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Lessons learned from ECMO support in pediatric patients with D-transposition of the great arteries: preoperative, intraoperative and postoperative

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ABSTRACT

Background Extracorporeal membrane oxygenation (ECMO) support on D-transposition of the great arteries (D-TGA) carries formidable challenges.

Methods A retrospective study was performed on pediatric patients with D-TGA supported by ECMO from July 2007 to December 2019. This study summarized the clinical experience of ECMO support in pediatric patients with D-TGA preoperative, intraoperative, and postoperative.

Results Overall, 16 children with D-TGA received ECMO support during this period. Two (2 of 16) were supported before cardiac surgery, 3 (3 of 16) were supported postoperatively in the intensive care unit, and 11 (11 of 16) failed to wean off cardiopulmonary bypass. Two cases of preoperative ECMO support for patients with D-TGA with an intact ventricular septum and restrictive atrial septum due to severe hypoxemia died. In this study, D-TGA with coronary artery malformation and other complicated deformities died (8 of 14), whereas uncomplicated D-TGA without coronary artery malformation all survived (6 of 14). The wean-off rate of ECMO patients supported in D-TGA was 62.5% (10 of 16), while the 30-day survival rate was 44% (7 of 16).

Conclusion Although a promising ECMO weaning rate was obtained, 30-day survival of this population was frustrating, mainly attributed to the original anatomy of coronary arteries and the concomitant deformities.

Summary box

What is already known about this subject?

- Extracorporeal membrane oxygenation (ECMO) is an effective support for severe conditions of congenital heart diseases perioperatively.
- While there are minimal reports on ECMO in D-transposition of the great arteries (D-TGA) in preoperative patients, there are more data on ECMO use in postoperative D-TGA.

What are the new findings?

- Management of ECMO support in patients with D-TGA is complicated.
- Coronary abnormalities and other concomitant deformities had an influence on the outcomes of the patients with D-TGA in the neonatal/infant intraoperative and postoperative subgroup.

How might it impact on clinical practice in the foreseeable future?

- Multiple imaging analysis of coronary artery both preoperative and on ECMO should be applied to improve survival rate in patients.
- Mode of ECMO support as well as the timing of the arterial switch operation may contribute to favorable outcome.

INTRODUCTION

D-transposition of the great arteries (D-TGA) is one type of cyanotic congenital heart disease that requires communication between systemic and pulmonary circulation for survival.[1 2] The initial clinical course, especially in patients with a restrictive atrial and intact ventricular septum (IVS), is often dramatic with a need for prostaglandin (PG) infusion to maintain an open arterial duct or balloon atrioseptostomy (BAS) and obtain hemodynamic stabilization. In institutes which are unable to execute BAS, a restrictive atrial and IVS may portend severe hypoxemia and unstable systemic circulation.[3] Since the first successful procedure of arterial switch operation (ASO) by Adib Jatene in 1975, it is now the standard treatment for D-TGA with the IVS (D-TGA/IVS) in the first few weeks of life.[4 5] Attributed to ASO, the mortality of D-TGA has been improved to over 90%. However, low cardiac output is the major cause of postcardiotomy death. Extracorporeal membrane oxygenation (ECMO) is a widely used mechanical support for severe cardiac or pulmonary failure in children.[6 7] Without the utilization of pediatric ventricular assist devices in China, ECMO remains the primary modality of mechanical support for neonatal and pediatric patients. Clinical experience in ECMO support with preoperative D-TGA is limited in current works of literature except

for a few case reports. We retrospectively summarized the clinical experience of ECMO support in pediatric patients with D-TGA.

METHODS

Patients

From July 2007 to December 2019, data of consecutive patients receiving a veno-arterial ECMO (VA-ECMO) or veno-venous ECMO (VV-ECMO) for pediatric ECMO patients supported in D-TGA were collected retrospectively in an affiliated university children's hospital. In this study, patients were divided into three subgroups: preoperative, postoperative neonatal/infant support (including intraoperative and postoperative) and late repair.

ECMO indication and management

Indications, implantation and routine management of VA-ECMO were as previously described.[8] The clinical criteria for respiratory failure requiring ECMO include DA–aO_2>605–620 torr for 4–12 hours, oxygenation index >35–60 for 0.5–6 hours, arterial oxygen pressure (PaO_2) <60 mmHg for 2–12 hours, metabolic acidosis and shock (pH <7.25 for 2 hours or with hypotension), and acute deterioration (PaO_2 <40 mmHg).[9] VV-ECMO implantation was performed via the right internal jugular vein with double lumen cannula.

