

# Extracorporeal circulation-from cardiopulmonary bypass to extracorporeal membrane oxygenation and mechanical cardiac assist device therapy: A constant evolution

The dramatic increase in human life expectancy in the modern era can be traced back to the immense advances in cardiovascular biology and medicine. Arguably, the biggest contributions have come from the remarkable evolution of open-heart surgery and cardiopulmonary bypass (CPB). Advances in these areas, however, could not have been possible were it not for the prodigious work of many investigators in apparently unrelated fields. The discovery of heparin by McLean and Howell in 1916 for example, followed by the first described use of protamine to neutralize heparin *in vivo* in 1939, laid the foundations upon what are now the well-established specialties of perfusion and cardiothoracic surgery.<sup>[1,2]</sup>

The specialty of cardiac surgery may have begun in 1896 with Ludwig Rehn's successful suture of a right ventricular stab wound. The early 1940's saw a handful of operations that did not need extracorporeal support-closure of patent ductus, coarctation repair, the Blalock-Taussig Shunt and mitral commissurotomy.<sup>[3-5]</sup> In the early 1950's Lewis published the first case report of atrial septal defect closure using hypothermia alone.<sup>[6]</sup> It soon became apparent that more complex operations on the heart and great vessels needed an artificial circulation, outside the body, to render the heart still and bloodless. John Gibbon at Jefferson Medical College deserves credit for the first successful demonstration of CPB (spurred by the death of a patient by fatal pulmonary embolism

following cholecystectomy) on May 6, 1953 for closure of an atrial septal defect.<sup>[7]</sup> In addition, C Walton Lillehei at the University of Minnesota and John Kirklin at Mayo Clinic worked simultaneously at refining techniques available at the time. The limiting factor in the early days of CPB proved to be oxygenation, with unacceptably high mortality from the rudimentary oxygenators available at the time. The biggest causes of CPB related death were from air embolism and coagulopathy. In the mid 1950's there were three types of oxygenators in use the vertical screen oxygenator (Gibbon and Kirklin), the bubble oxygenator (DeWall and Lillehei) and the rotating disc type (Kay and Cross).<sup>[8]</sup> Lillehei was a true pioneer, having invented the technique of "controlled cross circulation" (parent to child). Using this technique, he was the first surgeon to successfully close a ventricular septal defect, the first to perform total repair of tetralogy of Fallot, and the first to repair persistent common atrioventricular canal. He performed 45 operations using cross circulation and had 28 survivors.<sup>[9,10]</sup>

The first commercial heart-lung machine was the Mayo-Gibbon machine, which was the most widely used heart-lung machine of the 1950s and early 1960s. It was developed by Kirklin *et al.* at the Mayo Clinic, based on Gibbon design. Indeed, for a few years in the mid-1950's the only 2 centers performing cardiac surgery in the world (Lillehei at University of Minnesota and Kirklin at Mayo

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Address for correspondence: Dr. Harish Ramakrishna, Mayo Clinic, USA. E.mail: [Ramakrishna.Harish@mayo.edu](mailto:Ramakrishna.Harish@mayo.edu)

Clinic) were in the same state and only 90 miles from each other.<sup>[11,12]</sup> The Mayo-Gibbon machine was, for its time a relatively sophisticated device, with safety features that included an arterial filter, automatic control of arterial pH, high-pressure safety stops and an automatically activated occluder mechanism to maintain blood flow to the oxygenator.<sup>[13]</sup> Vacuum assisted drainage of the superior, and inferior venae cavae was responsible for initiation and maintenance of CPB. The machine needed 6 units of whole blood to prime. Oxygenation was provided by 14 wire-mesh screens, each 12 × 18 in. Oxygen flow into the oxygenator was constant at 10 L/min, and carbon dioxide flow to the oxygenator was controlled automatically by a pH meter to maintain a pH of 7.43–7.45. In a pioneering series of cases, CPB was maintained for 20–73 min and flows were on average 100 mL/kg/min. There was no heat exchanger, however, reflecting contemporary technology. Over the past 60 years, as perfusion techniques have grown more sophisticated with minimal morbidity and mortality, there are still few universally followed guidelines or standards to govern perfusion practices. Wide variations exist, internationally-in both technology and techniques for the conduct of CPB. These variations have been found to be associated with increased costs, neurologic outcomes, length of stay and mortality, as reflected by data published over the past decade.<sup>[14]</sup> Some key CPB related issues that have been shown to unequivocally affect outcome include appropriate blood pressure management on CPB, pump flows and oxygen delivery, temperature and glucose management, the role of pulsatility as well as recommended pH management as supported by the existing guidelines.<sup>[15-17]</sup>

