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;

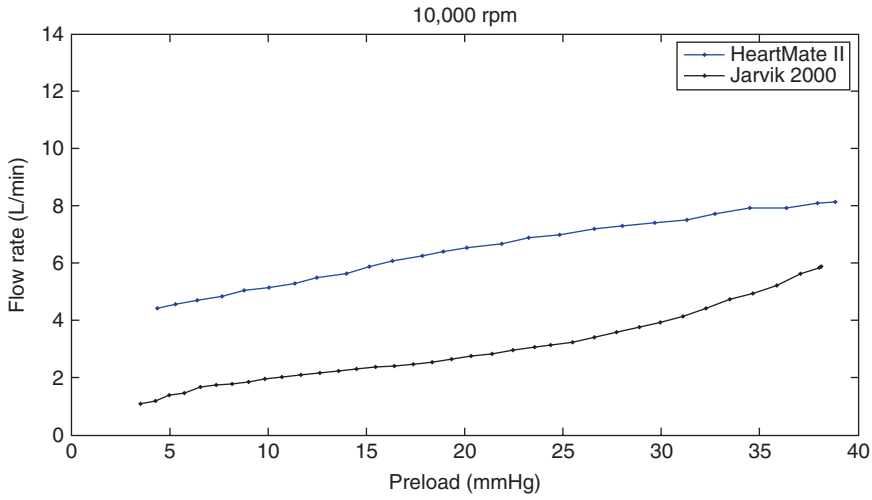

Fig. 1.2 Inflow sensitivity results in a Starling-like response without changing the pump speed

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

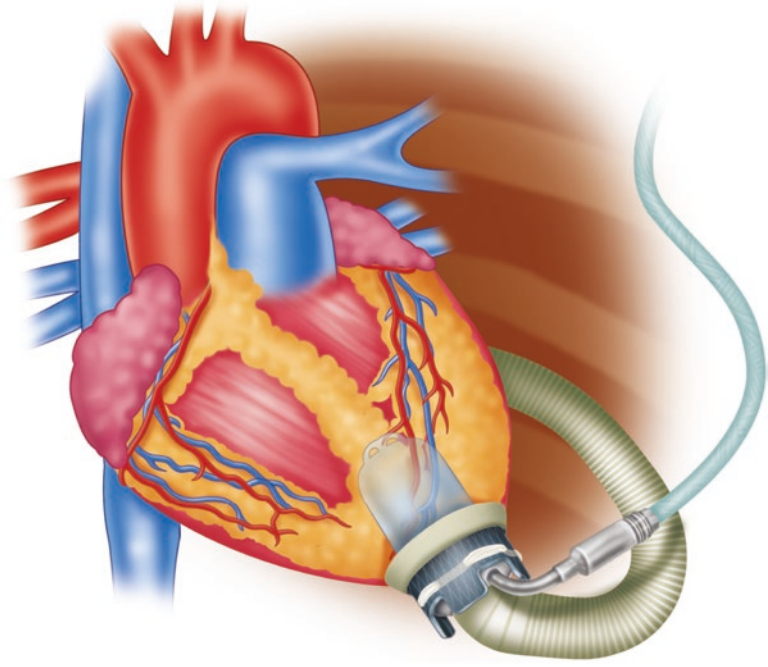

Fig. 1.4 Drawing of an implanted Jarvik 2000. This device was first placed in a patient in April 2000

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.

