Mechanical Circulatory Support for Advanced Heart Failure

A Texas Heart Institute/ Baylor College of Medicine Approach

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We would like to dedicate our book Mechanical Circulatory Support for Advanced Heart Failure: A Texas Heart Institute/Baylor College of Medicine Approach *to Dr. Denton A. Cooley.*

Dr. Cooley is considered to be the world's greatest heart surgeon. His accomplishments include expanding therapeutic potential for patients with congenital heart conditions, pioneering the artificial heart and heart transplantation, developing prosthetic heart valves, and establishing new methods for aortic aneurysm repair. In the words of Dr. Walt Lillehei, "Dr. Cooley was the first to demonstrate the safety of heart surgery with the heart-lung machine. He performed more heart surgery than any heart surgeon in the world every year from 1956 to 1994." Dr. Cooley also developed the first bundled services plan for cardiac surgery, called the CardioVascular Care Providers, which was influential in the structuring of cardiac services for Medicare.

Dr. Cooley founded the Texas Heart Institute (THI) in 1962 and was instrumental in THI rising to become one of the premier institutions for cardiac surgery in the world. Over 120,000 cardiac surgeries using the cardiopulmonary bypass circuit were performed at THI during Dr. Cooley's lifetime. Dr. Cooley published over 1400 scientific articles and was a member in more than 30 professional medical societies. He founded the Cullen Cardiovascular Surgical Research Laboratory, which under Dr. O.H. Frazier's leadership, a trainee and devotee of Dr. Cooley, was instrumental in developing nearly all of the left ventricular assist devices used in clinical practice today. Among his numerous honors and awards, Dr. Cooley received the Presidential Medal of Freedom from President Reagan in 1984 and the National Medal of Technology and Innovation from President Clinton in 1998, as well as the Lifetime Achievement Award in 2016 from the American Association for Thoracic Surgery.

It is our belief that every cardiologist, cardiac surgeon, and cardiac patient owes a great degree of gratitude to Dr. Cooley for his enormous contribution to the field. We are greatly honored to have been given the opportunity to dedicate our book to the memory of the late Dr. Cooley.

Respectfully,
Jeffrey A. Morgan, M.D.; Andrew B. Civitello, M.D.; and O.H. Frazier, M.D.

Foreword

I am proud and honored to have been asked to write this foreword. It seems only fitting that a book about mechanical circulatory support (MCS) should be published by experts from Baylor College of Medicine and the Texas Heart Institute (THI). Since the 1960s, these two institutions, at first separately and now jointly, have been involved in almost every major advance in this field.

Not so long ago, a book written in collaboration between THI and Baylor physicians would have been unimaginable. In 1969, professional rivalry between myself and Dr. Michael E. DeBakey, chairman of Baylor's Department of Surgery, caused me to resign my long-standing professorship at Baylor and devote my full attention to THI, which I had founded in 1962. Baylor and THI each continued to make outstanding contributions to cardiovascular medicine, but they lacked the advantage of a mutually beneficial collaboration. Not until 2007 was a cordial relationship reestablished. Instrumental in that reconciliation were Dr. George P. Noon of Baylor, Dr. O.H. Frazier of THI, and several other physicians at both institutions. In late 2007, Dr. DeBakey joined me in the THI research laboratory to watch Dr. Frazier implant a total artificial heart into a calf. The heart comprised dual MicroMed DeBakey left ventricular assist devices. This occasion marked a breakthrough in both MCS research and Baylor-THI relations. By the time of Dr. DeBakey's death, at age 99 in July 2008, the new rapport was firmly established.

In a modest way, this rapprochement might be compared to the ending of the twentieth-century "space race" between the US astronauts and the Soviet cosmonauts. Elsewhere, I have related how the space race influenced my response to the unique scientific challenge posed by the first TAH implantation [1]. With the end of the Cold War, former rivalries were laid aside, and old boundary lines were dissolved. Since then, unprecedented spaceflight cooperation between the USA and Russia has led to progress in education, research, and technology. Today, unprecedented cooperation between Baylor and THI is leading to advances in education, research, and patient care. The current book is a result—and a symbol—of that cooperation.

I congratulate Drs. Morgan, Civitello, and Frazier and all the other contributors to this superb volume, which covers every aspect of clinical cardiac support. The experience related here is based on the largest single-center MCS series in the USA. As a clear, comprehensive, and authoritative guide to device therapy, this book will be an indispensable resource for physicians,

other medical personnel, and anyone else interested in support of the failing heart.

Houston, TX, USA Denton A. Cooley, M.D.

Reference

1. Cooley DA. Some thoughts about the historic events that led to the first clinical implantation of a total artificial heart. Tex Heart Inst J. 2013;40(2):117–119.

Preface

The first successful LVAD was implanted by Dr. DeBakey at Baylor College of Medicine/Methodist Hospital in 1966. In 1968, Dr. Denton Cooley performed the first successful human heart transplant in the USA at Texas Heart Institute, St. Luke's Hospital. Dr. Cooley subsequently performed the first successful artificial heart implantation in 1969 at the Texas Heart Institute. The first LVAD as a bridge to transplant and the first combined heart/kidney transplant were also performed by Dr. Cooley in 1978 at the Texas Heart Institute. In 1988, Dr. Frazier implanted the first successful continuous-flow LVAD and has subsequently been instrumental in the development of nearly all continuous-flow devices used clinically, including the Jarvik, HeartMate 2, HeartMate 3, and HeartWare HVAD.

With the popularization of continuous-flow LVADs, mechanical circulatory support has evolved into the standard of care for patients with refractory, end-stage heart failure. Advancements in patient selection, device design, surgical techniques, and postoperative management have led to significant improvements in survival and a reduction in device-related complications, such as bleeding, infection, stroke, device malfunction, and device thrombosis.

Each chapter in our text *Mechanical Circulatory Support for Advanced Heart Failure: A Texas Heart Institute/Baylor College of Medicine Approach* was authored by staff members from the Texas Heart Institute, Baylor College of Medicine. Our LVAD program has grown significantly over the years with greater than 1300 LVADs implanted to date, including over 850 continuous-flow LVADs. Our goal in writing this text was to provide a framework for physicians evaluating patients for LVADs, caring for patients perioperatively, and/or managing patients with LVADs long-term by sharing the cumulative experience of the Texas Heart Institute, Baylor College of Medicine LVAD program.

Houston, TX, USA

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Andrew B. Civitello, M.D.
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History of Mechanical Circulatory Support

1

O.H. Frazier

This introduction focuses on the role of the Baylor College of Medicine (BCM) and the Texas Heart Institute (THI) in the evolution and development of heart replacement and circulatory assist technology. This is appropriate because both the first successful LVAD and the first successful artificial heart were implanted at these institutions in Houston, Texas. In addition, the initial experimental work on the continuous-flow pumps now in use (Jarvik, HeartMate II, HeartWare, Impella) began at our institute. My experience has been unique in this regard, as I have been personally involved in this journey from 1963 to the present. My only absence was during 1968–1970, when I served with an assault helicopter company engaged in active combat in the central highlands of Vietnam. In this same period (April 1969), Dr. Denton Cooley "relocated" Dr. DeBakey's artificial heart from BCM's labs to THI-St. Luke's Hospital and successfully implanted it as the first bridge to transplant with an artificial heart (or any device) (Fig. 1.1). Thereafter, Dr. DeBakey and Dr. Cooley did not speak to each other for more than 30 years. My friends who were in Houston at the time assured me that Vietnam was probably a safer place for me to be.

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The meaningful pursuit of heart replacement began in 1964 when Dr. Michael DeBakey secured funding, mainly through the auspices of then President Lyndon B. Johnson, to pursue the development of an artificial heart. It was unusual for the National Institutes of Health (NIH) to support such a project; in general, they confined their grants to pure research without any immediate clinical objective. So, this funding was unique in that regard and probably would not have been granted without Dr. DeBakey's leadership. Also, I remember well those heady times, when we were going to the moon, among other grandiose objectives. Creating an artificial heart, comparatively speaking, seemed like a simple side project.

The funding for the artificial heart went primarily to BCM, where I was then a medical student. During that time, BCM required us to participate yearly in research projects as part of our medical school education. Although I had no particular interest in surgery, my research projects, by sheer chance, began in 1963 with Dr. Domingo Liotta, who was developing heart replacement pumps. Dr. Liotta was mainly interested in the total artificial heart [1] but was primarily occupied with developing temporary left ventricular assist devices (LVADs). This work was initiated by Dr. DeBakey in 1964; it continued after 1972 in the THI research labs. This research initially was dedicated exclusively to pulsatile pumps. By 1989, the NIH had spent more than $266 million developing pulsatile pumps, and the companies contracted to develop this technology had spent at least as much. In all,

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Fig. 1.1 Domingo Liotta and the Liotta Artificial Heart (1969)

probably more than $450 million was spent by the NIH and an equal amount by the private companies on developing pulsatile pumps [2]. At the time, the pulsatile pumps seemed to be logical candidates for both temporary and total artificial heart development.

When I completed my surgery training at BCM in 1974, I renewed my direct involvement with the development of cardiac replacement pumps at THI. The work at THI at that time (1972–1980) was directed by Dr. Jack Norman, a capable Harvard-trained physician. This was the only research on pumps being conducted in the Texas Medical Center at the time; Dr. DeBakey had suspended work on the artificial heart in 1969 after his dispute with Dr. Cooley. Under Dr. Norman's direction, we implanted 22 intra-abdominal LVADs between 1976 and 1979, and one of the patients became the first to be bridged to transplant with an LVAD [3]. Unfortunately, none of the 22 patients were long-term survivors, but the pump itself worked well in all cases.

By the early 1980s, it seemed to me that the limiting factor in developing pulsatile pumps might be as simple as the durability of the membranes. The normal heart of an inactive adult beats approximately 100,000 times every 24 h. This poses quite a challenge to the membrane technology in pulsatile pumps, as well as to the additional technological complexity that a completely implantable total artificial heart would require.

The technological challenge of making this device fully implantable was further compounded by the fact that the left and right ventricles do not pump the same amount of blood. The left heart receives blood directly from the bronchial artery circulation; thus, in the normal adult, the amount of blood ejected from the left heart with each heartbeat is 1–2 cc more than the right heart [4]. This is not much, but in the course of a 24 h period, the difference amounts to more than 100,000 cc. This necessitated finding a way for a totally implantable artificial heart to adjust automatically for the imbalance between the left and right flow. The AbioCor total artificial heart addressed this problem primarily by shifting the blood to the right side when the left-sided pressures became elevated [5]. Although this solution seemed effective in the short term, its long-term application was never tested beyond one 17-month survivor.

The durability of the membranes seemed to be limited to about 24 months in the pump made by Thermo Cardiosystems, Inc. (TCI) and a bit longer in the Novacor pump. The Jarvik 7 total artificial heart had a similar durability problem.

By the mid-1980s, it became apparent to me that the best approach to the durability and flow imbalance problems would be a continuous-flow heart pump. Continuous-flow pumps are inherently inflow sensitive in that the higher the inflow becomes, the more they will pump (if the outflow resistance is constant) without increasing the pump speed (Fig. 1.2). This would allow more or less a physiologic Starling-type response, as well as physiologic adjustment, to control flow imbalance between the right and left heart.

However, probably the most pressing reason to pursue implantable long-term continuous-flow pumps was the durability problem. I realized that if a pump had only a 2-year life span, the pump could serve only as a prolonged bridge to transplant;

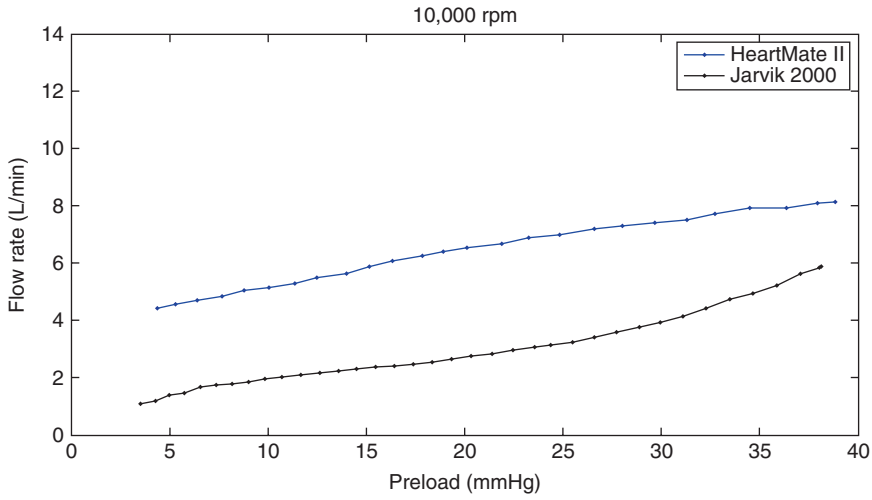

Fig. 1.2 Inflow sensitivity results in a Starling-like response without changing the pump speed

therefore, although the device could be lifesaving in individual cases, it would have no epidemiologic impact on the heart failure population. The problem of changing the pump every 2 years, or else simply adding another patient to the transplant list, was and remains a barrier to the further development of pulsatile pump technology.

I had become interested in continuous-flow pumps in the late 1970s and early 1980s, when I used the Biomedicus pump (a constrained vortex continuous-flow pump) in my extracorporeal membrane oxygenation patients, as well as for temporary LVAD support. I had used this pump in 1987 in a 9-year-old patient who became the first pediatric patient to be bridged to transplant. Using this device not only enabled our patient to survive, but as I stated in the discussion of the report of the case, it also "prompted us to speculate about broader application of nonpulsatile flow, to the development of fully implantable devices for long-term cardiovascular support of the terminal heart disease patient….*The potential for long-term benefit lies in meeting the requirements of the circulatory system with a nonpulsatile pump* [italics added]" [6].

Making a continuous-flow pump implantable seemed to be a significant challenge. During that era, I became involved in numerous debates and discussions at meetings on this subject. Skeptics of such implantable continuous-flow pump technology cited numerous potential problems, mechanical as well as physiologic. The physiologic aberration of the baroreceptor response and potential disruption of the juxtaglomerular response were only a few of the many physiologic changes that would be produced by implantable long-term continuous-flow pumps.

In addition to these physiologic challenges, there were two important engineering barriers that were thought to be insurmountable. In the mid-1980s, the only type of implantable continuous-flow pump available used axial-flow technology. Axial-flow pumps require bearings, and you could not have a nonlubricated bearing in the bloodstream (or anywhere else)—at least, that was the conventional thought. This was an engineering axiom. (In fact, the only nonlubricated bearings I know to be in use today are those in axial-flow blood pumps.) In addition, the pump speed required to produce significant flow seemed to be, by definition, a barrier to using axial-flow technology: Speeds of more than 2500 rpm in a small device were believed to be too damaging to the blood (the "Waring blender effect"), causing too much hemolysis to have any practical value in producing meaningful blood flow.

At a National Heart, Lung, and Blood Institute (NHLBI) contractor's meeting in Louisville,

Kentucky, in 1985, I was approached (separately) by Drs. Richard Wampler and Robert Jarvik. Although they were not acquainted, they were both looking independently at engineering solutions to this problem. Dr. Wampler showed me his concept for a temporary implantable continuous-flow device that would spin at 25,000 rpm (although at the time I thought he had said 2500 rpm). Shortly afterward, Dr. Jarvik showed me an implantable, long-term axial-flow pump that would use blood-washed bearings. I recommended to Dr. Jarvik that this smaller pump be placed in the ventricle to avoid the inlet problems that had plagued the pulsatile pumps. I agreed with both of these investigators, independently, to proceed with this research in our labs at THI. (Although I am not sure I would have proceeded with Wampler's design had I really understood that it spun at 25,000 rpm!)

Initial work with what Dr. Wampler called the Hemopump was very promising. This small pump—the size of the eraser on a #2 lead pencil (Fig. 1.3)—could produce 4–5 L of outflow. Furthermore, the device caused only minimal hemolysis in the experimental animal. Because of these promising experimental findings, we introduced this pump clinically in April 1988 in a patient dying of heart allograft transplant rejection [7]. We were able to support this patient with the Hemopump for 5 days, during which time we reversed his organ rejection. The patient survived this potentially mortal event and became a long-term transplant survivor. We used this pump in several more patients, with excellent results [8].

Fig. 1.3 The Hemopump, a tiny axial-flow pump designed to provide temporary circulatory support

The Hemopump became the first implantable continuous-flow pump to be presented to the US Food and Drug Administration (FDA) for approval. It was developed without any NIH funding. I funded the laboratory work (done in my lab), and Nimbus, a small research company, funded the manufacture of the pump. The company received the bulk of its money from investors who, naturally, wanted to apply this pump to the largest patient population possible. Therefore, for the initial clinical trial of this device (which had excellent results), the entry criterion was heart failure of any cause. The FDA, however, wanted more precisely defined entry criteria, and they recommended performing a new trial with such criteria. However, rather than fund further studies, the venture capitalists withdrew their funding and invested in a more profitable stent technology.

Fortunately, I found new support for the development of continuous-flow pumps in Helmut Reul, a German friend of mine who earned, at the University of Houston, what was probably the first Ph.D. in bioengineering. I had met him during his time in Houston, after which he had returned to Aachen, Germany, and initiated a research program. At a medical meeting in Germany in 1994, I advised him of the potential of the Hemopump technology and that it would not be further pursued in the United States. Subsequently, at his research base in Aachen, he began developing similar technology based on the Hemopump principle. The resulting device subsequently was acquired by the Abiomed company in Boston and is now in widespread use as the Impella pump, a temporary assist device.

Dr. Jarvik began working on long-term implantable axial-flow pump technology in my lab in 1985. The development was much more challenging than it had been for the Hemopump. The first few pumps made by Dr. Jarvik lasted only a short time before the nonlubricated bearing would accumulate debris and occlude the pump. However, after many revisions and experimental animal implantations, Dr. Jarvik produced

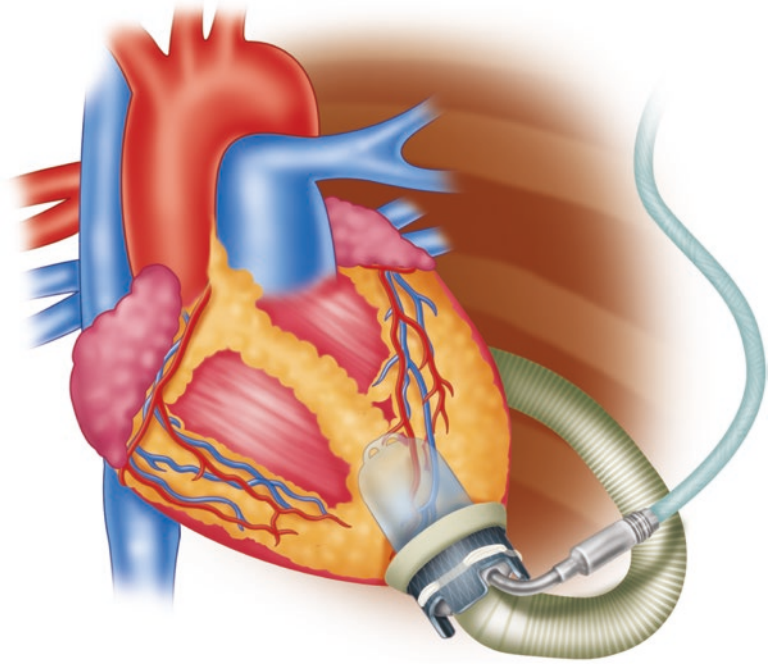

Fig. 1.4 Drawing of an implanted Jarvik 2000. This device was first placed in a patient in April 2000

a workable nonlubricated, blood-washed bearing in an axial-flow pump by the early 1990s [9].

This research showed the feasibility of continuous-flow implantable pumps for both long-term and temporary use. All of this research on continuous-flow pumps was funded internally with personal research funds of mine, by the Nimbus Company, and by Dr. Jarvik's company, Jarvik Heart, Inc. No NIH funding supported the feasibility studies performed in the 1980s and early 1990s. This work formed the foundation for all future clinical applications of continuous-flow blood pumps.

Soon after the initial clinical success of the Hemopump, the Nimbus Company also became involved with the development of an implantable long-term continuous-flow pump. Because I was the only clinician involved in developing this technology at that time, I was the medical advisor for both Dr. Jarvik's company[1] and the Nimbus Company, which was a very small research company based in Sacramento, California (Fig. 1.4).

At that time, the engineering leader at Nimbus was Dr. John Moise, a recognized expert and one of the best engineers in his field. He was struggling to develop a magnetically levitated axial-flow pump. At that time (the early 1990s), we were a small group—never more than 20 people—and we worked collegially with one another. I had shared Dr. Wampler's research success with the Hemopump with Dr. Jarvik, and I thought nothing of doing the same with Dr. Jarvik's success with blood-washed, nonlubricated bearings. Our primary goal was to make a pump that would ultimately benefit patients. I had never thought of or had any business interest in any of these projects.

I suggested to Dr. Moise that they put bearings on the rotor and not continue with the then futile attempts at creating a maglev axial-flow pump. He replied, politely, that I did not know anything about engineering and that you could not have a nonlubricated bearing in the blood-

[1]It may be of interest to note that Dr. Jarvik's company initially consisted of only Dr. Jarvik and his wife, Marilyn vos Savant, famed for having the highest recorded IQ according to the *Guinness Book of World Records*, making it without doubt the company with the highest average IQ in the world.

stream. But we had already shown in the Jarvik pump that blood-washed bearings were possible, so I stated that I did not know that it could not be done, that Dr. Jarvik did not know that it couldn't be done, and that, most importantly, there was a calf in Houston that had had the pump for more than 8 months and that seemed not to know that it couldn't be done. At that point, the Nimbus Company began working on what is now known as the HeartMate II.

In closing this section, I would be remiss in not emphasizing that this whole field (implantable continuous-flow pump technology) was initiated primarily by the engineering work of two individuals. Dr. Wampler showed that you could, in fact, use a pump speed of not only more than 2500 rpm but up to 25,000 rpm in the bloodstream without causing hemolysis. Dr. Jarvik's seminal contribution of creating a nonlubricated bearing was essential for the development of all axial-flow implantable continuous-flow pumps. I was privileged to work on both of these projects and have been fortunate to introduce both into the clinical arena. More than 40,000 continuous-flow blood pumps have now (as of mid-2017) been implanted in otherwise mortally ill patients. Other than the three of us, there was no one, to my knowledge, actively pursuing implantable continuous-flow pumps in the experimental animal at that time (the mid 1980s).

Development of Magnetically Levitated Centrifugal Force Continuous-Flow Pumps

The investor who initiated funding for continuous-flow, centrifugal force, bearingless pumps was Dr. Robert Fine, who, after earning his medical degree, had also obtained a master's degree in business and became a Wall Street broker specializing in medical investments. I had met him as a result of this involvement. He had successfully invested in the first pump to be approved (in 1994) by the FDA, the TCI pneumatic LVAD (which was developed in our facility). Dr. Fine then came to me and asked what I thought would further advance the field. I told him that I had been working experimentally and clinically with a short-term centrifugal force continuous-flow pump and if we could develop a long-term, magnetically levitated, bearingless, implantable pump, it would potentially be an important advancement in the field. I believed this because such a pump would not require the controversial blood-washed bearings at all. Even though Dr. Jarvik had shown the feasibility of blood-washed bearings, bearings still had the potential for wear. And although I anticipated that these pumps would last far longer than the pulsatile pumps, I believed they would have a finite life span of 5–10 years. (This has proved to be erroneous, because these pumps have now been in patients for longer than 10 years, and none of those that were properly fabricated and implanted have been pumped to failure.) However, I did see (and continue to see) the advantages of a magnetically suspended, bearingless centrifugal force pump. A particularly important advantage of this type of pump was that it could be easily implanted intrapericardially and therefore could be used for long-term right-sided, as well as left-sided, support.

Before this time, we had no right-sided long-term implantable pumps. The axial-flow pumps did not seem easily applicable to right-sided support, although I used a Jarvik pump successfully (in 2003) in the first patient to receive biventricular implantable pump support [10]. I knew the centrifugal force pump could be made flat so that it could easily fit inside the pericardium. Dr. Fine asked me to recommend an engineer who could work with him on this project, and I told him that, in fact, there were only two engineers in the world qualified to do so: Rich Wampler and Rob Jarvik. Although Dr. Jarvik was busy further developing his long-term pump, Richard Wampler had more freedom because the Nimbus Company, for which he worked, was no longer involved with the Hemopump.

Dr. Wampler subsequently began working on what ultimately became the first implantable centrifugal force pump, known today as the HeartWare. The company, originally called Kriton, reformed in the early 2000s and was renamed HeartWare, Inc. HeartWare began intro-

ducing its device clinically in Australia and Europe in 2005. Implantation of these pumps in the United States began in 2008, and this device became the first FDA-approved magnetically levitated rotary pump. It proved to be easily applicable to both right and left ventricular support. This pump has subsequently received widespread clinical acceptance and is recognized as an important contribution to the field.

Shortly after my encounter with Dr. Fine, I was at a meeting with Victor Poirier and Kurt Dasse, who were, at that time, the leading engineers with TCI. I had worked with them for more than a decade on developing pulsatile pumps. I suggested to them to also start looking at a magnetically levitated centrifugal-force pump. These two capable engineers began working on this project in the late 1990s. Their work eventually resulted in a short-term pump, the CentriMag, and an implantable maglev pump, the HeartMate III, being clinically introduced.

As noted earlier, the pump now known as the HeartMate II began with John Moise and the Nimbus Company, which eventually was absorbed into Thoratec. This pump underwent further development at Pittsburgh Medical School. Implantations began in Europe and Israel, with poor results. Vic Poirier brought me the pump. I pointed out that they had placed sintered titanium on the inside of the pump, causing it to become coated with a cellular layer and resulting in platelet activation. Both of these factors increased the potential for pump thrombosis.

The layering of the cellular elements, particularly mast cells, on the sintered titanium was well demonstrated in the early experience with the initial pulsatile pumps. However, the cellular layering was important in avoiding anticoagulation in these large pulsatile pumps. However, the much smaller continuous-flow pumps like the HeartMate II had little clearance. Therefore, the cellular layer formed was obstructive, and the increased turbulence and shear stress thus engendered promoted increased platelet activation. I agreed to implant the pump experimentally and then in patients if the sintered titanium was removed from the interior of the pump.

After this change was made, I implanted this iteration of the HeartMate II in experimental animals. After success in this, I implanted the first HeartMate II clinical pump in November 2003. This experience, I feel, is important to detail, as it shows the difficulty in developing these pumps. The slightest even seemingly inconsequential mistake may, despite good experimental results, turn into a clinical failure.

This was a well-run company, and once the HeartMate II was clinically reintroduced in 2003, it subsequently became the most widely used of all continuous-flow pumps. To date, more than 25,000 patients worldwide have been implanted with this device. Of these, 196 were supported for more than 8 years, including 135 patients who had the same device (i.e., never required pump exchange) for that entire period.

Another reason for the success of this pump is that its inflow cannula acts as a relative restrictor to pump inflow. This factor is important in ensuring a satisfactory reservoir, which is important for limiting inflow turbulence. Also, the position of the inlet cannula, designed by Vic Poirier, ensures that the cannula moves with the motion of the heart, thereby giving it further protection from pump inlet turbulence and consequent pump failure.

Clinical Application of Rotary Blood Pumps

After their feasibility was demonstrated in our lab, these pumps went directly to the manufacturers: Jarvik Heart, Thoratec for the HeartMate II, and HeartWare for the centrifugal force HeartWare pump. (The implantable Impella pump, a descendent of the Hemopump, was subsequently bought by Abiomed and is widely used for short-term support.) More than 150 hospitals in the United States alone are implanting these pumps. Another major reason for the widespread use of these small pumps was their ease of implantation, which was far greater than that of the much larger and more complicated pulsatile pumps. This allowed surgeons who had relatively little experience with continuous-flow pump technology to implant the pumps without difficulty.

These pumps' longer durability and reliability proved another important factor in their widespread acceptance.

The NIH spent $400–450 million in developing the pulsatile pumps, and the companies involved spent at least an equivalent amount. This involved more than 10 years of intense study of the physiologic parameters of the pulsatile pumps, which were, after all, intended to mimic the native circulation. The continuous-flow pumps, however, introduced an entirely new physiology. This significant alteration in the normal circulation contributes, in my opinion, to complications that our medical community has still not fully addressed.

Indeed, in the 1980s, there was much criticism from my medical colleagues as to the altered physiology these pumps induced. They voiced questions such as how will the pressure-sensitive baroreceptor response be affected, and what will its impact be on the normal blood pressure? This response would obviously be modified by a continuous-flow pump. In addition, the juxtaglomerular apparatus of the kidneys should also be affected, since they are believed to be pressure sensitive, as well. What would be the effect on the right heart function? Could it be impaired by the continuous unloading of the ventricle throughout the cardiac cycle? These and many other concerns were legitimately raised before this technology was clinically introduced.

The effects of continuous-flow pumps, particularly on the blood pressure, remain to be properly investigated. Earlier experience with the pumps from 2003 to 2005, particularly with the HeartMate II, saw hemorrhagic strokes in as many as 20% of patients. We determined that although the systolic blood pressure was diminished, the introduction of positive flow throughout diastole, when pressure is normally passive, could contribute to an altered but hypertensive state that would increase stroke risk. We addressed this complication by aggressively lowering the blood pressure, which dramatically reduced the incidence of this often fatal complication.

An additional problem results if the aortic valve is not opening. In this case, the pneumatic cuff will not yield an accurate blood pressure. The only pressure that can be measured—with the Doppler apparatus—is the systolic pressure. The actual pressure difference between systole and diastole remains unknown when the pulse is not present (unless there is an arterial pressure line). What contribution this abnormal physiology makes to continued pump thrombosis and the ever-present, although reduced, incidence of stroke has not been determined.

The phenomenon of gastrointestinal bleeding (GI) from arteriovenous malformations in the small and large bowel was first described by Heyde in 1958 in preterminal aortic stenosis [11]. We first reported GI bleeding in a minority of patients supported with the Jarvik pump. We thought that the decreased pulsatility induced by the continuous-flow pumps and the decreased pulsatility noted in patients with severe aortic stenosis could be related. This problem with GI bleeding remains. In our experience, it can generally be addressed by decreasing the pump flow, thereby increasing pulsatility. As the aortic valve opening time is increased, minimal anticoagulation is required; thus, this complication is usually managed successfully [12].

Numerous cases of complications have been associated with pump thrombosis. Nonetheless, more than 250 patients have survived with a single continuous-flow pump for more than 8 years, and 36 patients have been supported by the HeartMate II for more than 10 years. We know of no pump failures due to inherent mechanical flaws. Rather, all of the complications we see seem to be related to either the anatomic placement of the pump or other clinical factors, such as hypotension due to sepsis or hemorrhagic shock. Improper pump placement can result in turbulence at the inflow or obstruction at the outflow; either of these problems can contribute to stasis within the pump and increased platelet activation, both of which can promote pump thrombosis. This problem highlights the importance of proper implantation technique. So, clearly, these pumps have overcome the durability problem that was a barrier to the clinical application of the pulsatile pumps. However, the abnormal physiology induced by continuous-flow pumps remains to be addressed.

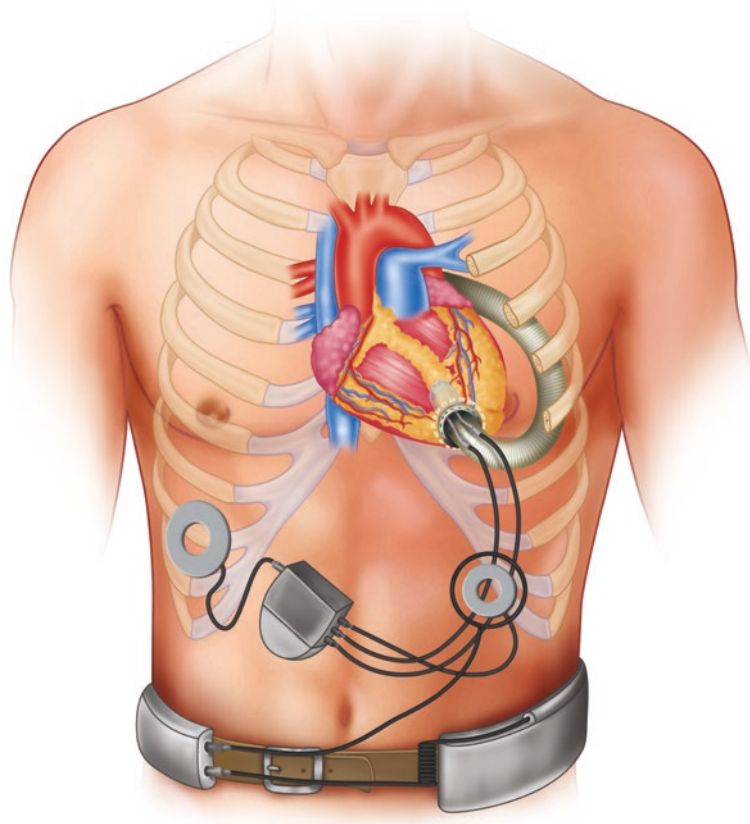

Fig. 1.5 The totally implantable version of the Jarvik 2000. Two power leads exit off the blood pump and are connected to the internal power and control unit. Primary and secondary transcutaneous energy transmission system (TETS) coils are placed in different locations in the abdominal wall. The external power and control are provided by the primary TETS, and the secondary TETS is for backup operation. (Reproduced with permission from Myers TJ, Gregoric I, Tamez D, et al. Development of the Jarvik 2000 intraventricular axial-flow left ventricular assist system. *J Congest Heart Fail Circ Support.* 2000;1(3):133–140)

I am hopeful that medical academic leaders, with NHLBI support, will be better able to understand the physiologic problems associated with this technology.

Many obvious problems could be addressed. The most persistent problem is that of driveline infection. The percutaneous driveline was the most expeditious and inexpensive approach in the feasibility studies. However, transcutaneous power, which is as old as Tesla, has proved effective in both the AbioCor and LionHeart pulsatile pumps and experimentally with the Jarvik (Fig. 1.5) [9, 13]. Intermittent speed control can be done rather simply and has already been shown with the Jarvik pump. This would insure a degree of pulsatility and perhaps lessen the problems of aortic insufficiency and GI bleeding.

If the aortic valve is closed, the pressure difference between systole and diastole cannot be directly measured without an arterial line. This difference should be maximized to minimize diastolic pressure. In fact, the pump speed (in rpms) should be minimized because these pumps are most effective as a true assist device and operate optimally at the lowest speed that can normalize circulation and maintain aortic valve opening (Fig. 1.6).

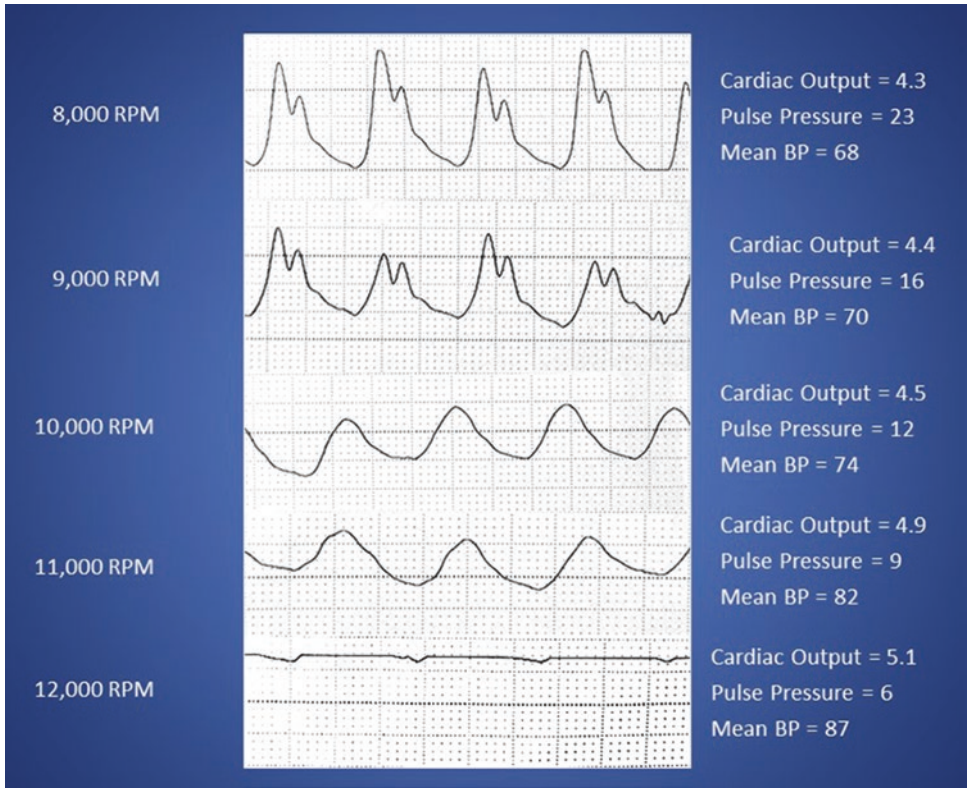

Fig. 1.6 Pulse pressure readings at various continuous-flow pump speeds. As pump speed is increased, the aortic valve ceases to open and close, and the rhythmic contraction of the heart has less influence on the pulse pressure as the pump takes on more of the workload

The Future

I began my original involvement in this field as a student under Drs. Michael E. DeBakey and Domingo Liotta. The goal was to develop an artificial heart. In 1965, Dr. DeBakey told me that by 1980, there would be "a hundred thousand Americans with a functional artificial heart." Likewise, NIH studies from the late 1960s predicted that a clinically practical artificial heart would be in widespread use by the mid-1980s (Fig. 1.7). But the problems associated with developing such a device proved to be far more formidable than was commonly assumed, on the basis of the perception at the time that an artificial heart could be a simple pump. The continuous-flow pumps now in widespread use as LVADs also may offer the best answer to total heart replacement. Many patients still would benefit from total artificial heart technology. In the 1970s, we developed a plutonium-powered internal battery that could power a 50-W pump for more than 82 years. Obviously, this was not pursued because we did not have a pump that would last more than 2 years. These continuous-flow pumps, in contrast, have not yet been pumped to mechanical failure, and their long durability evidences their potential as meaningful long-term pumps.

In 2005, Dr. William Cohn and I replaced the total heart in an experimental animal with two continuous-flow pumps [14]. We repeated these experiments numerous times and found that animals with continuous-flow pumps could perform well, grew normally, and had a normal activity response on the treadmill; many of them

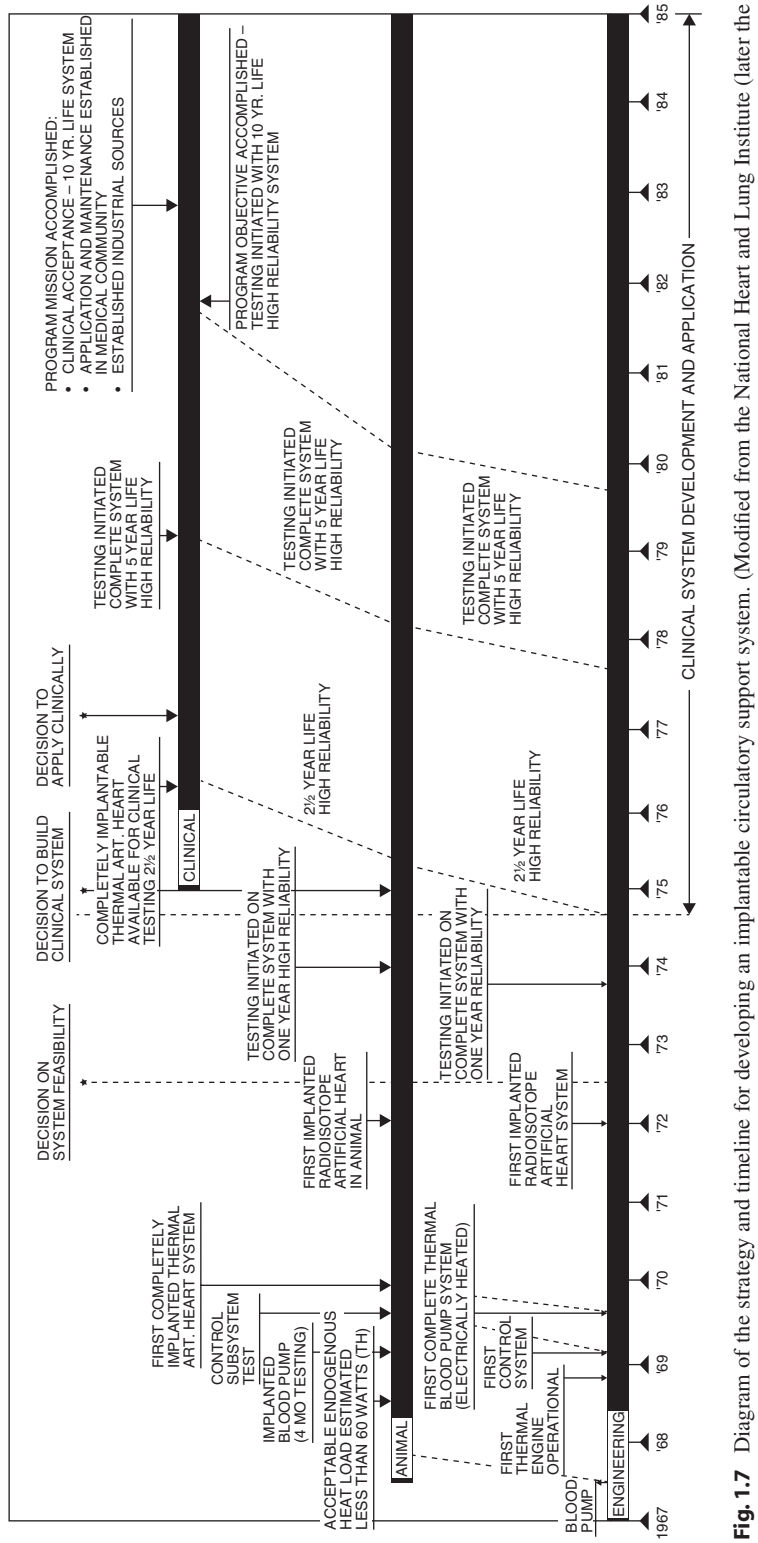

Fig. 1.7 Diagram of the strategy and timeline for developing an implantable circulatory support system. (Modified from the National Heart and Lung Institute (later the National Heart, Lung, and Blood Institute))

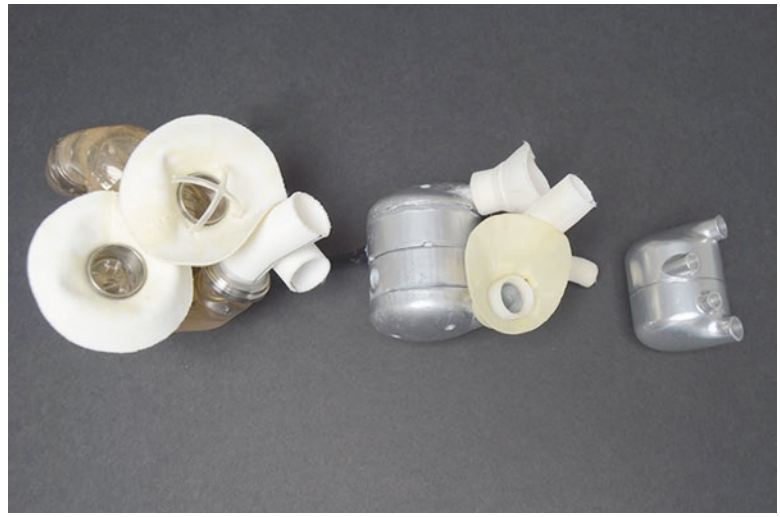

Fig. 1.8 The AbioCor totally implantable pump (*left*) compared with the BiVACOR centrifugal pump (adult, *center*, and child, *right*)

survived long term. We began working in 2012 with an investigator in Australia, Daniel Timms, who had devised a continuous-flow total artificial heart (Fig. 1.8). This pump is small but can produce up to 20 L of flow. It has only one moving part, which is magnetically levitated. It perfuses the pulmonary and systemic circulations simultaneously. We have demonstrated the feasibility of this pump in experimental animals and have even showed a Starling response, much like that of the normal heart, without changing the pump speed, when calves implanted with this pump are on the treadmill. This technology offers great promise for the future and for the meaningful prevention of premature death from the loss of natural heart function without the need for a heart transplant. I am confident that this technology will soon be available for clinical use.

This book primarily addresses the current widespread use of the continuous-flow pump. It is based on more than 50 years of experimental and clinical work and a single-center experience (one of the largest in the world) of more than 1300 pump implantations and 1500 heart transplants. In 2016, the number of continuous-flow pump implantations was twice that of heart transplants, and I am personally gratified to know that more than 40,000 of these pumps have been implanted in patients worldwide as a lifesaving effort. However, it must be reiterated that this represents a unique physiology never before encountered in mammalian species. We have patients doing well who have not had a pulse in more than 9 years and yet are totally asymptomatic. We must, however, study and address the complications seen with the use of this technology, in both its short-term and long-term application, to optimally benefit the heart failure patient.

In conclusion, I greatly appreciate the contributions of the THI faculty to the creation of this book—particularly Dr. Jeffrey Morgan—who, as a new arrival to our center, perhaps appreciates more than ourselves the more than 30 years of work on implantable continuous-flow pumps that originated here. I am glad to have had the opportunity to document the history of these pumps, as well as to highlight some of the early contributors to the field.

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2 Who Is an Appropriate Candidate for Long-Term MCS?: The Art of Patient Selection

Carol S.C. Lai and Andrew B. Civitello

Indications for MCS

Heart failure (HF) is a chronic and complex disease that has reached epidemic proportions worldwide. An estimated 6.5 million Americans have HF, and it is a leading cause of morbidity and mortality, with 50% mortality within 5 years of diagnosis [1]. Approximately less than 10% of this population will progress to advanced HF. These patients experience poor quality of life, frequent hospitalizations, and a 1-year mortality of 25–50% [2, 3]. Advanced HF is characterized by severe symptoms of heart failure with dyspnea and/or fatigue at rest or with minimal exertion, episodes of fluid retention, objective evidence of severe cardiac dysfunction, severe impairment of functional capacity, history of ≥1 HF hospitalization in the past 6 months, and the presence of all the previous features despite attempts to optimize therapy (Table 2.1) [4].

Patients with advanced heart failure refractory to medical management may be eligible for advanced therapy, including heart transplantation and mechanical circulatory support (MCS). Heart transplantation is considered the definitive therapy for advanced HF. However, shortage of donor organs and prolonged wait times remain a significant limitation. The development of MCS, such as the left ventricular assist devices (LVAD), has emerged as an effective and viable form of therapy. Though this field is quickly evolving, therapy with an LVAD is not free of complications, making appropriate patient selection imperative for successful therapy.

Generally, LVAD implantation is considered reasonable in "highly selected patients with advanced end-stage HF and an estimated 1-year mortality >50% with medical therapy" [5].

Four major indications for LVAD implantation exist: (1) bridge to transplantation (BTT), (2) destination therapy (DT), (3) bridge to recovery, and (4) bridge to decision. Bridge to transplantation is considered in patients with advanced HF who are candidates for heart transplantation but are hemodynamically unstable despite maximum medical therapy, including inotropes and intra-aortic balloon pumps. Due to hemodynamic instability, prolonged wait time, and increased risk mortality, they are too ill to wait for a donor

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Table 2.1 Definition of advanced heart failure [4]

1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction, shown at least by one of the following:
(a) Low LVEF (<30%)
(b) Severe abnormality of cardiac function on Doppler echocardiography with a pseudonormal or restrictive mitral inflow pattern
(c) High LV filling pressures (mean PCWP >16 mmHg and/or mean RAP >12 mmHg by pulmonary artery catheterization)
(d) High BNP or NT-proBNP plasma levels, in the absence of non-cardiac causes
4. Severe impairment of functional capacity shown by one of the following:
(a) Inability to exercise
(b) 6-MWT distance <300 m or less in females and/or patients aged ≥75 years
(c) Peak VO_2 < 12–14 mL/kg/min
5. History of ≥1 HF hospitalization in the past 6 months
6. Presence of all the previous features despite "attempts to optimize" therapy including diuretics, inhibitors of the renin-angiotensin-aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated

heart to be identified and require mechanical support in the interim. MCS in this population improves quality of life and reduces mortality [6]. In a multicentered trial, Frazier et al. demonstrated LVAD implantation improves NYHA functional class, organ dysfunction, and survival to transplantation compared to medical management in a cohort of transplant candidates. Furthermore, this survival benefit is sustained 1-year posttransplantation [7, 8]. Bridge to transplantation remains the most common indication for implantation [9]. However, due to the growing population of patients with advanced HF, scarcity of donor organs, and improved durability of the newer designed devices, there is an increasing trend toward LVAD implantation in patients for destination therapy. Destination therapy is offered as a permanent device in patients with advanced HF who are not candidates for heart transplantation. Like BTT, LVAD implantation as DT has also been shown to improve survival. The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial randomized 129 patients with end-stage HF who were not eligible for cardiac transplantation to LVAD therapy (HeartMate VE device) versus optimal medical management. LVAD therapy demonstrated a substantial survival benefit with 1-year survival of 52% versus 25% and 2-year survival of 23% versus 8%. Patients in the LVAD group also had improved quality of life, though they were two times more likely to develop serious adverse events including infection, bleeding, and mechanical failure of the device [10]. The development of newer left ventricular assist devices has further improved survival and quality of life. The HeartMate II trial randomized 200 patients with refractory HF who were ineligible for transplantation to the newer continuous-flow device versus pulsatile-flow device. Patients with the continuous-flow device demonstrated superior survival rates with 1-year survival of 68% versus 55% and 2-year survival of 58% versus 24%. While both groups had improvements in NYHA class and quality of life scores, the continuous-flow group had less major adverse effects [11]. Survival for continuous-flow pumps has continued to improve to an overall 1-year survival of 90% with 2-year survival of 70% [9, 12, 13]. Improved survival is not only secondary to advancements in LVAD technology but also to an improved understanding of heart failure, patient selection, surgical technique, and postoperative care [14]. Bridge to recovery is used in patients with potentially reversible etiologies of heart failure. LVAD implantation allows for recovery of myocardial function and is removed once the myocardium has recovered. Finally, bridge to decision is reserved for patients with hemodynamic instability requiring urgent mechanical support in which candidacy for transplantation or destination therapy cannot be made at the time of implantation. MCS at this time may allow for change in transplant eligibility with reversal of pulmonary hypertension, improvement in renal function and/or hepatic function, and weight loss.

General Criteria for MCS Patient Selection

Patients must undergo a comprehensive evaluation prior to LVAD implantations. The severity of heart failure must be assessed by the patient's clinical presentation, cardiopulmonary stress testing, and hemodynamic studies. Cardiac and anatomic factors are also evaluated such as right heart function, presence of arrhythmias, and anatomic and body size. Non-cardiac factors including coexisting life-limiting illness, psychosocial, and age-related considerations are also assessed. Patients must also be evaluated for cardiac transplant candidacy and LVAD operative risk.

General indications for LVAD implantation are based on inclusion and exclusion data from clinical trials. LVADs are indicated in patients with severe HF with NYHA functional IV symptoms and left ventricular ejection fraction <25%, who have failed response to optimal medical management. This includes beta-blockers and ACE inhibitors if tolerated, inotropes, and intra-aortic balloon pumps. In those who are not inotrope- or balloon pump-dependent and physically able, functional limitation is demonstrated with peak oxygen consumption ≤14 mL/kg/min [15]. Absolute contraindications include sepsis or current active infections, severe right heart failure, untreated and severe carotid artery disease, severe obstructive and/or restrictive pulmonary disease, irreversible severe cerebral injury, dialysis-dependent renal failure, elevated INR from liver failure or disseminated intravascular coagulation, any severe end-organ failure, heart failure expected to recover without mechanical circulatory support, and non-cardiac illness that would limit survival to less than 2 years. Relative contraindications include morbid obesity, small body size (BSA <1.5 m^2), chronic renal dysfunction but not dialysis-dependent, malnutrition, and severe or untreated mitral stenosis and aortic regurgitation. Of note, small body size may no longer be a contraindication as the newer devices are able to accommodate smaller body sizes [16].

Patient selection for LVAD remains a challenge as successful therapy is dependent on time of implantation and appropriate patient selection. The challenge lies with selecting patients with sufficient severity of illness to achieve a benefit while avoiding patients who are too ill or too early in the disease course to derive any benefit. Additionally, the risk of device-related complications including thromboembolic events, gastrointestinal bleeding, and infection must also be considered.

The National Institutes of Health-sponsored Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a US registry which has acquired data on patients with FDA-approved MCS devices. It has developed a validated classification scheme based on patients' hemodynamic status and has been established to predict outcomes in patients undergoing MCS. The classification scheme is felt to be more specific than NYHA classification and allows for optimal patient selection and timing. Moreover, it is easily assessed at the bedside (Table 2.2) [17].

Currently LVADs are approved by the FDA for INTERMACS profile 1–5, with the greatest amount of implants in patients with profile 1–2 [9].

Risk Scores

No single variable exists to select candidates for LVAD therapy. While the INTERMACS classification scheme has been shown to predict prognosis after MCS, it lacks specificity and objectivity. Furthermore, it does not incorporate severity of multi-organ dysfunction [18]. Several risk scores have been developed, which incorporate individual data. They have been shown to predict both mortality in advanced heart failure and survival after LVAD therapy.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was developed from a multi-institutional cohort of 5815 critically ill patients. The score consists of 13 variables including temperature, mean arterial pressure, heart rate, respiratory rate, partial pressure of arterial O_2 or A-a gradient, arterial pH, sodium, potassium, creatinine, hematocrit, white blood cell count, Glasgow coma score, and age. Patients with HF and an APACHE II score greater than 20 have been shown to have a significant increase in hospital deaths [19]. In a retrospective

Table 2.2 INTERMACS classification [17]

Level	Hemodynamic status	Time frame for intervention
1. "Crash and burn"	Persistent hypotension despite rapidly escalating support and eventually IABP and critical organ hypoperfusion	Within hours
2. "Sliding on inotropes"	Intravenous inotropic support with acceptable values of blood pressure and continuing deterioration in nutrition, renal function, or fluid retention	Within days
3. "Dependent stability"	Stability reached with mild to moderate doses of inotropes but demonstrated failure to wean from them due to hypotension, worsening symptoms, or progressive renal dysfunction	Elective over weeks to months
4. "Frequent flyer"	Possible weaning of inotropes but experiencing recurrent relapses, usually fluid retention	Elective over weeks to months
5. "Housebound"	Severe limited tolerance for activity: comfortable at rest with some volume overload and often with some renal dysfunction	Variable urgency, dependent on nutrition and organ function
6. "Walking wounded"	Less severe limited tolerance for activity and lack of volume overload. Fatigue easily	Variable urgency, dependent on nutrition and organ function
7. "Placeholder"	Patient without current or recent unstable fluid balance. NYHA class II or III	Not currently indicated

cohort of patients with advanced HF, each unit increase in the APACHE II score independently predicted death. Furthermore, patients with a medium APACHE II score of 11–20 had the greatest benefit from LVAD placement [20].

The Seattle Heart Failure Model (SHFM) was derived from a cohort of 1125 NYHA IIIb–IV patients. Twenty variables are weighted by hazard ratio: age, gender, NYHA class, weight, ejection fraction, systolic blood pressure, presence of ischemic cardiomyopathy, daily furosemide equivalent dose, inotrope use, statin use, allopurinol use, angiotensin-converting enzyme/angiotensin receptor blocker use, beta-blocker use, potassium-sparing diuretic use, implantable cardioverter defibrillator, hemoglobin, lymphocyte percentage, serum uric acid, serum cholesterol, and serum sodium. The SHFM has been updated specifically for LVAD patients with the addition of intra-aortic balloon pump and inotrope therapy. Web-based calculators are available to convert the SHFM score to a mortality estimation where a score > 3.53 is considered high risk with a 50% predicted survival at 6 months. SHFM has been shown to predict 1-, 2-, and 3-year survival in low- to high-risk HF patients [21]. The performance of the SHFM was applied to advanced HF patients referred for transplant by Kalogeropoulos et al. Overall, the SHFM accurately discriminates between low- and high-risk patients. However, in terms of absolute risk (observed versus predicted event rate), the model overestimates survival and underestimates risk, particularly in black patients and those with implantable devices. The adverse events in this case were primarily driven by death. The model showed improved calibration when evaluating for mortality alone [22]. One limitation of the SHFM is that the model is not developed from a cohort of patients being considered for MCS. However, when applied to the REMATCH database, in which patients with advanced HF were ineligible for cardiac transplant, the 1-year SHFM-predicted survival was similar to actual survival for both the medical and LVAD therapy groups [23]. Furthermore, the SHFM is able to predict important features of the patient's hospital course after LVAD implantation. Patients in the lower-risk group had shorter length of stay, higher rate of discharge, and discharge within 60 days of LVAD placement [24].

The REMATCH trial demonstrated that patients who were ineligible for cardiac transplant had improved 1-year survival with LVAD therapy compared to patients receiving optimal

medical therapy. The Destination Therapy Risk Score (DTRS) was derived from the DT registry in the post-REMATCH era. In an analysis of 222 patients who received pulsatile LVAD, nine preoperative risk factors were identified to predict 90-day in-hospital mortality by multivariable analysis. This includes platelet count ≤148, serum albumin ≤3.3, INR >1.1, vasodilator therapy, mean pulmonary artery pressure ≤25, AST >45, hematocrit ≤34%, BUN >51, and no intravenous inotrope use. Each variable is assigned a weighted risk score, creating a cumulative score ranging from 0 to 27. Patients can be stratified to four risk categories based on probability of 90-day mortality. The score offers good discrimination between low- and high-risk groups with a 1-year survival of 69% versus 13%. Limitations of the DTRS include generalizability as the registry is composed from an older population and predominantly Caucasian males. Mechanical ventilation, intra-aortic balloon pump, and patient size were also not represented in the model due to small sample size. Lastly DTRS was not applied to newer generations of continuous-flow LVADs [25]. This was examined by Teuteberg et al. who applied the DTRS to 1124 patients with continuous-flow LVADs for BTT and DT. The DTRS in this lower-risk cohort demonstrated modest discriminatory capacity for 90-day in-house mortality. The score was able to discriminate between those at low versus high risk, however failed to discriminate between low- and intermediate-risk groups. The ability of DTRS to predict 2-year survival was also examined. DTRS moderately predicted survival for DT populations stratified by risk group, though it was unable to predict survival in the BTT population [26].

The HeartMate II risk score (HMRS) was developed from patients enrolled either in the HeartMate II (HMII) BTT or DT clinical trials. The score used preoperative patient-specific factors for predicting 90-day mortality in LVAD candidates. In a multivariate analysis, age (per 10 years), albumin, creatinine, INR, and center volume demonstrated good discrimination and calibration in predicting 90-day mortality. Patients were able to be stratified to three risk categories. When comparing HMRS to DTRS, HMRS provided significantly higher risk discrimination in both DT and BTT populations and across all risk groups [27]. However, this could not be confirmed in a single-center study by Thomas et al. In this retrospective analysis of 205 patients who received HMII for either BTT or DT, the HMRS demonstrated poor discrimination in 90-day and 1-year survival across all risk groups [28].

The above risk scores were applied to a cohort of 86 patients with continuous-flow LVADs to determine their ability to predict mortality after LVAD implantation. INTERMACS appeared to differentiate high-risk populations if patients with profile 1 and 2 were combined. The APACHE II and SHFM scores successfully differentiated between high-risk and low-risk groups. The DTRS failed to show significant survival between low-risk and high-risk groups. Overall, the SHFM score was the best predictor of mortality [29].

The development of risk scores based on preoperative risk is a useful guide to patient selection. However, no single risk score has been shown to be conclusively predictive and must be used in context with the patient's clinical status.

Pulmonary Hypertension

Pulmonary hypertension is common in patients with advanced HF and is most commonly secondary to left heart disease. Pulmonary hypertension in this population is defined by mean pulmonary artery pressure ≥25 at rest and pulmonary arterial wedge pressure (PAWP) >15 mmHg assessed by right heart catheterization [30]. Pulmonary artery hypertension with elevated pulmonary vascular resistance (PVR) is considered a contraindication to heart transplantation when PVR >5 Wood units or the indexed pulmonary vascular resistance (PVRI) is >6 or the transpulmonary gradient exceeds 16–20 mmHg, due to the high risk of right ventricular failure posttransplantation [31]. This occurs because the grafted right heart is unable to tolerate an abrupt increase in pulmonary vascular resistance in the immediate postoperative period. The Cardiac Transplant Research Database has shown that preoperative vascular resistance is an

independent risk factor for early and late mortality after cardiac transplantation [32].

While pulmonary hypertension is a contraindication for cardiac transplantation, it is not considered a contraindication for LVAD therapy. In fact, LVAD implantation may improve the severity of pulmonary hypertension, thereby reversing a patient's contraindication to transplant candidacy. Numerous studies have demonstrated that LVAD implantation is safe and efficacious when used as bridge to transplant [33–35]. Tsuashita et al. conducted one of the largest studies evaluating the effect of continuous-flow LVADs on pulmonary hypertension as well as posttransplantation outcomes in patients bridged with LVADs. The study found that PVR decreased significantly post-LVAD implantation. This was also observed in patients considered to have severe refractory pulmonary hypertension. As a result, 66% of patients in this cohort, who would have otherwise not been candidates for transplantation, were able to have their eligibility reversed and undergo cardiac transplantation. Despite improvements in PVR post-implantation, patients with high PVR pre-LVAD implantation still had increased in-hospital mortality posttransplantation. A potential explanation for this finding is that the pulmonary vasculature undergoes heterogenous or incomplete remodeling and therefore is susceptible to early postoperative insult including myocardial ischemia, metabolic acidosis, hypoxemia, inflammatory response, or blood transfusion. Long-term survival posttransplantation, however, was similar in patients with high PVR pre-LVAD compared to those with low PVR [36].

Right Ventricular Failure

Right ventricular failure (RVF) after LVAD implantation is a cause of significant morbidity and mortality. It results in longer hospitalization, higher transfusion requirements, need for reoperation, and end-organ damage [37]. Concurrent placement of a right ventricular assist device (RVAD) for RVF has been identified as the most significant risk factor for death after implantation [38]. Several mechanisms contribute to RVF following LVAD implantation. Increased cardiac output from left ventricular unloading leads to increased venous return to the right ventricle, thereby unmasking preexisting right ventricular dysfunction. Left ventricular decompression may also result in leftward shift of the interventricular septum, decreasing septal contribution to right ventricle contraction [39].

The incidence of RVF ranges from 9.4 to 44%, depending on the definition of RVF [40]. The INTERMACS defines right heart failure as symptoms or findings of persistent right ventricular failure characterized by both of the following: (1) documentation of elevated central venous pressure (CVP) and (2) manifestation of elevated central venous pressure. Elevated CVP may be measured either directly (e.g., right heart catheterization) with CVP or right atrial pressure (RAP) >16 mmHg, findings of the significantly dilated inferior vena cava with the absence of inspiratory variation by echocardiography, or clinical findings of elevated jugular venous distension. Elevated CVP is manifested by clinical findings of peripheral edema, the presence of ascites or palpable hepatomegaly on physical examination or diagnostic imaging, or laboratory evidence of worsening hepatic or renal function. The severity of RVF may be further categorized as mild, moderate, severe, and severe-acute RVF (Table 2.3) [41].

Predicting patients at risk of developing RVF post-LVAD implantation would improve patient selection. It would also allow clinicians to implement strategies to avoid RVF. Several studies have identified predictors of post-implantation RVF (Table 2.4) [42–47]. However, predicting RV response to LVAD implantation remains challenging as there is no consensus among these studies, and the data is limited by different definitions used by each trial to define RVF.

Matthews et al. developed a RVF risk score (RVFRS) based on independent predictors of RVF. Each variable was weighted by odds ratio: vasopressor requirement (4 points), AST ≥80 (2 points), bilirubin ≥2 (2 points), and creatinine ≥3.0 (3 points). The RVFRS is calculated as the sum of the pointed awarded for the presence of each of the preoperative variables. Patients

Table 2.3 Right heart failure severity score [41]

Mild	– Post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators not continued beyond post-op day 7 after VAD implant
	– No inotropes continued beyond post-op day 7 after VAD implant
Moderate	– Post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond post-op day 7 and up to post-op day 14 following VAD implant
Severe	– Central venous pressure or right atrial pressure >16 mmHg
	– Prolonged post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond post-op day 14 following VAD implant
Severe-acute	– Central venous pressure or right atrial pressure >16 mmHg
	– Need for right ventricular assist device at any time following VAD implant
	– Death during VAD implant hospitalization with RHF as the primary cause of death

with a score ≥5.5 have a 15-fold greater risk of developing RVF compared to patients with a score ≤3.0. When compared to commonly used predictors of RVF-RVWSI, transpulmonary gradient, PVR, RAP, and PASP, RVFRS was shown to be superior [46].

Invasive hemodynamic monitoring also has a role in predicting RVF. Elevated CVP, low pulmonary artery systolic pressure (PASP), low RV stroke work index, low cardiac index, and elevated PVR have all been shown to be predictors of RVF. Interestingly, unlike cardiac transplantation, low PASP rather than high PASP is a predictor of RVF. Caution must be used however as hemodynamic parameters may fluctuate in unstable patients who may be on inotropes.

A novel hemodynamic marker, the pulmonary artery pulsatility index (PAPi), has been found to identify patients at high risk of developing severe RVF after inferior wall myocardial infarction [48]. PAPi is defined as [(systolic pulmonary artery pressure − diastolic pulmonary artery pressure)/central venous pressure]. When applied retrospectively to continuous-flow LVAD recipients, a higher PAPi (>2.0) was associated with lower rates of RVAD implantation. Interestingly, PAPi more strongly predicted early RVAD requirement when hemodynamics were measured on inotropes versus off inotropes. Furthermore, the predictive ability of PAPi remained valid regardless of the timing between right heart catheterization and LVAD implantation, where the maximum time was 6 months [49]. In another cohort of patients with continuous-flow LVADs, PAPi initially decreased in the immediate postoperative setting. However, in patients without RVF, PAPi significantly increased after 24 h. Therefore, PAPi may also be used as an indicator for right ventricular recovery following LVAD implantation [50].

Attempts have also been made to identify predictors of RVF by echocardiography. This is challenging due to the retrosternal position of the right ventricle and its complex geometry, as well as the lack of standardization of echocardiographic protocols [40]. Tricuspid annular plane systolic excursion (TAPSE) <7.5 mm [51], reduced right ventricular fractional change area (<35%) [52], short to long axis ratio ≥ 0.6, and more severe tricuspid regurgitation [53] have been found to be predictive of RVF in small, single-center studies. However, these parameters could not be validated in larger subsequent studies, potentially because measurements of these load-dependent values are made in patients under severe hemodynamic stress.

Strain, strain rate, and speckle tracking are promising predictors of RVF. Unlike standard echocardiographic predictors, strain imaging is less sensitive to loading conditions and can reasonably assess right ventricular systolic function. Strain imaging was applied to patients undergoing LVAD implantation. Global longitudinal right ventricular strain was found to be an independent predictor of RVF where a right ventricular free wall strain <−9.6% predicted RVF with 68% sensitivity and 76% specificity. When combined with the RVF score described above, it provided incremental value on its predictive ability [54]. The right ventricular function after left ventricular assist device (RFV-LVAD) study prospectively

Table 2.4 Preoperative risk factors for RVF

Study (first author)	*n*	VAD type	Definition of RVF	RVF incidence	Preoperative risk factors
Ochai [42]	245	Pulsatile	– RVAD implantation	9%	– Female gender (OR 4.5) – Preoperative circulatory support (OR 5.3) – Nonischemic etiology (OR 3.3)
Dang [43]	108	Pulsatile	– RVAD implantation – Inotropes/pulmonary vasodilator therapy ≥14 days	38.9%	– Female gender – Elevated intraoperative CVP (OR 1.2)
Drakos [44]	175	Pulsatile (86%), Continuous (14%)	– RVAD implantation – Inotrope therapy >14 consecutive days – Inhaled NO ≥48 h	44%	– Destination therapy (OR 3.3) – IABP (or 3.9) – PVR ≥4.3 WR (or 4.1) – PVR 2.8–4.2 Wu (or 3.0) – Higher RAP – Increased LV end-diastolic diameter – Lower platelets – Higher bilirubin
Fitzpatrick [45]	266	Pulsatile (98%), Continuous (2%)	– RVAD implantation	37%	– Cardiac index <2.2 L/min/m^2 (OR 5.7) – RVSWI <0.25 mmHg/L/m^2 (OR 5.1) – Severe pre-VAD RV dysfunction (OR 5.0) – Cr ≥1.9 (OR 4.8) – Previous cardiac surgery (OR 4.5) – SBP ≤96 mmHg (OR 2.9)
Matthews [46]	194	Pulsatile (86%), Continuous (14%)	– RVAD implantation – Inotrope therapy >14 days – Inhaled NO ≥48 h – Hospital discharge with inotrope therapy	35%	– Vasopressor requirement (OR 3.9) – AST ≥80 (or 2.1) – Bilirubin ≤2 (OR 2.4) – Cr ≥2.3 (OR 2.9)
Kormos [47]	484	Continuous	– RVAD implantation – Inotrope therapy >14 days after implantation – Inotrope support starting 14 days after implantation	20%	– CVP/PCWP >0.63 (or 2.3) – Preoperative ventricular support (OR 5.5) – Bun >39 (or 2.1)

AST aspartate aminotransferase, *BUN* blood urea nitrogen, *CVP* central venous pressure, *Cr* creatinine, *IABP* intra-aortic balloon pump, *LV* left ventricular, *NO* nitric oxide, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *RV* right ventricular, *RVSWI* RV stroke work index, *SBP* systolic blood pressure

evaluated LVAD candidates with standard echocardiographic parameters and strain imaging. Standard echocardiographic parameters included TAPSE, pulse tissue Doppler peak systolic velocity, right ventricular myocardial performance index, and right ventricular fractional area change. Preliminary findings revealed right ventricular global longitudinal strain was the most important predictor of RVF [55].

With available predictive risk factors for RVF, the goal for the clinician should be to optimize the patient prior to LVAD implantation as well as certain measures during implantation and postoperatively [56, 57]. In the preoperative stage, patients with evidence of right ventricular dysfunction should undergo aggressive treatment to reduce right ventricular wall stress with a goal of decreasing right atrial pressure to <12 mmHg. The benefit of reducing pulmonary artery pressure and pulmonary vascular resistance remains uncertain as they have been shown to be inconsistent predictors of RVF. Though they may be decreased with PDE5 inhibitors, this has yet to demonstrate a clear clinical benefit. Those who remain at high risk despite medical optimization should be considered for planned biventricular support or total artificial heart as elective right VAD implantation has been shown to have better long-term survival versus emergency implantation [58]. Intraoperatively, correction of tricuspid regurgitation has been theorized to improve right ventricular function, though this remains controversial. In a review of 2000 patients who underwent LVAD implantation, concomitant correction of moderate-to-severe tricuspid regurgitation did not reduce early death or right VAD requirement. In fact, this was associated with worse early postoperative outcomes including renal failure, dialysis, reoperation, transfusion requirement, and greater length of stay [59]. Surgical hemostasis during LVAD implantation is critical to minimize blood product transfusion, thereby preventing volume overload of the right ventricle [57]. Inotropic agents in the immediate postoperative period are essential due to increased preload to the right ventricle. Pulmonary vasodilators may also be employed to decrease right ventricular afterload. Optimization of pump speed also avoids excessive leftward shift of the septum, thereby decreasing venous return. If the right ventricle fails despite these measures and is unable to maintain adequate LVAD flow, implantation of a right VAD is necessary.

Renal and Hepatic Dysfunction

Renal dysfunction is common in patients hospitalized for heart failure. Acute kidney injury (AKI), defined as an increase in creatinine >0.3 mg/dL, is observed in 50% of patients admitted for acute decompensated heart failure and 70% of patients with cardiogenic shock [60]. AKI is an independent risk factor for all-cause mortality, cardiac-specific mortality, pump failure death, and increased hospitalization in patients with heart failure [61, 62]. The etiology of renal dysfunction in patients with heart failure is multifactorial due to intrinsic disease from chronic comorbidities and cardiorenal syndrome. In cardiorenal syndrome, poor cardiac output results in poor renal perfusion. Venous congestion is also thought to play a role via activation of the renin-angiotensin system and renal arterial vasoconstriction to maintain glomerular filtration rate (GFR). The autoregulatory capability cannot be sustained and GFR ultimately declines. Hemodynamic changes also result in decreased GFR secondary to inflammation, endothelial dysfunction, and anemia [63].

Not surprisingly, preoperative renal dysfunction is associated with complications and mortality post-LVAD implantation. While renal dysfunction is a relative contraindication for LVAD and dialysis dependence remains an absolute contraindication, renal function has been shown to improve after LVAD implantation. This is due to improved renal perfusion and correction of the neurohormonal dysregulation. Studies have shown patients who had recovery in GFR had a slightly increased survival compared to those who had no improvements in GFR. In fact, patients who had a recovery of GFR to that of >60 mL/min/1.73 m^2 had comparable survival to patients with normal renal function post-implantation. Positive predictors of improved renal function include the absence of diabetes, lower cardiac index preimplantation, lower body mass index, and use of intra-aortic

balloon pump. Negative predictors include older age and the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. These variables however have not been externally validated [64–66].

While the majority of patients will have improvements in renal function after LVD implantation, a subset of patients may develop AKI, which confers a threefold increased risk of 1-year mortality [67]. Factors such as acute blood loss, volume shifts, arrhythmias, and multiple vasoactive medications may negatively affect renal hemodynamics. Management in this scenario should focus on optimizing the patient's volume status, maintaining goal mean arterial pressure, balancing inotropic and vasopressor medications, and optimizing right ventricular systolic function [68]. Should renal function continue to decline, the indications for renal replacement therapy are the same as other patients without LVADs. However, the type of renal replacement therapy, hemodialysis versus peritoneal dialysis, vascular access, and hemodynamic monitoring during dialysis, remains challenging [69].

The etiology of hepatic dysfunction in patients with heart failure ranges from cardiac cirrhosis or congestive hepatopathy to ischemic hepatitis. Cardiac cirrhosis results from chronic and progressive right ventricular dysfunction. As discussed elsewhere, hepatic function is used in various risk scores to predict right ventricular failure. Ischemic hepatitis on the other hand is caused by cardiogenic shock or other hemodynamic collapse, which results in hepatocellular necrosis. Hepatic dysfunction is associated with increased morbidity and mortality. It is associated with coagulopathies resulting in increased risk of bleeding, vasodilation, and poor nutrition.

The Model for End-Stage Liver Disease (MELD) score is a scoring system, which measures the progression of liver dysfunction using creatinine, total bilirubin, and international normalized ratio (INR). The MELD score has been shown to successfully risk stratify patients and predict 1-year mortality in patients with heart failure [70]. As previously noted, elevated AST and bilirubin have also been associated with poor outcomes following LVAD implantation.

Like renal dysfunction, hepatic dysfunction has been shown to improve after LVAD implantation. Russell et al. showed a decrease in AST, ALT, and total bilirubin in patients after continuous-flow LVAD implantation. A more significant decrease was seen in patients with above-normal liver function prior to implantation [71]. This reduction in liver function was seen by 1-month and continued up to 1-year post-implantation [72].

Patient Size Considerations

Data shows that patients at both extremes of body mass index (BMI) are associated with worse outcomes after LVAD implantation. Cardiac cachexia, defined as BMI <20 kg/m^2 or <80% ideal body weight, is a common complication in patients with heart failure and portends a poor prognosis. This state is marked by poor nutritional status and hypoalbuminemia, which is independently associated with an increased risk of death from heart failure [73]. Cachexia prior to cardiac transplantation has also been associated with increased risk of morbidity and mortality posttransplantation [74]. Malnutrition increases the risk of postoperative complications such as infection and poor functional capacity. Interestingly, studies have shown that underweight patients who underwent LVAD implantation have no difference in survival compared to patients with normal BMI. However, underweight patients are at significantly higher risk of bleeding and procedure failure [75, 76]. Nevertheless, all candidates for LVAD therapy should undergo a nutritional assessment to develop a strategy customized to each patient [77].

Small body size defined as body surface area (BSA) <1.5 m^2 is considered a relative contraindication to LVAD implantation. This is the case as the older, pulsatile-flow generation LVADs are larger and can only be placed in patients with BSA >1.5 m^2. This limitation results in an underserved population of smaller adults, women, and children. The newer-generation, continuous-flow LVADs are much smaller. In fact, the HeartMate II is one seventh the size and one quarter the weight of the older-generation HeartMate XVE [78]. Therefore, the HeartMate

II has been approved to be implanted in patients with a lower limit of BSA at 1.2 m^2 and greater. There remains limited data available on implanting LVADs in smaller patients as few studies have a cohort of patients with a BSA <1.5 m^2. Ono et al. demonstrated no difference in survival at 1 year in a cohort of 104 Japanese patients with pre-LVAD BSA of <1.5 m^2 compared to patients with BSA >1.5 m^2. Both groups experienced a significant decrease in NYHA class. There was no difference in rate of thromboembolism; however, patients with BSA <1.5 m^2 were at increased risk of driveline infection [79].

Morbid obesity, defined as body mass index (BMI) >35 kg/m^2, is a relative contraindication for LVAD implantation, as it is associated with worse outcomes post-implantation. In a retrospective analysis of 3856 patients that underwent LVAD implantation as bridge to transplant, there was no difference in mortality across all BMI groups. However, there was a trend toward increased risk of infection and thromboembolism in patients with a higher BMI [80]. Another study also showed no differences in 1- and 2-year survival after LVAD implantation in all BMI groups, though obese patients had a higher incidence of sepsis and device-related infection as well as higher rate of rehospitalization [75]. The higher incidences of driveline infection may be secondary to excess adipose tissue in the abdominal area, resulting in less blood supply to the driveline area and therefore poor wound healing [81].

Morbid obesity is also a relative contraindication for heart transplantation as it is associated with worse outcomes posttransplantation. Therefore, weight loss is recommended to achieve a BMI ≤35 kg/m^2 before listing for cardiac transplantation [82]. A small study evaluated LVAD implantation in 19 obese patients with advanced heart failure as a "bridge to weight loss." Majority of obese patients experienced significant weight loss post-implantation and therefore reversal of their eligibility for cardiac transplantation [83]. However, this was contradicted in a larger study in which only 15% of obese patients were able to lose enough weight to be recategorized in a lower BMI group [80].

Age

The age cutoff for cardiac transplantation varies by transplant center. In general, it is agreed that patients less than 70 years old should be considered for cardiac transplants. Patients older than 70 years old may also be considered for transplantation, though they must be carefully selected [82]. Data on survival in the older post-LVAD population remains limited. Though there is no age cutoff for LVAD implantation, post-LVAD outcomes play an important factor in patient selection, particularly as there is an increase in older patients who are referred for LVAD therapy.

In a retrospective analysis of 55 patients who received HeartMate II as either bridge to transplantation or destination therapy, survival at 36 months was comparable between patients <70 versus ≥70 years of age. Both group of patients had improved quality of life and similar length of stay with no significant differences in adverse effects [84]. Another retrospective analysis evaluated outcomes in 128 patients implanted with continuous-flow LVAD for either bridge to transplantation or destination therapy. Patients were divided into patients <65 years of age and ≥65 years of age. In the bridge to transplantation group, patients ≥65 years old had a longer length of stay in the ICU. However, there was no difference in the two groups in terms of 1-year survival as well as 30-day adverse events including infection, re-exploration for bleeding, ischemic or hemorrhagic stroke, and renal failure. In the destination therapy group, patients ≥65 years old had a higher incidence of stroke. However, there were no significant differences in terms of survival at 2 years, length of stay, and other adverse events. In other studies, there was a trend toward decreased survival at 6 and 12 months in the older population, though this did not reach statistical significance. Nonetheless, adverse events remained comparable in both age groups [85, 86]. These studies suggest that age alone should not be used as criteria for exclusion of LVAD therapy.

It is felt that frailty rather than age may be a better measure to aid in patient selection for

LVAD therapy, as age itself has not demonstrated to be associated with worse outcomes. Though frailty is associated with advanced age, it is not confined to old age. Likewise, advanced age does not equate frailty. Frailty is defined as a "decrease reserve and reactivity to internal and external stressors—physically, psychologically, and socially" [87]. Markers of frailty include decline in lean body mass, strength, endurance, balance, walking performance, and low activity. Frailty has been shown to be predictive of both short- and long-term mortality, disability, and hospitalization when applied to patients with heart failure, coronary artery disease, and percutaneous coronary intervention [88].

Several screening tools are available to identify frailty, though this remains difficult as no gold standard definition exists. Perhaps the most widely used criteria to identify frailty is the Fried frailty phenotype. This was developed based on observations of progressive weakness and decline in activity in older adults. Frailty is defined with three or more of the following criteria: (1) weight loss, (2) weakness, (3) poor endurance, (4) slow gait speed, and (5) low physical activity (Table 2.5). The Fried frailty phenotype has been shown to be predictive of falls, hospitalization, disability, and mortality [89].

The Rockwood index is another screening tool to diagnose frailty. This uses multiple domains including disability, comorbidities, nutritional status, cognitive function, and physical performance. Though effective, this tool may be too difficult to apply in the clinical setting [90]. A simpler tool would be to use gait speed as a single measure of frailty. When compared with the Fried criteria and Rockwood index, gait speed alone was the strongest predictor of 6-month mortality in patients with coronary artery disease [91].

Table 2.5 Fried frailty phenotype [89]

Weight loss	Unintentional of >10 lb in prior year or ≥5% of body weight in prior year
Weakness	Grip strength in the lower 20% at baseline, adjusted for gender and BMI
Poor endurance and energy	Indicated by self-report of exhaustion
Slow gait speed	>6–7 s to walk 15 ft
Low physical activity	Weighted scores of kilocalories expended per week

Frailty defined with three or more of the above criteria

Frailty was applied to 99 patients undergoing LVAD implantation as destination therapy. Frailty was fined by the "deficit index," which consisted of 31 impairments, disabilities, and comorbidities. Patients were divided into tertiles based on deficit index ranging from frail, intermediate frail, and not frail. The study observed a stepwise increase in 1-year mortality with increasing deficit index. In fact, those in the highest frailty tertile had a threefold increase in death compared to those who were not frail. Frailty prior to LVAD implantation was also associated with increased risk of rehospitalization [92].

Psychosocial Evaluation

Psychosocial morbidity is common in patients with heart failure. Depression is the most common issue with a prevalence ranging from 15 to 36% [93]. Risk factors for depression in this population include female gender, living alone, and poor social support [94]. Depression is associated with increased mortality. Vaccarino et al. demonstrated patients with higher level of depressive symptoms had a higher rate of either functional decline or death at 6 months. Though noncompliance with medical regime likely contributes to increased mortality, it is not felt to play a significant role. Rather, depression may worsen heart failure prognosis via direct physiologic mechanisms [95]. Other psychiatric morbidities including anxiety, prior suicide attempts, drug or alcohol dependence or history of rehabilitation, and prior psychiatric hospitalization are also associated with poor survival [96].

Mood and anxiety disorders are also common after cardiac transplantation, particularly in the first year posttransplantation. Predictors of poor functioning posttransplantation include poor physical functioning at the time of cardiac transplant, pretransplant history of psychiatric disorder, poor social support, poor coping strategies, lower sense of personal control, and lower optimism. Collectively, this is associated with

increased mortality and risk of acute and chronic graft rejection and graft loss [97].

Psychological evaluation prior to LVAD implantation is essential for patient selection. Due to the complexity of care, candidates for LVAD must have both the cognitive and psychosocial abilities to care for themselves after receiving LVAD therapy. It is recommended that psychosocial selection criteria for LVAD implantation should follow heart failure transplant guidelines [98].

Structural Heart Disease

Left Ventricular Structure and Function

It is felt that dilated ventricles are better suited for LVAD implantation. Dilated ventricles allow the inflow cannula to be seated in the long axis of the left ventricle and avoid contact with the ventricular septum or free wall [16]. Patients with restrictive or hypertrophic cardiomyopathy have not been represented in LVAD trials, and therefore data remains limited. Topilsky et al. demonstrated LVAD implantation in this population may be feasible. In this study, eight patients with either restrictive or hypertrophic cardiomyopathy, who received LVAD placement, were evaluated. Myomectomy was performed at the time of LVAD insertion and enabled the placement of the inflow cannula. When this group was compared to patients with dilated cardiomyopathy, there was no difference in 1-year survival rates. However, the patients with restrictive or hypertrophic cardiomyopathy had increased rates of right ventricular dysfunction as suggested by right atrial pressures, decreased pump flow, and increased duration of inotrope use. One explanation of this finding is the possibility of myopathic involvement of the right ventricle and therefore preexisting pulmonary hypertension. Another explanation is increased "suck-down" events secondary to contact between the inflow cannula and intraventricular septum. Finally, there is concern that the myocardium may be too stiff; therefore, "suck-down" events may not be detected. Interestingly, when this cohort of patients was compared to patients with restrictive or hypertrophic cardiomyopathy without LVAD therapy, the LVAD group had slightly improved survival [99].

Valvular Heart Disease

Mechanical aortic valve is considered a relative contraindication to LVAD placement. Aortic valve immobility leads to stagnant blood flow near the valve, therefore increasing risk of thrombus formation and thromboembolism [16]. It is recommended that the mechanical valve be replaced with a bioprosthetic valve or the aortic valve prosthesis be patched with pericardium during LVAD insertion, though there is no consensus on which method is preferred. One small case series showed replacing a mechanical valve with a bioprosthetic did not offer any additional protection against thrombosis, and therefore patching the aortic valve prosthesis may be more beneficial [100, 101]. Another small case series examined outcomes between mechanical and bioprosthetic aortic valves at the time of LVAD implantation. Incidence of thromboembolism was low and comparable in both groups [102]. Similar results were seen in other small studies, where survival rates were similar to patients without mechanical valves [103–105].

Aortic stenosis does not require surgical intervention as LVAD flow is not dependent on the flow through the aortic valve [56]. More than mild aortic regurgitation on the other hand should be addressed at the time of LVAD implantation. Lower left ventricular pressures following LVAD implantation create a greater pressure gradient across the aortic valve, thereby worsening aortic regurgitation. The regurgitate flow produces a closed-loop system, which leaves the device ineffective for hemodynamic support. Furthermore, aortic insufficiency has been observed to progress even after LVAD implantation [106]. Diminished flow through the aortic valve results in diminished valve motion and fusion of the aortic valve commissures, resulting in worsening aortic valve insufficiency [107]. Current strategies to rectify aortic insufficiency include aortic valve closure, repair, and replacement with bioprosthesis. In a

retrospective analysis of patients with aortic insufficiency who underwent aortic valve procedure, aortic valve closure was associated with the highest 1-year mortality, followed by replacement, and then repair. Patients with aortic valve closure were more susceptible due to pump dysfunction as patients in this group become completely dependent on the pump [108].

