Transonic & Extracorporeal Life Support (ELS)

A little over a half century ago, the nation was transfixed by a struggle to save the life of Patrick Bouvier Kennedy, the infant son of President and Jacqueline Bouvier Kennedy. Five and a half weeks premature, Patrick, weighing 4 pounds 10 1/2 ounces, was delivered on Aug. 7, 1963. After birth he immediately began having trouble breathing and was transferred from Cape Cod to Boston Children’s Hospital where he was placed in a hyperbaric chamber. He died 39 hours later, a victim of hyaline membrane disease which was then the most common cause of death among premature infants (25,000 per year) in the United States. The disease is now known as infant respiratory distress syndrome (IRDS). In those days there were no neonatal intensive care units (NICU), and ventilators had yet to be used for premature babies.

This tragic death of the President’s son sparked interest in research on prematurity and, over the following decades, innovations from physicians, nurses and others led to bold and successful treatments for infants which gave rise to a new specialty, neonatology. Had Patrick been born today, his outcome most likely would have been positive due to the ground breaking work of neonatology pioneers such as Dr. Robert Bartlett of the University of Michigan who developed extracorporeal membrane oxygenation (ECMO) to treat IRDS.

**ECLS Origins**

The genesis of Extracorporeal Life Support (ECLS) and the development of the heart-lung machine for arresting the heart during cardiac surgery evolve from a common history. Driven by the death of a patient from a pulmonary embolus, Dr. John H. Gibbon developed a freestanding roller pump device for extracorporeal support which was first used in 1953 during surgery to assist repair of an atrial septal defect in an 18-year-old patient Cecilia Bavolek. The synthesis of silicone rubber in 1957 revolutionized the development of an artificial lung because the silicone was found to be strong enough to withstand hydrostatic pressure, yet still be permeable to gas transfer. The use of this silicone membrane oxygenator led to the use of the term extracorporeal membrane oxygenation (ECMO).

ECMO was introduced for the treatment of severe acute respiratory distress syndrome (ARDS) in the 1970s by Dr. Theodore Kolobow who pioneered the artificial membrane lung. In 1971, Dr. Donald Hill reported the survival of a 24-year-old polytrauma patient with ruptured aorta after a motorcycle accident. Even by today’s standards the patient would not have been considered a good ECMO candidate. Nevertheless, he was successfully treated on ECMO.

**Baby Esperanza & Robert Bartlett**

In 1976, interest in ECMO was revived after Dr. Robert H. Bartlett reported the first neonatal ECMO survivor, baby Esperanza. The baby’s mother, a poor, illiterate peasant from Baja, Mexico crossed the border and headed for Los Angeles, determined that her child would have a better life as a United States citizen. En route, she went into labor and was taken to Orange County Medical Center where her daughter was born. During delivery, the child had aspirated a large quantity of meconium and developed chemical pneumonitis. Even with maximal ventilatory support, the baby was unable to sustain adequate oxygenation.

When the situation was considered so hopeless that there was nothing to lose, Dr. Robert H. Bartlett, a thoracic surgeon who had been involved in developing the membrane lung, wheeled in a machine from the laboratory. The nurses named the baby Esperanza, meaning hope. After three days of bypass, Esperanza was weaned from bypass and recovered completely. A new era for treating babies with IRDS was born.
Best Practices during ECMO

Bartlett Used Transonic’s First Clamp-on Tubing Flowsensor

In 1987, Transonic launched an innovative breakthrough in the manufacture of Flowsensors with its first C-Series Clamp-on sensors designed for noninvasive sterile tubing. These sensors were the first of their kind to accurately measure flow within the walls of tubing.

Shortly after their introduction, Dr. Bartlett, by then director of the University Michigan’s ECMO program, incorporated the Transonic Tubing Flowsensor and its companion HT101DBLZ Flowmeter into his ECMO protocol as an independent safety measure of assuring the correct flow delivered to the patient. Richard Powers presented his validation of Transonic flow measurement as being an independent of temperature & hematocrit at the first Extracorporeal Life Support Organization (ELSO) meeting founded by Dr. Bartlett. Earlier, Dr. Thomas Depner (Univ. of CA at Davis) had studied the wear and cavitation of tubing at different pressure pump settings and recommended independent Transonic verification of delivered blood flow versus the pump occlusion setting in long blood pump procedures such as dialysis and ECMO.