Hemostatic management

In general, the activated clotting time was targeted to 160–200 s. The hematocrit was maintained at 30%–40% by packed red blood cell transfusion. Platelets were transfused when the patient's platelet count decreased to <100 × 10^9/L. Fibrinogen level was kept above 1.0 mg/dL. However, for those who failed to wean off cardiopulmonary bypass (CPB), bleeding was the major issue during the first 24 hours after surgery. Therefore, in case of massive bleeding, anticoagulation (heparin) administration was delayed until bleeding was under control; meanwhile, coagulation components, such as prothrombin complex and fresh frozen plasma, were transfused.

Definitions and data acquisition

All clinical variables of patients requiring ECMO support were collected retrospectively from our institutional database and from extracorporeal life support registry form files. The detailed definitions of coronary abnormalities are as previously described.[10] Other complicated deformities refer to the coexisting congenital cardiac malformations. Renal failure was defined as the presence of oliguria (<0.5 mL/kg/hour) or a tripling of creatinine value or with demand for hemodialysis. Neurological complications were recorded in the presence of clinical symptoms (eg, seizure, motor dysfunction, or radiological evidence for neurological deficit) or defect (eg, bleeding, stroke, or severe cerebral edema). Infection was diagnosed from positive blood cultures or sputum cultures that were ordered at the discretion of the treating intensivist. Vasoactive-inotropic score (VIS) was calculated as previously described.[8] Early mortality is defined as 30-day mortality after ECMO weaning, whereas late mortality is defined as death occurred more than 30 days after ECMO weaning. Intractable bleeding is defined as follows: surgical site bleeding that is unexpected and is prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associated reduction in hemoglobin level of at least 20 g/L (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 hours to the bleeding.[11]

Statistical analysis

Statistics were performed using the SPSS statistical software package (V.19; IBM). Shapiro-Wilk test was used to test the normality of the distribution. Continuous variables with normal distribution are expressed as mean±SD. Data with normal distribution were analyzed using t-test for two independent samples. Categorical variables were expressed as percentages and were analyzed using Fisher's exact test. All other data are described as medians [interquartile range (IQR)] and compared using a nonparametric test.

RESULTS

From July 2007 to December 2019, 43 children with congenital heart diseases received ECMO support, including 16 patients diagnosed with D-TGA. VA-ECMO was established in 15 patients, while VV-ECMO was run in the one with severe hypoxemia before surgery. The patients' ages ranged from 1 day to 3.5 years, with a median age of 0.75 months (IQR 0.1–1.28 months). Median weight was 3.35 kg (range from 2.7 to 11 kg, IQR 2.8–4.38 kg). Two (2 of 16) were supported before cardiac surgery, 3 (3 of 16) were supported postoperatively in the intensive care unit (ICU) including 1 case of extracorporeal cardiopulmonary resuscitation, and 11 (11 of 16) failed to wean off CPB. Pre-ECMO average VIS was 42±3, and pre-ECMO average lactate peak level was 10.8±1.6 mmol/L. Median ECMO duration was 85.5 hours (IQR 33.3–104.8 hours), ranging from 15 to 300 hours, and the median length of hospital stay was 23 days (IQR 17–62 days), ranging from 2 to 96 days. For those who underwent cardiac surgery, the mean CPB time was 294±17 min, and the mean aortic cross-clamp time was 128±9 min.

The wean-off rate of ECMO patients supported in D-TGA was 62.5% (10 of 16), while the 30-day survival rate was 44% (7 of 16). All coronary artery anatomy and concomitant deformities were confirmed by both echocardiography and CT angiography (CTA) before surgery. The anatomy of the patients was further confirmed during the surgical procedure. Patients on ECMO did not have an evaluation of coronary artery after surgery

