Artificial Organs

Invited Editorial

Eighth Istanbul Symposium on Pediatric Extracorporeal Life Support Systems and Pediatric Cardiopulmonary Perfusion

To improve the outcomes of pediatric extracorporeal life support (ECLS) and cardiopulmonary bypass (CPB) procedures in Turkey, we have established a series of conferences, called "Istanbul Symposiums." Since the first symposium in June of 2011, we have organized seven additional symposiums in Istanbul (1–3). The objective of this editorial is to share the latest results on pediatric ECLS and CPB patients with the *Artificial Organs* community.

The eighth Istanbul Symposium was held at the Medipol University on January 10, 2015. A multidisciplinary faculty including pediatric heart surgeons, pediatric intensivists, perfusionists, cardiologists, anesthesiologists, and scientists were invited to share their latest results (Fig. 1). The symposium was opened with welcoming remarks by Dr. Halil Turkoglu, the head of the cardiovascular surgery department at Medipol University, Istanbul, Turkey (Fig. 2). Dr. Akif Ündar presented his lecture about the basic principles of scientific research and the impact of the Istanbul Symposiums on pediatric ECLS and CPB patients in Turkey, along with future suggestions and recommendations (Fig. 3) (4–6). There were three specific panels at the eighth symposium:

1 Pediatric ECLS: 2015 update;
2 Latest developments on pediatric cardiac surgery and pediatric CPB procedures;
3 Role of perfusionists during ECLS and CPB along with hands-on wet-labs.

FIRST PANEL ON PEDIATRIC ECLS: 2015 UPDATE

The historical development as well as the current ECLS practice in Turkey was discussed by Dr. Atif Akcevin.

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ECLS experience at IMAEH

Dr. Sertaç Haydin presented their results and experience related to the management of complications in extracorporeal membrane oxygenation (ECMO) implementation at Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital (IMAEH). Seventy patients underwent ECMO support between March 2011 and January 2015 in this particular hospital. They changed their ECLS system from Medos Deltastream DP2 (Medos Medizintechnik AG, Stolberg, Germany) to Medos Deltastream DP3 (Medos Medizintechnik AG) after November 2012, and DP3 was used in a consecutive series of 45 patients (4.6% of all children undergoing congenital heart surgery during the same period). Their ECLS circuit consisted of a Deltastream DP3 diagonal pump head, a Hilite (Medos Medizintechnik AG) polymethylpentene diffusion membrane oxygenator, and Rheoparin (Medos Medizintechnik AG) coated tubing for both arterial and venous lines (Fig. 4). The Deltastream DP3 System can provide both nonpulsatile and pulsatile flow for pediatric ECLS. ECLS with the DP3 was performed in 45 patients. The median age and weight of the patients were 60 days (range 2–2920 days) and 3.7 kg (range 2.6–20 kg), respectively. Hemorrhage was the most common complication in patients who had successful weaning, whereas renal failure was the most common complication in unsuccessful weaning. Median ECMO duration was 5.6 days (range 4–41). ECMO was successfully discontinued (children survived and were able to maintain adequate hemodynamics more than 24 h following ECLS termination) in 31 (68.8%) patients. Nineteen (42.2%) patients survived to hospital discharge. Twelve patients (26.6%) died after successful weaning. During the study period, 13 patients received extracorporeal cardiopulmonary resuscitation (ECPR) for refractory cardiac arrest unresponsive to conventional cardiopulmonary resuscitation measures.

FIG. 1. Prof. Dr. Akcevin's welcoming remarks.

Successful weaning in this group was 53.8%, which compared favorably to a survival rate of 75% in non-ECPR patients. As a result of the shift to use DP3, revised ECMO protocol, and increased ECMO experience, significant improvement was observed in IMAEH clinical results. While the weaning success rate was 36% and the survival rate 20% before November 2012, 68.8% of patients were weaned, and 42.2% survived after this time. None of the patients experienced a mechanical component failure associated with the duration of ECLS. During the IMAEH study, the DP3 system could be used without any complications for up to 30 days.

