Avoidance of the clinical syndrome of acute right-sided heart failure after heart transplantation is, unfortunately, not possible. Clinical experience and the literature certainly suggest that a significant factor in the successful management of right ventricular (RV) failure is recipient selection. Moreover, threshold hemodynamic values beyond which RV failure is certain to occur and heart transplantation is contraindicated do not exist. Nor are there values below which RV failure is always avoidable. Acute RV failure will remain a difficult and ever-present clinical syndrome in the transplant recipient. Goals in the treatment of this clinical problem include:

1. Preserving coronary perfusion through maintenance of systemic blood pressure.
2. Optimizing RV preload.
3. Reducing RV afterload by decreasing pulmonary vascular resistance (PVR).
4. Limiting pulmonary vasoconstriction through ventilation with high inspired oxygen concentrations (100% FiO₂), increased tidal volume and optimal positive end expiratory pressure ventilation.

Inhaled nitric oxide is recommended before leaving the operating room in cases where the initial therapies have had little impact. Intra-aortic balloon counterpulsation is employed in patients with impaired left ventricular (LV) function and may be of benefit in patients with RV dysfunction resulting from ischemia, preservation injury or reperfusion injury. Optimal LV function reduces RV afterload and PVR. A proactive decision regarding RV assist device implantation is made before leaving the operating room and is highly dependent upon overall hemodynamics, size and function of the ventricles as seen on transesophageal echocardiography, renal function and surgical bleeding. Only through careful preoperative planning can this life-threatening condition be managed in the postoperative period. (J Am Coll Cardiol 2001;38:923–31) © 2001 by the American College of Cardiology

Registry data from the International Society of Heart and Lung Transplantation show that, despite advances in perioperative management, right ventricular (RV) dysfunction accounts for 50% of all cardiac complications and 19% of all early deaths in patients after heart transplantation (1).

Right ventricular dysfunction and pulmonary hypertension have long been considered vexing problems in cardiac surgery. As early as the 1950s, Guyton et al. (2) conducted experiments in an animal model of pulmonary hypertension. They demonstrated that, when the normal RV was exposed to increased pulmonary artery pressure, it would suffer acute failure, resulting in circulatory collapse of the animal.

In the 1960s at Stanford, several early post-transplantation deaths were due to acute right-sided heart failure (HF). It occurred in patients with pulmonary hypertension, reviving the idea that the normal (donor) right ventricle is unable to bear a sharp increase in its external workload. This led to a refinement in recipient inclusion criteria by excluding patients with severe pulmonary hypertension (2).

In 1971, Griepp et al. (3) first reported the relationship between elevated preoperative pulmonary vascular resistance (PVR) and the risk of death from acute RV failure after heart transplantation. Numerous other studies confirmed this association (4–6).

Subsequent analyses of larger numbers of patients confirmed PVR as an incremental risk factor for early death after heart transplantation. Indeed, preoperative pulmonary hypertension and increased PVR have not only been associated with post-transplant morbidity from acute RV failure and all-cause perioperative mortality, but they have also associated with other causes of postoperative morbidity, including post-transplant infections and arrhythmias (7,8).

Pulmonary hypertension, like arterial hypertension, is a phenomenon of diverse causes that include both increases in flow and in resistance across the pulmonary vascular bed. Patients with chronic HF may develop pulmonary hypertension for several reasons, including direct backward transmission to the lungs of increased left ventricular (LV) pressure resulting in a “reactive” increase in pulmonary pressure due to pulmonary vasoconstriction (9). This reactive pulmonary vasoconstriction may eventually lead to irreversible elevation of PVR. The exact time course for the development of pulmonary hypertension varies by HF etiology but usually will take years to develop.

Pulmonary hypertension and increased PVR are often used interchangeably. They are, however, two distinct physiologic events with important respective hemodynamic con-
sequences for the patient. The recognition that pulmonary hypertension may occur with or without reversible elevation of PVR is of key importance in predicting the success or failure of the transplanted heart.

