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Review Article

Heart failure therapies: new strategies for old treatments and new treatments for old strategies☆

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ABSTRACT

Heart failure, whether acute or chronic, remains a major health care crisis affecting almost 6 million Americans and over 23 million people worldwide. Roughly half of those affected will die within 5 years, and the annual cost exceeds $30 billion in the US alone. Although medical therapy has made some modest inroads in partially stemming the heart failure tsunami, there remains a significant population for whom medication is unsuccessful or has ceased being effective; such patients can benefit from heart transplantation or mechanical circulatory support. Indeed, in the past quarter century (and as covered in *Cardiovascular Pathology* over those years), significant improvements in pathologic understanding and in engineering design have materially enhanced the toolkit of options for such refractory patients. Mechanical devices, whether total artificial hearts or ventricular assist devices, have been reengineered to reduce complications and basic wear and tear. Transplant survival has also been extended through a better comprehension of and improved therapies for transplant vasculopathy and antibody-mediated rejection. Here we review the ideas and treatments from the last 25 years and highlight some of the new directions in nonpharmacologic heart failure therapy.

1. Heart failure

Heart failure, in general terms, is the inability of the heart to pump sufficient oxygen and nutrition to meet the metabolic demands of the body. Almost 6 million individuals in the United States alone are affected by heart failure, and roughly half will die within 5 years of the diagnosis [1]. While many can be effectively treated with pharmacologic intervention to boost cardiac output, many will continue to decline, eventually becoming refractory to medical therapies.

Indeed, despite significant improvements in our pharmaceutical bag of tricks, as well as increasing utilization of cardioverter–defibrillator and cardiac resynchronization therapies, heart failure patients who develop inotrope dependency still experience roughly 85% mortality after 2 years, with 50% dying within 7–10 months [2]. Such individuals clearly need advanced heart failure treatments, and for the last 20–30 years, mechanical devices and transplantation have become increasingly important mainstays in the clinical armamentarium. Left ventricular assist device (LVAD) either as a bridge-to-transplant or as destination therapy affords substantially better outcomes with 1-year survivals of over 80% and roughly 50% of recipients surviving over 4 years [2]. Even better is cardiac transplantation, with close to 90% 1-year survivals (somewhat worse if you have to wait for the transplant without benefit of an LVAD), with almost three-quarters of patients alive after 6 years [2].

Of course, none of this comes cheaply. Although a meta-analysis of 40 studies concluded that none really provided a good empirical assessment of relative costs of the various therapies [3], an outcomes analysis by Long et al. found that heart transplantation provides the overall best cost–benefit ratio—in either total life-years or quality-adjusted life-years—and in spite of a $1.0–1.2 M dollar total price tag. While the cost of purely medical management roughly averages a paltry $100 K lifetime total, that was in part because the patients did not live as long or as well. LVAD destination therapy, at approximately $400–600 K lifetime cost, seems at first blush to be a less costly option than transplantation. However, adjustments for life-years and quality-adjusted life years still make this significantly less cost-effective than medical management alone and especially compared to heart transplantation. Because cardiac biopsy remains the gold standard for assessing rejection in all these heart transplants (see later), an analysis showing the overall benefit of transplantation over all comers is good news indeed for cardiac pathologists!

Over the ensuing quarter century since the advent of mechanical support and orthotopic heart transplantation, there has been a wealth of refinements in both approaches. Some changes were developed based on earlier ideas, while many older treatments have had been materially improved through additional insights and innovations. We describe here several of these advances and treatments.

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2. Old ideas for heart failure: total artificial heart

The 1980s saw the development, to great fanfare, of the Jarvik-7, a total artificial heart. This was a dual ventricle device in which the chambers were pneumatically powered to produce a stroke volume of 100 ml and rates of 40–120 beats/min. The device used Bjork–Shiley tilting-disk valves and was attached to the atria and great vessels via Dacron grafts [4]. The initial excitement of this new development was soon tempered by the realization that the device was fraught with significant complications, particularly thromboembolism. Long-term survival on the device was rarely achieved, although it could be used as a bridge to transplantation [5]. This first-generation artificial heart never gained full integration into most hospital centers as other methods with better survival and reduced complications became more popular. These other methods are described here.

2.1. Old and new devices for acute heart failure

Acute heart failure, as a result of, for example, acute myocardial infarction, fulminant myocarditis, or postcardiotomy shock, can be managed by devices that are readily inserted to support the circulation and stabilize a critically ill patient [6]. Such devices range from the intraaortic balloon pump (developed by Dr. Adrian Kantrowitz in the mid-1960s), to extracorporeal centrifugal flow devices such as the CardiacAssist TandemHeart and Thoratec CentriMag, to intracardiac axial flow devices such as the Abiomed Impella. These devices can be deployed (and removed) percutaneously to provide immediate circulatory support, allowing the decompensated heart to potentially recover from an acute insult; generally, however, these are only advisable for short-term (hours to days) support. If the patient remains in refractory heart failure, one of the mechanical circulatory support (MCS) devices appropriate for long-term support discussed below may be subsequently employed.