Moderate to severe mitral stenosis should be replaced with a prosthetic valve at the time of LVAD implantation. Mitral stenosis after LVAD implantation results in reduced left ventricular filling and decreased LVAD flow. Pulmonary artery pressure also remains elevated, increasing the risk of right ventricular failure. Mitral regurgitation on the other hand does not generally require surgical intervention. LVAD implantation results in decreased left ventricular pressure, thereby reducing the severity of the regurgitant volume. A prosthetic or mechanical mitral valve is not considered a contraindication for LVAD implantation. There has been no increased risk of thrombus formation demonstrated [109].

Significant tricuspid has been shown to be a predictor of right ventricular failure after LVAD implantation. Correction of moderate or greater tricuspid regurgitation with either tricuspid valve repair or replacement at the time of LVAD implantation has been proposed to reduce the risk of right ventricular failure postoperatively. Maltais et al. demonstrated that tricuspid valve procedure (TVP) for moderate-severe tricuspid regurgitation produced right ventricular geometry changes consistent with reverse remodeling and improved right ventricular function [110].

The clinical benefits of concomitant tricuspid valve procedure were examined in a small cohort of patients with significant tricuspid regurgitation who received continuous-flow LVAD. Echocardiography after 1 month of implantation demonstrated reduced tricuspid regurgitation and right ventricular volume in the group who received concomitant TVP compared to the group who received LVAD alone. Postoperative right ventricular failure was also reduced in the TVP group. On the other hand, there was no difference in duration of hospitalization, need for rehospitalization, and 30-day or 1-year mortality between both groups [111]. However, these results could not be replicated by other studies. Saeed et al. demonstrated no difference in the incidence of right ventricular failure as well as long-term survival between patients who received concomitant TVP and LVAD implantation alone [112]. In addition, TVP has been also shown to be associated with increased risk of postoperative renal failure, greater transfusion requirement, reoperation, prolonged ventilation, prolonged ICU stay, and prolonged hospitalization. These inconsistences may reflect different management strategies for preoperative optimization in patients at risk of right ventricular failure [59]. Alternatively, there is also evidence that LVAD implantation may improve tricuspid regurgitation in a subset of patients due to left ventricular unloading and improvement in pulmonary artery pressures [113, 114]. Altogether, there has been no demonstration of a significant survival benefit to concomitant TVP. Though TVP improves the severity of tricuspid regurgitation, the data has failed to show a clinical benefit, and the risks and benefits of TVP should be carefully weighted before LVAD implantation.

Congenital Heart Disease

Intracardiac shunts including patent foramen ovale and atrial septal defects should be closed at time of LVAD implantation. Reduced left ventricular filling following implantation may result in right-to-left shunting and therefore thromboembolism [115, 116].

LVAD use in the adult congenital heart disease population is limited without established outcomes. Furthermore, implantation in this population may not be possible in this population due to their complex anatomy, presence of pulmonary hypertension and biventricular heart failure, and prior cardiac procedures. In patients following an atrial switch procedure with a failing systemic right ventricle, placement of a VAD into the right ventricle was shown to be successful. This is technically challenging though, as the right ventricle apex is not as well developed as the left ventricle apex. Furthermore, the trabeculae and

moderator band may obstruct the inflow cannula and must be carefully resected [117, 118].

Infections

Active infection is a contraindication for LVAD placement. Assessment for risk of infection must be assessed prior to LVAD implantation. This includes evaluating for leukocytosis or leukopenia, recent infections, BMI >40 kg/m^2, dental exam, indwelling catheters, and poor nutrition which is defined by prealbumin <15 mg/dL and BMI <20 kg/m^2 [119].

Infection is one of the most frequent adverse events following LVAD implantation. Driveline infections are the most common type of LVAD-associated infection. However, the severity of infection can range from driveline or pump pocket infection to sepsis.

Moving to Patients with Less Severe Heart Failure

LVAD implantation was initially reserved for patients with hemodynamic compromise and refractory heart failure, with the majority of recipients categorized as INTERMACS profile 1 and 2. However, this group is also associated with the highest 12-month mortality [9]. In a HeartMate II post-approval study, those with an INTERMACS profile 1–3 had a significantly lower survival at 24 months compared to patients in the INTERMACS 4–7 profile [120]. When patients with LVAD placement were stratified by INTERMACS profile, more patients with a higher INTERMACS profile survived to discharge compared with critically ill patients with a lower profile. Patients with higher INTERMACS profile also had a shorter length of stay [18]. Earlier implantation also confers other advantages such as reduced nosocomial infection and improved functional capacity prior to implantation [14]. Furthermore, health-related quality of life is significantly improved with LVAD therapy in all INTERMACS profiles [121].

This has led to an increasing trend to offer mechanical circulatory support to patients with less severe heart failure. Several studies have demonstrated patients who are inotrope dependent have superior outcomes with LVAD implantation when compared to patients receiving optimal medical therapy [10, 122]. However, outcomes in LVAD implantation in INTERMACS profile 4–7 are less established. The ROADMAP study is a prospective, nonrandomized, observational study comparing LVAD implantation versus optimal medical therapy in patients who are high risk but not inotrope dependent (INTERMACS 4–7). At 1 year, survival in the LVAD group was significantly higher than the optimal medical therapy group. However, this did not reach statistical significance on the intention to treat analysis. The LVAD group also experienced greater improvement and quality of life. Expectedly, adverse events were more common in the LVAD group. Bleeding was the primary driver in the LVAD group, while worsening heart failure was the primary driver in the optimal medical therapy group [123]. Earlier implantation may produce survival benefit and improve quality of life at the cost of increased adverse events, primarily bleeding.

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Optimization of Right Ventricular Function Preoperatively for LVAD Implantation

3

Salman Gohar, Samar Sheth, and Reynolds Delgado III

Introduction

Heart failure (HF) continues to place a significant burden on the current healthcare system. In 2012, the total direct medical cost for HF was $20.9 billion, and this is expected to increase to $53.1 billion in 2030 (representing a 2.5-fold increase). The majority of these costs are related to hospitalization [1]. Left ventricular assist devices (LVAD) were developed to provide end-stage heart failure patients opportunities to wait for a heart on a bridge-to-heart transplant (BTT) strategy or improve survival for those who were not eligible for heart transplantation on a destination therapy (DT) pathway. Since the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial reported a 48% reduction in risk of death in patients with advanced heart failure with the HeartMate XVE LVAD versus medical management, there has been an exponential increase in the number of mechanical circulatory assist devices for NYHA class IIIB/IV, stage D heart failure [2]. The HeartMate II study reported a significant survival advantage of continuous-flow ventricular assist devices (CF-VAD) over the older pulsatile HeartMate XVE device in a BTT strategy and opened the door for continuous-flow VADs (CF-VAD) that have since become standard of care [3].

Since 2001, more than 15,000 LVADs have been implanted in humans of whom more than 12,000 were CF-VADs. The current 1-year and 2-year survival with CF-VADs is 80% and 70%, respectively. Survival among DT patients continues to remain poor. In the recent era, survival with DT therapy at 1 and 3 years is 76% and 57%, respectively [4]. One way to minimize the risk is to affect immediate perioperative complications. Hence, once a patient has been selected as a candidate for LVAD, the patients must be optimized to prevent perioperative complications. RV failure after LVAD implantation is a serious complication associated with increased length of ICU and hospital stay [5] and 50% mortality at 1 year for those requiring a RVAD. From the seventh INTERMACS registry, RVF is associated with an immediate hazard for death; however, by 3 months, death rate decreases dramatically, highlighting the need to prevent RVF in the immediate postoperative period [4]. Although LVAD design has transitioned from pulsatile to continuous-flow devices,

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there has been no clinically significant reduction in RV failure [6]. Current reported incidence of RV failure after LVAD implantation remains between 20 and 50% depending on the patient series and is associated with overall poor clinical outcome.

This chapter aims to discuss the current definition of RVF after LVAD implantation as well as the current state of knowledge on its predictors, outcomes, and management. We will then discuss how to optimize RV function preoperatively from lessons learned during the history of mechanical support development and clinical research and, finally, via our own experience at the Texas Heart Institute.

Normal RV Anatomy

The right ventricle is designed to pump blood in a high-compliance, high-volume, and low-pressure system. It is approximately one-sixth the mass of LV with a paper-thin free wall and a septal wall shared with the LV. Unlike the conical left ventricle, the RV is a triangular-shaped structure in sagittal sections and crescent shaped in cross section [7]. It can be divided into a muscular trabeculated body (sinus) and a smooth infundibular outflow tract (Fig. 3.1). The intraventricular septum (IVS) also influences the RV shape. Under normal loading and electrical conditions, the IVS is concave to the LV during both systole and diastole (Table 3.1).

RV myocardium is composed of two layers: a superficial layer with circumferential fibers running parallel to the atrioventricular groove and a deep layer with fibers aligned longitudinally from base to apex. This differs from the LV, where oblique fibers are superficial, longitudinal fibers are in the subendocardium, and circumferential fibers are in between. The septum is shared and structurally similar to the LV, providing an intimate anatomic and functional relationship between the two, a basis for ventricular interdependence. Multiples studies have indicated that septal contribution to RV cardiac output is significant, ranging between 20 and 60% [8, 9]. Hoffman demonstrated that in a non-dilated RV, even after replacing the free wall with a noncontractile material (Dacron patch), the septum was able to maintain sufficient RV cardiac output for hemodynamic stability [10].

Normal RV Physiology

The RV contracts by three separate mechanisms, the first of which is an inward movement of the free wall followed by contraction of deeper longitudinal muscle fibers that draw the tricuspid annulus toward the apex and finally traction of the free wall from LV contraction generating a forward stroke volume. Normal baseline RV ejection fraction (RVEF) ranges from 40 to 76% and varies based on loading conditions [7].

RV function, like the LV, is affected by preload, afterload, and contractility. This complex relationship is best illustrated by differences in pressure-volume curves. The RV pressure-volume loop is more triangular in shape with the pulmonary valve opening early in systole once RV pressure reaches the low pulmonary pressure. As there is very little time spent in isovolumetric contraction, the loop assumes a triangular configuration in contrast to a square LV loop. This also hints to the fact that the RV performs primarily volume work [11] (Fig. 3.2).

The slope of the end-systolic pressure-volume relationship is called ventricular elastance and is a relatively load-independent measure of ventricular contractility. Dell'Italia demonstrated that the normal maximal RV elastance was 1.3 ± 0.84 mmHg/mL, four times lower than the LV. Consequently, the RV is more afterload sensitive than the LV [12]. This is demonstrated in the acute setting (i.e., massive pulmonary embolism), where RV stroke volume decreases significantly with sudden increase in pulmonary artery pressure.

Similar to the LV, in a normal RV, based on the Frank-Starling principle, an increase in preload improves contraction. However, in RV failure, the curves flatten and move down and to the right depict a drop in RV output with increase in preload (Fig. 3.3).

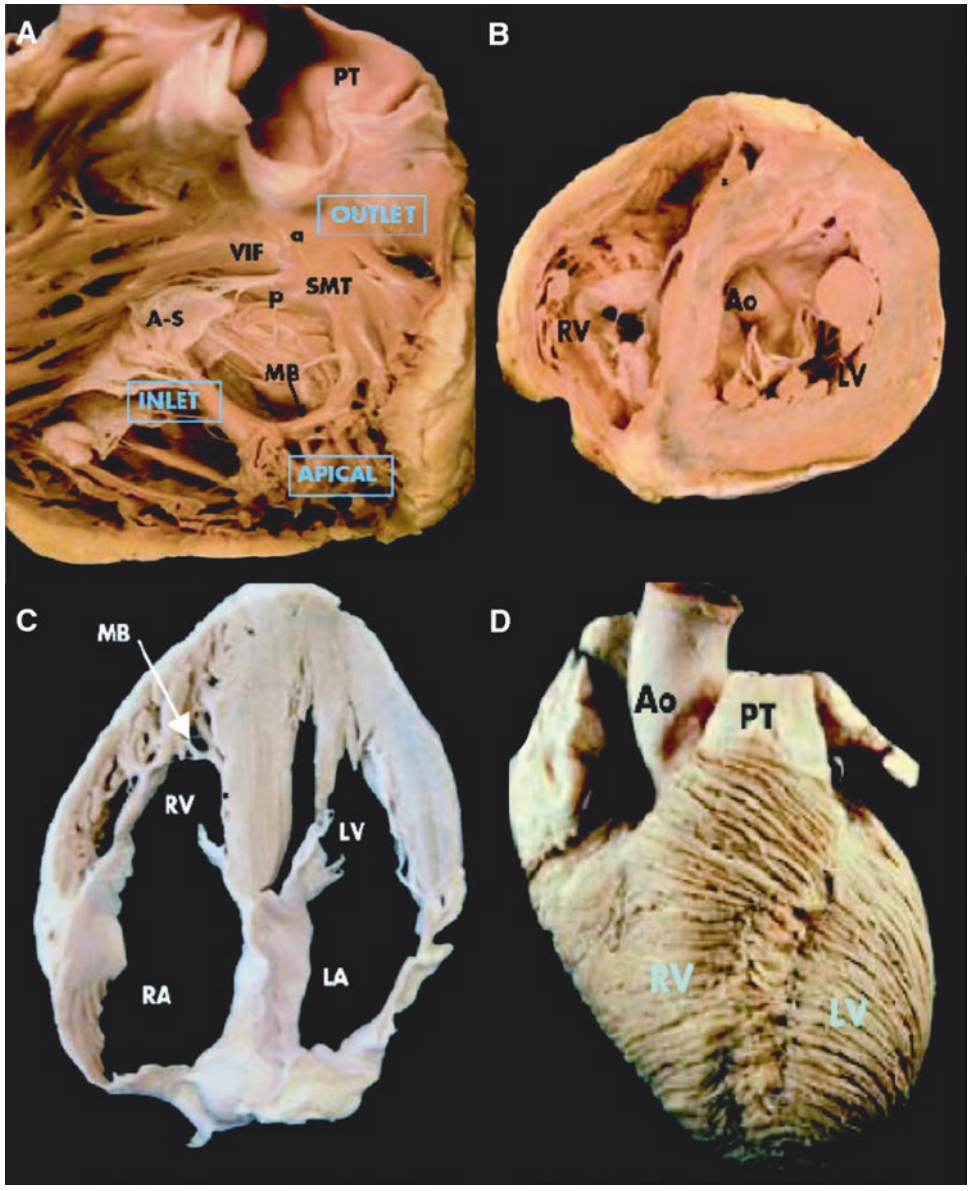

Fig. 3.1 (**a**) The inlet, trabeculated apical myocardium and infundibulum of the RV. The tricuspid and pulmonary valves are separated by the ventriculoinfundibular fold (VIF). (**b**) Short-axis plane of the RV demonstrating its crescentic shape. (**c**) The four-chamber anatomic plane of the heart showing the moderator band (MB) and the more apical insertion of the tricuspid valve. (**d**) Superficial muscle layer of the RV (dissection by Damian Sanchez-Quintana, University of Extremadura, Spain). SMT indicates septomarginal trabeculation with its anterior (a) and posterior (p) arm; *A-S* anterosuperior leaflet of the tricuspid valve, *PT* pulmonary trunk, *Ao* aorta, *RA* right atrium, *LA* left atrium (Reproduced with permission from Ho SY, Nihoyannopoulos P. Anatomy, echocardiography, and normal right ventricular dimensions. Heart. Copyright © 2006, BMJ Publishing Group Ltd)

The pericardium encases both ventricles and under normal circumstances provides an important protective barrier from overdistention and direct pathogen invasion. In addition, it also imparts a diastolic interdependence effect on both ventricles [13, 14]. Bernheim first hypothesized the impor-

Table 3.1 Structural findings of abnormal RV

Structural characteristics of RV		
Feature	Criteria	Interpretation
Dilation	Volume > 101 mL/m^2	Volume overload
	RV max SAX >43 mm	Pressure overload
	RVEDA/LVEDA >2/3	Intrinsic myocardial disease
D-shaped LV	[a]Eccentricity index >1	RV pressure or volume overload
		Diastolic D-shaped LV suggests RV volume overload
		Systolic D-shaped LV is RV pressure overload
Hypertrophy	Mass > 35 g/m	Pressure-overloaded RV
	RV infarction wall >5 mm	Hypertrophic cardiomyopathy infiltrative disease, exclude double-chambered RV
Aneurysm	Localized RV dilation	AVRD, RVMI; localized absence of pericardium
TV septal insertion	Septal insertion > 1 cm or 8 mm/m	Consider Ebstein's anomaly
Delayed hyperenhancement	Area of delayed contrast uptake and washout in MRI	Suggests myocardial fibrosis
Fatty infiltration	High-intensity signal on MRI	Consider ARVD

Haddad, F., et al., Circulation, 2008. **117** (11): p. 1436–48 [7]
RV max SAX indicates RV maximal short-axis diameter, RVEDA/LVEDA ratio of RV to LV end-diastolic area, *ARVD* arrhythmogenic RV dysplasia, *RVMI* RV myocardial infarction, *TV* tricuspid valve
[a]The eccentricity index measures the degree of septal displacement and is defined as the ratio of the minor axis diameter of the LV parallel to the septum to that perpendicular to it

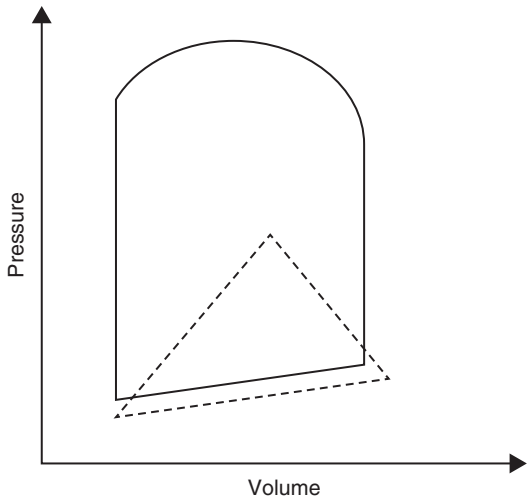

Fig. 3.2 The *solid line* depicts the square-shaped pressure-volume loop for the LV (*solid line*) and the triangular-shaped pressure-volume loop for the RV (*broken line*)

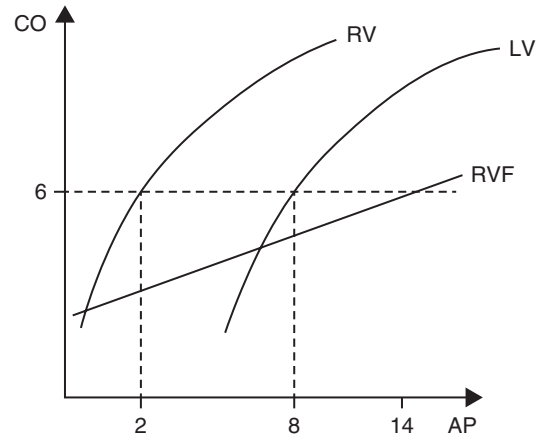

Fig. 3.3 Comparison of RV and LV Starling curves. LV requires higher atrial filling pressures (AP) to produce equivalent cardiac output (CO). In RV failure (RVF), the curve moves downward and to the right.

tance of the interventricular relationship [15]. Henderson and Prince later demonstrated that volume and pressure loading of one ventricle decreased the output of the other [16]. This was clinically demonstrated in 1956 by Dexter as deterioration of LV function in patients with atrial septal defects who developed RV pressure and volume overload,

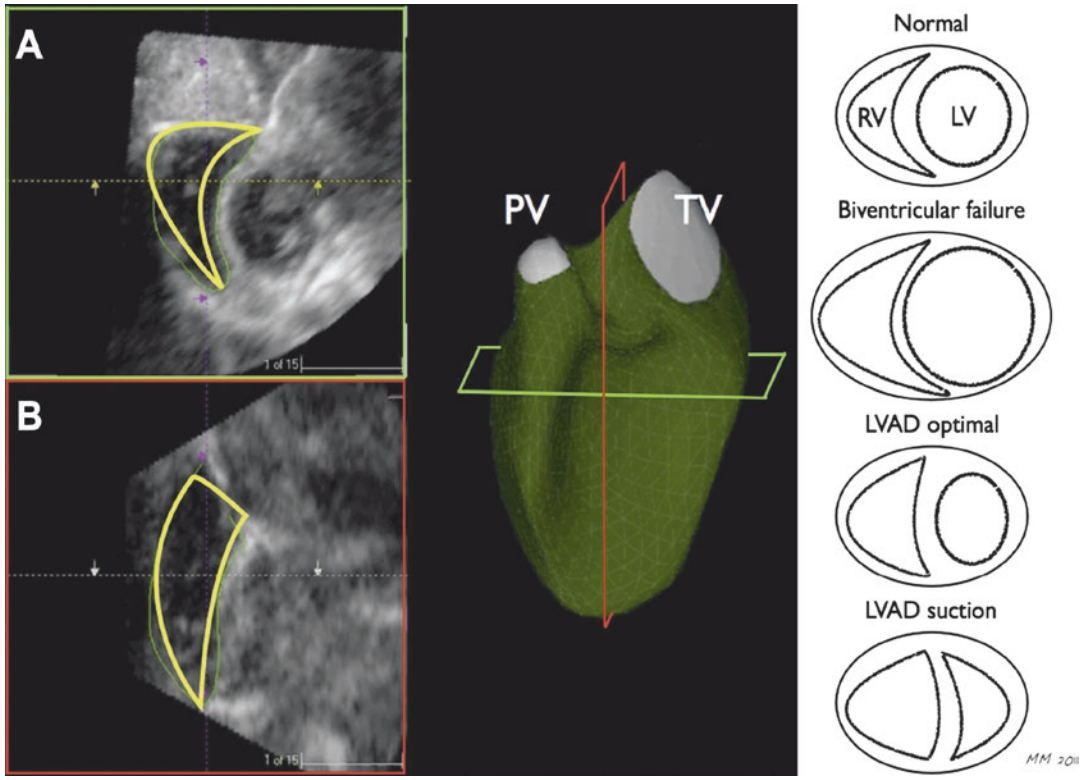

Fig. 3.4 RV size and function. Two perpendicular sections of a 3D TEE reconstruction of the right ventricle from tricuspid valve [TV] to pulmonary [PV] valve are shown. The cross section [**a**] demonstrates the crescent shape and the sagittal section and [**b**] the triangular shape of the RV. Ventricular interdependence between the left ventricle [LV] and RV during systole relies on interventricular septum position as shown in cross section for different clinical scenarios (Reproduced with permission from Meineri M, Van Rensburg AE, Vegas A. Right ventricular failure after LVAD implantation: prevention and treatment. Best Pract Res Clin Anaesthesiol. 2012)

a phenomenon called "reverse Bernheim effect" in which he postulated that the leftward septal shift resulted in impaired LV filling [17] (Fig. 3.4).

Measuring Normal RV Function

Multiple methods have been used to measure RV function clinically. Cardiac MRI is the most accurate tool to assess RV diastolic and systolic volumes as well as the RVEF [7]. By MRI, RVEF ranges 47–76%. A technique not used frequently is radionuclide angiography by which RVEF is usually 40–45%. Echo is least accurate in assessing RVEF but the most clinically used. Two-dimensional echo assessment by Simpson's rule can be used and correlates well with MRI; however, this is dependent on the quality of the images. RV fractional change area can be measured in four-chamber views and easily incorporated into most echo reports. Tricuspid annular plane systolic excursion (TAPSE) is another useful quantitative measurement of RV systolic performance [18, 19]. RV myocardial performance index, a ratio of isovolumic time interval to ventricular ejection time, doesn't involve ventricular geometry and is a load-independent measure of RV function. Finally, tissue Doppler imaging also allows for quantitative

Table 3.2 RV function echocardiography indices, Haddad, F., et al., Circulation, 2008. **117**(11): p. 1436–48 [7]

RV contractility indices			
Functional parameters	Normal value	Load dependence[a]	Clinical use
RVEF, %	61 ± 7% (47–76%)	+++	Clinical validation, wide acceptance
	>40–45%		Prognostic value in cardiopulmonary disorders
RVFAC, %	>32%	+++	Good correlates with RVEF
			Prognostic value in MI and bypass surgery
TAPSE, mm	>15	+++	Simple measure, not limited by endocardial border recognition: Good correlation well with RVEF
Sm annular, cm/s	>12	+++	Good sensitivity and specificity for RVEF <50%
Strain	Basal: 19 ± 6	+++	Correlates with stroke volume
	Mid: 27 ± 6		
	Apical: 32 ± 6		
Strain rate, s^{-1}	Basal: 1.50 ± 0.41	++	Correlates with contractility
	Mid: 1.72 ± 0.27		
	Apical: 2.04 ± 0.41		
RVMPI	0.28 ± 0.04	++	Global nongeometric index, index of systolic and diastolic function, prognostic value in PH and CHD
dP/dt max, mmHg/s	100–250	++	Not a reliable index of contractility
			More useful in assessing directional change when preload accounted for
IVA, m/s^2	1.4 ± 0.5	+	Promising new noninvasive index of contractility, studies in CHD
Maximal RV elastance mmHg/mL	1.30 ± 0.84	+	Most reliable index of contractility

RVFAC indicates RV fractional area change, *MI* myocardial infarction, *TAPSE* tricuspid annular plane systolic excursion, *Sm* tissue Doppler maximal systolic velocity at the tricuspid annulus, *RVMPI* RV myocardial perfusion index, *PH* pulmonary hypertension, *CHD* congenital heart disease

[a]Should be viewed as a general indication of load dependence

RV assessment. Finally, myocardial strain and speckle-tracking analysis can also be used to define RV function [20, 21] (Table 3.2).

Invasive hemodynamic assessment is the gold standard to assess RV function and can often tease out acute RVF from chronic RV dysfunction. Direct measurement of RA, RV, and PA pressures can clarify inconclusive noninvasive data. RV stroke work index (RVSWI), pulmonary artery pulsatility index (PAPi), and a RA to pulmonary capillary wedge pressure ratio have all been used to measure RV function [22] and predict RV failure post-LVAD implantation. At the Texas Heart Institute, we routinely use noninvasive parameters including TAPSE, tissue Doppler imaging (TDI), PAPi, and RA/PCWP ratio to aid in clinical decision-making (Table 3.3).

Table 3.3 Assessing normal RV performance using hemodynamic parameters

Parameter	Formula	Desirable value
RV size	N/A	RVEDV <200 mL, RVESV <177 mL
Central venous pressure (CVP)	N/A	<15 mmHg, 5 mmHg < PCWP
Transpulmonary gradient (TPG)	MPAP − CVP	<15 mmHg
Pulmonary vascular resistance (PVR)	MPAP − CVP/co	<4WU
RV stroke work index (RVSWI)	MPAP – CVP × (CI/HR)	>300–600 mmHg mL/m^2
Pulmonary artery pressure index (PAPi)	PASP − PADP/CVP	>2
Right atrial pressure to pulmonary capillary wedge pressure ratio	CVP/PCWP	<0.7

MPA mean pulmonary artery pressure, *CO* cardiac output, *RVEDV* RV end-diastolic volume, *RVESV* RV end-systolic volume, *PASP* pulmonary artery systolic pressure, *PADP* pulmonary artery diastolic pressure

Right Heart Failure Definition

The definition of RVF remains nebulous due to the use of inconsistent criteria in different publications. Some authors have described RVF as a need for intravenous inotrope or pulmonary vasodilator therapy for 14 days postoperatively and/or need for RVAD, while others defined it as simply a requirement for RVAD. Others still have used two or more of the following hemodynamic parameters to define RVF: central venous pressure greater than 16 mmHg, mean arterial pressure lower than 55 mmHg, cardiac index less than 2.0 L/min/m^2, inotrope support >20 units, and mixed venous saturation lower than 55%, all in the absence of cardiac tamponade [23–28].

According to the INTERMACS registry, RVF is present if symptoms or findings characterized by both elevation of central venous pressure (right atrial pressure > 16 mmHg on right heart catheterization, significantly dilated inferior vena cava with no inspiratory variation on echocardiography, and elevated jugular venous pressure) *and* manifestations of elevated CVP (peripheral edema, ascites, or hepatomegaly on exam or diagnostic imaging and laboratory evidence of worsening hepatic total bilirubin >2.0 mg/dL and renal dysfunction creatinine >2.0 mg/dL) are present [29] as illustrated in Table 3.4.

RV failure results from a number of reasons and similar to the LV can be both systolic and diastolic in nature. While the RV can accommodate increased preload, it is sensitive to increased afterload and elevations in PA pressures [29, 30]. As PA pressures increase due to worsening left-sided function, there is delayed pulmonary valve opening, leading to increased RV work and O_2 consumption. Moreover, this leads to progressive RV dilation, wall stress, and impaired coronary perfusion pressure. As the dilation progresses, geometry changes lead to tricuspid annular dilation and functional tricuspid regurgitation due to non-coaptation of leaflets. Abnormal septal activation also disrupts normal IVS function [29, 30]. Over time, if the heart failure remains untreated, cardiomyocyte stress and hypertrophy lead to irreversible apoptosis [29].

RV infarction due to obstructive coronary disease is another mechanism, which can lead to RVF although the incidence of RV infarct post-MI is low and is usually due to an isolated inferior wall MI. The likely reason for the lower incidence of ischemic RV failure compared to ischemic LV failure is probably lower RV wall stress and stroke work in addition to smaller mass requiring lower resting coronary flow and O_2 extraction [31].

Table 3.4 Interagency Registry for Mechanically Assisted Circulatory Support definition of right ventricular failure

Interagency Registry for mechanically assisted circulatory support definition of right ventricular failure	
RVF definition	Symptoms or findings of persistent RVF characterized by both of the following:
	– Right atrial pressure > 16 mmHg on right heart catheterization
	– Significantly dilated inferior vena cava with no inspiratory variation on echocardiography
	– Elevated jugular venous pressure
	Manifestations of elevated CVP characterized by:
	– Peripheral edema (>2+)
	– Ascites or hepatomegaly on exam or diagnostic imaging
	– Laboratory evidence of worsening hepatic (total bilirubin >2.0 mg/dL) or renal dysfunction (creatinine >2.0 mg/dL)
Severity scale	
Mild	Patient meets **both** criteria for RVF plus:
	– Post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators not continued beyond post-op day 7 after VAD implant
	– No inotropes continued beyond post-op day 7 after VAD implant
Moderate	Patient meets **both** criteria for RVF plus:
	– Post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond post-op day 7 and up to post-op day 14 after VAD implant patient meets **both** criteria for RVF plus:
	– CVP or right atrial pressure > 16 mmHg
	– Prolonged post-implant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond post-op day 14 after VAD implant
Severe	Patient meets **both** criteria for RVF plus:
	– CVP or right atrial pressure > 16 mmHg
	– Need for right ventricular assist device at any time after VAD implant
Severe acute	Death during VAD implant hospitalization with RVF as primary cause

CVP central venous pressure, *RVF* right ventricular failure, *VAD* ventricular assist device (Reproduced with permission [29, 47])

Pathophysiology of Right Heart Failure After LVAD Implantation

RV failure after LVAD implantation results from a complex sequence of events in the setting of underlying risk factors. Multiple mechanisms have been suggested. LV decompression and increased cardiac output increase venous return to the RV. Intraoperative volume resuscitation including blood transfusions also contributes to this increase in RV preload and can aggravate a decompensated RV [32]. Abnormal interventricular septum (IVS) geometry due to excessive leftward shift at high LVAD speeds can also worsen RV function due to loss of IVS contribution to RV output [33].

Ischemic injury is another mechanism seen after prolonged bypass times, coronary ischemia, and/or loss of coronary bypass grafts or coronary embolism. Between 30 and 64% of patients with advanced HF will have associated tricuspid regurgitation, which improves after LV decompression with a LVAD [34, 35]. However, a dilated tricuspid annulus or an incompetent valve generally worsens TR after LV decompression and increased preload. Severe TR further contributes to RV failure through the development of right-sided volume overload and reduced RV ejection. Although pulmonary artery pressures improve after LV decompression, perioperative ischemia-related pulmonary endothelial injury and transfusion-related lung injury often conversely increase pulmonary vascular resistance and can result in RV failure.

Supraventricular arrhythmias are seen in more than 20% of patients after LVAD implantation

and have been associated with twice the risk of RV failure [36]. More sinister rhythms like ventricular fibrillation have been associated with a 32% drop in cardiac output. Incessant postoperative VT can therefore adversely affect RV function in LVAD patients and should be avoided as far as possible [37].

Predicting Right Heart Failure After LVAD Implantation

Over the last three decades, many centers have worked to develop algorithms and risk scores to predict RVF after LVAD implantation. Early identification of high-risk patients remains important as it allows for the formulation of strategies to avoid RV failure. Unfortunately, most risk scores devised from retrospective, small single-center experiences provide a variable spectrum of predictors including hemodynamic, echocardiographic, biochemical, and intra- and postoperative parameters with no single model dependably forecasting RVF. Many early studies incorporated pulsatile devices in BTT cohorts and therefore did not accurately reflect outcomes in the current CF-VAD era. In addition, validation of many of these scores has demonstrated the modest real-world application [38]. In our center, we have noted that a preoperative, systemic inflammatory syndrome associated with a leukocytosis and thrombocytopenia may prime the RV for failure.

Hemodynamic Models

Fukamachi et al. reported RVAD support requirement for 11 out of 100 patients after HeartMate XVE pulsatile LVAD implantation. RVAD use was significantly higher in young, female patients with small BSA and those with myocarditis. There was no significant difference in the cardiac index, RV ejection fraction, or right atrial pressure between groups preoperatively. Low preoperative mean pulmonary arterial pressure (PAP) and RV stroke work index (RVSWI) were associated with the need for post-op RVAD. Survival to transplant was poor in the RVAD group, 27% vs. 83% in the no-RVAD group. However, the incidence and underlying mechanisms of RV failure changed after the introduction of continuous-flow LVADs (CF-LVAD) [39].

The right ventricular failure risk score (RVFRS) evaluated 197 patients undergoing HM II CF-LVAD implantations. Sixty-eight cases (35%) were complicated by postoperative RV failure. Points were given for need for vasopressors, elevation in aspartate aminotransferase (>80 IU/L), bilirubin (>2.0 mg/dL), and creatinine (>2.3 mg/dL). All were found to be independent predictors of RV failure. The odds ratios for RV failure for patients with an RVFRS of 3.0, 4.0–5.0, and 5.5 were 0.49 (95% confidence interval [CI], 0.37–0.64), 2.8 (95% CI, 1.4–5.9), and 7.6 (95% CI, 3.4–17.1), respectively, and 180-day survival of 90 ± 3%, 80 ± 8%, and 66 ± 9%, respectively ($P < 0.0045$) [40]. The different studies and RV failure risk models are listed in Table 3.5.

The HeartMate II risk model is the only large multicenter study with 484 patients, all of whom received CF-LVADs with results likely applicable in the current era. RVF in the trial was defined based on three groups; group 1 included those who needed RVAD support postoperatively, group 2 included those who required inotropes support for ≤14 days, and group 3 included patients who needed inotrope support for ≥14 days after implantation. Groups 1 and 2 together comprised the "early RVF" cohort, and group 3 was defined as "late RVF." The cumulative incidence of RVF was 20% with any early RVF noted in 13% of patients. The incidence of late RVF was 7%. The model found the CVP/PCWP ratio > 0.63, preoperative ventilator support, and BUN >39 mg/dL were independent predictors of RVF. Actuarial survival at 1 year was also significantly better for patients without RVF (79%) compared with that in patients requiring RVADs (group 1, 59%; P ¼ 0.004) or extended inotropes (group 2, 56%; P ¼ 0.007), whereas there was no difference for patients with late inotrope use (group 3, 75%; P ¼ 0.81). Decreased survival for patients with early RVF is evident in the grouped Kaplan-Meier survival curve (Fig. 3.5). Hospital length of stay for discharged patients was longer for those requiring an RVAD than for those without RVF (32 vs. 22 days,

Table 3.5 Clinical trials evaluating hemodynamic parameters for RV failure post-LVAD implantation (Reproduced with permission [47])

Study	*N*	VAD type	RVF definition	RVFi	Risk factors/scores	Outcomes
Ochai [27]	245	100% pulsatile VAD	Need for RVAD	9%	Pre-op circulatory support (OR 5.3)	
1991–2001					Female gender (OR 4.4)	
BTT 98%					Nonischemic etiology (OR 3.3)	
Drakos [40]	175	86% pulsatile VAD	Need for RVAD	44%	(1 point for each)	365-day post-LVAD survival:
1993–2008		14% CF-VADs	≥14 days inotropes		Destination therapy (OR 3.31)	≤5.0 = 83%
Single-center			iNO ≥ 48 h		Inotrope dependency (OR 2.47)	5.5–8.0 = 77%
Retrospective analysis					Obesity (BMI ≥ 30 kg/m^2) (OR 1.99)	8.5–12.0 = 71%
BTT 58%					IABP (or 3.88)	≥12.5 = 61%
					PVR	RVF % for risk score categories:
					1.8–2.7 Wu (or 1.95)	≤5.0 = 11%
					2.8–4.2 Wu (or 3.01)	5.5–8.0 = 37%
					≥4.3 Wu (or 4.14)	8.5–12.0 = 56%
					ACE or ARB (OR 0.49)	≥12.5 = 83%
					Beta-blocker (OR 1.60)	
Fitzpatrick [41]	266	98% pulsatile VAD	Need for RVAD	37%	Cardiac index (≤2.2 L/min/m^2) (OR 5.7) score 18	Total score ≥ 50 predicts need for BiVAD
1995–2007		2% CF-VADs			RSWI ≤0.25 mmHg/L/m^2 (OR 5.1) score 18	
Single-center					Severe pre-VAD RV dysfunction (OR 5.0) score 16	
Retrospective					Pre-op creatinine ≥1.9 mg/dL (OR 4.8) score 17	
					Previous cardiac surgery (OR 4.5) score 16	
					SBP ≤ 96 mmHg (OR 2.9) score 13	

(continued)

Table 3.5 (continued)

Study	*N*	VAD type	RVF definition	RVFi	Risk factors/scores	Outcomes
Dang [23]	108	100% pulsatile VAD	Need for RVAD, ≥14 days inotropes and/or pulmonary vasodilators	39%	Elevated intraoperative (OR 1.2)	
1996–2004						
BTT 73%						
Matthews [25]	197	86% pulsatile VAD	Need for RVAD/ ECMO	35%	Vasopressor use (OR 3.9) score 4	180 day post-LVAD survival for RVFRS
RVFRS		14% CF-VAD	≥ 14 days inotropes, inhaled iNO ≥ 48 h, or hospital discharge on an inotrope		AST ≥ 80 IU/L (OR 2.1) score 2	Total:
1996–2006					Bilirubin ≥2 mg/dL (OR 2.4) score 2.5	≥5.5 = 66 ± 9%
Single-center					Creatinine ≥2.3 mg/dL (OR 2.9) score 3	4.0–5.0 = 80 ± 8%
Retrospective						3.0 = 90 ± 3%
BTT 94%						
Atluri [28]	218	59% pulsatile VAD	Need for RVAD	23%	(1 point for each)	Score 0–1: LVAD only
2003–2011		41% CF-LVAD			CVP > 15 (or 2.0)	Score 2–3: May tolerate isolated LVAD with temp medical or RVAD support
CRITT score					Severe RV dysfunction (OR 3.7)	Score 4–5: BiVAD
					Pre-op mechanical ventilation (OR 4.3)	
					Severe tricuspid regurgitation (OR 4.1)	
					Heart rate > 100 beats/ min (OR 2.0)	
Kormos [26]	484	100% CF-LVAD	Need for RVAD, ≥14 days inotropes, late inotropes, later inotrope support starting >14 days after implant	20%	CVP/PCWP >0.63 (or 2.3)	365-day survival
Multicenter				Early RVF 13%	Pre-op ventilator support (OR 5.5)	No RVF = 78%
2005–2008					BUN >39 mg/dL (OR 2.1)	early RVF = 59%
Retrospective						
HM II BTT trial						
BTT 100%						

CRITT score [C]VP [R]V dysfunction [I]ntubation preoperatively [T]ricuspid regurgitation [T]achycardia; *RVFRS RV* failure risk score; *ACEI/ARB* angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, *iNO* inhaled nitrous oxide; RSWI

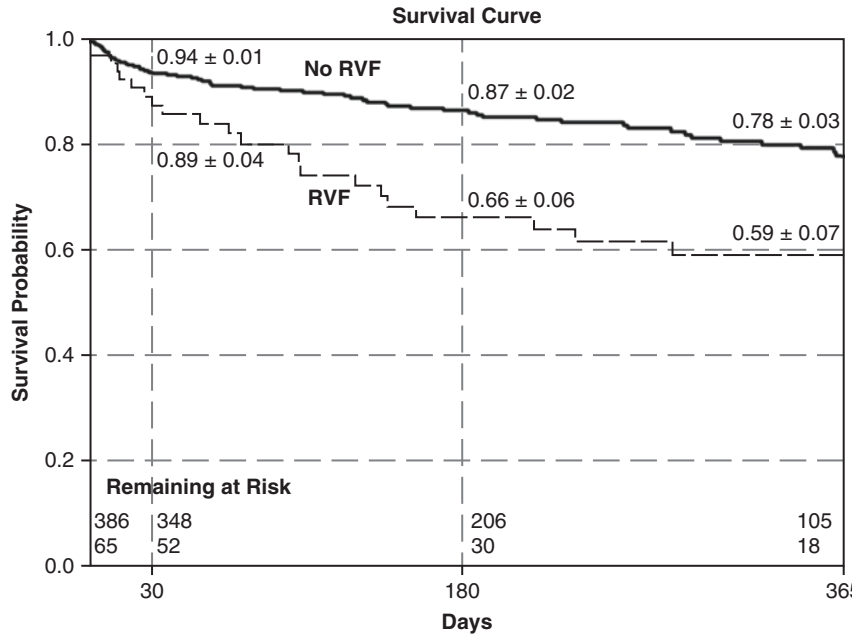

Fig. 3.5 HeartMate II LVAD indicating worse 1-year survival for patients with RVF (Modified from Kormos et al. [26])

$P < 0.001$). Those who required inotropic support for more than 14 days after LVAD implantation and those with late inotropic support had an average length of stay of 35 and 32 days, respectively. Thus, any RVF resulted in a significantly longer hospitalization time before discharge than seen in those without any RVF ($P < 0.001$) [26]. This trial indicates that patients with a significant preoperative RV dysfunction as characterized by a high-resting RAP to LAP ratio may be at higher risk for RVF after LVAD implantation and need closer monitoring. In addition, patients with established acute organ dysfunction especially if associated with a systemic inflammatory syndrome are very high-risk LVAD candidates as well.

Echocardiographic Models

Similar to hemodynamic parameters, various echocardiographic models have been used to predict post-LVAD RHF. Fitzpatrick et al. graded RV function on preoperative echo as none, mild, moderate, or severe. He noted that in addition to RV stroke work index (RSVWI), severe pre-op RV dysfunction was one of the strongest predictors of BiVAD placement [41]. However, semi-quantitative RV functional assessment on echocardiography is difficult to reproduce with potential for significant interobserver variability. Tricuspid annular plane systolic excursion (TAPSE) is a validated parameter of global right ventricular function. Puwanant et al. reviewed preoperative echo parameters in 33 patients and noted that TAPSE <7.5 mm was associated with increased risk of RVF with a 91% specificity and 46% sensitivity. Given the small cohort size with half devices pulsatile, extrapolation of the results remains limited in the CF-VAD era [42]. The RV/LV diameter ratio is a surrogate of disproportionate RV remodeling, similar to CVP/PCWP ratio. In a study involving 115 patients with CF-VADs, the RV-to-LV diastolic diameter (*R*/*L*) ratio was measured on transesophageal echocardiogram. The odds ratio of developing RVF was 11.4 in patients with an *R*/*L* ratio 0.72 (*P* 0.0001) [24] (Fig. 3.6). Another trial using transthoracic echocardiogram demonstrated a *R*/*L* ratio $\geq$ 0.75 and was associated with a fivefold increase in RVF. The *R*/*L* diameter ratio $\geq$ 0.75 (AUC = 0.68) was as optimal as the Matthews (AUC = 0.69) [25] and Kormos (AUC = 0.63) [26] risk scoring systems in predicting RVF alone and the composite of RVF and death [43].

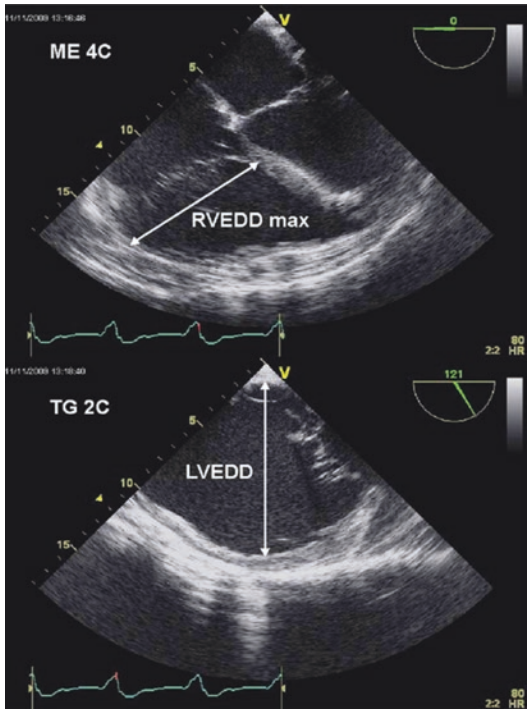

Fig. 3.6 *Upper panel*: mid-esophageal (ME) four-chamber view for measurements of right ventricular maximal end-diastolic diameter (RVEDD max). *Lower panel*: transgastric (TG) two-chamber view for measurements of left ventricular end-diastolic diameter (LVEDD). Both parameters are used for the *R*/*L* ratio calculation. A *R*/*L* ratio > 0.72 was associated with RVF (Reproduced with permission from Kukucka M et al. [24])

Strain imaging is a load-independent technique for measuring RV function. Although data is limited, many small studies have suggested decreased RV peak, and free wall longitudinal strain may predict RVF [21]. In a small study of 19 patients, speckle-tracking echocardiography was used to assess RV performance pre- and post-LVAD implant and noted that those with the lowest strain value pre-implant had worse function post-implant [44]. Quantitative 3D echocardiography (3DE) is a promising method for pre-LVAD RV assessment. Echocardiographic indices associated with RVF included 3DE indexed RV end-diastolic and end-systolic volumes (RVEDVI and RVESVI) and RV ejection fraction (RVEF). In a small study, preoperative RV volumes were associated with RVF in continuous-flow LVAD recipients, independently from hemodynamic correlates of RV function (RVSWI) [45].

Prevention of Right Heart Failure

Based on an understanding of RV physiology, many institutions have developed strategies to prevent post-LVAD RHF. These strategies are multifactorial as variables that relate to patient selection determine the need and type of medical plan prior to surgery. This can be thought of as optimizing the patient for LVAD implantation. What follows is our practice at the Texas Heart Institute (THI), which is informed by much of the previous discussion in this chapter. As such, it should not be considered a guideline or standard of care but rather a proposed pathway for practitioners to manage these complex patients.

Preload Optimization

In a study by Cordtz et al., the pathophysiologic steps leading to RVF after LVAD implantation were shown to initiate early on in the postoperative period as RVF incidence was related to the immediate cardiac index post-implant [46]. Based on the data presented earlier and our clinical experience, we have developed a uniform process to optimize RV function prior to LVAD implant.

Preoperative hemodynamic assessment and volume optimization with a PA catheter-guided strategy are recommended for patients at risk for RVF. The RV is a volume-dependent ventricle, and optimizing central venous pressure (CVP) is key to mitigate the risk of RVF. Volume optimization with aggressive diuresis and if needed ultrafiltration are the mainstay of therapy. A CVP > 16 mmHg has been associated with post-op RVF [25, 40, 47, 48]. At our institution, we use an aggressive diuretic regimen employing loop diuretic infusions in combination with thiazide diuretics to block the renal tubules in a multi-targeted approach.

In addition to increasing urine output, attempts should be made to limit blood product transfusions during surgery by correcting coagulopathies prior to surgery to reduce SIRS-associated PVR elevation. In a single-center study, with pulsatile LVADs, vitamin K given preoperatively was found to reduce bleeding and the need for blood product transfusions [49, 50]. For known

coagulopathies, we should proceed in conjunction with clinical pathology consultation to correct the bleeding diathesis prior to surgery.

Afterload Reduction

Optimization of RV afterload can further help improve hemodynamics and assist with weaning from cardiopulmonary bypass and chest closure. As noted earlier, the RV is very afterload sensitive, yet some reports suggest that this sensitivity increases further after LVAD placement [51, 52]. Attempts to reduce PVR prior to LVAD implant can lower the incidence of RV with likelihood of benefit [48, 49]. Pulmonary vasodilators including inhaled nitrous oxide (iNO) and phosphodiesterase-5 inhibitors have been used for RV afterload optimization during intraoperative and postoperative period. A prospective, randomized, double-blind, placebo-controlled, multicenter trial demonstrated that iNO initiated before weaning from cardiopulmonary bypass (CPB) and continued for 48 h post-LVAD implantation decreased mean pulmonary artery pressure (mPAP) and increased LVAD flow. However, it did not reduce the incidence of RVF, with most benefit seen in patients with higher mean pulmonary artery pressures and low pump flow during weaning from CPB [53]. Sildenafil is a phosphodiesterase-5A (PDE5) inhibitor with pulmonary artery vasodilatory properties. In patients with persistent pulmonary hypertension after recent LVAD placement, sildenafil use resulted in a significant decrease in PVR when compared with control patients [54, 55]. A recent systematic review noted insufficient evidence supporting PDE5 inhibitor use to attenuate RV failure in patients requiring an LVAD [56]. Lastly, strategies to avoid sudden elevation in pulmonary vascular resistance including hypoxia, hypercarbia, or severe acidosis should be implemented during peri- and early postoperative period. At THI, we initiate intraoperative iNO in all patients and oral phosphodiesterase inhibition in most patients to optimize PVR prior to surgery. These are continued into the postoperative period.

Inotropic Support

Perioperative inotropic support for a tired, distended RV is important to prevent postoperative RV failure. Milrinone and dobutamine are the two approved inotropes used for cardiac support. Milrinone is an intravenous PDE3 inhibitor that improves cardiac output by elevating intracardiomyocyte cAMP levels. It has a long half-life and has minimal effect on the heart rate. Its vasodilation of both the pulmonary and systemic vascular beds can result in hypotension at high doses, limiting its use in many situations. Dose adjustment is required in patients with renal dysfunction due to risk of toxicity. Dobutamine is a β-1 agonist with a short half-life. It increases both cardiac contractility and heart rate with some hypotension. In stable patients not on inotropes, given their negative inotropic effects, we recommend avoiding beta-blockers in the perioperative period at our institute.

Vasopressors are used cautiously in specific scenarios involving hypotension and post-op vasoplegia after LVAD implant. Epinephrine and dopamine are the two commonly employed agents for vasodilatory shock after LVAD implantation. They also possess some intrinsic inotropic properties and increase blood pressure by arteriolar and splanchnic vasoconstriction. We try to limit the overall duration of inotrope use given the association with increased mortality in clinical trials. Our inotrope weaning strategy at Texas Heart Institute (THI) involves vasopressor weaning first. The patient is aggressively diuresed during this time while PDE5is are uptitrated. Once clinical euvolumia is achieved (increase in BUN/Cr ratio and MvO2 > 60%), inotrope weaning is initiated and completed within a few days.

Sinus rhythm and AV synchrony are important in right ventricular function. A lack of sinus rhythm leads to suboptimal RV mechanical function [7]. There is strong evidence that cardiac resynchronization therapy in the appropriate patient population (LBBB, QRS >150, NYHA class III–IV) improves LV and RVEF and NYHA symptoms.

Temporary Mechanical Circulatory Support

RVF may still occur despite all necessary precautions after LVAD implantation. Prompt identification and surgical support in such scenarios can be crucial to improve long-term outcomes. Elective RVAD implantation has been correlated with better long-term survival than an emergent implant [57]. Concomitant RVAD implant at the time of LVAD implantation has also been shown to improve survival to transplantation in small studies [58].

Percutaneous ventricular assist devices (pVADs) are an important adjunct to medical therapy at THI. At our institution, we routinely utilize mechanical circulatory support for optimization of hemodynamics and end-organ function before durable LVAD implantation. Intra-aortic balloon pump (IABP) is associated with improved RV dysfunction in postcardiotomy shock [59]. It has also shown to improve LV and RV hemodynamics in patients with RV pressure overload [60, 61]. We utilize the balloon pump as a bridge to decision for both elective durable LVAD implantation and in critically sick ICU patients with slowly progressive cardiogenic shock. Our experience has demonstrated that IABP improves MPAP, PCWP, and RV geometry similar to previously published work [49].

Severe biventricular heart failure remains a difficult clinical scenario requiring complex management in the VAD era. In a small, single-center study, Ntalianis et al. demonstrated the prolong use of a sheathless femoral IABP (mean duration of 73 days), in 15 high-risk patients (INTERMACS 1 or 2). The study demonstrated an improvement in RAP, PAP, and cardiac index as well as improvement in echocardiographic indices of RVF (RVSWI, TAPSE). None of the six patients (40%) who were bridged to LVAD implantation developed post-implant RVF, while three patients who were weaned from the IABP preserved satisfactory RV function 6 months after IABP removal. An interesting finding from the analysis noted that patients with early shock seemed to derive the most benefit from the IABP [62]. At the University of Washington in St. Louis, 54 patients with cardiogenic shock prior to LVAD implant demonstrated clinical stabilization with an IABP, and outcomes post-VAD implant were improved as compared to those that did not and required escalation of therapy [63].

Femoral access for IABP is useful in emergent scenarios due to ease of access and caliber of vessel but has important limitations. Due to the need for limb immobilization, restriction on patient ambulation often leads to significant deconditioning. An alternative approach is axillary or subclavian (SCA) IABP insertion. In a single-center study from the University of Chicago, Tanaka et al. demonstrated the benefit of a subclavian (SCA) IABP. Ninety percent of the 70 patients who received a SCA IABP were bridged to either transplant, LVAD or recovery [60]. A statistically significant improvement in CVP, pulmonary artery pressure, wedge pressure, renal function, as well as cardiac index was noted with a median use of 21 days. Moreover, with the axillary balloon pump, the patients were able to ambulate and maintain muscle tone. We utilize IABP in patients with INTERMACS 2 extensively at our institution. Imamura et al. have also described a similar practice of insertion of IABP in all INTERMACS 2 patients <1 week prior to LVAD implantation. They demonstrated that compared to matched controls, patients who received an IABP had shorter ICU stays, improved markers of perfusion, and lower cost of care [64].

In those patients in which IABP is not an option or who are in acute profound shock, we have utilized the Impella pVAD (Abiomed) device series as a bridge to decision or bridge to LVAD. The Impella also may afford a period of time to precondition the RV to increase flows while also decreasing PA pressures. The Impella RP (Abiomed) is a small micro-axial percutaneously inserted pump that has been designed for short-term RV support and can assist with bridge to decision for long-term durable support without the need for significant surgery for implantation [65] (Fig. 3.7). Impella CP is a left-sided pVAD inserted across the aortic valve in the LV to optimize LV end-diastolic pressures. Its utility in RVF is questionable given the limited ability of the device to provide full cardiac output.

The Impella 5.0 (Impella) is a larger pVAD, which can deliver up to 5 L/min of flow and pro-

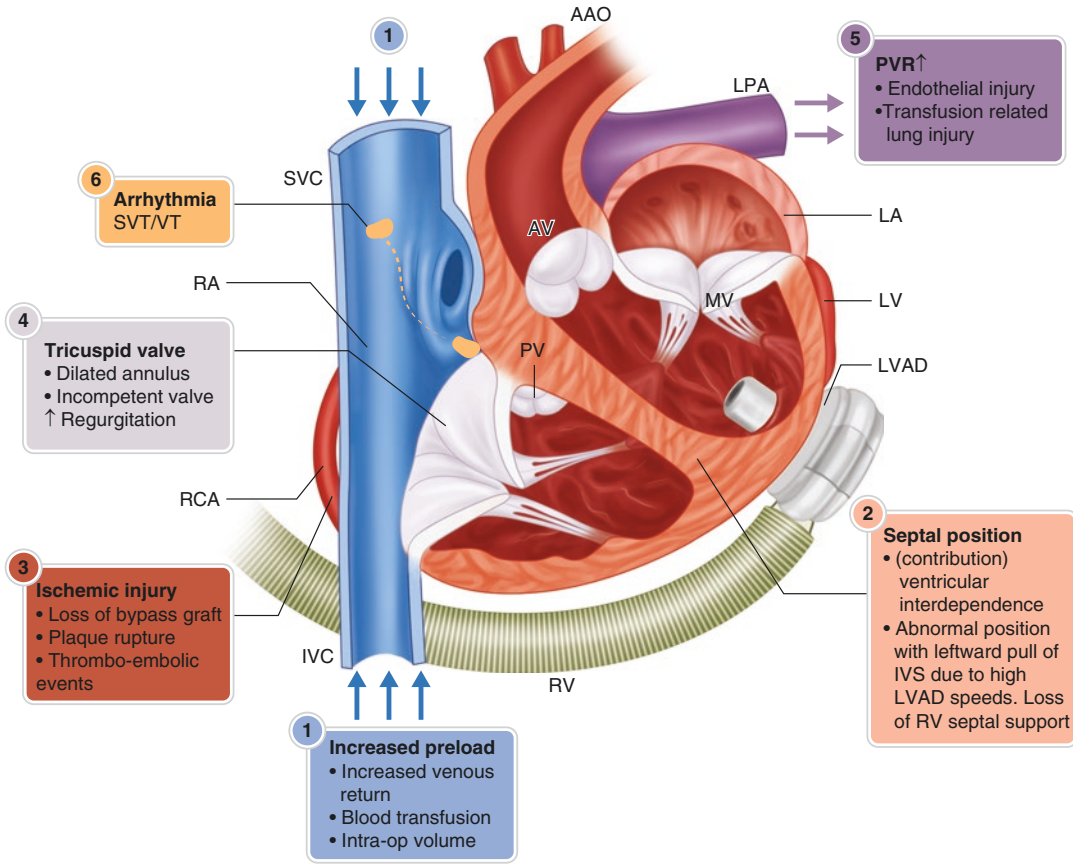

Fig. 3.7 Pathophysiology of RV failure after LVAD implantation

vide full cardiac support in cardiogenic shock. Its major limitation remains the need for surgery/vascular graft implantation for access. In a study involving 90 patients with abnormal renal or borderline RV function, 40 patients received the Impella 5.0 pVAD out of which 75% survived to transplant or LVAD. Of those who survived to LVAD, 87% survived to hospital discharge [66]. Hall et al. in Baylor University Medical Center, Dallas, and the Ochsner Clinic utilize the Impella 5.0 as the device of choice in patients with cardiogenic shock and high MELD scores. Their data demonstrates improved hemodynamics and end-organ function as demonstrated by improved MELD score [66, 67].

Similar to the axillary IABP [68], the Impella 5.0 pVAD can be inserted via the axillary artery via surgical graft if the vessel is of adequate caliber to facilitate mobilization [69] (Fig. 3.8). At THI, we utilize the Impella 5.0 as bridge to decision or bridge to transplantation where needed. We also frequently upgrade support from IABP to the axillary Impella 5.0 in patients with progressive cardiogenic shock and multi-organ failure.

For refractory shock and the need for escalation of therapy, the CentriMag (Thoratec, Pleasanton, CA) [70] and TandemHeart (CardiacAssist Inc., Pittsburgh, PA) [65] have successfully been used for temporary RV support. Both however require

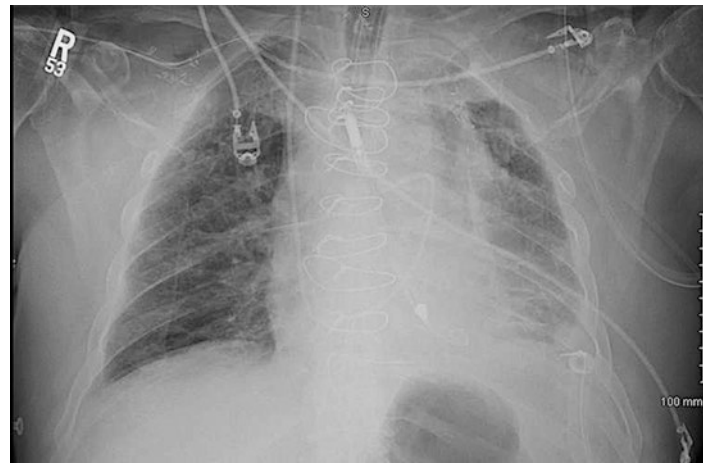

Fig. 3.8 Thoracic X-ray film of a patient shows an Impella 5.0 pump in the left ventricle, crossing the aortic valve, and the driving cable exiting from the right axillary artery (Reproduced with permission from Ann Thorac Surg. 2008 Apr;85(4):1468–70)

surgical implantation. Long-term durable biventricular support options include Thoratec PVAD and Syncardia Total Artificial Heart as bailout options on a BTT strategy. The use of TAH as a bridge to transplant has demonstrated a 79% survival to transplantation vs. 46% in patients not receiving a TAH in a small observational prospective study [71]. It is not currently approved for destination therapy. Detailed discussion on durable RVADs will be addressed in a later chapter.

Conclusion

Optimization of right ventricular function prior to LVAD implant is important and should be individualized for each patient. Early identification of high-risk patients remains critical for implementing strategies to avoid RV failure. Unfortunately, most RVF risk scores have been derived from small single-center retrospective trials and provide a variable spectrum of predictors with no single model dependably forecasting RVF. CVP/PCWP ratio > 0.63, preoperative ventilator support, and BUN >39 mg/dL are probably the strongest predictors of RVF along with TAPSE <7.5 mm on echocardiography. Perioperative management of RV failure should include preload optimization, afterload reduction, and inotropic support in all patients. RVF can still occur despite all necessary precautions, and prompt identification with early RVAD implantation may help improve long-term outcomes (Fig. 3.9).

It is still to be seen if in the future, minimally invasive surgery and off-pump pVAD implantation will mitigate the problem of right heart failure. The field of mechanical support for heart failure continues to grow however through clinical research and experience to improve outcomes and drive innovation. Interinstitutional collaboration experience in this field is expected to drive this growth further. This, combined with fast-moving innovation in the field, will likely improve RVF-related outcomes significantly in the future.

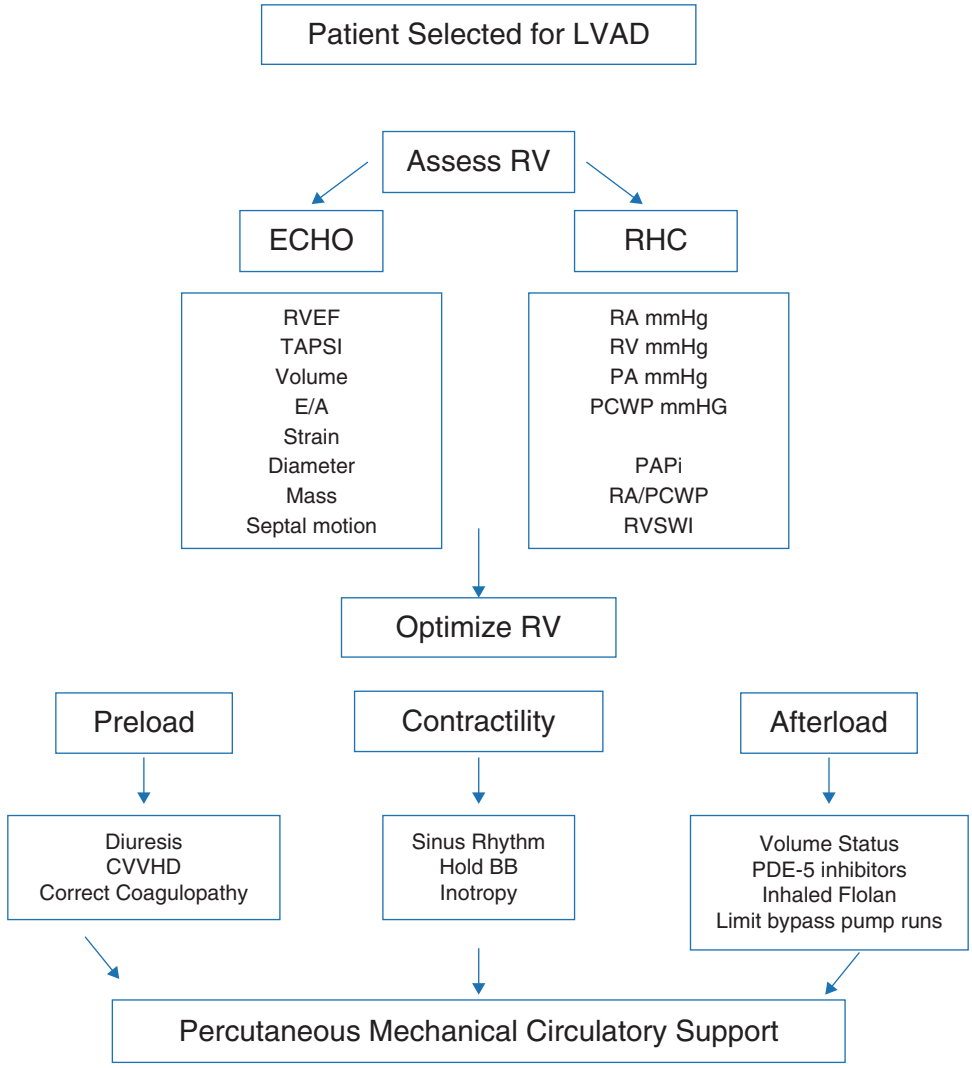

Fig. 3.9 Proposed algorithm for the prevention and management for RV failure after LVAD implantation

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Bridge-to-Bridge Strategies with IABP, Impella, and TandemHeart

4

Samar Sheth, Salman Bandeali, and Joggy George

Introduction

As our awareness of long-term consequences of advanced heart failure improves, there has been an institutional push to pursue durable solutions for these failing hearts. These solutions include left ventricular assist device (LVAD) implantation as a destination therapy or as bridge to transplantation, as well as listing for orthotropic heart transplantation.

Because pre-LVAD patients often have complex hemodynamics and multiple comorbid conditions, there have been multiple risk scores designed to risk stratify and predict outcomes of patients after LVAD implantation. Few of the most commonly used scores include the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile and the Heart Mate risk score [1, 2]. As the field continues to grow, heart failure programs across the country are currently working on better clarifying these risks and working on patient optimization prior to implant.

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Earlier implantation (early meaning in patients with ambulatory heart failure) is currently being evaluated and the data from the ROADMAP study (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients) is pivotal in demonstrating the benefit of early Heart Mate II LVAD implantation relative to optimal medical therapy. However in comparison to stable outpatient heart failure patients, there are still a number of patients who are admitted to the hospital with worsening heart failure and cardiogenic shock. This subset of patients includes long-term HF patients who have worsened over a period of time despite optimal medical therapy as well as patients presenting with cardiogenic shock secondary to acute myocardial infarction (AMI) or acute cardiomyopathies. Such patients with refractory cardiogenic shock, colloquially known as "crash and burn" [3, 4] could benefit from durable LVAD placement once they are stabilized.

Data from the seventh INTERMACS report suggests that the total number of patients receiving LVADs considered to be profile 1 is 15%, and this has remained stable since 2003 [5]. Those with profile 2 have gone from accounting for 43% of the implants to 37%, whereas those with profile 3 have increased from 22% to 28%. Data has shown that those patients with lower INTERMACS profiles have higher risk of death post implant and remain in the hospital longer [5,

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6]. The overall number of LVADs placed as rescue therapy has remained constant according to registry data but general trends suggest decreasing use in this setting. The mortality of such patients is significantly higher ranging anywhere between 60 and 84% [7, 8]. The poorer outcomes may explain why fewer patients with refractory shock (profile 1) are being considered for LVADs.

The Heart Mate risk score is a means of risk-stratifying patients across all INTERMACS profiles. Patients with higher INTERMACs profile can have a mortality risk similar or even higher than patients with a lower INTERMACS profile depending on the Heart Mate risk score [1]. Therefore, despite the higher risk of poor outcomes, a lower INTERMACS profile cannot and should not be considered a contraindication for durable LVAD implantation.

A significant number of patients we select at Texas Heart Institute® for LVAD implantation are INTERMACS profile 1 or 2.

As discussed in Chap. 3, we are strong proponents of temporary percutaneous mechanical circulatory support (pMCS) at the Texas Heart® Institute. While there is scarcity of data on risk stratification and postoperative outcomes of patients who get pMCS as a bridge to a durable LVAD or heart transplant [9], we employ this strategy to stabilize these patients with hopes of improving end organ function prior to a durable LVAD implant/heart transplant.

In this chapter, we plan to discuss our approach to patients in refractory shock and the use of pMCS as a bridge-to-bridge strategy.

Background

Cardiogenic shock is defined as inadequate end organ perfusion due to poor cardiac output in a setting of adequate circulatory volume. The clinical and hemodynamic parameters of cardiogenic shock defined in the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial are very well accepted and used. Hemodynamic parameters include: (a) cardiac index <1.8 L/min/m^2 without supportive measures or <2.2 L/min/m^2 with supportive measures, (b) pulmonary capillary wedge pressure of >15 mmHg, (c) systolic BP <90 mmHg for at least 30 min or SBP >90 mmHg on supportive measures [10]. In addition to hemodynamic parameters, clinical signs of pulmonary edema and impaired organ function are required with at least one of the following: altered mental status, cold clammy skin and extremities, oliguria, or serum lactate >2.0 mmol L^{-1} [11]. The decreased cardiac output leads to compensatory increase in circulatory volume. As the filling pressures in the heart increase, the stretch of ventricular wall further worsens the pumping function starting a cycle of decompensation. With further decreases in cardiac output, signs of multi-organ system failure and lactic acidosis ensue. Dr. Kapur writes "at this point the cardiogenic shock has transitioned from a potentially reversible problem to a more complex 'hemo-metabolic' problem that may not respond to traditional treatments" [12]. It is this multisystem organ dysfunction that is associated with poor outcomes after LVAD implant. In fact, scoring systems for shock related to systemic inflammatory responses and biomarkers (APACHE, SAPSII, SOFA, IL-6) do a better job of predicting outcomes than basic hemodynamic parameters for CHF [13–15].

The most common cause of cardiogenic shock is AMI (acute myocardial infarction), with an incidence of 10% [16, 17]. Data from the seventh INTERMACS registry suggests that as many as 50% of patients referred for LVAD are in cardiogenic shock [5]. Management of such patients lack large clinical trials and is mostly based on institutional experience and practices. Despite new revascularization techniques and treatment algorithms, morbidity and mortality among these patients remain significantly high [18]. While inotropes and vasopressors may help to improve hemodynamics, they increase myocardial demand, and this has been shown in multiple trials to be associated with increased mortality and morbidity. In such circumstances, institution of MCS can help lower myocardial demand and improve end organ perfusion as well as potentially reverse the damage.

The use of durable LVADs as rescue therapy for refractory cardiogenic shock has decreased; however, this has translated to the increased the use of pMCS devices as a means of stabilizing

the patients and preventing irreversible multi-organ failure.

Guidelines have recently started to include percutaneous MCS as options in high-risk PCI as well as cardiogenic shock. Given the limited direction however presented in the guidelines, in 2015 the Society for Cardiovascular Angiography and Interventions (SCAI) presented a consensus document on the use of MCS [19]. While the data on use in patients pre-LVAD is limited, it is reasonable to use nondurable MCS in patients falling into the INTERMACS category 1 and 2 [19]. However, the timing of initiation of hemodynamic support devices in these patients is not well studied. It should be noted that the majority of data on MCS and the hemodynamic effects evaluated are on that of the left ventricle and the patients we are discussing often have biventricular failure and MOSF which make the overall hemodynamic effects difficult to predict. Interestingly, data has recently shown that early use of MCS in patients with cardiogenic shock secondary to MI have an improved survival [20]. In fact, the earlier the device was implanted, even before the use of inotropes, the better the outcomes.

At Texas Heart® for our patients in cardiogenic shock we are rapid to escalate to nondurable MCS to improve end organ function and possibly post-LVAD outcomes. Moreover, for those patients with refractory shock or considered for salvage LVAD placement, we utilize MCS to stabilize these patients and provide a bridge-to-bridge decision.

Currently, our percutaneous MCS options include intra-aortic balloon pump (IABP), Impella, TandemHeart, and ECMO.

Intra-aortic Balloon Pump (IABP)

The IABP is the oldest and most commonly used hemodynamic support device. It is a pulsatile device that can either be inserted via the axillary artery or the common femoral artery and is used to augment pulsatile flow. It has two major components, the balloon catheter and the pump console. The catheter is a 7.5–8-French device with two lumens: a closed lumen with helium gas and a wire/pressure lumen. Helium is used due to its rapid transit into and out of the balloon in addition to the ability to absorb rapidly into blood in case of rupture. The balloon is triggered to inflate during diastole either by the ECG or pressure triggers. With the onset of systole, the balloon is rapidly deflated [12, 19, 21]. Tachycardia and or arrhythmia can effect timing of the pumps function and cause it to be ineffective, by either inefficient triggering or rapid deflation due to tachycardia [22, 23]. Inflation during diastole provides a displacement of blood in the aorta and hence increased pressure in the aortic root leading to increased coronary perfusion [21]. It should be noted however that in coronary arteries with fixed stenotic lesions there is no improvement in coronary flow [21, 24]. In systole, the rapid deflation of the device leads to a pressure sink thereby reducing LV afterload and increasing LV output.

Contraindications to placement include moderate or more severe aortic insufficiency as well as severe peripheral vascular disease. The majority of complications are vascular in nature and include limb ischemia, stroke, or access site issues. Thrombocytopenia has been seen due to platelet deposition on the membrane of the balloon or issues related to anticoagulation with heparin. If femoral IABP is selected, prolonged use can lead to complications associated with immobility.

Small trials have defined the safety of using IABP prior to LVAD placement as a bridge device [25, 26]. Recent literature has suggested however that the more dysfunctional the LV, the less benefit from the IABP [27]. The lack of overall benefit seen in the various IABP trials is likely because the subpopulation that would benefit the most is yet to be defined. In one particular study, ten patients referred for LVAD placement had an IABP placed. In those patients that were considered responders there was a 20% increase in cardiac index, lower SVR and lower right heart pressures [28]. In another small study 27 patients with non-ischemic cardiomyopathy had an IABP placed for cardiogenic shock. In patients that were considered responders (67%), within the first 24 h their urine output increased. In both responders and non-responders, lactate levels improved [29]. Interestingly, patients with higher

bilirubins or C-reactive protein (markers of systemic inflammation or end organ dysfunction) were more likely to be non-responders suggesting there is a point in the shock cascade in which the IABP will no longer be effective. In another study with similar design, IABP was placed prior to LVAD. In those patients who showed further decompensation (defined by the need for increased vasopressors and inotropes) had worse outcomes post LVAD [27, 30]. When the authors evaluated the difference in two populations, they noted that patients with contractile reserve, as defined by LV and RV power indices, were those most likely to respond to IABP. These trials suggest that early use of IABP is potentially of benefit in selected patients prior to LVAD placement.

As discussed in Chap. 3, IABP has been showed to improve both RV and LV function and can improve outcomes when placed prophylactically in patients with INTERMACS profile 2 [30]. But as mentioned above, the overall benefit of those in florid cardiogenic shock is debatable. Our approach at Texas Heart® Institute is to use IABP as a first-line bridge in patients with early cardiogenic shock to allow improvement in hemodynamics and reduce the use of vasopressors/inotropes. If patient's clinical status does not improve or worsens, the next step is to escalate support to stronger pMCS devices.

Impella (ABIOMED Inc., Danvers, MA)

The impella is a non-pulsatile continuous axial flow device based on the Archimedes screw pump that propels blood from the implanted chamber [31] .Unlike the IABP there is no triggering of this device by ECG or pressure. In fact, the flow generated is independent of ventricular function. There are currently three versions of the impella pump for left ventricular support: Impella LP 2.5 (low power), Impella CP (cardiac power), and Impella 5.0. The Impella 2.5 is a 12-French device placed via the femoral artery that has been studied extensively. It is FDA approved for cardiogenic shock and high risk percutaneous coronary intervention as demonstrated the PROTECT and PROTECT2 studies. In the ISAR-SHOCK trial (Impella LP 2.5 versus IABP in Cardiogenic Shock), the Impella LP 2.5 showed a greater increase in cardiac index and mean arterial blood pressure with a significant reduction in lactate; however, there was no difference in mortality and major adverse events between the Impella 2.5 and IABP arms [32]. The Impella CP is a 14-French device with limited data in the literature but has the ability to provide 3–4 L of blood flow (compared to 2.5 L by the Impella LP 2.5). The Impella 5.0 is usually placed via the axillary artery after placement of a graft and surgical cut down. It can however also be placed through the femoral artery.

While the Impella 2.5 pump is the device that was initially studied in trials and received an FDA indication, the use of device is decreasing at our institution. This is largely because both Impella CP and Impella 5.0 provide more cardiac output. In addition, the recent FDA approved indication for Impella CP in high-risk PCI and cardiogenic shock has resulted in most operators using the device as opposed to Impella 2.5.

Trials evaluating the Impella CP are limited. The IMPRESS (Impella CP versus IABP in Acute Myocardial Infarction Complicated by Cardiogenic Shock) trial recently published in October 2016 and compared Impella CP to the IABP in patients with cardiogenic shock secondary to AMI. There were interesting similarities to studies comparing Impella 2.5 with IABP. No difference in mortality was seen at 30 days and 6 months. However, notably 92% of the patients in the study had cardiac arrest that required resuscitation prior to pMCS implantation, and this may have affected the overall results [33]. In one small, single center trial the Impella CP pump was placed in 28 patients with refractory cardiogenic shock, mostly due to acute coronary syndrome. The estimated mortality rate based on SOFA scores was 87.1%; however, 36% of the patients survived, hence suggesting a benefit secondary to Impella CP placement [34].

The Impella 5.0 requires a surgical cut down given the device design. It is usually implanted using the axillary approach which can allow for patient ambulation. The Impella 5.0 has been

used as a bridge in small series of patients, the largest of which is from Dr. Hall's group in Dallas, Texas. They examined 40 patients with biventricular failure out of which 66% were INTERMACS profile 2 and placed them on Impella 5.0 support as a bridge therapy. Of these 75% survived to the next therapy (13 received cardiac transplant, 15 durable LVADs, 2 had systolic function recovery) [35]. This study demonstrated the efficacy of using Impella 5.0 device as a bridge to decision in patients with questionable benefit of LVAD placement, including those in the INTERMACS 1 profile. A single center German study also demonstrated the feasibility and benefit of the Impella 5.0 as a bridge in patients with INTERMACS 2 profile [36]. At a small trial at the Ochsner Clinic, the Impella 5.0 was used as a bridge to decision in patients with elevated MELD scores (marker of outcome for those undergoing VAD support). Prior to implant the MELD score was 21 and improved to 14 post implant thus suggesting improved end organ perfusion. Moreover, there was 70% success rate in bridge to decision and a 63% survival to discharge noted, which compared to historical outcomes of cardiogenic shock suggests a significant improvement [37]. All these trials and studies have resulted in impella pumps being the only pMCS pumps approved by FDA for cardiogenic shock and high-risk PCI.

Contraindications to placing an impella include severe peripheral vascular disease, mechanical aortic valve, or the presence of left ventricle mural thrombus. Common complications include access site bleeding and limb ischemia. Hemolysis occurs in the first 24 h in up to 10% of patients and can respond to device repositioning [38]. Persistent hemolysis can lead to AKI and is an indication for removal. While IABP has been shown to improve right ventricular function, data on RV improvement is limited with impella and hence one must be wary of RV function while the LV is being supported by impella.

Based on our institutional experience and practices at the Texas Heart institute, our first-line pMCS for the majority of INTERMACS profile 2 or higher is the IABP. However, we generally go straight to the Impella 2.5, CP, or 5.0 pump implantation in patients with INTERMACS profile 1. In cases of relative urgency and emergency, Impella 2.5 and CP are the devices choice given ease of placement and no requirement for a surgical cut down or general anesthesia. The approved duration of left ventricular support with Impella 2.5 and CP is 4 days. If we anticipate a prolonged course of hemodynamic support or if there is a requirement for greater LV unloading despite the presence of Impella 2.5/CP, the Impella 5.0 pump is chosen as the bridge to bridge.

TandemHeart (Tandem-Life, Pittsburgh, PA)

Our Center has one of the large TandemHeart experiences in the country. The left-sided TandemHeart is an extracorporeal centrifugal-flow pump that draws blood from the left atrium and returns it in the descending or ascending aorta. Removing blood from the left atrium reduces left ventricular preload and direct arterial return pressurizes the aorta improving mean arterial pressure. Of the various pMCS options, it is the most technically challenging as it requires transseptal puncture and placement of a large bore transseptal inflow cannula. There are four components to the system; the inflow cannula is a 21-French catheter placed via transseptal technique in the left atrium. The inflow cannula goes to a centrifugal pump, which can have an oxygenator added to the circuit if needed, and then this empties into the aorta. Depending on the placement of the aortic outflow cannula, there can be two opposite effects on the left ventricular afterload. If placed in the ascending aorta, afterload will increase along with an increase in LV stroke work. If placed in the descending aorta, there is an increase in retrograde perfusion of the great vessel, mesenteric and renal arteries thereby decreasing LV stroke work [39]. Similar to impella, left-sided tandem works independently of heart rate and native cardiac function. The total flow delivered can be affected by the size of the outflow cannula (15–19 French) but the TandemHeart pump has the potential to deliver 3–5 L of blood flow per minute. Given the pres-

ence of large bore outflow catheter through the femoral artery, an antegrade sheath is placed in the superficial femoral artery to perfuse the ipsilateral limb and limb ischemia.

A poorly functioning right ventricle is a relative contraindication to use of left side TandemHeart pump, as the RV is required to deliver blood to the left atrium. Severe aortic insufficiency and ventricular septal defect may also limit the utility of the pump. Left atrial thrombus is a contraindication to placement. In addition, the patient must be able to tolerate anticoagulation required for pump operation. Movement of the transseptal catheter can result in left atrial wall trauma leading to cardiac tamponade. It is sometimes difficult to secure the inflow cannula that traverses from the left atrium through the femoral vein. With unintended patient movement or patient repositioning, the cannula can retract into the right atrium leading to a large right to left shunt and systemic desaturation.

Our center has published extensively on the use of left side TandemHeart. In one series, 117 patients with refractory cardiogenic shock despite IABP placement were studied. As with other pMCS data sets, the majority of the patients were in cardiogenic shock due to ischemia. Similar to the IMPRESS trial, a large percentage suffered cardiac arrest, in this case 50%, prior to implant [40]. In this study, TandemHeart institution was associated with rapid improvement in hemodynamic parameters including improvement in mixed venous oxygenation, pulmonary capillary wedge pressure, and a decrease in creatinine. The TandemHeart investigators directly compared TandemHeart to IABP in patients with cardiogenic shock. Seventy percent of the patients enrolled were shock secondary to ACS. Compared to IABP in this trial, wedge pressure, creatinine, and cardiac power all improved. However, similar to impella trials, 30-day survival was not statistically different than the IABP arm [41]. Another study done at our center showed that left-sided TandemHeart is an effect bridge to more definitive therapy in those with end-stage cardiomyopathy [42, 43].

At Texas Heart®, many of the interventionalist are skilled at transseptal punctures as well as large bore access. In addition, we have perfusionists available so we are readily able to implant a TandemHeart in appropriate clinical situations. However, given ease of use we are likely to first implant an Impella CP.

Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO)

In patients with both cardiovascular and respiratory failure or who suffer from severe biventricular failure, VA-ECMO is the circulatory support of choice. Similar to the IABP it can be placed, if need be, at the bedside without fluoroscopic guidance. The circuit consists of an 18–22-French venous inflow cannula originating in the RA to a non-pulsatile centrifugal pump for blood propulsion to a 15–22-French arterial outflow cannula that ends in the aorta with a membrane oxygenator for gas exchange in series [12, 19, 21]. The device requires a full-time perfusionist for management. In order to ensure adequate retrograde flow, a right radial arterial line is required. Of the various percutaneous LVADs, VA-ECMO is the only to increase afterload. Often a second device for LV venting is required (IABP or impella). Large bore access sites for both venous and arterial limbs are required. The sizes of the cannulas used effect the amount of flow. As with TandemHeart, an antegrade sheath on the ipsilateral arterial side is required to ensure lower limb perfusion.

Access site complications are the major drawback to ECMO placement as bleeding is common. Blood products are often required which can interfere with future transplant options. Peripheral vascular disease and the inability to tolerate anticoagulation are relative contraindications to ECMO placement. Various scoring systems have been evaluated to determine the benefit of ECMO. Despite the utility and awareness in placing VA-ECMO, mortality of patients that receive the device still is as high as 50% [44].