THE ANATOMY AND PHYSIOLOGY OF THE RV

Anatomically, the RV can be divided into an inflow and outflow region. The crista supraventricularis is a muscular region that separates the inflow and outflow portions of the RV and is continuous with the tricuspid valve anterior leaflet, the interventricular septum and the RV free wall. The crista supraventricularis functionally integrates mechanical events during systole to narrow the orifice of the tricuspid valve and to cause the RV free wall to move toward the septum propelling blood into the lungs. The pattern and timing of contraction is different for the inflow and outflow portions. Contraction of the RV inflow region occurs before that of the outflow region, resulting in a peristaltic action. The earlier contraction of the inflow region may occur because of the presence of more Purkinje fibers. Contraction of the outflow region is of longer duration than the inflow region (10).

Herdt et al. (11) demonstrated that not only do these regions differ in embryological structure, but they also differ in response to inotropes. The outflow tract arises from the bulbus cordis, whereas the inflow tract arises from the ventricular portion of the primitive cardiac tube (11). The inotropic response of the outflow tract is greater than that of the inflow tract, perhaps as a mechanism to protect the pulmonary vasculature from high pressure (11).

The shape of the RV in cross-section is that of a crescent. The thin RV free wall embraces the interventricular septum along with the LV during contraction. The interventricular septum is pulled toward the LV with subsequent RV free wall flattening. While contraction of the LV involves radial constriction and longitudinal shortening, RV contraction involves free wall shortening and flattening (10). The smaller mass and lower systolic and diastolic pressures of the RV result in coronary blood flow during both systole and diastole.

The thin walls and crescent shape result in a highly compliant RV chamber, which is able to accommodate large increases in volume. However, the adaptive mechanisms of the RV are not well suited to large increases in pressure. The normal pulmonary vasculature provides a low-pressure system that can respond to great fluctuations in blood flow without a great change in pressure by the recruitment of underperfused pulmonary blood vessels along with further dilation of already perfused pulmonary blood vessels.

Formerly, the RV was viewed as a passive conduit connecting the venous circulation to the pulmonary circulation. As such, the RV was not considered to be as important as the LV in the maintenance of normal hemodynamics. It is now recognized that the RV and LV are interdependent and have similar vitally important functions. The ventricles share a common blood supply through the interventricular septum. The interventricular septal configuration may be altered during diastole if there is acute distention of either ventricle. Acute ventricular dilation will result in alterations to the opposing ventricle. These alterations will include changes in compliance, geometry and blood flow. For example, with acute failure of the RV from any cause, the RV will dilate, increase its wall tension and become ischemic and less compliant; and the interventricular septum will shift toward the LV, leading to a smaller underfilled LV (9,10).

PULMONARY HYPERTENSION AS A RISK FACTOR FOR HEART TRANSPLANT PATIENTS

Once a diagnosis of preoperative pulmonary hypertension has been defined by cardiac catheterization, it is important for patients to be subdivided further into those with “fixed” or “irreversible” PVR and those with “reactive” or “reversible” PVR. Reactive PVR may be discerned by measuring baseline hemodynamics followed by provocative therapy with pulmonary vasodilators and repeat hemodynamic measurements. Agents such as sodium nitroprusside, adenosine, prostacyclin and inhaled nitric oxide have been used for this purpose (11–14). Pulmonary vascular resistance, PVR index (PVRI), peak systolic pulmonary artery pressure (SPAP) and transpulmonary gradient (TPG) are hemodynamic measurements that should be evaluated carefully before transplantation. No one test can accurately predict outcome, but together, these evaluations are useful for risk stratification. Clearly, patients with reversible components to their pulmonary vasculature have a better prognosis than patients with fixed or irreversible pulmonary hypertension.

Michler et al. (15) have reported an approximately fourfold higher transplant mortality among patients with fixed pulmonary hypertension when compared with patients without pulmonary hypertension. Of particular importance, the transplant mortality for patients with reactive pulmonary hypertension remains high and does not fall to the level seen in patients without pulmonary hypertension (15,16).