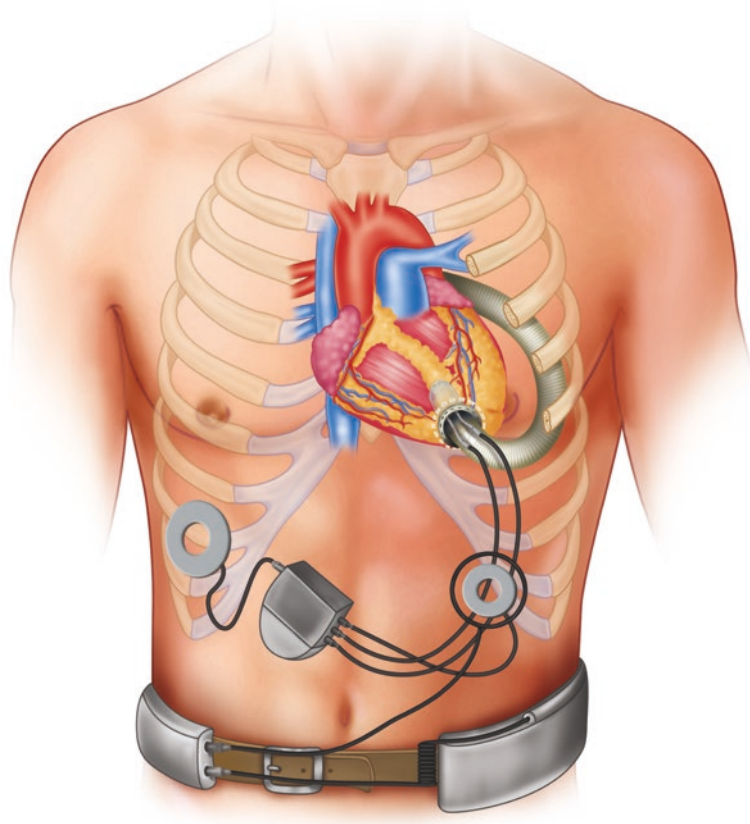

Fig. 1.5 The totally implantable version of the Jarvik 2000. Two power leads exit off the blood pump and are connected to the internal power and control unit. Primary and secondary transcutaneous energy transmission system (TETS) coils are placed in different locations in the abdominal wall. The external 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).

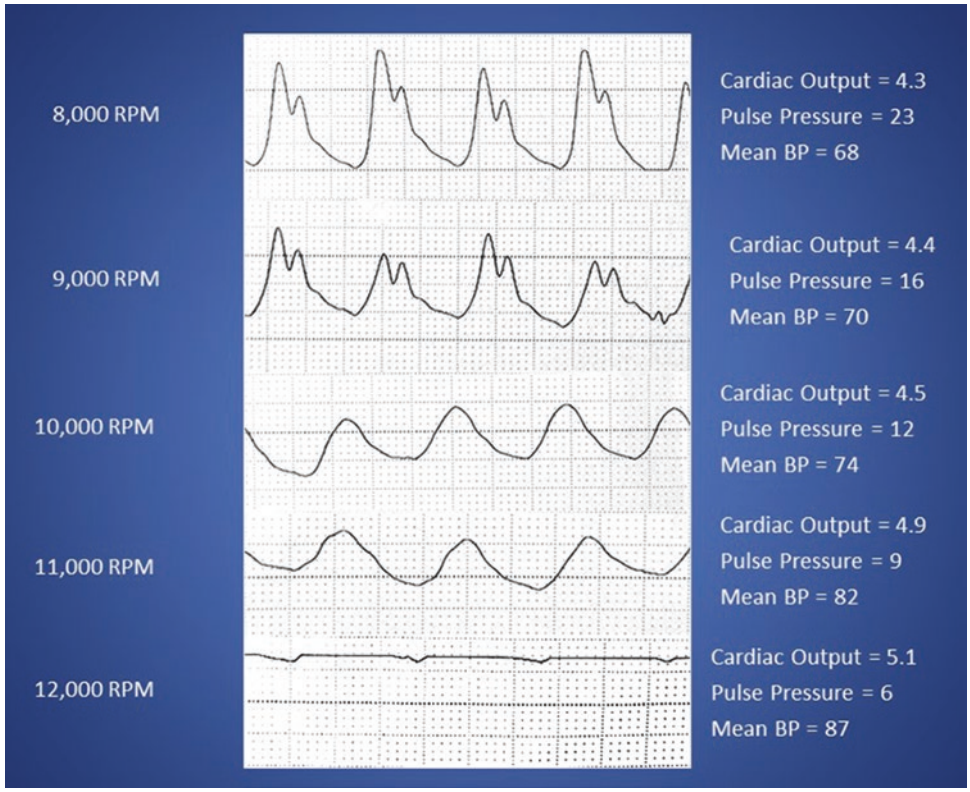

Fig. 1.6 Pulse pressure readings at various continuous-flow pump speeds. As pump speed is increased, the aortic valve ceases to open and close, and the rhythmic contraction of the heart has less influence on the pulse pressure as the pump takes on more of the workload