ECLS Experience at Medipol University

Dr. Arda Ozyuksel reported their initial experience with using the CPB membrane oxygenators in the ECMO setup in a subset of patients because of reimbursement problems related to the national healthcare system (7). They connected a RotaFlow centrifugal pump (Maquet Cardiopulmonary AG, Hirrlingen, Germany) to a Capiox FX05 or Baby RX05 CPB membrane oxygenator (Terumo Inc., Tokyo, Japan) and primed the system without heparin administration. They implemented eight oxygenators in five infants without leak or hemolysis. The replaced oxygenators were used for 81, 99, and

FIG. 2. Prof. Dr. Halil Türkoğlu and Prof. Dr. Atıf Akçevin, Co-Chairs of the Eighth Istanbul Symposium.

FIG. 3. Prof. Dr. Akif Ündar's opening lecture.

76 h, respectively. According to the January 2015 Extracorporeal Life Support Organization (ELSO) summary, the overall average run time for the cardiac ECMO implementation in the newborn and infantile periods were 146.1 ± 15.1 and 146.2 ± 20.3 h, respectively (8). Therefore, this system including a CPB oxygenator (instead of a ECLS) and a centrifugal pump can be an alternative circuit in case of reimbursement difficulties or the lack of availability of polymethylpentene oxygenators as also seen in the United States (9). However, there are several limitations of this alternative circuit, including risk of more microemboli delivery to the patient due to more frequent change of oxygenators, and more circuit setup time required rather than using a ready-to-plug-in circuitry. During the discussion section of Dr. Ozyuksel's presentation, Dr. Ündar also pointed out that the cost of pediatric and adult ECLS disposables in Turkey is two to three times more expensive compared with the same manufacturers in the United States (10).

FIG. 4. ECLS experience at IMAEH.

ECLS experience at Hacettepe University

Dr. Murat Tanyildiz shared the latest ECMO experience of the Hacettepe Ihsan Dogramaci Children's Hospital which is one of the most prestigious children's hospitals in Turkey. The first ECMO was done here in the pediatric intensive care unit in 2013 as an ECPR. ECMO was implemented in 10 patients since 2013 (Fig. 5). Median age was 32 months of age (range 6 months to 14 years). Median ECMO duration time was 6 days (range 7 h to 29 days). ECMO was implemented in six cases after cardiac surgery. The most commonly observed complication was bleeding (50%) along with heparin-induced thrombocytopenia (HIT) (40%). Overall survival rate was 60%, which is one of the highest survival rates compared with the other pediatric intensive care units in Turkey (1).

FIG. 5. ECLS experience at Hacettepe University.

Outcomes of ECLS patients in Turkey

The above institutions (IMAEH, Medipol Hospital, and Hacettepe University) are the leading ECLS centers in Turkey. Their ECLS outcomes are comparable with the most recent International ELSO Registry report (8). Based on the most recent January 2015 international summary, neonatal cardiac patients' ($n = 5810$) survival to discharge rate is 41% while pediatric cardiac patients' ($n = 7314$) survival has increased to 50%. However, most of other centers' ECLS outcomes in Turkey may not be as good as the above centers as previously reported (1).

Current ventilator strategies during ECMO

Following Dr. Tanyildiz's excellent lecture, Dr. Ayda Turkoz discussed the mechanical ventilator strategies during ECMO. Current evidence suggests that recent mechanical ventilation strategies improve survival in ECMO patients (11). Before the initiation of the mechanical ventilation, the ventilation parameters should be set by considering the alveolar strain, atelectrauma, and the applications which can limit and/or prevent overdistension. First, the tidal volume should be decreased to 6 mL/kg in protective (lung recruitment) strategy and to 4 mL/kg for ultraprotective ventilation strategy (lung rest) (11). In low tidal volume strategies, plateau pressure should be set at ≤20 cm H_2O. However, it is recommended to apply a moderately high level of positive end-expiratory pressure (PEEP) (≤10 cm H_2O) during low tidal volume ventilation in order to prevent alveolar collapse and nitrogen accumulation. Moderately high PEEP levels could be dangerous in patients with heart failure and acute respiratory distress syndrome on veno-venous ECMO, and could exacerbate right ventricular dysfunction and delay heart recovery (12,13). In order to decrease pulmonary oxygen toxicity, the fraction of the inspired oxygen at the ventilator should also be reduced to the minimal value to keep arterial saturation at >85%. The respiratory rate should be reduced depending on the tidal volume and ECMO gas flow settings. In pediatric patients, the tidal volume level and physiological PEEP titration should be monitored with transpulmonary pressure and tissue oxygenation. Further advanced studies are required to determine whether the use of noninvasive ECMO with awake mechanical ventilation leads to better outcomes instead of employing invasive "lung recruitment" and "lung rest" controlled mode of mechanical ventilation strategy (12,13).

