Improving Perioperative Outcomes in Patients with End-Stage Heart Failure

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In the United States alone, more than 4.5 million people are affected by heart failure, with more than 500,000 new cases diagnosed each year. Although cardiac transplantation remains the "gold-standard" surgical treatment for heart failure unresponsive to maximal medical therapy, the chronic shortage of donor hearts has necessitated clinical trials of other surgical options. Over the past two decades, research, technological progress, and extensive clinical experience have resulted in the application of ventricular assist device (VAD) technology to a broader population of heart-failure patients, as these devices have proven to be viable therapeutic alternatives for therapy of end-stage heart failure. All patients undergoing cardiac transplantation or VAD insertion have multiorgan dysfunction as a result of irreversible, severe ventricular dysfunction resulting in low cardiac output. Recently, fenoldopam has been described as a vasodilator that might be useful in patients with decompensated heart failure, particularly in the perioperative setting. As a selective dopamine-1 receptor agonist, fenoldopam causes vasodilation in the systemic, renal, mesenteric, coronary, and pulmonary vasculature. Potentially, the pharmacologic properties of fenoldopam could be successfully exploited in patients undergoing medical or surgical treatment of end-stage heart failure. Controlled randomized trials are needed to demonstrate improvement in cardiopulmonary or renal outcomes in such patients.

[Rev Cardiovasc Med. *2003;4(suppl 1):S29–S34*]

Key words: Cardiac surgery • Heart failure • Transplantation • Heart-assist device

In the United States alone, more than 4.5 million people are affected by heart failure, with more than 500,000 new cases diagnosed each year.[1] Coronary artery disease and cardiomyopathy are the most common etiologies of end-stage heart failure, although congenital and valvular heart disease also account for a small percentage of cases. Despite improvements in medical therapy, the annual mortality from end-stage heart failure continues to increase.[2] The 1-year mortality rate exceeds 50% in patients with New York Heart Association (NYHA) class IV symptomatology, and the 5-year mortality rate is approximately 70%.[3]

Surgical Therapy for End-Stage Heart Failure

The first heart transplants performed by Barnard in 1967[4] and by Cooley and associates in 1968[5] led the way for surgical treatment of patients with end-stage heart failure who were unresponsive to medical therapy. With the development of effective immunosuppression with cyclosporine in 1982, more than 55,000 successful heart transplants have been performed worldwide.[6] Despite the increasingly high-risk patient population selected for cardiac transplantation, survival rates remain satisfactory because of continuing advances in therapeutic immunosuppression, surgical techniques, and the diagnosis and treatment of allograft rejection.

Although cardiac transplantation remains the "gold-standard" surgical treatment for heart failure unresponsive to maximal medical therapy, the chronic shortage of donor hearts has necessitated clinical trials of other surgical options.[7] Experimental mechanical circulatory support systems were introduced at the Texas Heart Institute, in Houston, as a bridge to transplantation, demonstrating the feasibility of this approach.[8–10] Improvements in ventricular assist device (VAD) technology led to the first successful bridge to transplantation in 1984.[11] Over the past two decades, research, technological progress, and extensive clinical experience have resulted in the application of VAD technology to a broader population of heart-failure patients, as these devices have proven to be viable alternatives for therapy.[7,12] Consequently, clinicians are now confronted more frequently with the specialized perioperative and chronic care of patients who receive these devices.[13]

Such patients generally fall into three different categories. The first group consists of patients with severe myocardial infarction, myocarditis, or end-stage heart disease who are not expected to recover and need mechanical assistance until a heart transplant is available. The second group consists of patients who require ventricular assistance to allow rehabilitation of the ventricle, such as postcardiotomy shock, when the combination of maximal drug therapy and intra-aortic balloon pump mechanical assistance are unsuccessful. The third group consists of patients who require long-term assistance because of difficulty in locating a suitable donor or ineligibility for transplantation for other medical reasons.[14] Interestingly, there is a growing amount of evidence to suggest that, after a period of time with mechanical assistance, even patients with severe heart failure undergo some degree of myocardial recovery.[15–17] Left ventricular unloading with assist systems generates a "reverse-remodeling" process with resultant compliance changes, decreased dilation, and a well-documented histological rearrangement of myocytes.[18] Some patients have actually undergone successful weaning from mechanical cardiac support.[19]