At the Ohio State University, it is our practice to define “fixed” pulmonary hypertension (patients considered to be at high risk for transplantation) as those patients who, after

<table>
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<th>Abbreviations and Acronyms</th>
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<tr>
<td>cAMP = cyclic adenosine 3’5’ monophosphate</td>
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<tr>
<td>CVVHD = continuous venous-venous hemofiltration and dialysis</td>
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<tr>
<td>GMP = guanosine monophosphate</td>
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<td>HF = heart failure</td>
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<tr>
<td>LV = left ventricle, left ventricular</td>
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<tr>
<td>PVR = pulmonary vascular resistance</td>
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<tr>
<td>PVRI = pulmonary vascular resistance index</td>
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<tr>
<td>RV = right ventricle, right ventricular</td>
</tr>
<tr>
<td>SPAP = systolic pulmonary artery pressure</td>
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<td>TPG = transpulmonary gradient</td>
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proximate vasodilator therapy, have either a PVR $\geq 4$ WU, a PVRI $\geq 6$ WU/m$^2$ (particularly useful in the pediatric and small size patient population), an SPAP $\geq 60$ mm Hg or a TPG $\geq 15$ mm Hg (17–19). The patients who present the most cause for concern are those for whom several parameters are elevated. Importantly, each of these hemodynamic parameters may act independently. For example, a PVR = 4 WU may be seen in a patient with an SPAP = 40 mm Hg and a TPG = 12. Distinguishing whether a patient such as this can be successfully transplanted requires experience, careful preoperative therapy and monitoring, intuition and a measure of good luck.

Over the years, we have learned that there exists a group of patients who at first evaluation may be thought to have irreversible pulmonary hypertension, but who may be converted into the reactive category through vasodilator conditioning. “Vasodilator conditioning” is an aggressive sequence of long-term inotropic support (e.g., dobutamine or milrinone) followed by provocative testing, followed by the addition of a second inotrope, followed by provocative testing, all performed in an attempt to condition the pulmonary vasculature into a maximally dilated state. If the conditioning is successful, these patients may be considered for transplantation and, if accepted, should be maintained on this regimen until transplantation. These patients require intensive management after transplantation and remain at significant risk for acute RV failure.

The expectation is that a patient’s elevated pulmonary artery pressure and resistance will fall after transplantation. The time course for this appears to vary in the literature. For example, Bhattacharya et al. (20) evaluated post-transplant resolution of pulmonary hypertension and reported a continual decrease in hemodynamic indexes throughout the first year, with 80% of patients demonstrating normal PVR at one year.

The remarkable results seen with prostacyclin in the management of patients with primary pulmonary hypertension have prompted interest in using this agent in the preoperative conditioning of patients with secondary pulmonary hypertension stemming from chronic HF. Our team and others have seen dramatic clinical improvement in patients with congenital heart disease and Eisenmenger’s syndrome referred for heart-lung transplantation. These patients have exhibited subjective clinical improvement, elimination of cyanosis, improved RV function and increased exercise performance. Whether this improvement can be expected to be long lasting and whether these findings should prompt surgical correction of the cardiac defect combined with lung transplantation remain controversial. It should be recognized that long-term prostacyclin therapy is an extremely expensive therapy that should be reserved for situations in which other therapies have proved unsuccessful.

Unfortunately, normal preoperative PVR does not rule out the potential for increased PVR and acute RV failure after heart transplantation. Organ preservation and cardio-

pulmonary bypass have deleterious effects upon ventricular function, and it has been shown that cardiopulmonary bypass may result in an increase in PVR (21).

**TREATMENT OF RV FAILURE**

Right ventricular failure in heart transplant recipients is of multifactorial etiology. Most commonly, it results from coupling a donor heart not adapted to elevated pulmonary artery pressure and resistance to the increased afterload of pulmonary hypertension and increased pulmonary resistance in the recipient. Additionally, adaptation by the donor heart may be impaired by ischemia and reperfusion injury associated with organ preservation.

Right ventricular failure results in dilation, ischemia and decreased contractility. Decreased pulmonary blood flow and leftward septal shift subsequently leads to lower LV filling and reduced systemic cardiac output.

In order to optimize RV hemodynamics, one must consider the following manipulations. These include maximizing coronary perfusion through maintenance of aortic pressure, reducing preload to a distended and ischemic RV, decreasing RV afterload by reducing PVR, optimizing myocardial oxygen delivery and limiting ventricular oxygen consumption. Arrhythmias and atrioventricular conduction disturbances should be appropriately treated to maintain stroke volume of the right and left ventricles. Prevention of low cardiac output is mandatory. Effective therapy for RV failure remains very challenging.