Data for ischemic cardiomyopathy and ECMO to facilitate reperfusion has shown promising results but data on use in refractory cardiogenic shock is limited [45, 46]. In a single center trial of 87 patients who underwent extracorporeal life support (ECLS) implantation as a last treatment

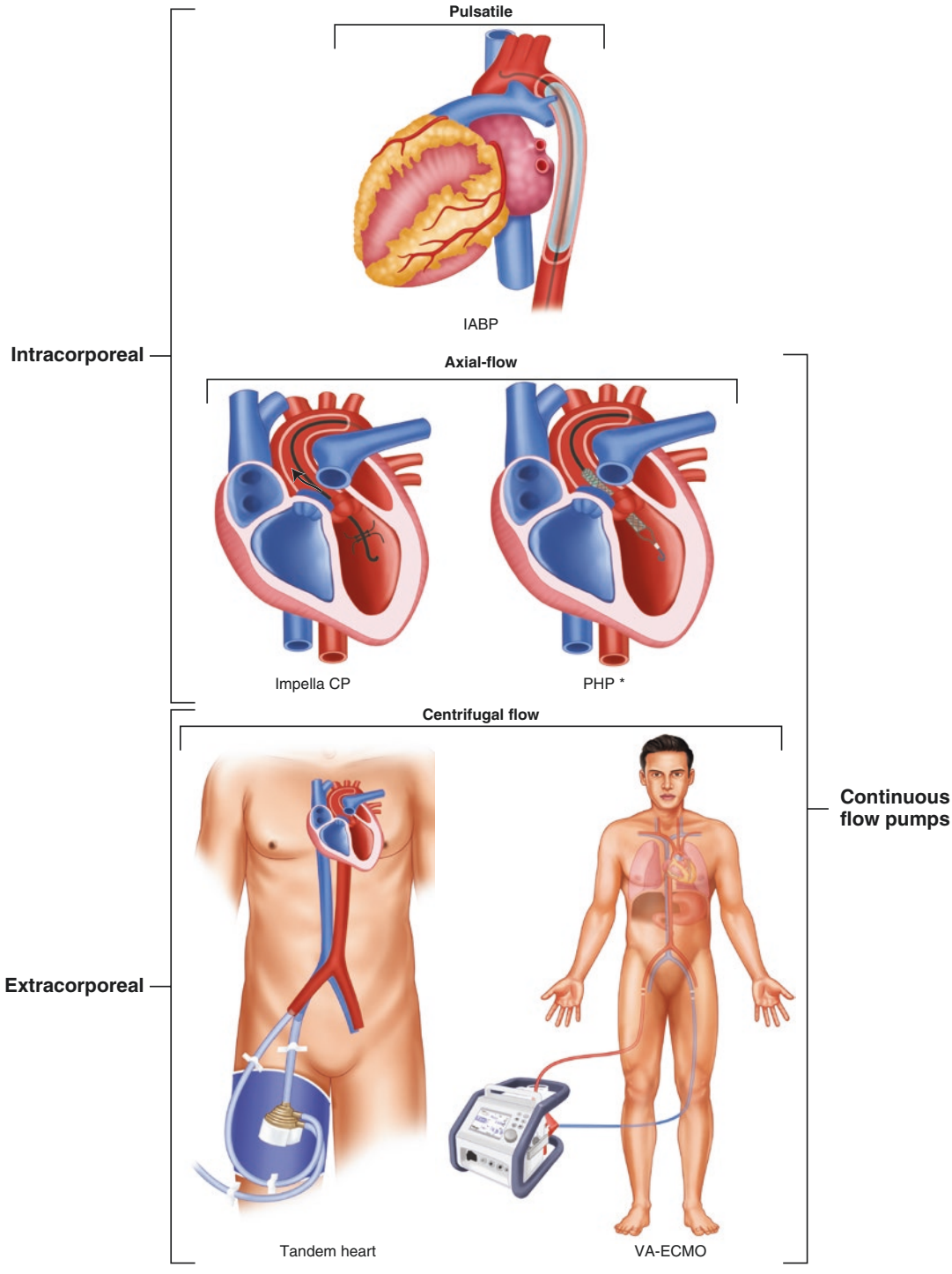
option for refractory cardiogenic shock, 60% of these were in shock secondary to acute coronary syndrome and 30% were due to a primary cardiomyopathy. It should be noted that in 31% of these patients, ECLS was implanted during CPR [47]. Patients with a higher lactate prior to implant or at 6 h post implant had a higher mortality rate. Moreover, patients with a pH closer to the normal range were more likely to survive. The overall survival rate was 47%. Thirty-eight percent of the patients died on ECLS and 12% died after explant [47]. In another single center study 15 pts with ECLS were bridged to LVAD. Eighty percent of these patients were INTERMACS 1. Fourteen patients improved with temporary cardiac support to INTERMACS profile 3. At the end of the study, 87% were still alive and none had right ventricular failure [48]. The study has an important implication that if unstable patients receive timely VA-ECMO implant they can be considered for durable LVAD if stabilized. In another study with similar findings, 58 consecutive patients undergoing LVAD implant were assessed and divided retrospectively into two groups: one group that required ECLS prior to placement of durable LVAD and the other that did not. APACHE III scores were higher in the ECLS group. During LVAD implant, larger number of patients in the ECLS arm required temporary right VAD placement and blood product transfusion as well as a prolonged intensive care unit course. However, survival between the two groups was similar [49].

At Texas Heart®, we use ECMO for *our crashing and burning* patients and will often have to add it to patients already on some other form of MCS such as IABP or impella. We try not to use ECMO as a bridge to LVAD unless the patients is awake and or has been fully consented for LVAD as we are proponents of a philosophy that no patient should "wake up with a VAD."

Conclusion

Patients in refractory cardiogenic shock, INTERMACS 1 and 2 have been shown to have poorer outcomes post-LVAD placement. We try and improve these outcomes by bridging these patients with percutaneous nondurable ventricular assist devices that improve cardiac output, improve end organ perfusion, and improve LV loading conditions. While the data on this strategy is limited, we have had good success with this approach and will continue to provide percutaneous mechanical circulatory support for our sickest patients as a bridge to further therapies.

DEVICE	CONTRAINDICATIONS	COMPLICATIONS
All devices	Severe peripheral vascular disease Irreversible neurologic disease Sepsis*	Bleeding Vascular injury Infection Neurologic injury
IABP	Moderate to severe aortic insufficiency Aortic dissection Abdominal aortic aneurysm Contraindication to anticoagulation*	Thrombocytopenia Thrombosis Obstruction of arterial flow due to malposition Aortic rupture or dissection Air or plaque embolism
ECMO	Mechanically ventilated >7 days Contraindication to anticoagulation	Thrombosis of circuit Upper body hypoxia due to incomplete retrograde oxygenation LV dilatation Systemic gas embolism
CentriMag	Contraindication to anticoagulation	Thromboembolic events Air embolism
TandemHeart	Ventricular septal defect Moderate to severe aortic insufficiency Contraindication to anticoagulation	Cannula migration Tamponade due to perforation Thromboembolism Air embolism during cannula insertion Inter-atrial shunt development
Impella	LV thrombus Moderate to severe aortic stenosis Moderate to severe aortic insufficiency Mechanical aortic valve Recent TIA or stroke Aortic abnormalities Contraindication to anticoagulation	Hemolysis Pump migration Aortic value injury Aortic insufficiency Tamponade due to LV perforation Ventricular arrhythmia


Pulsatile
IABP
Intracorporeal
Axial-flow
Impella CP
PHP *
Centrifugal flow
Continuous flow pumps
Extracorporeal
Tandem heart
VA-ECMO

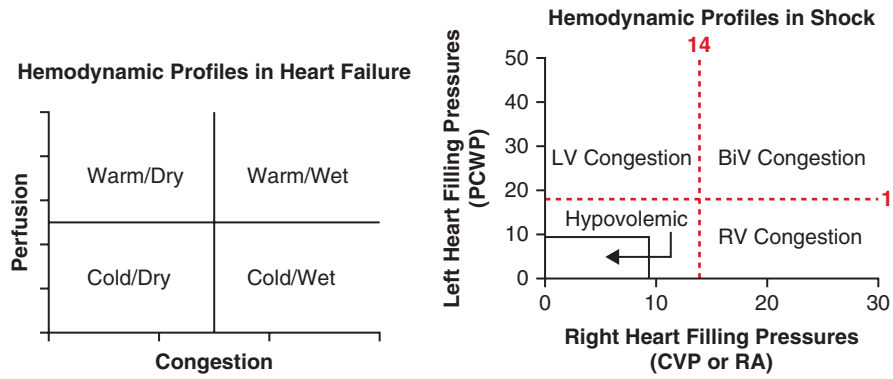


Table 2. Clinical applications for non-durable, percutaneously-delivered mechanical circulatory support

	Advanced heart failure / cardiogenic shock (refractory to IABP or ≥1 inotrope)										Acute MI	
	LV Failure			RV Failure		Biventricular Failure			Cardio-Pulm Failure		Killip IV MI	
	Recovery	Decision	DT-LVAD	Recovery	Decision	Recovery	Decision	DT-LVAD	Recovery	Decision	LV	RV
Impella CP	X	X	X								X	
Impella 5.0 (axillary)	X	X	X			X	X	X				
Impella RP (investigational)				X	X							X
TandemHeart LVAD	X	X	X			X	X	X	X	X	X	
TandemHeart RVAD				X	X				X	X		X
VA-ECMO				X	X	X + Vent	X + Vent	X + Vent	X + Vent	X + Vent		

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LVAD Surgical Implant Technique: Extraperitoneal Approach

5

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Introduction

As the number of LVAD implantations continues to rise and the technology advances, alternate approaches and new techniques have continued to develop. This chapter aims to not only summarize the steps common to the traditional LVAD implantation approach but also to introduce, explore, and summarize the increasing minimally invasive approaches, the variants in outflow graft (OG) anastomosis sites and their perceived benefits, and the varying approaches to "off-pump" LVAD implantation that circumvent the operative risks associated with the use of cardiopulmonary bypass (CPB).

Sections

1. Traditional Approach to LVAD Insertion
2. Minimally Invasive Implantation Techniques
3. Selection of Outflow Graft Anastomosis
4. Off-pump LVAD Insertion

Traditional Approach to LVAD Insertion

The process for inserting a LVAD through traditional approach using an extended sternotomy incision and placing the patient on cardiopulmonary bypass has 12 common steps which are introduced and summarized below.

Common Steps in LVAD Insertions

1. Skin incision
2. Creation of pre-peritoneal pocket
3. Device tunneling
4. Mediastinal exposure
5. Cannulation of the aorta and venous system
6. Cardiopulmonary bypass
7. Coring of the left ventricle, placement of core sutures, inserting inflow into apex
8. Outflow graft anastomosis to the ascending aorta
9. De-airing the device
10. Wean from CPB and actuation of LVAD

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11. Establishment of hemostasis
12. Closure of sternotomy and pre-peritoneal pocket

Primary Incision

In the traditional approach, the incision begins in the usual fashion used for sternotomy; starting at the sternal notch, the incision traverses downward at the midline; however, in lieu of ending at the xiphoid process, caudal extension progresses to create space for a pre-peritoneal pocket to accommodate the size of the particular device to be implanted. Sternotomy is then conducted with Bovie electrocautery with careful attention to avoid the pleural space and not to enter the peritoneal cavity.

Creation of the Pre-peritoneal Pocket

Creation of the pre-peritoneal pocket is generally conducted using one of two methods: by placing the LVAD posterior to the posterior rectus sheath or by placing the LVAD between the posterior rectus sheath and the muscle (Fig. 5.1). Taking down a portion of the hemidiaphragm is usually required to accommodate the device's size. Once the pocket has been developed, the LVAD is placed.

Device Tunneling

The LVAD is then screwed to the tunneler which is brought into the incision and through the fascia just left of the midline of the pocket. The tunneler is exited through a previously created incision in the right upper quadrant between the umbilicus and anterior iliac spine. The driveline exits with the "felt" portion remaining inside, and the LVAD is situated within the pocket.

Mediastinal Exposure

Insertion proceeds with division of the retrosternal fat and peri-thymic tissue utilizing the Bovie and clips. The pericardium is opened along the right side of the heart to the diaphragm and over the left apex, while the superior pericardium is brought over the aorta to the pericardial reflection. Pericardial stays secure the pericardium and provide exposure of the heart.

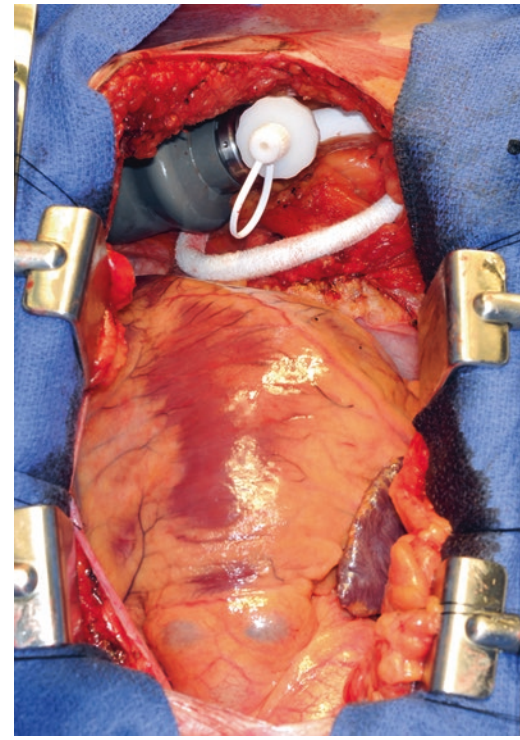

Fig. 5.1 Insertion of LVAD in extraperitoneal and extrapericardial pocket

Cannulation of Aorta and Venous System

Cannulation proceeds in the usual fashion using the right atrial appendage and ascending aorta for implantation. If concomitant valve work or ASD closure is to be performed, bicaval venous cannulation of the IVC and SVC is performed. When heparinization has progressed to an ACT of 400 s or higher, cannulation of the ascending aorta at the pericardial reflection is performed, and de-airing and securing of the cannula followed by line testing is performed. Venous cannulation is performed and connected to the circuit.

Cardiac Bypass

The patient is placed on CPB in the usual fashion and kept warm. Volume is removed from the heart and the field is flooded with CO_2.

Coring of Left Ventricle, Placement of Core Sutures, Inserting Inflow into Apex

In order to begin the coring process, the left ventricle apex is exposed and brought closer to the midline of the sternotomy. An incision in the apex is made left of the left anterior descending artery where the heart dimples. Coring proceeds with the coring knife directed toward the LV cavity (not the septum). Any large trabeculations and thrombus are removed from the ventricular cavity; next, 2–0 pledgets are placed in horizontal mattress circumferentially around the ventriculotomy (Fig. 5.2). The inflow cuff is then seated and tied into place with circumferential sutures (Fig. 5.3). BioGlue (CryoLife Inc., Kennesaw, GA) is applied to pledgets and along the inflow cuff. The cannula is inserted in the inflow housing and secured. The heart is returned to its normal position and the LVAD unit is rested into the pre-peritoneal pocket.

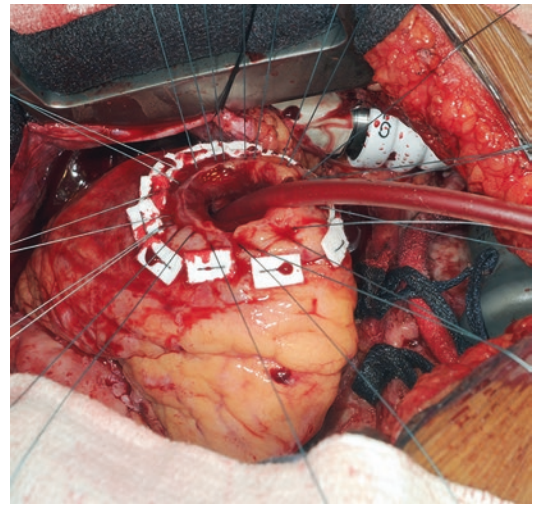

Fig. 5.2 Placement of LV apical LVAD sutures

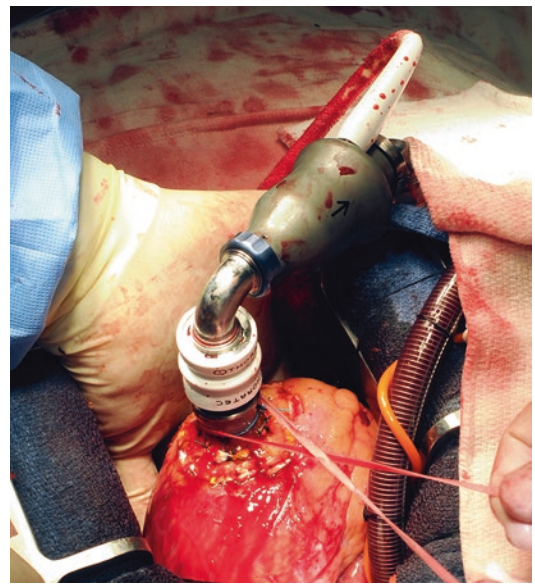

Fig. 5.3 Securing of LVAD inflow cannula

Outflow Graft Anastomosis to Ascending Aorta

The correct length for the outflow graft is measured and cut with a bevel edge. The aorta is partially occluded with side-biting clamp aortotomy proceeds. The OG is then anastomosed to the ascending aorta with mattress sutures which are tied, and BioGlue (CryoLife Inc., Kennesaw, GA) is applied to the single-layer running anastomosis (Fig. 5.4a–c). The graft is de-aired and clamped, and the anastomosis is checked for bleeding.

De-airing the Device Circuit

De-airing begins when the outflow housing is opened, and the heart is filled as the perfusionist replaces volume. Ventilation of the patient proceeds, and the head of the table is moved upward as the table's left side is tilted downward. The outflow graft is connected to the outflow housing, and a "de-airing" hole is placed in the outflow graft. The cross-clamp is kept distal to the de-airing hole on the graft (Fig. 5.5). Transesophageal echocardiography is used to monitor the de-airing process until its completion.

Inotropes are started for optimization of right heart function, and pressors (levophed and

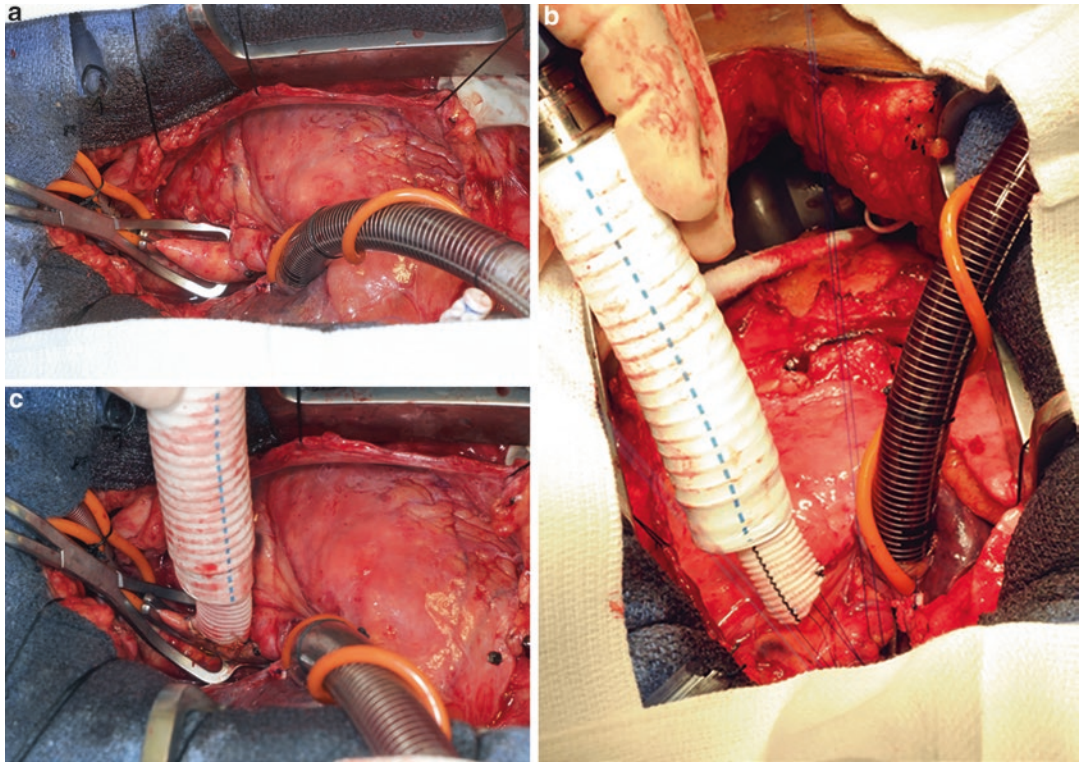

Fig. 5.4 (**a**) Side-biting clamp placed on ascending aorta for outflow graft anastomosis. (**b**). Evaluation of outflow graft anastomosis. (**c**) Removal of side-biting clamp from ascending aorta

vasopressin) are titrated as necessary to maintain hemodynamic stability and mean arterial pressures of 60–80 mmHg.

Weaning from CPB and LVAD Actuation

After placement of the LVAD, weaning off CPB is performed. The HeartMate II device speed begins at 6000 RPM once the CPB flow decreases to 2 L. The cross-clamp is released from the outflow graft to allow forward flow. As CPB weans, RPM is increased to reach between 8800 and 9600 RPM. Further, de-airing occurs through the hole in the outflow graft.

TEE assesses decompression of the LV and degree of mitral regurgitation, evaluates flow across the inflow and outflow cannula, monitors for the incidence of aortic insufficiency, assesses right ventricular function, and evaluates the interventricular septum, confirming that no bowing is present. These findings are used to adjust the RPM settings of the LVAD and optimize volume status and/or increase the dose of inotropes.

Establishing of Hemostasis

It is essential that all surgical, cannulation, and anastomoses sites are evaluated, and bleeding is addressed with pledgeted sutures. Nonsurgical bleeding is surveyed until full reversal of protamine and baseline ACT are reached, as this occurs light packing and the use of hemostatic agents may aid the process. Electrocautery may be used on soft tissue, LVAD pocket, and the sternum. Examination and proper control of bleeding in the LVAD pocket should be thorough and is necessary to proceed.

If diffuse coagulopathy and excess bleeding cannot be controlled with these methods, the

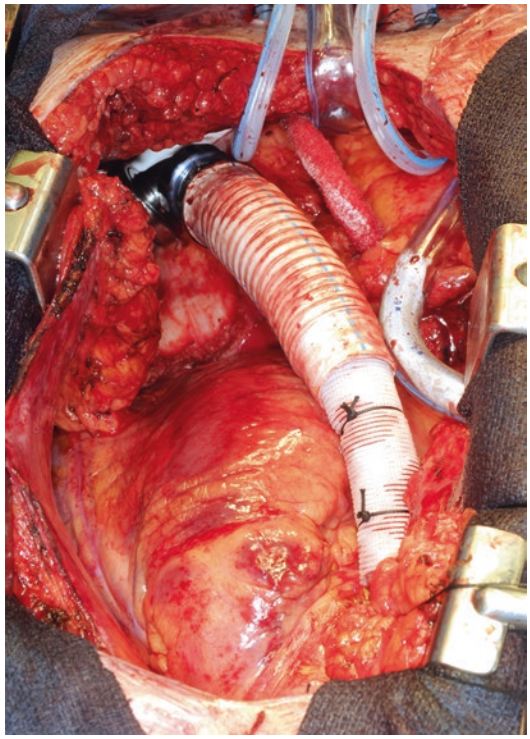

Fig. 5.5 LVAD in pocket, outflow connected to aorta, protective graft secured over outflow graft

mediastinum can be packed, and patch is placed over the sternotomy site with the plan to return to the operating room for true closure in 24 h after adequate resuscitation and resolution of the coagulopathy. A GoreTex pericardial membrane (Gore Medical Products, Flagstaff, AZ) is sutured to pericardial edges to minimize injury at reentry during reoperation (Morgan).

Closure of Sternotomy and Pre-peritoneal Pocket

Chest tubes are placed in the mediastinum and pleural space. Closure of the sternotomy proceeds in the usual fashion. Abdominal fascia is closed with interrupted figures of eight. The remaining layers and the skin are closed in the usual fashion.

Modifications of Technique for HVAD and HeartMate 3

For the HeartWare HVAD device and HeartMate 3, we do not create a preperitoneal pocket. The device is place intrapericardially. Thus, the sternotomy incision does need to extend beyond the xyphoid, like for HM2. Additionally, the left hemidiaphragm does need to be taken down to accomodate for the device. Unlike the HM2, where a "cut and sew" technique is used, for the HVAD and HM3, a "sew and cut" technique is employed. This involves identfying the LV true apex/dimple, marking it, placing the felt ring over it, with the center of the ring over the true apex, marking the outer portion of the ring, and then placing plegeted sutures circumferentially. After all sutures are placed, they are passed through the felt ring, the ring is seated, sutures are tied, and cut. A cruciate incision is then made in the LV apex, followed by spreading with a Tonsil clamp, followed by coring of the LV, followed by resection of LV trabeculae. The device is then inserted with the outflow graft clamped. The device is then secured in place while ensuring there is good apposition between the pump and felt ring, without a space. The device is then deaired. As side biting clamp is then placed on the ascending aorta and the proximal anastomosis is performed. For additional deairing, a hole is made in the outflow graft both proximal and distal to the clamp on the aotflow graft.

Other Techniques

As LVADs have become more widely used, techniques have been introduced and developed to decrease invasiveness of the procedure and eliminate the need for sternotomy and/or cardiopulmonary bypass (CPB). The following sections of this chapter will describe and compare the myriad of minimally invasive approaches to LVAD implantation and selection of outflow graft anastomosis sites in the minimally invasive approach and describe techniques used in "off-pump" LVAD implantation to avoid the use of CPB.

Minimally Invasive Approaches

The advent and successful use of minimally invasive methods of VAD implantation have the potential to improve the postoperative recovery in comparison to traditional sternotomy. Heart failure patients requiring VAD often have a host of other comorbidities such as poor pulmonary function, diabetes, malnutrition, obesity, and deconditioning that add to the risks of major surgery and can delay wound healing. The use of minimally invasive implantation therefore has the potential to decrease recovery time and avoid the stress of sternotomy.

In addition, minimally invasive techniques are ideal to avoid reentering the chest cavity after one or more prior sternotomies or to further preserve the sternotomy site in patients such as those in which the VAD is used in a bridge to transplant strategy. Owing to the large number of ischemic heart failure, which compromises the majority receiving LVADs in the Unites States, many VAD patients are likely to have one or more previous sternotomies for coronary artery bypass graft or valve repair/replacement surgeries. Minimally invasive techniques may be utilized in patient with prohibitive operative risk for sternotomy (Frazier). Thus, minimally invasive techniques can prevent the complications and increased operative time and stress caused by sternotomy.

The most common minimally invasive operative approach consists of implanting the VAD into the pre-peritoneal cavity through a left subcostal incision with the patient positions in left anterolateral thoracotomy. This approach is often paired with right mini-thoracotomy to gain access to the aorta. In Makdisi et al. [1] review of the literature, the most common surgical incision variations for minimally invasive VAD implantation incisions. The two incisions used for inflow are subdiaphragmatic or left thoracotomy, whereas outflow graft insertion site incision approaches are upper hemi-sternotomy, right mini-thoracotomy, and right upper hemi-sternotomy combined with a right mini-thoracotomy in a J-shaped incision, or axillary. When planning implantation combined with tricuspid or aortic valve work, an upper hemi-sternotomy should be used [2]. The most common cannulation strategy employed in minimally invasive procedures is femoro-femoro (Frazier [3], Ghosizad, [4]); however, central cannulation is still utilized [2] dependent on incisional approach and can even be done using the Seldinger technique (Anyanwu). Thus, there are a variety of both incisional approaches and cannulation site choices that can be utilized for minimally invasive VAD implantation.

Approach to minimally invasive implantation can be chosen strategically for specific operative goals. Popov et al. [4] have standardized their approach using a single left thoracotomy approach and describe its use as able to protect the outflow graft at the time of reentry and, by maintaining a short path of OG to the aorta on the side of the heart, to avoid creating difficulties dissecting the OG from the right AV groove as may be created by sternotomy approach. Cohn and Frazier [5] use a transdiaphragmatic approach for inflow cannulation and return of OG graft to the supraceliac aorta to avoid not only the peritoneal cavity but the mediastinum and the left hemithorax entirely.

One benefit of the minimally invasive techniques over traditional sternotomy is that this approach often allows for less extensive pericardiotomy. Often through the subcostal approach, the pericardiotomy extends along the base of the heart and apex. The pericardial sac over the right heart can then be left more intact. By avoiding opening of the pericardium over the right heart, it is thought that right heart function can be better preserved.

Cheung showed that the duration of CPB was on average 30 min less in minimally invasive cases as compared to the sternotomy group though there was no difference in ICU stay or hospital stay length or inotropic use. Frazier described shorter ICU stays and less 12-h blood loss for patients who underwent LVAD implantation through the subcostal as opposed to the redo sternotomy group. Sorensen et al. [6] showed that redo sternotomy predicted the use of RBC transfusion and increased ICU; in contrast patients that underwent minimally invasive implantation after prior sternotomy saw significant reductions in the need of the both.

Using minimally invasive techniques may lead to the possibility of avoiding full general anesthesia for implantation as it has been done for other non-cardiac surgeries. Bottio et al. [7, 8] have used paravertebral blocks combined with mild anesthesia in such cases and report successful extubation in the OR in 75% of cases with adequate pain control. The possibility of performing LVAD implantation in such a fashion would further support faster recovery times with less pulmonary complications in the LVAD population.

Approach to Outflow Graft Anastomosis

The site of outflow graft anastomosis varies depending on the surgical approach to exposure, patient anatomy and state of the native aorta, and surgeon preference. Makdisi and Wang [1] describe the most frequent outflow graft insertion sites to be to the ascending aorta, the axillary artery, the descending aorta, and the supraceliac aorta. Most surgical approaches make use of the ascending and descending thoracic aorta.

A simulation of the hemodynamics comparing outflow graft anastomosis to the ascending or descending aorta was undertaken by Kar et al. [9]. At high VAD outputs with output graft anastomosis to the descending aorta, areas of stagnation, which may be potentially thrombogenic in the native aorta, particularly in the region of the aortic root, were present which were not present when outflow graft anastomosis to the ascending aorta was simulated due to re-circulatory flow. This model correlated clinically with findings in Jarvik (2000) patients with descending aorta outflow anastomosis that showed stagnation on TEE while the aortic valve was not opening, whereas these areas were not present in patients with an ascending anastomosis even at high VAD speeds [9]. These findings and their clinical correlation suggest that the site of outflow graft anastomosis may affect both hemodynamics and the risk for thrombosis in VAD patients.

When the outflow graft is anastomosed to vessel sites other than the aorta, this often occurs in specific circumstances in which the native aorta is either hostile to graft anastomosis or is not necessarily readily accessible through the chosen incisional approach to implantation. Benefits of this technique include the ease of exposure and the low incidence of atherosclerosis in the vessels. Popov et al. [4] further postulate that OG to axillary artery anastomosis has the potential to reduce postoperative aortic regurgitation as the entry of blood flow from the OG is quite distal to the aortic root.

However, extra-aortic OG anastomosis does carry some considerable concerns relating to possible postoperative complications or undesired sequelae. One concern is the risk of the patient kinking the OG or the effects that elevate the arm may have on flow through the system. To prevent kinking, reinforced grafts with ring may be used [10, 11]. Cohn et al. [12] have found success in preventing kinking by using 10–15 cm of polytetrafluoroethylene (PTFE) to cover the OG before anastomosis to the descending or supraceliac aorta. Patients can be informed to avoid excessive elevation of the arm, and blood pressure should not be taken on the left arm to avoid potential disturbances to flow [11]. Magdy describes tunneling the outflow graft from the innominate under the IVC and innominate vein to protect it from direct contact with the sternum. If anastomosis to the left axillary artery tunneling occurred through the left 2nd intercostal space, then graft to graft anastomosis can be performed in the mediastinum (Magdy). When using the subclavian, the graft can be tunneled through the 1st intercostal space [11]. In addition, the use of the axillary proximal to the innominate has the potential for cerebrovascular complications; side-biting clamps are applied to the vessel to avoid this complication (Magdy).

Strategies can be employed to reduce swelling and excessive blood flow into the arm. For the purpose of avoiding excessive blood flow to the arm when anastomosing to the axillary artery, Bortolussi et al. [10] use double radial pressure monitoring and use restrictive distal anastomosis to ensure even pressure to both arms, have also described reducing distal axillary caliber if necessary with division of the artery and end-to-end

anastomosis to the outflow graft, and have documented the success of this technique with postoperative follow-up. Riebandt et al. [11], when performing anastomosis to the subclavian artery, avoid excessive blood flow to the arm by banding the subclavian when there is a pressure difference of 20 mmHg or more.

Off-Pump Insertion Techniques

The use of cardiopulmonary bypass is known to activate systemic inflammatory mediators. When conducting off-pump implantation, one should always be prepared to initiate CPB. The surgical team may choose to prepare sites for cannulation in advance should the necessity arise later in the procedure to minimize the time to emergent CPB.

When conducting off-pump LVAD implantation, it is crucial to create the best visualization of the LV apex possible to prepare for safe, quick, and accurate coring of the LV. Proper positioning, visualization, and uninhibited access to the site of LV coring must be ensured. Heparinization to targeted activated clotting time interval must be completed before this portion of the surgery. As this process is occurring without the use of CPB, it is absolutely essential that clean coring of the LV myocardium and rapid placement of the pump into the newly fashioned ventriculotomy proceed quickly, minimizing any loss of blood through the core. In lieu of placing packing underneath the heart to produce stabilization, other techniques may be used. The use of a suction device (like the Guidant XPOSE [Boston Scientific, Natick, MA]) in off-pump median sternotomy may be used to retract the heart into the surgical field [13, 14]. Cohn [15] have described an experimental technique that uses a vacuum stabilizer for the sewing ring with an over-the-wire vacuum-assisted myocardial coring tool, and an endoventricular occlusion balloon, that ensures exact, clean coring of the myocardium, while the balloon can tamponade the core site as the pump is navigated into place.

The whole operative team must be well coordinated at this point in the procedure, as the heart is still beating; steep Trendelenburg positioning is employed to limit the potential for air embolus. In order to further minimize this risk and optimize function of the heart, augmented fluid infusion rates and a bolus of inotropic drugs may be necessary [16]. Thus, the surgeons, assistants, and anesthesiology team must be focused and united in this monumental step of the procedure.

Given that proper off-pump technique is followed, the postoperative benefits of beating heart LVAD implantation can be delineated. Sileshi et al. [17] compared on-pump LVAD insertions to minimally invasive off-pump implantation with left hemi-sternotomy and left anterolateral thoracotomy patients and found statistically significant decrease in postoperative days on inotropes and substantially decreased need for perioperative and postoperative blood products. This study however compared the minimally invasive off-pump technique to traditional sternotomy implantation on CPB, therefore confounding the results. Yet, Gregoric et al. [3] found that with CPB use being the only variable, the average blood product requirement in the off-pump group was 7 units as compared to 26 units in the CPB group.

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LVAD Surgical Implant Technique: Infradiaphragmatic Approach

6

Jeffrey A. Morgan and O.H. Frazier

Introduction

The evolution of mechanical circulatory support (MCS) systems from early-generation volume-displacement pumps to smaller and more durable continuous-flow (CF) devices has dramatically reduced mortality rates and device-related complications. The advantages afforded by CF left ventricular assist devices (LVADs) have led to their widespread application in the treatment of severe heart failure. However, the perpetuation of implantation strategies developed in an era of pulsatile MCS makes some patients vulnerable to complications unique to CF physiology and design.

Proper orientation of the inlet cannula is an essential component of overall device function. Ideally, the mouth of the cannula should rest within the center of the left ventricular (LV) cavity, thus being free of potentially obstructive surfaces and oriented toward the mitral valve orifice. Traditionally, the pump inlet was inserted through the LV apex to take advantage of the longest measured span within the ventricle.

Surgeons at our institution have developed a method for implanting the HeartMate II along the diaphragmatic surface of the heart [1–3]. Although this method is a significant departure from traditional implantation techniques, it has proved valuable in both eliminating the need for a preperitoneal pump pocket and establishing a geometrically advantageous pump alignment.

Methods

A vertical midline incision is made, incorporating a 6-cm subxiphoid extension. Via a standard median sternotomy, the pericardium is opened both in the midline and along the length of the diaphragm. The anterior border of the diaphragm is then incised from the midline to the apex of the heart, providing access to the peritoneal cavity.

After systemic heparinization and initiation of cardiopulmonary bypass (CPB), the LV apex is brought out of the chest and controlled with a suction stabilizer device. The ventricular coring site is then identified approximately one third of the distance from the apex to the base of the heart (thus, anterior to the origin of the papillary muscles). The

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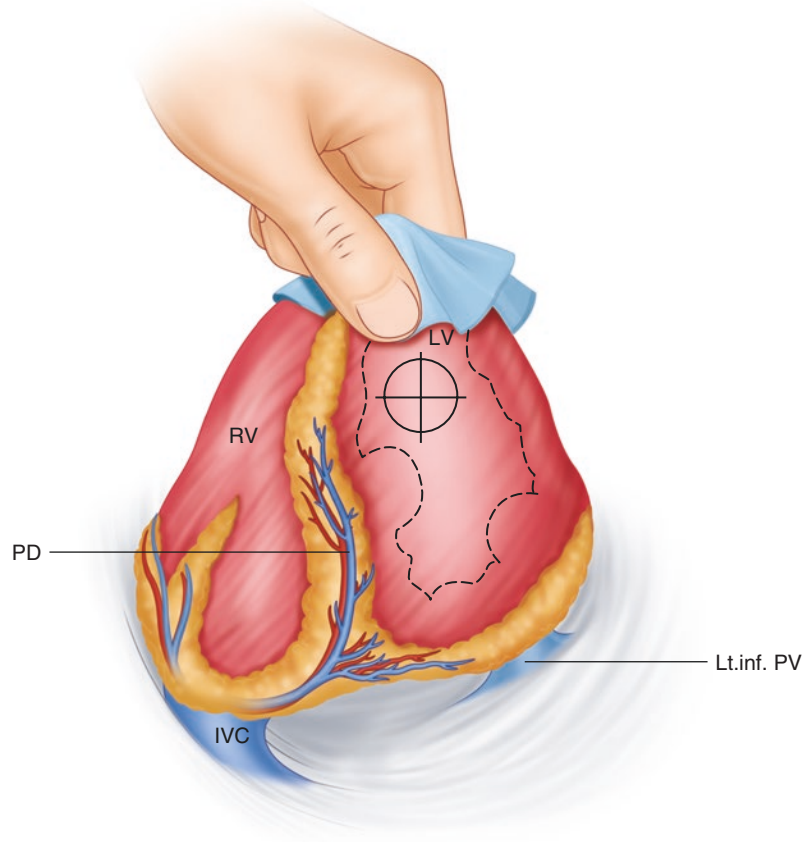

Fig. 6.1 The left ventricular (LV) apex is reflected in a cephalad direction to expose the diaphragmatic surface of the heart. The LV cavity is outlined by the *dotted line*, and the enclosed crosshair depicts "Frazier's point," the optimal location for transdiaphragmatic insertion of the inlet cannula (Modified from Gregoric ID et al. [6])

medial edge of the sewing ring is placed 0.5–1.0 cm lateral to the posterior descending artery to ensure a parallel orientation with respect to the short axis of the left ventricle (Fig. 6.1). The ventriculotomy is performed with a circular coring knife, taking care to stay parallel to the septum and to follow posteriorly in the direction of the mitral valve. The ventricular cavity must then be digitally explored and inspected for evidence of thrombus or obstructive trabeculae.

Next, the Silastic inflow cuff is secured in the standard fashion, using 12 pledgeted, full-thickness horizontal mattress sutures placed circumferentially around the coring site. Hemostasis around the inflow cannula is bolstered by using a large-caliber monofilament suture to place a full-thickness purse-string stitch through the pledgeted ring.

After a diaphragmatic myotomy has been created to correspond to the selected coring site, the inlet cannula is then guided through the diaphragm, inserted within the Silastic ring, and secured in place with two ratcheting cable ties. Proper orientation of the device is achieved by first pulling the pump housing into the abdomen until the heart lies flush with the diaphragm and then positioning the outflow graft to course above the left lobe of the liver. Our preference is to wrap the body of the pump in available omentum to protect the bowel from erosive injury.

The outflow graft then is measured and bevel cut with enough length to allow a gentle curve toward the right side of the chest without excessive redundancy. The outflow anastomosis is then performed in a standard end-to-side fashion with

the aid of a partial occluding clamp along the ascending aorta. After externalization of the driveline, the system is thoroughly de-aired by using a 19-gauge needle placed at the highest point of the outflow graft. Cardiopulmonary bypass flows are gradually decreased, the heart is allowed to fill, and the pump is started at its lowest setting (6000 rpm). The patient is weaned from CPB, which is eventually terminated with the aid of transesophageal echocardiographic guidance to allow optimization of LVAD speeds, chamber size, interventricular septal position, and right ventricular function.

Once proper function and orientation are verified, protamine is administered, the CPB cannulas are removed, and drains are placed in the mediastinum and pleural spaces. The bare portion of the outflow graft is covered with a 20-mm-diameter ringed Gore-Tex graft (Gore Medical, Newark, DE) to prevent kinking and damage during future sternal reentry. The defect in the diaphragm is partially reapproximated, and the sternum and soft tissues are closed in the standard fashion.

Discussion

Early in the development of MCS, inflow cannulation was performed through the LV apex to accommodate lengthy inlet-cannula designs. Although inlet conduits were eventually shortened in response to excessive inflow-graft occlusion seen in experimental testing, device implantation techniques changed little over time [4]. As a result, apical cannulation became standard practice after widespread adoption of the HeartMate XVE LVAD (Thoratec Corp.). Although care had to be taken at the time of implantation to avoid mechanical inlet obstruction, few complications arose from this orientation because of the obligatory preservation of a ventricular reservoir with pulsatile devices. Familiarity with this implantation technique resulted in its subsequent application to CF LVADs——a practice bolstered by the inclusion of an inlet cannula identical to that of the HeartMate XVE in the design of the HeartMate II. However, the unique physiology associated with CF technology necessitates consideration of specific anatomic and mechanical challenges associated with the use of these pumps.

Inlet placement along the diaphragmatic surface of the heart was first reported nearly 10 years ago, when surgeons from our institution described a subcostal approach for implanting the Jarvik 2000 pump (Jarvik Heart Inc., New York, NY) [5]. Although used sparingly, the procedure revealed both the feasibility and potential advantage of an alternative cannulation site for LVAD implantation. The HeartWare HVAD (HeartWare Inc., Framingham, MA) was developed in the Texas Heart Institute laboratories during the mid-1990s and was specifically designed to fit within the pericardial space. Whereas a familiarity with apical positioning led surgeons to prefer this method in early clinical trials, diaphragmatic implantation of the HVAD and HM3, as previously described elsewhere, is also performed at our institution [6].

Disclosures None of the authors has any commercial conflicts of interest.

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Intraoperative Anesthesia Management

7

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Introduction

Indications for left ventricular assist device (LVAD) placement have expanded in recent years. Bridge-to-transplantation (BTT) and destination therapy (DT) comprise the majority of indications, but an increasing number of patients are receiving LVAD support as a bridge-to-recovery (BTR) or even bridge-to-decision-making (BDM). While the development of short-term and percutaneously placed assist devices (e.g., Impella, TandemHeart) has changed the management of heart failure and post-cardiopulmonary bypass (CPB) cardiogenic shock, the anesthetic management for LVAD implantation is specialized even among cardiac procedures [1]. Indeed, LVAD candidates often present with not only cardiac failure but also secondary pulmonary, renal, and/or hepatic pathophysiology that impacts fluid regulation, coagulopathy, and drug pharmacokinetics. Moreover, the anesthesiologist will typically assume intraoperative responsibility for detecting intracardiac shunts, valvular dysfunction, right heart failure, and correct cannula placement via transesophageal echocardiography (TEE). This chapter will provide a framework for thinking about the anesthesiologist's preparation and management for intraoperative LVAD placement.

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Preoperative Evaluation and Considerations

The LVAD recipient is typically characterized by decompensated cardiac failure refractory to medical management. In addition to a severely reduced ejection fraction (EJ), these patients are often characterized by an elevated pulmonary vascular resistance, right ventricular (RV) dysfunction, coagulopathy, hepatorenal dysfunction, and decreased responsiveness to catecholamines. Thus, the preoperative exam informs an anesthetic plan tailored for a patient's comorbidities and provides the opportunity for a personalized informed consent.

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Cardiac Evaluation and Considerations

The cardiac evaluation encompasses not only the etiology of the heart failure but also perioperative assessment of LV and right ventricular (RV) function, valvular status, lesions with the potential for intracardiac shunting, arrhythmias, ventricular thrombus, and the presence of pulmonary hypertension. A history of previous surgeries is warranted as many LVAD candidates have undergone prior sternotomy which may influence the surgical approach to CPB cannulation and/or the potential for a subxiphoid or thoracotomy surgical approach [2]. If redo sternotomy is planned, there is a higher risk of both an increased perioperative transfusion requirement and iatrogenic cardiovascular injury.

Preoperative echocardiographic determination of LV internal dimension at end diastole (LVIDd) is essential, as the comparison to post-LVAD placement signifies the extent of LVAD-assisted LV unloading (Table 7.1) [3]. A small LVIDd (<63 mm) is associated with increased 30-day morbidity and mortality, and often encountered in smaller women and patients with infiltrative cardiomyopathies [3].

RV failure occurs in up to 30% of patients following LVAD placement and is a harbinger of a poor postoperative course complications [4–6]. There is no preoperative predictive model for RV failure with both good sensitivity and specificity; the right ventricular failure risk score (RVFRS) and TEE are often used together to identify potential high-risk patients for postoperative RV failure [4–7]. Postoperative RV failure following LVAD placement can be mitigated by concomitant placement of an RVAD, but the outcomes for these patients are substantially worse [8]. Therefore the presence of preoperative RV ischemic disease may warrant stenting or bypass grafting prior to LVAD placement. Preoperative inotropic support should be also considered if the RV is marginal [8].

The presence of pulmonary hypertension should be assessed preoperatively. Severe fixed pulmonary pressures used to be a contraindication for LVAD placement, but emerging evidence suggests fixed pulmonary hypertension secondary to left heart failure can improve significantly in the first 6 months post-LVAD placement [9]. Regardless, inhaled nitric oxide (iNO) and prostacyclin vasodilators should be available.

Given the advanced heart failure in this population, atrial and ventricular arrhythmias are common and not contraindications to LVAD placement. The majority of patients will present with automatic implantable defibrillators (AICDs) which will need to be deactivated in the

Table 7.1 Preimplantation TTE/TEE *red-flag* findings

Left ventricle and interventricular septum
Small LV size, particularly with increased LV trabeculation
LV thrombus
LV apical aneurysm
Ventricular septal defect
Right ventricle
RV dilatation
RV systolic dysfunction
Atria, interatrial septum, and inferior vena cava
Left atrial appendage thrombus
PFO or atrial septal defect
Valvular abnormalities
Any prosthetic valve (especially mechanical AV or MV)
>Mild AR
≥Moderate MS
≥Moderate TR or >mild TS
>Mild PS; ≥moderate PR
Other
Any congenital heart disease
Aortic pathology: Aneurysm, dissection, atheroma, coarctation
Mobile mass lesion
Other shunts: Patent ductus arteriosus, intrapulmonary

AR aortic regurgitation, *AV* aortic valve, *LV* left ventricular, *MS* mitral stenosis, *MV* mitral valve, *PFO* patent foramen ovale, *PR* pulmonary regurgitation, *PS* pulmonary stenosis, *RV* right ventricle, *TR* tricuspid regurgitation, *TS* tricuspid regurgitation

operating room, and external defibrillation pads placed. All pacemakers should be interrogated prior to surgery for battery life and underlying heart rhythm. Pacer-dependent patients should be placed in asynchronous mode.

Potential intracardiac shunts and valvular pathology should be ruled out by echocardiography. A patent foramen ovale (PFO) or other septal defect requires pre-LVAD implantation repair, as the transluminal pressure gradient post-LVAD predisposes a right-to-left shunt and intractable hypoxia. Similarly, moderate to severe aortic insufficiency (AI), moderate to severe mitral stenosis (MS), and severe tricuspid regurgitation (TR) are valvular lesions requiring repair prior to LVAD implantation.

Finally, the patient's cardiac medications should be reviewed for potential anesthetic interactions. ACE inhibitors' impact on afterload reduction, cardiac remodeling, and mortality in heart failure renders them a recommended medication for this patient population. However, their potential to blunt catecholamine response has been reported in the literature and may contribute to refractory vasoplegia. Withholding an ACE-I on the day of LVAD placement should be discussed.

Renal and Hepatic Function

Patients classified as NYHA III or IV experience a decrease in volume of distribution (VD) and reduced clearance of many intravenous medications by 50% or more [10]. Additionally, secondary renal and hepatic dysfunction are common in patients presenting for LVAD placement. The net result is that many common anesthetic drugs require dose adjustments. Both renal and hepatic end-organ functions can improve post-LVAD implantation, but their presence preoperatively are independently associated with worsened outcomes [11–13]. Elevated bilirubin is the laboratory value most strongly associated with mortality, and primary liver disease should be ruled out prior to LVAD placement. Pre-existing coagulopathy or electrolyte/acid-base imbalances should be corrected.

Other

Patients should have a complete preoperative neurologic exam to rule out deficits, an anesthetic history evaluation (assessing for personal or family anesthetic complications), and an airway exam. Difficulty in ventilation or intubation can result in a host of cardiopulmonary complications as hypoxia- or hypercarbia-related pulmonary hypertension and can precipitate cardiovascular collapse.

Preoperative Laboratory Testing and Imaging

Preoperative labs consisting of an ECG, CXR, pulmonary function tests, complete metabolic panel (including LFTs), complete blood count, and coagulation profile, including fibrinogen and a functional coagulation assessment such as a TEG or ROTEM, should be ordered. Echocardiogram and cardiac catheterization should assess the transpulmonary gradient, pulmonary vascular resistance, pulmonary vascular response to vasodilators, right ventricular function, cardiac output, valvular function, and LV filling pressures. Imaging including head, chest, and abdominal CT scans should be negative for malignancy, terminal process, or hemorrhage. Patients should be typed and crossed, and blood products should be immediately available in the operating room.

Consent/Family Discussions

Despite their success in extending the quality and duration of life for a vast majority of patients, LVAD placement comes with the assumption of significant risk for not only mortality but also prolonged ICU stay, renal failure, progressive cardiac failure, and fatal hemorrhage. Patients and their families need to be aware of this during the informed consent process, and the discussion should address the patient's wishes in the event of a catastrophic complication or decompensation. There is a high degree of family member confusion

at the time of end of life for LVAD patients given the complexity and life-sustaining nature of these devices [14].

Monitors

Large-bore peripheral IV access is recommended in patients with prior sternotomy. If present, an AICD should be inactivated in the OR, and external defibrillation pads placed. An arterial line should be confirmed prior to induction. A PA catheter recommended and is useful to measure ventricular pressures, mixed venous saturation, and CVP/PCMP ratio. Unlike the LVAD flow reading which is estimated and does not include the native heart's contribution, a PA catheter is also useful for cardiac output. Intraoperative TEE is useful for detecting factors that may affect VAD performance and patient outcome, including septal defects, aortic valve regurgitation, mitral stenosis, RV dysfunction, intracavitary thrombus, and aortic atheroma. Additionally, TEE is useful for confirming VAD cannulae positioning and cardiac de-airing.

Induction and Management Prior to Bypass

Induction and Preparation for Cardiopulmonary Bypass

End-stage cardiac failure patients presenting for LVAD implantation are often dependent on high circulating concentrations of catecholamines to maintain vasoconstriction. Acute decreases in LV preload or increases in LV afterload are poorly tolerated and should be avoided on anesthetic induction. Decreases in heart rate (HR) are especially deleterious, as these patients cannot compensate by increasing stroke volume [1]. Thus, these patients may benefit from low-dose norepinephrine or epinephrine infusion at the time of induction in order to maintain HR and CO.

Lidocaine and fentanyl are often given to blunt the sympathetic response to laryngoscopy. Etomidate is the most commonly used induction agent, but it comes with a risk of adrenal insufficiency. If this is a concern, ketamine can be used. Esmolol should be available to manage any tachycardia resulting from laryngoscopy. Increased time for circulation is required for onset of all intravenous medications, and intraoperative awareness is more frequent in patients undergoing cardiac surgery [15]. Maintaining cardiac output while restricting fluids to avoid unnecessary increases in RV end-diastolic pressure and maintaining adequate anesthetic depth are the pre-CBP goals.

Baseline labs including basic chemistry panel, arterial blood gas, and ACT should be obtained following induction. Hypokalemia and hyperglycemia should be addressed immediately. Antibiotics should be initiated at the time of skin prep (or earlier with vancomycin) and redosed accordingly during the procedure. Leukocyte-reduced blood should be available to reduce anti-HLA antibody production [16]. Replacement products for patients with an iatrogenic antithrombin III deficiency should be available.

Patients should be anticoagulated with heparin (300–400 units/kg) and an appropriate ACT (>350 s) confirmed with the surgeon and perfusionist prior to initiating CPB [17]. For patients with a suspected heparin resistance manifested by inappropriate ACT elevation, an additional dose of heparin may be administered. If this is unsuccessful, a presumed antithrombin III deficiency can be treated with antithrombin III concentrate or FFP if the former is unavailable. If the patient remains refractory to heparin or there is a contraindication to heparin, bivalirudin is the preferred substitute for use on CPB.

Intraoperative Transesophageal Echocardiography

The American Society of Echocardiography recommends a TEE checklist for both pre- and post-implantation (Table 7.2). TEE evaluation of the RV should begin with a qualitative assessment of size, tricuspid regurgitation (TR) severity, TR etiology (iatrogenic or secondary to dilated annulus), and ventricular motion from the tricuspid annulus to the apex, inclusive of the free wall [3, 18].

Table 7.2 Perioperative TEE protocol/checklist (Adapted with permission from [3])

Two-part exam
1. Preimplantation perioperative TEE exam
Goals: Confirm any preoperative echocardiography (TTE or TEE) findings; detect unexpected abnormal findings prior to LVAD implantation
Blood pressure: If hypotension is present, consider vasopressor agent to assess AR severity
LV: Size, systolic function, assess for thrombus
LA: Size, assess for LA appendage/LA thrombus
RV: Size, systolic function, catheters/leads
RA: Size, assess for thrombus, catheters/leads
Interatrial septum: Detailed 2D, color Doppler, IV saline contrast. ***Red flag:*** PFO/ASD
Systemic veins: Assess SVC, IVC
Pulmonary veins: Insepect
Aortic valve: ***red flags:*** >mild AR, prosthetic valve
Mitral valve: ***red flags:*** ≥moderate mitral stenosis, prosthetic mitral valve
Pulmonary valve: ***red flags:*** >mild PS, ≥moderate PR, if RVAD planned; prosthetic valve
Pulmonary trunk: ***red flags:*** Congenital anomaly (PDA, pulmonary atresia or aneurysm)
Tricuspid valve: TR, systolic PA pressure by TR velocity. **Red flags:** ≥moderate TR, >mild TS, prosthetic valve
Pericardium: Screen for effusion; consider constrictive physiology
Aorta: Root, ascending, transverse, and descending thoracic aorta; screen for aneurysm, congenital anomaly, dissection, or complex atheroma at each level
2. Postimplantation perioperative TEE exam
Goals: Monitor for intracardiac air; rule out shunt; confirm device and native heart function
Pump type and speed: Confirm
Blood pressure: Via arterial line; for hypotension (MAP of <60 mmHg), consider vasopressor agent before assessing AR severity and other hemodynamic variables
Intracardiac air: Left-sided chambers and aortic root during removal from CPB
LV: Size, inflow-cannula position and flow velocities, septal position. ***Red flags:*** Small LV (over-pumping or RV failure), right-to-left septal shift; large LV (obstructed or inadequate pump flows)
Inflow-cannula position: 2D/3D, assess for possible malposition
Inflow-cannula flow: Spectral and color Doppler (***red flag:*** Abnormal flow pattern/high/low velocities, especially after sternal closure)
LA: Assess LA appendage
RV: Size, systolic function. ***Red flags:*** Signs of RV dysfunction
RA: Size, assess for thrombus, catheters/leads
Interatrial septum: Repeat IV saline test and color Doppler evaluation of IAS (***red flags:*** PFO/ASD)
Systemic veins: (SVC, IVC)
Pulmonary veins: Inspect
Aortic valve: Degree of AV opening and degree of AR (***red flags:*** >mild AR)
Mitral valve: Exclude inflow-cannula interference with submitral apparatus; assess MR
Pulmonary valve: Assess PR, measure RVOT SV if able
Pulmonary trunk: (if applicable, demonstrate RVAD outflow by color Doppler); assess PR
Tricuspid valve: Assess TR (***red flags:*** >moderate TR); systolic PA pressure by TR velocity (if not severe TR)
Pericardium: Screen for effusion/hematoma
Aorta: Exclude iatrogenic dissection
Outflow graft: Identify conduit path adjacent to RV/RA with color and spectral Doppler (when able)
Outflow graft-to-aorta anastomosis: Assess patency/flow by color and spectral Doppler (when able). ***Red flags:*** Kinked appearance/turbulent flow/velocity > 2 m/s, particularly after sternal closure

2D two-dimensional, *3D* three-dimensional, *AR* Aortic regurgitation, *ASD* Atrial septal defect, *AV* Aortic valve, *CPB* Cardiopulmonary bypass, *IAS* Interatrial septum, *IV* Intravenous, *IVC* Inferior vena cava, *LA* Left atrium, *LV* Left ventricle, *LVAD* Left ventricular assist device, *LVOT* Left ventricular outflow tract, *MAP* Mean arterial pressure, *MR* Mitral regurgitation, *PA* Pulmonary artery, *PFO* Patent foramen ovale, *PDA* Patent ductus arteriosus, *PR* Pulmonary regurgitation, *PS* Pulmonary stenosis, *RA* Right atrium, *RV* Ventricle, *RVAD* Right ventricular assist device, *RVOT* Right ventricular outflow tract, *SV* Stroke volume, *SVC* Superior vena cava, *TEE* Transesophageal echocardiography, *TR* Tricuspid regurgitation, *TS* Tricuspid stenosis, *TTE* Transthoracic echocardiography

Systolic function and dilatation should be noted, as RV end-diastolic diameter was one of the two echocardiographic variables recently identified as independently predictive of RV failure [3, 19]. 3D volume assessment, tricuspid annular plane systolic excursion (TAPSE), global and regional RV fractional change area, and the maximum derivative of the RV pressure (dP/dt max) have also been mentioned as quantitative options for evaluating systolic function [3, 18]. However, these tools are not always available, and the techniques are challenging in this population [3]. At present there is no consensus on reliable predictors of RV failure following LVAD placement, but given the high morbidity and mortality associated with that event, thorough pre-bypass and postimplant examinations of both ventricles are imperative.

Any potential intracardiac shunt should be identified [3]. LVAD placement leads to a precipitous decline in LV and left atrial (LA) pressures, and a patent foramen ovale (PFO) or other septal defect could result in right-to-left shunting, systemic hypoxia, and paradoxical thromboemboli [3, 20]. Identification prior to bypass is essential because the repair may alter the surgeon's cannulation technique [18]. Our preferred technique for visualizing PFOs is via agitated saline in the mid-esophageal bicaval view. While pre-bypass identification is ideal, Valsalva maneuver is not always successful in identifying PFOs in patients with severe heart failure and elevated atrial pressures. Therefore confirming the absence of a PFO following LVAD placement is advised [18].

Valvular deficiencies need to be identified and often repaired prior to implantation. Aortic insufficiency (AI) is especially problematic. The LVAD decreases LV end-diastolic pressure, thereby increasing the aortic transvalvular gradient. Flow through the LVAD is increased compared to normal, but the systemic and coronary flow is inadequate because the leaky AV results in preferential LV filling [21]. Aortic stenosis is less of an acute problem, but an aortic valve that does not intermittently open increases the risk of pump thrombosis [18]**.** Similar examination should be done for the pulmonic valve in the event of RVAD placement and to identify the risk for RV overload in the event of pulmonic insufficiency. Unaddressed moderate or severe mitral stenosis will impair LVAD filling and can hamper RV function. Mitral regurgitation does not impact LVAD function. Finally baseline tricuspid regurgitation (TR) and annular dilatation should be noted because the LVAD's presence and its resultant LV decompression can worsen TR. Tricuspid repair or replacement should be considered if TR is moderate or severe [3].

Severe aortic atherosclerotic disease (atheroma >5 mm or protruding) and calcifications should be identified as they are associated with an increased risk of embolic events. Likewise atrial and ventricular thrombi should be ruled out in this population, as they are often located near the apical implantation site and may increase the risk of perioperative stroke [3, 18].

Management on Cardiopulmonary Bypass

General Anesthetic Management

While on bypass, blood pressure control is the primary goal with titration of vasopressors as necessary, favoring vasopressin and norepinephrine. In the event of refractory vasoplegia, there are case reports of success with methylene blue administration, which is hypothesized to inhibit guanylyl cyclase, although its use in small case series has not been shown to improve overall mortality [22]. Moreover methylene blue's pulmonary vasoconstrictive properties are concerning. Electrolytes, glucose, and hemoglobin should be monitored frequently. Some institutions recommend magnesium (4 g) and lidocaine (100 mg) loading prior to inflow cannula insertion to reduce ventricular arrhythmogenicity [23].

Cannula Positioning and De-airing

TEE can guide optimal positioning of the LVAD inflow cannula toward the mitral valve and away from the ventricular septum (Fig. 7.1). The tip

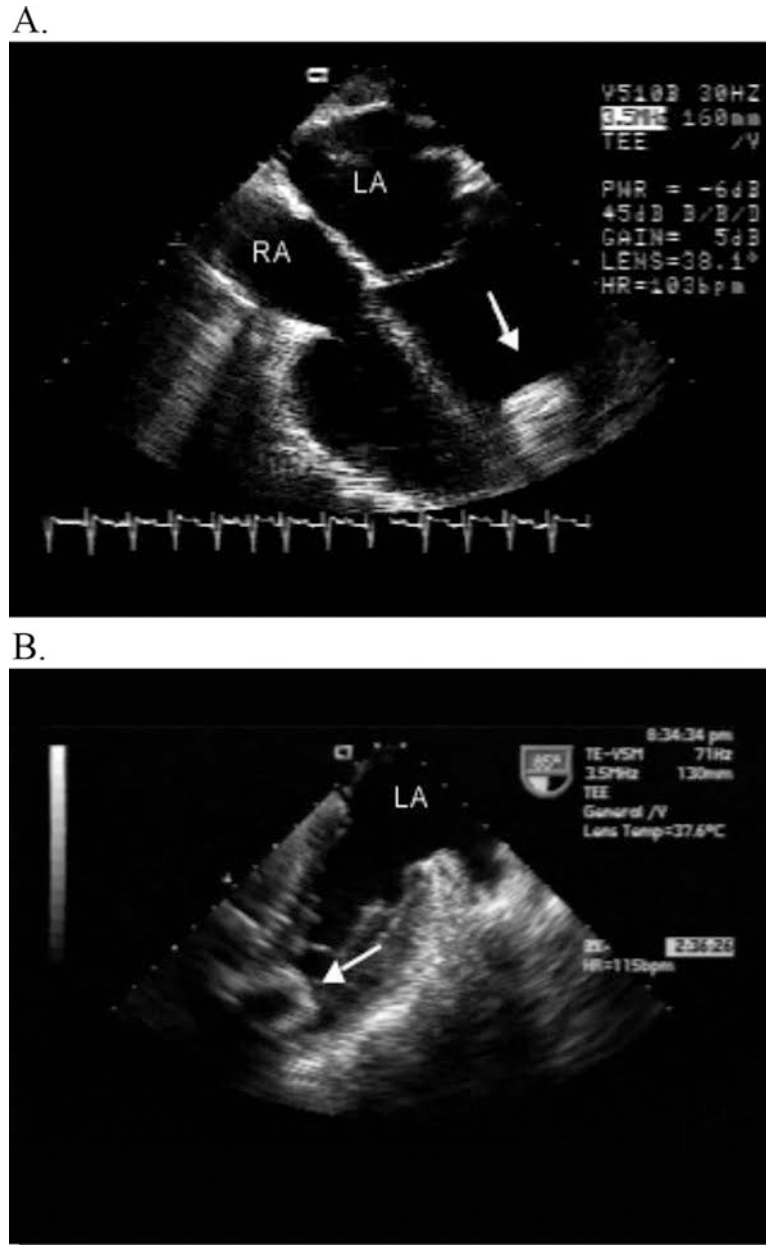

Fig. 7.1 TEE verification of LVAD inflow cannula (shown by *arrow*) placement (Panel **a**, **b**)

should rest in the center of the chamber, away from the ventricular free wall, to minimize suction events. Aortic dissection can occur, rarely, during suturing of the outflow graft to the aorta (Fig. 7.2). Intimal tears, aortic valve pathology, and true and false lumens can be assessed. When the LVAD is functional, outflow should be unidirectional and laminar; any flow >2 m/s should be caused for concern [3]. De-airing needs to occur before weaning from bypass [3]. Air migration into the right coronary artery can precipitate RV ischemia and failure, and air in the LVAD outflow track can result in a cerebrovascular event. Air should be excluded from the pulmonary veins, left atrium, LV, LVAD outflow graft, proximal ascending aorta, and right coronary sinus [3, 18].

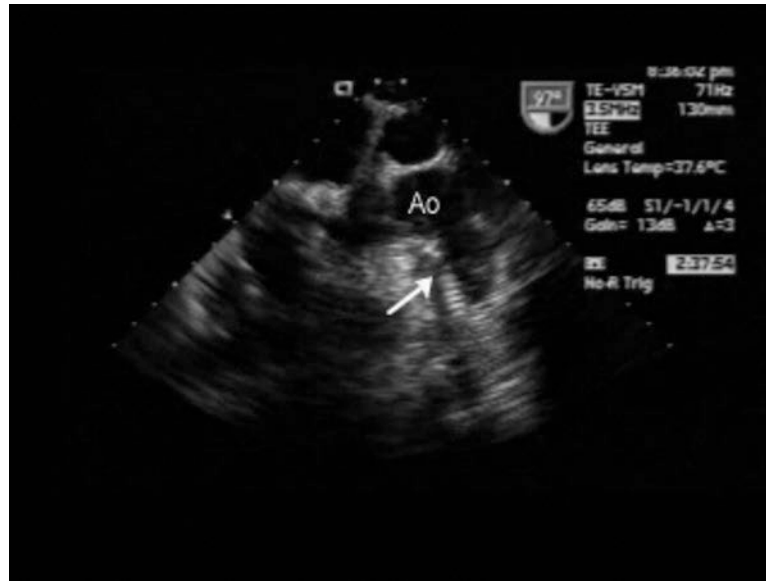

Fig. 7.2 TEE verification of LVAD outflow cannula placement (*arrow marks* outflow cannula entering into aorta (AO))

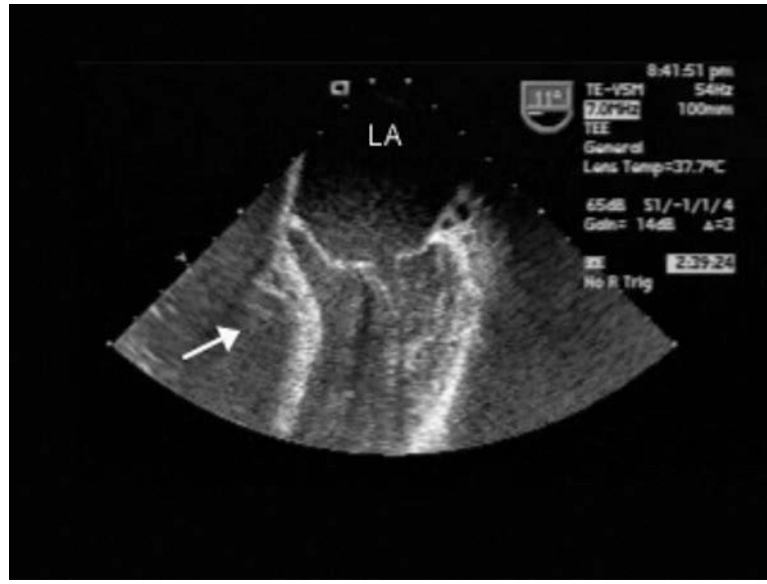

Fig. 7.3 TEE verification of right ventricular septal bowing (*arrow*) due to right ventricular failure and/or underfilling of the left ventricle

LVAD Speed Determination and Ventricular Function

Once the LVAD is implanted and functioning, the interventricular septum should be in a neutral to leftward position with the LV moderately decompressed [3]. Exaggerated decompression and significant leftward shift of the interventricular septum can predispose suction events and compromise RV contractility, whereas inadequate LV decompression and a rightward septal shift indicate inadequate LVAD flows (Fig. 7.3) [3]. The aortic valve (AV) should be evaluated for opening during systole. Fixed AV closure can be accompanied by adequate systemic flow but increases the risk of AV thrombotic events. A permanently closed AV may be inevitable in severe heart failure (opening is associated with degree of LVAD

support), repaired aortic insufficiency, or aortic stenosis, or it may be able to be ameliorated with speed changes on the LVAD device. Finally, the heart should be examined again for intracardiac shunts, aortic regurgitation, and right ventricular function [3].

Post-cardiopulmonary Bypass Management

Post-CPB implantation care now focuses on LVAD speed optimization, assessment and augmentation of RV function, and determining whether a BiVAD will be necessary. In conjunction with this, CPB-associated vasoplegia, hypertension, and coagulopathy will need to be treated. While hypertension is rare, it can impede systemic LVAD flow.

RV failure occurs in up to 30% of patients following LVAD placement and is a significant cause of morbidity and mortality [4–6, 24]. While an LVAD may provide RV afterload reduction, it can mechanically impair RV contractility and elevate RV filling pressures. Optimizing inotropes, reducing pulmonary afterload, and rectifying volume status offer the best hope for avoiding RVAD placement. However, if an RVAD is needed, it is best placed during the initial surgery as outcomes worsen for patients who need to return to the OR for RVAD placement as a subsequent operation [25].

Following bypass cessation and confirmed hemodynamic stability, protamine will be given to reverse heparin anticoagulation. An ACT should be <150 s. A full coagulation panel including PT, PTT, INR, fibrinogen, and TEG or ROTEM should be run. Derangements should be managed.

Special Situations

Minimally Invasive and Off-Pump Approaches

Minimally invasive and off-pump approaches to LVAD implantation are increasing in frequency [2, 23, 26, 27]. Sternal-sparing surgeries decrease the future sternotomy risk for patients awaiting a transplant and protect bypass grafts or previous repairs for congenital heart disease. Options cited in the literature include implantation via thoracotomy, hemi-sternotomy, and diaphragmatic approaches [23, 28, 29]. Anesthetic considerations for these approaches need to include potential for massive blood loss, ventilation strategies, and optimization of the left ventricular cavity for inflow graft placement in a systemically pumping heart.

An initial case series suggests blood product utilization may be less for patients undergoing implantation via thoracotomy than traditional sternotomy, but the potential for massive bleeding with reduced visualization is possible [23, 27]. With a thoracotomy approach, both single- and double-lumen tubes have been used successfully for patients, and the discussion regarding preference should happen with the surgeon prior to intubation. Patients for whom interrupted ventilation may result in decompensation, such as those with COPD, may be better candidates for double-lumen endotracheal tubes. Separately, a team from Vanderbilt cites an off-pump approach as a means of RV protection, as it spares pericardial opening and uncontrolled RV dilatation [23]. Moreover, the adenosine used in their technique (to assist with inflow cannula placement off-pump) is postulated to protect the RV further via adenosine-induced pulmonary vasodilatation [23].

Devices Placed Unexpectedly for Inability to Come Off Bypass

Short-term options for cardiac or cardiopulmonary support include extracorporeal VADs (i.e., Levitronix, Bio-Medicus, Abiomed AB5000) and extracorporeal membrane oxygenation (ECMO). Both benefit from TEE support to rule out intracardiac shunts and AI and confirm cannula placement. ECMO in the setting of significant post-cardiotomy bleeding is a challenge, and coagulation management will be adjusted based on the risk of ongoing bleeding vs. circuit thrombosis.

Percutaneous Devices Placed in the Catheterization lab

Percutaneous devices such as Impellas and TandemHearts are being used increasingly as a BTR or BTD in the catheterization lab. A BTD placement might involve the options of recovery, placement of a long-term LVAD, or transplant [30, 31]. The Impella in particular is also being invoked for support and cardioprotection during high-risk percutaneous interventions and ventricular tachycardia ablations. Despite the popularity of these devices, in general, they are short-term devices and do not provide the same level or duration of ventricular support as an LVAD.

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Perioperative Management of LVAD Patients

8

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A recent INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) annual report on the outcomes of patients who underwent continuous-flow left ventricular assist device (CF-LVAD) or biventricular assist device implantation showed that these patients had a 1-year survival rate of 80% [1]. Most of the mortalities occurred within the first 30 days after device implantation or during the postoperative period of the index hospitalization [1, 2]. The major causes of death during this period were as follows: 60–65% were due to multisystem organ failure (MSOF), which was driven primarily by poor oxygen delivery (DO_2) and, often, specifically by right heart failure (RHF) [1, 2]; 15–20% were due to embolic and hemorrhagic stroke [1, 2]; 10–15% were due to bleeding events [1, 2]; 5–10% were sepsis related [3, 4]; and approximately 5% were due to respiratory failure [3]. The remaining deaths were mainly due to device malfunction, arrhythmias, or other less common complications [3, 4]. Table 8.1 presents the notable postoperative complications and their frequency of occurrence. These data suggest that poor LVAD implantation outcomes can often be prevented or effectively managed. Therefore, diligent perioperative care is paramount to ensure positive outcomes for these patients.

This chapter will focus on the perioperative management of patients who have received one of the two prevalent and FDA-approved CF-LVADs: the HeartMate II (HM2), which was approved for bridge to transplantation in 2008 and for destination therapy in 2010, and the HeartWare HVAD (HW HVAD), which was approved for bridge to transplantation in 2012.

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Table 8.1 Early postoperative complications of left ventricular assist device (LVAD) implantation

Complication	% of cases
Right heart failure	10–39%; up to 50% when LVAD emergently placed
Respiratory failure	6–40%
Cerebral vascular accident	10–15%
Transient ischemic attack	4–12%
Delirium	10%
Renal failure	3–33%
Hepatic failure	2–8%
Arrhythmia	30–60%
Atrial	25%
Ventricular	22–52%
Thromboembolism	6% pulmonary or systemic vasculature
Hemolysis	3–5%
Infection	Up to 42% of index hospitalizations
Bleeding requiring transfusion	31–81%
Bleeding requiring reoperation	31%
Tamponade	15–28%

Preoperative Management of LVAD Patients

The perioperative management of an LVAD recipient begins with preoperative optimization of the patient's clinical status. Clear risk factors for poor outcomes after LVAD implantation have emerged over the past decade or so [1, 2, 5]. These are discussed in detail in Chap. 2. However, several of these adverse conditions are often, at least to some degree, remedial. Effective interventions for such conditions can sometimes allow for positive outcomes after LVAD placement. The recently published guidelines for mechanical circulatory support (MCS) from the International Society for Heart and Lung Transplantation provide a helpful summary of these preoperative treatment strategies [5]. Optimization of cardiac status, particularly addressing RHF, is a major focus of preoperative care. Right heart failure is discussed in separate chapters, but we discuss remediation strategies for other conditions below.

A substantial percentage of patients considered for LVAD implantation are malnourished or at risk for malnourishment through the pathophysiology of cardiac cachexia [6]. Indeed, only 10% of patients being evaluated for heart transplantation or LVAD implantation are considered to be "well nourished" [7], and insufficient nutritional status is associated with poor LVAD implantation outcomes [8]. Therefore, preoperative nutritional assessment of LVAD candidates is recommended, including at least a prealbumin screening and possibly more advanced measures of nutritional status, such as caloric expenditure, along with specific, nutritionist-directed interventions [6–9].

All unnecessary lines and catheters should be removed from patients who are to undergo LVAD implantation. A dental evaluation and treatment of any active or potential infections is also recommended before LVAD placement. In addition, any other active infections should be fully treated preoperatively [5, 10]. The administration of prophylactic antibiotics within 60 min of the incision and continued use for 48 h postoperatively has become standard practice [5, 11]. The most recent guidelines suggest that antibiotic regimens include coverage for both gram-positive and gram-negative organisms [5]. The most aggressive regimens, which we favor, include preoperative administration of vancomycin, a broad-spectrum cephalosporin, and fluconazole, followed by a 2-day course of vancomycin in combination with cephalosporin. Patients with a high preoperative risk for or who had a preoperative nasal swab positive for methicillin-resistant *Staphylococcus aureus* should be given rifampin and nasal topical mupirocin preoperatively and for 7 days postoperatively [4]. Standard topical skin preps should include the use of chlorhexidine solution [3, 12].

The function of major nonheart organs, including the kidneys, liver, and lungs, should be optimized preoperatively. Renal failure, depending on degree, is a major risk factor for poor LVAD outcomes [13–16]. In fact, end-stage renal disease requiring hemodialysis is currently considered a contraindication for LVAD implantation [5]. Therefore, it is generally recommended

that renal function be optimized before device implantation [5]. In the case of advanced congestive heart failure (CHF), renal perfusion is often compromised. In this circumstance, it is recommended that renal function be supported by optimizing the patient's hemodynamics with pharmacologic therapies and, perhaps, temporary MCS [5]. The evolving practice of using temporary MCS as a bridge to LVAD implantation in patients with MSOF is covered in another chapter, but early studies have suggested that such strategies are very promising [5, 17]. However, studies are needed to assess the specific strategy of targeting preoperative renal function to improve LVAD implantation outcomes. Volume overload, usually demonstrated by a central venous pressure (CVP) of ≥16, has been shown to increase the risk of poor LVAD implantation outcomes [18], and it has generally been agreed that CVP should be controlled preoperatively by using diuretics or hemodialysis techniques [5]. However, it is sometimes difficult to separate outright RHF and volume overload from renal dysfunction when conducting a study. Interestingly, volume overload has also been shown to increase the risk of acute kidney injury after LVAD implantation [13, 19].

Heart failure adversely affects liver function and can lead to liver injury by inducing both hypoperfusion (ischemic hepatitis) and venous congestion (leading to cardiac cirrhosis) [20–22]. Of these two possibilities, it appears that RHF and passive venous congestion have a more profound adverse effect. Advanced liver dysfunction can cause coagulopathy and vasodilation [20, 22]. It has been well established that patients with liver cirrhosis or a high model for end-stage liver disease (MELD) score are at high risk for adverse outcomes after LVAD implantation [20, 23–25]. In fact, recent data from a single-center study suggest that significantly elevated levels of aspartate aminotransferase and alanine transaminase and the need for a preoperative liver biopsy are powerful independent predictors of survival for HM2 and HW HVAD recipients [26]. Therefore, patients with abnormal liver function tests are recommended to undergo ultrasound evaluation of the liver, hepatology consultation, and possibly biopsy of the liver [5, 20]. Cirrhosis and having a high MELD score are considered contraindications for LVAD implantation [5]. Patients with these contraindications are typically suggested to undergo combined heart and liver transplantation [5, 20]. However, for patients with hepatic dysfunction that is not severe enough to exclude them from consideration for LVAD implantation, the current recommendations suggest pharmacologic improvement of hepatic perfusion and treatment of RHF [20]. As suggested for patients with renal failure, one strategy that may be successful for improving outcomes of patients with liver dysfunction could be to use temporary mechanical right and left heart support to improve or normalize liver function before LVAD implantation [20, 26]. A recent publication from a German hospital reported excellent outcomes (75% survival at 1 year) in a large cohort of relatively young patients (mean age, 35 ± 12 years) with acute hepatic failure who underwent HM2 or HW HVAD implantation [27]. Interestingly, 85% were on pharmacological support, and 41% were on some form of MCS going into surgery. For any patient with a demonstrated liver abnormality, we recommend administering vitamin K (10 mg, intramuscular or intravenous, though it is worth noting the risk of rare but potentially dramatic anaphylaxis with such) preoperatively, as well as maintaining vigilance for coagulopathy both intraoperatively and postoperatively, because the liver makes many of the key coagulation factors.

Pulmonary function is often impaired in patients with advanced heart failure due to interstitial and alveolar edema, cardiomegaly, pleural effusions, and secondary pulmonary hypertension, which can cause restrictive and obstructive lung defects, impaired gas exchange, decreased lung compliance, increased work to breath [28–32], and in the case of cardiac cachexia, respiratory muscle dysfunction. Studies correlating preoperative pulmonary function test results to LVAD outcomes are lacking. A limited number of studies have suggested that pulmonary function may be reduced after LVAD implantation, in spite of otherwise controlled CHF, particularly in HM2 recipients [31, 32]. Limited data suggest

that the HM2 device may affect diaphragm function [33], presumably because implantation requires transection of the left anterior hemidiaphragm and because the pump for the HM2 lies directly below the left hemidiaphragm, impairing its movement. However, there is substantial evidence correlating poor preoperative pulmonary function to adverse outcomes after cardiac surgery not involving ventricular assist device (VAD) implantation, and standard recommendations suggest optimizing pulmonary function before cardiac surgery [34, 35]. We recommend controlling pulmonary edema and any airway obstructions due to CHF or underlying obstructive lung disease as well as possible before the operation. However, again, no specific intervention studies have confirmed that this approach is beneficial. Additionally, preoperative respiratory muscle training may be beneficial for patients with advanced heart failure and respiratory muscle dysfunction, as has been shown for a high-risk cohort of patients undergoing general cardiac surgery [36].

Finally, coagulopathy and platelet dysfunction should be corrected before a patient undergoes LVAD implantation [5, 18]. Many LVAD candidates are on anticoagulation and antiplatelet regimens preoperatively (see "Bleeding and Hemostasis Considerations" section below).

Effects of Cardiopulmonary Bypass (CPB), Anesthesia, and Surgery on the Postoperative Course After LVAD Implantation

CPB

Immediately after CPB is initiated and the aortic cross clamp is placed, pulmonary capillary wedge pressure (PCWP) and pulmonary artery pressure (PAP) increase. This can cause pulmonary vascular endothelial dysfunction and result in pulmonary vasoconstriction and, ultimately, right heart strain when the patient is being weaned from CPB. However, a number of studies have demonstrated that pulmonary vascular resistance (PVR) actually declines immediately after CF-LVAD implantation and continues to decline over time [37].

Low cardiac output state, a well-recognized complication of CPB, is essentially characterized by poor ventricular performance [38]. The cause is thought to be multifactorial, including myocardial ischemia during cross-clamping, reperfusion injury, cardioplegia-induced myocardial dysfunction, and activation of inflammatory cascades, resulting in suppression of myocardial function. In our experience, patients who undergo LVAD implantation have the same complications, except that the LVAD, presumably, compensates for impaired left ventricular (LV) performance. The effects of LVAD implantation on the right heart are complex; these are discussed in Chap. 18.

Cardiac vasoplegia syndrome (CVS) is a form of vasodilatory shock that occurs in up to 44% of CPB patients [37]. This syndrome is caused by blood exposure to the CPB circuit and the consequent neurohumoral factor and inflammatory mediator activation. The clinical picture of CVS is typical of a systemic inflammatory response, with a low systemic vascular resistance and hypotension, but it can potentially be characterized by its resistance to typical vasopressor dosing [39]. Patients who undergo LVAD implantation are at greater risk of developing CVS, and it appears that CVS may more significantly affect the outcomes of LVAD recipients than those of typical cardiac surgery patients. A recent study showed that norepinephrine-resistant CVS is associated with a 25% mortality rate in patients who have undergone LVAD implantation [39]. Cardiac vasoplegia syndrome should be treated with vasopressors, particularly vasopressin and norepinephrine. For refractory cases, methylene blue, cyanocobalamin, and steroids may be used [39].

Another factor to consider during the postoperative care of LVAD recipients is the fluid shifts associated with CPB and surgery. When patients are initially placed on bypass, the circuit priming volume adds to the intravascular volume. On the other hand, intraoperative bleeding may decrease intravascular volume during surgery. For these reasons, it is very difficult to predict intravascular volume and, hence, right ventricular (RV) loading at the end of CPB. This is among the reasons

why it is standard to perform transesophageal echocardiography (TEE) at the termination of CPB and specifically important to view the right ventricle and intraventricular septum. The position of the septum and other aspects of the right ventricle are more fully discussed below, but essentially, a midline intraventricular septum is consistent with optimal intravascular volume and RV loading [40].

Anesthesia

Anesthetic agents and rewarming can compound the vasodilatory effects of CPB. Short-acting, less potent anesthetics are less likely to cause vasodilation. Some practitioners choose to avoid volatile agents altogether and use propofol instead. However, propofol can also significantly decrease systemic vascular resistance.

Surgery

Placement of the inflow cannula in the apical segments of the left ventricle causes increased LV dysfunction and loss of apical contractility. Analysis of LV tissue obtained up to a year after LVAD implantation showed persistent damage to myocytes and contractility derangements [41]. Because the majority of the LV contraction is based on twisting and untwisting of the apical portion to eject the blood, coring out the LV apex in order to place the inflow cannula invariably worsens LV contractility, compliance, and output. The loss of apical contractility adds to the decrease in inotropy seen once the LVAD is implanted [42], although LV function can certainly improve over time after LVAD implantation [43].

Coming Out of the Operating Room

Once the patient is stable and the LVAD speed has been set based on appropriate TEE imaging [40], it is time to transport the patient to the intensive care unit (ICU) and immediately begin cardiac intensive care management. All of our LVAD recipients leave the operating room with arterial and pulmonary artery catheters for monitoring pressure and measuring mixed venous oxygen saturation (MVO_2) and cardiac output by thermodilution. The patients are also on inotropic support, often consisting of low doses of milrinone and a catecholamine (usually dobutamine or epinephrine). As discussed in detail below, the inotropes are primarily for supporting the right ventricle, which is at risk of stress and decompensating after LVAD placement [44]. In addition, the patients are usually on vasopressors to treat CVS; a combination of vasopressin and norepinephrine is standard at our institution.

Postoperative Course, Complications, and Management

The postoperative period is often characterized by labile hemodynamics (typically caused by volume shifts), vasoplegia, and RV dysfunction. Partly as a consequence of this, major organ function can change quickly in the postoperative period. Not surprisingly, postoperative complications occur frequently after LVAD implantation. The major postimplantation complications are listed in Table 8.1. Because of the possible complications, our care model is for the anesthesiologist and surgeon to directly hand off the care of the patient to a postanesthesia care unit (PACU)/ICU intensivist and nursing team at the bedside. Typically, the required nurse-to-patient ratio is either 1:1 or 2:1 for these patients. It is imperative that all team members are well trained and experienced. The complexity and dynamic nature of the immediate postoperative course requires the proximate presence of the ICU team and clear lines of communication to the cardiologist and surgical team for best outcomes.

Pulmonary Considerations

As with any patient who has undergone cardiac surgery, the initial PACU assessment for LVAD recipients begins with an evaluation of gas exchange and pulmonary status; however, for

these patients, evaluation and management of mechanical ventilation, which virtually all LVAD recipients are on when they leave the operating room, is particularly important. Continuous-flow MCS, though not extensively studied, does not appear to affect the ventilation/perfusion relationships in the lungs or gas exchange [45]. Gas exchange is evaluated with hemoglobin oxygen saturation and arterial blood gas testing. However, the standard pulse oximetry test for assessing oxygen saturation of the blood may be unreliable in CF-LVAD recipients [46]. Obviously, the goal for the arterial hemoglobin oxygen saturation level is greater than 90% for optimal DO_2. The goal for the carbon dioxide arterial tension is to be near but not over 40 mmHg in order to optimize the acid-base balance. But for LVAD recipients, these goals are particularly important because failure to meet them will result in increased PVR [47], which can add afterload burden to a right ventricle already burdened by an increased preload from the increased cardiac output of the new LVAD. As discussed below and elsewhere, RHF is an extremely important complication to avoid in hearts with a newly implanted LVAD.

Physical exams and chest x-rays are used to assess for atelectasis and pulmonary edema, both of which can affect gas exchange. Both should be aggressively treated, but we are particularly diligent about correcting any significant atelectasis because it is a frequent consequence of cardiac surgery and can significantly increase PVR [34, 36]. Usually, we treat atelectasis by increasing either the ventilator-delivered tidal volume (Vt) or the positive end-expiratory pressure (PEEP), although sometimes therapeutic bronchoscopy is required in cases of airway obstruction.