Product Innovations

In 1993, MC3 contracted for an initial OEM for delivery of 6X Sterile Tubing Flowsensor and boards for an ECMO pump designed in Dr. Bartlett’s lab. This would later become the Asecor pump. The following year, Transonic introduced its first dedicated HT109 Tubing Flowmeter and first four-crystal “X”-sensors for sterile tubing. Designed for clinical use with bubble detection and multiple calibration capabilities for fluid type, temperature and tubing type, it quickly became the standard R & D flowmeter for pump developers and OEMs as well as a standard “must have” on ECMO shopping lists.

Within a couple of years, 30% of all ECMO centers in the USA use Transonic flowmeters to monitor flow to the patient for the duration of ECMO treatment.

Next Generation Flowmeter and Flowsensors Developed

A next generation dedicated HT110 Tubing Flowmeter was released in 1997 with improved measurement stability at low flow and higher frequency Flowsensors. This was particularly important for the low flow volumes (300–500 mL/min) of ECMO circuits. In addition, a full line of 4-crystal XL-series flowsensors was released. By providing an independent measure of delivered blood flow, the Transonic Tubing Flowmeter and its companion Clamp-on Flowsensors became an invaluable safety and quality device. It provides noninvasive, sterile measurements without any contact with the fluid or interruption of the tubing. In addition to its measurement stability at low flows, as used during ECMO, it also has a stable and low zero offset and its calibration can be adjusted on site. It has thus become the standard used by the biomedical industry by which they calibrate & validate other pumps.

These innovations paved the way for another Transonic specialty solution, Flowsensors to measure oxygen rich perfluorocarbon solution by Alliance in R & D liquid ventilator project in Dr. Bartlett and Dr. Hirschl’s lab at the University of Michigan. A decade later, Spectrum Medical followed suit by incorporating Transonic OEM flow measurement capability in its new ECMO monitor. They continued this practice when they launched their M4 Comprehensive Bypass Monitor in 2011.
ECMO Registry Established 1980

In the interim, back at the University of Michigan, Dr. John Toomasain created the Neonatal ECMO Registry to monitor the ECMO experience. By 1989, the Extracorporeal Life Support Organization (ELSO) was formed with the purpose of stimulating multi-institutional research in the field of acute lung injury and its therapy. Since its inception to support neonates in severe respiratory distress and infants with congenital cardiac defects undergoing surgery, ECMO has since been used to provide temporary (typically days to weeks) support of the pulmonary and/or cardiac circulation to more than 65,000 children and adults. There are currently approximately 160 ECMO centers in the Extracorporeal Life Support Organization (ELSO); 126 are in North America.

Today ECMO is an accepted treatment modality for neonatal, pediatric and adult patients with respiratory and/or cardiac failure, who:

- Fail to respond to maximal medical therapy,
- When there is an inability to wean from cardiopulmonary bypass after heart surgery,
- As a bridge to definitive therapy.

H1N1 Flu Virus Pandemic Sparks Adult ECMO Surge

The 2009/2010 H1N1 Flu virus pandemic sparked an increase in ECMO to treat adults struck with rapid, progressive Adult Respiratory Disease Syndrome (ARDS) within a day of the flu’s onset. ECMO is one of the last resorts for such life threatening complications. A study published in 2012 in the Journal of the American Medical Association reported that one hospital mortality rate for the 59 ECMO-referred patients was 24% versus 53% for the 59 non-ECMO-referred patients. In a report one a Oregon Hospital, H1N1 patients treated with ECMO had a 67% recovery rate and a 60% survival rate. All survivors were discharged to home.

Dedicated ELSA Monitor Optimizes ECMO Therapy

In 2004, a Phase I award of $100,000 from the National Institutes of Health (NIH) spurred Transonic’s development of a dedicated ECMO Monitor. The purpose of the grant was to develop a dedicated ECMO Monitor that used ultrasound dilution technology to derive measurement parameters. An additional $750,000 Phase II NIH grant was awarded Transonic in 2008 to continue this development of a Pediatric Cardiac Monitor for Extracorporeal Life Support.

The years of development culminated with the launch of the ELSA Monitor in 2014. The Monitor optimizes ECMO therapy in children and adults. In addition to measuring blood flow in the ECMO circuit, the ELSA Monitor, with infusion of a single bolus of room temperature isotonic saline, detects and quantifies recirculation in a VV ECMO patient.