Although numerous therapeutic options have been suggested, there is no single best approach to the treatment of RV failure. Key elements include judicious fluid infusion, inotropic support and high-inspired oxygen concentrations (100% FiO$_2$) to encourage pulmonary dilation. Optimizing RV preload should be considered if central venous pressure is $<$10 mm Hg, which would be unlikely. The administration of intravenous fluids, resulting in an increase in right atrial pressure without a concomitant increase in cardiac output, would suggest that no further volume replacement is necessary.

Isoproterenol and dobutamine are frequently used to increase contractility and reduce RV afterload. They are often inadequate to reverse RV failure, and they may induce arrhythmias as well as increase myocardial oxygen consumption. Various modes of pharmacological vasodilation have been described, including prostaglandins, beta-sympathomimetics, phosphorylase III inhibitors (milrinone), nitro compounds (nitroglycerin, sodium nitroprusside), alpha-adrenolitics (tolazoline, hydralazine), adenosine and inhaled nitric oxide. These vasodilators have all been used with variable degrees of success (Table 1). Vasodilator treatment is often complicated by hypotension, which may compromise RV coronary blood flow and, additionally, worsen RV failure (22–27). This is often why alpha-adrenergic agonists such as levarterenol are instituted as complementary therapy.

The goal in the treatment of RV failure is to dilate
### Table 1. Pharmacotherapy for Pulmonary Hypertension and Right Ventricular Failure After Heart Transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent Studied and Dosage</th>
<th>No. of Patients</th>
<th>Response</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Williams et al. (1995) (55)</td>
<td>Inhaled NO up to 70 ppm</td>
<td>5</td>
<td>Inhaled NO was used in patients with right ventricular failure after failed treatment with prostacyclin and sodium nitroprusside. All patients survived and were discharged from the hospital.</td>
<td>When 70 ppm NO and FiO₂ of ≥0.6 were used safety appeared confirmed.</td>
</tr>
<tr>
<td>Auler et al. (1996) (42)</td>
<td>Inhaled NO 20 ppm</td>
<td>10</td>
<td>Significant decrease in SVRI (p = 0.01), PVRI (p &lt; 0.05), PVR/SVRI (p = 0.0025), TPG (p = 0.05) and an increase in CI (p = 0.0007). No changes in MPAP, SAP, PWP, RAP.</td>
<td>Selective action of inhaled NO on pulmonary circulation confirmed.</td>
</tr>
<tr>
<td>Kieler-Jensen et al. (1995) (26)</td>
<td>Inhaled NO 5, 10, 20 ppm Prostacyclin 16 ± 2 ng/kg/min Prostaglandin E1 202 ± 27 ng/kg/min Sodium nitroprusside 1.0 ± 0.2 μg/kg/min</td>
<td>13</td>
<td>CO, SV, RVEDV, CVP were the highest with prostacyclin compared with both prostaglandin E1 and sodium nitroprusside. SVR and PVR were lowest with prostacyclin. PVR was highest with sodium nitroprusside. MPAP, TPG, CVP decreased with all treatments, but most pronounced effect was noted with inhaled NO 20 ppm.</td>
<td>Prostacyclin was the best choice for i.v. vasodilatory treatment in patients after heart transplantation. Inhaled NO is the only selective pulmonary vasodilator. Useful in cases of severe right ventricular failure associated with hypotension.</td>
</tr>
<tr>
<td>Kieler-Nielsen et al. (1993) (25)</td>
<td>Prostacyclin 12.4 ± 1.7 ng/kg/min Sodium nitroprusside 3.3 ± 1.7 μg/kg/min Nitroglycerin 6.6 ± 1.8 μg/kg/min</td>
<td>9</td>
<td>CO, SV, RVEDV, CVP were higher for prostacyclin than for nitroglycerin or sodium nitroprusside. PVR was lower for prostacyclin than for sodium nitroprusside. SVR was lowest for prostacyclin. PVR/SVR ratio did not differ for these three vasodilators.</td>
<td>Prostacyclin was a less efficient venodilator and a more efficient dilator of systemic resistance vessels. Prostacyclin was not more selective to the pulmonary circulation than nitroglycerin or sodium nitroprusside.</td>
</tr>
<tr>
<td>Pascual et al. (1990) (27)</td>
<td>Prostacyclin 0.5 up to 5.0 ng/kg/min</td>
<td>9</td>
<td></td>
<td>The use of prostacyclin enabled weaning from other drugs within 48 h. No side effects, no worsening of hemodynamics after discontinuation of prostacyclin.</td>
</tr>
<tr>
<td>Bauer et al. (1997) (19)</td>
<td>Prostaglandin E1</td>
<td>13 (Gr 1) + 19 (Gr2)</td>
<td></td>
<td>Prophylactic therapy of pulmonary hypertension with vasodilators in infants and children after heart transplantation was safe and effective in preventing right ventricular failure in the postoperative period.</td>
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<tr>
<th>Preop</th>
<th>Postop</th>
<th>Late</th>
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<tr>
<td>RAP</td>
<td>9 ± 6</td>
<td>7 ± 6</td>
</tr>
<tr>
<td>PAP</td>
<td>38 ± 10</td>
<td>32 ± 8</td>
</tr>
<tr>
<td>CI</td>
<td>1.6 ± 0.4</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>PVR</td>
<td>466 ± 91</td>
<td>421 ± 368</td>
</tr>
<tr>
<td>SVR</td>
<td>2,089 ± 290</td>
<td>1,318 ± 263</td>
</tr>
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Gr 2 (preventive therapy with prostaglandin E1 plus inotropic support started during weaning from cardiopulmonary bypass. Three of 19 patients died. Prostaglandin E1 initial dose was 50 ng/kg/min. Max dose 200 ng/kg/min used if PAP rose to a value higher than half of systemic pressure. Treatment was continued up to 48 h.)
pulmonary vessels and reduce PVR while maintaining systemic blood pressure and coronary perfusion. Except for inhaled nitric oxide, all other drugs currently used to treat pulmonary hypertension and increased PVR are nonselective vasodilators and may lead to systemic hypotension.