The rapid growth of extracorporeal technologies in the past decade is a testament to the pace of research and development in heart failure and mechanical cardiac assist devices. Mention must be first made of the dramatic growth in the field of extracorporeal life support as evidenced by the fact that that over a 2-year period, from early 2009 through May 2011, there were more than 1000 papers on extracorporeal membrane oxygenation (ECMO) reported on Medline, with the majority of ECMO usage related to multiple causes of respiratory failure and cardiac failure, particularly from H1N1 infection.<sup>[18]</sup> The trend, since then has continued-as demonstrated in a 2014 study, which reported a significant (433%) increase in ECMO utilization in adults within the USA alone from 2006 to 2011.<sup>[19]</sup> Aside from the H1N1 pandemic and the surge in veno-venous (VV) ECMO usage in

Australia and New Zealand, the other key stimulus for the use of ECMO has been the publication of the Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure (CESAR) trial.<sup>[20]</sup> The key finding in this trial was that the ECMO group showed significantly lower rates of death and disability 6 months after randomization (37% in ECMO vs. 53% in the mechanical ventilation group,  $P = 0.03$ ). More trials are underway, and we can expect to see more randomized data in the future reflecting the success of VV and venoarterial (VA) ECMO in the management of critically ill patients. Outcome data to date show a significant improvement from the past few decades. For example, a 2009 meta-analysis of cardiac arrest patients reported that, from 1990 to 2007, the survival rates for ECMO treated adults following cardiac arrest increased from 30% to 59%.<sup>[21]</sup> In the respiratory failure population, the Zapol trial in 1979<sup>[22]</sup> reported a 9.5% survival rate compared with 2009 CESAR trial (53%). The future will no doubt witness a significant increase in ECMO usage worldwide,<sup>[18]</sup> a key reason being significant improvements in circuit design, oxygenator technology and increasing portability of ECMO pumps. Growth areas in particular will be related to lung rescue and the increasing trend of using VV/VA ECMO as a bridge to lung transplantation, as well as the increasing popularity of “awake ECMO” in select high-risk patients, where the early use of ECMO allows for ambulation/rehabilitation and avoids all of the dangers of mechanical ventilation such as barotrauma, infection, and ventilator dependence [Figures 1 and 2]. Other areas that will see more use of ECMO will be as a means for rapid CO<sub>2</sub> removal in patients with severe chronic obstructive pulmonary disease/emphysema, acute respiratory distress syndrome and other causes of acute lung failure. Devices like the Novalung have already been shown to be successful in this regard.<sup>[23-24]</sup>

Finally, - it would be safe to say that the growth of new devices and technologies for the treatment of advanced heart failure has been phenomenal in the past decade. This promises to be the beginning of a new era in the surgical management of end-stage heart failure. For this group of patients, the gold standard of therapy has remained orthotopic heart transplantation, where current posttransplant survival rates are approximately 85% at 1-year, 80% at 2 years, and 75% at 5 years. However, there still remains a significant donor shortage, 8–10% of patients on the transplant list die every year. For this high risk, maximally-medically optimized group of end-stage heart failure patients,

mechanical assist devices are the key lifesaving option, along with the widespread use of implantable defibrillators (with cardiac resynchronization therapy) and outpatient inotropes [Figure 3].

Mechanical assist devices (ventricular assist devices [VAD's]) have had a long, successful history in the surgical management of heart-failure patients and are advancing beyond the third generation of devices. Figure 4 depicts the significant trends in VAD implantation for heart failure over the past decade. The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial, which was the first randomized trial, comparing VADs to medical management, published in 2001 showed a clear survival benefit for VAD patients (ineligible for heart transplantation) implanted with the first generation HeartMate XVE (Pleasanton, CA, USA).<sup>[25]</sup> At the present time, VAD implantation is reserved for bridging to heart transplant or as destination therapy in patients ineligible for heart transplantation. It can also be used a bridge to recovery in selected patients as well as a bridge to decision (which may be transplant, destination or recovery).