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Pathophysiology of End-Stage Heart Failure

All patients undergoing cardiac transplantation or VAD insertion have multiorgan dysfunction as a result of irreversible, severe ventricular dysfunction with an ejection fraction of approximately 10%–15%, resulting in low cardiac output. As such, these patients have a relatively fixed, low stroke volume and depend on an appropriate preload and heart rate to maintain marginal performance. Increasing preload further does not improve cardiac performance because the heart is on the flat or even descending limb of the Starling curve, and the preload reserve is exhausted.[13] In contrast, increasing afterload may dramatically decrease stroke volume, and, consequently, decrease cardiac output.

As the left and/or right ventricles fail, end-diastolic volume and myocardial fiber length increase. Eventually this results in cardiac dilation, increased left ventricular and pulmonary venous pressures, and pulmonary hypertension. These processes result in dyspnea and respiratory distress, with the need for supplemental oxygen. Other organ systems, such as the kidneys and liver, are compromised because of poor end-organ perfusion (low cardiac output) and chronic congestion (elevated venous pressures). Hepatic dysfunction is often present, with accompanying elevated prothrombin times and coagulopathy, as well as altered drug metabolism. Renal

dysfunction is also common, with decreased urine output and elevated creatinine and blood urea nitrogen levels. Although end-stage renal disease that requires chronic dependence on hemodialysis is usually a contraindication to cardiac transplantation or VAD implantation, moderate renal insufficiency resulting from low cardiac output does not preclude surgical therapy.[7] Continuous venovenous hemofiltration is often necessary in the postoperative period to facilitate fluid management in such patients. However, renal function usually improves as hemodynamics normalize, and the need for vasoconstricting drugs is reduced.

Compensatory neurohumoral mechanisms lead to sympathetic nervous system activation and persistent elevations in circulating catecholamines. Preload and peripheral vascular tone are maintained by activation of the renin-angiotensin-aldosterone system, resulting in increased sodium and water retention. Chronic circulating catecholamine elevations lead to myocardial β-adrenergic receptor downregulation, with decreased density and inhomogeneous distribution of receptors in myocardial tissue and resultant decreased responsitivity to positive inotropic agents.[20]

Pharmacologic Therapy for End-Stage Heart Failure

The therapeutic goals for treatment of severe heart failure are to increase cardiac output, reduce myocardial afterload, decrease sodium and water retention, and prevent thromboembolism.[21] Various combinations of inotropic agents, vasodilators, diuretics, β-receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, B-type natriuretic peptide (BNP), and anticoagulants are utilized to achieve these goals. For the purpose of this review, vasodilator therapy will be emphasized.

Vasodilator therapy is frequently needed to assess the responsiveness of pulmonary hypertension in patients with severe heart failure before heart transplantation.[22] Moreover, perioperatively, vasodilators are used to decrease afterload in order to augment cardiac output. In addition, vasodilators reduce preload, thereby reducing myocardial work and oxygen demand. A host of different systemically and locally active vasodilators have been used for these therapeutic end points, with varying degrees of success.[23] Such agents may have a cardioprotective effect following heart transplantation, in preventing right ventricular failure.[24] Care must be exercised to avoid a significant decrease in perfusion pressures by avoiding excessive lowering of blood pressure.