PANEL ON PEDIATRIC CARDIAC SURGERY AND PEDIATRIC CPB PROCEDURES

Dr. Halil Turkoglu shared his experiences regarding the historical development of cardiac surgery along with the CPB procedures in Turkey.

Dr. Ece Salihoglu discussed the recent updates on myocardial protection strategies in patients undergoing congenital cardiac surgery. Although a different management strategy is deemed necessary in pediatric cardiac surgery, most of the centers implemented myocardial protection methods with regard to their experience derived from adult cardiac surgery in the past. Normothermic CPB is not a routinely used technique in the era of congenital heart surgery; however, mild hypothermia is frequently used in simple procedures. Normothermic or hypothermic blood cardioplegia is the most frequent administration method in order to arrest the heart. However, in complex cardiac surgeries, a single or double-dose

administration of Del Nido (Compass-Baxter Healthcare Inc., Edison, NJ, USA) or HTK-Custodiol (Koehler Chemi, Alsbach-Haenlien, Germany) cardioplegia solutions provide a better myocardial protection along with a blood-free exposure of the cardiac chambers (14–16). The Del Nido cardioplegia protocol is not extensively used in Turkey, probably due to lack of regular procurement of the ingredients and proper delivery equipment. However, after a long period of experience in transplantation surgery, HTK-Custodiol solution has gained popularity in myocardial protection of the patients undergoing congenital cardiac surgery. The inevitable advantages of single or double-dose administration of these solutions include better myocardial protection along with a bloodless surgical exposure; however, increased familiarity of the surgical team and decreased costs of the solutions are mandatory in order to set a routine-based algorithm.

During the afternoon session, Dr. Alican Hatemi gave a speech on systemic inflammation during CPB. Following the general overview of CPB-induced systemic inflammation, the content was focused on "Blood-Surface Interactions and Aggregation of Serum Proteins during Extracorporeal Circulation." Based on the preliminary data of their research investigating the cause of the biochemical, immunologic, and clinical differences between phosphoryl choline-coated and conventional/noncoated extracorporeal circulation systems, Dr. Hatemi's group shifted their research through the etiology of these differences, by analyzing the protein aggregates on the extracorporeal circulation systems. Prominent protein bands present on the phosphoryl choline-coated lines but missing on the noncoated tubings were visualized and they were excised from the SDS-PAGE (Bio-Rad Laboratories, Hercules, CA, USA) electrophoresis gels, then were extracted and identified by MALDI-TOF (AB Sciex, Framingham, MA, USA) with Mascot software (Matrix Science Inc., Boston, MA, USA)—Swissport database (17). These preliminary data will be used for subsequent research activities on the development of modified extracorporeal circulation systems, aiming to reduce CPB induced inflammatory response.

Dr. Alkan-Bozkaya gave a lecture about the biomarkers used as early predictors for organ damage after cardiac surgery in pediatric population and she also mentioned their experience with the combined clinical application of routinely performed patient monitorization techniques in their cardiac surgery center at Medipol University (18).

International congenital cardiac surgery patients in Turkey

Dr. Salihoglu gave an informative speech about the cardiac surgery candidates admitted from foreign countries to congenital heart surgery centers. The contract-based patient admission program was initiated in 2009 with foreign congenital cardiac surgery candidates in Turkey. More than 6000 patients have been operated in eight cardiac surgery centers since this agreement was signed. The overall mortality is reported to be 1.7 to 5% (personal communication with all eight centers by Dr. Salihoglu). Eighty-five percent of the patients were admitted from Middle East countries, 10% from North Africa and Libya, and the rest of them from middle-Europe and Turkic Republics. The majority of the patients received healthcare with regard to the agreements signed with the Ministry of Health in the above-mentioned countries. These patients need detailed organization in terms of preoperative evaluation and accommodation along with their relatives, as well as postoperative discharge and follow-up. Moreover, infectious diseases that prohibit a fast-track surgical treatment are frequent in this patient population. There are basically two types of patients in this population: infants and children with congenital heart diseases, and adults with acquired cardiovascular diseases. Most of the patients in these population have congenital heart diseases; however, unusually late presentations such as tetralogy of Fallot in the fourth decade might be encountered. Unfortunately, some of these patients have significant adverse effects of the long-lasting morphological cardiac abnormalities, especially irreversible pulmonary hypertension and resultant Eisenmenger's Syndrome. Chromosomal abnormalities, congenital diseases other than the cardiovascular system, malnutrition, and chronic infections are common problems among these patients. The most common diagnosis among the adult patients are ischemic heart diseases and valvular pathologies; however, significant comorbidities such as uncontrolled diabetes mellitus, chronic renal failure, peripheral arterial disease, chronic obstructive pulmonary disease, congestive heart failure associated with diminished ventricular function, and obesity are encountered as well. In the last decade, Turkey has become an important destination for foreign cardiac surgery candidates, with increased experience of the cardiac centers related to preoperative evaluation of the diseases, management of the comorbidities, effective planning of the surgical treatment, and a well-scheduled follow-up program.

