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Reviews

The Physiologic Basis for the Management of Ventricular Assist Devices

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Summary: Mechanical ventricular assist devices are now approved as destination therapy for terminal heart failure. It is the purpose of this review to discuss the physiology of this technology that is considered in outpatient care. The currently available pulsatile devices are solely dependent of preload volume and, when placed in the automatic mode, can maintain physiologic cardiac outputs with exercise. However, because of their dependence on preload volume, there are unique physiologic consequences; device bradycardia represents volume depletion, device tachycardia reflects volume overload. The differential diagnosis of left ventricular assist device dysfunction includes native right ventricular failure, native left ventricular recovery, or other technical considerations. The management of biventricular mechanical support as well as arrhythmia management and the role of echocardiographic assessment in this unique patient population will be discussed. Expertise in outpatient management of such devices is now a requisite for subspecialists in heart failure. In the future, technical innovations may simplify management for professionals, patients, and their families.

Key words: ventricular assist devices, destination therapy, left ventricular assist devices, right ventricular assist devices

Introduction

The past 5 years have witnessed substantial refinement in the management of heart failure. Large randomized studies have defined the role of beta-adrenergic blocking agents, converting enzyme inhibitors, aldosterone antagonists, and angiotension II receptor blocking agents. In the same 5 years, substantial progress has been made in technologies to alter the natural history of heart failure. Implantable cardiac defibrillators and biventricular pacing have been documented to have an impact on prognosis and functional status. Yet, despite these pharmaceutical and technical innovations, cardiac transplantation continues to be the only standard therapy for truly "end-stage" heart failure, but it has a trivial epidemiologic impact. With 40,000–50,000 new cases of terminal end-stage congestive heart failure each year in the United States, cardiac transplantation will only be performed on 2,200 patients. Fewer patients received transplants in 2005 than in 2000; xenotransplantation and stem cell therapy remain theoretical considerations that will require years of additional research.[1]

In the same 5 years, substantial progress has been made in the clinical uses of mechanical support.[2–4] Left ventricular assist devices (LVAD) are proven bridges to cardiac transplantation. More important, the recent Randomized Evaluation of Mechanical Assistance Therapy as an alternative in Congestive Heart Failure (REMATCH) study clearly favors device implantation over maximum medical therapy for terminal heart failure.[5] Because of this landmark trial, the Food and Drug Administration (FDA) has recently approved LVAD as a permanent therapy for end-stage heart failure, that is, destination therapy. It is conservatively estimated that 5,000 to 10,000 patients in this country could be served with permanent device implantation. It is the purpose of this review to introduce unique management issues of this technology to the clinical cardiologist, emphasizing the physiologic aspects of the current mechanical support devices that might be clinically relevant in the outpatient setting.

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Current Ventricular Assist Technologies

There are four evolving ventricular assist device (VAD) technologies that should be considered.[6] Most relevant are the implantable pulsatile devices that are pneumatically driven or electrically powered. These devices are approved for outpatient care, have widespread use, and are the sole focus of this review. Axial flow pumps provide a continuous flow output as an experimental alternative to the pulsatile devices, and

percutaneous continuous-flow devices can be used in acute cardiogenic shock, obviating the need for emergency thoracotomy. Finally, intracorporeal orthotopic biventricular VAD systems are now FDA approved as a bridge to transplantation. The CardioWest™ Total Artificial Heart (TAH) (SynCardia Systems, Inc., Tucson, Ariz., USA) is placed inside the chest after both ventricles are removed and is one of only two devices that can provide simultaneous biventricular support.[7]

Indications for Implantation of Ventricular Assist Devices

Ventricular assist devices may be implanted as bridge to transplantation or, in specified and approved centers, as destination therapy. In the latter instance, patients have been excluded from transplant by conventional criteria, yet remain willing to consider all options for treatment of terminal heart failure. The criteria for device implantation are outlined in Table I, but will vary from center to center because of clinical experience.