via CTA or cardiac catheterization to diagnose residual lesions or other unrecognized pathologies. Demographic data and characteristics of this cohort are shown in table 1. Fourteen patients including both intraoperative and postoperative underwent arterial switch operation. Late arterial switch surgery was performed in a 4-year-old patient with D-TGA/IVS who was also diagnosed with left ventricular outflow tract obstruction (LVOTO), while other TGA/IVS cases were done within 2 weeks after birth. In the neonatal/infant intraoperative and postoperative subgroup, 7 of 13 patients had associated deformities (coronary and/or other associated anatomic lesions) and all 7 died. The other six patients had no associated deformities, and all survived. The most common complication was surgical site bleeding with an occurrence rate of 44%, followed by pneumorrhagia (19%), cannula site bleeding (19%), hemolysis (19%), infection (19%), disseminated intravascular coagulation (DIC) (6%) and renal failure (6%). Therefore, bleeding was intractable after surgery, which required transfusion of blood products, prothrombin complex concentrate as well as fibrinogen concentrate. Exploratory thoracotomy was implemented in surgical bleeding cases. In the meantime, intravenous heparin administration was delayed until bleeding was under control. Comparison of survivors and non-survivors in the neonatal/infant subgroup, both intraoperative and postoperative, was demonstrated in table 2. Concomitant deformities including coronary artery abnormalities and other deformities in this subgroup have a significant difference between survivors and non-survivors, but coronary artery abnormalities alone failed to reach statistical significance (p=0.07).

Early mortality

Out of 16 patients, 9 patients (56.3%) died within 30 days after ECMO weaning, including 2 preoperative cases.

Patients 1 and 2 were diagnosed with D-TGA/IVS with restrictive atrial septum who received ECMO support preoperatively. Patients presented with progressive hypoxemia after birth. Despite the initiation of intubation and PG E1 administration, a significant escalation in support, but no BAS was available in our hospital. Patient 1 who was supported by VV-ECMO on day 3 failed to establish adequate ECMO flow with an inappropriate double lumen cannula. Patient 2 initiated VA-ECMO on day 1 with the onset of cardiogenic shock. Pneumorrhagia occurred in the VA-ECMO neonate because of ECMO over perfusion to the lung through patent ductus arteriosus, which was near the arterial cannulation. The reflux of pulmonary flow was congested owing to restrictive atrial septum, leading to poor ECMO circulation flow.

Patients 6 and 7 were diagnosed with D-TGA with intramural left coronary artery. After revision of the left coronary artery, patients failed to wean from bypass and required ECMO support. ECMO was terminated because there were no signs of myocardial recovery.

Patient 8 was diagnosed with D-TGA with IAA. The patient died of anastomotic surgical bleeding 9 days after ECMO weaning.

Patient 11 was diagnosed with D-TGA with coarctation. This neonate went through bypass for more than 7 hours and was supported with a large dose of inotropes (VIS 96) for 12 hours after surgery. Then, the patient suffered cardiac arrest in the ICU, and ECMO was immediately initiated. However, ECMO was discontinued because of multiorgan failure and DIC.

Patient 12 was diagnosed with D-TGA with IAA. This neonate failed to wean off bypass and was switched to ECMO. Late intervention of thoracotomy for bleeding led to cardiac tamponade. ECMO was discontinued because of no myocardial recovery after this event.

Patient 13 was diagnosed with D-TGA with solitary coronary artery. The patient underwent uneventful surgery but with delayed sternal closure and died of sepsis on the 8th postoperative day.

Patient 15 was diagnosed with D-TGA with intramural left coronary artery. The patient died of sudden cardiac arrest 25 days after ECMO weaning.

Late mortality

The 42-month-old patient (patient 4) diagnosed with TGA/IVS, atrial septal defect (ASD), and LVOTO underwent late arterial switch procedure, but his left ventricle failed to adapt to high afterload postoperatively in the ICU. Twelve days after ECMO weaning, the patient suffered cardiogenic shock and was supported by left ventricular assist device (LVAD) (CentriMag) for 10 days. Afterward, the patient was successfully extubated, but he died 50 days after weaning off ECMO with signs of severe heart failure (massive pleural effusion and chylothorax).

DISCUSSION

In this study, we failed to support adequate circulation despite the use of ECMO in two cases with a preoperative diagnosis of D-TGA/IVS with restrictive atrial septum and without atrioseptostomy. We found coronary abnormalities and other concomitant deformities had an influence on the outcomes of the patients with D-TGA in the neonatal/infant intraoperative and postoperative subgroup. Although a promising ECMO weaning rate was obtained, 30-day survival of this population was frustrating.