End stage therapies include RV assist devices, extracorporeal membrane oxygenation and, of historical interest, pulmonary arterial counterpulsation.

GUIDELINES TO SPECIFIC DRUG THERAPIES

Isoproterenol. Isoproterenol, a nonselective beta-agonist, is a positive inotropic and chronotropic agent, and in therapeutic doses it increases cardiac output (28). However, in contradistinction to other inotropic drugs, isoproterenol produces pulmonary and peripheral vasodilation (28,29). As a pulmonary vasodilator, isoproterenol is one of the preferred inotropic agents in heart transplantation patients with elevated PVR. The dosage of isoproterenol should be reduced gradually because PVR may return quickly to elevated baseline levels after discontinuation of this drug.

Dobutamine. Dobutamine is primarily a beta-agonist with only minimal alpha-receptor agonist activity. This agent is, therefore, useful when further vasoconstriction is undesirable. At higher doses, dobutamine may induce tachycardia and atrial arrhythmias and increase oxygen demands. It is useful as an inotrope in patients with HF and elevated pulmonary artery pressures. The mechanism of action is through the cyclic adenosine 3'5' monophosphate (cAMP)-mediated intracellular pathway for inotropic stimulation.

Milrinone. Milrinone belongs to the class of drugs known as bipiridine phosphodiesterase III inhibitors. Their positive inotropic action is combined with a vascular smooth muscle-relaxing effect. The pharmacologic action of milrinone is mediated via the cAMP pathway; thus, it is independent of adrenoreceptor activity or increased catecholamine levels. Application of phosphodiesterase III inhibitors avoids stimulation of downregulated or desensitized beta-receptors, which may be seen commonly in HF patients managed with long-term dobutamine therapy before transplant. Unlike dobutamine, milrinone does not increase oxygen demand, presumably because milrinone reduces arterial afterload. Beta-agonists can be combined with phosphodiesterase inhibitors to produce synergistic hemodynamic effects as well as increasing cAMP levels via two separate, and possibly synergistic, mechanisms (30,31).

In an animal model of heart transplantation with pulmonary hypertension, it was demonstrated that intravenous administration of milrinone increased RV preload recruitable stroke work and decreased mean pulmonary artery pressure (31).