Implantable Pulsatile Devices

The pulsatile assist devices (PVADs) have generated the largest clinical experience as bridge to cardiac transplantation and destination therapy. The FDA-approved devices are summarized in Table II. The Thoratec® VAD system (Thoratec Corp., Pleasanton, Calif., USA) has external paracorporeal pneumatic pumping chambers and can be used for either univentricular or biventricular support. Because of the paracorporeal position of the pumping chambers, it is also utilized in the smaller adult and the pediatric population. Newer drive units now permit greater ambulation and hospital discharge. Long-term anticoagulation is required since the inflow and outflow valves are mechanical St. Jude valves.

The WorldHeart's Novacor® LVAS (WorldHeart Corp., Oakland, Calif., USA) and Thoratec's HeartMate® are implantable pulsatile univentricular assist devices that are electrically driven and hence fully portable. The size of the Novacor LVAS and the Thoratec HeartMate pumps precludes insertion in individuals whose body surface area (BSA) is < 1.5 m^2. The HeartMate develops an intrapump pseudointima with only aspirin, obviating the mandatory need for long-term warfarin anticoagulation. The inflow and outflow cannulas have porcine valves, and inflow valve durability has remained a technical challenge;[5] mechanical torque and intrapump pressure may be partially responsible for disruption of the inflow valve with resultant regurgitation.

Most large referral centers will have the paracorporeal Thoratec device and one of the electrically driven implantable devices available for use. The paracorporeal device will be considered in the smaller patient (BSA, 1.5 m^2) or when biventricular support is being considered. The electric pulsatile HeartMate device is approved for destination therapy.

The major long-term complications of any of the devices include device malfunction, infection, or thromboembolism. Careful echocardiographic studies may identify potential causes of device failure and prompt surgical intervention.[8] Meticulous attention must be given to avoid driveline infections or sepsis, and a therapeutic International Normalized Ratio (INR) of 2.5 to 3.5 is mandatory for the Thoratec HeartMate and the Novacor technology.

Variables of Ventricular Assist Devices

The PVADs have major variables to their function. These include mode of operation, device rate, drive pressure, vacuum pressure, and duration of systole for the pneumatic pump. The programmability of these variables does differ between devices.

The single most important of these variables for electric devices is the mode of operation. Devices may be placed in asynchronous mode, where the pumping rate of the LVAD is fixed and asynchronous to the native heart rhythm. This mode is generally used in the initiation of left ventricular support in the operating room. It may also be considered when weaning patients from the device, or when there is significant hemodynamic instability and preload and afterload are rapidly changing, that is, in the immediate postoperative period. A second mode of operation is the volume or automatic mode. In this instance, the LVAD continues to be asynchronous from the native rhythm and triggers systole when the LVAD is filled to approximately 90–95% of capacity (65–80 cc). In this mode, device rate and ultimately cardiac output depend

TABLE I Indications for placement of assist devices

Is patient a "bridge to transplant" or candidate for "destination therapy?"
Cardiac index < 1.5 l/min/m^2
Pulmonary capillary wedge > 25 mmHg on inotropic therapy
Systemic blood pressure < 80 mmHg on inotropic therapy
Continuous inotropic support and multiple inotropic drugs
Consideration of intra-aortic balloon counterpulsation
Impending renal or hepatic dysfunction

TABLE II Comparison of current left ventricular assist device (LVAD) technology for outpatient care

	HeartMate® XVE	WorldHeart Novacor®	Thoratec® VAD system
Position	Internal	Internal	External
Patient size	Large	Large	Medium/small
Power	Electric	Electric	Pneumatic
Capability	LVAD	LVAD	LVAD and/or RVAD
Duration	Years	Years	Possibly years
Anticoagulation	ASA	Coumadin	Coumadin

Abbreviations: RVAD = right ventricular assist device, ASA = aspirin.

upon passive filling of the device chamber. This mode of operation is used routinely, permitting increase in cardiac output through a physiologic range. A third operational mode is that of external asynchronous mode, in which the LVAD is synchronized to the patient's native rhythm. This is used in the rare instance when attempts are made to wean patients from mechanical support.