Mechanical ventilation can have three distinct effects on cardiac physiology through the effects of applied mean airway pressure (Paw) [34, 47]. First, increased Paw, via transmission of such pressure to the pleural space, can reduce the RV preload by discouraging venous inflow into the higher pressure chest cavity. Second, increased Paw can potentially cause the alveoli to overdistend, thereby causing compression of the pulmonary capillaries and increasing the PVR. Finally, increased Paw can decrease LV afterload via effects on LV wall tension. Our general approach is to assure a low peak airway pressure (<20 cmH_2O), as concerns about PVR and RHF are paramount. Typically, high RV preload and high LV afterload are dealt with by using interventions other than mechanical ventilation manipulation. The best postoperative ventilator management involves using settings that promote gas exchange, prevent and/or treat atelectasis, and avoid a high Paw. As of yet, no studies have specifically sought to determine the optimal ventilator practice in the LVAD postimplantation setting [44], so we follow standard post-cardiac surgery guidelines for ventilation management. Our usual mechanical ventilation mode is volume cycled with a Vt of 6–8 mL/kg and a PEEP setting of 5 cmH_2O. The respiratory rate is typically set at 10–12 breaths per minute, with a fraction of inspired oxygen (FiO_2) of 50% or titrated to an O_2 saturation level of >92%. Adaptive support ventilation, a newer mode of ventilatory support, has been used successfully to shorten the postoperative ventilator times of cardiac surgery patients [48]. Our preliminary experience with using adaptive support ventilation for LVAD patients has been good; however, close attention must be paid to gas exchange and the potential development of atelectasis and alveolar overdistension. As with other types of cardiac surgery patients, if LVAD patients demonstrate hemodynamic stability, rewarm properly, come out of anesthesia appropriately, and meet the basic mechanical ventilation weaning criteria, we aim to extubate the patient and remove the mechanical ventilation within 6–8 h of surgery. One caveat to note for the extubation of LVAD patients is that extubation may cause an increase in RV preload. That is, removal of the positive thoracic pressure of mechanical ventilation may increase venous return to the right ventricle, placing it at risk of decompensation. Therefore, it is important to monitor the CVP and RV function by echocardiography, along with other hemodynamic parameters, immediately after extubation of these patients. Prolonged postoperative respiratory failure (PPRF) (the definition for which varies but usually includes a mechanical ventilation requirement of at least 6 days) has been

reported to occur in 9–40% of LVAD recipients postimplantation [3, 49–53]. However, the exact causes of prolonged ventilation have not been well delineated in the literature. In our experience, conditions/procedures often associated with PPRF include poor DO_2 with MSOF, bleeding requiring reoperation, open chest, acute lung injury associated with MSOF, transfusions, and sepsis. Thus far, there have been no sophisticated studies evaluating the effects of CF-LVAD implantation on respiratory load and respiratory muscle power output in humans. Patients with PPRF should be cared for by following the same guidelines as above, but additionally, vigilance for ventilator-associated pneumonia should be increased, as these patients are at significant risk for this complication [3].

Hemodynamic and LVAD Function Considerations

As LVAD and total artificial heart technology progresses, there are likely to be significant advancements made in device auto adjustments to respond to the fluctuating hemodynamic states in the postoperative and other periods [54]. However, for now, the bedside hemodynamic assessments and interventions made by the care team during the immediate postoperative period are often critical to the outcomes of these patients. The initial postoperative assessment of hemodynamics consists of a review of the standard data presented in Table 8.2, including clinical parameters, catheter filling pressure, thermodilution cardiac output, and laboratory measurements (adequate and optimal values are provided). Additionally, the key LVAD operational parameters (displayed on the bedside inpatient LVAD monitors) and the important heart-LVAD interaction parameters (obtained by point-of-care echocardiography) are reviewed immediately after the operation (expected values are provided in Table 8.3).

The bedside inpatient LVAD monitors for the HM2 and HW HVAD are connected to the device controllers, which operate the pumps and serve as the user interfaces [55, 56]. The inpatient monitors are specifically designed to provide bedside clinicians with a real-time, optimized data display from the controllers. The LVAD speed, which refers to the revolutions per minute (RPMs) of the device's impellers, is the only set operational parameter for the devices. The HM2 is an axial-flow device that "pushes" blood through the pump casing, moving it from the inflow cannula through to the outflow cannula with a turning propeller. The propeller is turned by magnets and supported by mechanical bearings. In contrast, the HW HVAD is a centrifugal-flow device that "throws" blood from the pump. Specifically, this device takes in blood from the inflow cannula, pushes it between the blades of a rotating disk that is housed in the pump casing and levitated with magnets and hydrodynamic forces, and then throws it tangentially out the outflow cannula. The HW HVAD acts much like a discus thrower, who releases the disk after generating energy through a spinning motion [44, 55–57]. The HM2 operates at a set speed between 6000

Table 8.2 Postoperative hemodynamic parameters

	Adequate	Optimal
Cardiac index	2.2 L/min/m^2	≥2.5 L/min/m^2
Mean arterial pressure	60–90 mmHg	70–80 mmHg
Mixed venous oxygen	>50%	>70%
Central venous pressure	≤15 mmHg	5–10 mmHg[a]
Pulmonary artery occlusion pressure	≤15 mmHg	8–12 mmHg
Cardiac rhythm	–	Normal sinus rhythm
Lactate	<4 mmol/L	–
Hemoglobin	–	≥10 g/dL

[a]In right heart failure, central venous pressure may need to be higher for adequate preload

Table 8.3 Expected left ventricular assist device (LVAD) and echocardiography parameters after device implantation

Clinical screen of LVAD monitor	HM2	HW HVAD
LVAD speed	8000–10,000 rpm	2400–3200 rpm
LVAD flow	2.5–7 L/min	2.5–7 L/min
LVAD power	4–9 W	2.5–8.5 W
Pulsatility index	3.5–5.5	–
Pulsatility waveform	–	Δ flow >2–4 L/min

Bedside point-of-care TTE	HM2 and HW HVAD
Interventricular septum	Midline
Left ventricular size	Reduction of LVID by 20–30%
Right ventricular size	Variable effects on right ventricular size
Right ventricular function	Normal RV EFXN >45%
Inflow cannula	Directed at mitral valve
	Doppler: Turbulence minimal or less
Aortic valve opening	Every 2–3 beats
Aortic valve	Doppler: Regurgitation minimal or less
Mitral valve	Doppler: Regurgitation minimal or less
Tricuspid valve	Doppler: Regurgitation minimal or less
Pericardial effusion	Minimal and no evidence of right ventricular or right atrial collapse (a sign of tamponade)

HM2 HeartMate 2, *HW HVAD* HeartWare HVAD, *LVID* left ventricular internal diameter, *RV EFXN* right ventricular ejection fraction, *TTE* transthoracic echocardiography

and 15,000 RPMs, but the speed is usually set between 8000 and 10,000 RPMs. The HW HVAD can operate at a speed between 1800 and 4000 RPMs, but the usual setting is between 2200 and 3200 RPM. These speeds result in the typical optimal blood flow of between 2.5 and 6 L/min, but both devices can provide up to 10 L/min of flow. The power input to the pump is measured and displayed in wattage and varies according to the pump speed and volume or flow through the pump. For both devices, the flow displayed is an estimate that is calculated using an algorithm based on the speed and measured power of the device and is not directly measured [55, 56]. The only way to directly measure LVAD output is via Doppler TEE determination of flow at the outflow cannula. This data, together with the diameter of the outflow cannula, allows the output from the device to be calculated [58, 59]. The HW HVAD also uses hematocrit, a measure of blood viscosity (which is manually entered), to estimate flow. The default hematocrit is 30. Generally, the calculated flow is quite accurate for the HW HVAD over the usual range of speeds [57, 60]. However, flow estimation is much less accurate for the HM2, which shows substantial variability between patients [61, 62]. In the usual range of flows (i.e., 2.5–6 L/min), the calculated flow is typically 15–20% below the actual flow rate. However, for both devices, the accuracy of the calculated flows cannot be assured at high or low LVAD speeds or when there is an obstruction at the inflow or outflow cannula or within the pump [55, 56]. This is key to understanding and troubleshooting the devices. Both the HM2 and HW HVAD have a measure of pulsatility or variability in flow. It is important to understand that flow through these devices, like that through the heart, is determined, in part, by preload and afterload, as well as by the pump speed [3, 44, 55–58, 63]. Or to put it another way, the flow rate partly depends upon the differential pressure (or "head pressure") between the inflow and outflow cannulae. The pressure at the inflow cannula is equal to the pressure in the left ventricle, and the pressure at the outflow cannula is equal to the pressure in the proximal aorta. The equation for differential pressure (Diff P) is as follows:

$$\text{Diff P} = \left(\text{Pa} - \text{Pv}\right) + \text{delta P pump},$$

where Pa = pressure in the aorta, Pv = pressure in the left ventricle, and delta P pump is the change in pressure as blood flows through the pump (typically, this is negligible).

Flow rate is inversely related to the differential pressure. If the LV volume (and hence the pressure in the left ventricle and at the inflow cannula) increases, then the flow though the pump will increase. Similarly, if the LV volume decreases, then the flow will drop. If the LV

contractile force (and hence the pressure at the inflow cannula) increases, then the flow through the pump increases. If the pressure in the aorta (and hence at the outflow cannula) decreases due to low vasotone, then the flow will increase. If the aortic vasotone increases, then the flow will decrease. So, normally, although the speed is set, flow through the device is somewhat pulsatile, and the pulsatility is driven primarily by cyclical differences in LV pressure. It is important to note here that the HW HVAD and all the centrifugal-flow pumps are, by design, more sensitive to head pressure and usually demonstrate greater pulsatility. The design of these devices also makes them particularly sensitive to afterload. The HM2 provides a pulsatility index, whereas the HW HVAD displays a pulsatility waveform as a marker of pulsatility. The pulsatility index (PI) for the HM2 is calculated as follows (note that the value has no units):

$$\mathrm{PI} = \left(\text{flow max} - \text{flow min}\right) / \text{flow average} \times 10,$$

where the flow max and flow min are the averaged peak and valley flows over a 10- to 15-s interval and the flow average is the total averaged flow over this interval (refer to the device manual for the expected ranges).

The HW HVAD displays flow pulsatility as a continual waveform on the bedside monitor (refer to the device manual for ranges) [55, 56]. Pulsatility measures are used, along with other measures, to identify disturbances in preload and afterload conditions that affect flow of CF-LVADs.

Standard echocardiography windows (parasternal and four-chamber views) are usually adequate for the initial bedside point-of-care assessment by the intensivist [58, 59, 64]. The first and key echocardiography parameter to assess is the position of the interventricular septum. Fig. 8.1 demonstrates the optimal change in septal position after LVAD implantation (i.e., midline between both ventricles) [58]. When the septum is midline, the LVAD speed and flow are generally within the desired ranges, and the LV preload and afterload conditions are appropriate for the settings [44, 57–59, 64–66]. Septal midline position is consistent with an LVAD flow adequate enough to appropriately decompress the failing, distended left ventricle but not so high as to empty the left ventricle to the point where the inflow cannula is at risk of coming up against the LV wall and causing dynamic inflow obstruction. Furthermore, when the septum is at midline, the speed and flow are typically appropriate for optimal RV function. If the LVAD flow is too high, the septum is pulled leftward toward the overemptied and small left ventricle, causing the septal contribution of the RV contraction to be impaired. A leftward-shifted septum can also compromise tricuspid valve geometry (annular dilatation and chordae tendineae tension) and function (papillary muscle). If the LVAD flow is too low, the left ventricle is inadequately emptied, thus causing the left ventricle to enlarge and the septum to bulge rightward, similarly impairing the septal contribution to RV contraction. A leftward shift of the septum may also signal volume overload of the right ventricle. An overdistended right ventricle essentially "pushes" the septum leftward. An LVAD-driven increase in circulatory flow may cause the blood to be delivered at a higher pressure and volume than the right ventricle can pump through and into the pulmonary circulation. This may be due, in part, to a high PVR or poor RV function, as is common in patients with advanced heart failure before they undergo LVAD implantation, or to incompletely understood negative effects of LVAD implantation on RV function. Overdistention of the right ventricle can lead to a cycle of progressive RHF, which is among the most common and feared complications of LVAD implantation. Overdistension can force the right ventricle to operate on the descending limb of the Starling curve, producing RV wall stress and injury and a decrease in RV wall perfusion, creating conditions for ischemic injury. A midline septum also typically insures that the inflow cannula is appropriately aligned with the mitral valve to allow for unobstructed flow into the pump.

When determining the appropriateness of LVAD flow, other factors to assess, besides septal position, are the gross sizes of the left and right ventricles, especially in relationship to the preload

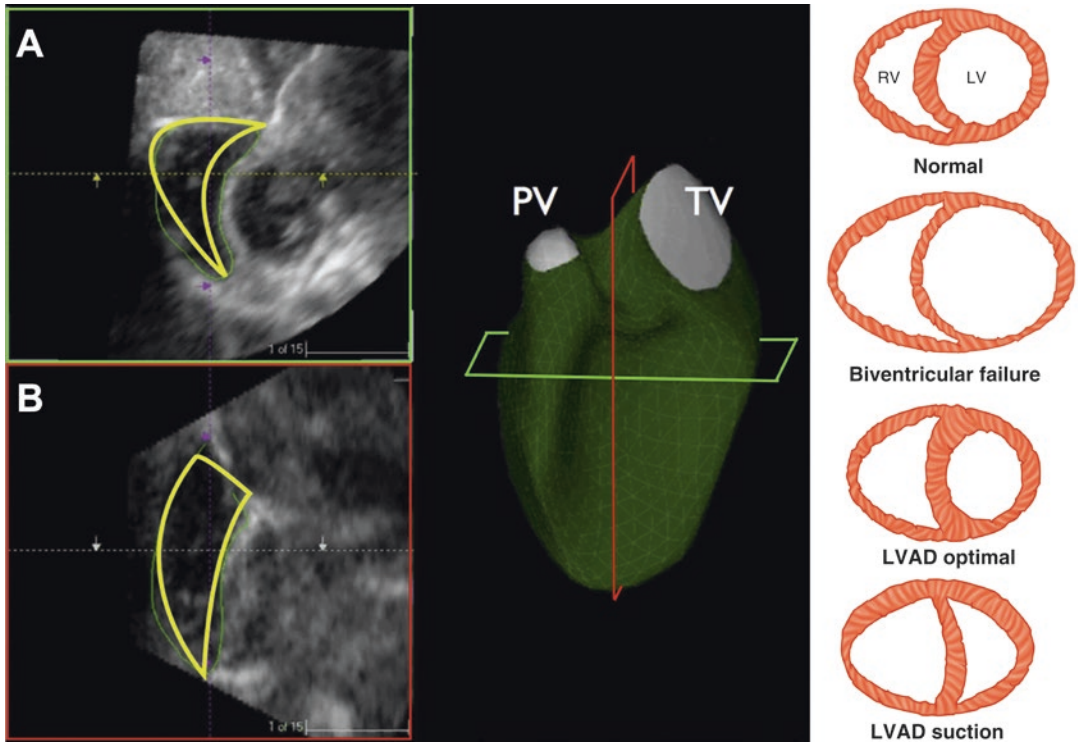

Fig. 8.1 Right ventricular size and function. Two perpendicular sections of a 3D transesophageal echocardiography reconstruction of the right ventricle from tricuspid valve (TV) to pulmonary (PV) valve are shown. The cross section (**a**) demonstrates the crescent shape and the sagittal section (**b**) the triangular shape of the right ventricle (*RV*). Ventricular interdependence between the left ventricle (*LV*) and RV during systole relies on interventricular septum position as shown in cross section for different clinical scenarios. Used with permission from Meineri et al. [58]

and afterload of the heart-LVAD system. An enlarged left ventricle may signal that the LVAD flow is too low to decompress the left ventricle or, alternatively, it may indicate a volume overload state with adequate DO_2 from the LVAD flow. In both of these circumstances, the right ventricle may be distended, as well, but it certainly would not be expected to decrease in size. An underfilled left ventricle may signify an LVAD speed too high for the volume state or RHF with an inability to deliver adequate preload to the left ventricle. In the latter case, the right ventricle would be expected to be distended.

On gross inspection, the LVAD inflow cannula should be directed at the mitral valve to allow for the most linear flow through the ventricle into the pump. Additionally, Doppler signals should show minimal turbulence at the inflow cannula, ruling out significant anatomic or thrombotic obstruction of the inflow cannula. The outflow cannula is usually difficult to visualize on a standard transthoracic echocardiogram (TTE).

Initial echocardiographic inspection by the intensivist should include visualization of the aortic and mitral valves, both by two-dimensional and Doppler imaging. Though somewhat controversial, it is generally recommended that the LVAD speed be adjusted to allow the aortic valve to open every two to three beats, if the DO_2 is otherwise adequate after LVAD implantation [59, 67]. When the LVAD speed is sufficiently low, enough blood is allowed to build up in the ventricle to be ejected through the valve, creating a parallel flow to the devices. This can help to minimize the risk of thrombus formation at or immediately above the valve and to decrease the chance of valve fusion due to disuse [67]. A fused aortic valve may eventually degenerate, and

under pressure from LVAD flow into the proximal aorta, become incompetent, eventually leading to aortic valve regurgitation. Left ventricular assist devices may also exacerbate pre-existing aortic valve regurgitation. After LVAD implantation, proximal aortic flow and pressure increase, typically along with a decrease in LV diastolic pressure due to LV unloading. The change in pressure gradient across the aortic valve can promote an increase in aortic valve regurgitation. Severe aortic valve regurgitation can lead to continuous recirculation of blood from the proximal aorta to the left ventricle and back to the proximal aorta again, thereby decreasing systemic DO_2 [59, 67]. As such, severe aortic valve regurgitation after LVAD implantation may prompt the need for surgical correction of the valve.

Moderate-to-severe mitral valve regurgitation is common in patients with dilated cardiomyopathy, occurring in 76% of the patients in one study [67, 68]. Mitral valve regurgitation is a function of annular dilation and LV end-diastolic pressure [67]. Left ventricular assist device implantation typically mitigates mitral valve regurgitation via LV unloading. Failure to do so may suggest that the LVAD inflow cannula is interfering with the mitral valve apparatus and that it may be necessary to decrease the LVAD speed or even surgically intervene.

Tricuspid valve regurgitation is also very common in patients with dilated cardiomyopathy (30–60% of cases, depending upon the series). This is due to the elevated PAP resulting from LV failure and a dilated right ventricle [67]. Typically, LVAD implantation would be expected to decrease PAP via LV unloading. However, persistent pulmonary vascular bed remodeling and pulmonary vasoconstriction from CPB may cause PVR to increase after the operation. This may contribute to RHF during the postoperative period. Significant tricuspid valve regurgitation should prompt at least pharmacologic treatment of pulmonary hypertension and possibly surgical correction of the valve.

Finally, after LVAD implantation, echocardiography should be performed to ensure that there is only a minimal amount of pericardial fluid. If pericardial effusion is significant, then the possibility of developing cardiac tamponade should become a concern. Tamponade is much more common in patients who have undergone LVAD implantation (occurring in 15–28% of patients) than in those who have undergone most other types of cardiac surgery. It is usually caused by postoperative bleeding into the pericardium or by a mediastinal hematoma extrinsic to the pericardial space. With either pathophysiology, the echocardiogram almost always shows collapse of the right atrium and right ventricle. Occasionally, the echocardiography signs of tamponade are atypical in this patient population [69], and other signs are used to diagnose tamponade (see discussion below).

The principal concern regarding hemodynamics during the postoperative period is poor DO_2, which is generally defined as having a thermodilution cardiac index of <2.5 (certainly when <2.2) [5] or otherwise is suggested by having a MVO_2 level of <70% (certainly when <50%) or a lactic acid level of 4 mmol or greater. Our algorithm for assessing poor DO_2 is presented in Table 8.4. This algorithm follows several recently published guides for assessing hypotension and low DO_2 in patients immediately after LVAD implantation [3, 5, 44, 58, 63, 64]. Essentially, our algorithm follows standard hemodynamic evaluation protocols by looking at cardiac preload and afterload (arterial vasotone), as well as "central" (cardiac equivalent in normal physiology) LVAD output or flow. The LVAD flow is key to our algorithmic assessment.

A decrease in LVAD flow during the postoperative period and a subsequent decrease in DO_2 caused by a decrease in LV preload is usually the result of bleeding. Bleeding requiring transfusion in this period is common, occurring in 31–81% of cases. Hemodynamically significant bleeding and other significant causes of hypovolemia are characterized by hypotension and low PCWP and CVP. Echocardiogram findings of this complication include diameter decrease or collapsibility of the inferior vena cava and possibly a leftward shift in the cardiac intraventricular septum, as the LVAD continues to unload the LV. However, the septum may maintain an appropriate midline position in this circumstance. In addition, the

Table 8.4 Decreased oxygen delivery: assessment and treatment

Low		↓CO, ↓MVO_2, ↑LA LVAD flow		High	
Volume depletion			**Severe aortic regurgitation**		
Hemodynamics		*Differential diagnosis:* – Hypovolemia – Bleeding *Treatment:* *Volume* – RBCs for Hgb ≥10 – Bolus 250 mL 5% albumin and reassess *Surgical* – Possible surgery for bleeding	Hemodynamics		*Differential diagnosis:* – Severe AR *Treatment:* *Device* – Trial ↓ speed *Surgical* – Aortic valve repair *Medications* – Nicardipine – Nitroprusside
MAP	↓		MAP	↓	
PCWP	↓		PCWP	↑	
CVP	↓		CVP	↑ or no change	
Echo findings			Echo findings		
IVC	↓		IVC	↑ or no change	
LV	↓		LV	↑ or no change	
RV	↓		RV	↑ or no change	
Septum	Midline or left shifted		Septum	Right shifted	
LVAD			LVAD		
PI	↓		PI	↑	
PP	↓		PP	↑	
RHF or PE			**Vasodilation**		
Hemodynamics		*Differential diagnosis:* – PHTN (SPAP ≥ 40) – RHF – TR – PE (massive or submassive) *Treatment (for RHF/PHTN):* *Device* – Trial ↓ speed *Pulmonary vasodilators* – NO/inhaled epoprostenol – Sildenafil – Milrinone *Inotropes for RHF* – Epinephrine – Dopamine – Dobutamine *Pulmonary embolism* – AC/possible catheter-directed therapy *Surgical* – Possible surgery for TR	Hemodynamics		*Differential diagnosis:* – Cardiac vasoplegia – Sepsis – Systemic inflammatory response syndrome *Treatment:* *Volume* – 250 mL 5% albumin or crystalloid and reassess *Medications* – Vasopressin – Levophed *Suspected sepsis* – Culture and use empiric broad-spectrum antibiotics
MAP	↓		MAP	↓	
PCWP	↓		PCWP	↓ or no change	
CVP	↑		CVP	↓ or no change	
Echo findings			Echo findings		
IVC	↑		IVC	↓ or no change	
LV	↓		LV	↓ or no change	
RV	↑		RV	↓ or no change	
Septum	Left shifted		Septum	No change or left shifted	
LVAD			LVAD		
PI	↓		PI	↓	
PP	↓		PP	↑	

Cardiac Tamponade				**Pump dysfunction (flow erroneously high)**		
Hemodynamics		*Differential diagnosis:* – Pericardial effusion – Mediastinal hematoma – Tension pneumothorax *Treatment:* *Surgical* – Pericardial window – Hematoma evacuation *Tension PTX treatment* – Tube thoracostamy *Note: PCWP may be ↓ early due to LV unloading, ↑ PCWP is a late finding		Hemodynamics		*Differential diagnosis:* – Rotor thrombosis – Mechanical failure of rotor *Treatment:* *Medication* – AC or thrombolytics *Surgical* – Pump replacement
MAP	↓			MAP	↓	
PCWP	↑*			PCWP	↑	
CVP	↑			CVP	↑	
Echo findings				Echo findings		
IVC	↑			IVC	↑	
LV	↓			LV	↑	
RV	Collapsed			RV	↑	
RA	Collapsed			RA	↑	
Septum	N/A			Septum	Right shifted	
LVAD				LVAD		
PI	↓			PI	↓	
PP	↓			PP	↑	
Increased LV afterload						
Hemodynamics		*Differential diagnosis:* – Hypertension – Vasopressors *Treatment:* – Stop or reduce vasopressors and/or start nicardipine or nitroprusside				
MAP	↑					
PCWP	↑					
CVP	↑ or no change					
Echo findings						
IVC	↑ or no change					
LV	↑ or no change					
RV	↑ or no change					
Septum	No change or right shifted					
LVAD						
PI	↓ or no change					
PP	↓ or no change					

(continued)

Table 8.4 (continued)

Low		↓CO, ↓MVO_2, ↑LA LVAD flow			High
Decreased pump function					
Hemodynamics		*Differential diagnosis:* – Speed settings too low – Suction event – Inflow/outflow obstruction – Pump obstruction Pump thrombosis Pump malfunction – Arrhythmia *Treatment:* *Device* – Trial ↑ speed *Suction event* – ↓ pump speed and give volume if indicated *Flow obstruction* – Advanced echo *Medication* – ↑ AC or thrombolytics for thrombosis *Surgical* – Possible surgical correction of obstruction or pump change *Arrhythmia control* – Medications or ablation techniques			
MAP	↓				
PCWP	↑				
CVP	↑ or no change				
Echo findings					
IVC	↑ or no change				
LV	↑ or no change				
RV	↑ or no change				
Septum	Variable				
LVAD					
PI	Variable				
PP	Variable				

AC anticoagulation, AR aortic valve regurgitation, CO cardiac output, CVP central venous pressure, echo echocardiography, Hgb hemoglobin, HTN hypertension, IVC inferior vena cava, LA lactic acid, LV left ventricle, LVAD left ventricular assist device, MAP mean arterial pressure, MVO mixed venous oxygen saturation, NO nitric oxide, PCWP pulmonary capillary wedge pressure, PE pulmonary embolism, PHTN pulmonary hypertension, PI pulsatility index, PP pump power, PTX pneumothorax, RA right atrium, RHF right heart failure, RBCs red blood cells, RV right ventricle, septum intraventricular septum, TR tricupid valve regurgitation

chamber sizes of both the left and right ventricle typically decrease. As with any hypovolemic state, the LVAD flow pulsatility would decrease, reflecting an underfilled LV and, hence, low LV intraventricular pressures. But in contrast to other causes of hypovolemia, bleeding would be expected to cause a decrease in the hemoglobin level, although this might not be the case with brisk bleeding. Chest tube output (from draining the mediastinum and, usually, the pleural cavities) is often the earliest and clearest indication of significant bleeding. Chest tube output rates >100 mL/h could indicate a significant bleed. Interventions for significant bleeding include reversal of platelet dysfunction and coagulopathy (see "Additional Hemostasis Considerations" below), volume resuscitation with red blood cells (leukoreduced to limit allosensitization in consideration of the future potential for cardiac transplantation) to achieve a hemoglobin level of >10 g/dL, and other volume-support therapies (5% albumin is favored) if red blood cells are not immediately available. It is critically important to continually assess the effects of the resuscitation by monitoring clinical parameters, laboratory measurements, filling pressures, echocardiography findings, and LVAD flow parameters, not only to determine the effect on DO_2 but also to avoid over-resuscitation, specifically RV overload. Such RV overload can lead to RHF, a key complication of perioperative bleeding [3, 44, 63]. Right ventricular failure leads to a decrease in DO_2 and is one of the primary causes of poor outcomes in these patients. The surgical team should obviously be apprised of significant bleeding and ultimately may need to take the patient back to the operating room if the bleeding is refractory to coagulopathy correction or is of such volume or duration to suggest the need for surgical intervention.

Other causes of hypovolemia during the postoperative period include over-diuresis and excessive volume removal by dialysis. These conditions are also treated with a volume expander, usually crystalloid, with the caveats delineated above.

Right ventricular failure during the postoperative period is common, occurring in 10–39% of patients and in even up to 50% when the VAD is emergently placed, and is a major driver of poor outcomes for LVAD patients [70]. Chapter 18 specifically deals with preoperative assessment for postoperative RHF risk and risk remediation strategies. However, it should be noted that RHF prediction models are still not highly sensitive or specific [58, 65, 66]. Additionally, therapy for RHF has evolved to the point where there are well established and even more effective treatment protocols involving volume management, device adjustment, medication, and MCS for the right ventricle. In fact, device support for the failing right ventricle is one of the most active areas of MCS research and development. As such, high vigilance to the development of RHF is warranted in the immediate postoperative period. Diagnostic indicators of RHF include a low DO_2, hypotension, low LVAD flow, a low PCWP, and a high CVP. Echocardiography findings consistent with RHF are a dilated inferior vena cava, a leftward-shifted intraventricular septum, a small left ventricle, and an enlarged right ventricle. Echocardiography measures of RV function may show impaired contractility. Additionally, substantial tricuspid valve regurgitation may be seen by Doppler echocardiography. Because the left ventricle is typically underfilled in this circumstance, device flow pulsatility can also be decreased.

Initial therapeutic maneuvers for RV decompensation include the following [3, 5, 44, 58, 63, 65, 66]:

- Promote RV volume unloading (typically if the CVP is >15 mmHg) by using diuresis or dialysis techniques (usually continuous renal replacement therapy) and/or by decreasing the overall circulatory flow and volume delivery to the right ventricle by decreasing the device speed.
- Promote RV afterload unloading by administering pulmonary vasodilators, typically inhaled nitric oxide and epoprostenol, as well as sildenafil. There are multiple new drugs available for treating pulmonary hypertension, including drugs in the prostacyclin, endothelin antagonist, phosphodiesterase inhibitor, and guanylate cyclase

stimulator classes. These have not yet been systematically studied in this population.
- Provide RV inotropic support with milrinone (which is also capable of vasodilating the pulmonary vasculature) and catecholamines, including epinephrine, dobutamine, and dopamine.
- If volume and medical treatments for RHF are unsuccessful, MCS of the right ventricle maybe be used for specific indications. The evolving selection of MCS devices for this purpose and the specific indications for use are discussed in Chap. 18 "Management of RV Failure After LVAD Implantation."

Massive or submassive pulmonary embolism can mimic RHF in LVAD recipients. Fortunately, it is an uncommon occurrence in these patients. Signs indicative of a pulmonary embolism include an echocardiogram showing a right-sided thrombus and failure of typical maneuvers to improve RHF. Pulmonary embolisms are diagnosed by finding a thrombus in the pulmonary arteries using imaging techniques, usually computerized tomography (CT) angiography but occasionally TEE or even TTE. The base therapy for these patients is anticoagulation, of course, but for patients who do not respond to standard anticoagulation protocols or who need emergent clearance of a hemodynamically threatening thrombus, we use catheter-based interventions to administer local lytic drug therapy, as well as thrombus fragmentation and suction removal techniques. We do not use systemic lytic therapy for LVAD recipients because of the high risk of causing major bleeding in the immediate postimplantation period. Rarely, patients may need to undergo surgical thrombectomy.

As previously mentioned, cardiac tamponade is not an uncommon postoperative complication that results from bleeding after LVAD implantation. Tamponade physiology causes a decrease in DO_2 and blood pressure and, if not addressed, can lead to cardiovascular collapse. It is primarily diagnosed by using echocardiography to show collapse of the right atrium and ventricle, often cyclically with the positive pressure ventilator cycle. Echocardiography also typically shows a distended inferior vena cava, and the CVP is elevated. Often, the PCWP is initially low, and the LV size is decreased due to ongoing LVAD unloading of a poorly filled left ventricle. However, elevations in PCWP and pulmonary artery diastolic pressure are usually late findings that are ominous for circulatory collapse [5, 69]. Pulsatility of the LVAD is also decreased in patients with tamponade due to the decreased LV filling. Treatment of cardiac tamponade almost always involves a return to the operating room to drain the pericardium or the mediastinal hematoma causing it, as well as to look for bleeding sites in need of surgical treatment. Occasionally, the tamponade may be relieved by percutaneous drainage.

Tension pneumothorax (PTX) physiology is very similar to that of cardiac tamponade and has similar effects on the hemodynamic profile of LVAD recipients. A key diagnostic indicator for PTX is an abrupt elevation of mechanical ventilator pressures. Clinical signs that may also suggest the presence of PTX include diminished hemithorax breath sounds and tracheal deviation. Although radiology remains the usual means for diagnosing PTX, thoracic ultrasound has a similar sensitivity and specificity, and point-of-care ultrasound testing is typically faster. Signs to look for include "lung pointing" and the "stratospheric sign" and the absence of the "sliding lung" sign and "B-lines." The treatment for PTX is immediate tube thoracostomy [71].

Vasodilation during the immediate postoperative period can result in poor DO_2 due to decreased filling volumes. Vasodilation can also promote an increase in DO_2 in LVAD recipients by decreasing afterload. Independent of the DO_2 effects, vasodilation can cause poor tissue perfusion by inducing maldistribution of blood flow (distributive shock) to the tissues. In LVAD recipients (as in all other patients), the net result of vasodilation on DO_2 to the tissues depends upon the net balance of these effects. The diagnosis of vasodilation can be suggested by a physical exam showing hypotension, a widened pulse pressure, or warm or overperfused skin, but the diagnosis is usually confirmed by a decreased systemic vascular resistance. The cause of vasodilation during the immediate postoperative

period is almost always cardiac vasoplegia (discussed in detail above). This is typically treated with vasopressors, including vasopressin and the catecholamines norepinephrine and phenylephrine. Rarely, methylene blue and steroids are used for refractory cases. Other causes of vasodilation are systemic inflammatory response syndrome from the operation itself and sepsis. For LVAD recipients who develop sepsis during the immediate postoperative period, the sources of infection are potentially the same as those of other patients who undergo similar procedures, such as those on ventilator support (e.g., pneumonia), those who have undergone device implantation (e.g., line infection and catheter-related urinary tract infection), or those who have undergone surgery in general (e.g., wound infection). De novo device-related infections can occur, but these usually take at least a couple of days to develop to the point of sepsis. However, in our experience, patients who undergo LVAD exchange because of device-related infection often manifest sepsis syndrome during the immediate postoperative period.

An elevated LV afterload (hypertension) can decrease LVAD flow and DO_2, particularly in patients who have received a HW HVAD, which is more sensitive to the differential pressure across the pump [45, 57]. In LVAD recipients, elevation of afterload is usually due to either the inotropes or the vasopressors typically administered postimplantation to provide RV support and prevent postoperative vasoplegia, although it can also result from intrinsic hypertension. The filling pressures and echocardiography profiles of these patients are similar to those of patients with CHF. Left ventricular assist device pulsatility may decrease if the afterload is high enough to substantially decrease the pressure differential between the left ventricle and the proximal aorta. It is important to note that having a high pump speed and flow can cause hypertension. So when the blood pressure and LVAD flow are elevated, one should consider decreasing the speed and flow. Having a mean arterial pressure above 90 has been associated with cerebral vascular accidents (CVAs) in this population [72].

There are many reasons why pump function may decrease, including controller dysfunction (either intrinsic or due to poor electrical connections to the power source or device), obstruction of the inflow or outflow of the pump, thrombosis in the pump rotors, mechanical failure of the pump impeller or bearings, significant arrhythmias, or cardiac arrest. A decrease in pump function will, in turn, decrease pump flow and can markedly decrease DO_2. In patients who experience such events, the hemodynamic profile is similar: the systemic blood pressure is usually, though not always, decreased, but the filling pressures, thermodilution cardiac output, and echocardiographic parameters look like those of patients with CHF. That is to say that the filling pressures increase, cardiac output decreases, and the left ventricle (and usually the right ventricle) dilates. Additionally, the pulsatility usually decreases with the overall drop in flow.

For both the HM2 and HW HVAD, the controller display shows alarms for battery failure, a poor connection to the electrical outlet, or "controller failure." These alarms respectively call for battery replacement, correction of the faulty electrical connection, or controller replacement. If the controller ceases to display data, it could be completely powerless (due to a battery and/or electrical connection failure) or it may not be working properly, in which case it should be replaced with a backup controller, which should always be immediately available. For both devices, the LVAD controller can be connected to a monitor that displays not only the alarms mentioned above but also pump flow, speed, power, and either pulsatility index (HM2) or a flow-time curve (HW HVAD), which serves as a "pulsatility wave." These parameters also have alarm functions that can be set for high or low values. Table 8.5 displays changes in these measures that can be used to help sort out pump-related malfunctions or physiologic derangement.

Obstruction of the LVAD pump inflow can be due to malpositioning of the inflow cannula, allowing anatomic structures of the left ventricle, such as the septum, to block flow. Additionally, intraventricular pathologies, such as ruptured

Table 8.5 LVAD troubleshooting

Monitored parameters		
Speed	Power	Flow
A constant speed should always be maintained by the controller unless there is a drop in power, most commonly from a suction event. Speed will decrease during a suction event. A suction event can be caused by (1) the pump speed being too high, (2) a decrease in preload, or (3) poor inflow cannula positioning	↓ *Power* Inflow/outflow obstruction Suction event Controller malfunction Power connection problem Decrease in preload Increase in afterload ↑ *Power* Thrombus/mechanical impairment of rotor Increase in preload Increase in inotropy Increase in pump speed Decrease in afterload	↓ *Flow* Decrease in preload Increase in afterload Decrease in speed Inflow/outflow obstruction ↑ *Flow* Increase in preload Decrease in afterload Increase in speed Mechanical impediment due to thrombus on rotor (erroneous high)

chordae tendineae, can block flow to the inflow cannula. Obstruction of the inflow cannula can be diagnosed with echocardiography (Table 8.6), CT angiography, or left heart catheterization with left ventriculogram. Obstruction of the graft outflow may be caused by graft kinking or twisting or by thrombosis. Echocardiography can be useful for diagnosing graft outflow obstruction (Table 8.6), but we have found CT angiography to be more helpful. It is more difficult to diagnose an obstruction within the pump itself or mechanical failure of the rotor because our imaging modalities (echocardiography and CT angiography) do not allow us to see inside the metal encased pumps. However, certain echocardiography findings can still be suggestive of these problems, especially when the imaging is done in conjunction with LVAD speed changes (Table 8.6). Specifically, if increasing the LVAD speed does not result in a decrease in LV volume, then there may be an obstruction in the LVAD pump [59]. Occasionally, internal pump obstruction can be diagnosed with the help of a left ventriculogram showing inflow to the pump and no outflow from the pump [73]. Specifics regarding the interventions for pump inflow, outflow, and internal obstructions are beyond the scope of this chapter. These interventions require input from cardiologists and surgeons, as well as an individualized strategy. However, depending upon the specific cause of the obstruction, the basic treatment options are anticoagulation, glycoprotein IIb/IIIa inhibitors, thrombolysis (significantly risky), catheter-based interventions, and surgical interventions (up to and including LVAD replacement) [74, 75]. Of note, the International Society of Heart and Lung Transplantation (ISHLT) has developed a clinical algorithm for treating LVAD thrombosis (as well as for making the diagnosis) [75].

Pump Stop

A complete pump stop is an immediately life-threatening event. An alarm will probably go off on the LVAD controller or monitor, but one may not if the controller is completely dysfunctional or disconnected from a power source. Clinically, a pump stop can be determined by auscultating over the device. If there is no mechanical hum, the device has stopped. As mentioned above, when there is a pump stop, the first assessment/intervention should be to examine the electrical connections of the driveline and power line to the controller. An emergent trial of controller change should be considered. If the connections are intact, a new controller trial has failed, and central cardiac output has ceased to be adequate (i.e., DO_2 and blood pressure are severely decreased or absent), then cardiopulmonary resuscitation (CPR) should be begun.

Table 8.6 Continuous-flow LVAD postimplant complications and device dysfunction detected by echocardiography

Pericardial effusion
With or without cardiac tamponade including RV compression. Tamponade*:* respirophasic flow changes; poor RVOT SV
LV failure secondary to partial LV unloading
(by serial exam comparison) a. 2D/3D: increasing LV size by linear or volume measurements; increased AV opening duration, increased left atrial volume b. Doppler: increased mitral inflow peak E-wave diastolic velocity, increased E/A and E/e′ ratio, decreased deceleration time of mitral E velocity, worsening functional MR, and elevated pulmonary artery systolic pressure
RV failure
a. 2D: increased RV size, decreased RV systolic function, high RAP (dilated IVC/leftward atrial septal shift), leftward deviation of ventricular septum b. Doppler: increased TR severity, reduced RVOT SV, reduced LVAD inflow cannula and/or outflow graft velocities (i.e., <0.5 m/s with severe failure); inflow cannula high velocities if associated with a suction event. Note: a "too-high" LVAD pump speed may contribute to RV failure by increasing TR (septal shift) and/or by increasing RV preload
Inadequate LV filling or excessive LV unloading
Small LV dimensions (typically <3 cm and/or marked deviation of interventricular septum toward LV). Note: May be due to RV failure and/or pump speed too high for loading conditions
LVAD suction with induced ventricular ectopy
Underfilled LV and mechanical impact of inflow cannula with LV endocardium, typically septum, resolves with speed turndown
LVAD-related continuous aortic insufficiency
Clinically significant—at least moderate and possibly severe—characterized by an AR proximal jet-to-LVOT height ratio > 46% or AR vena contracta ≥3 mm; increased LV size and relatively decreased RVOT SV despite normal/increased inflow cannula and/or outflow graft flows
LVAD-related mitral regurgitation
a. Primary: inflow cannula interference with mitral apparatus b. Secondary: MR functional, related to partial LV unloading/persistent heart failure Note: Elements of both *a* and *b* may be present
Intracardiac thrombus
Including right and left atrial, LV apical, and aortic root thrombus
Inflow cannula abnormality
a. 2D/3D: small or crowded inflow zone with or without evidence of localized obstructive muscle trabeculation, adjacent MV apparatus or thrombus; malpositioned inflow cannula b. High-velocity color or spectral Doppler at inflow orifice. Results from malposition, suction event/other inflow obstruction: aliased color-flow Doppler, CW Doppler velocity > 1.5 m/s c. Low-velocity inflow (markedly reduced peak systolic and nadir diastolic velocities) may indicate internal inflow cannula thrombosis or more distal obstruction within the system. Doppler flow velocity profile may appear relatively "continuous" (decreased phasic/pulsatile pattern)
Outflow graft abnormality
Typically due to obstruction/pump cessation a. 2D/3D imaging: visible kink or thrombus (infrequently seen) b. Doppler: peak outflow graft velocity ≥ 2 m/s[a] if near obstruction site; however, diminished or absent spectral Doppler signal if sample volume is remote from obstruction location, combined with lack of RVOT SV change and/or expected LV-dimension change with pump speed changes
Hypertensive emergency
New reduced/minimal AV opening relative to baseline exam at normal BP, especially if associated with new/worsened LV dilatation and worsening MR. Note: hypertension may follow an increase in pump speed
Pump malfunction/pump arrest:
a. Reduced inflow cannula or outflow graft flow velocities on color and spectral Doppler or, with pump arrest, shows diastolic flow reversal. b. Signs of worsening HF: including dilated LV, worsening MR, worsened TR, and/or increased TR velocity; attenuated speed change responses: decrease or absence of expected changes in LV linear dimension, AV opening duration, and RVOT SV with increased or decreased pump speeds; for HVAD, loss of inflow cannula Doppler artifact

2D, two-dimensional; 3D, three-dimensional; A, mitral valve late peak diastolic velocity; AR, aortic regurgitation; AV, aortic valve; BP, blood pressure; CW, continuous wave; E, mitral valve early peak diastolic velocity; e′, mitral annular velocity; HVAD, HeartWare ventricular assist device; IVC, inferior vena cava; LV, left ventricular; LVAD, left ventricular assist device; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MV, mitral valve; RAP, right atrial pressure; RV, right ventricular; RVOT, right ventricular outflow tract; SV, stroke volume; TR, tricuspid regurgitation

[a]Note: based on observational data. The "normal" outflow graft peak velocities are not well defined. Because the HVAD outflow graft diameter is smaller than that of the HM II device (see discussion in text). Therefore, the normal Doppler-derived HVAD outflow velocities may be somewhat higher on average than those observed for the HM II LVAD. Used with permission from Stainback et al. [59]

Cardiac arrest

There is debate as to whether CPR, administered by compressing the chest, is safe and effective in patients with an LVAD. If the device is not obstructed, patients may benefit from CPR because it may promote flow through the device. Even if the device is obstructed, CPR may promote flow through the aortic valve, unless, of course, the valve has been sewn closed. Although there would seem to be a risk of cannulae dislodgment and damage to the LVAD outflow conduit during CPR, a recent retrospective analysis of LVAD patients who received chest compressions for cardiac arrest did not support the theory that LVADs would be harmed by conventional resuscitation algorithms [76]. There have been cases published about alternative means of external CPR, like abdominal-only compressions. However, no studies have compared these alternative means of external CPR to conventional CPR. Further research is required to address both the safety and efficacy of chest compressions in this population.

Arrhythmias

Arrhythmias are common in the postoperative period, especially on day 1, occurring in 30–60% of patients [49, 51, 77–81]. The common arrhythmias are atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation. Atrial fibrillation and flutter can affect device output, predominantly by affecting RV filling and, consequently, LV preload, especially in patients with RHF. Atrial arrhythmias also increase the risk of thromboembolic events in this population [82]. The specific effect of atrial fibrillation or loss of sinus rhythm on RV function has not been well studied in this population. Many patients who undergo LVAD implantation have a history of atrial tachycardias. The causes of postoperative atrial fibrillation/flutter in LVAD recipients are the same as those for patients without a VAD: elevated atrial pressure from inadequate LV unloading or RHF, electrolyte disturbance (particularly potassium, magnesium, and acid-base disturbance), hypoxemia, myocardial ischemia, and drugs (particularly catecholamines). We manage atrial fibrillation by addressing the potential underlying causes and by using protocols provided in the guidelines recently published by multiple cardiac societies [83]. However, the aggressiveness of therapy is largely determined by the effects on device output and the strength of evidence suggesting that it is promoting RHF. The first pharmacologic agents used to control heart rate (target rate, 80–100 beats per minute) are beta blockers (typically esmolol and metoprolol). Calcium channel blockers are avoided because of their potential negative inotropic effects. In fact, careful monitoring for negative inotropic effects is warranted even when using beta blockers. In our practice, the typical second-line agent used to control heart rate is amiodarone. Rapid atrial arrhythmias that result in shock or acute RHF are treated with cardioversion. Amiodarone is also usually our first-line drug for pharmacologic cardioversion of atrial fibrillation or for keeping a patient in sinus rhythm once electrically converted. Atrioventricular node ablation and other ablation techniques may be needed for refractory arrhythmias [82].

Preoperative predictors of postoperative ventricular arrhythmias for patients undergoing LVAD implantation are a history of such arrhythmias, nonischemic cardiomyopathy, and increased age [78]. Interestingly, the preoperative INTERMACS profile has not been found to be predictive of postoperative ventricular arrhythmias. A recent multi-institutional study identified the following specific causes of postoperative ventricular arrhythmias in LVAD patients and their relative frequencies: inotropic agents (43%), suction events (whereby the septum is pulled up against the inflow cannula) (10%), electrolyte abnormalities (4%), ischemia (1%), and no specific cause (42%) [78]. Our experience has shown that an acute decrease in blood volume (usually due to bleeding, inadequate unloading of the left ventricle, or RHF) and device malpositioning can also precipitate ventricular arrhythmias. However, for a large percentage of patients, a specific cause is not readily identifiable. Notably, and in regards to this, there is evidence that LVAD implants can be arrhythmogenic themselves by directly creating

new areas of myocardial scarring around the inflow cannula insertion site and by altering myocardial ion channels. Conversely, LVADs can also decrease arrhythmogenicity (via LV unloading) in some patients [79].

Ventricular fibrillation is an immediate threat to life in patients without an LVAD. However, patients with an LVAD will often tolerate this rhythm acutely since device output and systemic DO_2, for the most part, do not depend upon LV contraction. If the LVAD receives adequate preload from a heart in fibrillation, essentially acting as a conduit for blood flow, it can deliver adequate output. However, the fibrillation may markedly decrease RV output (especially in patients with RHF) and, consequently, LV preload, which can lead to shock. Regardless of the immediate effects, ventricular fibrillation and ventricular tachycardia can ultimately result in RHF, although the exact mechanism for this is not clear and is likely multifactorial [78, 79]. Our approach to treating ventricular fibrillation and ventricular tachycardia includes an assessment for remedial causes. But, as with atrial fibrillation treatment, the aggressiveness of treatment for ventricular fibrillation and tachycardia depends on the effect of the rhythm on LVAD output and RV function. For acute, severe effects, we perform emergent external cardioversion. When ventricular arrhythmias are not emergently threatening, we use beta blockers and amiodarone as our primary pharmacologic interventions. Second-line agents include mexiletine, sotalol, and lidocaine. Ventricular arrhythmias refractory to treatment should prompt concern of possible device malpositioning and should be assessed with echocardiography and, perhaps, CT imaging. Electrophysiologic ablation may be required for ventricular arrhythmias not corrected with pharmacology or device repositioning. One important point of consensus to emerge from the literature recently is that, although implantable cardioverter defibrillators (ICDs) implanted preoperatively may ultimately be beneficial for select LVAD recipients, it is best to turn them off during the perioperative period. Those implanted preoperatively may unnecessarily fire quite frequently during the dynamic immediate postoperative period. Such frequent firing can lead to RHF [78, 79]. The ICD may eventually be turned back on, but reconsideration of the shock threshold is recommended. Cardiac resynchronization therapy (CRT) has been shown to improve outcomes in select advanced heart failure patients. At this time, few studies have assessed the effects of CRT on LVAD implantation outcomes. However, one recent study suggests that CRT, in situ, at the time of LVAD implantation improves ventricular arrhythmias and decreases ICD shocks in these patients [81].

Troubleshooting LVAD Malfunction by Using Echocardiography

Table 8.6, from the recently published guidelines on the echocardiographic assessment of LVADs, shows the problems associated with LVAD function and heart-LVAD interactions that can be found with echocardiography [59].

Bleeding and Hemostasis Considerations

Management of perioperative hemotherapy in patients requiring LVAD support is challenging for several reasons, including preoperative organ (hepatic and/or renal) dysfunction, the complex nature of the operative procedure, preoperative antithrombotic exposure, and postoperative anticoagulation requirement in a setting of high bleeding risk [84, 85]. Registry data show that the majority of LVAD patients require transfusion support, often characterized as large-volume transfusions [86, 87].

Preoperative Management

As a component of the preoperative evaluation, patients scheduled for LVAD implantation should be screened for factors associated with increased bleeding risk. A careful assessment of medical history should include previous spontaneous bleeding episodes, response to previous surgical

challenges, family history, and exposure to antithrombotic drugs. It is important to sort routine patients from those requiring in-depth input from a hematology consultant. Antiplatelet therapy with aspirin is routine for patients with ischemic heart disease and is typically maintained due to the associated benefits and the relatively low additional risk of perioperative bleeding [88]. In all but urgent cases, when the patient is on more potent antiplatelet agents (e.g., P2Y12 ADP receptor inhibitors), those agents should be withheld for the interval of the inhibitor effects (at least 5 days in the case of P2Y12 inhibitors), or the patient should undergo an evaluation of platelet function to determine if it is acceptable [89].

In many cases, routine laboratory testing is not recommended as a part of the preoperative assessment when the patient's medical history is not suggestive of a bleeding diathesis [86]. The international normalized ratio (INR) is a test designed primarily to monitor warfarin-based anticoagulation. Warfarin is typically dosed to achieve an INR value of 2–3. The INR has a nonlinear response to clotting factor activity, but it can be used to determine when clotting factor activity reaches the level required for hemostasis, which is approximately 30%. It is important to know the response of the INR to clotting factor activity in each facility due to the variation in response of different reagents: instrument pairs. Although the INR has not been shown to be a general predictor of perioperative bleeding in the preoperative evaluation of broad patient populations, it is used to determine reversal of warfarin effect and to assess the degree of hepatic derangement in patients with hepatic dysfunction [90, 91].

Patients who receive the anticoagulant warfarin before an operation should be treated with vitamin K to reverse the effects. The most effective way to administer vitamin K is intravenously [92]. Slow infusion should be used to avoid the risk of adverse reactions. Correction of the INR commences 6–8 h after intravenous therapy is begun. If there is ample time for correction (i.e., >24 h), oral vitamin K may be used. The half-life of warfarin (40 h) should be considered when reversing its effect. A second dose will be needed in most instances. For emergent correction of the effects of warfarin, treatment with prothrombin complex concentrates is preferred, the dosing for which is weight based and adjusted for INR category [93]. These agents promptly reduce the INR while minimizing the volume challenge associated with plasma-based correction. Plasma-based correction is slower and has been associated with an increased incidence of pulmonary reactions [94].

If a patient needs to undergo preoperative anticoagulation with a heparin analogue, unfractionated heparin is the easiest agent to manage. Given the short half-life of unfractionated heparin (1–2 h), it can be withheld for a short interval before surgery to achieve adequate operative hemostasis. Managing low-molecular-weight heparins (LMWH) is more challenging in the perioperative interval because of the longer half-life of these agents and the potential for impaired renal clearance, which would further prolong the anticoagulant effects of the LMWH. Patients managed with a LMWH should have the agent withheld for at least 12 h before an operation if a prophylactic dose is being used. If a therapeutic dose (1 mg/kg) of LMWH is being used, the dose administered within 12 h of an operation should be 50% of the standard dose to avoid the risk of bleeding [95]. Given the renal clearance mechanisms and possibility of decreased glomerular filtration rate in candidates for VAD implantation, we prefer to use unfractionated heparin in the immediate preoperative period.

Preoperative transfusion to bolster hemostatic potential is not typically used in mild coagulopathic states. Clinical staff should understand the relationships between coagulation parameters and hemostatic factor activity. For example, an INR value of 1.6 may be consistent with adequate procoagulant clotting factor activity (40–50%), depending on the reagent being used. A bleeding patient or a patient with severe congenital or acquired coagulopathy will need to be treated before the operation to prepare for the hemostatic challenge.

Operative Management

The operating room suite should have access to point-of-care or near-site coagulation laboratory testing to facilitate data-driven transfusion therapy. The use of these systems has been associated with reduced blood transfusions and improved patient outcomes [96, 97]. Important measures include prothrombin ratio/INR, fibrinogen, platelet count, and whole blood viscoelastic (VE) test parameters (e.g., Thromboelastograph [TEG®] R, TEG alpha, TEG MA, and TEG EPL). The TEG R value represents the time until initiation of clotting and is analogous to INR and partial thromboplastin time (PTT) data, although the correlation is not high [98]. The TEG alpha value reflects the reaction rate and is attributed to coagulation protein activity and fibrinogen content. The TEG MA value represents the maximum clot strength and is affected by platelet count and fibrinogen. The VE assays can be modified by inhibition of platelet activity. Viscoelastic fibrinogen results highly correlate with routine laboratory (Claus method) fibrinogen results. Estimated percentage lysis reflects fibrinolytic activity and is the only clinically available test of fibrinolysis at this time. We treat all patients undergoing CPB with antifibrinolytic agents. Therefore, we truncate our VE panel because the therapy will not be affected.

Traditional coagulation laboratory measurements and VE results may be used jointly or separately. We use both traditional point-of-care coagulation tests and VE assay measures in our center (algorithm in Fig. 8.2). Although a PTT test is useful for detecting an individual clotting factor deficiency (e.g., factor VIII, factor IX, or factor XI), it is of limited value in the perioperative setting for patients without a congenital factor deficiency. We use the difference in VE-based TEG R data (kaolin versus heparinase cups) to check for heparin effects after the initial anesthesia-managed point-of-care activated clotting time screen used for protamine titration. The thrombin time test may also be used to detect the effects of heparin, but this assay is typically only available in the main coagulation laboratory and, thus, not ideal for rapid decision-making. Point-of-care assays, such as activated clotting time or modified forms of this test, are routinely used in the operating room to assess for heparin effects [99].

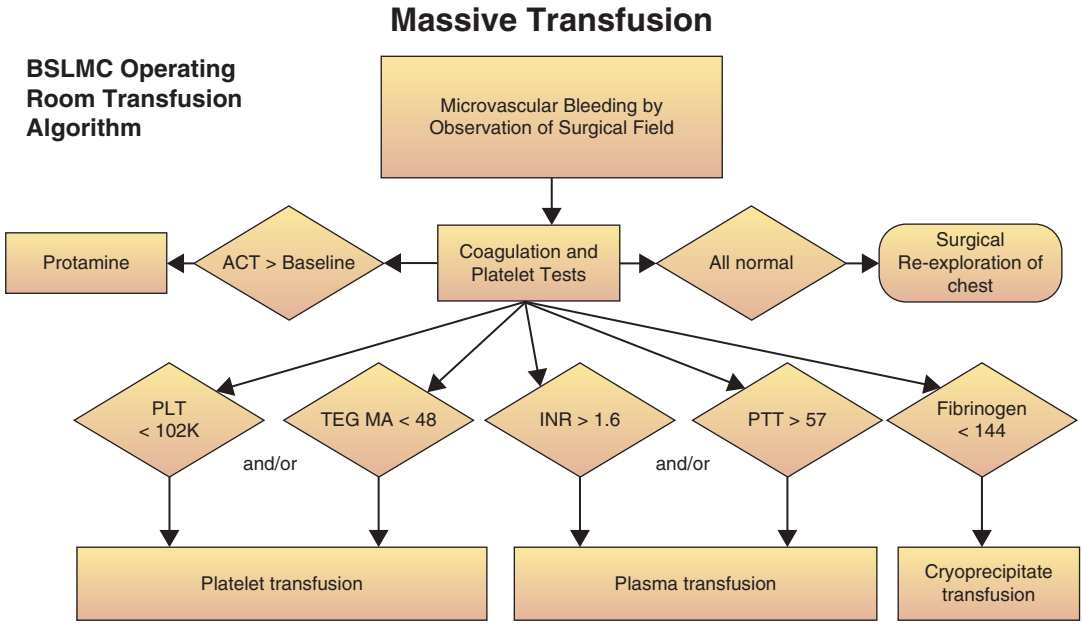

Fig. 8.2 Intraoperative transfusion algorithm. *ACT* activated clotting time, *INR* international normalized ratio, *PLT* platelet, *PTT* partial thromboplastin time, *TEG* Thromboelastograph

Postoperative Management

Patients should be transferred to the recovery room/ICU only when the bleeding rate has been controlled, which should be achieved by following a defined treatment algorithm involving surgical techniques and hemostatic therapy (Fig. 8.3). When the patient is admitted to the ICU, the coagulation system should be assessed using traditional coagulation assays and/or VE testing. Recent studies of cases involving frequent, large-volume bleeding show that careful attention to VE measures and maintaining optimal fibrinogen content is very helpful for optimizing hemostasis [100]. Data on optimal parameters for other measures are needed. Each team should know what the target INR should be for the critical therapeutic set points of 30–50% clotting factor activity. For example, at our center, an INR of 1.6 is considered an acceptable therapeutic target. There are no validated data regarding therapeutic thresholds for platelet count or PTT.

If bleeding is controlled on the first postoperative day, the management team should evaluate whether to initiate anticoagulation on the second postoperative day. We use reduced chest tube output (<0.5 mL × kg body weight) and lack of ongoing demand for red blood cells as gauges to help make this decision. Anticoagulation is typically initiated by administering unfractionated heparin because of its rapid onset. Unfractionated heparin should not be used at high doses to avoid bleeding; we start with a dose around 10–15 U/kg and then gradually increase it until a PTT of 50–60 s is attained. It is important for the team to know the dose response of their particular reagent system to unfractionated heparin. Although it has not been validated for this purpose, the difference in TEG R time between kaolin and heparinase cups can be effective for assessing onset of heparin activity. Anti-Xa activity may also be used to determine the effect of heparin therapy. On postoperative day 3, we typically begin administering aspirin (81 or 325 mg) and warfarin, with an INR goal of 2.5–3.5. In this setting, there is no need to rush to attain the therapeutic INR goal of 2–3, so a large initial loading dose is not recommended.

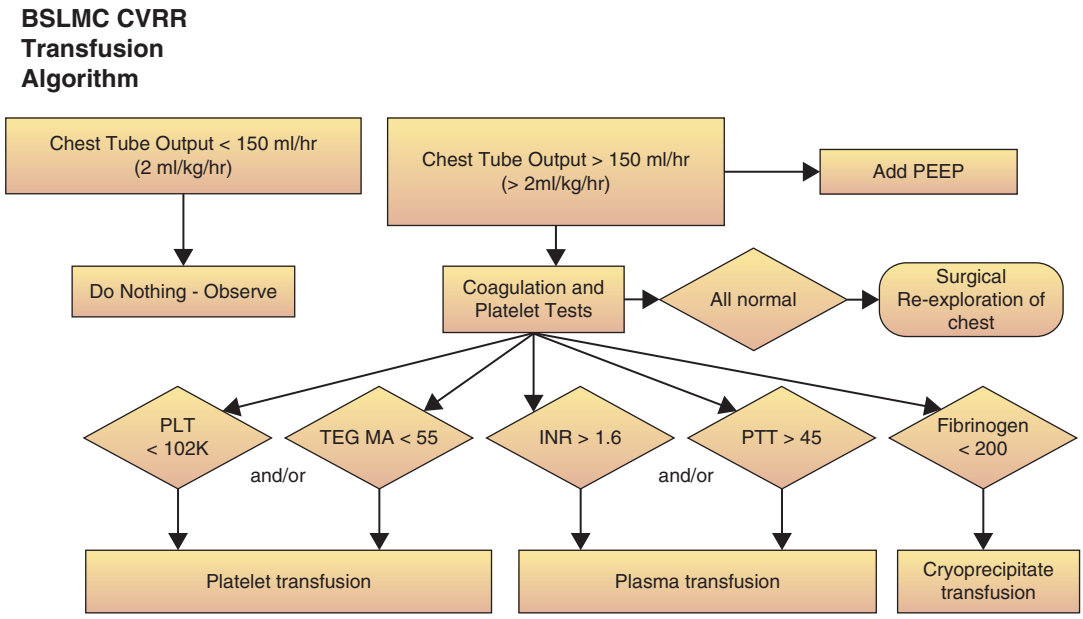

Fig. 8.3 Postoperative transfusion algorithm. *INR* international normalized ratio, *PEEP* positive end-expiratory pressure, *PLT* platelet, *PTT* partial thromboplastin time, *TEG* thromboelastograph

Additional Hemostasis Considerations

Alterations in von Willebrand Factor (VWF)

The high flow states that occur with VAD use have been associated with abnormal VWF multimer patterns and clinical bleeding [101, 102]. If unexpected bleeding occurs in the early postoperative interval, this possibility should be considered, and a laboratory assessment of VWF multimers should be performed. If bleeding occurs but measured coagulation parameters are normal, treatment with cryoprecipitated antihemophilic factor concentrate may be considered. It is helpful to have expert hematology consultants to aid in managing these issues.

Heparin-Induced Thrombocytopenia

Because unfractionated heparin is used for patients undergoing CPB and often for perioperative anticoagulation, staff caring for LVAD patients should be aware of the risk of heparin-induced thrombocytopenia, as well as the limitations of the heparin antibody test and the pitfalls related to inappropriate use this test [103]. In the context of cardiac surgery, especially in the setting of heart failure and the application of devices associated with increased platelet consumption (i.e., during the use of intra-aortic balloon pumps or extracorporeal membrane oxygenation or early after VAD implantation), the use of the heparin antibody test to assess a decrease in platelet count requires considerable caution. The 4T pretest probability score should be taken into account, and testing should be reserved when indicated by this index [104]. The heparin-PF4 ELISA test is a sensitive test for diagnosing heparin-induced thrombocytopenia, but it is nonspecific, frequently showing false positives. Reports have demonstrated a relationship between assay optical density (strength of test result) and true-positive status. Given the serious consequences of heparin-induced thrombocytopenia, specifically the need to alter the CPB approach and perhaps even limit access to transplantation, it would be wise to confirm the immunologic results with the serotonin-release assay (as is the practice in our hospital).

Postoperative Review of Systems

After the immediate post-LVAD implantation assessment to establish adequate gas exchange and hemodynamics, we perform a complete review of the systems at risk for complications. As part of this review, we perform a brief neurology exam to screen for a CVA when the patient wakes from anesthesia. The exam consists of a level of arousal assessment and a gross motor and sensory exam of the extremities. Cerebral vascular accident is one of the leading complications of LVAD implantation [1, 22, 105–107] and, as previously stated, is the second leading cause of death in the early postoperative period. Transient ischemic attacks have also been reported after LVAD implantation at an incidence rate of approximately 12% [3, 49, 51]. Specific risk factors for CVAs in LVAD recipients have been well described and include both hypotension and hypertension (MAP >90), infection, pump dysfunction or thrombosis, both excessive anticoagulation and insufficient anticoagulation [2, 72, 105, 107, 108], and heparin-induced thrombocytopenia. Outcomes of CVAs are worse for intracerebral hemorrhage than for ischemic CVAs and correlate, not surprisingly, with the extent of the neurological deficit [108]. An excellent protocol has been published regarding the management of CVAs in LVAD patients and the outcomes for such [107, 108]. These patients are generally managed by following standard CVA treatment guidelines, with some notable caveats. For intracerebral hemorrhages, the anticoagulation is reversed, and standard guidelines for surgical intervention are followed. For ischemic strokes, thrombolytics are not given in the perioperative period because of the risk of bleeding. However, patients with large-territory ischemic CVAs may benefit from catheter thrombectomy within 8 h of the event. Antiplatelet and anticoagulation therapies are instituted or continued for any CVA (or transient ischemic attack) that involves an infarct area of less than a third of the hemispheric volume. Infarcts involving a larger area are at risk for hemorrhagic conversion, so antiplatelet drugs and, particularly, anticoagulants are stopped. There are rare reports of spinal cord infarcts and peripheral nerve injuries after LVAD implantation,

as well [3]. Delirium is relatively common in these patients, occurring in 10% of them [109]. We manage delirium in the usual manner but have found dexmedetomidine to be a particularly helpful pharmacological therapy in the immediate postoperative period, and we use exercise physiologists and physical therapists to aggressively promote the mobilization of patients soon after extubation as a primary prevention strategy.

Renal failure has been shown to occur in 3–33% of patients after LVAD implantation, depending upon the series [3, 15, 16, 26, 51]. We monitor renal function by using standard indicators: urine output and serum creatinine level. The Foley catheter output is monitored particularly closely during the immediate postoperative period as the earliest marker of renal function. The standard of ≥0.5 mL/kg/h of urine output is used as preliminary evidence of adequate renal function. Creatinine measurement is used in the standard fashion to determine renal failure (50% increase above baseline or 50% decline in glomerular filtration rate). Evidence suggesting renal dysfunction prompts a standard evaluation to categorize the dysfunction as occurring from prerenal, renal (i.e., acute kidney injury), or postrenal problems; this is determined by performing a urinalysis, urine electrolyte tests, and sometimes an ultrasound assessment of the urinary tract. However, at the first sign of renal dysfunction, we also reassess DO_2 because inadequate DO_2 is the principal cause of renal failure in this patient population. If DO_2 is found to be inadequate (Table 8.4), we promptly intervene to correct this. In addition to being at increased risk for acute kidney injury due to poor DO_2, LVAD patients are specifically at risk for emboli to the kidney if adequate anticoagulation is not achieved and for LVAD-associated hemolysis [16]. We are particularly careful to avoid using potentially nephrotoxic drugs in the at-risk LVAD population. For this patient population, we use the standard indications to determine the need for hemodialysis, except that we often resort to using continuous renal replacement therapy quicker than usual for patients with RHF to control volume that is refractory to diuretics (Chap. 20). Continuous venovenous renal replacement therapy is the preferred form of renal replacement therapy during the postoperative period and has proven to be very effective [16, 110–113].

Postoperative liver dysfunction occurs in 2–8% of patients [3, 20, 23–27, 51]. Therefore, we monitor liver function tests during the postoperative period; in particular, we use the transaminases as early markers of liver dysfunction. Although liver dysfunction can be induced in these patients by sepsis or the use of toxic drugs, the primary causes of liver function that we look for are poor DO_2 and RV dysfunction, and any issues found are remediated accordingly and expeditiously. Progressive liver dysfunction can lead to encephalopathy, coagulopathy, and bleeding, as well as vasodilation [20, 24, 25].

Gastrointestinal bleeding is a very common complication of CF-LVAD implantation, occurring in 15–30% of patients [45, 114]. Although gastrointestinal bleeding is rare in the early postoperative period, the risk increases the longer an LVAD is implanted [45, 114]. The reasons for gastrointestinal bleeding are multifactorial and include the development of CF-LVAD-associated bowel angiodysplasia and coagulopathy, which can be caused by anticoagulant use or the loss of VWF due to the sheer stress from continuous flow. As part of our standard postoperative procedures, we provide either proton pump inhibitors or H2 blockers as a prophylaxis against gastritis.

Postoperative ileus is common, occurring in nearly 20% of patients. This risk can be mitigated largely by instituting early feeds (starting on postoperative day 2 or 3) and a bowel regimen [115]. It is helpful to remember that the patients undergoing LVAD implantation are often malnourished at the time of surgery, so it is important to ensure that these patients are well nourished during the postoperative period.

The most concerning hematologic complication of LVAD placement, aside from gastrointestinal bleeding (discussed above), is hemolysis. However, hemolysis is rare during the immediate postimplantation period, occurring in 3–5% of patients. Typically, hemolysis is associated with excessively high device speeds and, particularly, with device thrombosis [45, 116]. It is diagnosed by showing elevated levels of plasma-free hemo-

globin and lactate dehydrogenase [45, 116]. Consequences of hemolysis include anemia, decreased DO_2, elevated pulmonary and systemic vascular resistance, disordered coagulation, renal failure, and systemic inflammatory response syndrome. It is important to note that CPB itself can cause hemolysis, although it is mild and occurs in the immediate postoperative period [117, 118]. Heparin-induced thrombocytopenia syndrome (introduced above) is uncommon in LVAD patients but can be catastrophic by promoting pump thrombosis [119]. When heparin-induced thrombocytopenia is diagnosed or even strongly suspected, we immediately discontinue heparin and begin administering a direct thrombin inhibitor; bivalirudin has served us well for this purpose.

At this time, there are no known clinically significant effects of LVAD placement on the endocrine system [45]. However, hyperglycemia complicates the postoperative course of LVAD recipients, just as it does for patients who have undergone other cardiac surgeries and CPB. We know from many studies conducted over the past 15 years that patients whose glucose is controlled by continuous insulin infusions suffer less infections and have better outcomes [120]. Therefore, we employ standard post-cardiac surgery insulin protocols for these patients.

Prophylactic administration of antibiotics is recommended for 48 h after LVAD implantation, as described above. Surgical wounds and the driveline should be meticulously cared for by cleaning them with chlorhexidine daily and using sterile dressings. Recently, one group demonstrated good outcomes when using silver-impregnated gauze dressings [69]. Additionally, it has been shown that fixing the LVAD driveline in position by using various anchoring devices decreases the incidence of site infections [121]. However, for up to 42% of LVAD patients, the index hospitalization is complicated by infection; these infections are typically non-LVAD related [3, 4, 122–124]. In contrast, infections occurring after the initial hospitalization typically are LVAD related (driveline and pump pocket infections) [4]. The common infections seen during the initial hospitalization period include line-associated bacteremia, pneumonia, urinary tract infection, *Clostridium difficile* bowel infection, and sternal wound infection. Sepsis syndrome occurs in up to about 20% of patients and is associated with a very high mortality rate of approximately 50%. Recommendations to decrease the risk of these infections include early extubation (up to 18% of patients in this population on prolonged mechanical ventilation acquire pneumonia) [51] and removal of early invasive lines and Foley catheters [5]. Emerging data suggesting that the use of proton pump inhibitors is a risk factor for *Clostridium difficile* infection [125] has prompted some to consider avoiding these agents in favor of H2 blockers for gastritis prophylaxis. Other interventions used to decrease the risk of infection include early enteral nutrition and glucose control. We also practice thorough culturing and investigation of potential sources when early signs of infection appear, such as fever or elevated white blood cell count. It is hoped that evolving molecular markers for infection will allow us to identify infections in these patients even earlier. At the first signs of sepsis syndrome in these patients, we immediately institute empiric broad-spectrum antibiotic therapy, as has been a standard recommendation of infectious disease experts who work with these patients. Typically, vancomycin and either a third- or fourth-generation cephalosporin, advanced penicillin combination drug, or carbapenem is used; occasionally, depending upon the risk factors, antifungal therapy will be added [3, 4, 122–124].

Delayed Sternal Closure

The incidence rate of delayed sternal closure (DSC) has been reported to be 3–50% for LVAD patients [126]. Although recent series have shown rates in the lower range of these numbers, delayed sternal closure is much more common in LVAD patients than in the general population of adult cardiac surgery patients and is primarily associated with intraoperative bleeding and RHF severe enough to require RVAD implantation for hemodynamic support.

Risk factors reported for DSC include increased number and severity of preoperative morbidities in general and, more specifically, factors that increase the chance of bleeding and RHF. The risk of bleeding and DSC is increased in patients on IIb/IIIa inhibitors, with a high MELD score or renal failure, or supported by extracorporeal membrane oxygenation immediately before the operation. Our experience suggests that having a history of sternotomy increases the risk, as well. Patients who have DSC when undergoing LVAD implantation have been reported, in most studies, to have a significantly increased risk of mortality [126]. This is presumably due to the patients' higher acuity of illness going into the device implantation procedure and the complications necessitating DSC. However, there is also data suggesting that DSC is an independent risk factor for mortality in the LVAD population [126]. Why this would be is unclear, but it has been suggested that the higher incidence of sepsis in this group may be the prime driver [126].

Our specific approach to DSC) is to correct the coagulopathy and RHF that often precipitates the need for DSC, to keep the patient well sedated (and occasionally paralyzed) to decrease the risk of a movement-related sternal complication, to stringently enforce barrier protection, and to continue aggressive use of prophylactic antibiotics for the duration of time that the chest is open.

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9 Management of Fluid Balance and Perioperative Renal Complications

Whitson B. Etheridge and Sarah A. Shearer

Introduction

Renal disease and heart disease commonly coexist but also interact in a powerful way. Patients with end-stage heart disease (ESHD) have a high incidence of renal dysfunction [1]. In 84% of the patients in whom end-stage renal disease (ESRD) develops, left ventricular (LV) hypertrophy and diastolic heart failure are also present (Fig. 9.1) [2]. The most common cause of morbidity and mortality in ESRD patients is cardiovascular disease. Renal disease coexisting with cardiac disease is frequently due to underlying comorbidities, most commonly diabetes and hypertension. Systemic diseases (e.g., amyloidosis) may cause heart and renal disease or, less commonly, primary renal diseases that, although not the direct cause of heart disease, may worsen heart failure through hypertension and salt and fluid retention as the glomerular filtration rate (GFR) falls.

Chronic and acute heart failure patients frequently have renal dysfunction caused by a complex disease process that is broadly referred to as cardiorenal syndrome (Fig. 9.2). Renal and systemic ischemia and congestive nephropathy and hepatopathy from high central venous pressure (CVP) and low cardiac output cause neurohumoral stimulation with upregulation of the renin-angiotensin-aldosterone system and increased catecholamines, antidiuretic hormone, and inflammatory cytokines (Figs. 9.3, 9.4, and 9.5) [5–8]. Renal function may also be negatively affected by the use of diuretics, angiotensin II receptor blockers or angiotensin II-converting enzyme inhibitors, and intravenous contrast agents [6]. Over time, this leads to a decline in renal function with renal fibrosis [6]. ESHD frequently occurs in older patients and therefore in the presence of low renal reserve (nephronopenia) and chronic metabolic acidosis, both of which may cause renal fibrosis [9].

Preoperative abnormal renal function (i.e., GFR <60 mL/min/1.73 m^2) is associated with an increased incidence of acute kidney injury/acute tubular necrosis (AKI/ATN) and a reduced rate of survival 1 year after left ventricular assist device (LVAD) placement [10]. Other studies have confirmed that adverse outcomes are associated with preoperative renal dysfunction [10, 11]. An INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) risk score of 1 vs. 2 or 3 predicts poor renal outcomes [12]. Studies have shown that postoperative AKI/ATN is associated with the following preoperative

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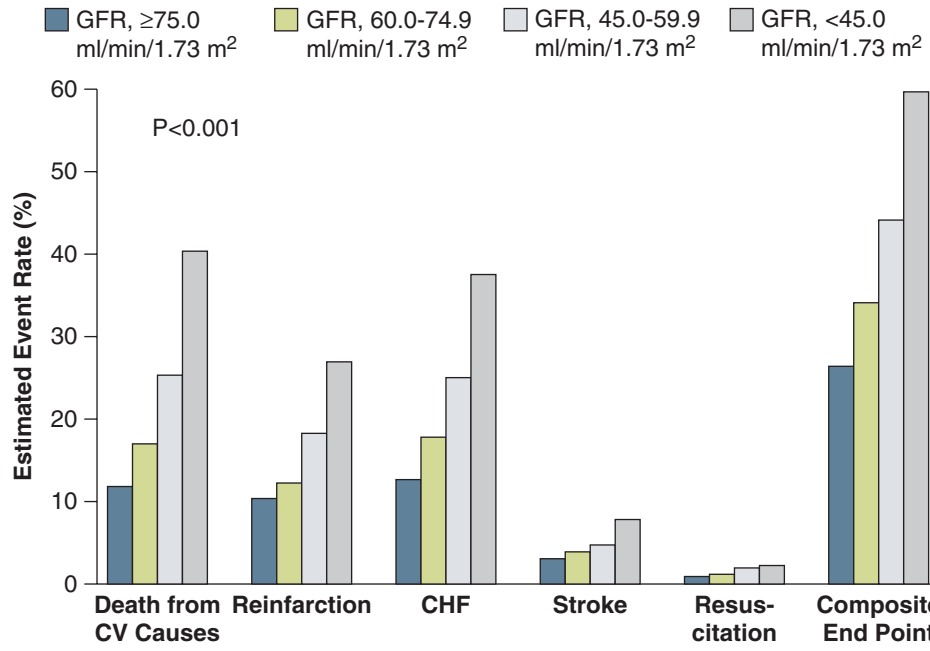

Fig. 9.1 Kaplan-Meier estimates of the rates of death at 3 years from cardiovascular (CV) causes, re-infarction, congestive heart failure (CHF), stroke, resuscitation after cardiac arrest, and the composite end point, according to the estimated glomerular filtration rate (GFR) at baseline. Modified from the original version [2, 3]

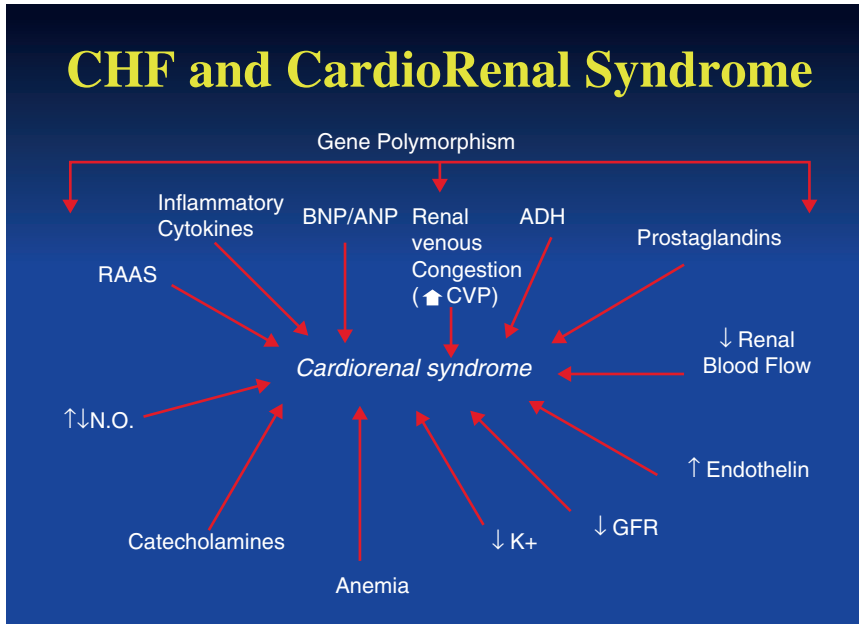

Fig. 9.2 Congestive heart failure (CHF) and cardiorenal syndrome

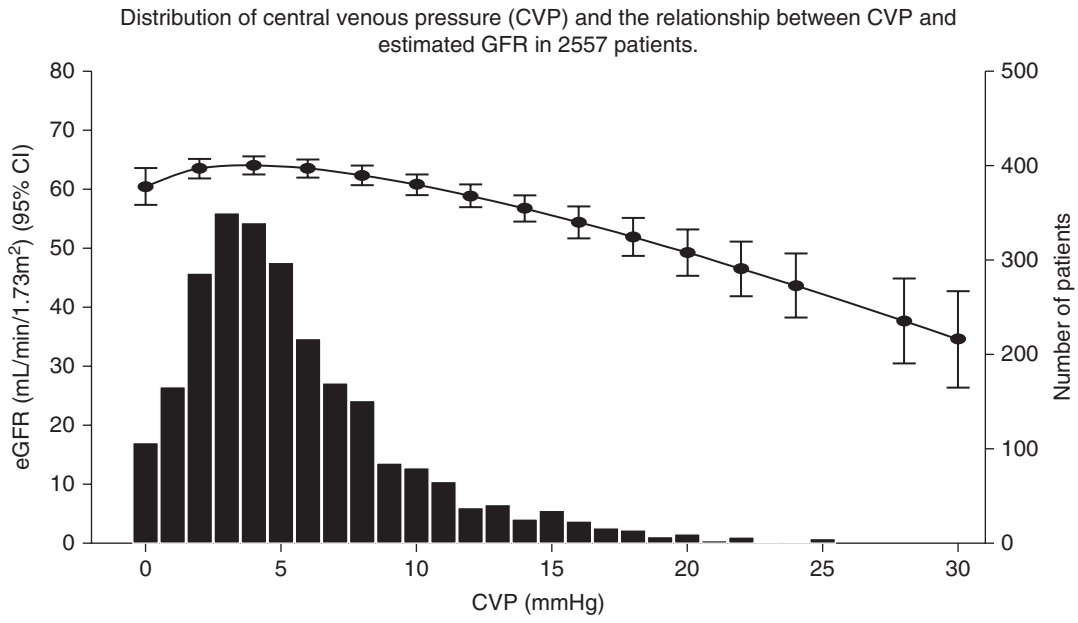

Fig. 9.3 Effect of increasing central venous pressure (CVP) on glomerular filtration rate (GFR) in rats with constant blood pressure. The curvilinear model had the following individual polynomial components for the relationship between CVP and estimated GFR (eGFR): first order, $Y = -25.8 \cdot (\text{CVP} + 1)/10$ (Wald 28.2, $p < 0.0001$), and second order, $Y = 35.7 \cdot ([\text{CVP} + 1]/10)^{0.5}$ (Wald 17.4, $p < 0.0001$). Modified from the original version [4]

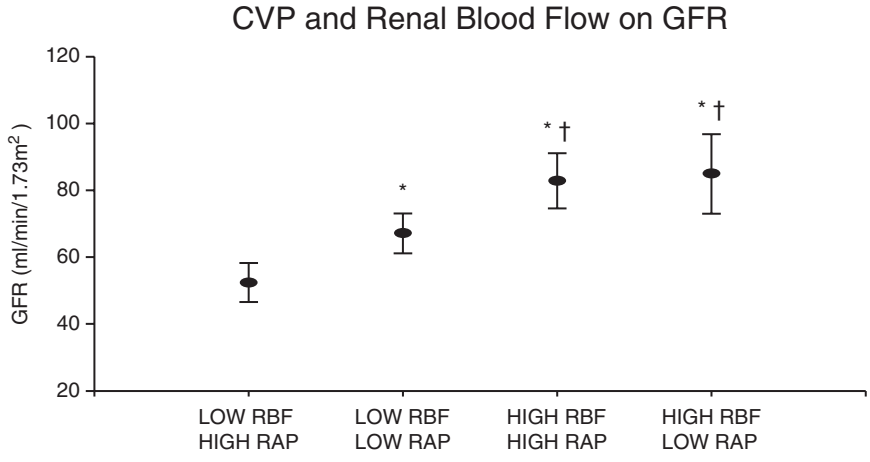

Fig. 9.4 CVP and renal blood flow on GFR. Modified from Damman K et al., Eur J Heart Fail 2007; 9:872–878

Pathophysiology of the relation between venous congestion and reduced glomerular filtration rate (GFR).

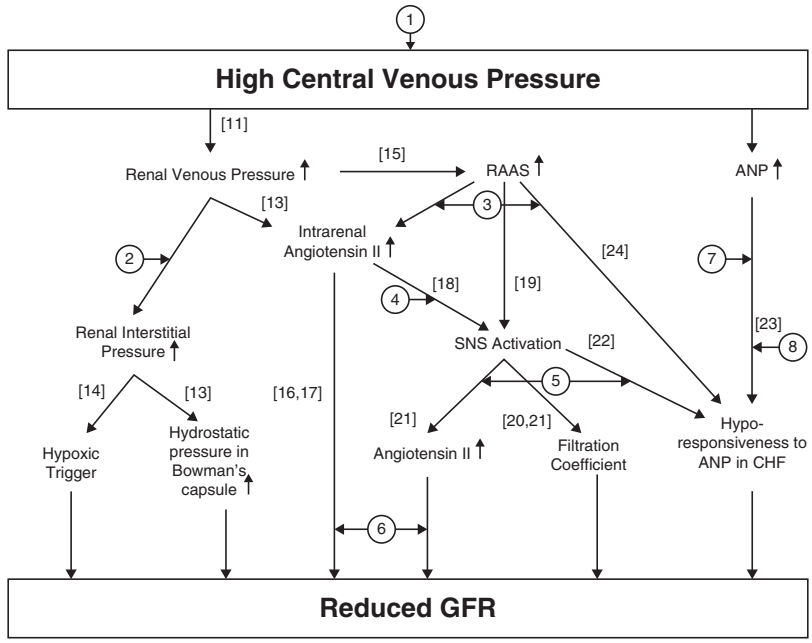

Fig. 9.5 Pathophysiology of the relationship between venous congestion and reduced glomerular filtration rate (GFR). *ANP* atrial natriuretic peptide, *SNS* sympathetic nervous system, *RAAS* renin-angiotensin-aldosterone system. Numbers in circles represent the targets for specific therapies as follows: (*1*) ultrafiltration, diuretics, sodium, and water restriction and arginine vasopressin receptor antagonists. (*2*) Ultrafiltration, diuretics, and sodium and water restriction. (*3*) Angiotensin II-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. (*4*) Statin therapy. (*5*) Beta-blocker therapy. (*6*) Angiotensin II receptor blockers. (*7*) Neutral endopeptidase inhibitors. (*8*) Urodilatin. Modified from the original version [5]

characteristics: angiotensin II-converting enzyme inhibitor or angiotensin II receptor blocker use, renal size <10 cm, older age, small left ventricle, and diastolic dysfunction with high CVP (both likely signs of right heart failure and known association of diastolic dysfunction with chronic kidney disease) (Table 9.1) [13–15]. However, in a review of 100 consecutive continuous-flow LVAD (CF-LVAD) implantations, Borgi and colleagues [14] did not find a statistically significant association between postoperative AKI/ATN and preoperative diabetes mellitus, hypertension, or renal dysfunction (7). The difference in these study findings may be attributed to the later era of the Borgi study, which has been proposed to be a period when patients received implants earlier in their disease process at a higher INTERMACS score. Operative and perioperative risk factors for AKI/ATN have been studied, and longer cardiopulmonary bypass (CPB) time (122 ± 55 vs. 78 ± 17 min), higher intraoperative blood loss and replacement (>1 L), and need for reoperation all increase the risk of postoperative AKI/ATN (Table 9.2) [13, 16–19]. Postoperative AKI/ATN is associated with a high risk of mortality, but death is most likely to occur within the first year after AKI/ATN, as the survival rate after the first

Table 9.1 Preoperative factors associated with postoperative acute kidney injury

1.	Glomerular filtration rate <60 mL/min
2.	INTERMACS score of 1 vs. 2 or 3
3.	Preoperative use of angiotensin II-converting enzyme inhibitors or angiotensin II receptor blockers
4.	Renal size <10 cm
5.	Diastolic dysfunction and high central venous pressure, likely reflective of right heart dysfunction

Table 9.2 Perioperative factors associated with postoperative acute kidney injury

1. Cardiopulmonary bypass time >90 min
2. Blood loss >500–1000 mL
3. Right heart dysfunction
4. Need for return to the operating room

year is not affected by the occurrence of postoperative AKI/ATN [15].