Thyroxine and glucagon may also increase adenyl cyclase activity, increasing cAMP and producing a similar effect on RV function (32–34). We have used both tri-iodothyronine (the active metabolite) and L-thyroxine in cases of severe RV failure, with anecdotal improvement in rare cases.
Prostaglandin E1 and prostacyclin. Prostaglandin E1 and prostacyclin are naturally occurring substances, with similar structures and short half-lives in the circulation. They are potent pulmonary vasodilators. Both agents are effective in the treatment of increased PVR and RV failure in patients after heart transplantation and in patients who receive RV assist devices (35–37). After intravenous infusion, prostaglandin E1 is almost completely cleared from the circulation during its first pass through the lungs. Prostacyclin also has a short half-life, but it is metabolized in the liver.

It has been demonstrated that prostaglandin E1 is at least as effective as nitroglycerin or nitroprusside in reversing pulmonary hypertension. In several reports, patients who responded to prostaglandin E1 treatment had postoperative mortality rates approaching patients without pulmonary hypertension (38–40).

In pediatric patients, Bauer et al. (18) demonstrated that the early administration of prostaglandin E1 had an advantage over delayed treatment of clinically evident RV failure. Early vasodilator therapy with prostaglandin E1 and the phosphodiesterase III inhibitor enoximone was introduced immediately before weaning from cardiopulmonary bypass, limiting pulmonary hypertension and RV failure.

A similar therapeutic profile has been observed with prostacyclin. When used in doses between 0.5 ng/kg per min to 5.0 ng/kg per min, prostacyclin had few side effects. Importantly, hemodynamic conditions were stable after the discontinuation of prostacyclin. The addition of prostacyclin in patients with pulmonary hypertension has been credited with the ability to wean other vasodilatory drugs within a short period of time.

Kieler-Jensen et al. (26) compared the hemodynamic profile of prostacyclin with sodium nitroprusside and nitroglycerin showing that postoperative vasodilation with prostacyclin was associated with a higher stroke volume and cardiac output compared with nitroprusside and nitroglycerin. Prostacyclin infusion also resulted in pronounced systemic vasodilation without lowering central filling pressures. In a second study by Kieler-Jensen et al. (26), they demonstrated that the pulmonary vasodilatory effect of prostacyclin was more pronounced than that seen with nitroglycerin but was comparable to the effect seen with nitroprusside. However, the systemic vasodilation caused by prostacyclin was more pronounced than that seen with either sodium nitroprusside or nitroglycerin. In essence, prostacyclin was no more selective for the pulmonary circulation than nitroprusside but was a significantly more effective systemic vasodilator than either nitroglycerin or sodium nitroprusside.

When the hemodynamic effects of prostaglandin E1, nitric oxide and nitroprusside were compared, it was demonstrated that both systemic and PVR were lowest, while stroke volume and cardiac output were highest with prostacyclin. On the other hand, nitric oxide was the only selective pulmonary vasodilator and, therefore, the only agent not associated with the addition of an alpha agonist to support systemic blood pressure.

Adenosine. Adenosine is a pulmonary vasodilator with a very short half-life. It is primarily used as a provocative agent in the preoperative evaluation of patients with pulmonary hypertension. The vasodilating action of adenosine is mediated through membrane A2 receptors on pulmonary vascular smooth muscle cells with subsequent activation of adenyl cyclase and release of cAMP. Adenosine is cleared from the circulation by adenosine deaminase after a single pass through the lungs. The selective action of adenosine on the pulmonary circulation results from its very short plasma half-life (< 10 s), limiting the amount of adenosine that reaches the systemic circulation.

Adenosine is a suitable diagnostic agent to determine reversibility of pulmonary hypertension in patients awaiting heart transplantation. Adenosine lowers the transpulmonary gradient and PVR, but its clinical application for long-term therapy is limited due to its effect of increasing pulmonary capillary wedge pressure and the risk of inducing pulmonary edema. Therefore, it is rarely used in the management of acute RV failure resulting from pulmonary hypertension.

Interestingly, Fullerton et al. (41) used 50 μg/kg per min of adenosine to treat pulmonary hypertension in a group of patients after valve replacement and coronary bypass surgery without inducing systemic hypotension. However, others have shown that, when adenosine is infused in higher doses (70 mg/kg per min to 100 mg/kg per min), systemic vasodilation has been shown to occur (42–44).