Device rate for mechanical support can also be programmed. A back-up device rate must be established if the patient is placed in the volume or the external asynchronous mode. Back-up rates are usually 50 to 60 beats/min. There are additional unique considerations for the Thoratec PVADs; duration of systole must be adjusted to permit for proper diastolic filling; device systole should be 25 to 30% of anticipated rate in order to keep the ejection duration constant, be it in the volume or asynchronous mode. Another variable will be drive pressure, the internal device pressure that leads to blood ejection. High drive pressures will compensate for variations in systemic blood pressure, and inadequate drive pressure will not properly eject blood, promoting stasis or thrombosis. The drive pressure is usually set approximately 100 mmHg above the systolic pressure; hence, a drive pressure of 230 to 245 mmHg for LVAD and 140 to 160 mmHg for right ventricular assist devices (RVAD). The final physiologic variable for pneumatic systems is the vacuum pressure, which assists with filling of the VAD and helps to overcome the intrinsic resistance from the inflow tubing length. The vacuum is usually adjusted to −25 to −40 mmHg.

Physiology of Ventricular Assist Devices

There is unique physiology established with the insertion of a mechanical pump into the circulatory system. First, two competing and parallel systemic pumps are created. They compete for the same blood volume returning through the left atrium and face the same systemic vascular resistance. It is imperative to long-term management to remember that an LVAD is solely preload dependent. With complete LVAD filling, cardiac output becomes defined by heart rate. If the LVAD is effectively draining and decompressing the native left ventricle throughout the cardiac cycle, the native ventricle should act as a passive conduit to filling of the mechanical pump and contribute little to systemic cardiac output through the native aortic valve. In fact, if the native left ventricle does contribute to systemic cardiac output by providing a stroke volume to open the aortic valve at rest, it suggests inadequate decompression of the native ventricle and device dysfunction.

The physiology of biventricular support is more complex and provides new insights to common clinical assumptions. In this instance, there are four ventricles that compete for the same preload volume. The two right-sided pumps and two left-sided pumps are independent of each other. Conventional clinical wisdom about the integration of right and left ventricular function overlooks that fact that left atrial return is greater that right atrial return. There is free communication between the bronchial circulation and the pulmonary capillary bed; hence, bronchial arterial flow, part of left ventricular output, returns to the left atrium via the pulmonary veins. Since mechanical devices are noncompliant without a physiologic Starling curve and cannot change stroke volume, the rate of preload filling determines output. If left atrial return is greater than right atrial return, mechanical left ventricular output must be greater than mechanical right ventricular output. This simple principle of mechanical support challenges decades of hemodynamic assumptions that the right and left ventricular outputs are equal.

Unique Clinical Consequences of Ventricular Assist Physiology

The absolute dependence of LVAD function on preload volume and the passive conduit of the native left ventricle create unique clinical scenarios. First, failure of the native right ventricle will result in delivery of an inadequate preload to the LVAD and a subsequent low output state. This may be the purest clinical example of right ventricle failure begetting left ventricular failure, rather than vice versa. Second, recovery of function of the native left ventricle can be perceived as dysfunction (inadequate filling) of the mechanical ventricle since the native ventricle's competition for the same preload may result in a reduction in the mechanical pump's output. Finally, function of either native or mechanical ventricle provides unique insights into the function of the other competing chamber and can be assessed by echocardiogram.[8]

The complexity of biventricular support physiology engenders separate concerns. First, native right ventricular recovery can occur independent of native left ventricular recovery. In this instance, it would be inappropriate to remove the RVAD if the patient were still dependent on LVAD support. Second, if right-sided (RVAD + native right ventricular) output equals or exceeds total left-sided (LVAD + native left ventricular) output, left atrial pressure precipitously rises and immediate pulmonary edema may result. Finally, the complexity (atrial or ventricular inflow cannulation) and number of insertions (two in-flow and two outflow cannulae) compounds the number of technical concerns that can arise with malfunction of either or both mechanical ventricles.