Studies have shown that CF-LVAD placement can often lead to postoperative liver and renal recovery, especially for (but not limited to) patients with mild preoperative renal dysfunction (e.g., creatinine levels between 1.4 and 1.9 mg/dL) [10, 11, 20–30]. Despite an early recovery in GFR (measured by serum creatinine) in patients after CF-LVAD implantation, a late (i.e., greater than 1 year post implantation) decline in GFR (measured by an increase in serum creatinine) has been observed. The reason for this decline is unclear [10, 23, 31–35]. Possible causes include low muscle mass at the time of implantation with a subsequent increase in muscle mass, continued (albeit less intense) neurohumoral and inflammatory cytokine stimulation, and hypertensive damage from the "new physiology" of chronic high diastolic perfusion. Animal and human studies have shown an abnormal inflammatory response in the arterial wall after exposure to a CF-LVAD [36–43]. Notably, at higher pump speeds, low-grade continuous hemolysis occurs, which has been proposed as a cause of chronic hemoglobinuria, reduced availability of nitric oxide, and oxidative stress with peritubular inflammation [16, 18]. In an ovine model, micro-emboli have been seen in the renal microvasculature [17].

Most contemporary pumps are continuous-flow assist devices. Therefore, this chapter will focus on the care of patients with renal dysfunction after placement of a CF-LVAD. Currently, ESRD is an exclusion criterion for destination therapy (DT) LVAD placement, so patients with ESRD have been approved for LVAD placement only if they have been approved for dual-organ transplant or bridge to transplant (BTT). The number of patients in whom ESRD develops after LVAD implantation for DT has grown. We will discuss the successful care of these post-LVAD patients with ESRD by a specialized dialysis clinic and management team.

Other renal-related syndromes in LVAD patients are worthy of attention in this new and relatively unstudied physiology, which is characterized by minimal pulsatile flow with high diastolic and low systolic pressure and low-grade, continuous hemolysis. Postoperative mediastinal and pericardial tamponade is a cause of sudden oliguria. Partial-flow constriction from a clot, pannus over the inflow, or "kinking" of the inflow cannula or the aortic graft that causes acute or subacute massive hemoglobinuria in the presence of reduced cardiac output can cause AKI [43]. Renal or splenic infarcts may develop in patients, accompanied by acute pain syndrome. Hyponatremia often continues after LVAD implantation, and, although not yet studied, correction may lead to improved functional status.

The First 48 h

Performing LVAD surgery generally requires the patient to undergo CPB. As in all cardiovascular surgeries, limiting CPB time to <90 min can help prevent postoperative AKI [13]. Perioperative bleeding is a confounding complication with a progressive increase in the risk of AKI with >500–1000 mL of blood loss and replacement [13]. Right heart dysfunction after LVAD placement is a common risk factor for postoperative AKI because of the reduced cardiac output and high venous pressure [6, 7, 14]. Pulmonary hypertension frequently develops in patients with chronic heart failure; in fact, an LVAD is usually placed as DT or as a "bridge to candidacy" in patients with increased pulmonary vascular resistance (>4 WU) to allow pulmonary pressure to normalize so that transplantation can be considered. Right ventricular failure causes high right-sided pressure and increased CVP. Right heart failure may be affected by the LVAD itself, as discussed in Chap. 18. The septum may be displaced to the left, adversely affecting right ventricular function. This is dependent on the LVAD pump speed and its effect on the anatomy of the

left ventricle. Ideally, to help protect the septum, the pump is adjusted so that the aortic valve opens with each beat and the left ventricle remains mildly dilated. High venous return with increased pump flow may further overload the right ventricle and cause dilation and strain, especially if there is not a concomitant reduction in the pulmonary pressure and cardiac output. The end result may be right ventricular failure and increased central and renal venous pressure. This outcome may be further complicated by tricuspid regurgitation, which is common in chronic heart failure, especially in patients with high preoperative pulmonary artery (PA) pressure. Congestive hepatopathy and nephropathy are also common and may worsen renal function and cause a poor diuretic response (Figs. 9.3, 9.4, and 9.5) [5–8, 14].

Low systemic blood pressure in postoperative LVAD patients compounds right heart failure and high central and renal venous pressures. Causes of low systemic blood pressure include sedation, pain medications, and frequent use of vasodilatory inotropes and pulmonary vasodilators. A continuous-flow pump cannot pump against high pressure, so it is important to keep the systemic pressure high enough to provide adequate renal perfusion, taking the adverse effects of high venous pressure into account. Care should be taken, however, not to increase the systemic pressure high enough to reduce output from the continuous-flow pump [44].

The nephrologist should confer closely with the intensivist, cardiologist, and LVAD surgeon. The best plan for accomplishing this is to perform daily team rounds.

In the immediate postoperative period, we minimize the use of casual fluid (i.e., fluid given as a carrier for drips, medications, and electrolytes) and administer therapeutic fluid according to a weight-based protocol by using a balanced electrolyte solution with some bicarbonate equivalent rather than normal saline. Postoperative volume-related weight gain has been associated with poor outcomes [45], and fluid-restricted protocols in the postoperative period have been associated with either worse [46] or improved [47] outcomes. González-Fajardo and colleagues [48] have shown improved outcomes in patients undergoing abdominal vascular surgery with the use of a fluid-restricted protocol [45]. In addition, at CHI/St. Luke's Texas Heart Institute, we are initiating a trial of a fluid-sparing regimen in CF-LVAD patients. The goal PA pressure is <45 mmHg, and the goal CVP is initially <12 mmHg and is reduced to <10 mmHg once the patient is hemodynamically stable. Milrinone is often required to support right ventricular function and to lower PA pressure. In patients with a low GFR, which affects milrinone clearance, drug accumulation may cause low systemic and renal perfusion pressure. For patients with a low GFR (<30–40 mL/min/1.73 m^2) or low urine output (<0.5 mL/kg/h), we prefer to reduce the milrinone dose to <0.25 μg/kg/min, but we confer regularly with the cardiology team (Table 9.3) (Figs. 9.6 and 9.7) [50].

Although diuretics generally are not recommended early because of the risk of venous dilatation, low blood pressure, and reduced LV filling, loop diuretics may be necessary to prevent severe volume overload, especially in patients with right heart dysfunction [51]. Judicious fluid management, however, should be the mainstay of fluid therapy.

In patients with fluid overload, pulmonary congestion, and high right-sided filling pressures, we initiate loop diuretics while minimizing fluid intake. The latter requires coordination with the pharmacy and members of the intensive care unit (ICU) team. A low dose of a loop diuretic (20–40 mg of furosemide or 0.5–1 mg of bumetanide) is given, while the patient's response and blood pressure are monitored. The dose can then be

Table 9.3 Fluid therapy choice in the AKI ICU

Alternatives	
Drug	Hazard/disadvantages
0.9% saline	Acidosis, ?AKI
Lactated Ringer's	Hypotonic, Ca++
Plasmalyte	Gluconate, acetate
Albumin	Cost, ?AKI
HES	AKI, bleeding, pruritus
Gelatin	Anaphylaxis

AKI acute kidney infection

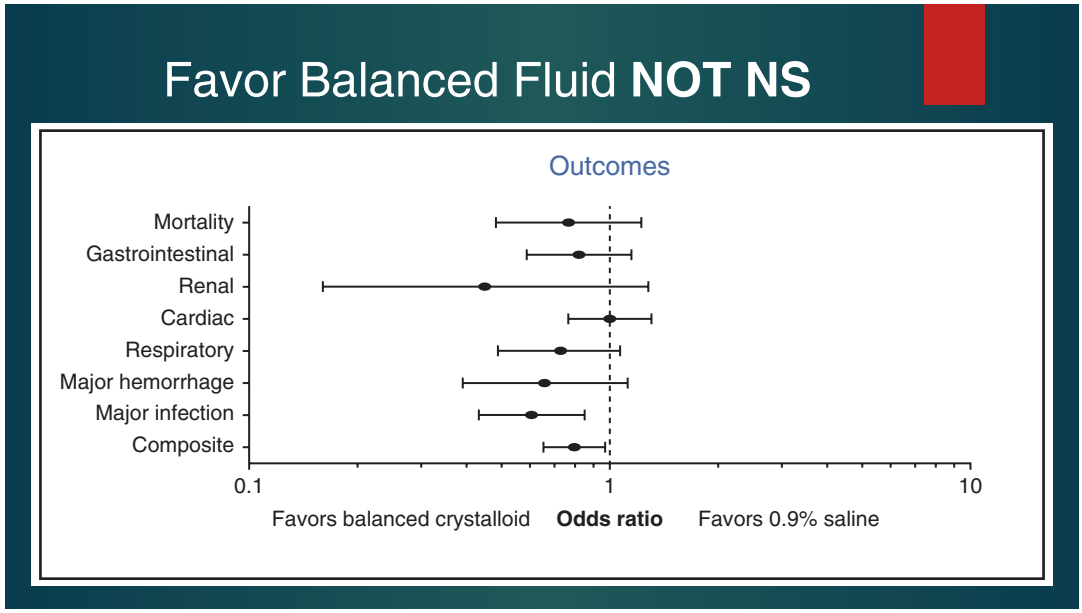

Fig. 9.6 Favor-balanced fluid *not* NS. Modified from Shaw, et al. Ann Surg. 2012 Mar 30

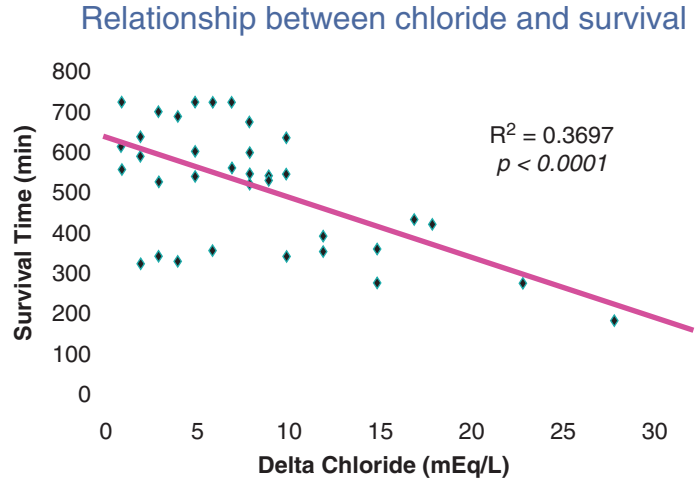

Fig. 9.7 Relationship between change in chloride and survival time. Modified from original [49]

titrated either with higher intermittent doses or with a continuous drip (5–20 mg/h of furosemide or 0.25–1 mg/h of bumetanide). For patients who do not respond, we confer with the team to ensure that no other cause for low renal perfusion pressure can be identified (e.g., excessive sedation, pain medication, vasodilators such as milrinone, or tamponade). A lack of response, again, may indicate a poor right heart function or a need to increase the LV output, and the cardiologist may need to make pump speed adjustments. These adjustments may be made under echocardiographic or PA catheter guidance. The next step that we have found helpful is the addition of a distal tubule blocker (usually chlorothiazide, 250–500 mg administered intravenously). Loop diuretics and distal tubular blockers cause alkalosis and hypokalemia. We use potassium chloride, carbonic anhydrase inhibitors, or amiloride in this situation. Amiloride has a shorter half-life

Table 9.4 Ideal hemodynamics for renal function

1. Central venous pressure <10 mmHg
2. Pulmonary pressure <45 mmHg
3. "Mean arterial pressure" 70–80 mmHg
4. Adequate cardiac output to ensure stable and normal end-organ function; patient should be awake, alert, and neurologically stable (confer with cardiology)

Table 9.5 Acute oliguria after continuous-flow LVAD implantation

1. Lower urinary tract obstruction
2. Severe right heart dysfunction with decreased cardiac output
3. Tamponade due to mediastinal bleeding
4. Bleeding (look for hemothorax)
5. Pump malfunction, inflow or outflow obstruction (rare in the postoperative period)
6. Sepsis- or drug-induced hypotension (consider milrinone)

and a more immediate onset than mineralocorticoid inhibitors and will ameliorate alkalosis and hypokalemia as well.

From a renal perspective, ideal postoperative values include a CVP of <10 mmHg, PA pressure of <45 mmHg with the LVAD adjusted so that the valve is opening, and a mean systemic pressure of 70–80 mmHg, as well as an even fluid balance (Table 9.4).

A sudden reduction in urine output should trigger suspicion of bleeding, especially bleeding into the mediastinum with functional tamponade or into the pleural space with a sudden reduction in cardiac output or mean pressure. Tamponade will usually be associated with increased central pressures, but this is occasionally subtle and may cause low urine output, even in the setting of a minimal change in PA pressure and CVP. Right heart dysfunction is always a consideration; thus, we further emphasize the importance of conferring with the LVAD team (Table 9.5). Often, an adjustment of inotropic drugs or pump speed is successful. However, the patient may require reoperation for bleeding and pericardial decompression or placement of a right ventricular support device, but we have a standard action plan (Table 9.6).

Table 9.6 Acute oliguria after continuous-flow LVAD implantation: action plan

1. Ensure that the bladder is decompressed
2. Look for a sudden decrease in hemoglobin levels
3. Confer with the ICU team to adjust pump or drips
4. Perform chest radiography: computed tomography or echocardiography
5. Check urine indices, if appropriate
6. Look for nephrotoxic drugs

Acute Oliguria Post Continuous-Flow LVAD

1. Lower urinary tract obstruction
2. Severe RH dysfunction with decrease in cardiac output
3. Tamponade/due to mediastinal bleeding
4. Bleeding/look for hemothorax
5. Pump malfunction/inflow or outflow obstruction—rare in post-op period
6. Sepsis or drug-induced hypotension—consider milrinone

If the above-described measures do not improve the patient's condition, intervention with renal replacement is necessary. For patients who remain on the ventilator and need fluid removal, we prefer to use continuous renal replacement therapy (CRRT), which allows more continuous ultrafiltration (UF) adjustment with excellent clearance. At our institution, we often keep the patient on CRRT in the operating room to control fluid volume and electrolytes. Our ICU nurse, who is familiar with the patient, manages CRRT in the operating room. Adjustments are made by the anesthesia team, but the nephrologist is always available.

We have found that the blood flow rate does not affect blood pressure or hemodynamic stability, so we recommend adjusting this rate as close to 300 mL/min as possible to prevent system thrombosis. The clearance, which is controlled by the dialysate flow and the dialysate content, is based on the concentrations of blood urea nitrogen, creatinine, and potassium, as well as the acid-base status, just as in the standard ICU patient. However, we prefer a dialysate and UF fluid flow of at least 35 mL/kg/h (Fig. 9.8).

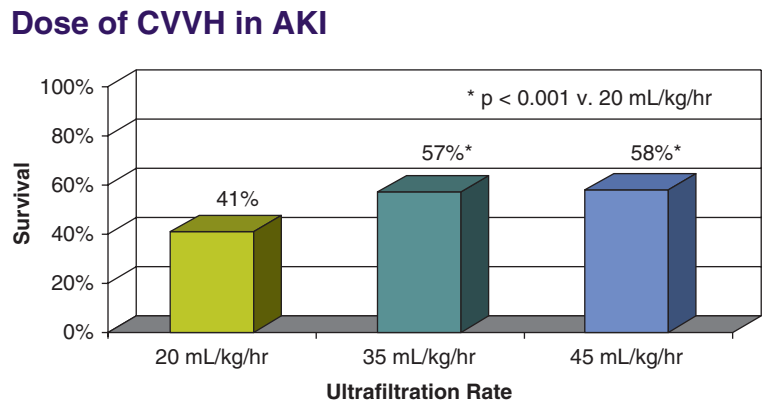

Fig. 9.8 Dose of CVVH in AKI. Modified from [52]

Table 9.7 Benefits of nocturnal prolonged intermittent renal replacement therapy

Early mobilization during the day when PT/OT staff are available
Radiological or surgical procedures can be performed during the day
Less anxiety for patients

Potassium replacement should be given by an enteral route if the patient has a feeding tube and the gastrointestinal tract is functional. Using this route reduces the amount of fluid that needs to be removed. Venous access is obtained through a standard percutaneous line, unless the patient is on extracorporeal membrane oxygenation (ECMO), in which case the arterial and venous lines can be placed in line with the ECMO circuit. The nephrologist should monitor the patient closely because UF and dialysate needs can change frequently. The cardiologist and the intensivist should be allowed to alter the UF rate on a short-term basis, but we recommend that the nephrologist see the patient at least twice per day and closely coordinate care with the other members of the ICU team. Once the patient is stable (and especially if the patient is off mechanical ventilation), we recommend initiating periodic intermittent renal replacement, shift dialysis, sustained low-efficiency dialysis (SLEDD), or standard hemodialysis (SHD) (Table 9.7).

Continuous-Flow Physiology for the Nephrologist and Dialysis Nurse

In a CF-LVAD patient, blood pressure does not have the same meaning as it does in a patient without an LVAD. Although we typically monitor and record a "mean pressure" or, in some patients, an actual systolic pressure, we do so with the understanding that there is not an actual mean blood pressure. Because the flow is continuous, there is no true diastole. The physiologic measures we are interested in for CF-LVAD patients are the degree of filling of the left ventricle and the systemic flow. Similar to the non-LVAD patient, less blood is available for systemic perfusion as the volume in the left ventricle decreases. The Doppler and the audible or palpable pulse are monitored to detect a change in the flow with a ventricular contraction. In the case of the palpable or audible pulse, there is enough blood in the ventricle and a strong enough contraction to open the valve (note that the palpable pulse and the Korotkoff sounds are from the closure of the aortic valve). When the valve opens, blood flows through the pump and also from the ventricle through the aortic valve (parallel flow). When the contraction is very weak or the ventricle is less full—which can occur during UF—the valve may remain closed, but a Doppler pulse can be detected because the ventricle continues to contract and increase input (albeit less) to the pump with each beat. Only two values

on the LVAD monitor are actually measured and displayed on the pump: the speed in revolutions per minute (RPMs) and the power in watts. Power is increased by the amount of flow across the pump or by an increase in pump speed and is decreased by a decline in the flow across the pump or a decline in speed. The flow is derived from a formula that is based on the power (because the power is dependent on flow) in both the HeartMate II (HMII) and the HeartWare ventricular assist device (HVAD). The HMII also displays the pulsatility index (PI), a value that can be helpful to the dialysis team.

A variation in power can be caused by an increase or decrease in the speed set by the cardiology team, a change in the contractile force of the ventricle, a change in the systemic vascular resistance (which can increase or decrease the afterload), or a change in the fluid volume delivered to the pump through the left ventricle. An increase in power or flow will occur rhythmically with a ventricular contraction (whether the aortic valve opens or not), when a fluid bolus is given or when the patient is overloaded with fluid. In the HMII, the variation in power with each cardiac cycle is measured, and a larger power change is reflected by a higher PI. During the UF process and as the ventricle is emptied, we can anticipate that less blood will be available with each beat. Less augmentation of the power during ventricular systole vs. diastole may result in lower power overall, a lower power variation from beat to beat, and a lower PI for the HMII, and just lower power for the HVAD.

SLEDD, Shift Dialysis, and SHD in the LVAD Patient

During the dialysis process, the primary concerns of the nephrologist and the dialysis nurse are the changes in LV filling and systemic flow reflected in the "pressure." The pump speed is set by the cardiology or surgical team. Dialysis nurses add or increase inotropes or adjust vasopressors only with a direct order from a physician on the care team. A decrease in power generally signifies reduced flow across the pump; if the power falls below a set point, then a "low-flow" alarm activates. In extreme cases, the patient can have what is termed a "suction event" that can cause ventricular tachycardia. The current hypothesis is that this occurs because the ventricle is empty and the inlet cannula touches the ventricular wall.

The nurse can sometimes palpate or auscultate a pulse (as noted above) if the valve is opening, or there may be an arterial line to record a systolic pressure. More often, the arterial line has been removed, and the nurse will need another way to detect a change in the left ventricle filling (i.e., blood pressure). This can be done by using a standard pressure cuff, generally placed on the arm in the usual fashion, to detect the first appearance of an audible or palpable pulse or by detecting a Doppler signal, if the valve is not opening. To monitor the patient during dialysis, the power and—indirectly—the flow and PI (in the HMII) are watched closely, along with the blood pressure. Small reductions in power, flow, and PI (in the HMII) are expected during UF. We generally accept a 5–10% reduction in power or PI as normal, but this variation is dependent on the patient and the clinical situation. The nephrologist and the cardiologist will need to confer on these limits and discuss parameters with the dialysis nurse. After the patient has achieved a physiologic dry weight, patients generally remain stable on renal replacement therapy. We usually set a "mean pressure" limit of 60–70 mmHg for patients on SHD, shift dialysis, or SLEDD, but this limit is variable. A low-flow alarm or a suction event with ventricular tachycardia requires urgent attention. The patient should be given 3–5 mL/kg of intravenous fluids, and the nephrologist and the cardiologist should be notified. Ventricular tachycardia is usually tolerated for a short time and generally resolves with volume replacement. Chest compressions should not be performed.

Postoperative patients who are still taking pain medication and may also be on vasodilatory inotropes have low systemic vascular resistance, making UF difficult without a pressor. Using a dialysate with a sodium concentration of 145 meq/L and/or a calcium concentration of 3 meq/L will allow more UF by increasing cardiac output, vasoconstriction and better right ventricular filling, and blood pressure. We use this "modeled" dialysate on a short-term basis until the patient is stable, and then we switch to a more standard dialysate.

Patients may be on pressor agents, but, as noted, these agents are generally adjusted by a physician only unless adjustment is part of the order set.

Two situations warrant special consideration. First, patients with severe aortic insufficiency may have the aortic valve closed at the time of operation and, therefore, will have pulsatility through the pump but no dicrotic notch on the arterial tracing. As a result, these patients will generally not have a palpable pulse or Korotkoff sounds, and the nurse will need to rely on the Doppler pressure reading. Second, some patients will need biventricular support. As with one pump, the speed of both pumps will be set to optimize the hemodynamics of the patient. Overpumping of the right side can cause pulmonary congestion or a perfusion injury of the lungs. Once the patient is stable, the guidelines for monitoring the patient are essentially the same as those previously described for patients with an LVAD only.

Most patients are already anticoagulated; therefore, we do not add an anticoagulant. This aspect of care is managed by the cardiology team.

In summary, the dialysis nurse should monitor the degree of LV filling by using the tools available. This includes monitoring the pressure with the standard cuff, palpation, or auscultation, the Doppler pulse, and, if discussed with the nephrologist or team, the power, flow, or PI (in the HMII). Reduced power, flow, or PI indicates reduced LV filling. When writing the dialysis orders, the nephrologist should instruct the nurse on the expected UF volume and hemodynamic parameters. Although an expected "pressure" value is determined on the basis of experience with the individual patient, the "mean pressure" is typically kept at >55–65 mmHg. Occasionally, especially early in the initiation of intermittent treatment, we may ask the nurse to also monitor the power or PI for a sudden decrease and notify the nephrologist or the cardiologist of any considerable (i.e., 20–30%) change.

If the low-flow alarm is activated, this indicates an urgent situation in which the LV volume has become dangerously low (see above), and the power and therefore the measured flow have decreased to critically low levels (the "low-flow" alarm threshold is set by the LVAD team). Volume replacement should be administered immediately, and UF should be stopped. In some patients, a "suction event" may occur with a brief episode of ventricular tachycardia that is usually terminated with the fluid treatment. The nurse should notify the cardiologist and nephrologist. Because many patients are still sedated or on pain medications and may have low systemic vascular resistance, we have sometimes found it necessary to use low-dose pressor agents to prevent peripheral blood pooling and to maintain LV return. This is an important option to consider in the ICU, but we always confer with the cardiologist first. In addition, during dialysis and UF, some patients may benefit from a small increase in pump speed, which is set by the cardiologist only. Alternatively, some patients because of a small-sized left ventricle or unusual inflow cannula may require a reduction in pump speed during treatment to prevent ventricular collapse and recurrent low flow or suction events and accompanying symptoms of syncope. Again this is coordinated through the LVAD team. After the patient is out of the ICU, using dialysate with increased sodium concentration, sodium modeling, or even increased calcium concentration may be necessary on a short-term basis. The potassium is adjusted on the basis of the patient's pretreatment potassium level (as usual).

Using the above plan, extending the standard treatment to 4.5–5 h is sometimes required to achieve the necessary UF, especially in patients with right heart dysfunction or a small ventricle.

Although many patients have recovered after 30 days, others continue to require renal replacement therapy. We declare these patients as having ESRD and prepare them for outpatient dialysis. Late recovery, however, is possible, and we continue to monitor their renal function and urine output.

Transitioning the Patient to Outpatient Dialysis and ESRD Care

The literature on ESRD in LVAD patients is sparse, but we expect this unique patient population to increase in number. The expected increase is attributed to the growing number of LVADs

Table 9.8 End-stage renal disease (ESRD) in patients after acute kidney injury (mean age <60 years)

Author	Journal	Patients	ESRD (%)
Schmidt R	AJKD 2008	Meta-analysis	31
Thakar CV	AJKD	110	70
Palevsky PM	NEJM	533 survived	66
Kurella Tamura M	NEJM	3702	>24

implanted as BTT in patients with ESRD awaiting dual-organ transplant and LVADs implanted as DT in patients who develop ESRD after ATN post-op CF-LVAD implant (an estimated 50% risk). This is in line with studies performed in the population of surgically treated patients as a whole (Table 9.8). In addition, the number of patients living with an LVAD is expected to increase. Thus, more patients will be experiencing a slow decline in renal function over time—even after initial improvement after LVAD implantation—and will need long-term renal replacement therapy. As the population of patients with ESRD grows and ages, more patients will present with or develop cardiac disease and will be referred for dual-organ transplant. These patients may require an LVAD as BTT and will continue to need outpatient dialysis.

An increase in the number of LVAD patients with ESRD will pose unique challenges in disease management. ESRD is complex, and patients can face psychological barriers. Many patients arrive at the outpatient clinic with the belief that their renal dysfunction was caused by heart disease and that they will recover, when in fact (as noted above) there may be only a 50% chance of recovery. If patients reach the point of discharge without recovery, then the chance of recovery may be even lower. The overly optimistic expectation of patients can be exacerbated by optimism of the LVAD team and the nephrologist for eventual renal recovery. The most important result of this is contribution to delayed or poor education of the patient and family in ESRD care and management. In addition, patients often interpret urine output as evidence of impending renal recovery, which—along with the above mentioned insufficient disease education—contributes to poor compliance, missed treatments, and large fluid weight gains between treatments. Eventually the patients realize that their kidneys will not recover. In these patients, there is a high incidence of psychosocial complications such as depression and disrupted family structure, which is not surprising given that education is prioritized in LVAD care at the expense of poor ESRD education. We have adopted a multidisciplinary team approach that includes working with the LVAD team, nephrologists trained in LVAD care, and ESRD social workers and prioritizing referral of patients to a designated LVAD/dialysis clinic. Educating patients before they are discharged has played a crucial role in promoting both dialysis awareness and acceptance.

Most dialysis patients are referred for SHD. Although peritoneal dialysis has been reported to have satisfactory outcomes, experience with this technique has been limited. Theoretically, peritoneal dialysis may have several advantages, but this form of treatment has not been well studied and will most likely be limited to patients with an intrathoracic pump or a pre-peritoneal-positioned LVAD [51, 53].

Access

Dialysis is generally initiated with a temporary catheter that is transitioned to a permanent catheter, tunneled into the internal jugular vein. A permanent arteriovenous access, however, may have been placed by the time of outpatient planning and discharge. The patient, patient's family, and health-care providers should be educated about the risks of intravenous catheters. This concern may be heightened by the theoretical risk of pump infection, but this has not been well studied, and actual pump infection is rare.

For outpatient ESRD treatment, including the treatment of LVAD patients with ESRD, the ideal access is an arteriovenous (AV) fistula (AVF). We avoid placing an AV access on the side of an automatic implantable cardioverter-defibrillator because there is a risk of angioedema. In a review by Patel et al. [1], the authors discuss the issue of

access in LVAD patients with ESRD and conclude that an AV graft is the best option for these patients, not an AVF. The authors base their recommendation on the theoretical concern that the thin walls of the native vein would not receive the typical pulsatile flow from an artery and, as a result, would not mature in a CF-LVAD patient. Our experience, however, does not agree with this conclusion. We have seen satisfactory maturation of fistulas, even in patients with low pulsatility, so fistula remains our preferred access. Nonetheless, we have not had a fistula in a patient with a surgically closed aortic valve. Even in patients who do not have a palpable pulse, our nurses have been able to palpate the fistula by virtue of the bruit, and cannulation has not been a serious obstacle. Coagulation plays an unknown role in the patency of the fistula, but the failure of warfarin to maintain patency in patients with multiple access thromboses suggests that the role of anticoagulation may be minimal. Some patients are off anticoagulation because of gastrointestinal bleeding, and they are treated as any other patient with an AVF who is not on chronic anticoagulation. The requirement for warfarin in most patients with a CF-LVAD complicates the placement of AV access because this surgery requires heparin "bridging" so that the patient is anticoagulant-free on the day of surgery. Therefore, as part of our education and preparation process, we place an AV access before the patient's original discharge. Our surgeons are trained in access placement in these patients.

Dialysis Monitoring

In the literature, it has been suggested that blood pressure monitoring in CF-LVAD recipients is either inaccurate or not feasible. This would present an obstacle for patients undergoing outpatient dialysis because patient monitoring would be much more time consuming and would require the added expense of using a Doppler machine. Most patients have enough pulsatile flow to allow for automated blood pressure readings. This, of course, requires some degree of residual LV function and valve opening and closing, as noted in a review by Patel et al. [1] When combined with a standard patient assessment, monitoring with an automated cuff is sufficient for most patients. Patient monitoring during dialysis can be adjusted on an individual basis and usually remains very stable. The disappearance of pulsatility may indicate that the UF rate needs to be reduced, but in our experience, patients usually do not become unstable.

Patient behavior and increased fluid and salt intake have presented more of a challenge than the actual physiologic nuances of monitoring the patient's blood pressure. Just as in non-LVAD patients, the standard assessment of pretreatment volume in LVAD patients is critical. An increased rate of fluid removal reduces pump power and flow. Just as in non-LVAD patients, the rate of UF needs to be controlled. UF should be limited to 10 mL/kg/h. Patients are instructed that if they gain more than their allowable weight goal, dialysis time will need to be increased accordingly.

There are three special circumstances that occur infrequently but may need additional attention. Patients with aortic insufficiency may require surgical closure of the aortic valve, in which case there will be no palpable or audible pulse. For these patients, we recommend that a Doppler instrument be used to detect and monitor a "mean pressure," understanding again that that there is not a true mean pressure in CF-LVAD patients. The same may be true in the group of patients who have poor LV function and an aortic valve that does not open regularly. Occasionally, a patient will require a right and left continuous-flow pump. In general, these patients are stable, and it is recommended that they be treated the same as the abovementioned patients, whether there is valve opening or not. Finally, LVAD patients will occasionally have continuous ventricular fibrillation or tachycardia. These patients will generally have a closed aortic valve and should be treated accordingly. In our experience, these patients are stable on dialysis and can be assessed with a standard exam, taking into account the skin color, level of consciousness, and presence of diaphoresis. We have not had a patient with continuous ventricular tachycardia or fibrillation on outpatient dialysis. Communication

with the LVAD team is critical. We have a designated case manager for our LVAD patients on outpatient dialysis.

The dialysis team should be familiar with the increased risk of gastrointestinal bleeding, primarily from AV malformations of the small bowel. Any sudden decrease in hemoglobin should alert the renal team and prompt a referral to the LVAD team managers. We initiate our erythropoiesis-stimulating agent protocol in LVAD patients if they are on anticoagulation. For those not on anticoagulation, we discuss the case with the cardiology/LVAD team because there may be some increased risk of thrombosis.

In conclusion, hemodialysis and—though experience with it has been limited—peritoneal dialysis are satisfactory treatment modalities for CF-LVAD patients in whom ESRD develops after implantation or for CF-LVAD patients who are already on dialysis (currently only patients approved for dual-organ transplantation). The dialysis team should have a basic understanding of continuous-flow physiology, and it is preferable to have clinics and case managers dedicated to the care of these patients. Monitoring the hemodynamics of patients on dialysis has not been difficult, with the standard exam and assessment before treatment and the use of the standard blood pressure cuff to monitor the "mean pressure." Our preferred access is AVF. Patient education and training before the initial discharge should include information on dialysis and ESRD, in addition to standard LVAD training. Patient satisfaction is good, with a low hospitalization rate after CF-LVAD implantation. Some patients have chosen to remain on dialysis instead of pursuing dual-organ transplantation.

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Chronic Management of Patients with Left Ventricular Assist Devices

10

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Introduction

Implantable left ventricular assist device (LVAD) use has continued to increase since the first long-term placement of such a device in 1988. Following this event, the FDA approved implantable LVADs in 1994 as a bridge to transplantation. Due to a perpetual shortage of available organ donors for end-stage congestive heart failure (CHF) patients, durable LVAD implantation is now also used for destination therapy (DT) since 2002 after it received approval from the FDA. These populations of patients require close monitoring and continued management of congestive heart failure.

Initial devices attempted to preserve pulsatile flow such as the HeartMate XVE device, which used a central blood chamber and inflow-outflow conduits separated by 25 mm porcine valves. The Texas Heart Institute (THI) was key in the development and testing of the device with successful implantation in 1991. However, continuous-flow LVADs have shown to be more durable and now have replaced older models. As technology improves, the size of these devices has decreased from the larger XVE device, weighing 1250 g requiring intraperitoneal implantation, to much smaller devices such as the HeartMate II (390 g) and HeartWare HVAD devices (160 g) (Figs. 10.1 and 10.2) [1]. Currently, FDA-approved continuous-flow devices include the axial-flow HeartMate II (Thoratec, Pleasanton, CA) and the centrifugal-flow HeartWare HVAD (HeartWare International, Framingham, MA). In addition, HeartMate III is a continuous-flow centrifugal device that is currently under investigation in clinical trials (Fig. 10.3). Given the increased use of continuous-flow devices, we will review care and use of all the above devices.

The HeartMate II device (Thoratec, Pleasanton, CA) was initially approved for use as a bridge-to-transplant (BTT) therapy in 2008 and then as a destination therapy (DT) for patients not eligible for transplant in 2010. HeartWare became approved as a BTT device in 2012 and is currently completing trials to obtain DT approval. Increasing use of LVADs for DT has been seen in the most recent Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data, which recorded an increase in patients receiving DT devices from 28.3% in the 2008–2011 era to 45.7% in 2014. However, approximately 60% of patients still receive an LVAD as a BTT therapy with immediate listing for heart transplantation or plans to place on the list in the near future [2].

Those receiving a device as DT have been demonstrated to have improved survivals compared to

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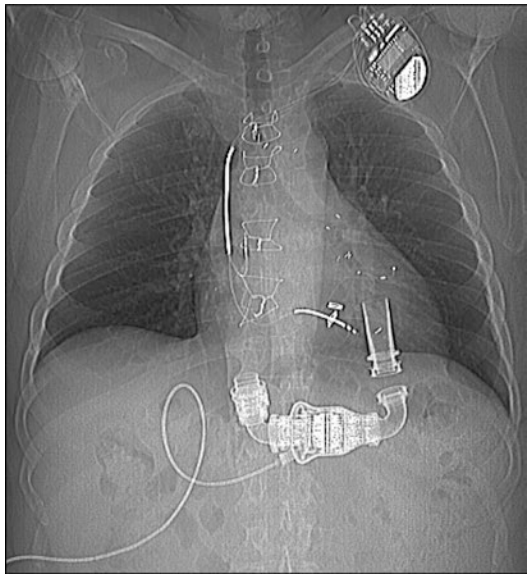

Fig. 10.1 HeartMate II left ventricular assist device. CT scan film demonstrating appearance of the device on radiography, which is important to recognize in patients with long-term devices in place. The inflow cannula is seen entering the left ventricle, and the pump is positioned outside the pericardial space

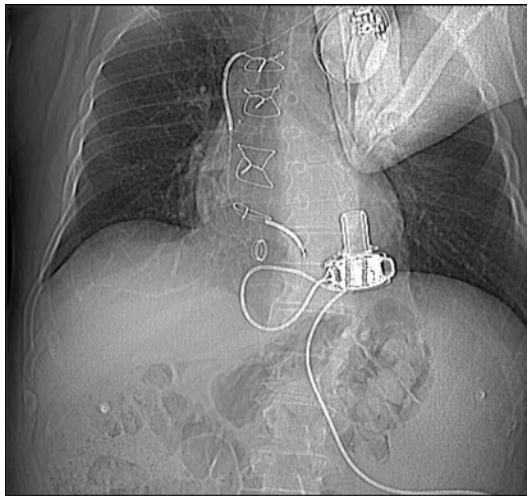

Fig. 10.2 HeartWare HVAD left ventricular assist device. CT scan demonstrates the appearance of the device. The pump is implanted in the pericardial space

those end-stage heart failure patients who have no intervention. For DT patients, after implantation of an LVAD, there is estimated survival of 76% and 57% at 1 year and 3 years, respectively. Technical improvements in continuous-flow

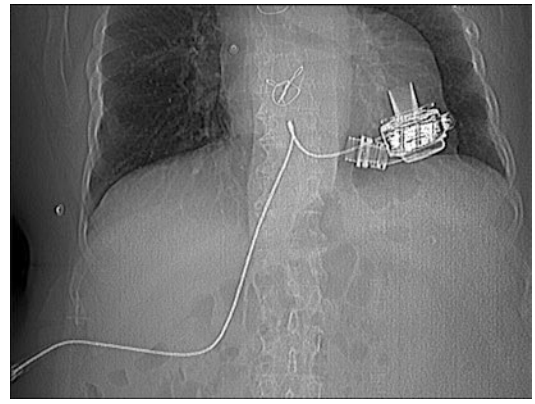

Fig. 10.3 HeartMate III left ventricular assist device. CT scan images shown. The device is implanted in the pericardial space. Compared to the HVAD, it is larger with a shorter inflow cannula

LVADs have improved long-term survival in patients with end-stage heart failure who receive a device for a BTT or DT indication. According to the most recent estimates, combined survival at 2 years with either an axial or centrifugal LVAD is 83%. Despite improvements in devices, challenges continue to emerge in the management of these patients.

Device Management

General Management

Current generation devices utilize a single part rotor in either an axial-flow rotor or centrifugal design to counter earlier generation complications of mechanical failure, but the continuous flow of these devices changes the nature of monitoring this subset of patients. While speed is the main parameter adjusted in an LVAD patient based on their hemodynamic status, there should also be continued optimization of the CHF regimen, mean arterial pressure, and possibly newly initiated anticoagulation regimen. This should include maintenance of optimally tolerated neurohormonal blockade, volume optimization, and afterload reduction.

After implantation of an LVAD, monitoring of the device parameters and alarms can provide insight into the function and hemodynamic status of the patient. HeartMate II device parameters

include speed (RPMs), power (Watts), pulsatility index (PI), and estimated flow (L/min). These parameters should be measured and recorded at each visit to assess for trends or acute changes in LVAD function. Additionally, review of any recent alarms and the timing of those alarms is an important evaluation of an LVAD patient. The specific interpretation of alarms will be reviewed later in this chapter.

Generally flow and power carry a linear relationship compared at a given speed. However, this may not hold true in certain clinical situations. Given the linear relationship between flow and power, flow is a calculated number based on a direct measurement of the power. Therefore, if the power increases due to mechanical failure, it may not truly reflect increased flow from the LVAD. For example, when a thrombus is present in the inflow cannula, it can produce an increase in power without increased flow due to the obstruction by the thrombus. This may cause some confusion related to reported device readings as both power and flow will be incorrectly reported as increased. Similarly, if there was outflow obstruction, this would cause a decrease in flow as well as erroneously low power.

The PI is a measure of the assistance the LVAD is providing to the LV and is provided in a range from 1 to 10. The PI is a specific parameter for only the HeartMate devices. This PI is calculated based on flow pulses during systole, which are sensed by the LVAD and averaged over duration of 15 s. Lower values indicate the pump is contributing more to systemic flow and will translate to less pulsatility, whereas higher values indicate less pump contribution to this flow and higher pulsatility. PI values should remain relatively constant, and a decrease should lead clinicians to consider a decrease in circulating blood volume. Significant increases in PI should prompt further evaluation for possible fluid retention, hyperdynamic states (such as sepsis), significant aortic valvular insufficiency, and, in rare instances, cardiac recovery.

Additionally, after implantation, the necessary speed of the LVAD should be evaluated at each visit based on mean arterial pressure, echocardiography, and, if necessary, further testing such as a right heart catheterization (RHC). The speed should be aimed to maintain peripheral pressure and perfusion while minimizing right ventricular (RV) overload, aortic regurgitation (AI), or left ventricular (LV) collapse [3, 4]. Since RV function, AI, and LV size are dynamic factors, frequent assessment should occur at least every 6 months following implantation of an LVAD or sooner if symptoms arise.

Role of Hemodynamic Assessment

A reduction in exertional capacity is a characteristic feature of advanced heart failure. The use of cardiopulmonary exercise testing (CPET) in patients with severe left ventricular impairment prior to cardiac transplantation or LVAD placement will demonstrate a markedly reduced exercise time and peak oxygen consumption. Patients with marked reduction of VO2 below 14 mL/kg/min have been demonstrated to have a reduced survival when compared to those with left ventricular impairment and a VO2 greater than 14 mL/kg/min [5]. While completion of CPET is typically completed prior to cardiac transplantation, its use is also recommended in patients after implantation of an LVAD. It may be useful in providing clinicians an objective assessment of exercise capacity as well as helping guide recommendations for exercise regimens. Studies have consistently demonstrated improvement in exercise time in the first 6–8 weeks following LVAD implantation; however, there has been variable response to VO2. Age may be a large predictor of VO2 improvement with patients reaching only 50–60% of their age- and sex-predicted VO2 after LVAD implantation [6, 7].

Current guidelines recommend regular interval testing of hemodynamics by right heart catheterization, particularly in those patients awaiting transplantation. Serial evaluation can identify those patients with pulmonary hypertension (pHTN), which when irreversible has been associated with a higher risk of allograft dysfunction [8–10]. No specific recommendations currently exist on the interval of testing; however, data has suggested that those with pHTN on right

heart catheterization 2–3 months after LVAD implantation are at the greatest risk for persistent or progressive pHTN in the following 6 months. In addition, there appears to be little predictive value of a right heart catheterization prior to LVAD implantation and development of pHTN following surgical implantation.

Right heart catheterization has also proven useful for hemodynamic-guided LVAD optimization and diagnosis of inadequate pump speed, right heart failure, or volume overload. Studies have demonstrated the ability to decrease pulmonary capillary wedge pressure and central venous pressures as well as increase cardiac output/index by evaluating increasing pump speeds while in the catheterization lab [11]. Interval evaluation may also provide a way to differentiate patients with persistent heart failure symptoms into categories of right heart failure (relatively normal PCWP with persistently elevated central venous pressures) versus those with left-sided volume overload (persistently elevated PCWP despite increasing pump speeds) (Fig. 10.4). Also some patients may respond to increasing pump speeds with decreasing PCWP and central venous pressures suggesting inadequate LVAD speeds. While hemodynamic improvements have been achieved with right heart catheterization-directed studies, no direct correlations have been drawn to symptomatic improvement or decreases in morbidity and mortality.

Echocardiography

This section will identify the basics of echocardiography in the chronic management of patients following implantation of an LVAD, while prior chapters will address preoperative assessment and issues immediately postoperatively. Transthoracic echocardiography (TTE) is essential in the optimization of LV decompression, reduction of aortic insufficiency, and evaluation of possible device malfunction. Using standard echocardiographic views, 2D measurements, color Doppler, and spectral Doppler can collectively be used to provide LV size, valvular function, and interrogation of inflow/outflow cannulae. Guidelines by the American Society of Echocardiography recommend surveillance TTE at postoperative week 2 and at 1, 3, 6, and 12 months if the patient remains clinically stable. Evaluation should then take place every 6–12 months thereafter [12].

Measurement of the left ventricular internal diastolic dimension (LVIDd) is an important parameter in the assessment of LV unloading following LVAD implantation. While end-diastolic volumes as obtained by Simpson's method of disks have in some cases been shown to be a more accurate measurement of LV unloading, reproducibility can be an issue due to shadowing from the outflow cannula of the LVAD. Therefore, the use of the parasternal long-axis images to obtain the LVIDd has been found to be the most reproducible measurement. Following LVAD implantation, approximately a 15% reduction in LV size has been shown to be expected at 3 months post-LVAD [13, 14]. This data was obtained solely in HM II patients; therefore variation may exist between devices.

In regard to LV ejection fraction, serial measurement can provide clinicians data to evaluate for myocardial recovery or worsening over time. As mentioned above, measurement of LVEF by Simpson's method of disks is the recommended method; however, it can be difficult due to shadowing in the apex from the LV outflow cannula, paradoxical septal motion, or significant regional wall motion abnormalities. Therefore, in cases when endocardial visualization is difficult, the use of alternative methods including LV fractional shortening, LV fractional area change, or the Quinones method has been suggested (for the latter bearing in mind the LV apex should be considered akinetic due to the presence of the LV inflow cannula) (Table 10.1). It is important to remember that these methods are not validated in patients with LVAD in situ.

Assessment of the aortic valve mobility is an alternative parameter in serial evaluation of LV unloading. If LVAD speed is set above which allow aortic valve opening, it may lead to aortic regurgitation (AR) which impairs LVAD function. This occurs as a continuous loop of flow from the LV outflow cannula to the aorta followed by regurgitation back into the LV. Therefore, significant

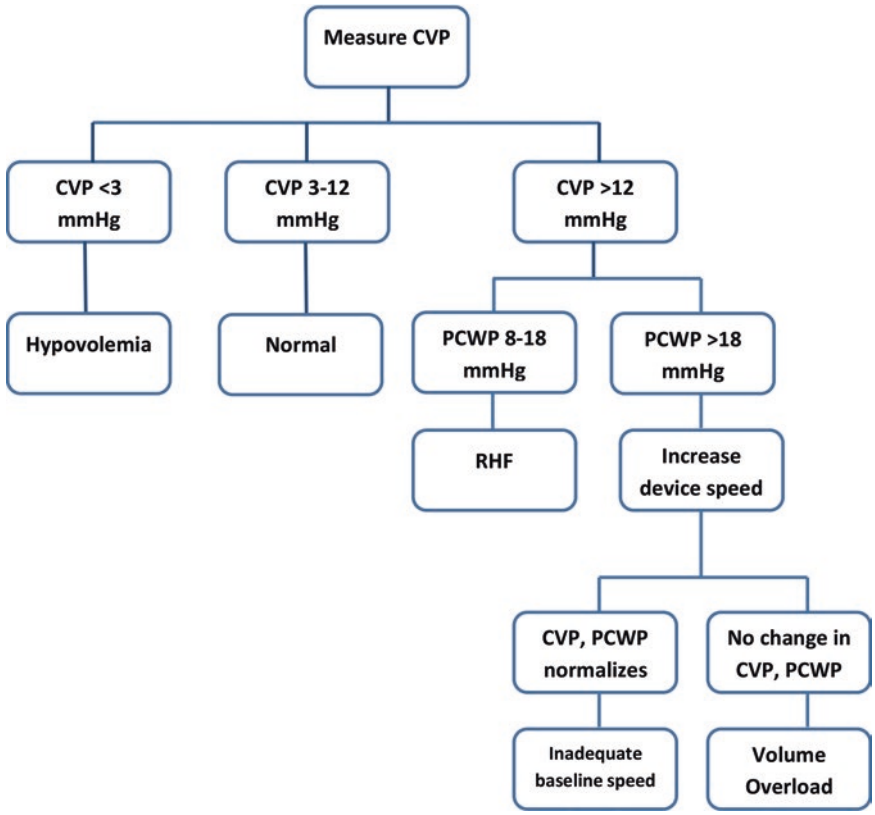

Fig. 10.4 Interpretation of right heart catheterization in LVAD patients. *CVP* central venous pressure; *PCWP* pulmonary capillary wedge pressure; *RHF* right heart failure

AR can affect the unloading of the LV and thus LVAD effectiveness. Development of AR has important implications in morbidity and mortality, which will be discussed in more detail later in this chapter. Additionally, if the aortic valve remains closed, it can predispose patients to aortic root thrombus and/or fusion of the aortic valve cusps).

Assessment of the aortic valve during LVAD surveillance TTE should begin with evaluation of opening of the valve. This is most accurately achieved with the use of M-mode echocardiography by recording the aortic valve in up to 5–6 cardiac cycles, as the valve can open with every cardiac cycle, open intermittently, or remain closed with every cycle. While aortic valve opening can occur with each cardiac cycle, it may only occur for a short duration. Therefore, the duration of aortic valve opening should also be addressed by averaging the duration of opening in multiple cardiac cycles, usually in milliseconds (ms).

Parameters for defining the severity of AR have not been specifically validated; however, the use of prior guidelines is generally followed. When there is a vena contracta of ≥0.3 cm or an AR jet width of >46% of the LVOT diameter, there is likely at least moderate if not severe AR. The AR may also be present during only diastole, nearly continuous when it extends into systole, or continuous when it is holodiastolic and holosystolic. Due to the ability of AR to be present into systole and the extracardiac circuit of the LVAD, neither the pressure halftime nor the presence/absence of aortic diastolic flow reversal is a reliable method to quantitate AR.

Mitral regurgitation (MR) is also regularly evaluated on surveillance TTE after LVAD implantation as it can have implications for device management. Quantification of the severity of MR can be made based on the general echocardiography guidelines. Importantly, the

Table 10.1 Alternative methods of evaluation of LVEF in LVAD patients

Method	Equation	Benefits	Limitations
Fractional area change (%)	FAC = [(end-diastolic area − end-systolic area)/(end-diastolic area)]	Can be used in the absence of adequate apical visualization	Less reliable in the setting of significant LV wall motion or distortion (i.e., aneurysm)
Fractional shortening	FS = [(LVIDd − LVIDs)/(LVIDd)]	Can be used in the absence of adequate apical visualization	Less reliable in the setting of significant wall motion or LV distortion (i.e., aneurysm)
Quinones method	LVEF = [($LVIDd^2$ − $LVIDs^2$)/($LVIDd^2$)]	Decreases error by using multiple areas of measurement	Less reliable in the setting of significant wall motion or LV distortion (i.e., aneurysm)

FAC fractional area change; *FS* fractional shortening; *LVIDd* left ventricular internal diastolic dimension; *LVIDs* left ventricular internal systolic dimensions; *$LVIDd^2$* indicates measurement of eight different LV dimensions at different levels in the parasternal long axis, four-chamber, and long-axis views of end diastole; *$LVIDs^2$* indicates measurement of eight different LV dimensions at different levels in the parasternal long axis, four-chamber, and long-axis views of end systole

presence and severity of MR can be an indicator of adequate unloading provided by an LVAD. Appropriate LVAD speeds will ideally lead to reduction in LV size and in turn the mitral annulus. This reduction in the mitral annular size will improve coaptation and thus reduce mitral regurgitation. However, if mitral regurgitation is persistent despite increasing LV unloading, evaluation for LVAD malfunction should be sought as the outflow cannula may interfere with the submitral apparatus in some cases.

The tricuspid and pulmonic valves are reliably interrogated using standard methods in patients following LVAD implantation. Tricuspid regurgitation (TR), present in moderate to severe ranges, can provide indirect data on the function of the LVAD. Assuming the absence of a concurrent right ventricular assist device, significant TR in appropriate clinical scenarios can suggest inadequate LV unloading, RV dysfunction, or excessive LV unloading leading to intraventricular shift and distortion of the tricuspid valve morphology. The presence of significant TR should therefore prompt review of serial changes in LV size, ejection fraction, measures of RV function, and intraventricular motion.

Lastly, TTE can be useful in the evaluation of the inflow and outflow cannula of the LVAD. The inflow may be visualized in the parasternal long axis or LV four-chamber views and should be evaluated for its position in reference to the septum or submitral apparatus. Flow through the cannula can also be interrogated using pulsed and continuous wave Doppler and should be obtained over 3–4 cardiac cycles. Normal Doppler waveforms will be pulsatile due to the contribution of the LV to flow even if the aortic valve is closed (Fig. 10.5). Doppler velocities should also be ≤1.5 m/s, and when higher flows are present, it may indicate obstruction or the presence of thrombus.

Evaluation of the aortic outflow graft anastomosis is more difficult but can be seen in the modified parasternal views, which focus on the ascending aorta. In cases where this is not sufficient, positioning patients in the right lateral decubitus position and obtaining right parasternal views may be helpful. Spectral velocities through the graft can be used in calculation of flow using velocity time integral (VTI) and outflow graft area method, keeping in mind that velocities can vary between graft sizes. For example, HeartMate II tends to have a larger outflow graft (16 mm) than HeartWare devices (10 mm). In general, flows >2 m/s are considered abnormal for the outflow graft, and further evaluation for obstruction should be undertaken.

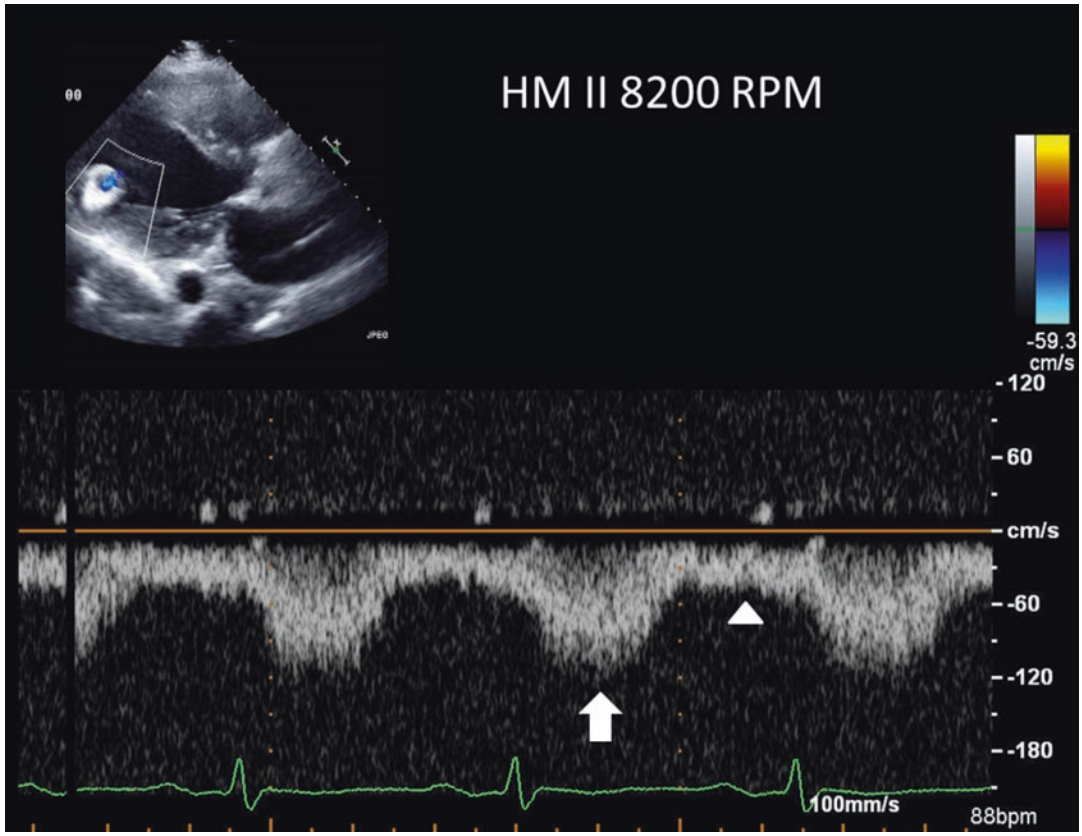

Fig. 10.5 Pulsed wave Doppler is seen of a HeartMate II inflow cannula. Although it is a continuous-flow device, contribution of left ventricular contraction leads to a systolic peak (*lined arrow*) and a diastolic nadir (*arrow head*). Typically these can be obtained in a standard four-chamber echo view or from the parasternal long view (*upper left panel*). Velocities should be ≤1.5 m/s

Optimization of a patient's LVAD speed can be completed in asymptomatic ambulatory patients using TTE to obtain the above parameters. These optimization studies, sometimes referred to as a "speed change" echo, can be obtained by completing a TTE study at the baseline speed and either lower or incrementally increasing speeds. At each speed, the patient's mean pressure as well as echo parameters should be obtained, including LVIDd, septal position, frequency/duration of aortic valve opening, and quantitative or qualitative AR, MR, and TR. It should be noted that if a thrombus is visualized in the aortic root, the LVAD speed should not be changed as it can aid in mobilization of the thrombus, especially at lower speeds.

HeartMate II and HeartMate III Device Parameters

After implantation of a HeartMate II or HeartMate III device, patients will receive a system controller with two sets of batteries, a primary operating set, and a backup. Additionally, the patients will have a system controller and a power base unit (PBU). A control monitor is required at the initial implantation and subsequent encounters to review settings and alarms but is not a required component for discharge. Patients will be educated during their admission on the operation of the system controller, which has several display icons and buttons seen on the face (Fig. 10.6). There are two buttons, which include the "Test Select" and "Silence Alarm" buttons, which

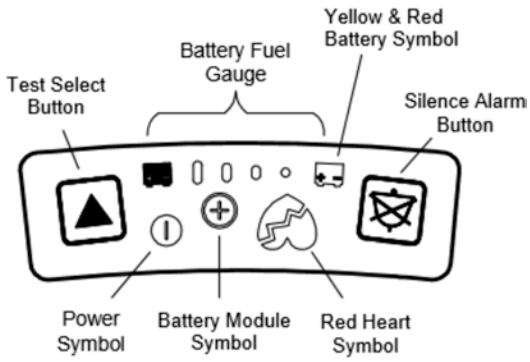

Fig. 10.6 HeartMate II control system

allow patients to interact with the system. Lighted icons on the controller include a power symbol, battery symbol with fuel gauge, battery module symbol, and red heart symbol.

The battery symbol and fuel gauge are the most vital for day-to-day patient usage. The gauge has four green markers, which can provide an approximate amount of battery life remaining. When all four are lighted, it signifies that 75–100% of the battery energy remains with a reduction of 25% of battery energy with the loss of each marker. When a single green lighted marker remains, it signifies <25% of battery energy remains, and once the battery symbol appears as a yellow or red indicator, it signifies <15 min or <5 min of battery energy remains. Not all patients can be provided with similar durations of battery life as this can vary depending on the set speed or the age of the battery. Higher set speeds will deplete a battery more quickly, and as the battery ages, it will hold its charge for less time.

As previously described, the LVAD speed, flow, power, and pulsatility index are displayed when the device is hooked to the control monitor and can be adjusted by the clinician through this interface (Fig. 10.7). The minimum and maximum operating speeds for the HeartMate devices are 6000 and 15,000 RPMs, but typical operating speeds usually range between 8800 and 10,000 RPMs. When making speed adjustments or speed optimization on TTE, incremental changes of 200–400 RPMs are used.

HeartMate II and HeartMate III Device Alarms

Several alarms can occur within the HeartMate II and HeartMate III systems and are divided into hazard alarms and advisory alarms. The former type of alarm is the more critical of the two and can indicate imminent or current loss of support from the device. Hazard alarms are indicated by a continuous alarm tone and illumination of either the red battery or heart symbols. When the red heart symbol is illuminated with a continuous alarm tone, this indicates low flow (≤2.5 L/min) or pump off. It should prompt evaluation of the pump connections between the controller and power source. Illumination of the red battery symbol indicates a low-voltage situation and should prompt the user to replace current batteries. In this situation, the system will revert to a power saver mode in which the RPMs will drop to 8000 despite the current settings. Lastly, if a continuous audio tone is present without an illuminated indicator, it suggests the system is not receiving power and should lead the operator to check the connections between the controller and power source or change the current battery.

Advisory alarms indicate a change in the condition or minor malfunction of the system, which will have little to no effect on hemodynamic support. Instead of a continuous alarm tone, advisory alarms will emit alarms lasting seconds with or without illumination of indicators on the controller. A yellow battery illumination with one beep every 4 s indicates a low-voltage advisory with a battery life of <15 min. This should prompt the user to change the battery or switch to an alternate power source. Similarly, when the battery powering the controller is depleted, a yellow battery alarm symbol will appear and alert one beep every 4 s; this requires replacement of the battery. If the power lead is disconnected, an alarm will beep every second with green illumination of the power button and flashing of the green fuel gauge lighting. In this situation, the power cord should be promptly reconnected. Lastly, if the module provides one alarm tone every 4 s with no warning light, this is an indication that the pump is operating below the low speed limit. If appropri-

Fig. 10.7 HeartMate II display panel. The pump speed, pump power, pulsatility index, and pump power are displayed

ate, the patient should be connected to the system monitor and the speed adjusted. Additionally, if the system reverts to the backup operating system, two alarm tones will be provided in 1 s followed by 2 s of silence with no illuminated alarm indicators. In this situation, the system controller should be replaced.

A daily self-test should be completed on the system controller to ensure proper operation of the device. A self-test is accomplished by pressing and holding the "test select" button for at least 3 s at which time all indicators should light up and a continuous alarm tone should be heard. It is during this time the patient or clinician completing the test should ensure all indicators are functioning properly. If malfunction of the alarm system occurs, it will emit a 1-s tone every other second, or if malfunction of the controller is present requiring replacement, it will emit an audio tone of two beeps every second, and no indicators will light up. If a normal self-test is performed, the alarm tone and indicators will turn off 5 s after releasing the "test select" button. The LVAD will remain in its set parameters throughout the self-test.

HVAD Device Parameters and Waveform Analysis

The HVAD device when implanted comes equipped with two sets of batteries, a battery charger and a controller. Unlike the HeartMate devices, patients receive a touch screen tablet monitor at discharge, which allows for monitoring of device function and adjustment of parameters if needed. Recommended device speeds range from 2400 to 3200 RPM, which correlate to approximately 3–8 L of flow. Speeds can be set as low as 1800 RPM; however, these are not generally used except for during initial implantation when patients are being weaned from cardiopulmonary bypass. Speeds higher than 3200 RPM are associated with higher risk of LV suction events.

The HVAD controller face has two push buttons and four indicators as well as a display. Buttons include the "alarm mute" and "scroll" buttons, while indicators include AC/DC indicator, battery 1 and 2, and alarm indicator. A patient must be connected to two power sources through the controller at all times, and this may

include two batteries or a single battery and an AC/DC adapter. The battery icons on the controller include a battery symbol with four boxes, which will illuminate green when a fully charged battery is connected. As battery energy is depleted, the boxes sequentially no longer illuminate and indicate the percent of battery energy remaining. For example, when three boxes remain, there is 50–74% of battery energy remaining, two boxes is 25–49% of energy remaining, and one box is <25% energy remaining. Depending on whether one or both batteries are depleted, different alarms may sound, and this will be discussed in the subsequent section.

The "home screen" seen on the HVAD touch screen monitor will display important parameters that can help assess and evaluate the current condition of the patient and pump. From the top left hand of the screen down will be displayed the pump flow (L/min), speed (RPM), and power (Watts) (Fig. 10.8). Immediately to the right of this display bar appear five touch responsive icons which allow the clinician to navigate between display screens. From top to bottom, these include the "home screen," "alarm screen," "trend screen," "system screen," and a monitor power icon. Each of these allows for review of current settings, review of alarms, review of temporal trends in flow/speed/power, and adjustment of LVAD speed or patient data, respectively.

Lastly, the home screen includes two real-time waveforms, which display the pulsatility of both the flow and power. Normal pulsatility of the flow should include a variation of at least 2 L/min from peak to trough in the waveform. In addition, the minimum value of flow should be greater than 2 L/min. Deviations of normal waveforms may provide suggestion of pump or hemodynamic dysfunction such as with regurgitant lesions, pump thrombosis, or suction events. When regurgitant lesions arise, such as aortic insufficiency, the pulsatility waveform may take on a large variability with trough flows reaching negative flow rates. In contrast, in patients with suction events or a small, decompressed LV, there may be decreased variability due to the outflow cannula abutting the LV wall and reducing blood intake. Since the waveform display on the home screen may provide only short periods of assessment, it can be useful to review the waveform from longer time periods through the trend screen which

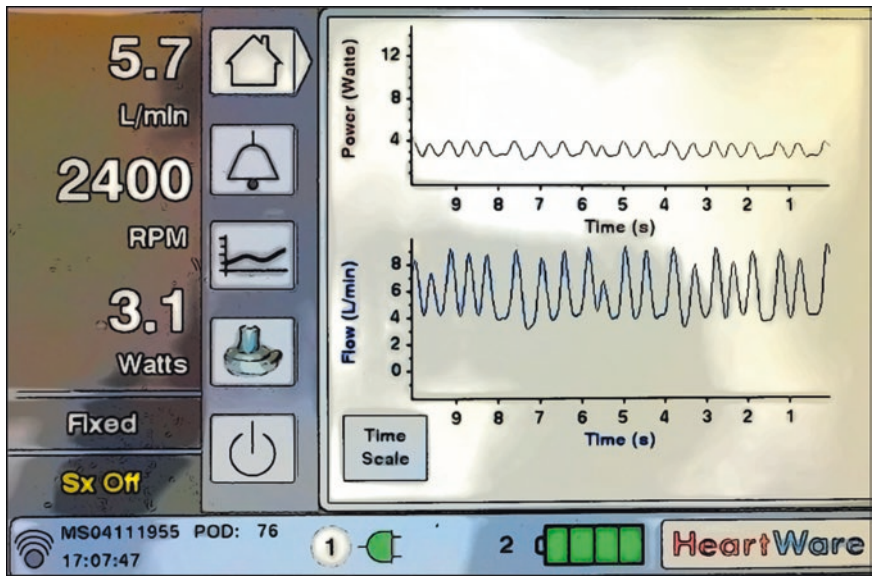

Fig. 10.8 HeartWare HVAD waveform display

can retrieve data from the prior 60 min, 4 h, 24 h, 14 days, or 30 days.

HVAD Device Alarms

Device alarms on the HVAD device can be separated into low-, medium-, and high-priority alarms. Each alarm has a separate set of indicators and alarm tones, and the controller will produce a text message to indicate the exact source of malfunction.

High-priority alarms indicate immediate action is needed as loss of support has occurred or is imminent. For all alarms, the alarm indicator will be illuminated in a flashing red color, and a continuous alarm tone will sound which cannot be muted. Situations in which high-priority alarms occur include when the driveline is disconnected or the connector is broken, when there is controller failure, or when both battery sources have limited time remaining. In each of these, the controller will produce a two-line message, for example, if there is controller failure, the first line may read "VAD Stopped" and the second line "Change Controller."

Medium-priority alarms will produce a flashing yellow illumination of the alarm indicator and a low-volume tone which will increase in volume over the next 1 min if not silenced. This type of alarm can indicate a low-flow situation, suction events, electrical fault, or high voltage of the device. Typically these alarms prompt the patient to call the clinician for further instructions. Text messages may include "Low Flow" in line 1 and "Call" in line 2. Low-priority alarms will produce a constant yellow illumination of the alarm indicator and a low-volume tone which will increase after 5 min if not silenced. These alarms occur when one of two power sources is low, for example, one of the two batteries connected. It will also occur when one power source is disconnected from the controller. Text messages may include "Low Battery 1" in line 1 and "Replace Battery 1" in line 2. For complete review of text provided with each potential alarm, clinicians should review the HeartWare Instruction Manual.

Heart Failure Management

Implantation of an LVAD provides hemodynamic support and reduces myocardial work improving symptoms and the functional class of CHF patients. This support also provides unloading of LV and can allow for recovery of LV function in some cases [15–17]. Pharmacologic therapies that augment the renin-angiotensin-aldosterone system and sympathetic nervous system have also been shown to improve LV function, decrease fibrosis, and improve heart failure symptoms. Importantly, mortality has been shown to be reduced in CHF patients in large randomized trials using angiotensin-converting enzyme (ACE) inhibitors [18–21], angiotensin receptor blockers (ARB) [22, 23], β-blockers [24–27], mineralocorticoid antagonists [28, 29], and the most recently validated angiotensin-neprilysin inhibitor (ARNi) and sacubitril/valsartan combination [30].

At this time, no large randomized controlled trials have been completed to evaluate pharmacologic therapies in patients with LVADs. Generally, the use of diuretics, ACE inhibitors/ARBs, and β-blockers is encouraged for the management of volume overload, hypertension, and tachyarrhythmia, respectively. Mineralocorticoid antagonists may also be used to limit the need for potassium replacement in LVAD patients with adequate renal function. However, given the lack of direct evaluation of neurohormonal blockade in LVAD patients, the 2013 ISHLT guidelines provide a Class I indication for the use of these agents for the above indications and with only a level of evidence C (expert opinion) [8].

Small studies have evaluated the use of combination therapies for LV recovery in LVAD patients. One single-center study initiated maximally tolerated lisinopril (maximum dose 40 mg daily), carvedilol (maximum dose 50 mg twice daily), spironolactone (maximum dose 25 mg daily), and losartan (maximum dose 100 mg daily) in 15 nonischemic cardiomyopathy patients after device implantation. The patients were followed by echocardiography every 2 weeks for 6 months to evaluate end-diastolic LV size with the device on and off. Once it was determined, maximal LV recovery had occurred, and the patients were switched to clenbuterol at a maximally tolerated dose of

700 μg three times daily in addition to bisoprolol. At the end of the study, 11 patients were able to undergo device explantation with an improvement in LVEF from 12 ± 6% to 64 ± 8% ($p = 0.001$) and end-diastolic diameter from 75.1 ± 16.3 mm to 55.9 ± 8.3 mm ($p = 0.002$). The remaining four patients did not meet the criteria for explantation but underwent transplantation. The survival rate among those after explantation at 1 and 4 years was 90.1% and 81.8%, respectively [31].

Right Heart Failure

Incidence of Late RV Failure

Right ventricular failure (RVF) can be seen in patients after LVAD implantation and carries a poor prognosis for these patients. Early right heart failure is a common complication following implantation and has been studied more frequently in the literature. However, patients may present months to years after their incident admission. Generally, these patients develop signs of increased peripheral edema, elevated liver enzymes due to hepatic congestion, increasing diuretic requirement, and decreased LVAD flow and/or pulsatility. The incidence of late RVF has been studied in a few small cohorts and demonstrated a variable incidence between 11 and 45%; however, definitions of RVF varied significantly among studies [32, 33].

Varying severity of RVF has been defined previously by the level of therapy needed for the patient. Those with mild RVF have two of four signs of elevated central venous pressure (CVP) by Swan-Ganz measurement (>18 mmHg), cardiac index <2.3 L/min/m^2, ascites or moderate to severe peripheral edema, or evidence of elevated CVP by physical examination or echocardiography. Mild RVF can usually be treated with increasing doses of diuretics. Moderate RVF has been defined as those meeting the mild criteria and requiring inotropic support or pulmonary vasodilators for a duration of >1 week at any time following LVAD implantation. Severe RVF is defined in those patients that necessitate a right ventricular assist device.

The etiology of late RVF has not been fully elucidated, but it may be due to hemodynamic changes following LVAD implantation. Early RHF has been associated with increases in cardiac output, which directly increases preload and may increase the work of the right ventricle. In addition, the geometry of the heart can be changed when the left ventricle is decompressed and/or the interventricular septum is shifted leftward. However, given that these changes are more acute after implantation of an LVAD, they are unlikely to contribute to the late presentations of RHF. Studies have shown that baseline measurements of CVP and CVP/PCWP ratios are similar among those who develop RHF implicating other mechanical stressors [33, 34]. Therefore, one common link between those who develop late RHF has been readmission for tachyarrhythmia, bleeding, and infection or progression of tricuspid regurgitation and pulmonary hypertension [33, 35].

Pulmonary Vasodilators in Pulmonary Hypertension and Right Heart Failure

Prior evidence has shown a direct correlation with pulmonary hypertension and transplant mortality [36] which has led to the International Society of Heart and Lung Transplantation to provide a relative contraindication to cardiac transplantation in patients with a pulmonary vascular resistance (PVR) >3 Woods units (WU). Studies have documented the success of pulmonary vasodilators in lowering PVR in patients after implantation of an LVAD with both sildenafil and bosentan; however, their effects on outcomes remain unclear. Additionally, safety concerns have been raised for the use of endothelin receptor antagonists (ERAs) in patients with CHF due to results from the Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) trial in which a large proportion of patients had elevation of their transaminases without significant clinical benefit.

In a retrospective study by LaRue et al., 50 patients were treated with bosentan after LVAD

implantation. Predominantly these patients were recipients of HeartMate II devices, and 70% were implanted with a BTT strategy. Therapy was started at a median of 37 days after LVAD implantation and continued for a median of about 16 months. A target dose of 125 mg twice daily was achieved in 78% of patients with a statistically significant decrease in 6-month follow-up BNP, total bilirubin, and alkaline phosphatase. A significant decrease in PVR was also noted by echocardiography measurement with a mean reduction of 1.4 Woods units (WU) (3.93 ± 1.53 to 2.58 ± 1.05, $p < 0.0001$). Of note, three patients discontinued the medication due to elevated liver transaminases, but all had normalization after discontinuation of the mediation [37].

Hypertension Management

As in those patients who are at risk or have developed CHF, hypertension management is of clear benefit. In addition, emerging evidence suggests blood pressure control is of importance to prevent device complications or malfunction. Due to the increasing use of continuous-flow LVADs, most blood pressure goals are reported as achievement of a goal mean pressure given the loss of pulsatility. Validation of blood pressure measurements by dopplerable flow has been shown to be correlated with both systolic blood pressure and mean arterial pressure when validated to simultaneous intra-arterial measurement [38, 39]. Measurement can be taken at the brachial artery with a pulse wave Doppler as the first indication of flow when a sphygmomanometer is slowly deflated after obtaining occlusive pressure. This type of pressure is more accurate than obtaining measurement from an automated blood pressure cuff or palpable pulsation, especially in those patients who do not achieve aortic valve opening at optimal speeds.

The International Society for Heart and Lung Transplantation (ISHLT) provides recommendations for blood pressure goals in patients with durable mechanical circulatory support devices. In those with pulsatile devices, they recommend a blood pressure goal of a systolic blood pressure less than 130 mmHg and a diastolic blood pressure of <85 mmHg. In patients with nonpulsatile support devices, they recommend a mean BP goal of <80 mmHg. These recommendations both come with a level of evidence of "C" as they are provided as a recommendation of expert opinion.

Recent studies in patients with CF-LVAD have shown that achieving mean BPs <80 mmHg is correlated with decreased incidence of hemorrhagic stroke, thromboembolic events, and aortic regurgitation. One retrospective study included 123 patients who were at 30 days from CF-LVAD implantation and in the outpatient setting. End points including intracranial hemorrhage, thromboembolic events, or moderate to severe aortic insufficiency were evaluated. Based on at least ten outpatient Doppler-derived blood pressure readings, subjects were stratified to either a controlled (<80 mmHg), intermediate (80–90 mmHg), or high (>90 mmHg) group. Based on the results 18 months after LVAD implantation, there were 97%, 86%, and 70% survival-free from combined adverse events in each of the controlled, intermediate, and high groups, respectively [40].

Aortic Insufficiency and Valvular Heart Disease

Greater than mild AI after LVAD implantation has been demonstrated to occur in 25–31% of patients at 1 year [41, 42]. This finding has been demonstrated to lead to worsening of heart failure symptoms and increased LVAD flows due to the continuous circuit that occurs between the LVAD and the LV [43]. A proposed etiology for this clinical entity stems from the continuous positive pressure the outflow graft places on the aortic side of the valve and the negative pressures the inflow cannula has on the LV side of the valve which lead to remodeling, fusion of the aortic valve leaflets, and eventually incompetence [44, 45]. Current therapies for significant AI include medical management, aortic valve repair, aortic valve closure, or aortic valve replacement.

Predictors for development of significant AI have been evaluated in both preoperative and postoperative LVAD patients. Significant preoperative

predictors appear to include the use of continuous-flow devices, lower body mass, lower preoperative ejection fraction, and female gender [41, 46, 47]. Interestingly, the presence of AI at baseline has not been identified as a risk factor for progression after LVAD implantation. Postoperatively, greater risk is conferred for AI in patients with higher LVAD speeds, smaller LV size, lack of aortic valve opening, and presence of AV commissural fusion [41, 47–49].

Medical management for significant AI is generally aimed at afterload reduction. AI leads to increased LV diastolic pressures and increased LVAD flow; however, when LVAD speeds are increased to compensate, this may contribute to widening of transvalvular gradient (by increasing the systemic diastolic pressure and decreasing the LV diastolic pressure). These hemodynamic changes are favorable for worsening of the AI and promotion of aortic valve remodeling. Reduction of the LVAD speed may actually improve AI by allowing at least intermittent aortic valve opening, but if systemic pressures are too high, end-organ perfusion may suffer. Therefore, afterload reduction is the preferred treatment, aiming for the ISHLT recommended goal of a mean arterial pressure of ≤80 mmHg. Antihypertensive therapies are reviewed in prior sections of this chapter.

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Surveillance Echocardiography for LVAD Patients

11

Raymond F. Stainback

Introduction

Guidelines have been previously published for the use of echocardiography during each of the various phases of care for left ventricular assist device (LVAD) patients [1]. This chapter focuses on the use of surveillance echocardiography either before hospital discharge or during routine scheduled follow-up appointments. Surveillance examinations can confirm individual patients' baseline echo parameters, which can later be used for problem solving if the patient presents with new abnormal signs or symptoms. Also, surveillance examinations can detect abnormalities of the native heart and pump malfunctions (Table 11.1) that might otherwise remain occult, particularly in less active patients. This chapter provides educational material for mechanical circulatory support (MCS) medical and technical staff team members, along with example imaging protocols and reporting worksheets that can be modified to fit an LVAD center's existing internal standards.

Substantial portions of this material were adapted from Stainback RF, Estep JD, Agler DA, et al. Echocardiography in the management of patients with left ventricular assist devices: Recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2015; 28(8):853–909. Used with permission.

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Role of Echocardiography After LVAD Implantation

The significant variability among individual patients' clinical courses after LVAD implantation precludes taking a "one-size-fits-all" approach to postimplantation echocardiography. Nevertheless, an overall framework can be recommended to improve patient care while addressing the efficiency of both the LVAD clinic and the echocardiography laboratory. Surveillance echocardiography generally refers to standard transthoracic echocardiography (TTE) imaging that is performed in the echocardiography lab, in the LVAD clinic, or at the bedside.

In LVAD-supported patients, surveillance echocardiography is performed at the pump's baseline speed setting and includes LVAD-specific views and Doppler flow assessments, in addition to all the elements of a standard TTE exam for heart failure (HF) patients. If an LVAD optimization protocol is added, further limited imaging can be performed at pump speeds above or below the baseline speed to optimize LVAD and native heart function, although standards for optimal pump speeds may vary among centers and according to patient-specific variables.

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Table 11.1 Continuous-flow LVAD postimplant complications and device dysfunction detected by echocardiography

Pericardial effusion
With or without cardiac tamponade including RV compression. *Tamponade*: respirophasic flow changes; poor RVOT SV
LV failure secondary to partial LV unloading
(by serial exam comparison)
(a) 2D/3D: increasing LV size by linear or volume measurements; increased AV opening duration, increased left atrial volume
(b) Doppler: increased mitral inflow peak E-wave diastolic velocity, increased E/A and E/e′ ratio, decreased deceleration time of mitral E velocity, worsening functional MR, and elevated pulmonary artery systolic pressure
RV failure
(a) 2D: increased RV size, decreased RV systolic function, high RAP (dilated IVC/leftward atrial septal shift), leftward deviation of ventricular septum
(b) Doppler: increased TR severity, reduced RVOT SV, reduced LVAD inflow cannula and/or outflow-graft velocities (i.e., <0.5 m/s with severe failure), inflow-cannula high velocities if associated with a suction event. Note: a "too-high" LVAD pump speed may contribute to RV failure by increasing TR (septal shift) and/or by increasing RV preload
Inadequate LV filling or excessive LV unloading
Small LV dimensions (typically <3 cm and/or marked deviation of interventricular septum toward LV). Note: may be due to RV failure and/or pump speed too high for loading conditions
LVAD suction with induced ventricular ectopy
Underfilled LV and mechanical impact of inflow cannula with LV endocardium, typically septum, resolves with speed turndown
LVAD-related continuous aortic insufficiency
Clinically significant—at least moderate and possibly severe—characterized by an AR proximal jet-to-LVOT height ratio >46% or AR vena contracta ≥3 mm; increased LV size and relatively decreased RVOT SV despite normal/increased inflow-cannula and/or outflow-graft flows
LVAD-related mitral regurgitation
(a) Primary: inflow-cannula interference with mitral apparatus
(b) Secondary: MR functional, related to partial LV unloading/persistent heart failure
Note: Elements of both a and b may be present
Intracardiac thrombus
Including right and left atrial, LV apical, and aortic root thrombus
Inflow-cannula abnormality
(a) *2D/3D*: small or crowded inflow zone with or without evidence of localized obstructive muscle trabeculation, adjacent MV apparatus, or thrombus; malpositioned inflow cannula
(b) *High-velocity* color or spectral Doppler at inflow orifice. Results from malposition, suction event/other inflow obstruction: aliased color-flow Doppler, CW Doppler velocity >1.5 m/s
(c) *Low-velocity* inflow (markedly reduced peak systolic and nadir diastolic velocities) may indicate internal inflow-cannula thrombosis or more distal obstruction within the system. Doppler flow-velocity profile may appear relatively "continuous" (decreased phasic/pulsatile pattern)
Outflow-graft abnormality
Typically due to obstruction/pump cessation
(a) 2D/3D imaging: visible kink or thrombus (infrequently seen)
(b) Doppler: peak outflow-graft velocity ≥2 m/s[a] if near obstruction site; however, diminished or absent spectral Doppler signal if sample volume is remote from obstruction location, combined with lack of RVOT SV change and/or expected LV-dimension change with pump speed changes
Hypertensive emergency
New reduced/minimal AV opening relative to baseline exam at normal BP, especially if associated with new/worsened LV dilatation and worsening MR. Note: hypertension may follow an increase in pump speed

(continued)

Table 11.1 (continued)

Pump malfunction/pump arrest	
(a)	Reduced inflow-cannula or outflow-graft flow velocities on color and spectral Doppler or with pump arrest shows diastolic flow reversal
(b)	Signs of worsening HF, including dilated LV, worsening MR, worsened TR, and/or increased TR velocity; attenuated speed-change responses: decrease or absence of expected changes in LV linear dimension, AV opening duration, and RVOT SV with increased or decreased pump speeds; for HVAD, loss of inflow-cannula Doppler artifact

2D two dimensional, *3D* three dimensional, *A* mitral valve late peak diastolic velocity, *AR* aortic regurgitation, *AV* aortic valve, *BP* blood pressure, *CW* continuous wave, *E* mitral valve early peak diastolic velocity, *e′* mitral annular velocity, *HVAD* HeartWare ventricular assist device, *IVC* inferior vena cava, *LV* left ventricular, *LVAD* left ventricular assist device, *LVOT* left ventricular outflow tract, *MR* mitral regurgitation, *MV* mitral valve, *RAP* right atrial pressure, *RV* right ventricular, *RVOT* right ventricular outflow tract, *SV* stroke volume, *TR* tricuspid regurgitation. Adopted and modified from Estep et al. [15]

[a]Note: based on observational data. The "normal" outflow-graft peak velocities are not well defined, because the HVAD outflow-graft diameter is smaller than that of the HM-II device (see discussion in text). Therefore, the normal Doppler-derived HVAD outflow velocities may be somewhat higher on average than those observed for the HM-II LVAD

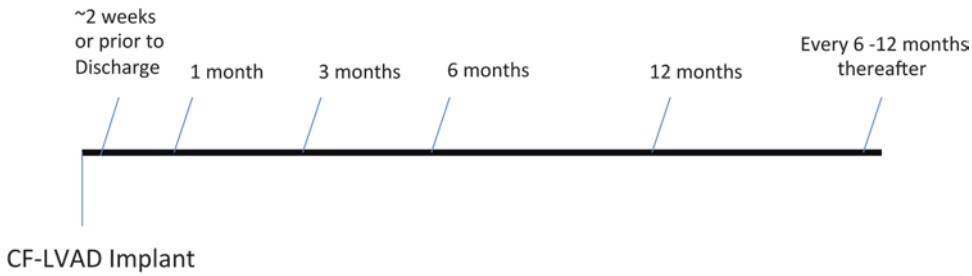


Fig. 11.1 Sample schedule for initial and follow-up surveillance echocardiography of patients with no evidence of device malfunction

Patients with an uncomplicated postoperative course (i.e., absence of HF symptoms, successful weaning from intravenous pharmacologic inotropic and vasopressor agents within 14 days, absence of LVAD controller alarms, and no serologic evidence of hemolysis or infection) should undergo follow-up surveillance TTE at prespecified intervals. Periodic LVAD surveillance echo exams are recommended, to establish patient-specific "baseline" parameters for both LVAD and native heart function. An LVAD surveillance echo exam should be considered at approximately 2 weeks after device implantation or before discharge from the index hospitalization (whichever occurs first). Additional routine surveillance TTE should be considered at 1, 3, 6, and 12 months after implantation and every 6–12 months thereafter; however, at this time, no outcome data support a specific timetable. Figure 11.1 summarizes a reasonable sample schedule for timing postimplantation surveillance TTE.

Comparing serial surveillance exam results with each other (for an individual patient) or to population-based benchmarks can also help the examiner understand a patient's response to LVAD therapy over time. Moreover, surveillance data may allow early diagnosis of occult native heart abnormalities (e.g., development of LVAD-related aortic regurgitation [AR]) or device-related problems, including a drift from previously optimal device speed settings. When surveillance TTE is coordinated with the patient's routine LVAD clinic visits, HF specialists can integrate the information obtained into their clinical assessments and care plans. A putative benefit of routine LVAD surveillance echocardiograms (with optimization protocols when indicated) is better patient outcomes, including early detection and treatment of

complications and fewer hospitalizations for recurrent HF.

Key Points

- Patients with an uncomplicated postoperative course should undergo LVAD surveillance echocardiography at predetermined intervals after LVAD implantation to assess the patients' response to mechanical circulatory support (MCS) therapy and to screen for the development of subclinical complications.
- When possible, LVAD surveillance echocardiography should be coordinated with routine LVAD clinic visits.

Clinical Data Acquisition Standards and Sonographer Reproducibility

Before initiating any LVAD echo exam, sonographers should always annotate the LVAD type and baseline LVAD speed in rotations per minute (rpm) on the imaging screen (Fig. 11.2), in addition to the standard patient demographic data. If the device speed is changed, this should be noted during the exam. The device type and speed information should also be routinely incorporated into reporting templates.