Inhaled nitric oxide. Nitric oxide is a gaseous biological mediator released by the vascular endothelium. It is a potent, rapidly acting and selective pulmonary vasodilator. Inhaled nitric oxide decreases PVR and pulmonary pressure without affecting systemic vascular resistance (45,46).

Nitric oxide exerts its vasorelaxation action by stimulating cyclic guanosine monophosphate (GMP) release in smooth muscle cells. Because the half-life of cyclic GMP is < 1 min, the vasodilating action of nitric oxide essentially ends when inhaled nitric oxide is withdrawn. Nitric oxide is quickly inactivated by hemoglobin, forming methemoglobin, nitrate and nitrite ions (47). The fact that nitric oxide is inactivated directly in the lumen of the vessel limits its effect to the vascular smooth muscle adjacent to the alveolar unit. The affinity of hemoglobin for nitric oxide is 3,000 times greater than that for oxygen. Nitric oxide is a labile agent with a half-life of 111 ms to 130 ms, which depends on the ambient oxygen concentration.

It is the oxidation of nitric oxide to NO2 that is responsible for its toxicity. The concentration of inhaled nitric oxide should be closely monitored. The Occupational Safety and Health Administration has established a limit of 5 ppm per 8 h per 24-h interval as the upper limit of safe human exposure (48).

Auler et al. (49) suggested using inhaled nitric oxide immediately after heart transplantation to prevent RV failure. In addition to selective pulmonary vasodilation,
inhaled nitric oxide can improve hypoxemia by improving the ventilation perfusion relationship as a result of its delivery as an inhalational agent. This improvement in oxygenation is produced with lower doses of inhaled nitric oxide than that required to induce vasodilation.

In contrast, the intravenous nonselective pulmonary vasodilators dilate all blood vessels of the lung. Thus, nonselective pulmonary vasodilators can lead to ventilation perfusion mismatch and increased shunt fraction as a consequence of vasodilatation and increased pulmonary blood flow to regions of poorly ventilated lung. Since nitric oxide is delivered as an inhalation agent, it only reaches ventilated regions of the lung, dilating those blood vessels and resulting in better ventilation perfusion matching.

**Assist devices.** The goal in the treatment of RV failure is to provide adequate support of the transplanted heart permitting time for recovery. Excellent long-term function may be expected. Initial results with RV assist devices in the treatment of RV failure were poor (50,51). With experience, the midterm results with RV assist devices have been somewhat more promising.

One important observation has been that implantation of an RV device reduces elevated right-sided pressures in patients who survive the removal of the device. Failure to reduce central venous pressure was a negative predictor for survival. In addition, the RV assist device improved organ function (normalization of transaminase levels, urine output, relieved hepatic congestion) in those who were found to survive. Ideally, RV assist devices should be implanted early to avoid end organ damage and should be continued for sufficient time for the patient to show signs of recovery, that is, a decrease in central venous pressure and diastolic pulmonary artery pressure (52).

Our experience has confirmed the critical importance of kidney function to outcome. It is our routine practice to splice into the Abiomed (Danvers, Massachusetts) RV assist device tubing, the connectors necessary for continuous venous–venous hemofiltration and dialysis (CVVHD). This is performed even if a patient appears to have adequate renal function, since one must anticipate the potential for renal dysfunction and failure. If we have chosen to insert a Thoratec (Pleasanton, California) RV assist device, we will insert the necessary CVVHD catheters in the femoral vessels before leaving the operating room. The ability to remove volume from the circulation has been a major advance in the critical pathway for these desperately ill patients.

It is our opinion that the selection of a right-sided device depends on three issues: 1) anticipated duration of device implantation, 2) expectation for early endotracheal tube extubation and mobility of the patient, and 3) cost. Both devices are similar in terms of ease of insertion and device management. Patients on the Thoratec device are easier to mobilize and ambulate, and this device is better suited to long-term implantation. Cost considerations are institutionally dependent but are clearly influenced by time in use of the device. Complications of circulatory assist devices include infection, bleeding, coagulation abnormalities, multiple organ failure and neurological complications.

Of course, the most difficult question to answer is when to insert an RV assist device. In our experience, the routine use of nitric oxide has reduced the incidence of RV failure requiring right-sided circulatory support. Nevertheless, this clinical syndrome continues to occur, and the decision regarding implantation of an RV assist device remains a difficult one.