2.2. Old and new devices for chronic heart failure

The number of patients with chronic heart failure (of whatever etiology) refractory to medical management is a continually expanding population; in the US today, there are an estimated 250,000–500,000 such patients—a total that outpaces the availability of donor hearts for potential transplantation (2500 annually in the United States and stagnant) by over two orders of magnitude. MCS devices can be used in patients with chronic heart failure as (a) a bridge to transplantation, where the patient may be a good transplant candidate but will likely die or suffer significant end-organ damage before a suitable donor organ is identified; (b) the definitive, permanent heart failure therapy or "destination therapy" for patients who are not transplant candidates; or (c) a bridge to recovery in a small number of patients for whom mechanical unloading of the heart provides an opportunity for cardiac remodeling of a sufficient degree to obviate the need for further MCS.

The first generation of ventricular assist devices (VADs) consisted of pulsatile devices whose pumps could be implanted fully within the peritoneal cavity or resided outside of the patient. Examples of implantable pulsatile LVADs included Thoratec HeartMate XVE (Fig. 1A) [7] and Novacor Ventricular Assist System [8]; the Thoratec PVAD [9] is an example of a paracorporeal VAD. These devices generally consisted of a flexible polymer pumping bladder or diaphragm actuated by a pusher plate to allow filling and emptying of the pumping chamber. Valves on the inflow and outflow aspect of the pump ensured unidirectional flow of blood.

The second generation of VADs consists of implantable continuous axial flow devices, where the long axis of the impeller is parallel to the direction of blood flow. Examples of such devices include Thoratec HeartMate II (Fig. 1B) [10], BerlinHeart INCOR [11] (pumps reside within the peritoneal cavity), and Jarvik 2000 FlowMaker [12] (the pump is intraventricular). These second-generation devices are much smaller, making implantation easier and allowing smaller patients to receive them; they are also more durable than the first-generation devices. Since these are all *continuous flow* devices, the pumps themselves do not impart pulsatility to the blood, resulting in reduced pulse pressure for the patient; algorithms are being developed for some devices to vary the speed of the pumps to add some degree of pulsatility, which may ultimately prove to be beneficial.

The third generation of VADs consists of implantable continuous centrifugal flow devices, where the impeller creates a centrifugal force to add kinetic energy to the flowing blood. Examples of such devices include HeartWare HVAD [13] (Fig. 1C), Thoratec HeartMate III [14], and Evaheart LVAS [15]. These pumps generally reside on the epicardial surface of the heart, obviating the need to enter the abdomen for implantation. The impellers are magnetically levitated within the housing which further enhances durability, and some devices can provide pulsatile flow.

2.3. New total artificial heart

In contrast to VADs which augment ventricular function while leaving the native ventricles in place, mechanical devices that entirely replace the native heart are termed total artificial hearts. The SynCardia Total Artificial Heart [16] (a descendant of the Jarvik-7 device used in the 1980s) is one such device; it is used predominantly as a bridge to transplant.

2.4. Complications of MCS devices

The major complications of MCS devices are thrombosis and/or thromboembolism, hemorrhage, infection, and interactions with host tissue. Virchow's triad dictates that thrombosis risk increases in the presence of an abnormal blood-contacting surface, abnormal flow, or intrinsic hypercoagulability. All patients with MCS technology will obviously have a nonphysiologic blood-contacting surface within the device and some measure of nonphysiologic flow. The newer device designs aim to minimize these factors, but patients with current MCS devices are still required to be on anticoagulation regimens to prevent thrombosis, usually warfarin, with or without an antiplatelet agent. Even so, device-associated thrombosis still poses a significant risk to MCS patients (Fig. 1D). Recent data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) show that freedom from pump thrombosis for patients receiving the HeartMate II device from April 2008 to June 2014 is 95% at 6 months, 93% at 12 months, and 89% at 24 months [17]. On the flip side of this coin, increasing the level of anticoagulation increases the risk of bleeding. Hemorrhage, especially of the brain and gastrointestinal tract, continues to be a significant problem in device recipients; gastrointestinal bleeding was seen in 29.6% of continuous flow LVAD patients (with an event rate of 0.18 per patient year) in a recent 9-year single-institution study [18]. Interestingly, patients with continuous flow devices can also develop acquired von Willebrand factor deficiency, thought to be secondary to high shear forces within the devices; this further limits the effectiveness of the platelet arm of the clotting cascade and predisposes to hemorrhage. Fortunately, the risk of major hemorrhage has declined with improved device designs, anticoagulant therapies, patient selection, blood pressure management, and surgical methods.

Infection accounts for significant morbidity and mortality following the prolonged use of cardiac assist devices; it can occur either within the device or associated with percutaneous drivelines. In a prospective postapproval study of the HeartMate II device, device-related infection affected 19% of patients (event rate, 0.22 per patient-year), which was significantly lower than the 35% of affected patients (event rate, 0.47 per patient-year) in the pivotal trial [19]. Susceptibility to infection is potentiated by not only the usual prosthesis-associated factors but also by the multisystem organ damage from the underlying disease, the periprosthetic culture medium provided by postoperative hemorrhage,