In the last decade, ACE inhibitors have become central to the management of chronic heart failure. ACE inhibitors combine both venous and arteriole dilator activity and improve the prognosis in these patients.[25] ACE inhibitors may attenuate many of the neuroendocrine processes associated with cardiac failure. These agents are administered chronically and in the preoperative period. Also, the nitrates (eg, nitro-

Main Points

- Despite improvements in medical therapy, the annual mortality from end-stage heart failure continues to increase.
- Cardiac transplantation is the ultimate surgical treatment for intractable heart failure, but a chronic shortage of donor hearts has led to clinical trials of other surgical options.
- Because ventricular assist device (VAD) technology today is applied to a broader population of heart-failure patients, clinicians are confronted with the specialized perioperative and chronic care of patients who receive these devices.
- Various combinations of inotropic agents, vasodilators, diuretics, β-receptor antagonists, angiotensin-converting enzyme inhibitors, B-type natriuretic peptide (BNP), and anticoagulants are utilized to increase cardiac output, reduce myocardial afterload, decrease sodium and water retention, and prevent thromboembolism.
- Fenoldopam is a vasodilator that has been approved for short-term clinical use in the management of severe hypertension, including malignant hypertension with deteriorating end-organ function.
- As a selective dopamine-1 receptor agonist, fenoldopam causes vasodilation in the systemic, renal, mesenteric, coronary, and pulmonary vasculature.
- Fenoldopam has potential for use in the medical management of acutely decompensated heart failure and pulmonary hypertension as well as perioperatively for the management of patients undergoing surgical procedures to treat end-stage heart failure.
- Well-controlled, randomized trials are clearly needed to demonstrate improvement in renal and/or cardiopulmonary outcomes in such patients.

glycerin and sodium nitroprusside) are suitable for perioperative use and may be useful for relieving the symptoms of pulmonary edema by reducing ventricular filling pressures and afterload. In addition, perioperatively, pulmonary vasodilators (eg, intravenous prostaglandin E_1, or BNP, or inhaled nitric oxide) are used to decrease right ventricular afterload, as guided by pulmonary arterial pressures.

Fenoldopam for End-Stage Heart Failure

Recently, fenoldopam has been described as a vasodilator that might be useful in patients with decompensated heart failure, particularly in the perioperative setting. Fenoldopam, a benzazepine derivative, is the first selective dopamine-1 (DA_1) receptor agonist that has been approved for clinical use. Administered parenterally, it acts predominantly as a vasodilator in peripheral arteries and as a diuretic in the kidneys. The U.S. Food and Drug Administration has approved it only for short-term use (up to 48 hours) in the management of severe hypertension, including malignant hypertension with deteriorating end-organ function.[26] Clearly, however, it has potential for other indications, including the medical management of acutely decompensated heart failure and pulmonary hypertension[22,27] as well as perioperatively for management of patients undergoing surgical procedures to treat heart failure.[28]

As detailed elsewhere in this issue, peripheral dopamine receptors are of two different types: DA_1 and DA_2.[29] DA_1 receptors are located postsynaptically on the smooth muscle of systemic, renal, coronary, cerebral, and mesenteric arteries, as well as the pulmonary vessels.[30] Vasodilation results from activation of DA_1 receptors through an increase in cyclic adenosine monophosphate production, and thus of adenyl cyclase. As a selective DA_1 receptor agonist, fenoldopam causes vasodilation in the systemic, renal, mesenteric, coronary, and pulmonary vasculature.[31,32] The presence of DA_1 receptors in human coronary and mammary arteries, and in saphenous vein smooth muscle, has been demonstrated using immunocytochemical techniques.[33] In one study, administration of fenoldopam (0.1 μg/kg/min) resulted in a small, nonsignificant increase in left internal mammary artery blood flow in patients undergoing elective coronary revascularization.[34] Also, agonism of dopaminergic-1 receptors in the pulmonary bed has been demonstrated to result in clearance of lung edema.[35] Thus, theoretically, the use of fenoldopam could not only reduce pulmonary vascular resistance, but could also enhance the clearance of lung fluid.[22]

Each of these effects would be beneficial in patients with decompensated heart failure. Potentially, the pharmacologic properties of fenoldopam could be successfully exploited in the perioperative period for patients undergoing surgical procedures for treatment of end-stage heart failure. However, there are no randomized, controlled, outcome studies addressing the cardiopulmonary effects of fenoldopam.