ELSA Quantifies Recirculation

Recirculation of flow through the cannulas can severely limit the effectiveness of ECMO. With an injection of a small volume of saline, the ELSA Monitor can measure the percentage of recirculation that is occurring in the line.

ELSA Verifies Delivered Blood Flow

As with the earlier dedicated Tubing Flowmeters and Flowsensors, the ELSA Monitor measures true delivered blood flow through ECMO tubing using “gold standard” transit-time ultrasound technology. By comparing actual delivered blood flow to the pump’s reading, any flow limiting cause such as incorrect cannulation placement can be identified on their spot and corrected before a problem occurs.

Oxygenator Blood Volume

A clot in an ECMO circuit can be catastrophic if not detected early. The challenge for the ECMO team is to maintain a blood flow level and concentration sufficient enough to prevent a clot in the oxygenator while not inducing bleeding in fragile patients.

With an injection of a small volume of saline, the ELSA Monitor measures oxygenator blood volume to identify early clot formation in the oxygenator of the ECMO circuit that will allow a wider window of opportunity to perform an oxygenator change-out.

H1N1 Flu Virus Pandemic Sparks Adult ECMO Surge
HOW THE ELSA MONITOR WORKS

DIFFERENTIAL TRANSIT-TIME ULTRASOUND
A clip-on sensor transmits beams of ultrasound through the blood line many times per second. Four transducers pass ultrasonic signals back and forth, alternately intercepting the flowing blood in upstream and downstream directions. The ELSA Monitor derives an accurate measure of the changes in the time it takes for the wave of ultrasound to travel from one pair of transducers to the other ("transit time") resulting from the flow of blood in the vessel. The difference between the upstream and downstream transit times and the area of the tubing provide a measure of volume flow.

ULTRASOUND INDICATOR DILUTION:
The velocity of ultrasound in blood (1560–1590 m/sec) is determined primarily by its blood protein concentration. The Transonic® ELSA Monitor and Flow/dilution Sensors measure ultrasound velocity. A bolus of isotonic saline (ultrasound velocity: 1533 m/sec) introduced into the blood stream dilutes the blood and reduces the ultrasound velocity. The sensor records this saline bolus as an indicator dilution curve.

RECRYCLATION
When a saline bolus is injected upstream from the arterial Flowsensor, the ELSA Monitor identifies the saline concentrations at both Flowsensors. The ratio of indicator concentrations equals recirculation (Fig. 3).

OXYGENATOR BLOOD VOLUME MEASUREMENT
When a saline bolus is injected upstream from the oxygenator, the time that the indicator takes to travel through the oxygenator is proportional to its blood volume.

OXBV = Qb * MTT; where Qb is blood flow through oxygenator and MTT is mean transit time of indicator through the oxygenator.

Percent change of OXBV (%) in time can be expressed: OXBV% = OXBV/OXBV0*100%, where OXBV0 is the value of OXBV measured at any moment in the ECMO process. OXBVI – initial OXBV measured at the beginning of the ECMO process when oxygenator is free of clots.

A decrease in oxygenator blood volume over time reflects poor oxygenator performance and the onset of clotting within the circuit.

Fig. 2: Recirculation and Oxygenerator Volume Measurement: Saline is introduced into the arterial sensor of the ECMO circuit. The venous sensor measures the diluted concentration of blood from each recirculation and oxygenator blood volume are calculated.

UNIVERSITY OF MICHIGAN EXPERIENCE

The University of Michigan has largest single cohort of reported ECMO patients. Two thousand patients were managed with ECMO from 1973 to 2010. Of the 2,000 patients, 74% were weaned from ECLS, and 64% survived to hospital discharge.

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>SURVIVAL TO HOSPITAL DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>700 84%</td>
</tr>
<tr>
<td>Children</td>
<td>239 76%</td>
</tr>
<tr>
<td>Adults</td>
<td>353 50%</td>
</tr>
</tbody>
</table>

CARDIAC FAILURE PATIENTS (ARDS)

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>SURVIVAL TO HOSPITAL DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>361 45%</td>
</tr>
<tr>
<td>Adults</td>
<td>119 38%</td>
</tr>
</tbody>
</table>

COMPLICATIONS

The most common complication during ECMO was bleeding at sites other than the head, with an incidence of 39%. Intracranial bleeding or infarction occurred in 8% of patients, with a 43% survival rate. The least frequent complication was pump malfunction, with a 2% incidence.