The absolute dependence on preload volume for either mechanical ventricle raises another dimension to their management that is counterintuitive to conventional clinical wisdom. When placed in the automatic (volume) mode, mechanical ventricle systole will be triggered when the pumping chamber is full. Therefore, the mechanical pumping rate is determined by the rate of filling. If there is volume depletion, the device will fill more slowly and cardiac output will fall. If there is volume overload, the device will fill faster and become "tachycardic," resulting in a greater cardiac output. In contrast to normal physiology, device tachycardia means volume overload, device bradycardia means volume depletion. In the outpatient management of assist devices, patients carefully monitor device rates in the automatic mode and will often vary diuretic dose depending on device rates and their im-

plications for preload volume; device rate of 75 to 80 beats/min is optimal; slower rates often reflect excess diuresis, higher rates volume overload.

Differential Diagnosis of Poor Device Function

The ideal hemodynamic profile following left ventricular assist device implantation should include a cardiac index > 2.2 l/min/m^2, systemic blood pressure > 90 mmHg, < 140 mmHg, and left and right atrial pressure < 10 mmHg, with adequate urine output. Any significant variation to the expected norm should raise a specter of pathophysiologic considerations unique to this patient population.

When malfunction of any ventricular device occurs, initial attention will focus on the implanted technology, surgical placement of the cannula, controlling circuitry, and adequacy of alarms.[9] If defects in such are excluded, understanding the principles of ventricular assist physiology allows one to establish an interesting differential diagnosis. If there is inadequate filling of the mechanical left ventricle, acute volume depletion secondary to bleeding, tamponade, or diuresis must be immediately excluded. Another common etiology of reduced LVAD output is native right ventricular failure; this scenario can present a major clinical problem; it may be justification for parental inotrope support—inotropic support of a native right ventricle to permit normal function of a mechanical left ventricle. The presurgical dilemma is, therefore, whether or not to provide concomitant RVAD support to avoid this post LVAD implant situation. A third differential diagnosis to decreased output of a mechanical left ventricle is recovery of the native left ventricle, for the native ventricle may compete with the mechanical pump for a given preload and provide a systemic stroke volume. Finally, clinicians must always question the adequacy of the valves that are part of a mechanical heart. Regurgitation of either the inflow valve (the "mitral" valve) or the outflow valve (the "aortic" valve) will present as volume overload and device tachycardia. In this instance, the pump itself is not dysfunctional but is rather working to accommodate the regurgitating volumes from dysfunctional valves.

Diagnosis and Management of Device Valve Dysfunction

The LVAD rate in the volume mode will also provide insight into the function of the inflow and outflow device valves. In the case of the HeartMate, these tissue valves are prone to regurgitation; inflow valve regurgitation is far more common than outflow valve regurgitation. Predisposing factors in inflow valve regurgitation include valve and conduit design, distortion of the conduit, infection, and the development of inappropriately elevated intrapump isovolumic pressures. The differential diagnosis to the elevated LVAD rate seen with inflow valve regurgitation includes any cause of volume overload, including renal failure, aortic valve insufficiency, or shunting. Inflow valve regurgitation should always be suspected when there is sudden inappropriate LVAD tachycardia (when in the volume mode); dyspnea and hemolysis may follow. The diagnosis can generally be determined by echocardiography or by cardiac catheterization with hemodynamic assessment and angiography. Outflow valve regurgitation is far less frequent and is usually secondary to infectious destruction. Finally, increased resistance to outflow may occur as a result of systemic hypertension, obstruction above the outflow valve at the site of anastamosis to the aorta, kinking of the conduit, and outflow valvular stenosis from fungal vegetation or thrombus.

Surgical therapy of device valve dysfunction must be considered once the diagnosis is made. While outflow valve regurgitation requires repeat sternotomy with all the attendant complications, inflow valve replacement can be accomplished by an abdominal incision over the inflow conduit. Inflow valve regurgitation can also be managed by several unique therapeutic strategies. First, the LVAD should be switched to the asynchronous mode and heart rate reduced to approximately 75, thereby reducing the torque on the inflow cannula and preserving pump longevity. However, this change must be done cautiously since the LVAD will not be adequately decompressing the rapidly developing preload seen by the native heart. As a consequence, filling pressures will rise and pulmonary edema can result. Second, conventional therapy for volume overload should be maximized with conventional vasodilator and diuretic therapy. Finally, synchronizing the PVAD with any native QRS contractions in the external asynchronous mode reduces the hemodynamic burden of inflow valve regurgitation by establishing two competitive systoles. These manipulations may be sufficient for improving the functional status of patients who are not candidates for inflow valve replacement.