Biomedical engineering

During the meeting, Dr. Kerem Pekkan, the principal investigator of a recently established bioengineering research laboratory at Koc University, presented their current work dedicated to congenital heart disease patients and pediatric cardiovascular engineering. The Pekkan laboratory is supported by the European Research Council and European Molecular Biology Organization (EMBO) and National Science Foundation that houses state-of-the-art experimental and computational infrastructure for conducting multidisciplinary research that is valuable for clinicians, with the objective of improving the health and quality of life of children who suffer. Current research activities of this laboratory are: embryonic cardiovascular mechanics (19); pediatric and adult congenital heart diseases (20,21); reproductive biomechanics and cardiovascular maternal health (22); and bio-inspired engineering analysis and design (23).

ROLE OF PERFUSIONISTS DURING ECLS AND CPB ALONG WITH HANDS-ON WET-LABS

The last panel of the symposium was about the role of perfusionists during ECLS and CPB along with hands-on wet-labs. Perfusionist Halime Erkan from IMAEH presented their pediatric CPB protocol (24–26). Since 2010, 1500 congenital cardiac cases were performed at the IMAEH. Capiox FX05 oxygenators with integrated arterial filters were used during this time period. Before 2014, the main strategy for pediatric CPB was moderate to deep hypothermia, then it was changed to normothermic CPB. Their group started to use cold crystalloid cardioplegia (Custodiol) instead of cold blood in the second half of 2014, and they also added pulsatile flow to these changes. Inotrope doses decreased dramatically following this protocol. Cardiac recovery following cross-clamp release improved and the need for ultrafiltration during or after CPB decreased. Perioperative and postoperative course has become more straightforward. It is likely that a better pediatric CPB strategy is possible with normothermic pulsatile flow by using a pediatric oxygenator with an integrated arterial filter. This could benefit by the addition of Custodiol in terms of decreasing myocardial edema and providing a clear surgical field.

Perfusionist Aydin Kahraman from Medipol University gave a speech on common complications encountered during the implementation of ECMO, primarily focusing on the air embolism arising from the equipment. Perfusionist Sibel Aydin from Kartal Kosuyolu Thoracic and Cardiovascular Surgery Training and Research Hospital also shared the most recent ECLS results in pediatric patients (1).

Poster presentations were moderated by Drs. Alkan-Bozkaya and Ersoy. At the end of the meeting, a practical approach for the setting and priming of the pediatric ECMO system was implemented at the "wet-labs" for perfusionists. A multimedia DVD including the ECMO circuit setup and priming, along with several recent ECLS publications was also shared with all participants at the eighth symposium.

Artificial Organs

Based on Dr. Malchesky's recent editorial entitled "Artificial organ technologies around the world," Turkish cardiovascular clinicians and scientists submitted articles to *Artificial Organs* as first authors between 2004 and 2013 more than most countries (27). In fact, Turkey was listed as seventh (after USA, Japan, China, Germany, Korea, and Italy) out of 57 countries. In a separate study, Dr. Altan Onat from Istanbul University pointed out that *Artificial Organs* is the #10 most frequently published journal by Turkish cardiovascular clinicians in 2013 (28).

CONCLUSIONS

During the past 3.5 years, outcomes of pediatric CPB and ECLS patients were improved by a multidisciplinary team approach in Turkey. In particular, a few ECLS centers now have similar survival rates with the ELSO centers. More clinicians prefer "evidence-based approach" for selecting the CPB and ECLS disposables and techniques for their patients ever than before. *Artificial Organs* is one of the leading journals for cardiovascular clinicians and scientists in Turkey as well. Istanbul symposiums will continue to train more young clinicians and scientists for pediatric cardiovascular research in Turkey.

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