Blood Pressure

The patient's blood pressure (BP), which reflects peripheral vascular resistance, is an important parameter that greatly influences ventricular unloading and the observed echocardiographic findings. Therefore, BP should be recorded just before the exam and immediately afterward if pump speed changes were made. Patients with a continuous-flow LVAD (CF-LVAD) have a reduced and narrowed pulse pressure and may not have a palpable pulse. Therefore, cuff-based BP assessment may be difficult or impossible. In the intensive care unit, BP may be obtained from invasive arterial monitoring devices. In other circumstances in which no pulse is present, a mean arterial BP can be obtained with a standard BP cuff, along with a handheld audible Doppler device for detecting brachial or radial artery flow [2]. Note that the arterial Doppler-derived BP reading lies between the systolic pressure and the mean arterial BP [3]. For practical purposes, if the patient has a pulse (i.e., the aortic valve [AV] is opening), the Doppler-derived BP is the same as the systolic BP. If the patient does not have a pulse (i.e., the AV is not opening), the Doppler BP is considered to be the mean arterial BP.

A current BP measurement is necessary for accurate echo interpretation and for safety reasons during "speed change" protocols, particularly when changing to higher speed settings. Susceptible patients may develop clinically significant hypertension in response to increased LVAD flow, and a mean arterial pressure of <85 mmHg is recommended [4]. Hypotension is generally defined as a mean arterial pressure of <60 mmHg and may be associated with traditional symptoms or signs of hypoperfusion. With CF-LVADs, one challenge is that a sonographer (or some other trained and available individual) needs to be facile at obtaining an arterial Doppler-derived BP reading. To facilitate the care of CF-LVAD recipients, better BP monitoring techniques may be needed [5].

Key Points

- Although BP readings can be challenging to obtain in LVAD patients, this variable is important because it significantly influences echo findings and their interpretation.
- In the absence of a palpable pulse, BP measurement may require audible Doppler interrogation by an appropriately trained individual before the echo exam.
- Susceptible patients can have marked hypertension after the LVAD pump speed is increased. Therefore, BP measurement should be repeated after a significant pump speed increase, particularly if the patient's BP is elevated at the baseline pump speed.

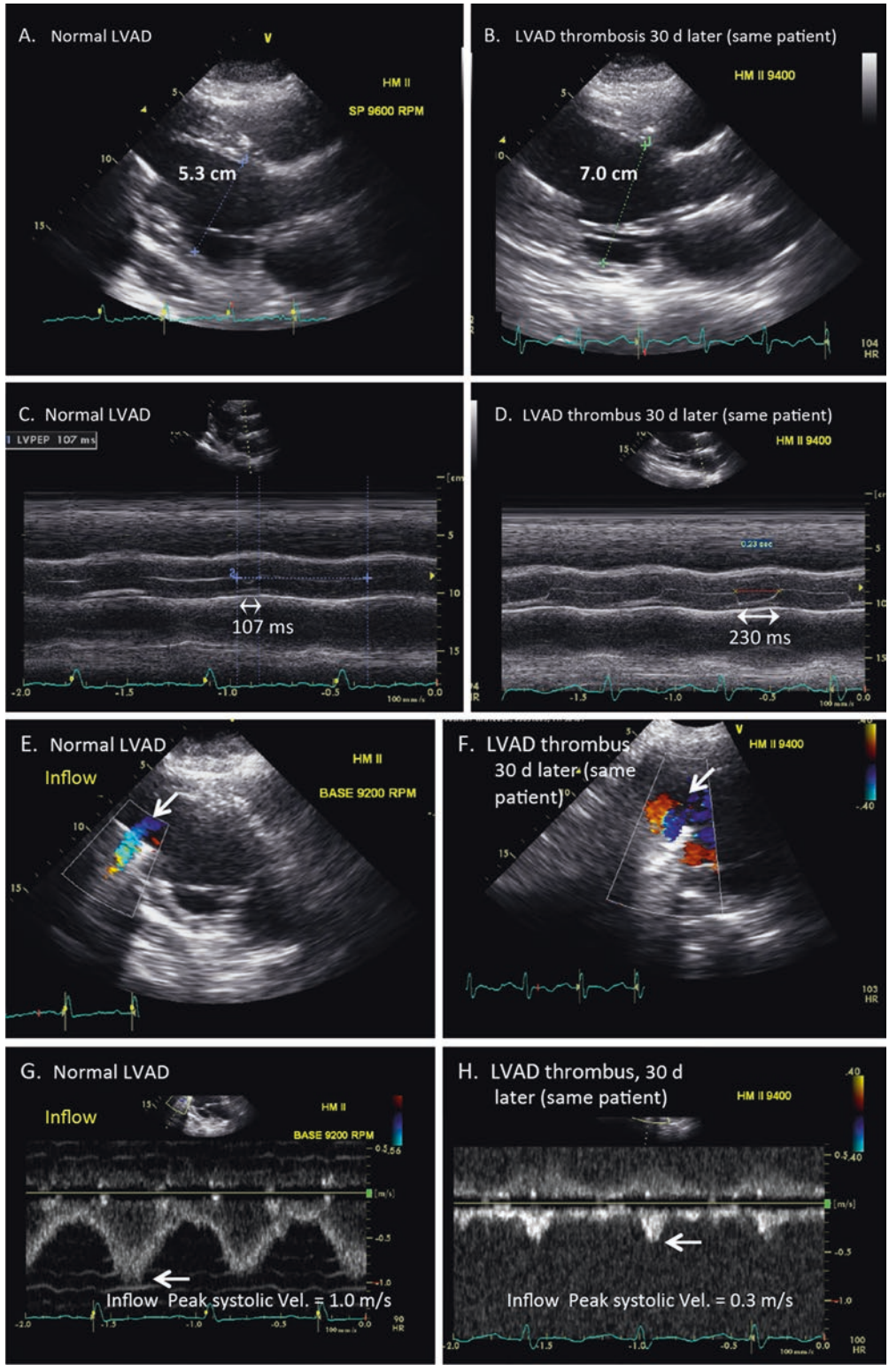


Fig. 11.2 Side-by-side comparison of multiple imaging metrics in the same patient before and after HM-II LVAD impeller thrombosis. (**a**) LVIDd, normal LVAD; (**b**) increased size by LVIDd after LVAD thrombosis; (**c**) AV M-mode, minimal opening (107 ms) during normal LVAD function; (**d**) markedly increased AoV opening duration

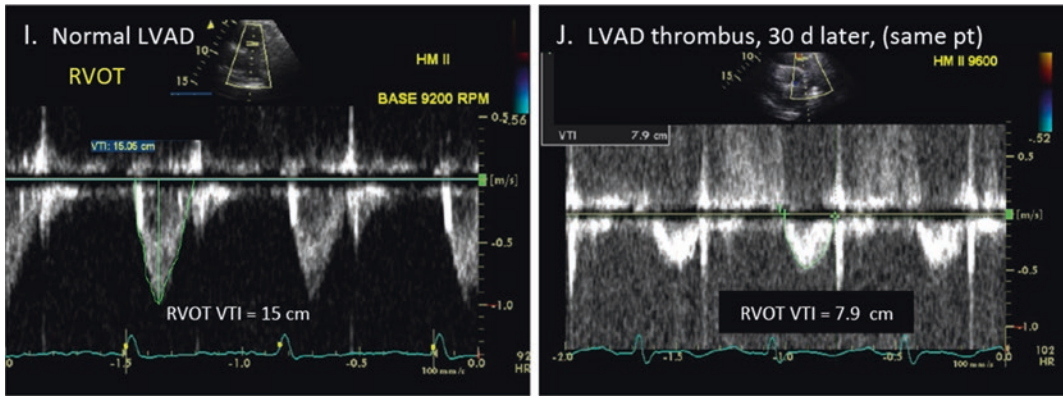


Fig. 11.2 (continued) (230 ms) after internal LVAD thrombosis; (**e**, **g**) inflow-cannula color-flow (*arrow*) and pulsed Doppler images, respectively, during normal LVAD function; (**f**, **h**) very-low-velocity inflow-cannula systolic flow on color-flow (*arrow*) and pulsed Doppler images, respectively, with nearly absent diastolic flow (view **h**) after development of impeller thrombosis; (**i**) RVOT pulsed Doppler VTI = 15 cm during normal LVAD function; (**j**) RVOT pulsed Doppler VTI = 7.9 cm after LVAD thrombosis. *Inflow* inflow cannula; *vel.* velocity

- A mean arterial BP of <85 mmHg is recommended.
- Hypotension is generally defined as a mean arterial pressure <60 mmHg. It may be associated with traditional symptoms or signs of hypoperfusion.

LV Size and Systolic Function

Linear and volumetric approaches for determining LV size and systolic function in non-LVAD patients have been described by Lang and colleagues [6]. These methods may or may not be appropriate for LVAD patients, as outlined below.

LV Size

As mentioned above, the left ventricular internal dimension at end-diastole (LVIDd) from the 2D parasternal long-axis image is considered the most reproducible measure of LV size in LVAD recipients (Fig. 11.2a, b). In patients with a normally functioning CF-LVAD, severely depressed native LV function, and altered mitral valve opening, determining end-diastole may be difficult. In this scenario, correlating the images to the electrocardiographic signal can be helpful. Additionally, using a microbubble contrast agent should be seriously considered when endocardial definition is insufficient for accurate LVIDd measurement [7]. Previous data from HeartMate II (HM-II)-supported outpatients in stable condition suggest that the LVIDd is probably at least 15% lower than the preimplantation value 3 months after implantation [8, 9]. Care must be taken to correlate LV end-systolic versus end-diastolic diameters with the electrocardiographic signal. Paradoxically, the LVIDd may be smaller than the left ventricular internal dimension at end-systole (LVIDs); this is an important finding, as it may indicate excessive LVAD unloading, severe right ventricular (RV) dysfunction, or both.

Left ventricular volumes, as determined by the Simpson's biplane or single-plane method of disks (Fig. 11.3), reflect the LV size more accurately than do linear measurements. However, measuring the LV size by volume may be technically challenging after LVAD implantation because of apical shadowing/dropout associated with the inflow cannula. This is one reason why postimplantation LV volumes assessed by echocardiography are smaller than those assessed by

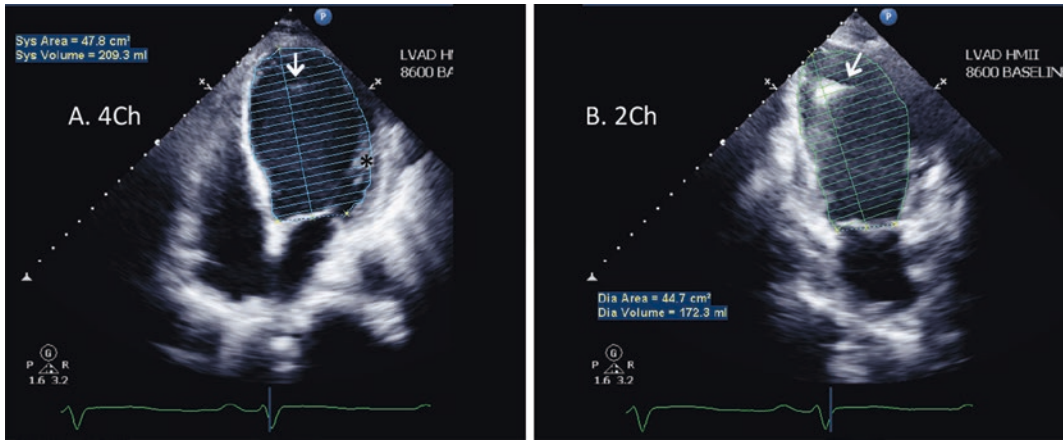


Fig. 11.3 Left ventricular end-diastolic volume (LVEDV), as measured by Simpson's biplane method of disks. This method is preferred for LV size assessment when possible. Simpson's single-plane LVEDV method (using the best-/least-foreshortened (**a**) four-chamber [4Ch] *or* (**b**) two-chamber [2Ch] view) may suffice for LV size assessment and may be superior to linear measurements (e.g., Fig. 11.2). The inflow cannula (*arrow*) and anterolateral papillary muscle (*Asterisk*) are excluded from the endocardial tracing. *Note:* In view **b**, aneurysmal remodeling of the LV apex (relative to the LV base), which would cause underestimation of LV size by parasternal long-axis-view linear measurements (e.g., Fig. 11.2a, b)

cardiac computed tomography [10]. A reasonable LV diastolic volume assessment is possible in many ambulatory LVAD patients, and this metric can be incorporated into the surveillance exam, particularly at the baseline pump speed setting. However, LVIDd measurement, being more expediently acquired and reproducible, is practical for tracking the relative LV size over time at a baseline pump speed (e.g., Fig. 11.2a, b vs. Fig. 11.3) and in the context of a speed-change exam (see below) for quick problem solving. That the serial LVIDd measurement (combined with the degree of AV opening) can be used as a surrogate marker for the degree of LV unloading in CF-LVAD patients seems intuitive and is supported by the limited available literature, which is derived primarily from HM-II studies. However, robust outcome data are limited, and applicability to patients with a HeartWare LVAD (HVAD), from whom there is less evidence, has not been demonstrated at this time [11].

LV Systolic Function

Accurately determining LV volumes is challenging after device implantation. So, too, is accurately and meaningfully assessing overall LV systolic function from the patient's LV ejection fraction (LVEF). The limitations of LVEF measurement are both technical (with regard to imaging quality) and physiologic. The LV endocardium may be difficult to visualize because of apical foreshortening, apical shadowing from the device, or acoustic dropout (signal attenuation). Physiologic challenges related to the LVAD include enhanced interventricular dependence and discordant septal and inferolateral wall motion, which can vary considerably in the same patient at different pump speeds. If the LV endocardium, including the apex, can be adequately visualized, with or without a microbubble contrast agent, the preferred method for calculating the LVEF is the biplane method of disks (modified Simpson rule; Fig. 11.3) [6]. Although other parameters for LV systolic function can be considered, LVEF is an important surrogate because it can reveal possible LV worsening or recovery. Therefore, surveillance and recovery LVAD exam reports should include an LVEF assessment, even if only a qualitative assessment is possible. However, LVAD support markedly reduces LV afterload, an important determinate of LVEF. Therefore, the value of LVEF for

determining systolic function during LVAD support must be taken into consideration during clinical decision-making.

Other methods: In patients with suboptimal apical but adequate parasternal views, the following methods for measuring LV systolic function may be considered, although their accuracy has not been validated in LVAD patients:

1. The LV fractional area change (FAC) method at the mid-papillary muscle level on 2D short-axis views: FAC (%) = [(end-diastolic area − end-systolic area)/(end-diastolic area)] [12].
2. The Quinones method for determining the LVEF [13], with the assumption of an akinetic apex given the presence of the apical inflow cannula.
3. The LV fractional shortening (%) method: FS = [(LVIDd − LVIDs)/(LVIDd)], where FS = fractional shortening and LVIDs = the LV internal dimension at end-systole [6], which has been used in LVAD patients [10, 14].

The linear and volume measurements of systolic function noted above represent possible methods of tracking the course of individual patients, serving as their own controls, over time. However, routinely using the three methods described above may not be feasible or advisable for many LVAD patients because of segmental wall motion abnormalities, exaggerated paradoxical septal motion, ventricular dyssynergy, or ventricular septal shift, the extent of which could change at varying pump speeds in the same patient. Note that calculating the LVEF from the LV stroke volume is not recommended, because many LVAD patients have beat-to-beat variations in this parameter [15]. Previous data suggest that most outpatient HM-II recipients in stable condition have persistent moderately to severely depressed LV systolic function during the first 6 months after device implantation [8, 9].

Key Points

- After CF-LVAD activation, the LVIDd may be the most reproducible measure of LV unloading that can be tracked over time and at different pump speeds.
- The LV end-diastolic volume is a more accurate representation of LV size than is the LVIDd.
- After LVAD implantation, measuring LV volumes and the LVEF can be technically challenging. When the LVEF needs to be obtained (particularly to assess for LV recovery), the Simpson biplane method of disks is recommended for use when possible.

LV Diastolic Function

It can be assumed that LVAD patients have markedly abnormal baseline diastolic function. Although the standard LV diastolic function parameters [16] can (and, in the context of clinical research, should) be measured and included in the report, there is a paucity of data validating their clinical usefulness in patients receiving LVAD support. However, the LVAD echo report should not include an assessment of LV diastolic function, which has not been validated in LVAD-supported patients. Using certain acquired diastolic parameters could be helpful, particularly when they are correlated with symptoms in individual patients. This should be done at the discretion of the interpreter, because these parameters may reflect changes in the degree of LV unloading when compared with data recorded during previous examinations or at different pump speeds during the same exam.

Previous data suggest that the mitral E velocity (cm/s), left atrial volume (mL), pulmonary vascular resistance (Wood units), and pulmonary artery systolic pressure (mmHg) are significantly reduced and that the mitral deceleration time (ms) is significantly prolonged in outpatients whose condition is stable 3–6 months after HM-II implantation [8, 9]. How these parameters should be integrated into postimplantation clinical management is currently unclear, as is their prognostic value for patient outcomes. For clinical LVAD echo reporting purposes, a practical approach at this time may be to use the following (or a similar) statement: “Interpretation of the degree of LV diastolic

dysfunction (presumed abnormal) is not provided because of continuous-flow LVAD support."

Key Points

- It can be assumed that LVAD patients have markedly abnormal baseline diastolic function.
- How LV diastolic parameters should be integrated into the interpretation and report of an LVAD echocardiography examination and any resulting treatment decisions is currently undefined, as is these parameters' prognostic value for patient outcomes.

RV Size and Systolic Function

Many of the standard measures of RV size and systolic function [17], including linear dimensions, RV FAC, tricuspid annular plane systolic excursion (TAPSE), and right-sided cardiac output, can feasibly be measured in LVAD patients [8, 18, 19]. However, recent data suggest that the correlation of TAPSE with overall RV systolic function may be weaker after cardiothoracic surgery, so this variable may have less clinical utility than the other measures [20]. Current data regarding the expected response of RV systolic function after LVAD implantation are conflicting: one study showed a significant improvement in RV FAC at 3 months [9], but another study did not show a significant difference in this parameter at either 1 or 6 months [8].

Valvular Assessment

Aortic Valve

Evaluating and reporting the degree of AV opening (if any) are important because it is affected by several other parameters, including LVAD speed, native LV function, volume status, and peripheral vascular resistance. In addition, whether the AV opens may have clinical implications. Whereas recent guidelines recommend that the LVAD speed be set low enough to allow at least intermittent AV opening [21], opening may not occur at any LVAD speed in patients with extremely poor native LV function. The frequency of AV opening is most accurately assessed by recording multiple (5 or 6) cardiac cycles at a slow M-mode sweep speed (e.g., 25–50 mm/s) (Fig. 11.4); the valve should be characterized as opening with every cardiac cycle, opening intermittently, or remaining closed [15, 22].

Many HF teams also request that the duration of AV opening be measured (in ms) from the same M-mode acquisitions. This parameter may vary from beat to beat, so it is best to measure several beats and report an average value. When the AV opening duration is relatively constant, a faster sweep speed (e.g., 75–100 mm/s) may be appropriate (Fig. 11.4). An important potential pitfall of using M-mode to assess the presence and duration of aortic cusp separation is illustrated in Fig. 11.5. In this example, AV semilunar cusp conformation, combined with cardiac translational motion or slightly off-axis imaging, can create the false appearance of aortic cusp separation when the cusps are not actually separating. Careful attention and the additional use of color M-mode may be useful in difficult cases to avoid M-mode "pseudo AV opening" or an exaggerated AV opening duration. However, in some cases of "minimal" AV opening, the duration of AV cusp separation and the duration of forward systolic flow are not always the same, and using color M-mode can help to document this finding (Fig. 11.6).

In patients whose AV remains closed, it is important to evaluate for aortic root thrombus, which may be transient or associated with commissural fusion. Continuously closed aortic cusps have been associated with the development of aortic root thrombosis and LVAD-associated AR [23], as discussed below. Fusion of the aortic cusps, either surgical or secondary to chronic aortic cusp closure, can be recognized on speed-change echocardiograms (discussed below).

New-onset ("de novo") AR is found in approximately 25–33% of patients 12 months after LVAD implantation [24, 25] and is a key finding, given its adverse effects on LVAD performance and its association with morbidity and mortality [26–28]. Several studies suggest that persistent AV closure is a risk factor for de novo

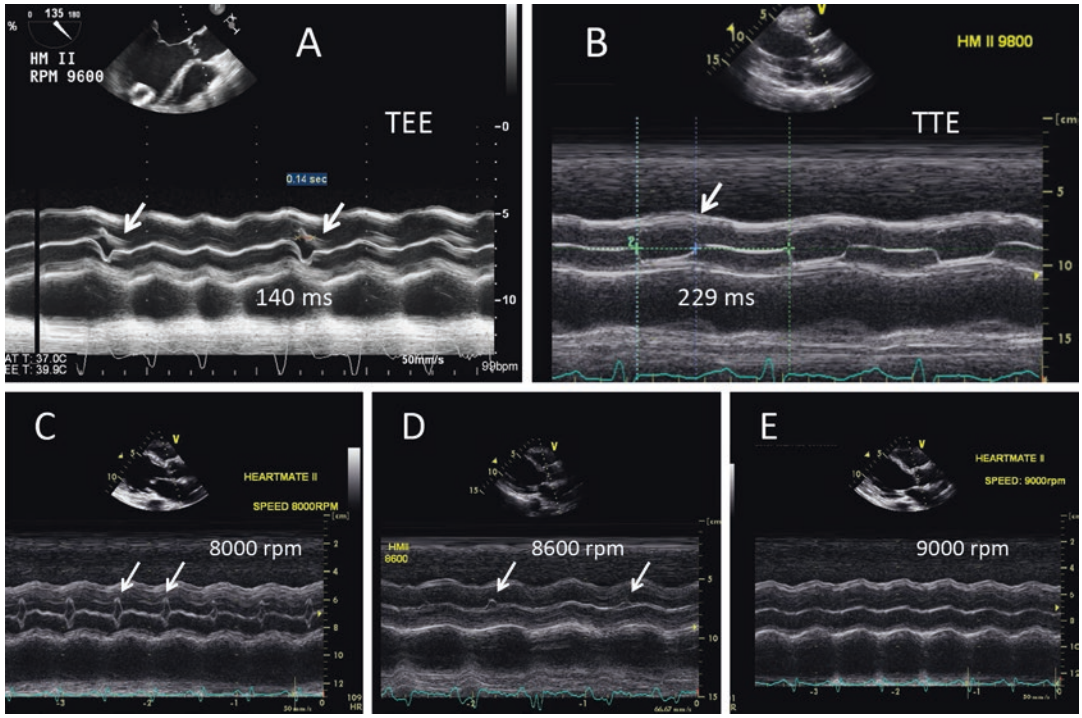


Fig. 11.4 The duration of AV opening during LVAD support can be easily measured by using M-mode during either TEE (**a**) or TTE (**b**). In view **a**, the AV "barely opens" intermittently (*arrows*); this maybe related, in part, to an arrhythmia and suggests normal LVAD function at a pump speed of 9600 rpm. In view **b**, there is near-normal AV opening, with durations of >200 ms; this may be an abnormal finding at a high LVAD pump speed (9800 rpm). (**c**–**e**) The expected progressively reduced duration of AV opening in the same patient during a ramp (speed-change) echo exam at different HM-II pump speeds: In view **c** (8000 rpm), the AV "barely opens," in view **d** (8600 rpm), the AV "opens intermittently" (*arrows*); in view **e** (9000 rpm), the AV "remains closed"

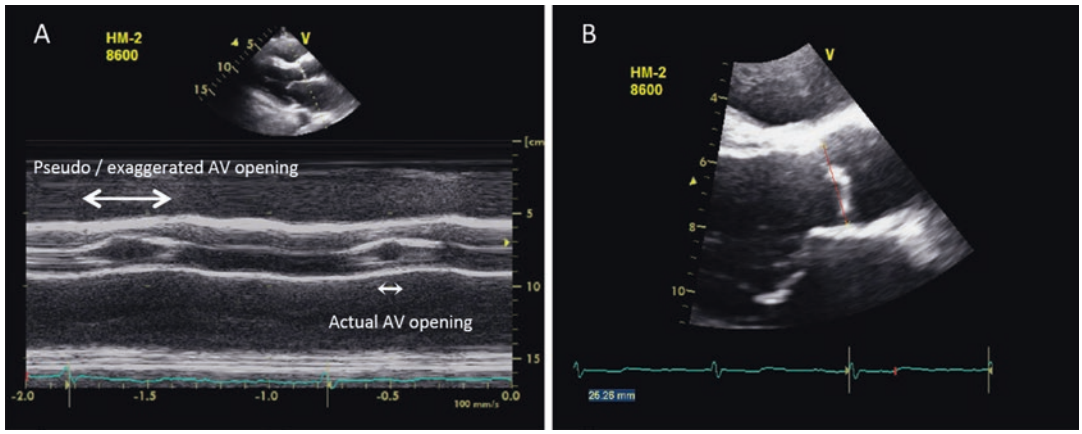


Fig. 11.5 Images suggestive of an exaggerated or "false" AV opening duration, as assessed by M-mode. This artifact should be suspected when the aortic cusp opening shape is fusiform (**a**). Although the apparent M-mode AV opening duration in this case appeared to be >200 ms (*arrows*), there was, in fact, little or no AV opening. (**b**) This error was due to several factors, including the semilunar shape of the AV cusps, placement of the interrogating cursor to the left of the cusp closure line (view **b**: *red line*), and translational motion of the aortic root. This pitfall could have negative implications when the examiner relies solely on M-mode for selecting the AV closing speed during an LVAD optimization protocol. M-mode should not be used in isolation. False M-mode AV opening can be identified by correlating M-mode findings with the 2D image and color M-mode (in the presence of AR) to validate the extent of AV opening

AR after LVAD implantation, even when no aortic root thrombus is present (Fig. 11.7) [24, 29, 30]. Standard methods for quantifying AR [31] may be challenging to use after LVAD implantation. In the absence of definitive cutoff criteria to define mild, moderate, and severe AR after LVAD implantation, one should perform an aggregate assessment based on duration (predominantly diastolic vs. continuous AR flow by spectral Doppler), AR jet vena contracta width (significant AR vena contracta ≥3 mm, see Table 11.1), the presence or absence of holodiastolic flow reversal in the descending thoracic aorta on suprasternal notch views, jet height relative to the LV outflow tract (LVOT), comparative LVAD and native-circuit flow measures (Figs. 11.8 and 11.9), and LV chamber size. Additionally, significant AR noted on LVAD surveillance echocardiography can be further evaluated with device controller data and the cardiac response during LVAD problem-focused echocardiography with speed changes, as described below.

Key Points

- Recording multiple cardiac cycles with color M-mode at a sweep speed of 25–50 mm/s is recommended to accurately assess the frequency and duration of AV opening.
- Persistent AV closure can be associated with aortic root thrombus and de novo AR.
- If aortic root thrombus is suspected, decreasing the LVAD pump speed (e.g., during a planned speed-change exam) should be avoided, because it could result in sudden AV opening.
- After LVAD implantation, AR is not uncommon. Assessment of AR severity is partly based on careful color Doppler analysis in the parasternal long-axis view.

Mitral Valve

As noted above, LV unloading generally leads to reduced mitral valve annular dilatation, improved leaflet coaptation, and, ultimately, reduced mitral regurgitation (MR) severity. Persistence of significant MR after LVAD support begins may indicate inadequate LV unloading or inflow-cannula malposition and interference with the subvalvular apparatus. If MR is present, it can be quantified by standard methods [32]. Incidental post-LVAD MR may also represent LVAD malfunction and should be discussed with the clinical team.

Tricuspid and Pulmonary Valves

Like MR, moderate or greater tricuspid regurgitation (TR) is an important finding on LVAD surveillance echocardiography, because this condition can be associated with insufficient LV unloading (functional TR), excessive LV unloading with a leftward shift of the interventricular septum (e.g., a suction event), elevated systolic pulmonary pressures, or intrinsic RV systolic dysfunction. Distinguishing among these causes by using echocardiographic parameters is discussed in further detail below. Regardless of the cause, TR after LVAD implantation can generally be assessed with standard methods [32]. Furthermore, the native pulmonary valve typically remains functionally normal after LVAD implantation and can be interrogated by using standard methods when significant stenosis or regurgitation is suspected [31, 32].

Interventricular Septal Position

The end-diastolic interventricular septal position, which is dependent on the interventricular pressure gradient, should be routinely reported as neutral, leftward-shifted, or rightward-shifted. A leftward shift can be due to elevated RV end-diastolic pressures, reduced LV preload, or LV over-decompression resulting from excessive LVAD speed; differentiation among these causes is further discussed below. A rightward shift is generally due to elevated LV end-diastolic pressures resulting from an inadequate LVAD speed setting, pump dysfunction, severe AR, or an increased LV afterload.

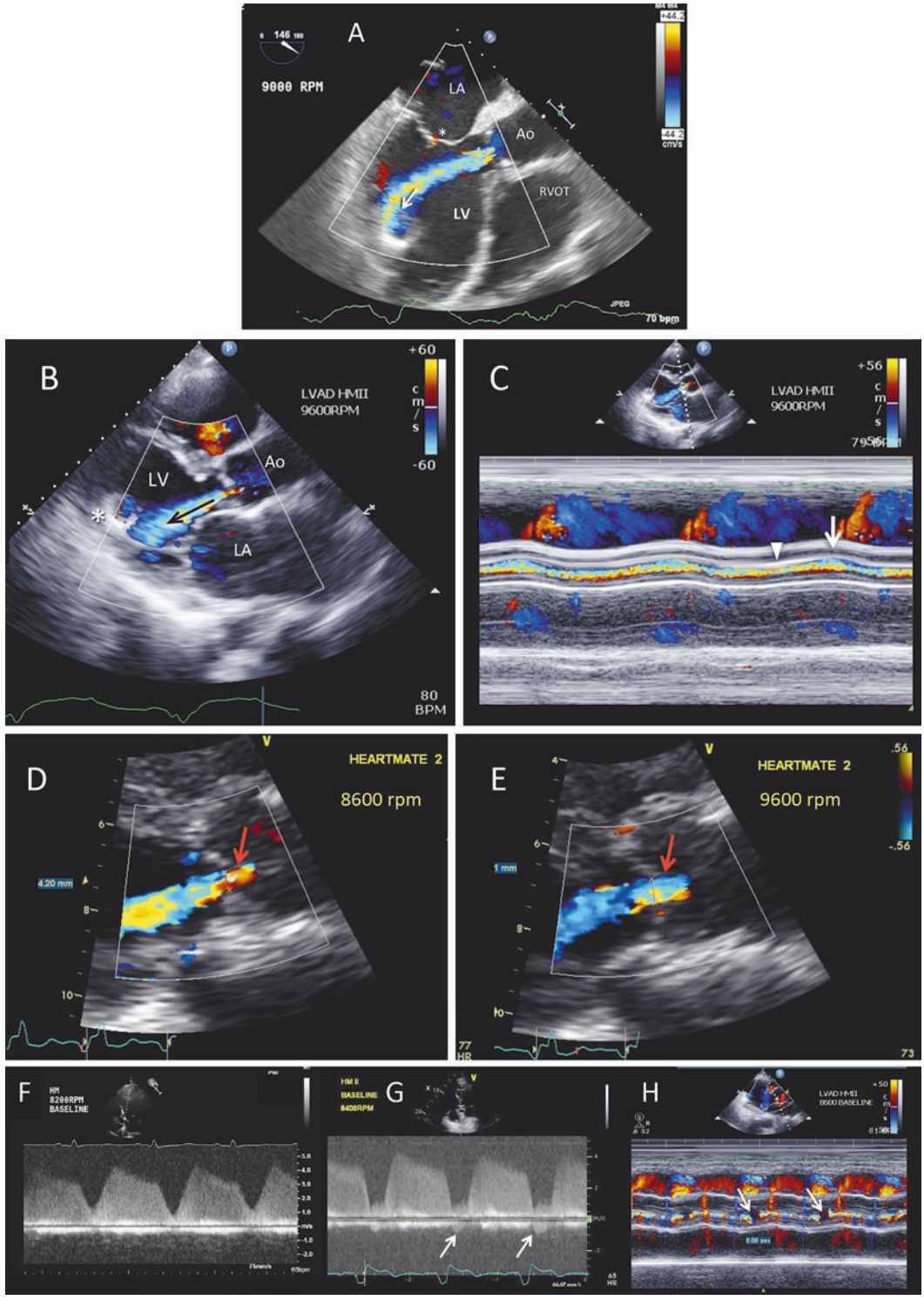


Fig. 11.6 Assessment of AR. (**a**) TEE shows at least moderate—and possibly severe—continuous AR during LVAD support. The AR vena contracta (VC) is clearly >3 mm, and the jet width/LVOT width is clearly >46%. Color-flow Doppler reveals inflow-cannula systolic entrainment of the AR jet (*arrow*). A closed MV and trace MR (*Asterisk*) are

Inflow-Cannula and Outflow-Graft Interrogation

Inflow Cannula

Usually, the apically inserted inflow cannula can be adequately imaged in standard or modified 2D parasternal and apical TTE views. The sonographer's objective is to reveal the inflow cannula's location and orientation in relation to the interventricular septum and other LV structures. The inflow cannula can often be visualized with 3D echo techniques, and this approach can be used as a complementary imaging method by examiners experienced in 3D imaging. As noted above in the section on perioperative TEE, color Doppler interrogation of a properly aligned inflow cannula should reveal laminar, unidirectional flow from the ventricle to the inflow cannula, with no evidence of turbulence or regurgitation [33]. Pulsed and continuous-wave (CW) spectral Doppler interrogation may require "off-axis" modification of a standard parasternal, apical, or short-axis TTE view to achieve true coaxial alignment between the sampling beam and inflow-cannula flow; such interrogation should additionally reveal the flow to have a low peak velocity (<1.5 m/s). Because of native LV contractility, cannula flow generally remains pulsatile to some degree even when the AV does not open [9, 15]. Recording both the peak systolic and the nadir diastolic velocities over at least 3 or 4 cardiac cycles is recommended (Figs. 11.10 and 11.11).

The inflow cannula should be routinely interrogated with CW spectral Doppler at the baseline pump speed and particularly during speed-change exams (discussed below) to screen for inflow obstruction. Note that in many cases, a normal inflow-cannula spectral Doppler flow-velocity profile can be contaminated by low-velocity diastolic AR or mitral inflow (Fig. 11.12). Moreover, during TEE evaluation of the inflow cannula, the CW Doppler signal can be contaminated by MR (Fig. 11.5c). The HVAD inflow-cannula flow velocities typically cannot be evaluated by using either color or spectral Doppler because of a characteristic Doppler artifact (Fig. 11.13) related to the inflow cannula's direct connection to the adjacent impeller housing.

Outflow Graft

In contrast to inflow-cannula imaging, visualizing the outflow graft requires the use of atypical echocardiographic windows. The terminal portion of the outflow conduit and its anastomosis to the aorta can generally be visualized from a high left parasternal long-axis view (Figs. 11.8 and 11.14). The midportion of the outflow graft is best visualized from a right parasternal view while the patient is in a right lateral decubitus position. Color Doppler and spectral Doppler interrogations are usually possible from these views; as with the inflow cannula, recording both the peak systolic and nadir diastolic velocities over at least 3–5 cardiac cycles is recommended

Fig. 11.6 (continued) indicative of marked systolic AR. RVOT, right ventricular outflow tract. (**b**, **c**) During LVAD support, at least moderate continuous AR (*arrow*) is observed in the transthoracic parasternal long-axis view with color Doppler (**b**) and color M-mode imaging (**c**); the inflow cannula is denoted by an asterisk. In view **c**, note the variance in the early systolic (*arrowhead*) versus late systolic (*arrow*) AR VC width, as shown by M-mode. This finding is not consistent among different patients; it is likely influenced by several variables and by the fact that the AV cusps can exhibit augmented systolic opening, despite AR, at speeds close to (but less than) the AV "opening speed." (**d**–**e**) The AR VC width may increase at higher pump speeds in the same patient, as seen here. This may partially be due to an increased systemic arterial pressure at higher pump speeds, which presumably increases the AR volume. At both speeds, the VC is >3 mm, indicating at least moderate—and possibly severe—AR. The VC width is 4.2 mm at 8600 rpm in view **d** and is 5.7 cm at 9600 rpm in view E (HM-II LVAD). (**f**) "Continuous" holosystolic and holodiastolic AR, as detected by continuous-wave Doppler (TTE apical 5-chamber view). (**g**) Continuous-wave Doppler (TTE apical 5-chamber view) reveals nearly continuous AR, which significantly extends into the electrical and mechanical systolic period with a brief period of AV systolic forward flow (*arrows*). (**h**) Color M-mode shows minimal AV opening, with a brief duration of low-velocity systolic forward flow (*arrows*). (**i**) TTE parasternal long-axis view of an AR jet on color-flow Doppler imaging (*arrow*). (**j**) The AV opens widely, with forward flow that interrupts AR. However, the AR period extends into the electrical and mechanical systolic period (*arrows*) during HVAD pumping at 2600 rpm

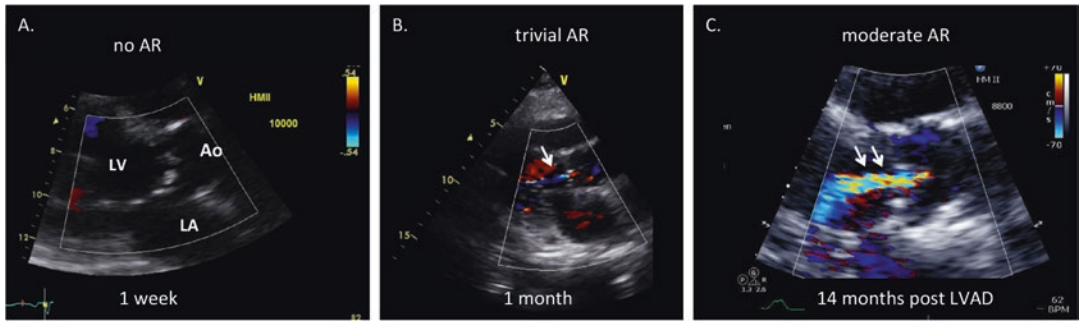
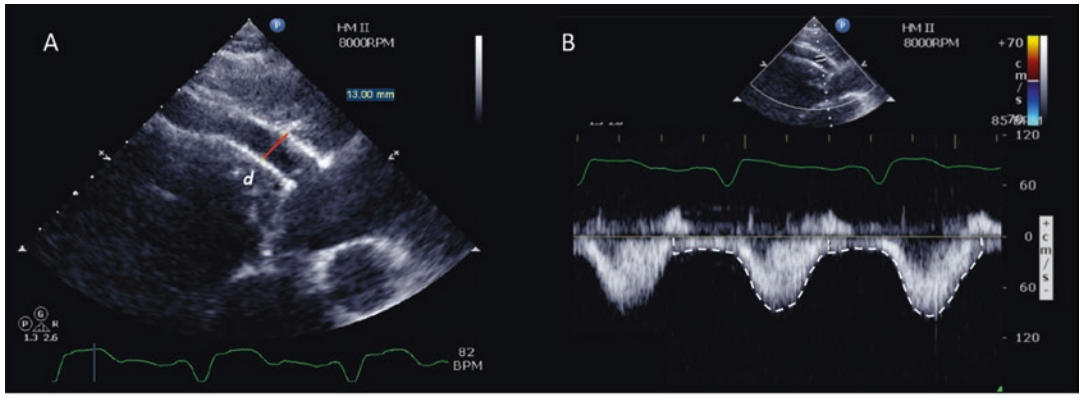


Fig. 11.7 De novo AR after LVAD implantation. This condition progressed from no AR on the baseline surveillance study exam at 1 week (**a**) to trivial AR (*arrow*) at 1 month (**b**) to at least moderate AR (*arrows*, VC >3 mm) at 14 months (**c**). All images are transthoracic parasternal long-axis views with color Doppler. In this patient, the AV never opened at any pump speed during the LVAD support period; aortic root thrombus was not present



LVAD output = (outflow graft $d/2)^2$ x $\prod$ x outflow graft VTI x HR

- For irregular HR or variable stroke volumes, average 3-5 cycles
- Average outflow graft VTI = VTI (throughout *n* cardiac cycles) / *n*
- *Because of continuous flow, the LVAD VTI includes the area under curve for both the systolic and the diastolic periods as shown in B, in which case n = 2.* ($\prod \sim 3.14$)

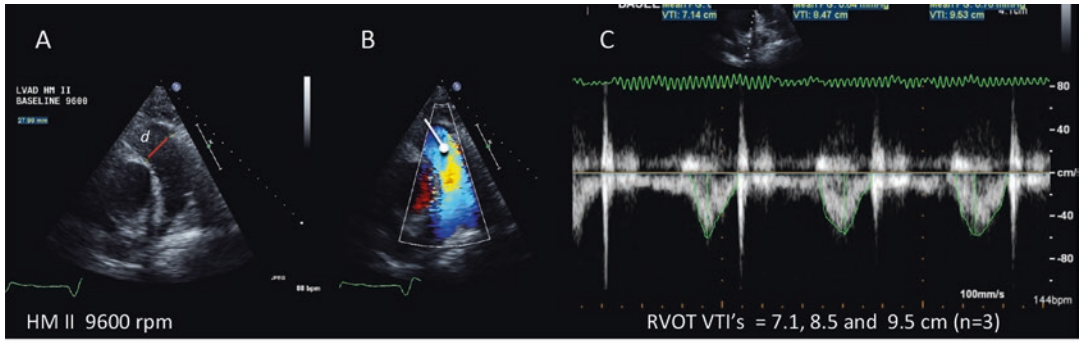
This example: *n = 2 cycles; VTI_1 = 21.2 cm, VTI_2 = 23.6 cm; HR = 82 bpm; d_{graft} = 1.3 cm*

VTI avg = (21.2 + 23.6) / 2 = 44.8 / 2 = 22.4 cm
LVAD Stroke volume = $(1.3\ cm/2)^2$ x $\prod$ x 22.4 cm = 29.7 ml
LVAD Cardiac output = 29.7 ml x 82 bpm = 2,435 ml / min = 2.4 L/min

Note: Although potentially useful, this type of imaging may be challenging to obtain in routine practice.

Fig. 11.8 Direct Doppler measurement of LVAD flow from the distal outflow graft, as evaluated by TTE (**a**). Flow (stroke volume and cardiac output) within the outflow graft (LVAD output) can be derived by measuring the graft's diameter (*arrow*) and the pulsed Doppler VTI at the same location, proximal to the anastomosis site (**b**)

(Fig. 11.14), depending on the uniformity of the spectral Doppler signal. Note that the outflow-graft flow-velocity profile will appear either above or below the baseline in the spectral Doppler display, depending on the sonographer's positioning of the sample volume direction (caudad vs. cephalad) within the graft. There is no standard recommendation for a positive-versus-negative outflow-graft display other than to provide the most coaxial alignment and to ensure that the flow direction (caudad vs. cephalad) is apparent. In some patients, the outflow graft may



Total cardiac output (LVAD + Native LVOT) = RVOT $d/2^2$ x π x RVOT VTI x HR

Fig. 11.9 The total cardiac output (combined LVAD flow output and native LVOT flow output [if any]) is the same as the RVOT cardiac output. The RVOT cardiac output is measured by using standard imaging techniques including (**a**) measurement of the RVOT (pulmonary annulus) diameter (d). Color-flow (**b**) and spectral Doppler (**c**) studies are performed to rule out significant pulmonary regurgitation and to measure the RVOT VTI. *Note:* In the case shown above, the RVOT VTI is low (7–9 cm) at a relatively high HM-II pump speed of 9600 rpm; this was consistent with a low cardiac output, which was due to an obstructed (kinked) outflow graft. It may be useful to average 3–5 VTIs, depending on their variability

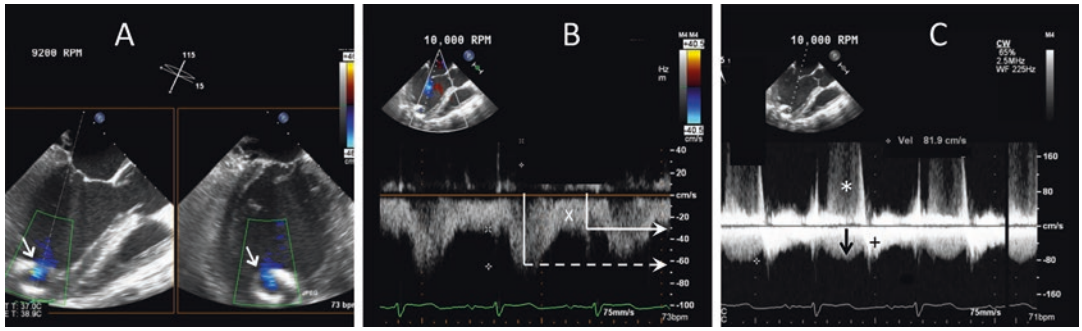


Fig. 11.10 After LVAD implantation, (**a**) TEE shows that the inflow cannula is somewhat directed toward the ventricular septum (*arrow*). This can be acceptable but may predispose to inflow-cannula obstruction after sternal closure or later reduction in LV size. However, cannula position and flow velocities are shown to be acceptable (*normal*) in this case. Simultaneous orthogonal plane imaging reveals unobstructed, laminar inflow-cannula flow on 2D and color-flow Doppler (*blue*) examination. (**b**) Pulsed Doppler interrogation of the inflow cannula shows a typical continuous, systolic dominant inflow pattern. *Dashed arrow* = peak systolic velocity; *X* = nadir diastolic velocity. (**c**) Continuous-wave spectral Doppler interrogation of the inflow cannula (to screen for inflow obstruction) shows normal inflow-cannula systolic flow (*black arrow*); "+" indicates a hybrid signal that results from overlapping of continuous diastolic inflow-cannula flow and diastolic MV inflow; "*" indicates MR velocity

be visualized in subcostal or sternal notch views, depending on the body habitus. At similar flow rates, normal flow velocities within the HM-II outflow graft (16-mm diameter) are somewhat lower than those within the smaller-caliber HVAD outflow graft (10-mm diameter). Otherwise, phasic holosystolic and holodiastolic laminar flow-velocity patterns should be similar between the two devices. The outflow-graft pulsed Doppler time velocity integral (TVI) combined with the expected or measured outflow-graft area may be used to measure LVAD flow directly (see Fig. 11.8 and the discussion below).

Key Points

- When 2D imaging is inconclusive, 3D echocardiography can help delineate the

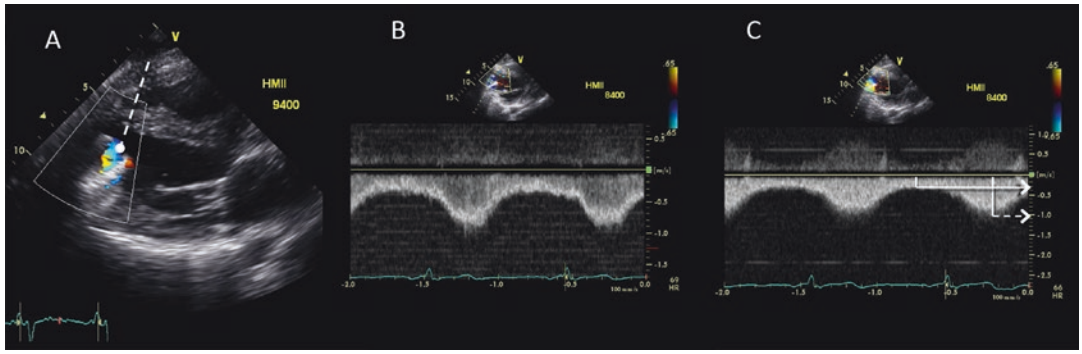


Fig. 11.11 Normal HM-II inflow-cannula flow, assessing which, in this case, required using a modified parasternal long-axis view for coaxial alignment of the sampling volume. (**a**) Color-flow Doppler with pulsed Doppler sample volume at the inflow cannula's inflow zone. The color-flow and pulsed spectral Doppler profiles (**b**) are consistent with laminar flow. (**c**) Peak systolic velocity = 1.0 m/s (*dotted arrow*) and nadir diastolic velocity = 0.3 m/s (*solid arrow*) as assessed by continuous-wave spectral Doppler (Normal peak inflow velocities are typically <2 m/s)

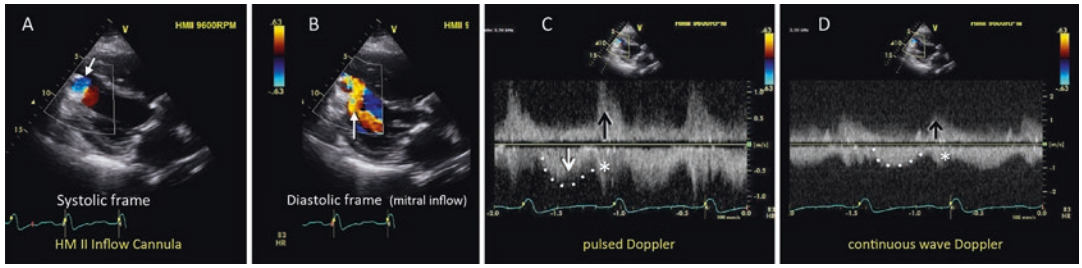


Fig. 11.12 (**a**) HM-II inflow cannula, systolic frame, showing normal color Doppler inflow (*blue*, *downward arrow*). (**b**) HM-II inflow cannula, diastolic frame, with color Doppler showing prominent diastolic mitral inflow (*orange*, *upward arrow*) in a patient with a previous mitral annuloplasty repair. (**c**) Pulsed Doppler examination of the inflow cannula shows normal systolic inflow (*dotted line*). However, prominent bidirectional diastolic velocities are present because of mitral inflow (*arrow*) and interaction between the cannula and the adjacent interventricular septum (*Asterisk*). (**d**) Continuous-wave Doppler shows a similar pattern and rules out obstruction. *Note:* Hybrid/contaminated inflow-cannula Doppler signals may also be observed with AR jets. These types of low-velocity, normal-variant, contaminated inflow-cannula spectral Doppler patterns can be explained with color Doppler and should not be confused with higher-velocity signals (typically >2 m/s), which could signify inflow obstruction. Nonetheless, the pure continuous diastolic inflow, as shown in Fig. 11.11, is not seen, and the diastolic nadir velocity cannot be reported

relationship of the inflow cannula to the interventricular septum and other LV structures.

- In patients with an HM-II LVAD, peak systolic and nadir diastolic inflow-cannula and outflow-graft velocities can be derived from coaxially aligned spectral Doppler.
- HM-II inflow-cannula peak systolic flow velocities are typically <1.5 m/s. Higher velocities suggest possible inflow-cannula obstruction.
- HVAD inflow-cannula velocities cannot be accurately measured because of a characteristic Doppler artifact.
- Peak systolic and nadir diastolic inflow-cannula and outflow-graft velocities should be derived from 3 to 5 cardiac cycles, depending on the regularity of the spectral Doppler contour.
- Outflow-graft velocities of >2 m/s at any level may be abnormal and suggest possible obstruction, although benchmark data are lacking.

Native Heart Versus LVAD Flow Assessment

In the absence of significant pulmonary valve regurgitation, the net cardiac output (combined native LV outflow and LVAD conduit flow) is the same as the right-sided cardiac output. The

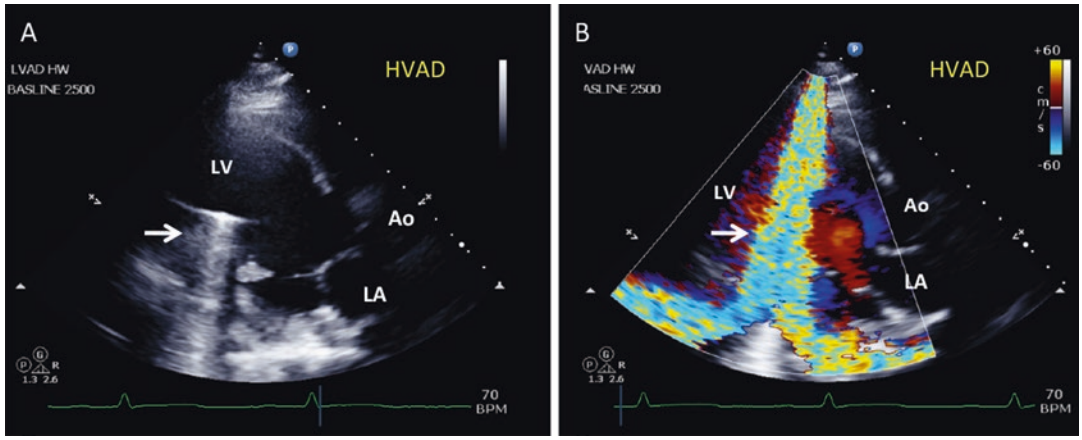


Fig. 11.13 HVAD inflow-cannula artifact. (**a**) Artifact (*arrow*) is visible in a 2D parasternal long-axis view on TTE. (**b**) Typical color-flow Doppler artifact (*arrow*) associated with the HVAD inflow cannula. This artifact prohibits spectral Doppler interrogation of the inflow cannula. Inflow-cannula flow must be surmised by other means (e.g., outflow-graft and RVOT flow, AV opening, LV size changes during pump speed changes)

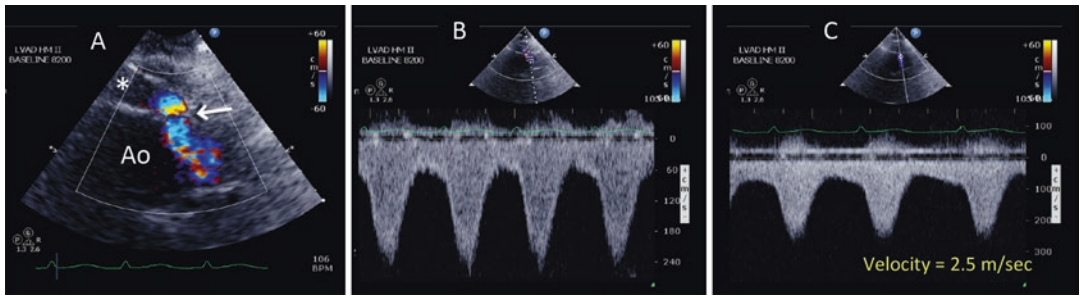


Fig. 11.14 Mild stenosis of the LVAD outflow graft-to-ascending aorta anastomosis site, as assessed by TTE with color and spectral Doppler. (**a**) 2D image: outflow graft (*Asterisk*). The aliased color Doppler signal reveals the site of anastomotic stenosis (*arrow*). (**b**) Pulsed Doppler examination of the anastomotic region shows turbulent flow and an abnormally high peak systolic velocity. (**c**) Continuous-wave Doppler reveals an abnormally high anastomotic velocity of 2.5 m/s

right-sided output is calculated by using the following commonly applied equation: RVOT cardiac output = RVOT pulsed Doppler VTI × [3.14 × (RVOT diameter/2)^2 × HR] (Fig. 11.9), where RVOT is the right ventricular outflow tract, VTI is the velocity time interval, and HR is the heart rate. When the AV does not open and there is no significant AR, the RVOT-derived cardiac output is the same as the LVAD cardiac output. When the AV opens significantly and an adequate LVOT VTI can be measured with pulsed Doppler (and in the absence of significant AR), the LVAD cardiac output should equal the RVOT-derived cardiac output minus the LVOT cardiac output. In patients with significant AR and no AV opening, the LVAD flow can be assumed to be significantly greater than the RVOT-derived cardiac output, owing to a blind loop of LVAD-to-aorta flow as described above. In cases of greater than mild AR, it may be useful to calculate the LVAD cardiac output directly by measuring flow within the outflow graft with pulsed Doppler and the following equation: LVAD output = outflow-conduit VTI × [3.14 × (outflow-graft diameter/2)^2 × HR] (Fig. 11.8) [9, 34, 35], although this approach has not been well validated for the HVAD. When using this formula, accuracy can be increased by measuring the outflow-graft diameter (area) directly at the site of Doppler interrogation,

rather than using the manufacturer's reported graft diameter (which could cause overestimation of flow) [9]. The aortic regurgitant volume would then equal the LVAD stroke volume, measured directly, minus the RVOT-derived stroke volume, as described above and in Fig. 11.9. These Doppler methods can be useful for validating normal or abnormal LVAD flows reported by the device's controller (see discussion of alarms, below) or detecting problems early, in advance of an alarm report.

Key Points

- In the absence of AV opening, significant AR, or significant PR, the RVOT Doppler-derived cardiac output equals the LVAD cardiac output.
- If the AV opens and the LVOT cardiac output can be measured, the LVAD cardiac output can be calculated as the difference between the RVOT and LVOT outputs.
- In patients with significant AR and no AV opening, it may be best to directly compute the LVAD cardiac output by using pulsed-wave Doppler in the outflow graft. An estimate of regurgitant volume can then be computed by subtracting the RVOT cardiac output.

Echocardiography with Speed Changes and Safety Concerns

"Speed-change testing" is part of either an optimization protocol or a problem-focused (ramp) exam, both of which are outlined below. Before a speed-change exam is initiated, the patient's anticoagulant status should be considered.

Speed-change testing is typically performed only if a patient has been receiving therapeutic doses of warfarin or parenteral anticoagulation therapy. Risks of performing speed changes include embolic events associated with sudden AV opening (return to pulsatile flow) in the event of undiagnosed aortic root thrombus or the potential liberation of peripheral or internal pump thrombi, particularly at lower pump speeds. In general, strong consideration should be given to deferring speed-change exams if baseline imaging shows a possible intracardiac or aortic root thrombus.

An experienced and knowledgeable member of the MCS team should be immediately available to solve potential problems and recognize key safety endpoints (discussed below) before an optimization or problem-focused echo exam is initiated. In the case of an optimization exam, unless the supervising MCS medical staff member or an experienced echocardiography medical staff member is actively supervising the exam, the ordering HF team must indicate prospectively what speeds should be tested, which echo parameters should be measured at each speed, what defines the "optimal" LVAD speed for that particular patient, and what the LVAD speed should be at the conclusion of the study. A structured ordering template can facilitate this process; a representative template is shown in Table 11.2, which also outlines reasons to stop a speed-change (ramp) test. These reasons include (1) completion of the test; (2) a suction event (at higher speeds); (3) new symptoms, including palpitations, dizziness, chest pain, shortness of breath, and headache, which may be related to hypoperfusion or hypotension; (4) hypertension; (5) and cannula flow reversal. Because increasing the pump speed can markedly increase the mean arterial BP, the BP should be rechecked at higher pump speed settings [36]. At lower pump speeds, particularly in patients with an elevated mean arterial pressure (hypertension), outflow-graft flow reversal can occur. The inflow-cannula color and spectral Doppler exam should be repeated at each new pump speed to establish the following parameters: (1) the expected progressive decrease in the peak systolic and nadir diastolic flow-velocity ratio with increasing pump speed (Fig. 11.15), (2) possible flow reversal (at lower speeds as mentioned or with pump arrest [Fig. 11.16]), (3) inflow-cannula flow obstruction (Figs. 11.17 and 11.18: suction event), and (4) diminished or absent change in the flow-velocity profile at varying speeds in the case of internal pump thrombosis or other mechanical obstruction (Fig. 11.2) or significant AR.

Table 11.2 Sonographer checklist/ordering worksheet: LVAD-specific demographic data, image acquisition, and safety considerations particular to "speed-change" echo exams (optimization, problem solving/ramp studies)

√	Study type being ordered
	• *Surveillance, initial* (± optimization, preoperative/discharge)
	• *Surveillance, post-discharge* (± optimization, number months post: 1, 3, 6, 12, every 6–12 thereafter)
	• *Problem solving at baseline speed only*
	• *Problem solving at baseline + other speed settings*
	• *Recovery*
	Ordering/responsible physician identified
	Implantation date documented
	Symptoms noted (if applicable)
	Device alarms: if present, type of alarm identified
	Other key clinical history/information related to indication noted
	Anticoagulation therapy adequate if low pump speeds tested
	LVAD name noted on worksheet and annotated on screen
	LVAD speeds (baseline and changes) noted on worksheet and annotated on screen
	Blood pressure (cuff or Doppler) noted on worksheet and annotated on screen *(obtained by designated trained individual at time of exam)*
	Designated person to change pump speed available
	Supervision: appropriate staff to perform speed changes; safety endpoint recognition (e.g., low flow, suction event, hypo-/hypertension)
	Endpoints for speed-change exams • Protocol completion • Hypotension • Hypertension • New symptoms • Device alarm • Signs of a suction event – Decrease in LV size (typically <3 cm) – Interventricular septum shifting leftward – Impeded flow into inlet cannula – Worsening TR due to septal shifting, RV enlargement, or both – Cessation of AV opening – Increased severity of AR (when present at baseline) • Signs of low cardiac output • Aortic root thrombus (lowering speed could open AV) • Cannula flow reversal (at low pump speeds)

AR aortic regurgitation, *AV* aortic valve, *LV* left ventricular, *LVAD* left ventricular assist device, *TR* tricuspid regurgitation

During screening for inflow obstruction, both pulsed and CW spectral Doppler interrogations of the inflow cannula are useful at baseline speed and at each higher pump speed. When possible, Doppler evaluation of the outflow graft is useful at baseline speed, but it may not be needed when pump speed is changed (e.g., during optimization or problem-focused exams, discussed below) unless the baseline values are abnormal or the information might be otherwise relevant for clinical problem solving. The outflow-graft Doppler exam is of greater importance for HVAD patients, because HVAD inflow-cannula velocities cannot be measured with Doppler.

LVAD Optimization Echocardiography

The LVAD optimization echo exam (with speed changes) is generally performed in asymptomatic or minimally symptomatic patients with no device alarms or other clinical indicators of abnormal LVAD or cardiac function. Optimization echocardiography for the LVAD consists of routine comprehensive TTE, first at the baseline speed setting (Table 11.3) and then with stepwise incremental adjustments to the LVAD speed (in rpm). At each new speed, prespecified echocardiographic parameters (Tables 11.4 and 11.5) are collected that reflect LVAD function, native LV function, or both (e.g., LVIDd, interventricular septal position, AV opening frequency/duration, TR or MR severity) [15, 26, 36].

HM-II Speeds

The minimum and maximum speed settings for the HM-II LVAD are 6000 and 15,000 rpm, respectively. The speed can be changed in 200-rpm increments. Although patient dependent, the recommended range of speeds for normal pump operation is 8800–10,000 rpm [37]. With the HM-II pump, speed changes for optimizing device function are usually made in small increments of 200–400 rpm.

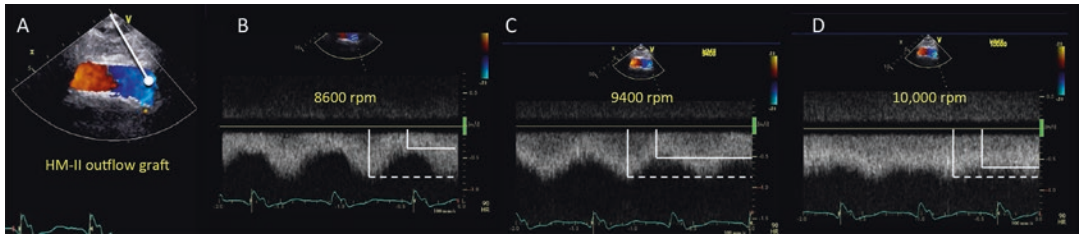


Fig. 11.15 LVAD outflow graft, mid right parasternal window, on TTE. The flow velocity within the outflow graft should appear laminar, with a characteristic diminution of the peak systolic velocity (*dotted line*) and increase in the nadir diastolic velocity (*solid line*) as the pump speed is systematically increased (narrowing of the pulse pressure). *Note:* A similar diminution of the peak systolic velocity and increase in the nadir diastolic velocity occurs as the pump speed is systematically increased in the absence of any provoked inflow obstruction

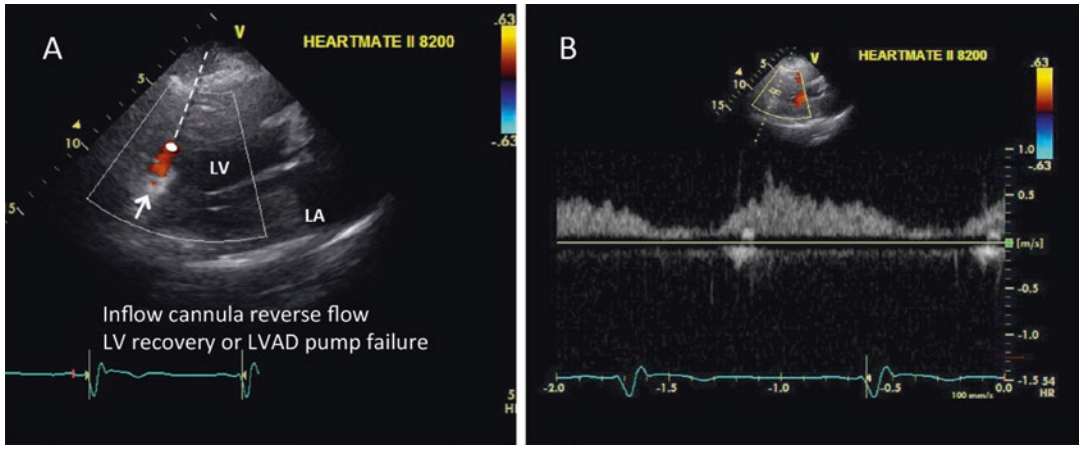


Fig. 11.16 TTE, in the modified parasternal long-axis view, shows HM-II inflow-cannula diastolic flow reversal in a normally functioning LVAD at a relatively low pump speed (8200 rpm) in a patient with significant LV recovery. (**a**) Color-flow Doppler image. The inflow cannula is denoted by an arrow. (**b**) Pulsed spectral Doppler image of the inflow cannula shows reduced systolic forward flow but pandiastolic regurgitant flow (aorta to left ventricle) due to improved diastolic recoil. *Note:* A similar Doppler pattern is seen with LVAD pump arrest, although such arrest is associated with symptoms and echocardiographic signs of HF

Fig. 11.17 (continued) the ventricular septum is bowed toward the left. (**b**) Aliased color-flow Doppler image of the inflow cannula. (**c**) Aliased high-velocity pulsed spectral Doppler image of the inflow cannula. (**d**) Continuous-wave spectral Doppler examination of the inflow cannula shows irregular flow, with systolic velocity "spikes" of up to 3.5 m/s during tachycardia (HR = 154 bpm). (**e**) Right parasternal TTE view of the outflow graft shows low-velocity laminar flow, as evaluated by color Doppler. (**f**) Pulsed Doppler of the outflow graft shows an irregular pattern low-velocity flow consistent with variable degrees of severe inflow-cannula obstruction. (**g**) Apical four-chamber view shows severely dilated right-sided chambers, a tiny LV cavity, and right-to-left bowing of the interventricular septum (*arrows*), with associated severe TR on color-flow Doppler (**h**). The asterisk denotes a pacing lead

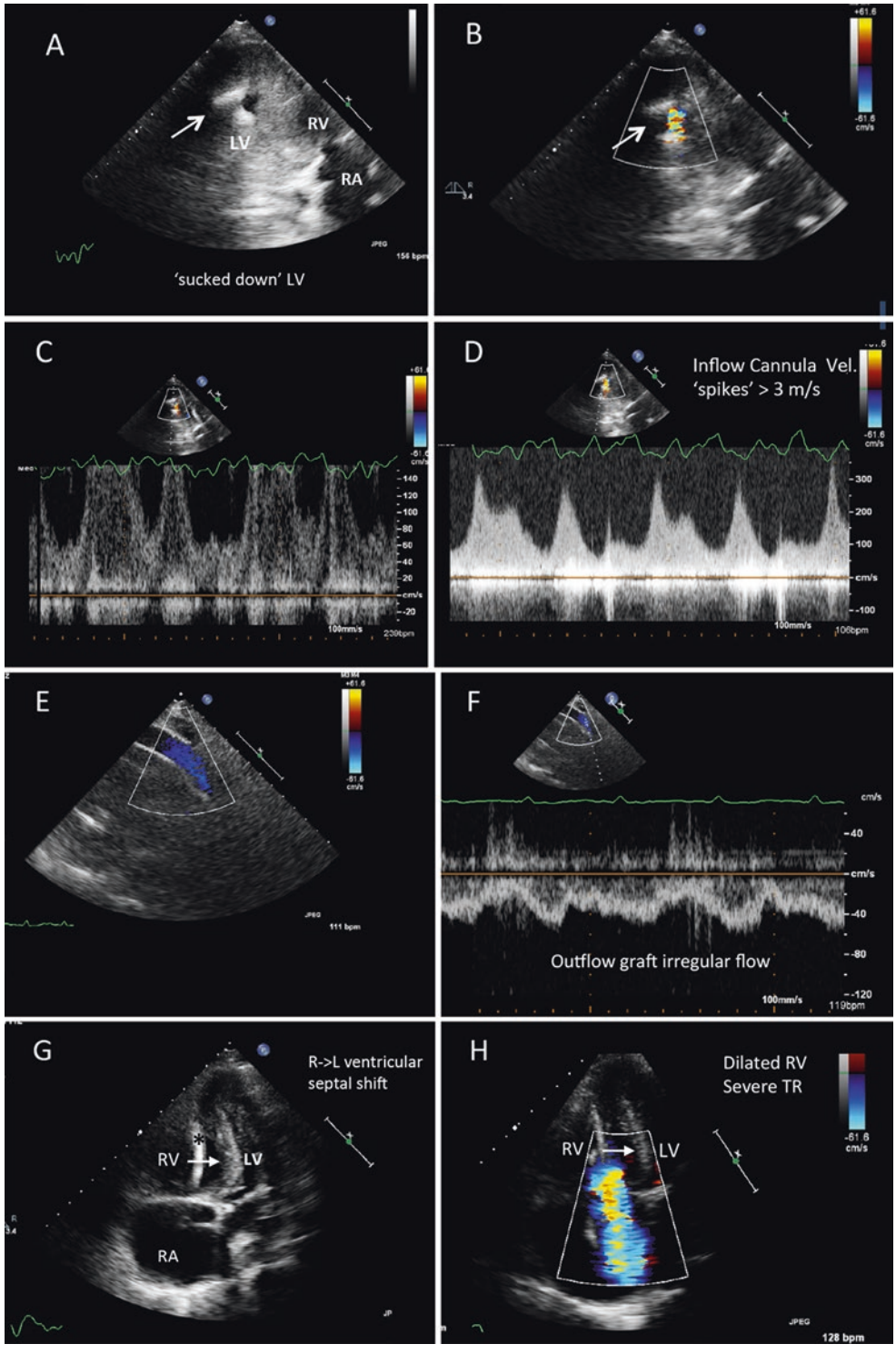


Fig. 11.17 Suction event at a relatively low pump speed (HM-II, 8200 rpm), consistent with severe RV failure. (Because this condition was refractory to medical management, the patient received an RVAD after this exam.) (**a**) Modified parasternal RV inflow tract view. The tiny LV cavity is "sucked down" around the inflow cannula (*arrow*), and

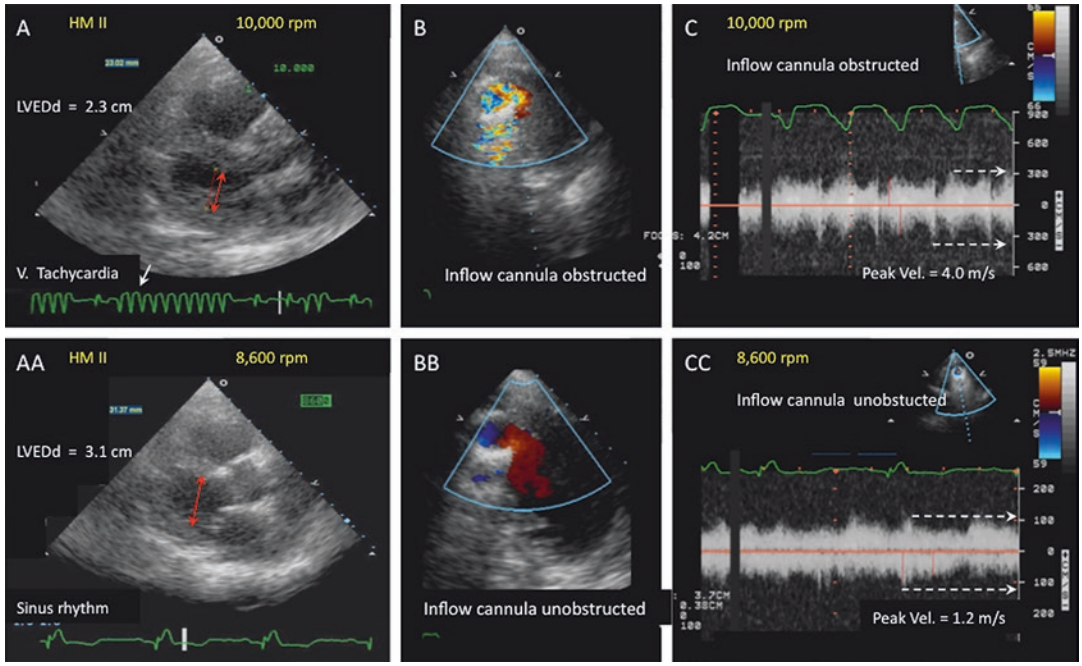


Fig. 11.18 Mechanical ventricular tachycardia due to a suction event at a high pump speed (10,000 rpm), due to new hypovolemia resulting from a gastrointestinal illness. (**a**) Small LV chamber size (LVEDd = 2.3 cm, *red arrows*), with frequent nonsustained ventricular tachycardia (*white arrows*). (**b**) Turbulent, aliased inflow-cannula inflow, as assessed by color Doppler. (**c**) Complex, "spiky," high inflow-cannula inflow velocities up to 4 m/s on continuous-wave Doppler examination. (**aa**) Reducing the pump speed (to 8600 rpm) immediately increased the LVEDd (to 3.1 cm, *red arrows*) and eliminated the ventricular tachycardia (by reducing mechanical contact between the ventricular septum and the inflow cannula). Normal low-velocity inflow-cannula flow is observed on color-flow (**bb**) and continuous-wave Doppler (**cc**) at the reduced pump speed. The LV size remained small (3.1 cm) because of the hypovolemia, which later resolved. *Note:* Mechanical ventricular tachycardia can also be associated with excessive inflow-cannula angulation toward the septum or other endocardial surfaces after sternal closure, particularly at higher pump speeds

HVAD Speeds

The minimum and maximum speed settings for the HVAD are 1800 and 4000 rpm, respectively. The speed can be changed in 20-rpm increments. The recommended range of speeds for normal pump operation is 2400–3200 rpm. With this device, speed changes for optimizing device function are usually made in small increments of 20 or 40 rpm [4].

Some LVAD implantation centers have chosen to include an optimization (speed-change) protocol in all LVAD surveillance echo exams. Others have chosen to include the optimization protocol in the initial surveillance echo examination (typically performed at index hospitalization discharge or 2 weeks after LVAD implantation) and then only as needed when a routine surveillance echo (without speed changes) reveals a less-than-optimal LVAD speed according to predefined criteria [19, 26]. It is important to note that using echocardiography to optimize the LVAD speed is relatively new, and the effect of echocardiography-guided LVAD speed optimization protocols on short- and long-term clinical outcomes is currently unknown. Table 11.6 shows summary benchmark echocardiography parameters from three cohorts of patients from three different institutions, beginning before LVAD implantation and extending up to 12 months afterward.

Table 11.3 LVAD surveillance echo protocol: standard comprehensive TTE (or TEE) with additional LVAD-specific parameters

Blood pressure (if no pulse, Doppler-derived mean arterial pressure), pump type, and baseline speed
Degree of aortic valve opening/closure
Ventricular and interatrial septal position
LV inflow cannula • Location • Note optimal view for visualization • Flow type • Flow direction • Peak systolic and diastolic flow velocities (pulsed Doppler) • Velocity flow pattern
LV outflow graft • Location/note optimal view for visualization • Flow type • Flow direction • Peak systolic and diastolic flow velocities (pulsed Doppler) • Velocity flow pattern
LVAD output • Outflow-graft pulsed Doppler VTI • Cross-sectional area as calculated from the measured cannula diameter or from the known cannula diameter
Total cardiac output • RVOT pulsed Doppler VTI • Calculated cross-sectional area from the RVOT diameter
Pericardium: effusion/hematoma
Post-VAD placement *red flag* **echo findings**
• Ventricular and/or atrial septal shift from midline • Intracardiac shunt • Excessive increase in cannula velocities • Mechanical cannula obstruction • Cannula suction event • Worsening aortic or mitral regurgitation • Cardiac thrombus • Pericardial hematoma/effusion, with or without tamponade • RV dysfunction (multiple parameters in aggregate) – Enlarged RV cavity size – RV systolic dysfunction (qualitative, quantitative as far as possible) – Moderate or severe TR – Elevated RA pressure

LV left ventricular, *LVAD* left ventricular assist device, *RA* right atrial, *RV* right ventricular, *RVOT* right ventricular outflow tract, *TEE* transesophageal echocardiography, *TR* tricuspid regurgitation, *TTE* transthoracic echocardiography, *VTI* velocity time integral

Refer to Table 11.1 for guidance regarding the possible implications of abnormal/"red flag" findings

Determining the "Optimal" LVAD Speed

The definition of optimal LVAD speed varies among implantation centers. However, there is a general consensus among centers that the optimal speed lies between "minimum" and "maximum" speeds, defined as follows:

- The minimum speed is defined by echocardiography parameters as the speed below which the LVIDd (measured in cm) exceeds its baseline value. The interventricular septum may be shifted rightward, MR may become more prominent, AV opening may occur or become more frequent or sustained, and estimated right atrial and systolic pulmonary artery pressures may increase. Clinically, the minimum speed is

Table 11.4 LVAD optimization/ramp echo protocol

Perform baseline LVAD surveillance study (annotate BP, pump type, baseline pump speed)
At baseline pump speed, acquire the following: • LVIDd in the parasternal long-axis view • RV VTI (to calculate cardiac output) in the parasternal short-axis view • AV opening by 2D and M-mode in the parasternal long-axis view (color Doppler M-mode if needed) • 2D imaging in the parasternal long- and short-axis views • Color Doppler examination of AR and MR in the parasternal long-axis and apical views • Color Doppler examination of TR in the RV inflow and apical four-chamber view • Standard mitral valve PW Doppler inflow parameters • Positioning of the interventricular and interatrial septa
Decrease pump speed to as low as **8000 rpm (for HM-II)** *Or* Decrease pump speed to as low as **2400 rpm (for HVAD)** • Wait 2 min • Repeat data acquisition
Increase pump speed by **400 rpm (for HM-II)** *Or* Increase pump speed by **20–40 rpm (for HVAD)** • Wait 2 min • Repeat data acquisition
HM-II: continue to increase pump speed in **400-rpm** increments to a pump speed of up to **12,000 rpm** or until endpoint (below), acquiring data at each stage ***HVAD:*** continue to increase pump speed in **20- to 40-rpm** increments to a pump speed of up to **3200 rpm**, or until endpoint (below), acquiring data at each stage
Endpoints • Completion of test • Suction event: decrease in LV size (typically <3 cm), ± ventricular ectopy, ± inflow-cannula intermittent obstruction, leftward ventricular septal shift, worsening TR • Symptoms including, but not limited to, palpitations, dizziness, chest pain, shortness of breath, or headache • Hypertension (e.g., MAP > 100 mmHg or symptoms) • Hypotension (e.g., MAP < 60 mmHg or symptoms)

Note: inflow-cannula color and spectral Doppler (including CW Doppler) should be evaluated at each pump speed to test for obstruction. Outflow-graft Doppler evaluation is needed at baseline but is optional at speed changes if LVAD function is normal. When abnormal conditions are being evaluated, additional parameters may be assessed when possible, such as outflow-graft velocity profile/stroke volume (e.g., for obstruction, to assess AR volume) and outflow-graft-to-aortic anastomosis to assess obstruction or flow reversal

2D two dimensional, *AR* aortic regurgitation, *AV* aortic valve, *BP* blood pressure, *HM-II* HeartMate II, *HVAD* HeartWare ventricular assist system, *LV* left ventricular, *LVAD* left ventricular assist device, *LVIDd* left ventricular internal diameter at end-diastole, *MAP* mean arterial pressure, *MR* mitral regurgitation, *PW* pulsed Doppler, *RV* right ventricular, *TR* tricuspid regurgitation, *TV* tricuspid valve, *VTI* velocity time integral

that speed below which the patient's functional capacity is reduced, congestion develops, or end-organ function worsens.

- The maximum speed is defined echocardiographically as the speed above which the interventricular septum shifts leftward or impedes flow into the inflow cannula. Tricuspid regurgitation may worsen owing to the leftward interventricular septal shift with tricuspid valve annular distortion or RV enlargement, the AV may cease opening, and AR (when present) increases. Some or all of these changes above the maximal speed may constitute a "suction event," with low-flow alarms (see below).

To provide a margin of safety, implantation centers that view maximal LV unloading as paramount in HF management define the optimal LVAD speed as being just below the maximum

Table 11.5 Speed changes: LVAD optimization or problem-focused (ramp) protocol worksheet

CF-LVAD type: **Implantation date:** **[PT INR = _____** **PTT = _____]**

Previous echo exam date and significant findings:

- *Optimization protocol*. Optimal speed based on MCS center's own standard; sample order sets include the following: (a) attain at least intermittent AV opening, (b) attain neutral IVS position and/or mild or less MR, (c) attain complete AV closure to maximize LV unloading, *or* (d) adjust speed to below the maximum speed associated with complete AV closure and the minimum speed associated with more prominent MR and rightward IVS
- *Problem-focused protocol. Indication for exam*: sample order sets include the following indications:
  (a) Smoldering left- and/or right-sided heart failure
  (b) Screen for pump function in patients with hemolysis and suspected pump thrombosis
  (c) Other LVAD alarm troubleshooting

Pump speed (rpm)	BP	AV opening (y/n/intermittent)	LVIDd (cm)	RVOT VTI (cm)	Significant AR (y/n)	Significant MR (y/n)	Significant TR (y/n)	TR velocity (m/s)	MV peak E velocity (m/s), DT (ms)	IVS direction L/R/neutral	(a) Symptoms (y/n) (b) Evidence of inflow- cannula obstruction (y/n)

Reason for termination: **Final speed setting = ____ rpm**	(E.g., signs of inflow-cannula obstruction, hypotension, hypertension, worsening RV or LV function)
Final BP = _____ mmHg	

Note: parameters measured at each speed setting may vary according to an implantation center's internal standards. After examination at the baseline pump speed, most of the needed parameters at subsequent pump speeds can be obtained primarily from parasternal views in most cases, as a limited exam.
AR aortic regurgitation, *AV* aortic valve, *BP* blood pressure, *CF* continuous flow, *DT* deceleration time, *E* early diastole, *INR* international normalized ratio, *IVS* interventricular septum, *LV* left ventricular, *LVAD* left ventricular assist device, *LVIDd* left ventricular internal diameter at end-diastole, *MCS* mechanical circulatory support, *MR* mitral regurgitation, *MV* mitral valve, *PT* prothrombin time, *PTT* partial thromboplastin time, *RVOT* right ventricular outflow tract, *TR* tricuspid regurgitation, *VTI* velocity time integral

Table 11.6 Magnitude and time course of echo LV parameter changes induced by CF-LVAD unloading

Variable	Pre-LVAD	Post-LVAD 1 month	Post-LVAD 3 months	Post-LVAD 6 months	Post-LVAD 12 months
	Study 1 ($N = 21$)	Study 1 ($N = 21$)	–	Study 1 ($N = 10$)	–
	Study 2 ($N = 63$)	–	Study 2 ($N = 63$)	Study 2 ($N = 63$)	–
	Study 3 ($N = 80$)	Study 3 ($N = 68$)	Study 3 ($N = 47$)	Study 3 ($N = 32$)	Study 3 ($N = 20$)
LV parameters					
LV diastolic diameter					
Study 1 (mm)	66 ± 11	55 ± 11**	–	52 ± 11*	–
Study 2 (mm)	68 ± 9	–	56 ± 11*	57 ± 12	–
Study 3 (cm/m^2)	3.2 (2.9, 3.6)	2.8 (2.3, 3.2)	2.9 (2.4, 3.4)	2.8 (2.2, 3.4)	2.6 (2.2, 3.0)*
LV systolic diameter					
Study 1 (mm)	58 ± 10	47 ± 12	–	43 ± 13	–
Study 2 (mm)	61 ± 9	–	47 ± 13*	49 ± 13	–
Study 3 (cm/m^2)	3.0 (2.6, 3.3)	2.6 (2.0, 3.1)	2.6 (2.1, 3.1)	2.5 (1.8, 2.9)	2.3 (1.9, 2.8)*
LV end-diastolic volume					
Study 1 (mL)	242 ± 108	127 ± 68*	–	113 ± 45*	–
Study 2	–	–	–	–	–

(continued)

Table 11.6 (continued)

Variable	Pre-LVAD	Post-LVAD 1 month	Post-LVAD 3 months	Post-LVAD 6 months	Post-LVAD 12 months
	Study 1 ($N = 21$)	Study 1 ($N = 21$)	–	Study 1 ($N = 10$)	–
	Study 2 ($N = 63$)	–	Study 2 ($N = 63$)	Study 2 ($N = 63$)	–
	Study 3 ($N = 80$)	Study 3 ($N = 68$)	Study 3 ($N = 47$)	Study 3 ($N = 32$)	Study 3 ($N = 20$)
Study 3 (mL/m^2)	113 (94, 141)	77 (54, 109)*	86 (62, 106)*	86 (52, 108)*	69 (45, 93)*
LV end-systolic volume					
Study 1 (mL)	191 ± 93	100 ± 66*	–	82 ± 42*	–
Study 2	–	–	–	–	–
Study 3 (mL/m^2)	3.0 (2.6, 3.3)	2.6 (2.0, 3.1)*	2.6 (2.1, 3.1)	2.5 (1.8, 2.9)*	2.3 (1.9, 2.8)*
LV ejection fraction (%)					
Study 1	22 ± 5	25 ± 13	–	29 ± 10	–
Study 2	19 ± 7	–	26 ± 12*	27 ± 14	–
Study 3	17 (14, 23)	20 (15, 30)	20 (14, 26)	25 (18, 33)*	22 (15, 31)
LV mass					
Study 1	–	–	–	–	–
Study 2 (g)	383 ± 113	–	295.9 ± 188*	314 ± 134	–
Study 3 (g/m^2)	114 (93, 146)	95 (71, 114)**	92 (63, 118)**	111 (74, 134)	77 (50, 104)*
LV diastolic parameters					
LA size					
Study 1 (mm)	*47 ± 7*	37 ± 9**	–	42 ± 13	–
Study 2 (mL/m^2)	*69 ± 30*	–	42 ± 15*	–	–
Study 3 (mL/m^2)	*46 (35, 54)*	28 (22, 36)*	32 (23, 38)*	25 (19, 39)*	28 (18, 38)*
E-wave					
Study 1 (cm/s)	*96 ± 23*	73 ± 27**	–	66 ± 12**	–
Study 2 (cm/s)	*98 ± 35*	–	100 ± 160	80 ± 20	–
Study 3 (cm/s)	*100 (80, 110)*	80 (60, 100)*	80 (70, 100)	80 (70, 110)	100 (60, 120)
E/A ratio					
Study 3	*2.8 (2.1, 4.1)*	2.2 (1.2, 3.6)	1.5 (1.0, 2.9)*	1.6 (1.3, 2.2)**	1.7 (1.0, 3.3)
Mitral DT					
Study 1	*124 ± 39*	180 ± 53**	–	164 ± 24	–
Study 2	*132 ± 27*	–	188 + 70*	166 ± 48	–
Study 3	*133 (112, 165)*	175 (137, 220)*	178 (141, 212)*	172 (121,220)*	170 (157, 225)
Tissue Doppler e′ (cm/s)					
Study 1	–	–	–	–	–
Study 2 (septal e′)	*4 ± 1*	–	4 ± 1	–	–
Study 3 (septal e′)	*4 (3, 6)*	6 (5, 9)*	7 (5, 9)*	7 (4, 9)*	7 (6, 10)**
(lateral e′)	*8 (5, 11)*	9 (7, 10)	9 (6, 11)	10 (7, 13)	12 (8, 12)
E/e′ (ratio)					
Study 1	–	–	–	–	–
Study 2 (septal e′)	*26 ± 11*	–	20 ± 9**	13 ± 7	–
Study 3 (septal e′)	*23 (16, 30)*	13 (9, 19)*	12 (9, 16)*	12 (9, 19)*	15 (7, 17)**
(lateral e′)	*14 (9, 19)*	9 (16, 13**)	10 (6, 12)	9 (7, 13)	10 (6, 11)

Study 1 Lam et al. JASE 2009 [8], *Study 2* Topilsky et al. JASE 2011 [9], *Study 3* Drakos et al. JACC 2013;61:1985–94.
Values are mean ± SD for studies 1 and 2 and median (25th, 75th percentiles) for Study 3.
Study 2 *P* values only provided comparing pre-LVAD and post-LVAD 3-months measurements. *A* mitral valve late peak diastolic velocity, *CF* continuous flow, *DT* deceleration time, *E* mitral valve early peak diastolic velocity, *e′* mitral annular velocity, *LA* left atrial, *LV* left ventricle, *LVAD* left ventricular assist device
*$P < 0.01$ versus pre-LVAD; **$P < 0.05$ versus pre-LVAD

speed, even when the AV remains closed (typically at least 400 rpm below the maximum speed for the HM-II [37] and at least 40 rpm below the maximum speed for the HVAD). Implantation centers that desire AV opening will, when possible, choose a lower "optimal" LVAD speed, at which AV opening occurs either intermittently or during every cardiac cycle, combined with other echocardiographic data to suggest clinically adequate (if not maximal) LV unloading. A subset of these centers may elect to maximize the AV opening duration. As noted above, Table 11.5 provides a typical set of parameters that can be measured at each speed during an LVAD optimization exam, including LVIDd, interventricular septal position, AV opening frequency/duration, MR severity, TR severity and velocity, and cannula flow velocities.