CONCLUSION

The Michigan experience concluded that ECLS saves lives of moribund patients with acute pulmonary and cardiac failure in all age groups.


Summary

The spotlight on the tragic death of Patrick Kennedy, the infant son of President and Mrs. John Kennedy, in August 1963 from hyaline membrane disease (now known as severe respiratory disease) ignited focus on the care of premature infants. Increased NIH funding for research on the diseases of the newborn resulted in the specialty of neonatology and creation of the modern neonatal intensive care unit, or NICU.

ECMO Pioneer — Dr. Robert Bartlett
Fifty years ago there were few treatment options for infants, children or adults with severe respiratory disease syndrome. Due to the herculean and innovative efforts of pioneers such as Dr. Robert Bartlett, treatment by extracorporeal membrane oxygenation also came into being and has continued to evolve. It remains a last ditch effort to treat neonatal, pediatric and adult patients who are suffering from severe respiratory syndrome and/or cardiac failure who are not responding to other medical treatments. But ECMO eventually reduced infant mortality from 80% to 25% for critically ill infants with acute reversible respiratory and cardiac failure unresponsive to conventional therapy in conditions such as persistent pulmonary hypertension, meconium aspiration, and sepsis.

January 2015 ESLG Registry Statistics

PATIENTS TOTAL SURVIVED TO DISCHARGE OR TRANSFER SURVIVED TO ECMO

<table>
<thead>
<tr>
<th>Neutinal</th>
<th>27,128</th>
<th>84%</th>
<th>74%</th>
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<tbody>
<tr>
<td>Cardiac</td>
<td>5,810</td>
<td>62%</td>
<td>41%</td>
</tr>
<tr>
<td>Urgent CPR</td>
<td>1,112</td>
<td>64%</td>
<td>40%</td>
</tr>
<tr>
<td>Pediatric</td>
<td>6,659</td>
<td>66%</td>
<td>57%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>7,314</td>
<td>66%</td>
<td>50%</td>
</tr>
<tr>
<td>Urgent CPR</td>
<td>2,370</td>
<td>56%</td>
<td>41%</td>
</tr>
<tr>
<td>Adult</td>
<td>7,008</td>
<td>65%</td>
<td>57%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>5,603</td>
<td>56%</td>
<td>41%</td>
</tr>
<tr>
<td>Urgent CPR</td>
<td>1,657</td>
<td>39%</td>
<td>28%</td>
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<tr>
<td>TOTALS</td>
<td>65,171</td>
<td>71%</td>
<td>59%</td>
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Flow Pioneer — Transonic
Hand in hand with the evolution of ECMO has been Transonic’s development of Flowsensors that can clamp on sterile tubing and measure the volume flow inside the tubing. The first Transonic Tubing Flowsensors were introduced in 1987. Incremental improvements in the sensors, which now have a 4 ”X-style” crystal configuration, has expanded the measurement capability in tubing circuits. The 300–500 mL/min low flows typical to ECMO circuits can now be measured accurately with minimal zero offset with XL-Flowsensors.

Flow Innovations — Dedicated ELSA Monitor
The first dedicated Tubing Flowsensors measured delivered blood flow only and added an independent safety measure to ECMO procedures.

Now, the new ELSA Monitor adds additional measurement capability for clinicians. Recirculation in dual catheter VV ECMO circuits and oxygenator blood volume which has been shown to indicate oxygenator clotting can also be quantified.

With measurements from the ELSA Monitor the clinician can optimize ECMO delivery by verifying delivered pump blood flow and identifying and diagnosing flow limiting causes that might lead to hemolysis.

Catheter performance can be enhanced by establishing a maximum pump setting before recirculation occurs; using known values for flow and recirculation to minimize the length of ECMO runs; identifying cannula migration through high recirculation rates and possible cardiac output failure during VV ECMO.

Oxygenator clotting can be detected by a progressive decline of oxygenator blood volumes.

Again, through ongoing collaborations with clinicians who bring their measurement needs to Transonic, Transonic’s innovative and cumulative engineering know how generates measurement devices such as the a dedicated Tubing Flowmeter with XL clamp-on Flowsensors that maintain sterility within circuitry and now the ELSA Monitor to offer measurements that help to ensure better patient outcomes.

REFERENCES

1) NY Times JULY 29, 2013, Lawrence K Altman, M.D.
24) https://www.elso.org/