There can be other catastrophic technology failures. Motor failure (primarily from ball bearing wear), ruptured diaphragms, and fractured power cables have been reported and can be successfully approached with the proper surgical expertise. Ball bearing wear, in particular, can be followed to some extent by examining the intake filter for particulate matter unique to the bearings.[10]

Arrhythmia Management for Ventricular Assist Devices

Arrhythmia management of VADs also presents unique clinical challenges. In fact, uncontrollable ventricular arrhythmias can be an indication for LVAD support. Although most dysrhythmias are well tolerated, they may compromise the filling and therefore the output of the pumps. In general, rapid ventricular arrhythmias may be clinically well tolerated, but the device output inevitably falls to some degree, and native right ventricular function may become compromised. Although not generally emergent, cardioversion and maintenance of sinus rhythm is recommended when ventricular arrhythmias are present. The management of implantable cardiac defibrillators (ICD) is variable, but the defibrillation feature is frequently inactivated while maintaining monitoring capacity of the ICD. Finally, all dysrhythmias may predis-

pose to thromboembolism and often necessitate the introduction of warfarin anticoagulation.

Echocardiography and Ventricular Assist Devices

Echocardiography of the native heart and of the LVAD becomes essential in the evaluation of LVAD function and understanding two competing ventricles.[8] The device itself is impossible to visualize, but significant inferences as to its function can be made from echocardiography. If the native ventricle is serving as a passive conduit, minimal aortic valve motion is seen; normal excursion of the aortic valve suggests either malfunction of the mechanical support system or return of native left ventricular function. Decompression of the left ventricle is also anticipated with proper functioning of an LVAD. If left ventricular size has not been reduced, it can be inferred that there may be inadequate ventricular decompression. Finally, a detailed Doppler analysis of the LVAD inflow cannula is required for the evaluation of suspected inflow valve regurgitation.

Criteria for Device Explantation

The ultimate impact of this technology on failing native ventricles is unknown and the subject of current clinical investigations. There may be patients with long-term VADs who will be considered for device explantation.[11, 12] Some investigators hypothesize that full ventricular decompression will promote myocyte regeneration and function,[13] and others suggest that ventricular decompression with supplemental beta agonist therapy (clenbuterol) will lead to ventricular recovery.[14] Patients with healed myocarditis or stunned but recovered myocardium following reperfusion therapy for an acute myocardial infarction might also be considered for device explantation.[15] The clinical criteria for device explantation are still in evolution, and potential suitability is best initially explored by echocardiography and concomitant invasive hemodynamic assessment. Those patients who have opening of the aortic valve or only partial decompression of the left ventricle, with a diastolic diameter < 6 cm, may have adequate left ventricular function to support device removal. Functions of the right and left ventricle in the automatic mode and the asynchronous/fixed rate mode must be compared. The response to dobutamine echocardiography while in the asynchronous mode (rate of 50) provides additional insight into myocardial reserve and inducible mitral regurgitation. If noninvasive data are encouraging, then more definite physiologic data are mandatory before an irrevocable surgical decision. This should include exercise test with oxygen consumption while in the asynchronous mode at a rate of 50, and then full hemodynamic assessment with right and left heart catheterization with the LVAD turned off and only after full heparinization to prevent thrombus formation. However, contemporary experience suggests that device explantation and long-term survival are uncommon and are not routinely sought in most centers.

Conclusion

The use of ventricular assist devices for destination therapy of end-stage heart failure ushers in a new era of clinical expertise and knowledge about outpatient management. We anticipate rapidly expanding outpatient needs as the technology improves and donor supply for cardiac transplantation remains limited. The principles reviewed here are an initial insight into the physiology of the technology and the inherent complexities that will inevitably evolve. One can also hope that rapid evolution of the technology will also simplify care for the patients, their families, and all their healthcare providers.

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