Implementing safe and consistent LVAD surveillance echocardiography in a busy clinical environment with changing medical and technical staff can be challenging. Accordingly, the following implementation tools have been included. Table 11.3 is an "LVAD surveillance echo protocol" that provides a checklist for exam setup, LVAD-specific parameters, and "red flag findings." Laboratory leaders may edit this protocol into their existing standard heart failure examination protocol for a "baseline speed surveillance echo protocol." Table 11.4 can be used when an LVAD optimization/ramp protocol is needed. Table 11.5 is a "speed-change worksheet" that can be used to help organize data for interpretation and reporting purposes. The LVAD data are typically first obtained at the baseline pump speed and then at subsequent speeds determined by the supervising physician. The data columns can be edited to conform to a lab's internal standards. Typically, an LVAD examination at the baseline pump speed requires a similar time allotment as a standard non-LVAD examination once sonographers become familiar with these devices and given some of the technical limitations on obtaining standard images as outlined above. Data acquired at subsequent pump speeds can be streamlined considerably when not all data columns are required according to a center's own protocol. On the other hand, data collection may need to be more comprehensive at each pump speed if certain problems are suspected on the basis of baseline speed findings.

In summary, the components and timing of an LVAD surveillance examination have only been recently defined by consensus in the recent recommendations from the American Society of Echocardiography [1]. There remains little outcomes data with regard to optimal speed settings. Ideally, a program of routine surveillance echocardiography examinations could confirm normal device function or detect occult device or native heart abnormalities that could be addressed early on to prevent hospitalization for recurrent heart failure or to identify patients who may require more frequent monitoring. Implementing consistent and safe surveillance exam protocols can be a challenge, and it is hoped that the material and implementation protocols herein might be a helpful starting point for creating a more efficient LVAD patient care plan.

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Diagnosis of Device Thrombosis

12

Cyril Varughese, Ajith P. Nair, and Jordan Chaisson

Introduction

As continuous-flow left ventricular devices become more streamlined and smaller, pump thrombosis and hemolysis are emerging as serious complications following device implantation. Initial studies involving continuous-flow left ventricular assist devices (LVAD) revealed an incidence of pump thrombosis following initial implantation at 0.014–0.03 events per patient-year [1]. Additional studies reviewing data from around 2005 to 2007 reported 4% of patients with pump thrombosis [2]. More recent analysis of INTERMACS data has shed further light in revealing possible risk factors, such as age, gender, and BMI, which might make a patient more prone to developing pump thrombosis [3]. One challenge that clinicians face following LVAD implantation remains balancing anticoagulation therapy with risk of bleeding. Anticoagulation and antiplatelet therapy varies from institution to institution, but the primary goal remains balancing a patient risk of bleeding with their risk for pump thrombosis. The primary marker most centers utilized still remains the international normalized ratio (INR) with typical goals ranging from 2 to 3 or even 2.5–3.5 with patients who might be at higher risk from pump thrombosis. Current guidelines from ISHLT recommend an INR of 2.0–3.0 with HeartMate II and HeartWare devices. However, despite aggressive anticoagulant therapy, a patient might still be prone to developing device thrombosis, which with early detection can play a key role with overall survival.

Etiology

Although no single entity has been known to produce left ventricular assist device thrombosis, several factors together may play a role for thrombus formation in select patients. First assessment should focus on identifying those patients that might be predisposed to thrombus formation. Usually risk assessment for pump thrombosis is performed prior to device implantation based on various institutions' guidelines. Those individuals already at high risk (hypercoagulable state, autoimmune disease, malignancy) are not a direct contraindication for mechanical circulatory support but do warrant a thorough investigation prior to device implantation. A patient's body weight can also play a role for potential pump thrombosis. Just as prior studies have identified poor

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outcomes in low BMI patient population (<18.5 kg/m^2), those patients with obesity or even morbid obesity have been shown to be at higher risk for pump thrombosis [3, 4]. Prior retrospective studies reviewed patients with a BMI greater than 30 with increased risk for pump thrombosis [3]. Analysis of INTERMACS data identified female gender as having early phase incidence of pump thrombosis; however, this may have been secondary to smaller LV cavity size [3]. Even after device placement, vigilance must be maintained to evaluate additional factors that may predispose a patient to thrombus formation. Following LVAD implantation, driveline infection and/or pump pocket infections tend to promote prothrombotic states that can lead to an increased risk for pump thrombosis [5].

In addition to assessing a patient's inherent risk for pump thrombosis, external factors can play a role in predisposing to thrombus formation. One key component to minimize pump thrombosis remains tight anticoagulation management. In one review of various LVAD implantation centers, an increase incidence of pump thrombosis in one part was thought to be secondary to lower anticoagulation goals [6]. Anticoagulation therapy can become difficult if the patient's risk of bleeding increases as in the setting of an acute gastrointestinal bleed. Usually in an effort to reduce the incidence of GI bleeding, pump speeds are reduce to maintain some semblance of pulsatility. An indirect result of this can be less blood moving through the pump, which prevents adequate heat dissipation from the motor itself leading to an increased risk of thrombus formation. Simulated low axial flow in HeartMate II pumps demonstrated prothrombotic states once flows were decreased below 3.8 lpm which supported prior studies suggesting lower flows promoting increase risk for pump thrombosis [7, 8]. In addition to maintaining adequate anticoagulation goals and speed adjustments, evaluating the device itself becomes crucial to determine if specific positioning of the inflow or outflow graft may predispose to pump thrombosis. Initially textured surfaces of the HeartMate XVE ventricular assist device minimized incidence of pump thrombosis due to development of a thin biofilm layer decreasing thrombin deposition. Unfortunately similar textured surfaces on the inflow cannula of new left ventricular assist devices have not been able to replicate the prior effect to a degree.

Locating Pump Thrombosis

Identifying the region of pump thrombosis can also be challenging. Usually mechanical continuous-flow pumps can be divided into three areas of interest for thrombosis: the inflow, pump, and outflow graft. Laboratory testing can be useful to aid with diagnosing pump thrombosis, but 2D echocardiography and CT angiography are also helpful to identify the location of pump thrombosis.

Positioning of the inflow cannula usually can be assessed with 2D echocardiography. Typically angulation of the inflow cannula medially toward the interventricular septum or next to papillary muscles can predispose to obstruction near the inlet. Depending on specific hardware type, direct visualization of inflow cannula can be limited by acoustic dropout from echocardiography. Continuous wave Doppler directed toward the inflow cannula with velocities >1.5 m/s has been suggestive of inflow obstruction or even suction event [9]. Identifying thrombosis in the pump itself can be difficult due to limitations with imaging. Severe streaking artifact on CTA of the chest from the metallic motor housing makes direct visualization of pump thrombosis difficult. Usually evaluation of the motor housing itself is accomplished by direct visualization in the operating room or disassembly of the device at the manufacturing site.

In a similar fashion of evaluating the inflow graft, the outflow graft of a continuous-flow LVAD can be visualized through CTA with 3D reconstruction (Fig. 12.1). This can aid the clinician to determine if any kinks are present obstructing flow through the outflow graft. Two-dimensional echocardiography can also assist in evaluating LVAD outflow graft velocities. Typically Doppler flow tends to accelerate if obstruction is present to levels >2 m/s [9].

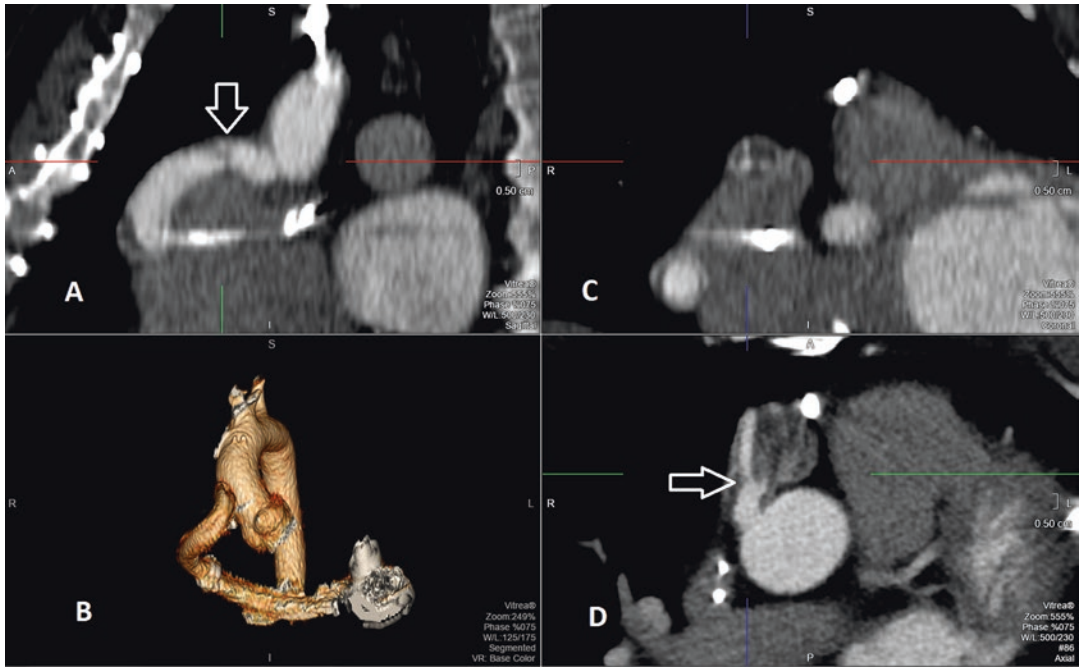

Fig. 12.1 CT angiogram with 3D reconstruction of left ventricular assist device. (**a**) Following contrast administration, filling defect can be seen along the distal portion of outflow graft. (**b**) Complete 3D reconstruction of LVAD, outflow graft, and ascending aorta. (**c**) Orthogonal visualization of outflow graft. (**d**) Further visualization of filling defect in distal outflow graft consisted with thrombosis

Diagnosing Pump Thrombosis

Evaluating a patient for acute thrombosis usually starts with a clinical evaluation but ultimately requires a culmination of laboratory testing in addition to various imaging modalities (Fig. 12.2). One of the primary goals for laboratory testing remains validating the presence of hemolysis. Clinical signs may be present that coincide with lab results suggestive of hemolysis. Patients may describe darkened urine from increased hemoglobin destruction due to active hemolysis from pump thrombosis. When pump thrombosis forms, reduced forward flow develops, preventing adequate unloading of the left ventricle. Soon the patient may experience similar symptoms of decompensated heart failure they felt prior to device implantation. Once these clinical factors are present, active evaluation of pump thrombosis must be performed starting with laboratory analysis. In one retrospective study, hematological markers were a better marker to predict pump thrombosis before imaging or pump parameters were identified [10]. Most advanced heart failure centers routinely screen patients with left ventricular assist devices by checking lactate dehydrogenase (LDH) levels [11]. Long-term monitoring of a patient's LDH level is key to evaluate trends that may suggest a gradual pump thrombosis versus an acute event. LDH levels tend to remain elevated but stable in the former whereas levels can rise abruptly in the latter. Typically once levels are greater than 2–2.5 times, partial or complete pump thrombus formation should be excluded. Also plasma-free hemoglobin levels are another laboratory test to identify active hemolysis. Typically two separate levels that are greater than 40 mg/dL are suggestive of ongoing hemolysis. Combining an elevated LDH and plasma-free hemoglobin reading with other common markers for hemolysis such as reduced levels of hemoglobin, hematocrit, and haptoglobin and increased indirect bilirubin lev-

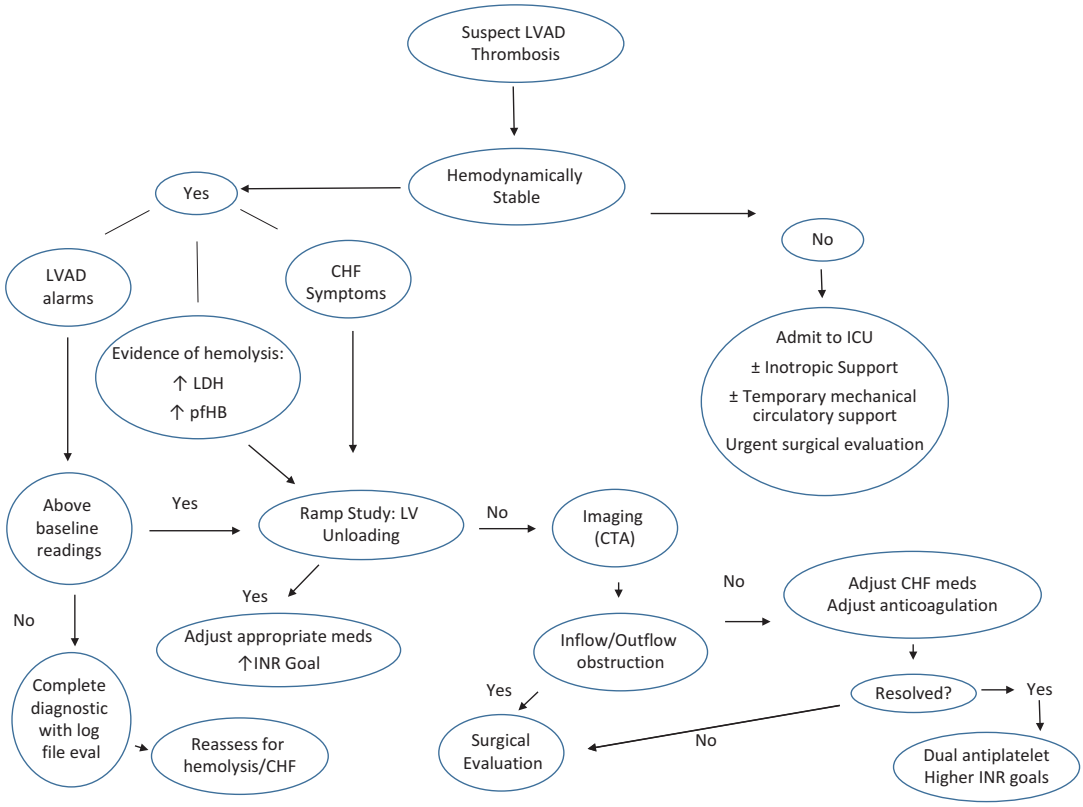

Fig. 12.2 Flowchart for diagnosing and managing acute pump thrombosis. Abnormal LVAD alarms include power readings >10 W or readings greater than 2 W above patient's baseline. Evidence for hemolysis would be elevated LDH levels 2–2.5 times the upper limit of normal and plasma-free hemoglobin (pfHb) > 40 mg/dL

els is strongly suggestive of ongoing hemolysis from pump thrombosis.

In addition to laboratory testing for hemolysis, various imaging studies can be utilized to evaluate LVAD positioning and ability to unload the left ventricle. The first imaging study to perform on a patient with a suspected pump thrombosis should be a chest x-ray. The chest x-ray can be useful to not only evaluate pulmonary congestion from decompensated heart failure but also to evaluate any kinking or malposition of the inflow cannula. In addition to the standard chest x-ray, CTA of the chest becomes useful in evaluating the inflow and outflow graft. As mentioned above, positioning of the inflow cannula can be visualized with CT angiography as well as LV cavity size and possible location of pump thrombosis. The outflow graft can also be adequately visualized to determine if any specific segment has thrombus formation or kink present. Most patients with acute pump thrombosis tend to have elevated creatinine levels due to ongoing hemolysis, which can make ordering a CTA difficult due to the need for intravenous contrast. However, the risk of worsening renal perfusion from a low cardiac output state is also an important factor to consider when working up a patient with an acute pump thrombosis.

Two-dimensional echocardiography can be a useful tool when evaluating a patient with suspected pump thrombosis. When pump thrombosis occurs, adequate unloading of the left ventricle becomes difficult. As a result, left ventricular end-diastolic dimensions can increase which is one sign of pump malfunction if the left ventricular size is larger than previous baseline studies at similar speeds. Mitral regurgitation is also a useful parameter seen on 2D

echocardiogram which can help in determining if adequate LV unloading is occurring at certain pump speeds. While there may be some mild mitral regurgitation at baseline speeds in a normal functioning LVAD, theoretically increasing the LVAD speed should unload the LV sufficiently to reduce or minimize the presence of mitral regurgitation. Once pump thrombosis occurs, adequate LV unloading is not possible at higher speeds, so severity of mitral regurgitation may persist despite higher VAD settings. The aortic valve can be another structure seen on 2D echocardiography that can assist in determining if adequate LV unloading is occurring at higher speeds. At higher speeds, normal functioning left ventricular assist devices should unload the left ventricle to the point that a majority of blood flow is directed toward the LVAD instead of the left ventricular outflow tract. As a result, minimal aortic valve opening is seen at higher LVAD speeds suggestive of adequate pump function. Caution should be used when performing a ramp study on a patient with suspected pump thrombosis. Depending on the location of thrombus, distal embolization can occur once speed adjustments are made. Usually HeartMate II LVADs are increased by 200 rpm, while HeartWare HVAD speeds are increased by 20 rpm increments. Initial studies reviewing the use of ramp echocardiography evaluation were helpful with HeartMate II LVEDD slope relationships but did not correlate well when extrapolated to HVAD function [12].

In some instances when adequate information is not obtained from CTA or 2D echocardiography, cardiac output and hemodynamics assessed from right heart catheterization can assist in determining if adequate LV unloading is occurring with various pump settings. One advantage to right heart catheterization versus 2D echocardiography or CTA is the ability to measure both left- and right-sided pressures. Specific protocols for ramp right heart catheterization studies may vary from institution to institution; however, similar to ramp echocardiogram study, various measurements such as cardiac outputs, pulmonary capillary wedge pressures, and right-sided filling pressure can be obtained at various speeds. With a normal functioning pump, at higher speeds, cardiac output increases, PCWP decreases, and right-sided filling pressure may increase due to higher preload.

Left ventricular device power surges or changes in pulsatility index can also serve to assist in diagnosing pump thrombosis. Typically pump thrombosis usually causes high power spikes with low a low pulsatility index. Caution should be used in avoiding making clinical decisions based on single pump parameter changes but evaluate changes in LVAD settings compared to a patient's baseline. Typically pump thrombosis causes elevated power readings >10 W or sustained readings greater than 2 W above a patient's baseline [13]. Recent studies regarding pump thrombosis recommend identifying multiple factors such as active hemolysis, symptoms of decompensated heart failure, abnormal imaging or ramp studies, and/or abnormal pump readings to help in making the diagnosis.

Management and Treatment

Sudden thrombus formation leading to pump stoppage can be life-threatening depending on how much native cardiac function still exists. For those patients completely dependent on their left ventricular assist device to maintain cardiac output (i.e., oversewn aortic valve), acute thrombus formation leads to profound hemodynamic instability and possible death. Early detection and management become critical to stabilize the patient and identify further therapeutic options.

The first step in managing a patient with pump thrombosis is assessing the patient for hemodynamic stability (Fig. 12.2). As mentioned above, those patients fully dependent on cardiac output from their assist devices can clinically deteriorate rapidly. These patients usually require inotropic support and in some cases temporary mechanical circulatory support. Those patients who are in shock and are not responsive to medical therapy require emergent surgical evaluation for pump exchange and should not be delayed to minimize end organ damage. In addition to inotropic support, attention must be focused on anticoagulation

therapy. The first line of anticoagulation therapy remains IV heparin infusion; if contraindications are present or thrombus does not resolve, then consideration must be given for direct thrombin inhibitors. Laboratory testing can be used to diagnosis hemolysis, which can be trended to determine if pump thrombosis persists or is resolving. Once a patient has become hemodynamically stable, further assessment can be performed on the pump itself in addition to ramp studies to determine if appropriate LV unloading is occurring.

If symptoms of hemolysis resolve with adjustment to anticoagulation and antiplatelet regimen, then careful evaluation must be undertaken to determine if pump thrombosis has truly resolved. Serial ramp echocardiographic studies may be necessary to verify adequate LV unloading, and symptoms of hemolysis should resolve. In these select patients, higher INR goals with additional antiplatelet therapy may be required to minimize future risk of device thrombosis. In certain circumstances when devices are implanted as bridge to transplant, patients who present with active hemolysis, pump device dysfunction, or visually detected pump thrombosis may qualify for UNOS 1A transplant status.

A majority of patients with pump thrombosis will ultimately require surgical replacement. Multiple factors can play a role in the approach for surgical removal of a pump such as bleeding risk, underlying pulmonary disease, BMI, and any ongoing infections. One common discussion that occurs when surgical replacement of the pump is deemed necessary is the risk associated with resternotomy. A resternotomy approach to surgical removal and replacement of an LVAD is one approach to consider if complete visualization of the device is required. Performing a sternotomy is particularly useful if inflow cannula position needs to be replaced or the entire pump requires exchange. This approach is particularly helpful if concern for outflow graft thrombosis is present. However, this approach does have several risk factors associated with it in a patient who may have already undergone prior open-heart procedures. Due to buildup of scar and inflammation dissection, planes can become difficult to visualize and the risk of bleeding increases with subsequent sternotomies. However, a recent study comparing postoperative complications in patients with resternotomy versus primary sternotomy found similar results between the two groups [14]. Another surgical approach for replacement of left ventricular assist device, particularly HeartMate II, is the subcostal approach. If pump thrombosis is thought to be located to inflow cannula and sternotomy can be avoided, then the subcostal approach is generally considered for surgical removal [15].

Conclusion

Left ventricular assist device thrombosis is a complication that clinicians practicing in advanced heart failure centers should be comfortable managing. While each institution may have its own protocol for management of pump thrombosis, a clear understanding of precipitating factors and further clinical workup can become helpful in making a prompt diagnosis. Early diagnosis and stabilization of the patient can lead to better postoperative outcomes following surgical replacement.

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13 Device Exchange: THI Technique Involving a Left Subcostal Approach

Tadahisa Sugiura and Masashi Kawabori

Introduction

Continuous-flow left ventricular assist devices (CF-LVADs) are being used to support patients with end-stage heart failure for longer periods because of both longer transplant waiting times and the use of these devices as destination therapy. Longer durations of support make CF-LVAD exchange more common. In this chapter, we present our technique of HeartMate II (St. Jude Inc., St. Paul, MN) pump exchange through a left subcostal approach.

Preoperative Considerations

A CF-LVAD exchange is planned in cases of pump thrombosis, pump infection, or driveline issues. A preoperative complete system workup is mandatory before all exchange cases [1]. Physical examination, medical history, and medication compliance should be reviewed. Echocardiography should be performed in all patients to assess hemodynamics. A computed tomography scan is necessary for planning surgical strategy. From this information, the surgeon should consider whether total or partial replacement of the device is required. If only isolated pump exchange is planned, it can be performed by a left subcostal approach.

Optimization of patient's condition is mandatory before the surgery. If the patient's hemodynamic status is compromised, inotropic support or temporary mechanical circulatory support should be started immediately. Mechanical respiratory support and pulmonary vasodilators such as nitric oxide and epoprostenol are useful for managing right heart failure. A Swan-Ganz catheter can be used to assess cardiac function and optimize volume status. Major neurological issues should be ruled out before the operation.

Patients with an active pump infection require aggressive preoperative antibiotic therapy. Any coagulation abnormalities should be corrected and anticoagulant effects should be reversed before the procedure.

Technique of Pump Exchange Through a Left Subcostal Approach

We perform isolated pump exchange through a left subcostal approach by a technique that does not require sternotomy [2]. The exchange can be completed without CPB if sufficient hemodynamic parameters can be maintained at a pump speed of approximately 6000 rpm; nonetheless, a femoral artery is exposed in case CPB becomes

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necessary. A left subcostal incision is created two fingerbreadths below the left costal margin, from the midline to the mid-axillary line, extending through the abdominal musculature to the pump pseudo-capsule. A heavy-duty self-retaining retractor (Thompson Surgical Instruments, Inc., Traverse City, MI) is necessary for adequate exposure (Fig. 13.1a). One arm is used to pull the left costal margin anteriorly and cephalad, and a second arm is used to retract the left side of the rib cage laterally. The incision is often extended several centimeters to the right of the midline, and the rib junction is resected to expose circumferentially the connection between the outflow-graft collar and the detachable outflow bend-relief. The bend-relief is detached, and dissection is performed around the outflow graft to make enough space for a vascular clamp to be applied (Fig. 13.1b). Excessive traction of the outflow graft should be avoided because this can damage the graft, making it vulnerable to stenosis.

Next, additional dissection is done around the inflow cannula to allow a vascular clamp to be applied across the white silicone elastic bellows between the sintered titanium inflow cannula and the pump. When the vascular clamp is placed, the bellows and graft are compressed to temporarily occlude inflow (Fig. 13.1c). The old driveline is dissected circumferentially for several centimeters so that the driveline can be easily transected before the pump is removed.

Heparin is administered systemically, and pump speed is gradually decreased to slowly wean the patient from the HeartMate II. Transesophageal echocardiography is used to determine whether hemodynamic stability can be maintained for 10–15 min without CF-LVAD support. Inotropes and vasoactive agents are used as needed. Patients with extremely poor LV function may require CPB.

The new driveline is tunneled through the abdominal wall and brought out in a suitable position. The inflow components included with the new pump are not used; if they are already attached to the new pump's housing, they should be removed. Two vascular clamps are placed on the exposed portion of the outflow graft and on the silicone elastic bellows, and the old driveline is transected. The outflow collar is rotated counterclockwise to detach the outflow graft (Fig. 13.1d). Surgeons often need a tubing clamp to loosen the collar. The inflow collar is held with a tubing clamp (Fig. 13.1e), while the old pump housing, now disconnected from the pump outlet and the driveline, is rotated counterclockwise to unscrew it from the old inlet components (Fig. 13.1f).

The new pump is then attached to the old inflow and outflow components. If the patency of the inflow segments is uncertain, the vascular clamp on the silicone elastic bellows can be released for a heartbeat to ensure brisk backflow of the blood. This maneuver can cause air entrainment, but this is unlikely to happen because these patients have elevated LV diastolic pressure. If the inflow becomes partly obstructed, the surgeon should consider starting CPB and repairing the inflow, either through the existing subcostal incision or by performing a redo sternotomy. We attach the new pump to the old inflow components by holding the inflow collar firmly with a tubing clamp, then screwing the new pump into the collar by rotating the entire pump clockwise. We keep the driveline from interfering with the attachment process by rewinding the new pump housing several turns counterclockwise before engaging the screw threads on the inflow collar.

The outflow graft is then attached to the new pump, and we confirm the patency of the graft. Typically, we do this by releasing the outflow-graft clamp to ensure brisk arterial backflow. However, in some cases, we instead measure the pressure inside the graft by inserting a needle through the graft proximal to the clamp and attaching the needle to a transducer. Any difference between the pressure within the graft and the systemic arterial pressure is a sign of outflow-graft stenosis, potentially indicating outflow-graft repair.

A 19-gauge needle is inserted into the outflow graft for de-airing. The LVAD pump is

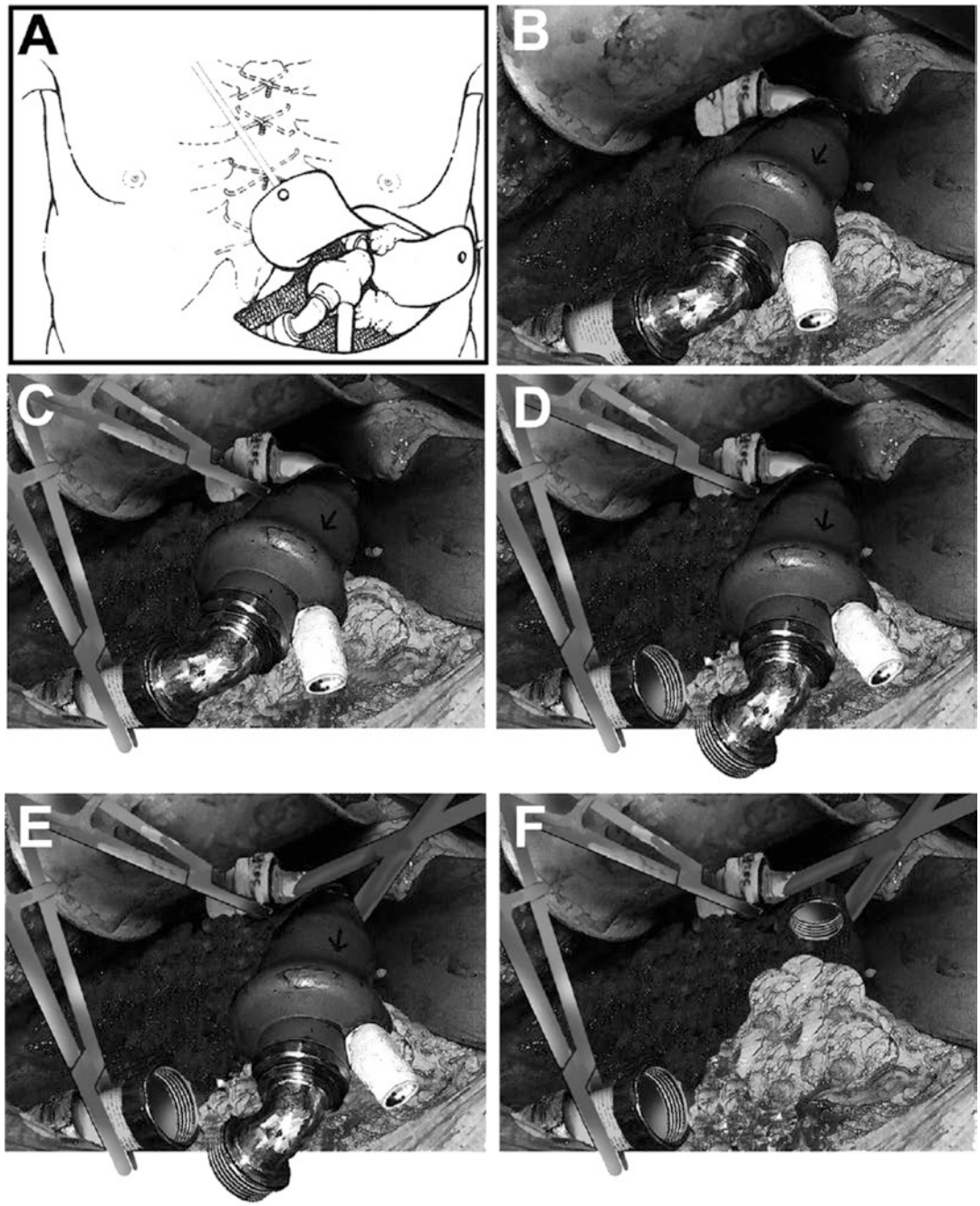

Fig. 13.1 (**a**) The pump is exposed through an extended left subcostal incision. A self-retaining retractor is invaluable in visualizing the white silicone rubber bellows that surrounds the pump inlet graft. (**b**) The bend-relief is disconnected from the pump outlet so that the outflow graft can be exposed. After hemodynamic stability is ensured, the pump power is turned off, and the driveline is cut. (**c**) Clamps are immediately placed on the outlet graft and the silicone rubber inflow bellows to prevent retrograde flow through the nonfunctioning pump. (**d**) The outflow graft is unscrewed from the curved titanium tube at the pump outlet. Brisk backflow is confirmed by transiently releasing the clamp to ensure adequacy of the outflow graft. (**e**) A pump clamp is used to firmly grasp the collar at the pump inlet. (**f**) While the collar is held, the pump is rotated counterclockwise until it can be removed from the inlet. Brisk bleeding from the inlet is confirmed by transiently releasing the clamp on the inflow bellows to ensure adequacy of the pump inflow. The new pump is implanted by performing these steps in the reverse order

initiated, and the pump speed is gradually increased, while transesophageal echocardiography is used to monitor hemodynamics and LV size. Protamine is administered to maintain hemostasis. The wound is closed in layers in the standard fashion.

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14 Mechanical Circulatory Support to Bridge to a Long-Term Continuous-Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation

Chitaru Kurihara

Introduction

Over the past decade, the use of left ventricular assist devices (LVADs) for long-term therapy has increased exponentially [1–3]. In addition, the indications for implantation of mechanical devices have expanded over time and now include cardiogenic shock, bridge to transplant (BTT), bridge to decision, and destination therapy (DT). On the basis of their features, devices can be separated into various subcategories of use, including short-term versus long-term devices and assist devices versus complete heart replacement (i.e., total artificial heart). This chapter will focus on the use of LVADs for long-term support as BTT and will cover critical factors relating to types of devices, including the use of short-term mechanical circulatory support (MCS) to bridge to BTT, and the importance of patient selection.

Patient Selection

Prudent patient selection is a critical element in achieving good clinical results with LVAD support. Analysis of the Texas Heart Institute/Baylor College of Medicine clinical LVAD database indicated that low preoperative levels of albumin or prealbumin and a high Model of End-Stage Liver Disease-eXcluding INR (MELD-XI) score are predictors of poor patient outcomes after LVAD implantation (Fig. 14.1a–c). Preoperative malnutrition has been shown to increase postoperative morbidity and mortality in patients who undergo cardiac surgery [4]. The preoperative diagnosis of malnutrition could help identify patients who may benefit from improving nutritional status before implantation surgery. It is also important to implant LVAD in patients before development of end-organ failure.

Contraindications for LVAD implantation include irreversible end-organ failure, particularly renal, hepatic, and respiratory, which are uniformly independent predictors of poor outcome [5–7]. Severe, unrecoverable neurological dysfunction is also a contraindication for LVAD implantation. Systemic sepsis poses a significant risk to patients who undergo LVAD implantation because it can cause a profound, refractory, vasodilatory state and an increased incidence of infections such as device-related endocarditis [8, 9]. Patients who have had sepsis should have two negative blood cultures over a 1-week period before LVAD implantation to indicate that the infection has been cleared from the bloodstream. Another contraindication for LVAD implantation is the presence of a malig-

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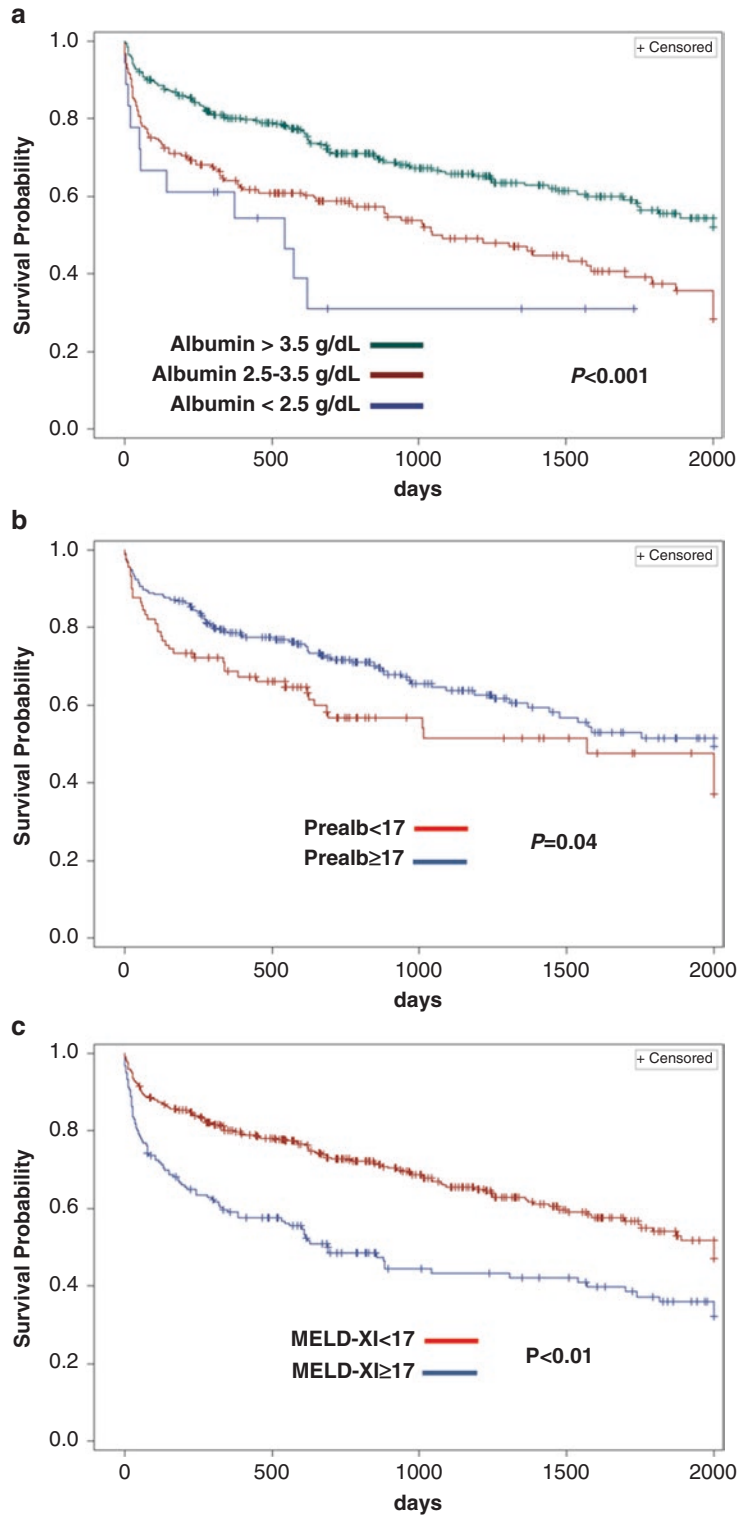

Fig. 14.1 (**a**) Survival curves for patients who had normal albumin levels (≥3.5 g/dL), moderate hypoalbuminemia (2.5–3.5 g/dL), and severe hypoalbuminemia (<2.5 g/dL) before undergoing implantation of a continuous-flow left ventricular assist device. (**b**) Survival curves for patients who had preoperative prealbumin levels ≥17 or <17 after implantation of a continuous-flow left ventricular assist device. (**c**) Survival curves for patients who had preoperative MELD score ≥17 or <17 after implantation of a continuous-flow left ventricular assist device

nancy leading to a life expectancy of less than 2 years. Each of these cases requires individual attention and evaluation for appropriate decision-making. A patient with human immunodeficiency virus (HIV) infection who is compliant with medical therapy and who has a normal CD4 count and undetectable viral levels should be considered for LVAD implantation.

Types of Devices

Using Short-Term MCS

Data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profiles indicate that mortality and morbidity rates are worst in profile 1 patients (critical cardiogenic shock). Because INTERMACS profile 1 patients have a poor survival (ranging from 65 to 76% at 1 year), the patient population undergoing LVAD implantation is shifting from INTERMACS profile 1 toward those with less severe illnesses such as INTERMACS profiles 2 or 3. In 2008, 30% of LVAD implantations in the INTERMACS registry were performed in profile 1 patients, whereas that percentage decreased to 15% in 2013. Therefore, short-term MCS has become a necessary component of the therapeutic strategy for patients in cardiogenic shock, and implanting a short-term MCS device as a bridge to decision has gained popularity. This approach is used to stabilize the patient's hemodynamic status and improve end-organ function, thereby reducing the surgical risk associated with implanting an LVAD [10, 11]. Ideal strategy with short-term MCS would reduce surgical risk before LVAD implant with stabilizing hemodynamics and improving end-organ function. The most commonly used short-term MCS device is the intra-aortic balloon pump (IABP); other forms of MCS include the TandemHeart (CardiacAssist Inc., Pittsburgh, PA), Impella (Abiomed, Danvers, Massachusetts, MA), venoarterial extracorporeal membranous oxygenation (VA-ECMO), and CentriMag (Thoratec Corporation, Pleasanton, CA) devices.

Appropriate patient selection is the central tenet of the current paradigm of MCS. Indeed, compared with more stable patients on medical therapy, inotrope-dependent patients with rapid deterioration and end-organ dysfunction have unacceptable outcomes, including a 1-year mortality rate of nearly 50% among those who survive to discharge while receiving long-term LVAD support [12, 13]. Patients who receive short-term MCS before LVAD implantation are sicker at baseline than LVAD-only patients, and short MCS is used to optimize patients' condition before LVAD placement and to increase their suitability as long-term MCS candidates. Despite their poorer condition at baseline, MCS-supported patients had similar outcomes to LVAD-only patients, suggesting that short-term MCS decreases preoperative risk and achieves outcomes similar to those using LVAD support only. In a meta-analysis of data from patients with cardiogenic shock who were randomly assigned to receive a percutaneous ventricular assist device (p-VAD, including TandemHeart and Impella) or IABP support, outcomes were similar between the groups, although p-VAD support appeared to improve hemodynamics [13, 14]. Clinical criteria for using MCS are difficult to determine, but in our center, short-term MCS is initiated when patients show signs of significant hemodynamic instability or end-organ dysfunction, such as renal or respiratory failure, despite maximum medical support. Previous studies suggest that VA-ECMO is as safe and effective as a p-VAD to bridge patients to more advanced therapies such as heart transplantation or long-term LVAD support [15–18]. However, patients with VA-ECMO had only a 40–50% rate of survival to recovery or next therapy. One potential advantage of p-VADs over ECMO is that their design and mechanism of action allow direct ventricular unloading, thereby reducing the myocardial oxygen demand and the workload of the failing heart [19]. In contrast, a sizable proportion of patients supported with ECMO may develop refractory pulmonary edema, necessitat-

ing ventricular decompression secondary to increased afterload [20].

Using Long-Term MCS

Axial Flow Pump for Long-Term Mechanical Support: Thoratec HeartMate II

The most commonly used pump at our institution is the Thoratec HeartMate II LVAD (HM II; Thoratec Corp.), which is an axial flow rotary pump constructed of titanium. Smaller than the Thoratec HeartMate XVE (XVE; Thoratec Corp.), the HM II pump housing is implanted in the peritoneal space and requires a less invasive operative approach. It can provide flow up to 10 L/min at pump speed of 6000–15,000 RPM, with inflow via the left ventricular apex or diaphragm and outflow via the ascending aorta. A small percutaneous driveline exits the skin in the right upper abdomen. Patients are placed on systemic anticoagulation with warfarin and antiplatelet therapy with aspirin to prevent thromboembolic events. The Food and Drug Administration (FDA) has approved the HM II for BTT and DT.

Centrifugal Pump for Long-Term Mechanical Support: HeartWare

The HeartWare HVAD (HVAD; HeartWare International Inc., Framingham, MA) is a centrifugal pump that has no mechanical bearings and that weighs 145 g, with a displaced stroke volume of 45 cm^3. It can provide flow up to 10 L/min at 2000–3000 RPM. The device is implanted in the pericardial space without the need for an abdominal incision. The inflow cannula is integrated into the left ventricle. A single, flexible driveline (4.2 mm in diameter) exits the anterior abdomen. The HVAD is approved by the FDA for BTT and DT.

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Outcomes Using LVADs for Destination Therapy

15

Priyanka Sen and Selby Oberton

Introduction

Most recent estimates cited by the AHA suggest that >250,000 patients in the United States are in end-stage heart failure that is medically refractory [1]. This is a staggering number when compared to the >2000 transplants that are performed annually in the United States [2]. Implantation of a left ventricular assist device (LVAD) as destination therapy (DT) is a hopeful alternative for those who qualify. Approved for use as destination therapy, continuous-flow LVADs are quieter and more streamlined and involve fewer moving parts that may fail, giving them more longevity than their pulsatile counterparts and more suitability for long-term use [3]. Though far superior than optimal medical therapy alone, LVADs are not without their problems which include but are not limited to bleeding, infection, thromboembolic events, and pump thrombosis [4]. The use of risk stratification to carefully select patients and time of LVAD implantation may help minimize the potential complications [5, 6] and help predict outcomes after implantation [1, 7].

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In this chapter, we aim to present a summary of the work of landmark trials that have studied the outcomes of LVADs used for DT.

Survival

REMATCH was the first landmark trial to demonstrate that implantation of an LVAD (HeartMate vented electric device (HM VE LVAD)) as DT provided a significant survival advantage compared to optimal medical therapy (OMT) in patients with end-stage heart failure who were ineligible for cardiac transplantation [8]. Conducted between 1998 and 2001, it randomized 129 patients (68 to the LVAD and 61 to the OMT arms) who were deemed ineligible for transplantation with NYHA class IV heart failure symptoms, LVEF < 25%, either peak oxygen consumption <12 mL/kg/min or dependence on IV inotropic infusion, OMT use for at least 60 of the last 90 days, and a projected life expectancy of less than 2 years. Analysis of the patients randomized to the HM VE LVAD and OMT arms demonstrated a rate of survival at 1 year of 52% in the device group and 25% in the OMT group ($p = 0.002$) with a median survival advantage of 8.5 months [8]. This amounted to a RR of 48% in the primary endpoint of death from any cause and therefore an absolute risk reduction of 27% at 1 year (Fig. 15.1) [8]. The HM VE LVAD as DT was thus touted to have a remarkable treatment

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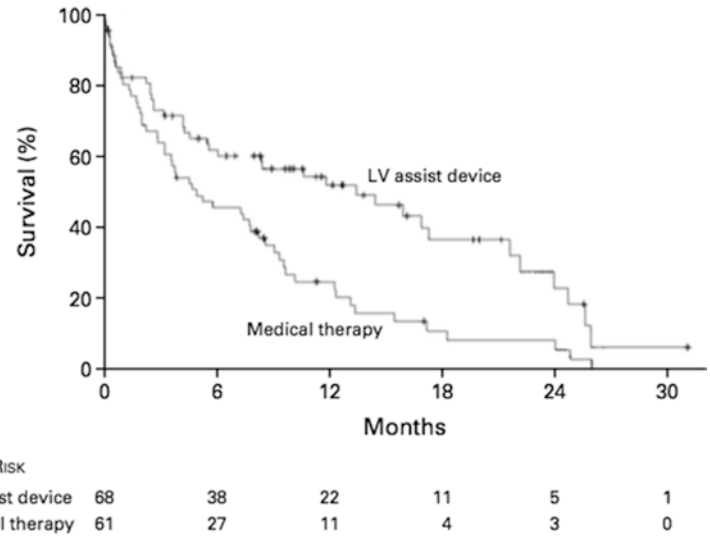

Fig. 15.1 Taken from the REMATCH trial, this Kaplan-Meier analysis depicts a reduction of 48% in the risk of death from any cause (primary endpoint) in the group that received the LVAD versus the group that received optimal medical therapy alone [7]

effect nearly four times that of beta-blockers or an ACE inhibitor, which individually had been estimated to prevent 70 deaths for every 1000 patients [8].

At the time of its publication, the REMATCH trial was noteworthy for having enrolled heart failure patients with the most severe clinical and hemodynamic compromise and mortality rates to date [1, 9]. An unanticipated 71% of patients were on inotropic infusions at the time of randomization [9]. Post hoc analysis of the outcomes of patients on and off intravenous inotropic therapy at the time of randomization confirmed that the patients on inotropes derived a near doubling of survival benefit from LVAD implantation with a 1-year survival of 49% and 24% in the LVAD and OMT groups, respectively ($p = 0.0014$) [9]. Survival of patients on baseline inotrope therapy was equal to or better than that in the OMT group at all times, even in spite of the predicted excess of perioperative mortality due to LVAD implantation [9]. The difference in 1-year survival rates was, however, not statistically significant between the LVAD (57%) and OMT (40%) groups who were not on intravenous inotropic support at baseline ($p = 0.55$) [9]. It was thus concluded that LVAD implantation was most beneficial for the sickest patients with advanced heart failure.

Enhancements in LVAD design based on lessons learned from the REMATCH trial led to the development of the HeartMate XVE (HM XVE). In a nonrandomized, prospective trial, Lietz et al. studied the outcomes of 280 patients who were implanted with the modified HM XVE between 2001 and 2005 for DT [1]. This study aimed to investigate the impact of this improved pulsatile-flow LVAD on DT outcomes and to identify clinical predictors portending worse prognosis that could then be made into a risk score to stratify DT candidates. Rates of survival were 86.1%, 56.0%, and 30.9% at 30 days, 1 year, and 2 years after LVAD implantation, respectively [1]. The high 1-year survival rates among recipients of HM XVE as DT were corroborated by a smaller, albeit nonrandomized trial. This study by Long et al. compared the survival of 48 recipients of the HM XVE at four of the highest volume centers participating in the Thoratec DT registry with that seen in the historical LVAD arm of the REMATCH trial [10]. It found a statistically nonsignificant but nonetheless remarkable 40% decline in the rate of death per patient year from any cause in the HM XVE arm as compared to the HM VE arm of the REMATCH trial [10]. The lesser mortality rates were attributed to improved LVAD design and patient management protocols from years of experience.

While pulsatile-flow LVADs had earned acceptance as therapy for refractory heart failure, their limited long-term durability and large pump size created a need for the simpler and smaller design of continuous-flow LVADs (CF-LVADs) [4, 11]. The HeartMate II trial was among the earliest of studies that looked at the outcomes of CF-LVADs, which were being tested only as a bridge-to-transplant at the time. By 180 days of the study, 100 of the 133 patients implanted with a HM II had either undergone cardiac transplantation, had significant cardiac recovery, or were still on ongoing mechanical support while remaining eligible for transplantation [11]. Although the results of a study on BTT patients cannot be directly applied to DT patients, as the degree of severity of heart failure and associated comorbidities making a patient ineligible for transplant and hence a DT patient make for a much sicker population, this study did show the promise of CF-LVADs.

The staggering results of REMATCH and other trials individually comparing the survival benefit among patients implanted with improved pulsatile-flow LVADs and continuous-flow LVADs begged the need for a head-to-head comparison of pulsatile-flow and CF-LVAD therapies. Conducted between 2005 and 2007 and using similar eligibility criteria as the REMATCH trial which have since been adapted into the CMS (Center for Medicare and Medicaid Services) criteria [12], this multicenter trial randomized 200 DT patients to either CF-LVAD (HeartMate II) or pulsatile-flow HeartMate XVE groups [13]. The primary endpoint of a composite of survival at 2 years, free of disabling stroke (stroke with a Rankin score > 3) or the need for reoperation to replace the device, was achieved by 46% and 11% in the HM II and HM XVE groups, respectively, with $p < 0.001$ [13]. Subgroup analysis of 1- and 2-year survival rates showed similarly significant results of 68% and 58%, respectively, in the CF-LVAD group and 55% and 24%, respectively, in the pulsatile-flow LVAD group (Fig. 15.2) [13].

Adverse Events

While both continuous and pulsatile-flow LVADs demonstrated significant survival benefits in patients with end-stage heart failure who were ineligible for transplantation, their use was not without complications. In the REMATCH trial, for instance, patients randomized to the device

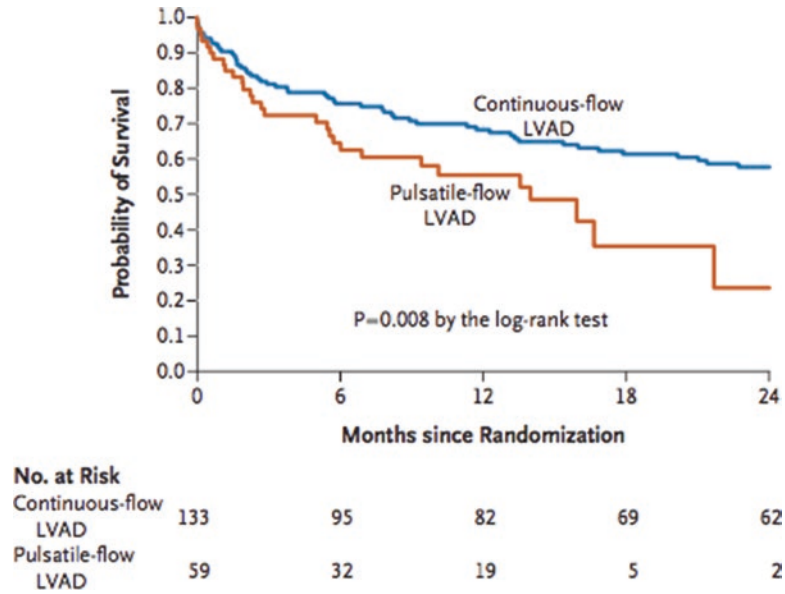

Fig. 15.2 Taken from the HeartMate II destination therapy trial, this Kaplan-Meier analysis depicts the striking superior survival rates seen up to 24 months after implantation of the continuous-flow HeartMate II compared to the pulsatile-flow HeartMate XVE [12]

group were 2.35 times as likely as those in the OMT group to suffer a serious adverse event [8]. Infection, suspected malfunction of the LVAD, non-neurologic bleeding, and neurologic dysfunction were the most common adverse events associated with the LVAD group [8].

Infection

Infection was by far the most frequent adverse event in LVAD studies and, in the era of pulsatile pumps, was particularly commonplace. The REMATCH trial stated that 28% of patients implanted with HM VE developed infection within the first 3 months, with most cases related to a local driveline tract and pocket infection. While most could be treated with local antibiotics, sepsis still claimed 17 of 68 lives [8]. A comparison of the results of HM XVE and HM II recipients showed that CF-LVADs significantly reduced the rates of LVAD-associated infections by 50% as well as that for non-LVAD-associated local infections and sepsis [13]. The larger area of surgical dissection required for implantation of a pulsatile-flow LVAD and the percutaneous driveline were felt to be the most likely causes of increased infection risk associated with pulsatile-flow pumps [11, 13, 14]. Additionally, CF-LVADs lack the compliance chambers, polyurethane membranes, and prosthetic valves that may become niduses for infection [15]. Indeed, the transition to the use of CF-LVADs and the higher cumulative experience of LVAD management at high-volume centers correlated with reduced overall LVAD-associated infections. Institutional changes to use management guidelines, abdominal binders to stabilize the percutaneous driveline, and antibiotic prophylaxis likely contributed to reduced rates of infection with LVADs over the years [10, 14, 16].

LVAD Dysfunction

Suspected LVAD dysfunction was the second most common adverse event seen in the REMATCH trial, amounting to a 35% probability of device failure in 24 months. Within the device group, ultimately, 10 of the 68 patients required replacement [8]. Largely due to improvements in LVAD design, CF-LVADs unsurprisingly fared better in this regard. As the HeartMate II study showed, fewer patients in the HM II group required reoperation to repair or replace the pump than those in the HM XVE group ($p < 0.001$) [13].

Non-neurologic Bleeding

Non-neurologic bleeding has also been a vexing problem with LVADs. Balancing the risk of device-related thromboembolic events with an increased propensity for bleeding due to anticoagulation and the theorized increased development of acquired von Willebrand syndrome and arteriovenous malformations in the setting of chronically low pulse-pressure has been a struggle with LVAD management [17, 18]. In the REMATCH study, even despite a lack of routine anticoagulation, the frequency of bleeding within the first 6 months following implantation with the HM VE was as high as 42% [8]. During the early trials using HM II for BTT, some centers had adopted a stringent antiplatelet and anticoagulation regimen of aspirin and dipyridamole with a postoperative heparin bridge to warfarin to achieve a target international normalized ratio or INR of 2.0–3.0 [11]. But this regimen resulted in a significantly increased rate of bleeding events, especially in the early postoperative period [11]. A comparison of HM II with HM XVE outcomes showed that both types of LVAD were associated with ten times the rate of bleeding as thromboembolic events, even though only those assigned to the HM II group were anticoagulated [13]. Based on these results, many centers have since reduced the targeted INR to 1.5–2.5 for continuous-flow LVADs and have eliminated the heparin bridge [14].

Neurologic Events

Surprisingly, despite a lack of routine anticoagulation use in the LVAD group of the REMATCH trial, 76% of patients were free of serious neuro-

logic events [8]. Only 10% of patients in the device group suffered an ischemic stroke [8]. The low percentage was attributed to the textured surfaces of the HM VE [8]. Comparison of the HM XVE and HM II recipients showed similar rates of ischemic stroke between the two groups of 14% and 17%, respectively [13]. In fact, while on Coumadin targeted to an INR of 2.0–3.0, the HM II patients suffered a similar rate of ischemic stroke as that among other patients with advanced heart failure and atrial fibrillation who are not on device support [13].

Overall, head-to-head assessment of pulsatile and continuous-flow LVADs showed significant reductions in the rate of major adverse events among CF-LVAD patients including device- and non-device-related infections, RV failure, respiratory failure, renal failure, and cardiac arrhythmia [13]. The study concluded that implantation of CF-LVADs as compared to pulsatile-flow devices among advanced heart failure patients being considered for destination therapy significantly improved the chance of survival free of stroke and the need for reoperation for device repair or replacement at 2 years [13].

An understated confounder of the results which showed an overwhelming superiority of CF-LVADs when compared to pulsatile-flow models was the increased clinical experience that was gained during the early years of device development in the management of these complicated patients. A follow-up study using the same patient pool from the REMATCH trial but followed for an additional period of 375 patient-months found lesser rates of adverse events among the group of patients that had been enrolled during the second half of the trial [14]. A study of 377 patients who were implanted with the HeartMate I generation of LVADs (HM VE and XVE) for DT a rising trend in 1-year survival rates related to the center volume of DT surgeries performed [16]. However, when preoperative DT risk score adjusted analysis of 1-year survival rates showed that DT center volume was not an independent predictor of survival, it was surmised that other factors related to center experience such as better patient selection and improved perioperative treatment accounted for the difference [19].

Causes of Death

The primary causes of death among patients with the pulsatile HeartMate VE were sepsis (41%) followed by LVAD failure (17%) instead of terminal heart failure which accounted for the majority of deaths in the optimal medical therapy group of the REMATCH trial [8]. A trial looking at HM XVE recipients in the post-REMATCH era found that the majority of in-hospital deaths (79%) occurred within the first 3 months [1]. During a minimum follow-up period of 2 years after LVAD implantation, the leading cause of death was hemorrhagic stroke which was seen in 9 and 10% of patients in the pulsatile and continuous-flow recipients, respectively [13]. This was followed by right ventricular failure which occurred in 8 and 5% of the pulsatile and continuous-flow LVAD recipients, respectively [13]. External power interruption, respiratory failure, cardiac arrest, and bleeding each accounted for 3–4% of the rest of the mortalities in the HM II group [13]. The estimated 1- and 2-year survival rates in this group were 68% and 58%, respectively [13].

Risk Score for Survival to Hospital Discharge and 1-Year Post HM XVE

Risk scores and risk calculators have become an important tool in patient selection for LVAD and in the education of patients that are interested in LVAD. In the cases in which the LVAD is used as destination therapy, the patient as well as the physician must be aware of risk for in-hospital mortality and 1-year outcomes. The authors of the post-REMATCH era [1] developed a risk score that can assist the discussion. Although the HeartMate XVE LVAD was used during the trial, the data does support the notion that sicker patient pre-LVAD implant does worse. Using univariate and multivariable analyses, the results were able to predict the risk factors for 90-day in-hospital mortality following LVAD. Table 15.1 shows the nine variables used in the multivariable model.

Each variable was assigned a weighted risk score and the cumulative risk score was calculated for each patient. A maximum score that can

Table 15.1 Multivariable analysis of risk factors for 90-day in-hospital mortality after LVAD as DT [6]

Patient characteristics	Odds ratio (CI)	*p*	Weighted risk score
Platelet count ≤148 × 10^3/μL	7.7 (3.0–19.4)	<0.001	7
Serum albumin ≤3.3 g/dL	5.7 (1.7–13.1)	<0.001	5
International normalization ratio >1.1	5.4 (1.4–21.8)	0.01	4
Vasodilator therapy	5.2 (1.9–14.0)	0.008	4
Mean pulmonary artery pressures ≤25 mmHg	4.1 (1.5–11.2)	0.009	3
Aspartate aminotransferase >45 U/mL	2.6 (1.0–6.9)	0.002	2
Hematocrit ≤34%	3.0 (1.1–7.6)	0.02	2
Blood urea nitrogen >51 U/dL	2.9 (1.1–8.0)	0.03	2
No intravenous inotropes	2.9 (1.1–7.7)	0.03	2

Table 15.2 Operative risk categories and risk score for 90-day in-hospital mortality after LVAD implantation as DT, survival to hospital discharge, and 1-year survival [6]

			In-hospital mortality within 90 days			Survival, %		
Operative risk categories	Risk score	No.	Observed, *n*	Predicted, *n*	% probability (CI)	To discharge, %	90 days	1 year
Low	0–8	65	2	1.6	2 (1.1–5.4)	87.5	93.7	81.2
Medium	9–16	111	12	13.7	12 (8.0–18.5)	70.5	86.5	62.4
High	17–19	28	10	7.9	44 (32.8–55.9)	26	38.9	27.8
Very high	>19	18	22	22.8	81 (66.0–90.9)	13.7	17.9	10.7

be obtained was 31. The patients were then divided into four operative risk categories based on probability of mortality during the hospitalization. Table 15.2 and Fig. 15.3 provide the in-hospital mortality and survival for DT-LVAD patients receiving a HeartMate XVE LVAD.

Therefore, the cumulative risk score for in-hospital mortality after LVAD surgery ranged from 81% in the lowest-risk candidates to a high probability of postoperative death and 11% 1-year survival in the highest-risk candidates.

Quality of Life and Functional Status

A number of studies have shown that survivors of LVAD implantation had a sustained improvement in their quality of life and functional status. At 1 year since the time of surgery, the survivors of HM VE implantation had a median NYHA functional class of II versus IV in the medical therapy group ($p < 0.001$) [8]. The same study showed significantly better scores on the physical-function and emotional-role subscales of the SF-36 and the Beck Depression Inventory in the device arm when compared to the medical therapy group [8]. A follow-up study by Stevenson et al. showed that even the most gravely ill subset of patients from the REMATCH trial who had been on inotropic support at the time of device implantation reported a decline in the Minnesota Living with Heart Failure Quality of Life Score of 77 at the time enrollment to 41 by 1 year suggesting less impairment [9]. The HeartMate II study for destination therapy showed that 80% of patients with CF-LVAD had an NYHA functional class of I or II at 24 months and doubled the mean distance on the 6-min walk test [13]. Members of both the pulsatile and CF-LVAD groups demonstrated a statistically significant ($p < 0.001$) improvement by over 30 points in their scores from baseline on the Minnesota Living with Heart failure and Kansas City Cardiomyopathy questionnaires after follow-up of up to 12 months for the pulsatile-flow group and up to 24 months for the CF-LVAD group [13].

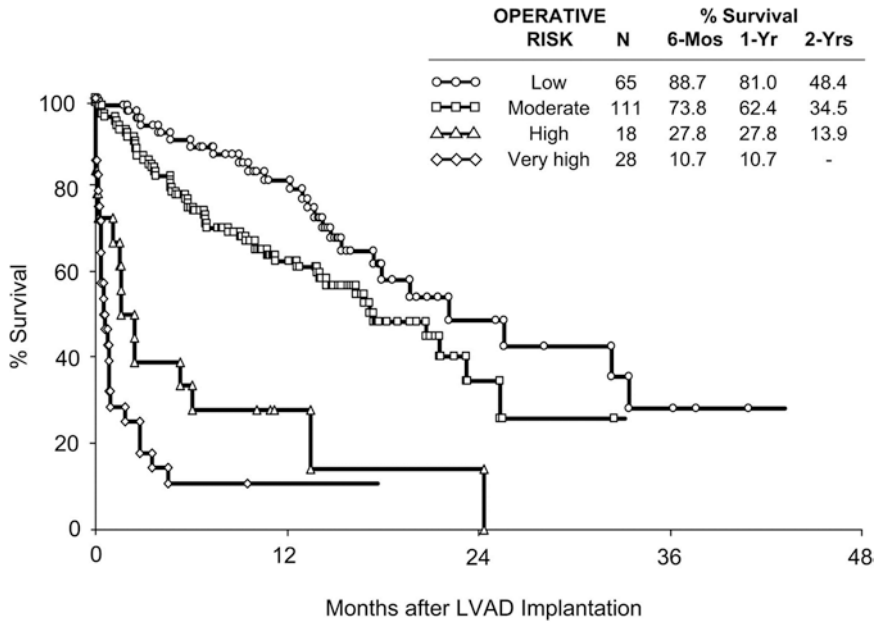

Fig. 15.3 Survival after LVAD implantation [6]

LVAD Durability

The lack of long-term durability was a concern beginning with the initial LVAD models as was mentioned briefly before. Pulsatile pumps were notably bulky with a large-diameter percutaneous lead and pump and thus required a large patient habitus to accommodate the device and extensive surgical dissection for implantation [11, 13, 20]. In the REMATCH trial which used the HeartMate VE, though no device had failed by 12 months of follow-up, the probability of device failure was quoted to be 35% by 24 months [8]. The HM VE was fraught with inflow-valve failure, late erosions of the outflow graft due to kinking, rupture of the lining, motor failure, and wear on the bearings [8]. The HeartMate XVE was an upgrade with a better designed inflow valve and outflow graft. Used in the post-REMATCH trial by Lietz et al., the HM XVE exhibited a median time of LVAD support on the first pump of 18.6 months [1]. During the follow-up period ranging from 1 day to 3.6 years (mean 10.3 months), 24.6% of patients either required LVAD replacement because of device end of life or expired as a result of pump failure [1].

CF-LVADs addressed some of the problems that were noted with the pulsatile models. With only a single moving part, the internal rotator, the design was much simpler [20]. The HM II destination therapy trial showed that 9% of the patients who were supported by HM II required pump replacement compared to 34% of those who had received a HM XVE ($p < 0.001$) [13]. Of the 59 patients who were initially implanted with a PF-LVAD, 20 patients required a total of 21 pump replacements: 3 were replaced with an alternate PF-LVAD and 18 with a CF-LVAD. The most common reasons for replacement were bearing wear, valve malfunction, and infection [13]. Of the 133 patients who received a CF-LVAD initially, only 12 patients required a total of 13 pump replacements [13]. A pump replacement rate of 6 events per 100 patients in the CF-LVAD group was approximately one-eighth the incidence seen in the pulsatile-flow group of patients, and the most common reason was damage to the percutaneous lead [13].

Hospitalization

Among HeartMate VE recipients, the mean number of days spent in the hospital was 88 as opposed to 24 in the medical therapy group of the REMATCH trial [8]. In the HM II destination therapy trial, the median length of stay after LVAD implantation was 28 days in the HM XVE group and 27 days in the HM II group [13]. Significantly, Slaughter et al. noted a 38% relative reduction in the rate of rehospitalization among continuous-flow LVAD recipients as compared to pulsatile-flow LVAD recipients [13].

Psychosocial Characteristics and Outcome Predictors

Psychosocial factors play a key role in the management of LVAD patients and can affect the outcomes. Depression is often given the most attention since the incidence is consistently higher than the general population. Prevalence and severity of depression in heart failure vary considerably from 11–25% in outpatients to 35–70% among inpatients [21–23]. Although some studies have shown an increased risk of death and hospitalizations in patients with HF and depressive symptoms, other failed to show any associations [24]. One study looked at specific psychosocial characteristics in 136 DT-LVAD patients and the association with all-cause readmission and death. In the retrospective analysis, there was no statistically significant difference in the risk of death in regard to a multitude of psychosocial characteristics. They did note current tobacco users had lower risk of readmission (adjusted HR, 0.57; 95% CI, 0.38–0.88). On the other hand, illegal drug use (HR, 1.55; 95% CI, 1.01–2.35) and depression (HR, 1.77; 95% CI, 1.40–2.22) had a higher readmission risk [25].

Elderly (>70 years old)

Given the increasing aging population and increasing incidence of heart failure, there will be a large number of elderly patients presenting with end-stage heart failure needing advance heart failure therapies. Heart transplant is usually not a viable option in this age group. Unfortunately, they are left with only optimal medical therapy. LVAD has become an option for this age group but often with significant risk. This patient group is often left out of randomized control trials or not the main focus which makes advising and educating these patients about the risk of implant difficult. However, a recent retrospective study analyzed patients ≥70 years old. Taken from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), Atluri et al. looked at 590 patients >70 years old (565 pts 70–79 years old, 25pts >80 years old) who received a continuous-flow left ventricular assist device (CF-LVAD) and compared them to <70 years old patients. These 70+-year-old patients were healthier and hemodynamically stable evident by their INTERMACS score and dependence on inotrope. They were more common to undergo re-sternotomy for the LVAD implant and have worse renal function on presentation. Length of stay and mean bypass time were the same as compared to patients <70 years old. Adverse events after LVAD implant revealed a significant increase in stroke (2.3% vs. 0.9%, $p = 0.01$) in the elderly when compared with younger, increased risk of gastrointestinal bleeding (19.84% vs. 13.39%, $p < 0.001$). Rehospitalization (62.17% vs. 63.9%, $p = 0.5$), renal dysfunction (14.72% vs. 12.78%, $p = 0.2$), respiratory failure (21.06% vs. 20.07%, $p = 0.9$), and right heart failure (14.31% vs. 14.23%, $p = 0.9$) were similar in both groups. Interestingly, there was a much lower incidence of driveline infection among the elderly when compared with younger patients (5.7% vs. 12.6%, $p < 0.001$). Survival (Fig. 15.4) was significantly different but acceptable, 1 year (75% vs. 81%, $p < 0.001$) [26].

As more scoring systems come about and the frailty index evolves, this patient cohort will soon gain an understanding on the outcomes and incidence of adverse events. More importantly with a study such as ROADMAP, early LVAD implant may help this population greatly.

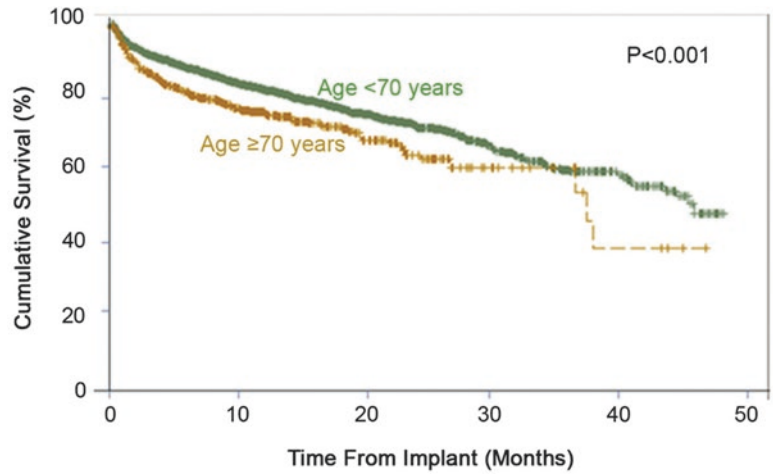

Fig. 15.4 Kaplan-Meier analysis for cumulative survival undergoing LVAD in patients less than 70 or 70 and greater [25]

Recovery

Mechanical volume and pressure unloading induced by LVADs allow reversal of stress-related compensatory responses triggering structural and functional reverse remodeling. In theory, this would allow for cardiac recovery and explant of the LVAD. However, studies are limited specifically in the destination therapy group [27]. INTERMACS data suggest less than 5% of patients in the DT group (553 total in the study) recovered cardiac function [28].

Transplant from Destination Therapy

Transplant in the destination therapy group is uncommon but can occur. There are patients who received a destination therapy device and transplant ineligible for various reasons. As age was the most common reason precluding patients in the REMATCH trial from cardiac transplantation, no patients enrolled in that study underwent transplantation [8]. However, a study of HM XVE DT recipients during the post-REMATCH era showed that 47 patients (17%) underwent heart transplantation after a mean mechanical support time of 10.2 months [1]. Transplant eligibility occurred due to the reversal of pulmonary hypertension in 12, 5-year cancer survival in 5, recovery of renal function in 4, weight loss in 3, resolution of infection in 4, and correction of other issues in 16 patients [1]. In the HeartMate II destination therapy trial, transplantation was ultimately possible in 9 of 66 patients in the pulsatile-flow LVAD group and 17 of 134 patients in the continuous-flow LVAD group mainly due to a significant drop in pulmonary pressures [13]. Based on data from INTERMACS as reported by Teuteberg et al., 14.6% of patients in the destination therapy group were deemed eligible for transplant. At 6 months, 1% of DT group received a transplant, and at 2 years only 6% of DT population received a transplant [28].

Conclusions and New Directions

The large discrepancy between the rising incidence of medically refractory heart failure and the limited supply of available heart transplants is a challenging issue that will have to be dealt with in the coming years. LVADs placed for destination therapy provide a means to mitigate the situation. However, not enough LVADs are placed as destination therapy to meet the projected demand for them. This may be due to an unawareness in the general medical community about this technology or due to a perception that LVADs serve a palliative option.

Trials comparing pulsatile-flow LVADs to medical therapy alone in transplant-ineligible patients have demonstrated the superiority of LVADs in terms of lengthening survival though at the cost of increasing adverse events. The bulkiness and fragility of earlier LVAD models were addressed by the simpler design of the continuous-flow LVADs which were less prone to adverse events such as device infections, pump thrombosis, cardiac arrhythmia, and RV failure than pulsatile models. However, the nonphysiologic continuous flow was attributed to increased rates of non-neurologic bleeding.

The next generation of left ventricular assist support systems promises more compact design, more physiologic flow, and fewer hemocompatibility-related adverse events. Unlike the standard axial-flow HeartMate II, the new HeartMate 3, a magnetically levitated centrifugal continuous-flow pump with intrinsic pulsatility, and the HeartWare, a small intra-pericardial centrifugal-flow pump with magnetic levitation and hydrodynamic design, both lack bearings [29, 30]. They were made with the idea that eliminating the bearings may reduce friction and risk of thrombosis associated with other LVADs. The 6-month follow-up of patients enrolled in the MOMENTUM 3 trial comparing the outcomes of patients who received HeartMate 3 versus HeartMate II for bridge-to-transplant and destination therapy showed that HeartMate 3 patients exhibited greater survival free of hemocompatibility-related adverse events defined as any nonsurgical bleeding, thromboembolic event, pump thrombosis, or neurological event [29, 31]. The ENDURANCE trial which compares the HeartWare HVAD against the HeartMate II for destination therapy has proven the non-inferiority of the HeartWare HVAD in the primary endpoint of survival at 2 years free from disabling stroke or device removal for malfunction or failure [30, 32].

Durable LVAD for destination therapy is not without its risk. Considering the high mortality rate among patients who are on medical therapy alone awaiting heart transplantation, the increased adverse events balanced by increased survival rates associated with LVADs may be a necessary trade. We look forward to future directions of LVAD design that may one day minimize risk, improve quality of life, and obviate the need for heart transplant altogether.

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Cardiac Regenerative Strategies for Advanced Heart Failure

16

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Abbreviations

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CADUCEUS	Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (phase 1 trial)
cTnT	Cardiac troponin T
ES	Embryonic stem cells
FGF	Fibroblasts growth factor
GFP	Green fluorescence protein control
GMT	Gata4, Mef2c, Tbx5 cardio-differentiating factors
iCM	Induced cardiomyocyte
iPS	Induced pluripotent stem cells
mRNA	microRNA
PAD	Peripheral arterial disease
SCIPIO	Stem cell infusion in patients with ischemic cardiomyopathy (phase 1 trial)
VEGF	Vascular endothelial growth factor

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Introduction

Congestive heart failure, caused by a loss of cardiac function typically as a result of myocardial ischemia or infarction, is the common end point for advanced coronary artery disease and is the leading cause of mortality from heart disease [1]. Current therapies for end-stage coronary artery disease, including transplant or assist devices, are associated with considerable morbidity, limiting cost and/or availability, and aggregate 5-year mortality rates of 50% [2–4].

Despite some evidence of limited endogenous myocyte replication or regeneration from resident stem cells, native adult cardiac muscle does not effectively regenerate itself de novo after cardiomyocyte death. Strategies have therefore been devised to administer exogenous stem cells or reserve cells (e.g., embryonic stem cells, mesenchymal stem cells, or skeletal myoblasts) into the

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infarct zone to enhance cardiac function. Stem cell clinical trials have however been largely disappointing, likely due to inadequate implant phenotypes and/or poor implant survival and engraftment into the host myocardium [5, 6]. Given that post-infarct ventricular remodeling is characterized by the replacement of cardiomyocytes with fibroblasts, a new strategy utilizing genetic reprogramming to regenerate (induced) cardiomyocytes (iCMs) from endogenous scar fibroblasts has thus evolved as an intriguing new therapeutic paradigm for treating patients with congestive heart failure arising from end-stage coronary artery disease.

More specifically, the seminal finding that cellular reprogramming strategies could be used to produce induced pluripotent stem (iPS) cells from adult somatic cells was soon followed by findings that iPS cells could be redifferentiated into cells with a cardiomyocyte-like phenotype. The more recent discovery that "transdifferentiating" transcription factors could be administered to reprogram adult somatic cells (fibroblasts) into "induced cardiomyocyte" (iCM) cells suggests that in situ autologous cardiomyocyte regeneration that completely bypasses stem cell or (potentially immunogenic and/or tumorigenic) iPS staging is possible [7, 8].

"Direct" reprogramming thus offers the exciting opportunity to convert cardiac fibroblasts into functional iCMs in situ and transform scar tissue into functional myocardium. Knowledge that has been garnered from the false starts and disproved premises of many of the therapeutic angiogenesis and stem cell trials conducted over the past two decades will hopefully provide a solid starting point for well-designed studies to test the potential clinical efficacy of this new strategy—one that is based on sound selection of delivery vectors, routes of delivery, and regulation of "dosage" [9–11].

Strategies for Cardiac Regeneration

The cardiac regeneration strategies that are the most extensively studied to date include: (1) angiogenic therapy, (2) exogenous (stem) cell implantation (e.g., using hematopoietic, bone marrow, or myoblast cells), (3) direct reprogramming strategies, and (4) resident progenitor cell and cardiomyocyte replicative stimulation strategies [9–13]. The remainder of this chapter will focus on the first three of these.

Recent analyses of these efforts suggest that the poor survival of exogenous stem cell implants in the hostile, ischemic milieu of the myocardial scar is in large part related to the absence of an adequate blood supply to nourish these relatively great metabolic needs of these cells compared to that of the resident fibroblasts and poor engraftment of these exogenous cells in the host syncytium [5, 6]. Following consequently marginal improvement, at best, in cardiac function in stem cell clinical trials, current rationalization for the mechanism of action of stem cell implantation centers on proposed angiogenic and other paracrine effects of these cells upon host cardiomyocytes and other cells, rather than the primary contractile or physio-mechanical contributions of implanted cells [14].

In comparison, although the direct administration of angiogenic factors has been shown to induce myocardial vascularization in animal models and some clinical trials, it is improbable that angiogenesis therapy alone cannot improve the function of myocardial scar and on contractile scar fibroblasts [9, 10, 15, 16]. Thus, as depicted in Fig. 16.1, a rational myocardial regeneration strategy could incorporate prevascularization of myocardial scar with angiogenic therapy, followed by direct, in situ reprogramming of resident scar fibroblasts into induced cardiomyocytes, obviating entirely the challenges of exogenous cell delivery and engraftment into the host myocardium.

Cardiac cellular reprogramming describes the process by which cardio-differentiating (transcription) factors or the genes encoding them can be administered to terminally differentiated cells in order to reprogram them into cardiomyocyte-like cells. The scientific principles underlying this strategy were dramatically put forth in the revolutionary work of Nobel laureate Yamanaka, who used the transcription factors Oct4, Sox2, Klf4, and c-myc to reprogram terminally differentiated cells into induced pluripotent stem (iPS) cells [17]. Capitalizing on this strategy, Srivastava

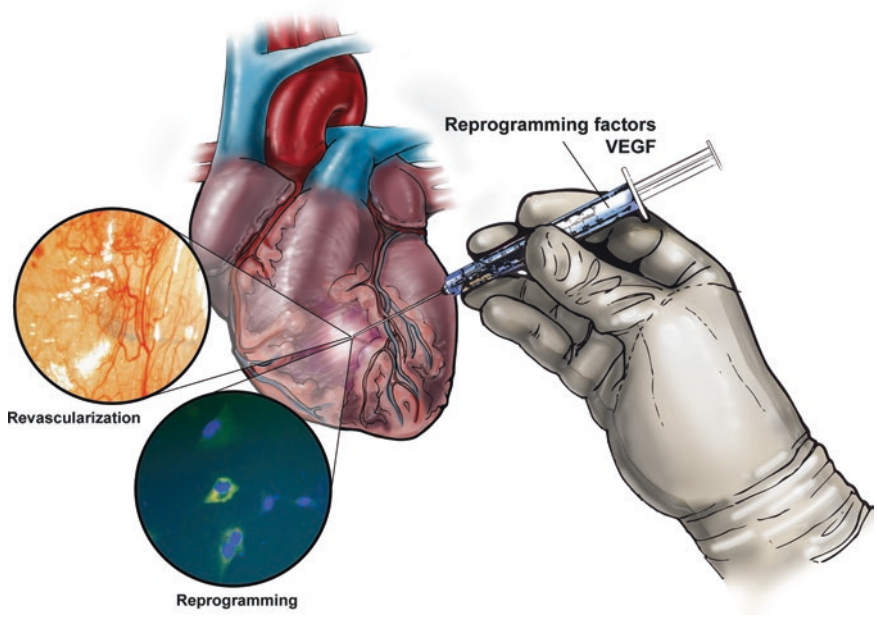

Fig. 16.1 Multimodal strategy for cardiac regeneration. Printed with permission from Baylor College of Medicine

et al. soon thereafter showed that cardiac fibroblasts could be *directly* reprogrammed into induced cardiomyocytes (iCMs) using the cardiodifferentiating factors Gata4, Mef2c, and Tbx5 (GMT), which were able to bypass a pluripotent intermediate state [11]. Most importantly, the administration of GMT into infarcted myocardium has more recently been shown to yield significant improvements in post-infarct ventricular function and fibrosis in rodent models [18]. Since this time, a variety of gene- and small molecule-based strategies have been successfully tested in vitro and in vivo, as described below.

Angiogenesis-Based Therapies

The goal of *therapeutic angiogenesis* is to "biologically bypass" an occluded vessel in coronary artery disease (CAD) or peripheral arterial disease (PAD) by forming collateral blood vessels, thereby relieving ischemia. The notion of therapeutic angiogenesis for coronary and peripheral arterial diseases originates from the seminal work by Dr. Judah Folkman in the early 1970s, who demonstrated that growth factors were responsible for tumor angiogenesis [19]. These growth factors are most commonly identified today as the angiogenic peptides vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [9, 10].

Not long following Folkman's discovery, compelling preclinical data in animal models demonstrated that angiogenic protein or gene delivery improved peripheral and myocardial collateralization, as well as peripheral perfusion and cardiac function [20, 21]. Since then, numerous trials involving over 2000 patients and utilizing administration of angiogenic proteins and their genes (e.g., VEGF-A 121, 165, and 189, FGF-1, and FGF-4) for the treatment of coronary and peripheral vascular disease have yielded mixed results [10, 22–24].

Likely, the disappointing outcomes of angiogenic therapy trials were often due to inappropriate or ineffective routes of administration (e.g., intravascular vs. intramyocardial) that provided inadequate tissue concentrations of angiogenic agents and/or were due to inappropriate end points (e.g., relatively low-resolution myocardial perfusion studies vs. PET or treadmill exercise testing) [9, 10, 13, 14]. These limitations

frequently confounded data interpretation, leading many to dismiss the promise of angiogenic (gene) therapy. The unfortunate death of study patient Jesse Gelsinger, who received an abnormally high dose of adenovirus therapy for treatment of ornithine transcarbamylase deficiency, likewise led to a brief moratorium on all gene therapy in the United States, which nevertheless led to a prolonged period of diminished enthusiasm for gene therapy trials [25, 26].

Despite these challenges in this new area of drug development, retrospective analyses of the angiogenic gene therapy clinical trials have yielded useful insights that offer new opportunities for advancing this field. First, it appears clear that the type of angiogenic vector utilized (i.e., protein, plasmid, or virus) is critical to achieving an appropriately therapeutic angiogenic factor "dose" sufficient to induce angiogenesis [27, 28]. In this regard, angiogenic protein delivery typically produced disappointing results likely due to the relatively short half-life and the dose-limiting side effect of hypotension associated with large systemic dosing. Plasmid delivery likewise seems to be ineffective due to its low transduction efficiency into cells and transient expression. In contrast, adenoviral delivery of angiogenic factors allows for a higher transduction efficiency of cells and prolonged expression of genes up to weeks after administration without integration into the genome. Accordingly, trials incorporating adenoviral-mediated delivery were and may prove to be more effective in inducing angiogenesis than are those testing other agents [10, 29–33].

The use of intracoronary vs. direct intramyocardial delivery of angiogenic factors also likely undermined therapeutic efficacy, as did the choice of appropriate tissue treatment targets [15, 28]. More specifically, direct intramyocardial delivery generally yielded more favorable outcomes compared to intracoronary delivery likely because of the more favorable pharmacokinetics of "drug delivery" via this more localized approach compared to the more diffuse, systemic delivery of drug associated with intracoronary or intravascular delivery (Table 16.1) [15]. Parenthetically, the latter also confers the additional potential risk of disseminating angiogenic factors throughout the body, potentially producing "off-target" effects.