The current status of VAD therapy across most VAD centers in the USA is almost exclusively represented by continuous flow pumps which either function as axial flow devices (Heart Mate 2 Thoratec, USA) or centrifugal rotary pumps which are magnetically levitated and bearingless and include the HeartWare HVAD, (HeartWare International, USA) and DuraHeart, (Terumo Inc., USA). The latter group of devices have thinner drivelines, no pump pockets, no heat or friction generation and overall greater durability. All of the currently available devices, however, have their limitations; adverse events are common, with varying rates of bleeding, infection, sepsis, right ventricular failure, stroke and pump thrombus. Gastrointestinal bleeding remains a particularly troublesome issue in continuous-flow left ventricular assist device patients and has been attributed to a combination of arteriovenous malformations in the gut accompanied by Von Willebrand factor deficiency in these patients.

The new generation of VAD's will be significantly smaller, less invasive, designed with an emphasis on durability and patient mobility/lifestyle, with a tendency for more percutaneous devices (like the current Impella and TandemHeart) and devices placed

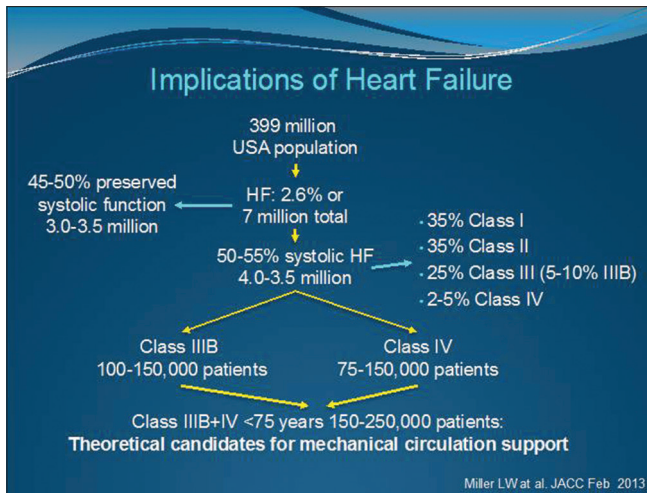


**Figure 1:** The cardiohelp

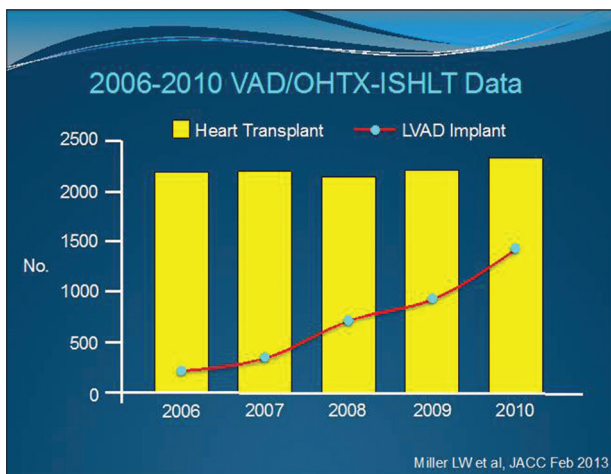


**Figure 2:** Potable, awake extracorporeal membrane oxygenation for selected high-risk patients

without the need for CPB (Circulite, Circulite Inc., NJ, USA). Pumps implanted over the next decade



**Figure 3:** Potential usage of ventricular assist device's in heart failure patients



**Figure 4:** Increasing ventricular assist device utilization in the past decade

will be designed for intraventricular or intravascular operation (intravascular micro-axial design). In addition, advances in wireless technology and transcutaneous energy transfer will herald a new era of driveline-less pumps (doing away with driveline infections and trauma, both a significant source of morbidity in VAD patients) as well as devices that will have the capacity for remote monitoring like pacemakers and defibrillators of the current day. More importantly, evidence of biologic recovery following VAD implantation continues to accumulate, with reductions in neurohormonal activation, cytokine release, improvements in myocardial calcium handling and histologic evidence of myocardial recovery (as noted in explanted hearts in patients bridged to transplantation).<sup>[26,27]</sup> In the not too distant future, one might well expect heart transplantation to be replaced by technologies such as those described above.

**Harish Ramakrishna**

Division of Cardiovascular and Thoracic, Anesthesiology, Mayo Clinic, United States

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