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

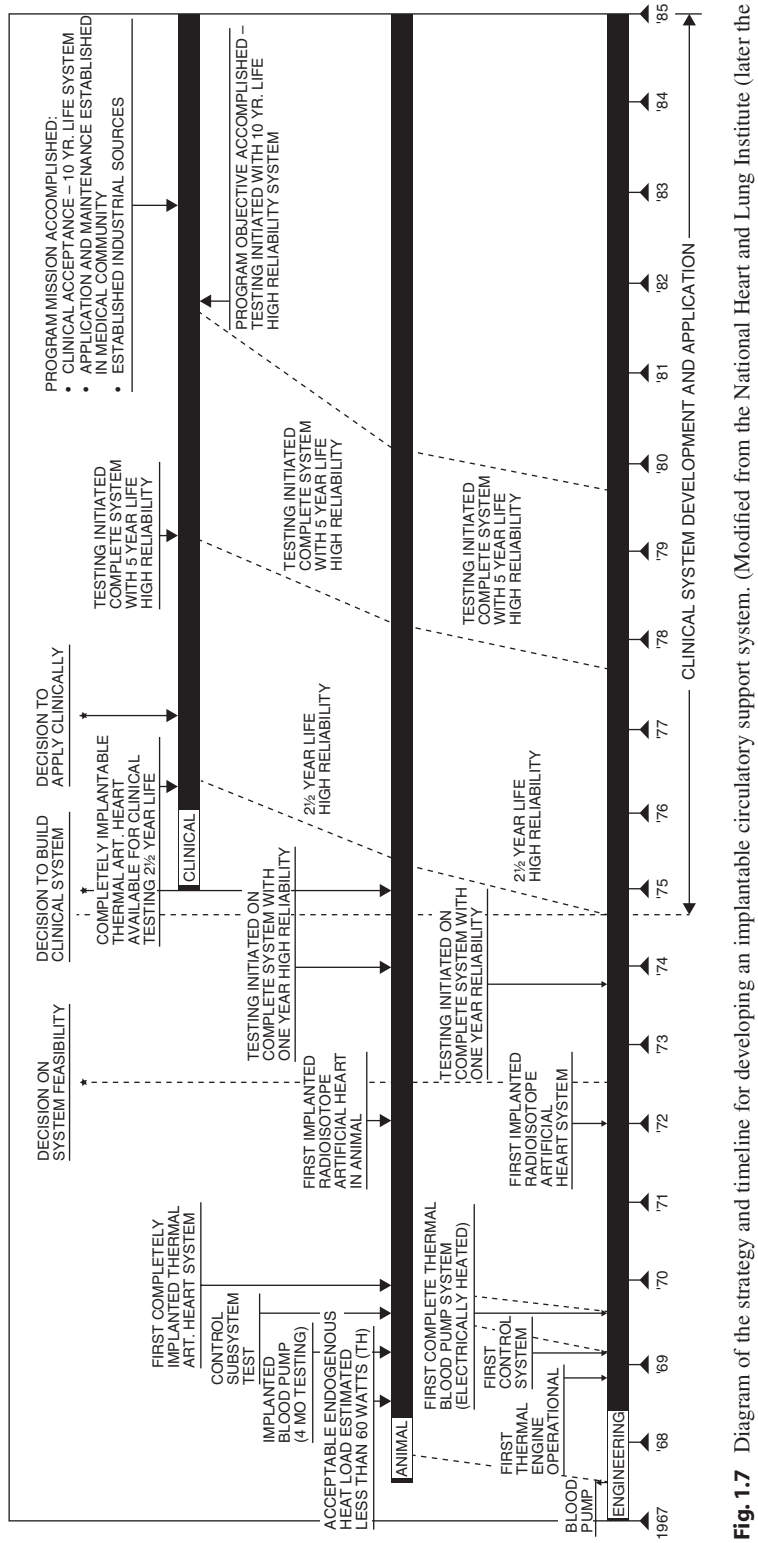

Fig. 1.7 Diagram of the strategy and timeline for developing an implantable circulatory support system. (Modified from the National Heart and Lung Institute (later the National Heart, Lung, and Blood Institute))

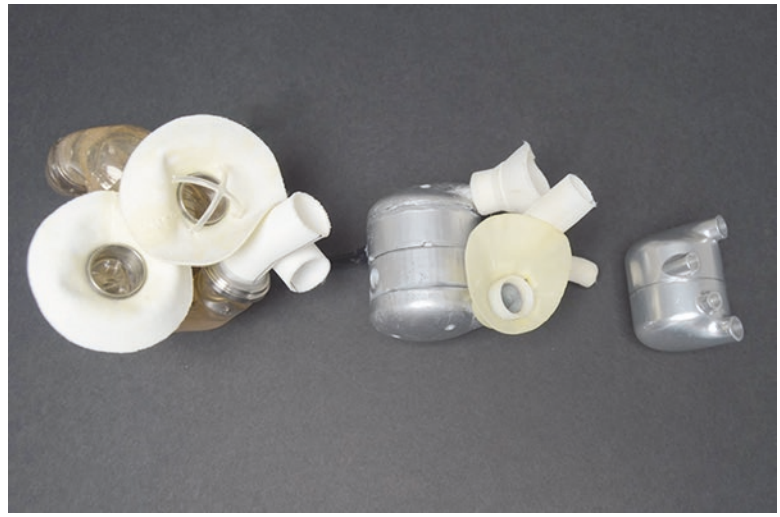

Fig. 1.8 The AbioCor totally implantable pump (*left*) compared with the BiVACOR centrifugal pump (adult, *center*, and child, *right*)

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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