Likewise, the application of angiogenic therapies to peripheral vascular vs. coronary disease creates the challenge of effectively treating vascular obstruction at multiple levels over a relatively vast tissue territory (i.e., central inflow disease, diffuse intermediate-level vascular obstruction, and peripheral outflow obstruction), compared to more "geographically" localized coronary disease requiring less total amounts and distribution of drug delivery. The treatment of coronary disease may thus represent an ideal target for angiogenic therapy. While these considerations may seem obvious in retrospect, the failure to consider these basic pharmacokinetic principles often led to analytic generalizations about negative trial outcomes to the entire field and (mis)perceptions that angiogenic therapy was ineffective.

A number of the early angiogenesis trials were also dismissed because they lacked placebo controls and objective, clinically relevant end points, such as electrocardiographic changes associated with exercise treadmill testing [16]. Paradoxically, while inclusion of such placebo controls was relatively easy with (pharmacokinetically ineffective) intravascular trials, performing sham surgery to allow (more effective) direct intramyocardial delivery in patients with end-stage heart disease poses an ethical dilemma [15]. Unfortunately, this led many observers to discredit the positive findings demonstrated by (non-placebo) intramyocardial-based trials, despite positive objective data such as changes in ischemia levels based on ECG data. While a randomized, placebo-controlled trial may ultimately be necessary to conclusively verify the clinical benefit of angiogenic therapy, the development of a uniform study protocols with objective, validated end points, more efficient methods of gene delivery, and improved methods to determine total gene delivery into the target tissue may well offer a pathway to effectively test this new biologic treatment for patients with vascular disease [9, 10, 15, 27, 28].

Table 16.1 Representative cardiac angiogenesis clinic trials

Trial title	Author, year	Study design	Sample size	Follow-up	Vector	Delivery	Agent	Results
Direct myocardial injection[a]								
	Symes et al.,[b] 1999	Phase I	20	90 days	Plasmid	Epicardial; minithoracotomy	VEGF-165	(+) Angina (nitroglycerin use) (+) Perfusion (SPECT) (+/−) Coronary angiography
	Rosengart et al.,[c] 1999	Phase I	16	6 months	Adenovirus	Epicardial; minithoracotomy	VEGF-121	(+) Angina class (+) (+) Exercise duration (+) (+) Perfusion (sestamibi)
	Vale,[d] 2000	Phase I	13	60 days	Recombinant protein	Epicardial; minithoracotomy	VEGF-165	(+) Angina (+) Exercise duration (+) Perfusion (NOGA)
	Losordo et al.,[e] 2002	DB-RCT	19	12 weeks	Plasmid	Endocardial; NOGA	VEGF2	(+) Angina class (+) Exercise duration (+/−) Perfusion (NOGA/SPECT)
Euroinject One	Kastrup et al.,[f] 2005	DB-RCT	80	3 months	Plasmid	Endocardial; NOGA	VEGF-165	(−) Angina class (−) Perfusion (SPECT/NOGA)
REVASC	Stewart et al.,[g] 2006	RCT	67	26 weeks	Adenovirus	Epicardial	VEGF-121	(+) Angina (+) Exercise duration
NORTHERN	Stewart et al.,[h] 2009	DB-RCT	93	6 months	Plasmid	Endocardial; NOGA	VEGF-165	(−) Angina class (−) Exercise duration (−) Perfusion
Intracoronary delivery[a]								
Intracoronary	Laham et al.,[i] 2000	Phase I	52	180 days	Recombinant protein	Intracoronary	FGF-2	(+) Angina score (Seattle) (+) Exercise treadmill (+) Ischemia (MRI)

(continued)

Table 16.1 (continued)

Trial title	Author, year	Study design	Sample size	Follow-up	Vector	Delivery	Agent	Results
	Hendel et al.,[j] 2000	Phase I	14	60 days	Recombinant protein	Intracoronary	VEGF-165	(+/−) SPECT
FIRST	Simons et al.,[k] 2002	DB-RCT	337	180 days	Recombinant protein	Intracoronary	FGF2	(−) Angina class (−) Exercise time
AGENT-2	Grines,[l] 2003	DB-RCT	52	8 weeks	Adenovirus	Intracoronary	FGF4	(−) Angina class (−) SPECT
VIVA	Henry et al.,[m] 2003	DB-RCT	178	120 days	Recombinant protein	Intracoronary	VEGF	(−) Angina class [(+) at high dose] (−) Exercise time (−) SPECT
AGENT-3, AGENT-4	Henry et al.,[n] 2007	DB-RCT	532	12 months	Adenovirus	Intracoronary	FGF4	(−) Angina class (−) Exercise time

+, Statistically significant change; +/−, nonsignificant improvement; −, no improvements detected

DB-RCT indicates double-blind, randomized controlled trial, *CABG* coronary artery bypass graft, *SPECT* surface photon emission computerized tomography, *REVASC* randomized evaluation of VEGF for angiogenesis, *NORTHERN* NOGA angiogenesis revascularization therapy: assessment by radionuclide imaging, *FGF* indicates fibroblast growth factor, *MRI* magnetic resonance imaging, *FIRST* FGF initiating revascularization trial, *AGENT* angiogenic gene therapy trial, *VIVA* VEGF in ischemia for vascular angiogenesis

Note. Adapted from Tables 1 and 2 in Rosengart TK, Fallon E, Crystal RG. Cardiac Biointerventions: Whatever Happened to Stem Cell and Gene Therapy?, *Innovations: Tech in Cardiothoracic Surgery*, May/June 2012; 7(3): 173–179. Please see this reference for further information, including citations for these trials. Reprinted with permission from Wolters Kluwer

[a]Does not include combined interventions (e.g., adjunct to CABG); includes latest of multiple reports on each trial

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Stem Cell Implantation

Given the low regenerative capacity of cardiomyocytes (<1% per year), replacement of cardiomyocytes with exogenous stem cells (embryonic, bone marrow-derived, or induced pluripotent) following myocardial infarction has received much attention over the past two decades. Bone marrow-derived hematopoietic progenitor cells were the first to be implanted, resulting in over 100 phase I-II trials including thousands of patients. Despite the promising safety profile of these cell implants, several meta-analyses revealed that bone marrow-derived progenitor cell implantation therapy led only to a non-clinically relevant increase (i.e., not greater than 2–4%) in left ventricular ejection fraction [7, 8, 34, 35]. This negative outcome has been attributed to the low survival of implanted cells, poor engraftment into the native myocardium, and the formation of immature cardiomyocyte structures (Table 16.2) [36]. The modest improvement in ejection fraction seen in these trials has more recently been alternatively ascribed to the secretion by implanted cells of paracrine signals that might support resident myocyte survival, neovascularization, recruitment of endogenous cardiac progenitor cells, or cardiac remodeling induced by these implants rather than their differentiation into nascent cardiomyocytes [12, 35, 37].

The use of embryonic stem (ES) cells, which possess a potentially more favorable degree of plasticity and proliferative capacity than bone or circulation-derived stem cells, is not ideal as a stem cell therapy for obvious ethical reasons, as well as the risk of immune-mediated rejection necessitating immunosuppression and the formation of heterogeneous cardiac cell subtypes (ventricular cardiomyocytes, atrial cardiomyocytes, or pacemaker cells) or other aberrant tissues such as teratomas [14, 38].

Given these concerns, induced pluripotent stem (iPS) cells, which can be derived directly from the patient and reimplanted into infarcted myocardium, have emerged as potentially more suitable candidates for cell-based regeneration. The advantages of using iPS cells include their similarity to ES cells, unlimited proliferative capacity, reduced risk of immune-mediated rejection, and, of course, more ethically sound procurement [38, 39]. The disadvantages of iPS cells include the cost needed to generate patient-specific iPS cells and their immature development of sarcomeric structures following implantation, immature electrophysiologic properties, electrical ectopy, and the formation of a heterogeneous mixture of cell types, as well as the same implant survival and integration challenges associated with all cell implants into the hostile milieu of the infarcted myocardium [14, 38]. While the implantation of iPS cells into animal infarct models has been shown to lead to 10–15% increases in left ventricular ejection fraction, these results, as with other cell implants, may thus likely not be translatable to clinical efficacy [40–45].

In the context of these mixed results, efforts are currently underway to improve implant cell survival through improved mechanical adherence strategies (e.g., using engineered tissue scaffolds and adhesive biogels) and improved vascularization of the tissue bed to enhance implanted cell survival (e.g., using angiogenic pretreatment) [39, 46–50].

Direct Cardiac Cellular Reprogramming Studies In Vitro

Given the challenges associated with cell implantation therapies for cardiac regeneration, the advent of direct cardiac cellular reprogramming represents a significant potential advancement for this field as it capitalizes on the presence of endogenous, quiescent cardiac fibroblasts to generate induced cardiomyocytes (iCMs), avoiding nearly all of the challenges posed by exogenous cell implant strategies [6]. In general, this entire field seeks to capitalize upon the identification and administration of the differentiating factors associated with early embryonic cardiac development.

The first iterations of direct cardiac reprogramming using administration of the cardiodifferentiating transcription factors Gata4, Mef2c, and Tbx5 (GMT) yielded reprogramming efficiencies of about 7%, as evidenced by expression of the cardiomyocyte marker cardiac tropo-

Table 16.2 Summary of current cardiac regenerative strategies

	Bone marrow-derived stem cells	Induced pluripotent (iPS) cells	Direct cardiac reprogramming
Type of therapy	Cell implantation	Cell implantation	Gene therapy
Survival of cells	Low	Low	Unknown beyond 12 weeks
Characterization of cells	Immature sarcomeric structures	Immature sarcomeric structures	Mature sarcomeric structures
Oncogenic risk	Low	High	None
Risk of immunorejection	High if allogeneic source	Low (viral reprogramming factors)	Low (viral reprogramming factors)
Improvement in ejection fraction[a]	+2–5%	+10–15%	+10–25%
Advantages	Proven safe in phase I/II trials	Ex vivo expansion of cells, lower immunorejection risk (patient-specific cells)	Avoids cell implantation, uses endogenous cardiac fibroblasts
Disadvantages	Marginal improvement in ejection fraction, complicated acquisition and delivery of cells, low cell survival, arrhythmia, potential for teratoma	Cardiac subtype heterogeneity, arrhythmia, teratoma, poor engraftment, low cell survival	Human cells resistant to reprogramming, no long-term studies (>12 weeks)
Modifications/future research	Tissue scaffolds or improved vascularization to improve cell survival, new delivery techniques	Tissue scaffolds or improved vascularization (VEGF, omental flap) to increase cell survival	Non-viral vectors, epigenetic modifications, simpler combinations of factors

[a]Represents the difference between treated vs. untreated (control) groups for each regenerative strategy

nin T (cTnT), with an even smaller subset of contractile iCMs [11]. In order to enhance the reprogramming efficiency and the maturation of iCMs, several modifications have been proposed, including the improvement of the cardiodifferentiating gene cocktail and incorporation of downregulation of native fibroblast gene expression (Table 16.3).

Consistent with the results of the angiogenesis trials, it was quickly established that efficient delivery of reprogramming factors, not surprisingly, improved the efficacy of reprogramming. The use of a "triplet" GMT vector which resolved the challenge of target cells needed to be infected by three different viruses each encoding for a single reprogramming transgene, for example, resulted in a twofold increase in reprogramming efficiency (based on % $cTnT^+$ cells), more mature sarcomeric structures (immunofluorescence), and a threefold improvement in post-infarct ventricular function when compared to the use of the original "singlet" GMT vectors [51, 52]. Optimized reprogramming transgene dosing via differential overexpression of Mef2c in relation to Gata4 and Tbx5 provided by stoichiometric rearrangement or fusion of the MyoD domain to Mef2c has likewise been shown to result in a higher proportion of contractile iCMs, reemphasizing the principle that the correct "dosing" of genes is important [53, 54].

The addition of new potent select cardiodifferentiating factors to the original GMT formula has also produced improvements in efficacy. The addition of Hand2 [55], Nkx2.5 [56], Myocardin, and/or Mesp1 [57] to GMT has, for example, been shown to increase the reprogramming efficiency and the contractile characteristics of iCMs [57–59]. Other reprogramming factor cocktails have also been favorably tested (Table 16.3).

"Erasing" the preexistent somatic cell signature of target cells by downregulating native fibroblast gene expression has also been shown to

Table 16.3 In vivo and in vitro reports of direct cardiac reprogramming

Cell type	Reprogramming factors	Vector	Contractile iCM	Reprogramming efficiency (% cTnT$^+$)	In vitro	ΔEF%
Murine						
CF, DF	Gata4, Mef2c, Tbx5 [11, 18]	RV, LV	●	8%	●	+10
CF	Gata4, Mef2c, Tbx5 [51]	RV	○	7%	●	[a]
CF, TTF	Gata4, Mef2c, Tbx5 [53, 71]	RV	●	10%	●	+21
CF, TTF	Gata4, Mef2c, Tbx5 [85]	LV	○	–	○	
CF, TTF	Gata4, Mef2c, Tbx5, Hand2 [55]	RV	●	25%	●	+21
MEF, TTF	Gata4, Mef2c-MyoD fusion, Tbx5, Hand2 [54]	RV	●	21%	○	
CF, TTF, MEF	Gata4, Mef2c, Tbx5, Hand2, Akt1 [86]	RV	●	30%	○	
MEF, CF	Gata4, Mef2c, Tbx5, Hand2, Nkx2.5 [56]	LV	●	5%[b]	○	
MEF	Gata4, Tbx5, Myocardin [58]	LV	○	26%[b]	○	
MEF	Mef2c, Tbx5, Myocardin [59]	LV	○	10%	○	
MEF	Gata4, Mef2c, Tbx5, Myocardin, SRF, Mesp1, SMARCD3 [57]	LV	○	30%[b]	○	
CF	miR-1, miR-133, miR-208, and miR-499 [66, 67]	LV	○	–	●	[c]
CF, MEF	Gata4, Mef2c, Tbx5, Hand2, Nkx2.5, SB431542 (TGFβ inhibitor) [62]	LV	●	17%[b]	○	
MEF, CF, TTF	Gata4, Mef2c, Tbx5, Hand2, miR-1, miR-133, A-83-01 (TGFβ inhibitor) [63]	RV, AV	●	60%	○	
MEF, TTF	Oct4, small molecules (SB431542, CHIR99021, Parnate, Forskolin) [68]	LV	●	–	○	
MEF, TTF	Small molecules (CHIR99021, RepSox, Forskolin, VPA, Parnate, TTNPB) [69]	–	●	–	○	
CF, TTF	Gata4, Mef2c, Tbx5, Bmi1 shRNA [65]	RV	●	30%	○	
MEF, TTF	Gata4, Mef2c, Tbx5, FGF2, FGF10, VEGF [74]	RV	●	3%	○	

(continued)

Table 16.3 (continued)

Cell type	Reprogramming factors	Vector	Contractile iCM	Reprogramming efficiency (% cTnT⁺)	In vitro	ΔEF%
Rat CF	Gata4, Mef2c, Tbx5, VEGF [52, 73]	LV, AV	○	8%	●	+15
Other						
MEF, Human CF	Gata4, Mef2c, Tbx5, miR-133, Mesp1, Myocardin [60]	RV, LV	●	30%	○	
Human DF	Ets2, Mesp1 [87]	RV	○	–	○	
Human CF, DF	Gata4, Mef2c, Tbx5, ESRRG, Mesp1, Myocardin, ZFPM2 [75]	RV	○	12%	○	
Human CF, DF	Gata4, Tbx5, Hand2, Myocardin, miR-1, miR-133 [61]	RV	●	20%	○	
Human CF, DF	Gata4, Mef2c, Tbx5, Myocardin, Mesp1 [76]	RV, LV	○	6%	○	
Human DF	Small molecules (CHIR99021, A83-01, BIX01294, AS8351, SC1, Y27632, OAC2, SU16F, JNJ10198409) [70]	–	●	6%	○	

ΔEF% represents the difference or improvement in ejection fraction between GMT-treated groups and control groups
RV retrovirus, *LV* lentivirus, *AV* adenovirus, *CF* cardiac fibroblasts (neonatal or adult), *DF* dermal fibroblasts, *TTF* tail tip fibroblasts, *MEF* mouse embryonic fibroblasts
Reprinted with permission of Springer. *Current Treatment Options in Cardiovascular Medicine*, Direct Cardiac Cellular Reprogramming for Cardiac Regeneration, (2016) 18: 58, Patel V, Mathison M, Singh VP, Yang J, Rosengart TK
[a]Inagawa et al. demonstrated formation of sarcomeric structures in fibroblasts (IF for α-actinin and cTnT) following administration of intramyocardial GMT
[b]Addis et al. and Ifkovits, % cells that express Troponin T-GCaMP-GFP (calcium reporter) by immunofluorescence (IF). Christoforou, % cells that express Tnnt2 (precursor gene for cTnT) by flow cytometry. Zhou et al. % Tnnt2 cells by IF
[c]Jayawardena et al. showed reduction in fibrosis and improvement in cardiac function (echocardiography) by other metrics such as increased fractional shortening and decreased left ventricular dimensions

favor the formation of iCMs. Muraoka et al. and Nam et al., for example, demonstrated that microRNA-133 (miRNA-133)-mediated suppression of Snai1, a key activator of pro-fibrotic genes, improved reprogramming efficiency at least fivefold in murine and human fibroblasts [60, 61]. Similarly, Ifkovits et al. and Zhao et al. demonstrated that small molecule inhibitors of key pro-fibrotic pathways, transforming growth factor-β (TGF-β) or Rho-associated kinase, substantially enhanced reprogramming efficiency and quality, as evidenced by the percentage of contractile cells and maturation of sarcomeric structures [62, 63]. By combining multiple cardio-differentiating factors and multiple inhibitors of pro-fibrotic genes, Zhao et al. reported a reprogramming efficiency of nearly 60% (% cTnT⁺ cells by flow cytometry) in mouse embryonic fibroblasts, many of which were contractile.

As such efforts will only increase the complexity and number of constituents in reprogramming factor cocktails, which would be difficult to deliver in vivo, efforts are also underway to consolidate the number of factors by silencing the intrinsic epigenetic barriers that oppose reprogramming [64]. Zhou et al. demonstrated

that silencing Bmi1, an epigenetic regulator, results in derepression of cardiogenic genes Gata4, Nkx2.5, Isl1, Pitx2, Tbx20, and Hand2, enhancing both the efficiency and quality of reprogramming when combined with GMT [65]. Similarly, we have shown that silencing the "anti-plasticity gene" p63 alone results in derepression of Gata4, Mef2c, and Tbx5 and upregulation of cardiomyocyte-specific markers [Patel et al. 2016, unpublished].

While most reprogramming approaches have utilized integrative lentiviral or retroviral vectors, many have reported that non-viral, transient expression of reprogramming factors is sufficient for cardiac reprogramming. Jayawardena et al. described that transient transfection of fibroblasts with miR-1, miR-133, miR-208, and miR-499 reprograms cardiac fibroblasts into iCMs, as evidenced by the formation of sarcomeric structures, demonstration of spontaneous calcium fluxes, and, most importantly, improvement in post-infarct ventricular function (increased fractional shortening and reduction in ventricular dimensions) [66, 67].

Consistent with these findings, small molecules regulating Wnt signaling, TGF-β signaling, and various other pathways may also reprogram murine and human fibroblasts into iCMs [68–70]. Additionally, we have demonstrated that non-integrative adenovirus-mediated delivery of GMT reprograms murine cardiac fibroblasts into iCMs [Mathison et al. 2016, unpublished]. Therefore, cardiac cellular reprogramming is also possible using non-viral vectors or small molecules, both of which are likely more ideal for clinical use than the use of chronic expression vectors.

Direct Cardiac Reprogramming Studies In Vivo

Despite the low in vitro efficiency of reprogramming (~10% $cTnT^+$ cells) demonstrated in initial studies, in vivo studies have demonstrated about a 10–20% improvement in ejection fraction and 50% reduction in fibrosis in rodent infarct models, providing the most convincing evidence for the potential clinical benefit of cardiac cellular reprogramming [18, 52, 55, 71]. Given these findings and the observation, for example, that up to 35% of infarct border zone cardiac fibroblasts may be reprogrammed into iCMs, it has been postulated that the in vivo microenvironment is more permissive to the formation of mature cardiomyocytes than is that provided in cell culture [18]. The in vivo milieu may, for example, include unknown paracrine signaling pathways as well as electrical and mechanical stimuli likely to promote the maturation of iCMs [18, 51, 52, 55, 67, 71]. Collectively, these studies indicate that the reprogramming of cardiac fibroblasts or other non-myocytes into iCMs can result in improved post-infarct ventricular function and decreased fibrosis in vivo [18, 55, 72].

In the context of these encouraging in vivo data, we have further shown that optimization of in vivo results and potentiation of the effect of reprogramming cocktails such as GMT may be obtained by adjuvant prevascularization of the ischemic, scarred myocardium (with VEGF), resulting in enhanced iCM population density and greater improvement in post-infarct ventricular function (17% vs. 4% relative increase in ejection fraction) [73]. A subsequent study by Yamakawa et al. confirmed that VEGF and FGF also activate multiple cardiac transcriptional pathways (p38 mitogen-activated protein kinase and phosphoinositol 3-kinase/AKT pathways) in cardiac fibroblasts, which may further enable the maturation of iCMs [74].

Future Directions in Cardiac Reprogramming

Although direct cardiac reprogramming has moved closer to clinical implementation, significant barriers still need to be addressed. Most notably, human cardiac fibroblasts are more resistant to reprogramming than are those of lower-order species and are, for example, almost completely resistant to reprogramming with GMT alone [60, 61, 70, 75, 76]. This finding is likely due to a more complex cardiac gene regulatory network and greater epigenetic constraints

imposed on the human species relative to murine models [64]. In this regard, a systematic evaluation of reprogramming barriers in human cells revealed that approximately 956 genes are opposed to reprogramming, regulating a multitude of functions including transcription, chromatin modifications, and various cellular functions [77].

While most attempts to overcome such barriers have simply included the addition of more cardio-differentiating factors or anti-fibrotic agents, some strategies to overcome the epigenetic constraints have been reported, including suppression of Bmi1 [65] or p63 [Patel et al. 2016, unpublished]. However, our understanding of epigenetic regulation in cardiac reprogramming is very limited, and extensive investigation is still needed. Encouragingly, our recent observations suggest that a porcine model may be an appropriate surrogate to investigate the resistance of human cells to reprogramming [Singh et al. 2016, unpublished].

The long-term survival of iCMs and demonstration of sustained improvement in post-infarct ventricular function beyond 12 weeks are other significant considerations in the potential clinical applicability of this strategy. Whether GMT-mediated reprogramming prevents or reverses ventricular remodeling is an intriguing additional consideration derived from early studies. In this regard, further investigation is needed of the intriguing observation that reprogramming factors induce an unexpected 50% reduction in post-infarct fibrosis [18, 55, 67, 71, 73], far exceeding the extent of iCM generation. The potential mechanisms underlying this observation are largely unexplored. Finally, while most studies have utilized immediate administration of GMT following coronary artery ligation, reflective of an acute infarct model [18, 51, 55, 67, 71], an increased focus on delayed administration studies reflective of the clinically relevant scenario of established scar is still needed [52, 73].

Cardiac Regenerative Strategies Using Endogenous Cardiomyocytes or Cardiac Stem Cells

Efforts to force (normally quiescent) adult human cardiomyocytes back into a replicative state, mimicking the persistent replicative state of lower vertebrates such as zebrafish and neonatal mice, represent a final potential myocardial regenerative strategy now being investigated. Cardiomyocyte cell cycle reentry has been attempted using miRNAs, cyclins, growth factors including FGF, and other small molecules [12]. Adenoviral-mediated administration of cyclin A2 has most prominently been demonstrated in murine and porcine infarct models to induce cardiomyocyte proliferation with improvements in cardiac function (~27% by echocardiography in porcine models) [78–80]. While these initial reports are compelling, therapeutic use of these factors may incur the risk of neoplastic transformation, which has yet to be investigated.

Initiatives to isolate and induce the ex vivo expansion of cardiac stem cells, which are usually quiescent but activated following myocardial injury, represent one more cardiac regeneration strategy under investigation [81, 82]. In the stem cell infusion in patients with ischemic cardiomyopathy (SCIPIO) phase 1 trial, right atrial biopsies were performed at the time of coronary artery bypass grafting, with subsequent intracoronary infusion of these cardiac stem cells 4 months later. This intervention resulted in a 14% increase in left ventricular ejection fraction compared to baseline and a reduction in infarct size 12 months following treatment [83]. Similarly, the intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS) phase 1 trial utilized percutaneous endomyocardial biopsies to generate cardiac stem cells for infusion and established safety data for further trials [84]. Obstacles to clinical implementation

of these techniques include the costly expansion of cardiac stem cells and similar difficulties to that seen with stem cell implantation, as well as challenges in differentiation into other cardiac subtypes, potential for arrhythmia, and electromechanical integration.

Conclusions

Initial disappointments in the field of cardiac regeneration have resulted in the formation of a more rigorous, tempered research methodology, which has significantly influenced novel regenerative strategies such as direct cardiac cellular reprogramming. In comparison to cell-based interventions for cardiac regeneration, direct cardiac cellular reprogramming boasts a significant advantage by utilizing endogenous cardiac fibroblasts, thereby offering a higher chance of nascent cardiomyocyte survival, maturation, electrophysiological integration into the host syncytium, and durable long-term results. Optimal cardiac cellular reprogramming strategies will likely utilize a multimodal approach involving upregulation of cardio-differentiating factors, inhibition of profibrotic gene expression, and induction of angiogenic factors as exemplified in our iteration shown in Fig. 16.1.

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Long-Term Complications of Ventricular Assist Devices

17

George V. Letsou

Heart failure is a common affliction in developed countries. Approximately 2% of all adults in industrialized countries have heart failure, and the prevalence rises to 6–10% in adults older than 65 [1]. Of the 23 million people who have heart failure worldwide, approximately 5.8 million live in the United States [2]. The risk of death is approximately 35% in the first year after diagnosis and then falls to approximately 10% each year after that [3]. Orthotopic heart transplantation is the treatment of choice for end-stage heart failure, but a limited donor pool restricts the number of cardiac transplantations that can be performed worldwide to approximately 4000 per year [4]. Therefore, mechanical circulatory support is an area of intense interest.

The first successful implantation of a mechanical cardiac assist device was performed in 1963 in Houston [5] several years before the first successful heart transplant. Progress with different mechanical cardiac assist devices proceeded intermittently until the influential Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial in 2001. In that trial, 129 patients with severe heart failure and a life expectancy of less than 2 years on optimal medical therapy were randomly assigned to undergo either maximal medical management or surgical implantation with a pulsatile-flow HeartMate Vented Electric (XVE) left ventricular assist device (LVAD). The 1-year survival rate was 52% in the surgical group and 25% in the medical group. The 2-year survival rates were 23% and 8%, respectively. However, patients with a surgically implanted LVAD had a nearly twofold increase in the rate of long-term adverse events, including infection, hemorrhage, and device malfunction [6]. The survival advantage associated with LVAD support was impressive, but improving LVAD reliability and durability was clearly necessary.

In a subsequent trial in 2009, patients with an implantable pulsatile-flow device were compared with patients who had a continuous-flow device. Two hundred patients with a left ventricular ejection fraction <25%, a peak oxygen consumption <14 cc/kg/min, New York Heart Association (NYHA) class IIIb or IV symptoms, or the need for inotropic therapy or intra-aortic balloon pump counterpulsation were randomly assigned to undergo implantation with either the first-generation pulsatile HeartMate XVE or the newer continuous-flow HeartMate II device. Actuarial survival was significantly greater in the continuous-flow HeartMate II group than in the pulsatile-flow HeartMate XVE group (68% vs. 55%, respectively, at 1 year and 58% vs. 24%, respectively, at 2 years) (Fig. 17.1). The adverse

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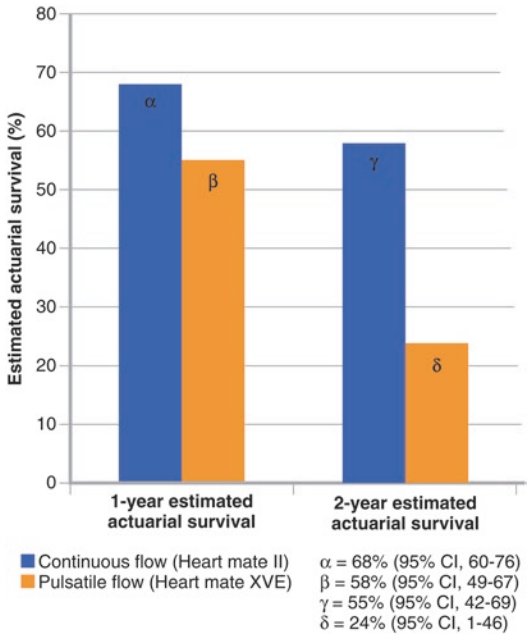

Fig. 17.1 Estimated actuarial survival (continuous-flow LVAD therapy vs. pulsatile-flow LVAD therapy). Modified with permission from Hindawi Publishing Corporation [33]

event rate was significantly lower in the continuous-flow group (Fig. 17.2) [7]. Continuous-flow pumps offered the greater durability that investigators had been searching for.

Mechanical cardiac assist devices have become significantly more reliable, but still have problems. The most common complications of long-term VAD implantation include pump thrombosis, mechanical failure necessitating device replacement, stroke, LVAD-related infection, sepsis, bleeding requiring blood transfusion, cardiac arrhythmia, renal failure, and aortic valve insufficiency. Each of these issues will be addressed in the following sections. Complications after the implantation of continuous-flow devices will be emphasized because those devices accounted for more than 90% of pumps implanted in 2015.

Pump Replacement and Thrombosis

The greater durability of continuous-flow LVADs led to an increase in the use of device implantation to treat heart failure. In the current era, more LVADs are implanted than hearts are transplanted. According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, between 2012 and 2014, the number of continuous-flow pumps implanted as a bridge to transplantation increased from 404 to 734, and the number implanted as destination therapy increased from 983 to 1108 [8].

Rates of mechanical failure markedly decreased in the continuous-flow era. In the pivotal study by Slaughter et al. [7] in 2009 that compared pulsatile-flow and continuous-flow devices, pump replacement for malfunction (including events such as a driveline fracture) was necessary for 9% of implanted continuous-flow pumps and 34% of implanted pulsatile-flow pumps. There were no primary pump or bearing failures in patients with a continuous-flow LVAD. However, pump thrombosis occurred in 4% of patients with continuous-flow pumps but in none of the patients with pulsatile-flow devices [7].

The findings of other studies have shown the reliability of continuous-flow devices and freedom from replacement. In one retrospective study [9], replacement of the device for failure or thrombosis was required for only 3.8% of patients. However, studies of earlier continuous-flow devices, such as the Jarvik 2000 and the DuraHeart, have documented device replacement rates as high as 14% [10]. In the latter series, thrombosis was the most common indication for replacement (66%), followed by driveline infection (10%), and other problems (22%).

When VAD replacement is required, outcomes are not compromised. Of 469 patients who underwent 546 continuous-flow LVAD implantations from December 1999 to December 2013, 14% required the exchange of one continuous-flow LVAD for another [10]. Survival was not significantly different between the exchange and non-exchange groups (Fig. 17.3).

In 2013, two separate reports documented an increase in the incidence of HeartMate II pump thrombosis that seemed to have begun in 2011 [11, 12]. These reports estimated the risk of pump thrombosis at 6 months to be 6–12%, a substantially greater risk than was previously reported. Another report indicated that the HeartWare device may also have a higher-than-expected pump thrombosis rate of 8% [13]. Many of the

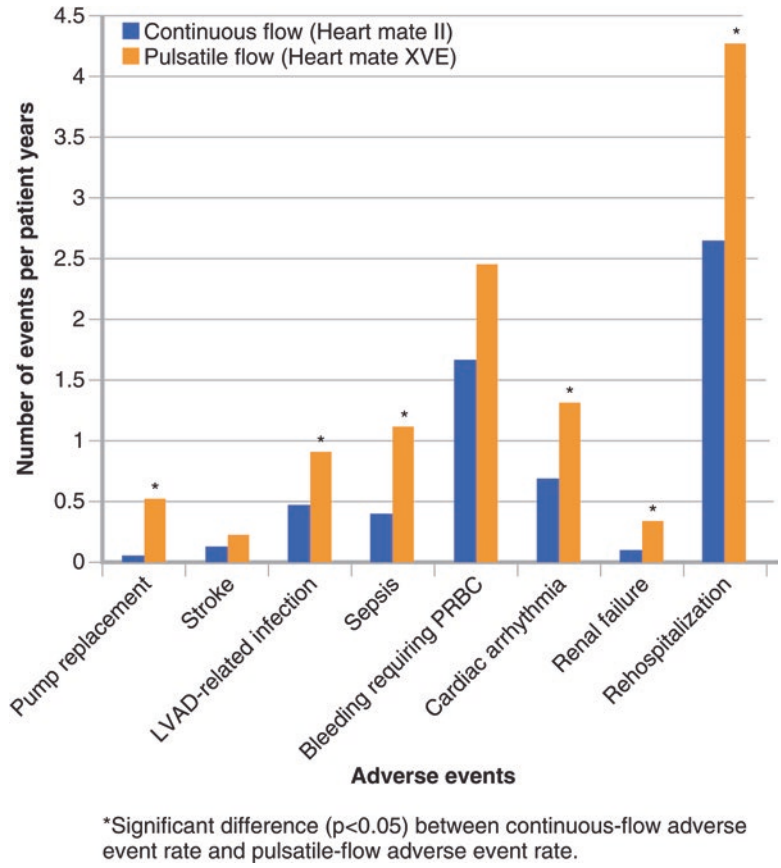

Fig. 17.2 Comparison of adverse event rates of continuous-flow LVADs and pulsatile-flow LVADs. *Significant difference ($p < 0.05$) between continuous-flow adverse event rate and pulsatile-flow adverse event rate. Modified with permission from Hindawi Publishing Corporation [33]

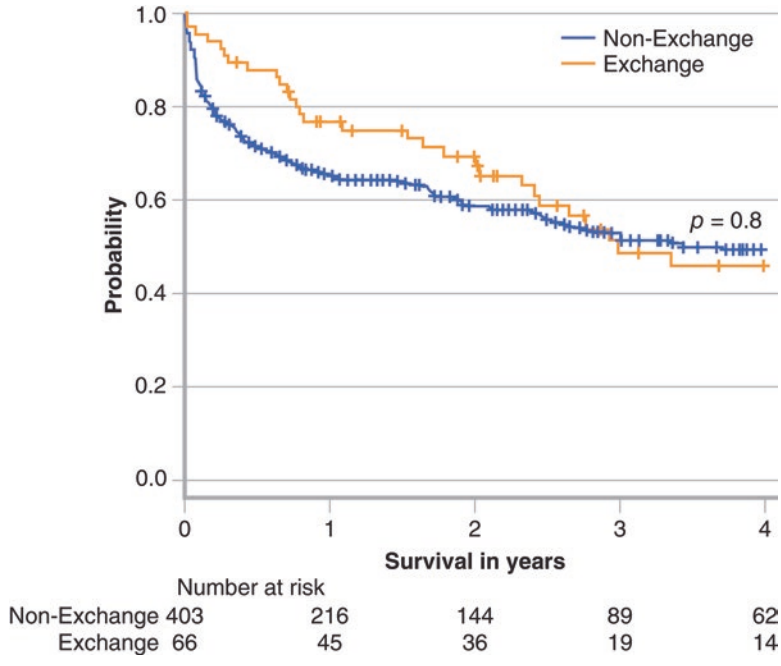

Fig. 17.3 Kaplan-Meier analysis of survival (VAD exchange vs. no VAD exchange). Survival from time of primary VAD implantation to time of most recent follow-up. Modified with permission from Elsevier [10]

events occurred within 6 months of implantation. Although these rising rates of thrombosis were not initially associated with a decrease in survival, they were associated with substantial morbidity, the need for pump exchange, and increased healthcare costs.

Suggested explanations for the increase in pump thrombosis rates included mechanical defects in the devices and suboptimal inflow cannula geometry, but these theories were not independently supported. Other possible contributing factors included clinical management issues, such as the use of lower levels of anticoagulation to minimize gastrointestinal (GI) bleeding and the reduced use of heparin bridging after implantation to minimize postoperative bleeding. The lowering of pump speeds to facilitate aortic valve opening and minimize aortic valve commissural fusion may have also been a possible contributing factor.

After these reports, management strategies were changed to emphasize heparin bridging after device implantation and to increase postoperative anticoagulation. Despite the increased awareness of the problem, actuarial freedom from pump thrombosis decreased progressively from 2009 to 2013. Freedom from pump thrombosis at 6 months fell from 98% in 2010 to 92% in 2013 [14]. In 2014, freedom from pump thrombosis improved to a level approaching that of 2011. Subsequent analyses of data provided by the INTERMACS database suggested that pump thrombosis rates remain elevated when compared to those reported before 2011 [15]. In this INTERMACS analysis, the most important predictors of pump thrombosis and pump exchange were age at the time of implantation and body mass index. Patients younger than age 72 and those with a body mass index greater than 25 kg/m^2 were at increased risk. In this analysis, pump thrombosis was associated with an elevated mortality risk of 18% at 1 month after the first thrombosis and 37% at 1 year after the first thrombosis.

To prevent pump thrombosis, methods of early detection and intervention have been adopted, including the monitoring of lactate dehydrogenase (LDH) levels as a measure of hemolysis and possible thrombosis. In addition, nonoperative management with anticoagulant and thrombolytic therapy has been introduced, with success rates approaching 80% in some series with centrifugal continuous-flow pumps [16]. Nonoperative therapeutic strategies have included the use of heparin, direct thrombin inhibitors, and platelet glycoprotein IIb/IIIa inhibitors, as well as local and systemic thrombolytic therapy with tissue plasminogen activator (tPa).

Compared with pulsatile-flow pumps, continuous-flow pumps offer greater durability and have been a clear step forward in improving LVAD outcomes. Although mechanical failure is much less common in patients with continuous-flow pumps, pump thrombosis occurs in 4–10% of these patients, posing substantial challenges. Appropriate attention to anticoagulation protocols is important. In many cases, monitoring LDH levels and early intervention (beginning with augmented anticoagulation and thrombolytic therapy) can successfully prevent pump thrombosis. If pump replacement is necessary, acceptable results and survival can be anticipated.

Stroke and Thromboembolic Events

Cerebrovascular events are a substantial cause of morbidity and mortality after implantation of either a continuous-flow or a pulsatile-flow VAD. In 2009, a randomized trial in which continuous-flow and pulsatile-flow LVADs were compared showed that the incidence of stroke was 17% in the continuous-flow group and 14% in the pulsatile-flow group. However, the number of strokes per patient year was only 0.13 in the continuous-flow group and 0.22 in the pulsatile-flow group. This incidence of stroke in the continuous-flow group was similar to that in patients with end-stage heart failure who do not have mechanical support [7].

Other studies have documented similar stroke rates after continuous-flow LVAD implantation. A review of 150 patients who underwent continuous-flow LVAD implantation revealed a stroke rate of 18% [17]. The anticoagulation

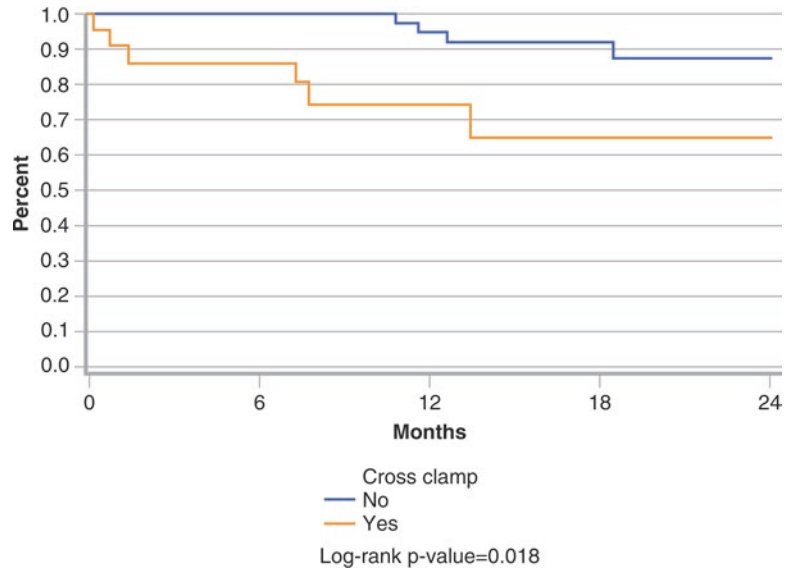

Fig. 17.4 Freedom from stroke (clamped or arrested vs. unclamped). Modified with permission from Wolters Kluwer [18]

protocol in this study included aspirin (81 mg/day) and warfarin (target international normalized ratio [INR] of 2.0–2.5). In the 32 patients who died, stroke was the second most common cause of death (n = 8). Six patients had hemorrhagic strokes, and two had embolic strokes.

Risks factors for stroke include high blood pressure, infection, pump thrombosis, GI bleeding, aortic cross-clamping with cardioplegic arrest during implantation, and insufficient or excessive anticoagulation.

A review of 100 consecutive continuous-flow pump implantation cases revealed a stroke rate of 12% [18]. Patients who had a stroke had a significantly higher prevalence of diabetes (66% vs. 41%), previous stroke (17% vs. 5%), and use of aortic cross-clamping with cardioplegic arrest during LVAD implantation (50% vs. 20%) than did patients without stroke (Figs. 17.4 and 17.5). Notably, the mean INR at the time of stroke was subtherapeutic in all four patients who had embolic strokes. Mortality within 30 days of stroke was 25%. A University of Minnesota review of 230 patients in whom a HeartMate II continuous-flow LVAD was implanted as a bridge to transplant revealed a stroke rate of 17%. Of those stroke cases, 49% were embolic and 52% were hemorrhagic. Diabetes and hypertension were not risk factors for stroke in this study, but prior cardiac surgery and infection were associated with a higher risk of stroke. Stroke compromises survival [18–20]: 12 months after implantation, survival in the stroke group was significantly lower (71%) than that in the nonstroke group (82%) (Fig. 17.6) [20].

In a Columbia University Medical Center review of data from 301 patients who underwent implantation with continuous-flow LVADs from 2008 to 2015, strokes occurred in 40 (13%). The study emphasized appropriate characterization of the type of stroke. A clear distinction was made between ischemic stroke and primary intracerebral hemorrhagic stroke, which probably have different etiologies. Unlike patients in other studies, these patients were classified as having ischemic stroke, ischemic stroke with hemorrhagic conversion, or intracerebral hemorrhagic stroke after the careful review of the clinical presentation and radiologic findings. In this study, ischemic stroke—presumably caused by embolic disease originating from the LVAD—was the most frequent cause of death, occurring in 32 of the 40 patients who had a stroke; the remaining 8 patients had an intracerebral hemorrhage. On the basis of the Columbia protocol, continuous-flow LVAD patients were maintained on a regimen of aspirin (81 mg/day) and warfarin

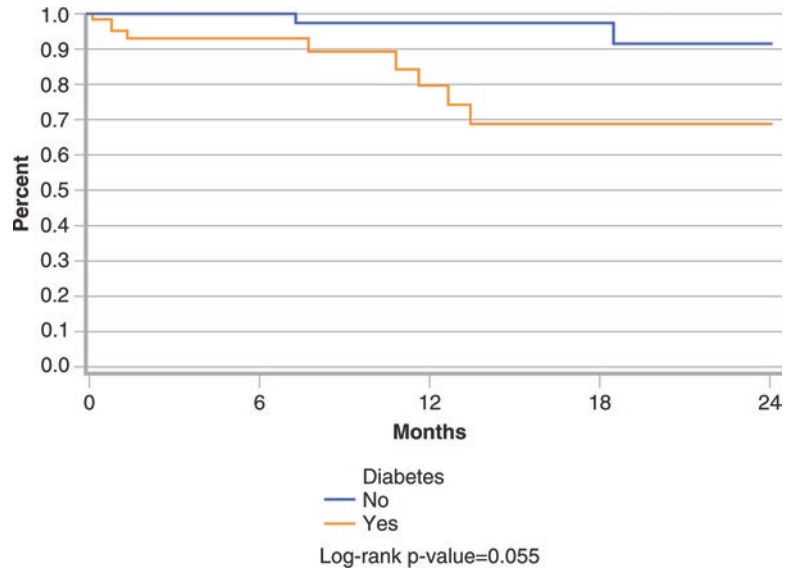

Fig. 17.5 Freedom from stroke (patients with diabetes vs. patients without diabetes). Modified with permission from Wolters Kluwer [18]

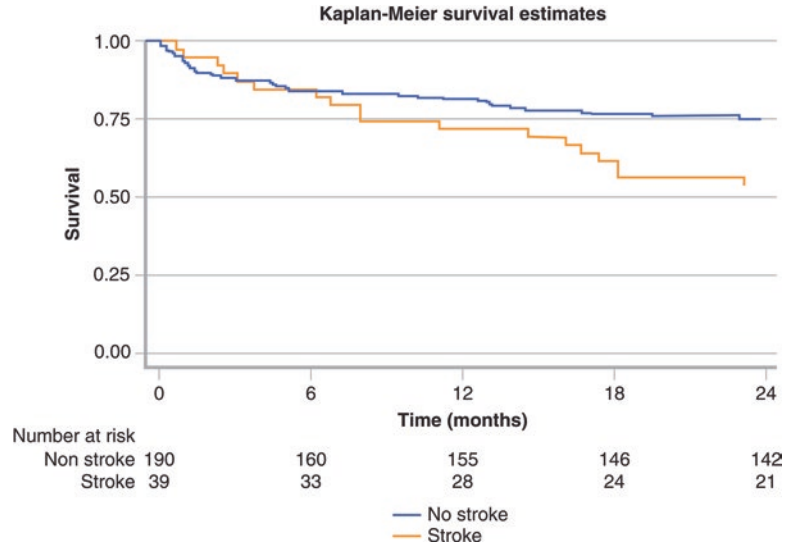

Fig. 17.6 Actuarial survival rates after HeartMate II implantation. Modified with permission from Elsevier [20]

(target INR of 2.0–2.5). However, a substantial proportion of stroke patients had an INR at the time of stroke that was either subtherapeutic or above the target range. For several patients, warfarin had been discontinued for various reasons. In-hospital mortality was 50% after intracerebral hemorrhagic stroke and 28% after ischemic stroke. Survival correlated with the severity of the stroke, which was assessed clinically by using the National Institutes of Health Stroke Scale. Ischemic stroke patients often recovered sufficiently to proceed to transplant or discharge [21].

Identifying optimal anticoagulation strategies continues to be an important area of investigation. Studies by John et al. [22] and Katz et al. [23] showed that reduced amounts of anticoagulation may be acceptable. In the study by John et al. [22], 45 patients who received the HeartMate II were anticoagulated with aspirin and warfarin, but 41 of those patients had a mean INR less than

2.0. Among the 21 patients who had a mean INR less than 1.6, only one stroke occurred [22]. In the intriguing study by Katz et al. [23], 94% of patients receiving reduced anticoagulation (i.e., only aspirin, only warfarin, or no agents at all) because of bleeding complications were free from ischemic stroke at 1 year [23].

Early thrombus formation after LVAD implantation is likely a risk factor for stroke. To minimize this risk, appropriate attention to anticoagulation with heparin is important in the early postoperative period. With prolonged circulatory support, the risk of stroke may be increased by comorbidities such as atrial fibrillation, appropriate aortic valve closure, and the anatomic position of the inflow cannula, device, and outflow graft. Stroke is a multifactorial problem that develops in approximately 10–20% of patients with continuous-flow LVADs. Hemorrhagic stroke is typically more lethal than ischemic stroke.

Bleeding

Bleeding is the most common specific adverse event for patients with a continuous-flow device. According to the 2009 study by Slaughter et al. [7], 81% of patients had bleeding that necessitated a packed red blood cell transfusion.

Bleeding in the immediate surgical period is common. Approximately 75% of patients undergoing LVAD implantation require blood transfusion. Re-exploration for bleeding is necessary for 20–30% of patients [24]. Reoperation for bleeding is associated with illness severity in these compromised patients. Often, patients undergoing LVAD implantation have significant comorbidities and have been anticoagulated preoperatively. Some degree of platelet dysfunction, as well as hepatic dysfunction, is common. Optimizing the patient's hemodynamics and overall condition preoperatively is important for minimizing perioperative bleeding.

Gastrointestinal bleeding is common during the recovery period after LVAD implantation. In an early experience with a continuous-flow LVAD, 3 of 21 patients (14%) developed GI bleeding [25]. Gastrointestinal bleeding may be more common after continuous-flow pump implantation than after pulsatile-flow pump implantation. In a review from the University of Minnesota, GI bleeding developed in 12 of 55 patients (22%) who underwent implantation with a continuous-flow pump, whereas only 3 of 46 patients (7%) who underwent implantation with a pulsatile-flow pump had GI bleeding [26]. A similar predisposition to bleeding after continuous-flow pump implantation was seen in a study from Washington University. The incidence of GI bleeding in 61 patients who underwent implantation with a HeartMate II continuous-flow pump was 21% [27]. The overall incidence of GI bleeding after continuous-flow pump implantation is typically between 15 and 30%.

The most common sources of GI bleeding after continuous-flow pump implantation are arteriovenous malformations and ulcers. Arteriovenous malformations were somewhat more common than ulcers in both of the above-mentioned series. Bleeding episodes are often significant and necessitate transfusion but typically are not lethal. Management with aggressive medical therapy, including endoscopic intervention, is often effective, but repeated interventions are frequently necessary.

The mechanism of increased bleeding is unclear and multifactorial. Many investigators have suggested that a possible cause is acquired von Willebrand factor (vWF) deficiency, which is characterized by a reduction in high molecular weight multimer production after continuous-flow pump implantation. Rapidly rotating continuous-flow pumps may cause vWF to deform and degrade into smaller proteins that are then cleared from the bloodstream. Previously asymptomatic GI lesions, such as arteriovenous malformations or ulcers, may then become prone to bleeding. In a study performed at Duke University and the University of Minnesota, acquired vWF deficiency was documented in all 37 patients who underwent axial continuous-flow pump (HeartMate II) implantation between July 2008 and April 2009 [28]. However, only 10 of the 37 patients developed clinically significant GI bleeding.

Despite the differences in pump conformation and rotation speed between centrifugal and

axial continuous-flow pumps, the implantation of either type of pump generally results in a similar decrease in levels of high molecular weight multimers of vWF. In a review of 102 consecutive implantations in Leipzig and Hannover, Germany, a 34% decrement in plasma levels of high molecular weight multimers of vWF was observed after implantation of a centrifugal continuous-flow pump (HeartWare), compared with a 30% decrement after implantation of an axial continuous-flow pump (HeartMate II) [29].

Other likely mechanisms that may contribute to postoperative bleeding after continuous-flow pump implantation include the mechanical destruction of platelet proteins, increased shear stress on blood elements by the pump rotors, and decreased pulse pressure. Therapeutic anticoagulation after continuous-flow pump implantation usually involves antiplatelet agents and warfarin; however, an optimal anticoagulation regimen remains to be determined. Strategies to minimize postoperative bleeding include lowering the postoperative target INR and reducing the use of antiplatelet agents.

An intriguing strategy for reducing postoperative bleeding is altering the pump speed to induce pulsatility. In a study of 134 patients from the Utah Transplantation Affiliated Hospitals (UTAH) program, nonsurgical bleeding was more than fourfold higher in patients with a lower pulsatility index than in patients with a higher pulsatility index [30].

Bleeding complications after continuous-flow LVAD implantation are common. Early bleeding is usually secondary to perioperative surgical factors, including severity of patient illness and comorbidities. After the patient recovers from surgical implantation, GI bleeding is frequent. Gastrointestinal bleeding may be related to an acquired VWF deficiency or to the anticoagulation regimen. Pulsatility may also play an important role in bleeding complications. Heightened attention to these factors is important for minimizing bleeding complications.

Infections

Infection after LVAD implantation is a serious cause of patient morbidity and mortality. Compared with pulsatile-flow pumps, continuous-flow pumps have a markedly lower overall rate of infection. In the clinical trial by Slaughter et al. [7], the number of infectious events per patient year was almost 50% lower for patients with continuous-flow pumps (0.48) than for patients with pulsatile-flow pumps (0.91). This lower rate of infectious events after the implantation of a continuous-flow pump was an important factor in reducing the overall readmission rate for patients after LVAD implantation. The lower rate of overall infectious complications associated with the use of continuous-flow pumps is likely related to the elimination of the large pump pocket.

Most infections in the continuous-flow pump era are driveline infections. All continuous-flow and pulsatile-flow pumps employ a percutaneous driveline to carry electrical signals and energy from the controller and battery unit to the pump. This places the patient at risk for infection at the driveline entrance site and along the subcutaneous tunnel of the driveline leading to the pump. To minimize complications from infection, a Dacron cuff surrounds the driveline. Antibiotic-impregnated drivelines have been used to minimize infectious complications. Nevertheless, driveline infections occur in approximately 15–30% of LVAD recipients.

Driveline infections are most commonly due to *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Each of these bacterial species accounts for approximately one-third of infections. Fungal infections are unusual. Many infections remain localized to the driveline exit site. Most infections begin superficially and either remain localized or progress to involve the entire driveline [31]. Infections occur at a steady rate of approximately 2% per month after LVAD implantation. After 24 months, a driveline infection may have developed in as many as 30% of LVAD recipients (Fig. 17.7).

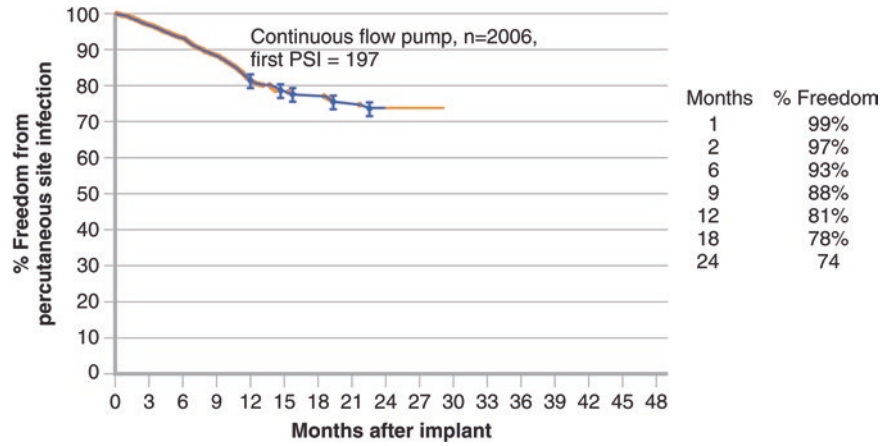

Fig. 17.7 Freedom from driveline infection in continuous-flow LVAD recipients. Time (months) from LVAD implantation to the first percutaneous site infection. Error bars show standard deviation. Modified with permission from Elsevier [32]

Although driveline infections are often perceived as benign events, they are associated with a distinct increase in mortality and hospital readmission rates. In studies by Koval et al. [31] and Goldstein et al. [32], approximately 10% of patients in whom driveline or percutaneous site infections developed eventually died, with sepsis as the most common cause of death. The most common cause of death in patients with a driveline infection is disseminated sepsis. Antibiotic therapy can be effective in a minority of these cases, but device removal and replacement can be required. The definitive treatment for driveline infection or pump infection is heart transplantation. Despite immunosuppression in the transplant recipient, subsequent infection is not common.

Driveline infection is an unusual surgical infection in that it is not typically associated with traditional surgical risk factors, such as diabetes, acuity of illness, and malnutrition. Younger age seems to be an important predisposing factor. Many driveline infections occur after patients are discharged home. All of these associations suggest that localized minor trauma that occurs as an outpatient (which may be more likely for younger patients) is an important risk factor for driveline infection. Better outpatient support and driveline care should thus be emphasized.

Evidence-based interventions that have been shown to decrease the rate of driveline infection include preparing the surgical site with an appropriate antibiotic agent, properly sterilizing and disinfecting equipment, minimizing operating room traffic, and using appropriate ventilation systems. In addition, appropriate glucose control in diabetic patients is important during the perioperative period. Specific measures for postoperative driveline care have been proposed, but none have been shown objectively to decrease the incidence of infection. Driveline infection is a morbid event that should be taken seriously and prevented if possible.

Conclusion

Mechanical cardiac assist devices continue to be developed as an effective treatment for the large population of patients living with heart failure. Continuous-flow pumps have been a major advancement. Nevertheless, long-term challenges remain, including reducing rates of pump thrombosis, stroke, bleeding at sites distant from the heart, and infection. Further attention to these issues will be necessary as newer mechanical cardiac assist devices are introduced.

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18 Right Ventricular Failure in Patients Undergoing LVAD Placement

David Kuten and Joggy K. George

Introduction

The introduction of left ventricular assist devices (LVADs) has proven to reduce morbidity and mortality in patients with advanced heart failure [1]. Despite their benefits, LVADs are associated with a host of adverse events. These include right ventricular failure (RVF), which is a particularly common and morbid complication when it arises in the early postoperative period. The hemodynamic consequences, both positive and negative, of LVAD therapy on the right ventricle are addressed in greater detail elsewhere in this text. Briefly, although the right ventricle benefits from LV decompression of the pulmonary circulation, it remains vulnerable to multiple insults related to LVAD-induced hemodynamic changes, in addition to the complications associated with major cardiac surgery.

The impact of RVF on patient outcomes was recognized early in the clinical experience with LVADs. A 2002 report found that almost one-third of HeartMate XVE recipients had RVF, which was associated with a higher incidence of end-organ dysfunction, longer intensive care unit stays, and greater mortality [2]. RVF remains a morbid complication in the era of continuous-flow devices. Data from the initial HeartMate II bridge-to-transplant trial show that patients were significantly less likely to survive to transplant, recovery, or ongoing device support if they had RVF [3]. In this chapter, we discuss issues related to early RVF, including its evolving definition, myriad of causes, incidence, predictors, and diagnosis. Particular attention is paid to the prevention and management of RVF.

Definition

The right heart serves both as a low-pressure reservoir for blood as it returns from the systemic circulation and as a pump filling the left heart via the pulmonary circulation. RVF is caused by an inability to perform one or both of these important roles. In patients with an LVAD, RVF translates into an inability to preserve the low-pressure state of the right heart, resulting in Fontan-like physiology, and failure to maintain adequate preload to the left heart. The INTERMACS criteria for RVF require documentation of elevated central venous pressure (CVP) and clinical manifestations of venous congestion [4]. The INTERMACS classifies early RVF as mild if the patient requires inotropes, inhaled nitric oxide, or

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intravenous pulmonary vasodilators for less than 7 days after implantation, and RVF is classified as moderate if such therapies are required for 7–14 days. Early RVF is classified as severe if CVP is greater than 16 mmHg, and the patient requires these therapies for more than 14 days after LVAD implantation. RVF is considered severe and acute if the patient requires an RV assist device (RVAD) or dies during the index hospitalization with RVF as the primary cause of death.

Etiology

The right ventricle is uniquely vulnerable to early LVAD hemodynamic alterations for reasons related to its underlying anatomy and physiology. The anteriorly positioned right ventricle is a thin-walled, highly compliant structure with a complex shape that is affected by neighboring structures and is critical to its function [5]. RV contractility depends on the function of the RV free wall and the interventricular septum, which, in turn, is highly dependent on LV function. As a result, the right ventricle is exquisitely affected by changes in loading conditions in both ventricles, as well as septal position.

RV function benefits from the decrease in RV afterload caused by reduced LV end-diastolic pressure and pulmonary artery pressure with LVAD therapy. However, leftward shift of the interventricular septum with reduced LV filling pressures may diminish RV contractility [6]. Moon et al. [7] elucidated the effect of acute LV unloading on interventricular septal position and function in a canine model by clamping left atrial pressure between 0 and 2 mmHg, thereby reducing LV pressure (mean reduction, 30%) [7]. As a result of this intervention, the septum moved leftward and flattened. Functionally, both systolic septal thickening and systolic septal output (the product of septal thickening and heart rate) were reduced. However, an earlier study by the same group calls into question the impact of these changes. Among eight dogs that underwent LVAD implantation, the reduction in RV contractile function caused by septal displacement was counterbalanced by reduced RV afterload and increased RV preload, such that RV power output and RV myocardial efficiency were unchanged [8]. Thus, the overall significance of changes in septal geometry is not completely understood and may be affected by an individual patient's unique physiologic milieu, including the degree of RV afterload reduction observed after LVAD implantation.

In addition to these structural alterations, the RV is exposed to an increase in preload resulting from augmented cardiac output after LVAD placement. Although a healthy, highly compliant right ventricle can tolerate increases in preload, particularly with a concomitant reduction in RV afterload, factors such as baseline RV dysfunction and significant tricuspid regurgitation (TR) may impair the right ventricle's ability to compensate. TR due to annular dilatation, in particular, may deteriorate with increased RV preload. A 2011 study of 176 patients who underwent either pulsatile or continuous-flow LVAD implantation without tricuspid annuloplasty found that TR did not improve in the immediate postoperative period and that patients with at least moderate TR required longer inotropic support, had longer hospitalization, and had a trend toward poorer survival [9]. Almost 10% of patients with significant preoperative TR required temporary RVAD support, whereas none of the patients with insignificant TR required such support.

Along with these LVAD-specific factors, the usual complications of cardiac surgery can also cause RV dysfunction. For instance, myocardial ischemia in the RV distribution can be caused by intraoperative air emboli, which preferentially affect the right coronary artery because of its anterior location. In patients with ischemic cardiomyopathy, ischemia can also result from the exacerbation of epicardial obstructive disease due to perioperative increases in myocardial demand. In addition, pericardial tamponade due to postoperative bleeding can impair RV filling, resulting in venous congestion and diminished LV preload.

Another potential cause of RVF is sustained tachyarrhythmia, which can disproportionately affect the unsupported right ventricle. A 2015 publication by Garan et al. [10] found a high

incidence of ventricular arrhythmia in the period immediately after continuous-flow LVAD implantation. Among 162 patients enrolled between 2012 and 2014, 38 (23%) had ventricular arrhythmia. The investigators found that patients with ventricular arrhythmia had RVF at a higher rate than those without arrhythmia (44.7 vs. 23.4%; $P = 0.01$).

Interestingly, findings suggest that appropriate implantable cardioverter-defibrillator (ICD) shocks may be inherently detrimental in such patients. Among Garan and colleagues' 129 patients with ICDs, 25 had ICD shocks and 13 had antitachycardia pacing (ATP) for malignant arrhythmia. ICD shocks were associated with RV dysfunction, evidenced by increased CVP and initiation of therapy for RVF in 8 of the 25 patients. In contrast, none of the 13 patients who received ATP had RV dysfunction. Also informatively, the authors report that 43% of the arrhythmia events were associated with inotropic medications, implicating perioperative vasoactive medications in the onset of ventricular arrhythmia with resultant RVF.

Incidence

The reported incidence of RVF after LVAD placement varies, in large part, according to how RVF is defined in each study, the comorbidities of the study cohort, the type of LVAD used, and the medical therapies available to the treating clinicians. In a 2002 publication detailing the experience of 69 recipients of a HeartMate XVE at Columbia University, the authors report a 30% incidence of RVF, which they define as inotrope use for more than 14 days or need for RVAD support [2]. Patients with RVF had higher postoperative rates of mortality and certain morbidities, including bleeding requiring reoperation and renal failure. In 2006, the same institution reported a 38.9% incidence of RVF, similarly defined, among 108 patients [11]. Of the 42 patients with RVF, 14 required RVAD insertion. Whether continuous-flow LVADs might reduce the high incidence and morbidity of RVF in patients with pulsatile LVADs was investigated in a 2008 study comparing outcomes after HeartMate XVE and HeartMate II implantation at Johns Hopkins Hospital [12]. Consistent with the aforementioned studies, early postoperative RVF was defined as the need for inotrope or inhaled pulmonary vasodilator therapy for more than 14 days, or RVAD insertion. Among 77 patients included in the study, the investigators found similar incidences of RVF in those supported by pulsatile and continuous-flow devices (41.2% vs. 34.9%; $P = 0.63$). The authors posit that their increasing use of inhaled pulmonary vasodilators and inotropes to facilitate diuresis toward the end of the study period may have biased the results. To this point, patients with a continuous-flow LVAD were more likely to receive milrinone (rather than epinephrine) than were patients with pulsatile devices. Furthermore, HeartMate II recipients were less likely to require RVAD insertion than HeartMate XVE recipients.

A larger, multicenter experience with the HeartMate II among 484 patients in the initial bridge-to-transplant trial of that device found a 20% incidence of RVF [3]. Here, RVF was defined as the need for RVAD insertion (7% of patients), continuous treatment with inotropes for more than 14 days (6%), and the need for inotropic support beginning 14 days after device implantation (6%). Thus, only 13% of patients had early postoperative RVF. Consistent with previous reports, the authors found that outcomes were worse in patients with RVF. A smaller, single-center experience published contemporaneously found an even lower incidence of RVF (2 of 40 patients), which was similarly defined [13]. Study investigators posit that the lower incidence of RVF in these modern cohorts with axial-flow devices may relate to a confluence of several factors, including the more favorable hemodynamic impact of these newer devices on the right ventricle, better patient selection and preoperative optimization, and refined postoperative management.

In summary, although RVF in the early postoperative course is less common in the era of continuous-flow LVADs than it was in the era of pulsatile devices, the incidence of postoperative RVF remains high.

Predictors

Given the morbidity associated with RVF in LVAD-supported patients, investigators have sought to identify clinical, hemodynamic, biochemical, and echocardiographic risk factors for its development. Risk calculators incorporating a multitude of parameters have also been developed. The studies conducted to date are limited by small sample size, retrospective design, and inclusion of patients with pulsatile LVADs.

Clinical predictors of RVF were first described in a large cohort by Ochiai et al. [14], who in 2002 published the Cleveland Clinic experience with 245 patients who received a pulsatile LVAD. The authors found that risk factors for postoperative RVAD placement, which was performed in 23 patients, included female gender (odds ratio [OR] 4.5), nonischemic cardiomyopathy (OR 3.3), and pre-LVAD circulatory support (OR 5.3). The authors speculate that patients with nonischemic cardiomyopathy are more likely to have preoperative biventricular failure than those with ischemic cardiomyopathy. Subsequent studies that included patients with both pulsatile and continuous-flow LVADs have identified additional clinical predictors such as preoperative intra-aortic balloon pump, mechanical ventilation, and vasopressor administration, suggesting that preoperative cardiovascular and pulmonary instability plays an important role in the development of RVF [12, 15, 16].

Hemodynamic predictors of RVF have been investigated, as well. Ochiai et al. [14] found that low RV stroke work index (RVSWI), but not elevated pulmonary artery pressure, was a risk factor for RVAD placement. That poor preoperative RV contractility, as reflected by low RVSWI, can predict RVF in patients undergoing LVAD support was supported in a 2006 study from Columbia, which reported a lower intraoperative systolic pulmonary artery pressure in patients with right heart failure than in unaffected patients (51 ± 11 vs. 58 ± 11 mmHg; $P = 0.047$) [11]. Of note, this study identified elevated intraoperative CVP as an even stronger hemodynamic predictor of RVF (23 ± 8 vs. 17 ± 6 mmHg; $P = 0.017$). Kormos et al. [3], in their analysis of the HeartMate II bridge-to-transplant trial data, found that an elevated (i.e., >0.63) CVP-to-PCWP ratio was more predictive of RVF than was elevated CVP alone, implicating RV dysfunction, as opposed to left-sided congestion, as the culprit of RVF. Predictably, these authors also found that a low RVSWI was associated with RVF.

Biochemical predictors of postoperative RVF include those suggestive of elevated CVP, such as elevated bilirubin and transaminase levels and markers of renal insufficiency, including elevated blood urea nitrogen and creatinine levels [3, 16].

The usefulness of preoperative transthoracic echocardiography in identifying patients at risk for RVF after LVAD implantation has been investigated in a few small cohorts. One study of 33 patients found that reduced tricuspid annular motion predicted postoperative RVF, whereas Tei index, RV fractional area change, and right atrial dimension were not predictive [17]. A subsequent study published in 2011 found that among 40 patients with various LVADs, more severe preoperative tricuspid insufficiency correlated with RVF [18]. A 2013 study of 55 patients identified three predictors of RVF: a reduced RV fractional area change, elevated estimated right atrial pressure, and low left atrial volume index; here, tricuspid annular motion was not predictive [19]. The disparate findings of these studies reflect their small sample sizes, variable definitions of RVF, and diverse patient populations.

Given the varied contributors to RVF in patients undergoing LVAD, multiple investigators have attempted to develop a weighted risk calculator. In 2008, Matthews et al. [16] published a risk prediction model developed from data obtained from 179 LVAD-supported patients at the University of Michigan. Multivariate risk factors for RVF (defined as inotrope use for >14 days postoperatively, inotrope use at discharge, inhaled nitric oxide use for >48 h, or the need for a mechanical RVAD) included vasopressor use and serum levels of creatinine >2.3 mg/dL, bilirubin >2 mg/dL, and AST >80 IU/L. The factors were compiled into a weighted risk calculator that classifies patients' risk of postoperative RVF as low, intermediate, or high. A more recently published risk score designed to predict

need for biventricular assist device (BIVAD) support is based on patient data collected at the University of Pennsylvania between 2003 and 2011 [20]. The investigators identified five multivariate predictors of postoperative RVF: CVP >15 mmHg, severe preoperative RV dysfunction, preoperative intubation, severe tricuspid insufficiency, and tachycardia. A risk calculator was created that assigns each factor a 0 or 1 and sums the results to produce a single score; higher scores correspond with greater risk of RVF. Although we do not systematically use these risk scores, it is our opinion that they attest the overall acuity of a patient's condition, which is the primary driver of RVF.

Prevention: Preoperative

Instituting measures to prevent RVF in patients who are identified as high risk is essential. However, the difficulty of identifying patients who will ultimately develop RVF requires that, in all patients, clinicians optimize hemodynamics preoperatively and maintain a high index of suspicion for RV dysfunction during the postoperative period. An algorithm summarizing our approach to the prevention and management of RVF is provided (Table 18.1).

Preoperative measures to prevent RVF include invasive hemodynamic monitoring, volume optimization, the perioperative use of pulmonary

Table 18.1 Prevention and management of RVF in patients undergoing LVAD placement

Preoperative measures		
Risk stratification		
Low	Moderate	High
Limit fluids		
	Pulmonary vasodilators	
	Cardiac inotropes	
		Consider elective RVAD
Operative measures		
Preventive	High-risk patient/early RVF	Fulminant RVF
Limit transfusion		
Expeditious operative time		
TEE-guided optimization of pump speed		
Optimize electrolytes/pH balance		
	TEE-guided titration of vasodilators and cardiac inotropes	
	Consider elective RVAD	
	If severe TR, consider elective tricuspid annuloplasty	
		Insert central RVAD
Postoperative measures		
Preventive	Early RVF	Fulminant RVF
PA-guided volume and inotrope management		
Limit arrhythmias		
Limit RV preload		
	Rule out reversible causes: • VT • RV hematoma • Epicardial ischemia • Increased preload	
		Insert RVAD • Elective: central or peripheral • Emergent: VA-ECMO

vasodilators and inotropic medications, and careful selection of patients who could benefit from empiric BIVAD support. We commonly employ indwelling pulmonary artery catheters in patients awaiting LVAD implantation in order to titrate therapies. As mentioned, pulmonary artery pressure alone may not be as useful as the overall hemodynamic picture, including pulmonary vascular resistance, RVSWI, and the ratio of CVP to PCWP.

Optimizing volume status before LVAD placement is important. We strive to attain the lowest right and left heart filling pressures that the patient can tolerate from a hemodynamic and renal standpoint. The choice of strategy for achieving this goal is informed by the individual patient's hemodynamic stability, renal function, and degree of volume overload. Intravenous loop diuretics, usually administered via a continuous drip, with or without thiazide diuretics, are the mainstay of diuresis. Often, patients are already receiving low-dose inotropes, which can potentially improve renal perfusion. In patients who are profoundly volume overloaded or who have severe renal dysfunction, ultrafiltration with continuous renal replacement therapy is necessary, with the goal of reducing filling pressures.

When used judiciously, preoperative percutaneous LVAD support can optimize organ perfusion and decompress both ventricles. Although we have experience with the TandemHeart (CardiacAssist, Inc., Pittsburgh, PA) and the femorally implanted Impella (Abiomed, Danvers, MA), using these devices necessitates bedrest. We have, therefore, begun to use axillary intra-aortic balloon pumps and the Impella 5.0 more frequently.

A particularly controversial topic in the perioperative management of LVAD recipients is that of empiric placement of BIVADs in select patients. Proponents argue that, although RVAD implantation for RVF is associated with increased morbidity, planned BIVAD placement improves outcomes in high-risk patients. A 2010 report from an Italian group describes a strategy of planned BIVAD placement in which central RVAD is used at the time of LVAD placement in patients at high risk of RVF [21]. All of the six patients described in the report were successfully weaned from RVAD support by postoperative day 18 and were successfully discharged with an LVAD alone.

The advent of percutaneous RVADs (Impella RP and TandemHeart) is actively changing the discussion as it relates to the prophylactic use of temporary RVADs. Schmack et al. [22] describe a practice of prophylactic RVAD support with the TandemHeart, using the Protek Duo cannula, in patients at risk for RVF. Potential benefits of this device include its lower invasiveness, the mobility it affords to patients, and that it can be explanted without reoperation. The authors do not specify in how many patients this strategy has been used or on what basis patients were deemed high risk for RVF. Although we have used percutaneous devices in the postoperative period after RVF has developed, we have not yet used them prophylactically in high-risk patients. We hope that future improvements in preoperative risk prediction models for RVF will help us to select patients who are most likely to benefit from such a strategy.

Another controversial issue is whether patients with severe tricuspid annular dilatation benefit from undergoing tricuspid valve annuloplasty concomitantly with LVAD placement. In a 2014 single-center study involving 101 patients who underwent LVAD implantation, 14 patients who had concomitant tricuspid valve repair (all of whom had moderate or greater TR) were found to have greater survival, but not less severe RVF, than patients with similarly severe valvulopathy who did not undergo annuloplasty [23]. A 2015 meta-analysis of six observational studies with a total of 3249 patients found no difference in survival or RVF rates in LVAD recipients who underwent concomitant tricuspid valve repair versus LVAD implantation alone [24]. We do not routinely perform tricuspid annuloplasty concomitantly with LVAD implantation at our institution.

Prevention: Postoperative

By the nature of their underlying disease, patients who undergo LVAD placement are uniformly high risk with regard to major cardiac surgery. Thus, they are particularly susceptible to intraoperative

complications such as air embolus into the right coronary artery, aggressive transfusion of blood products, and ischemia and vasoplegia associated with prolonged cardiopulmonary bypass. Expeditious procedural times and paying scrupulous attention to intraoperative bleeding while limiting transfusion are imperative. Intraoperative transesophageal echocardiography (TEE) is invaluable for optimizing cannula placement and initial pump speed.

On returning to the recovery unit, patients must be hemodynamically optimized. Acid-base status and electrolytes should be monitored and corrected as needed. Volume status should be assessed with invasive hemodynamic monitoring. We strive to maintain a CVP as low as can be hemodynamically tolerated through the aforementioned use of diuretics and, if needed, ultrafiltration.

Postoperative arrhythmia, while tolerated by the left ventricle, is a potential source of RV dysfunction. Patients who develop supraventricular or ventricular tachyarrhythmia should be aggressively treated with intravenous antiarrhythmics and, if necessary, synchronized cardioversion. A search should be undertaken for the underlying cause of the postoperative arrhythmia, such as high pump speeds with septal interference, suboptimal cannula positioning, electrolyte abnormalities, postoperative pericardial bleeding, or RV ischemia. Vasopressor administration should be minimized. The best time to resume tachytherapy in patients with defibrillators is not clear. We typically resume tachytherapy immediately; however, if a patient requires multiple defibrillations, adjustments may be required, including increasing the defibrillation threshold or turning off shocks altogether.

Echocardiographic guidance is necessary to optimize pump settings and, thus, hemodynamic conditions. We use intraoperative TEE to select initial device settings, and we obtain serial transthoracic echocardiograms in the early postoperative period to ensure that increases in pump speed are well tolerated. Although we frequently use ramp or "speed-change" studies to evaluate cardiac response to various pump speeds in patients with an LVAD, caution should be taken in performing such a study during the early postoperative period because high speeds may induce unnecessary RV strain. Consequently, we prefer to evaluate only one or two incrementally higher speeds, paying close attention to echocardiographic and invasive indicators of RV function.

The prophylactic use of pulmonary vasodilators after LVAD implantation in high-risk patients is appealing. The effects of inhaled nitric oxide in LVAD patients with elevated pulmonary vascular resistance (PVR) were explored in 2011 by Potapov et al. [25], who randomly assigned 150 patients with preoperative PVR greater than 200 dyn*s/cm^{-5} to receive either inhaled nitric oxide or placebo. Patients who received inhaled nitric oxide had less RV dysfunction, time on mechanical ventilation, and need for an RVAD than the placebo-treated patients, but these differences did not reach statistical significance. Whether prophylactic use of inhaled prostacyclins, such as epoprostenol and iloprost, may be protective has not been investigated in a placebo-controlled trial. One group that administered epoprostenol to 37 consecutive LVAD recipients found that it reduced pulmonary pressures whether it was initiated before or during weaning from cardiopulmonary bypass [26]. Whether this strategy improved clinical outcomes has yet to be determined. Despite the lack of high-quality evidence to support their use, we have a low threshold for initiating either inhaled nitric oxide or epoprostenol administration in patients who are perceived to be at high risk for RV dysfunction after LVAD placement.

In addition to targeted pulmonary vasodilators, cardiac inotropes are frequently used in the perioperative period to enhance RV support. Milrinone, a phosphodiesterase III inhibitor that increases cardiac inotropy and causes pulmonary and systemic vasodilation by increasing tissue levels of cAMP, has a particularly appealing hemodynamic profile. However, when not used selectively, intravenous milrinone can cause systemic hypotension. Inhaled milrinone has recently been explored as an alternative formulation that may not have this adverse effect. Haglund et al. [27] have described their experience with using inhaled milrinone in ten consecutive patients who underwent HeartMate II LVAD implantation.

The authors note a reduction in pulmonary pressures and no episodes of sustained hypotension. In addition, institutional costs were significantly lower with the use of inhaled milrinone than with the use of inhaled nitric oxide. At our institution, LVAD patients frequently begin receiving intravenous milrinone, usually in conjunction with low-dose epinephrine, dobutamine, or both, on weaning from cardiopulmonary bypass. The adverse effects of these medications, including their proarrhythmic properties, are well-known; thus, the risks and benefits of their use in an individual patient should be continuously reassessed by using all available hemodynamic information.

Management

Should RVF develop after LVAD implantation despite preventive measures, it must be quickly identified and aggressively managed. Any of the aforementioned reversible causes should be excluded, and electrolyte levels, acid-base status, and cardiac rhythm should be optimized.

Here, again, transthoracic echocardiography is crucial to optimizing LVAD speed and identifying reversible causes of RVF, such as pericardial effusion. Absence of arterial pulsatility and aortic valve opening, along with septal bowing into the left ventricle, suggests that the LVAD's pump speed may be too high. Reducing pump speed in such cases relieves RVF by reducing RV preload and allowing the interventricular septum to assume a midline position, particularly if there is septum-cannula interference causing suction events and ventricular ectopy. Patients with evidence of RVF may need to be able to tolerate some degree of incomplete LV decompression in the early postoperative period.

As mentioned previously, we have a low threshold for administering pulmonary afterload-reducing agents as patients wean from cardiopulmonary bypass. We typically continue to give patients inotropic agents, including milrinone, dobutamine, and epinephrine, during the early postoperative period; individual regimens are determined by hemodynamic profile and clinician preference. Evidence for the efficacy of these agents in patients with RVF after LVAD is mainly extrapolated from the general cardiac surgery literature. In 2002, Kihara et al. [28] described the use of intravenous milrinone in two patients with RVF after LVAD. Used at low doses to avoid systemic hypotension and malignant arrhythmia, milrinone was associated with clinical benefit and avoidance of RVAD placement in both patients. A more recent retrospective study of 149 patients who underwent continuous-flow LVAD implantation at Henry Ford Hospital found that, among 18 patients who developed postoperative RVF, mortality was no different when patients were treated with prolonged milrinone; on the other hand, patients who required RVAD support had poorer survival [29]. We consider milrinone, dobutamine, and epinephrine first-line agents in the management of postoperative RVF, and we typically begin administering them either prophylactically or at the first signs of RV dysfunction.

Although randomized studies are lacking that could validate the use of pulmonary vasodilators in patients with RVF after LVAD, observational reports support their use. A 2012 report by a Greek group describes the use of combination treatment with inhaled nitric oxide and iloprost in seven patients with RVF refractory to inotropic support with dobutamine and epinephrine [30]. The authors describe significant reductions in PVR and mean pulmonary artery pressure, along with increased tricuspid annular velocity as measured by echocardiogram, without a clinically significant drop in mean arterial pressure. None of the patients required RVAD support. A 2014 study supporting a strategy of liberal pulmonary vasodilator use in unselected LVAD patients (91% received inhaled nitric oxide, iloprost, oral sildenafil, or some combination of these) found that, among six patients with postoperative RVF, none required an RVAD [31]. Five of the six patients received inhaled nitric oxide, and all six received iloprost and sildenafil. At our institution, we have a similarly low threshold for using pulmonary vasodilators in high-risk patients, especially those with postoperative indicators of RVF.

In patients who are not selected for a strategy of planned BIVAD support, an RVAD is inserted

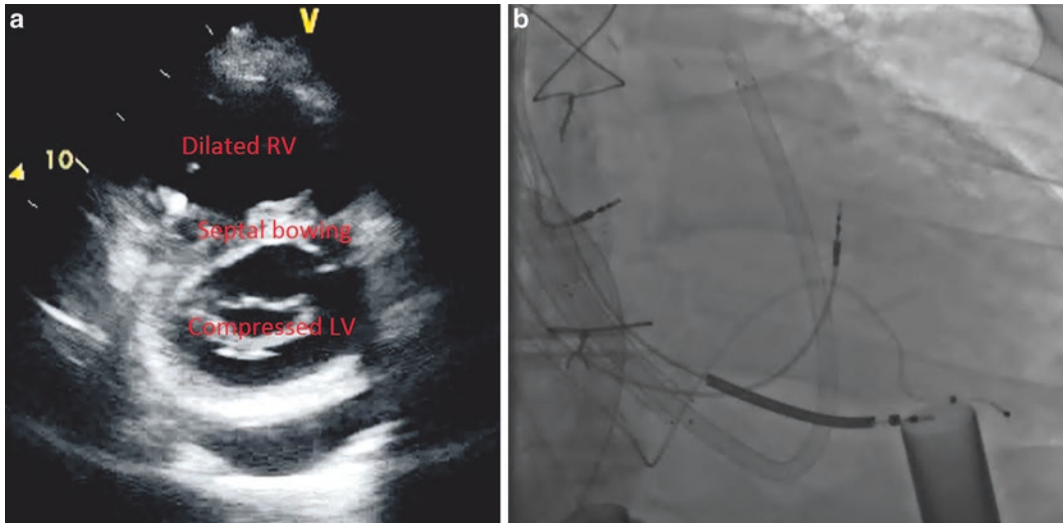

Fig. 18.1 TandemHeart Protek Duo placed for RVF following LVAD. (**a**) Post-LVAD TTE demonstrating LV compression by the RV. (**b**) Tandem Protek Duo placed in the cath lab

when the aforementioned medical therapies for RVF are ineffective. Frequently, this decision is made during the LVAD insertion procedure when the patient cannot be weaned from cardiopulmonary bypass despite aggressive use of inotropes and pulmonary vasodilators, and RV function is severely reduced on visual inspection. In such cases, the surgeon may elect to insert a temporary RVAD centrally.

Once the patient is in the recovery unit, options for mechanical RV support include extracorporeal membrane oxygenation (ECMO), percutaneous RVAD support, and returning to the operating room for central RVAD placement. We reserve ECMO for patients experiencing complete cardiopulmonary collapse, in which case femoral cannulation can be performed and full support initiated at the bedside. As mentioned earlier, percutaneous temporary RVAD support is an increasingly attractive option. Available devices include the Impella RP and TandemHeart, both of which we have used in cases of refractory RVF as a bridge to RV recovery or permanent RV support. Inserted through the femoral vein, the Impella RP is a 22 Fr pump on an 11 Fr catheter and is capable of producing flows greater than 4 L/min. The TandemHeart pump offers the benefit of an oxygenator to facilitate early extubation; when used with the Protek Duo dual-lumen catheter, it can be placed through a single jugular access site, enabling patient ambulation (Fig. 18.1).

Options for permanent RV support are limited. Currently, patients who require durable biventricular support are considered candidates for the SynCardia Total Artificial Heart (SynCardia Systems, Inc., Tucson, AZ) or temporary RVAD support as a bridge to cardiac transplantation (Fig. 18.2).

Conclusion

RVF is a common and morbid complication seen in the early postoperative period. Although numerous demographic, biochemical, hemodynamic, and imaging predictors of early RVF have been identified, no patient is immune from this adverse event. Thus, with the expanding use of LVADs in an increasingly sick patient population, it is critical that the clinician make efforts to prevent RVF and identify early clinical and hemodynamic signs as they develop. Further, the

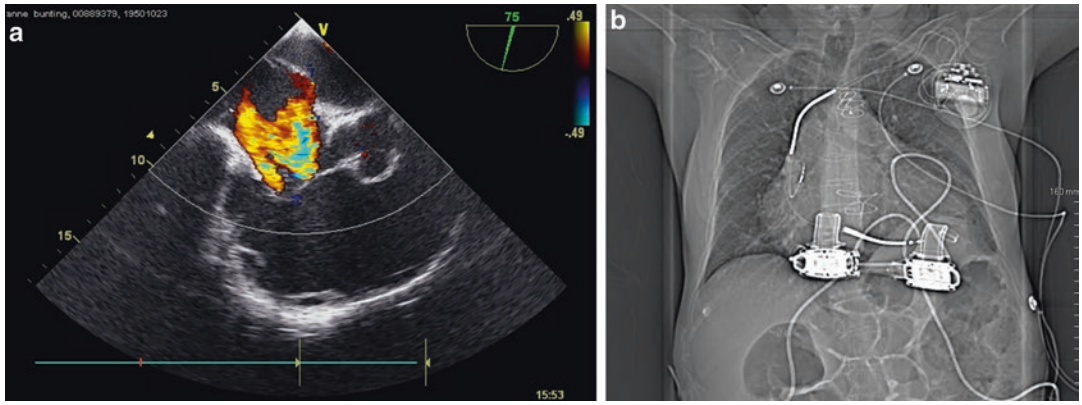

Fig. 18.2 HeartWare RVAD placed for RVF following LVAD. (**a**) RV dilatation and severe TR by intraoperative TEE immediately following LVAD placement. (**b**) Following immediate implantation of HeartWare device in the RV position, biventricular support was tolerated for 9 months pending successful heart transplant

clinician must be familiar with the growing arsenal of medications and mechanical interventions available for the timely and effective management of RVF.

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