Fenoldopam also causes a natriuretic and diuretic effect in hypertensive as well as normotensive subjects through increased renal plasma flow and stimulation of specific DA_1 receptors in the tubules of the kidney.[36] No proven therapeutic agents exist for the treatment of acute renal failure. Although "low-dose" dopamine has been studied extensively, there is no clear experimental or clinical evidence to support its use, either to prevent or to treat acute renal failure.[37,38] The lack of a consistent effect with low-dose dopamine may be attributable in part to its simultaneous interaction with renal DA_2- and α_1-receptors. Stimulation of these receptors decreases renal blood flow, glomerular filtration rate, and sodium excretion.[39,40] These effects may offset those of DA_1 antagonism. Unlike dopamine, fenoldopam has no DA_2, α-adrenergic, or β-adrenergic agonism. When administered to patients with hypertension, fenoldopam reduces blood pressure in a linear, dose-dependent manner.[26] Despite the reduction in renal perfusion pressure that normally occurs with acute blood-pressure decreases, glomerular filtration rate and renal blood flow are maintained or increased during fenoldopam infusion.[41,42] The utility of fenoldopam as a potential renal protective agent is enhanced by the fact that at low doses, dilation of the renal vascular bed is achieved without inducing or aggravating systemic hypotension in normotensive subjects.[26,36]

The lack of a consistent effect with low-dose dopamine may be attributable in part to its simultaneous interaction with renal DA_2- and α_1-receptors.

Mathur and colleagues[36] demonstrated that, at the lowest dose of fenoldopam studied (0.03 μg/kg/min), significant renal blood flow increases occurred without changes in systemic blood pressure or heart rate. At 0.1 and 0.3 μg/kg/min, systolic blood pressure did not change; however, diastolic blood pressure was slightly but significantly lower in

the fenoldopam group than in the placebo group. None of the effects of fenoldopam were altered by volume status. Therefore, fenoldopam may be useful in preventing or treating renal insufficiency, even in patients who are not hypertensive. Evidence of the benefits of administering fenoldopam in animals with renal damage is accumulating.[26] However, unfortunately, to date, there are no current clinical data addressing renal outcomes, either in patients with end-stage heart failure or in other patient groups.

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At the Texas Heart Institute, fenoldopam (0.05–0.1 μg/kg/min) is used in most cardiac surgical procedures involving cardiac transplantation or insertion of a VAD. The infusion is started prior to cardiopulmonary bypass (CPB) and is continued into the postoperative period. The lowest dose has minimal vasodilatory effect, although increasing the dose beyond 0.1 μg/kg/min readily creates the desired amount of vasodilation for heart-failure patients. Prior to CPB, fenoldopam may be administered alone or in combination with other agents, eg, inotropes. After either transplantation or VAD insertion has been accomplished, inotropic support of the right ventricle and reduction of pulmonary vascular resistance become critically important, because without a functioning right ventricle (or at least a right ventricle and pulmonary circuit that do not obstruct flow), the left heart will not receive the preload needed to provide adequate cardiac output. Both goals may be aided by the use of inotropes such as milrinone, dobutamine, isoproterenol, or epinephrine, or with agents such as BNP, prostaglandin E_1, or inhaled nitric oxide, which have a more direct effect on the pulmonary circuit. Furthermore, some patients manifest very low systemic vascular resistance, either as an unwanted result of agents used for right ventricular support or as a syndrome associated with severe heart failure.[43] Although norepinephrine is sometimes effective, vasopressin, which has systemic effects, but relatively little effect on pulmonary vasculature, has proved useful in low doses.[43,44] Therefore, combinations of various agents, including fenoldopam, are common in the post-CPB and postoperative periods.

In time, fenoldopam may be administered as a standard protective agent for patients undergoing surgical therapy for end-stage heart failure, as well as for patients in other clinical situations known to lead to impaired renal function. However, well-controlled, randomized trials are clearly needed to demonstrate improvement in renal and/or cardiopulmonary outcomes in patients undergoing medical or surgical treatment for end-stage heart failure. ■

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