Usually, cyanosis occurs within a few days after newborns with D-TGA/IVS were born. Among these, neonates with reduced pulmonary and systemic blood mixing opportunities (TGA-IVS with restrictive foramen ovale and/or closure of the ductus arteriosus) become symptomatic with extreme cyanosis early after birth, leading inevitably to severe hypoxia and acidosis.[12] Most of these neonates can be stabilized until their arterial switch operations by means of PG and BAS, while in some institutions the BAS cannot be fulfilled in cath lab. At the most severe end of the spectrum, progressive

Table 1 Demographic data and characteristics of pediatric patients with D-transposition of the great arteries supported by ECMO

No.	Diagnosis (preoperative)	Operation	Age	Weight (kg)	Location/mode of ECMO	Indication for ECMO	Duration on ECMO (h)	Successful decannulation	Outcome
Preoperative									
1	TGA, restrictive ASD, PDA		3 d	2.7	ICU/VV-ECMO	Hypoxemia	15	No	Death
2	TGA, restrictive ASD, PDA		1 d	3.5	ICU/VA-ECMO	Hypoxemia	21	No	Death
Postoperative									
3	TGA, VSD, ASD, PDA	ASO, VSD repair, ASD repair, PDA ligation	1 mon	4.5	OR/VA-ECMO	Failure to wean off CPB	71	Yes	Discharge
4	TGA, ASD, LVOTO	ASO, ASD repair, LVOT fibromyectomy	3 y 6 mon	11	ICU/VA-ECMO	Low cardiac output	72	Yes	Death
5	TGA, ASD, PDA	ASO, ASD repair, PDA ligation	3 d	3	OR/VA-ECMO	Failure to wean off CPB	85	Yes	Discharge
6	TGA, ASD, PDA, intramural left coronary artery	ASO, ASD repair, PDA ligation	3 d	3	OR/VA-ECMO	Failure to wean off CPB	108	No	Death
7	TGA, VSD, ASD, PDA, intramural left coronary artery	ASO, VSD repair, ASD repair, PDA ligation	15 d	2.7	OR/VA-ECMO	Failure to wean off CPB	300	No	Death
8	TGA, IAA, VSD, PDA	ASO, aortic arch reconstruction, VSD repair, PDA ligation	1 mon 12 d	2.7	OR/VA-ECMO	Failure to wean off CPB, hypoxemia	67	Yes	Death
9	TGA, ASD, PDA	ASO, ASD repair, PDA ligation	3 d	2.8	OR/VA-ECMO	Failure to wean off CPB	86	Yes	Discharge
10	TGA, VSD, ASD, PDA	ASO, VSD repair, ASD repair, PDA ligation	1 mon 6 d	4	OR/VA-ECMO	Failure to wean off CPB	22	Yes	Discharge
11	TGA, coarctation, VSD, PDA	ASO, aortic arch reconstruction, VSD repair, PDA ligation	1 mon 21 d	3.5	OR/VA-ECMO	Cardiac arrest	19	No	Death
12	TGA, IAA, VSD, PDA	ASO, aortic arch reconstruction, VSD repair, PDA ligation	6 d	4.5	OR/VA-ECMO	Failure to wean off CPB	169	No	Death
13	TGA, VSD, ASD, PDA, tricuspid regurgitation, solitary coronary artery	ASO, VSD repair, ASD repair, PDA ligation, tricuspid valvuloplasty	1 mon 9 d	3.5	OR/VA-ECMO	Failure to wean off CPB	89	Yes	Death
14	TGA, VSD, ASD, PDA	ASO, VSD repair, ASD repair, PDA ligation	1 mon 6 d	3.2	OR/VA-ECMO	Failure to wean off CPB	142	Yes	Discharge
15	TGA, VSD, ASD, PDA, intramural left coronary artery	ASO, coronary artery bypass grafting, VSD repair, ASD repair, PDA ligation, pacemaker implantation	1 mon 3 d	4.7	ICU/VA-ECMO	Low cardiac output	95	Yes	Death
16	TGA, ASD, PDA	ASO, ASD repair, PDA ligation	9 d	2.8	OR/VA-ECMO	Failure to wean off CPB	92	Yes	Discharge

ASD, atrial septal defect; ASO, arterial switch operation; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; IAA, interruption of aortic arch; ICU, intensive care unit; LVOTO, left ventricular outflow tract obstruction; OR, operation room; PDA, patent ductus arteriosus; TGA, transposition of the great arteries; VA-ECMO, veno-arterial ECMO; VSD, ventricular septal defect.