The lesson we have learned over the years is to begin with a careful and stepwise review of all hemodynamic parameters after the institution of maximal inotropic and vasodilator support. The assessment includes a review of RV and LV function and size by transesophageal echocardiography, the status of mediastinal bleeding, oxygenation, presence of arrhythmias and urinary output. This assessment invariably takes place after several unsuccessful attempts to separate the patient from cardiopulmonary bypass and approximately 1 h after removal of the aortic crossclamp. By this time the surgeon and anesthesiologist generally have a “feel” for whether or not there is any improvement in the patient’s clinical condition. With this clinical assessment clearly in mind, the observation of a small hyperdynamic LV, a dilated RV, marginal urine output, atrial or ventricular arrhythmias, or coagulopathy, should stimulate the team to insert an RV assist device. Since a coagulopathy will require ongoing aggressive volume resuscitation with blood products, one can anticipate worsening of pulmonary hypertension and pulmonary edema from the volume infusion. This is likely to further worsen RV failure and its secondary effects on cardiac output and end organ perfusion. We have come to the opinion that it is safer and easier to err on the side of RV assist device insertion, recognizing the possibility of early removal, as opposed to waiting until the patient develops low output syndrome, arrhythmias, congestion and renal dysfunction/failure.

**Oversizing of the donor heart.** At one time it was common practice for patients with significant preoperative pulmonary hypertension to receive donor hearts from patients with body weights equal to or greater than that of the recipient. It was believed that the larger the donor, the greater the ability of the heart to adapt to a recipient’s elevated PVR. It was also believed that oversizing helped in the early adaptation of the donor heart and improved the outcome of orthotopic heart transplantation in recipients with preoperative pulmonary hypertension (53,54). However, several investigators, including Constanzo-Nordin et al. (55) demonstrated that the outcome of recipients given smaller hearts was similar to that of those given larger hearts. Moreover, they demonstrated that oversizing donor hearts did not improve the outcome of orthotopic heart transplantation for recipients with reversible preoperative pulmonary hypertension. In fact, they suggested that oversizing the donor heart in patients without pulmonary hypertension might increase mortality. This issue remains controversial and many investigators including Yeoh et al.
Management algorithm for acute RV failure in cardiac transplant patients. Avoidance of this clinical syndrome is, unfortunately, not possible. Clinical experience and the literature would suggest that a significant element in the successful management of RV failure is recipient selection. The literature confirms the absence of threshold hemodynamic values beyond which RV failure is certain to occur and heart transplantation is contraindicated. Neither are there values below which RV failure is avoidable.

Pulmonary hemodynamic indexes represent a spectrum of values traditionally thought to have a direct linear relationship with postoperative mortality; the higher the value, it was postulated, the more likely postoperative morbidity and mortality. Data described herein, however, soften this notion and, instead, suggest that the relationship between elevated preoperative pulmonary hypertension/resistance and postoperative complications and death is but an association—direct but not exact and by no means linear. Therefore, it becomes the independent decision of clinicians and their respective heart transplantation programs to establish guidelines for pulmonary hemodynamic thresholds beyond which a patient is ineligible for transplantation, as we have done at our institution.

Acute RV failure will remain a difficult and ever present clinical syndrome in the transplant recipient. Goals in the treatment of this clinical problem include:

1. Preserving coronary perfusion through maintenance of systemic blood pressure.
2. Optimizing RV preload.
3. Reducing RV afterload by decreasing PVR.
4. Limiting pulmonary vasoconstriction through ventilation with high inspired oxygen concentrations (100% FIO2), increased tidal volume and optimal PEEP ventilation.

At the Ohio State University, fluid administration, milrinone, levophed and isoproterenol are mainstays of the initial therapy. Inhaled nitric oxide is instituted before leaving the operating room and is highly dependent on preoperative planning can this life-threatening condition be managed in the postoperative period.

REFERENCES


Reprint requests and correspondence: Dr. Robert E. Michler, Professor and Chief, Cardiothoracic Surgery and Transplantation, Ohio State University Medical Center, 410 West 10th Avenue, North Doan Hall, N-847, Columbus, Ohio 43201-1214. E-mail: miche1.1@osu.edu.