Table 2 Comparison of survivors and non-survivors in neonatal/infant subgroup, both intraoperative and postoperative

Characteristics	All (n=13)	Survivors (n=6)	Non-survivors (n=7)	P value
Age (mon), mean±SD	0.8±0.2	0.7±0.2	0.9±0.2	0.463
Gender (male), n	11	5	6	1.0
Weight (kg), mean±SD	3.5±0.2	3.4±0.3	3.5±0.3	0.769
Coronary artery abnormalities, n	4	0	4	0.07
Concomitant deformities, n	7	0	7	0.001*
CPB time (min), mean±SD	303±15	298±13	307±26	0.139
Cross-clamp time (min), mean±SD	130±10	116±16	142±12	0.721
VIS before initiation of ECMO, mean±SD	41±4	36±7	45±4	0.277
VIS on ECMO, mean±SD	32±3	31±6	34±4	0.705
ECMO duration (d), mean±SD	89±21	83±16	121±34	0.363
Ventilation time (d), mean±SD	19±4	18±6	19±6	0.914
ICU stay (d), mean (IQR)	23 (18–56)	20 (14–61)	19 (12–38)	0.073
Hepatic failure, n	1	0	1	1.0
DIC, n	1	0	1	1.0
Bleeding events, n	9	3	6	0.266
Hemolysis, n	2	2	0	0.192
Infections, n	2	0	2	0.462

Concomitant deformities include coronary artery abnormalities and other deformities (such as interruption of aortic arch and coarctation).
*P<0.05.
CPB, cardiopulmonary bypass; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; VIS, vasoactive-inotropic score.

cardiogenic shock occurs in patients with a high risk of end-organ injury, even cardiac arrest. In this condition, patients are unsuitable to undergo the surgery immediately and require extracorporeal oxygenation support preoperatively.[13] Unfortunately, only a few successful reports are available on these patients.[14] Although two preoperative ECMO supports failed in our study, lessons learned still need to be discussed for future success. A thoughtful approach with regard to the mode of support (veno-arterial vs veno-venous), management of extracorporeal support, as well as the timing of the arterial switch operation, may be beneficial for the outcome of patients. For example, atrioseptostomy cannot be performed in our center; so we will evaluate the neonates with D-TGA/IVS and restrictive atrial septum immediately after they are born, and decision for surgery will be made as soon as it is on demand. For the patient presenting with progressive hypoxemia and cardiogenic shock leading to oxygen debt, VA-ECMO was the first choice for saving multiple end-organ failure. On the other hand, if the patient's cardiac function was stable, veno-venous support may be beneficial. First, it returns oxygenated blood to the right atrium, where most of it enters the right ventricle (RV) and aorta. Second, placing the ECMO circuit in parallel to the systemic circulation is physiologically identical to the TGA post-BAS condition. Third, it spares the carotid artery by internal jugular vein cannulation. Once the patient's hemodynamic condition is stable and oxygen debt is paid off after a short duration of support (mainly lasting more than 24 hours), the arterial switch operation can be scheduled to avoid complications related to the support.

Some patients with D-TGA need cardiopulmonary function support due to left ventricular dysfunction or to combined pulmonary hypertension. For these patients, VA-ECMO can provide whole cardiac and pulmonary function assistance to help them overcome difficulties. For simple D-TGA with left ventricular dysfunction, there are two main reasons for the reversible low left ventricular cardiac output following ASO: first, myocardial ischemia/reperfusion injury during extracorporeal circulation surgery leads to cardiac dysfunction; second, the postoperative left ventricle was the original functional RV, which functioned as RV with low afterload before surgery and could not adapt to the left ventricular function of the systemic circulation with much higher afterload after surgery. Such patients with D-TGA with satisfying surgical correction have good coronary artery blood supply but are temporarily unable to adapt to systemic circulation load. Although the temporary cardiac function is severely impaired, it can generally recover within 4–6 days after ECMO support.[15] However, the morbidity and mortality of children with D-TGA combined with coronary artery malformations (including intramural, solitary coronary artery, and mono-coronary ostium) are high.[4 16–18] In these cases, coronary artery transfer is difficult, and it is probable to cause myocardial ischemia due to cardiac infarction of the distal portion. Therefore, the mortality

of the patients is greatly increased and the outcome of ECMO support is also unsatisfactory. Coronary problems, such as kinking, stretching, or thrombosis, will have a profound effect in these patients, and even sudden cardiac death may occur after ECMO weaning.[18] For such cases, there is a great challenge for the surgeon, and it is necessary to fully evaluate the satisfaction of the coronary artery transfer operation when considering the ECMO indications. It has been reported that patients who require postoperative ECMO and undergo cardiac catheterization or CTA for diagnosing residual lesions or other unrecognized pathologies have better outcomes. And, the sooner the better.[19 20] Unfortunately, our patients in this study had not undergone cardiac catheterization or CTA on ECMO, which should be changed in the future.

TGA combined with LVOTO as well as aortic arch deformity are risk factors of ASO death.[21–24] TGA with aortic arch obstruction (AAO) is of low incidence in congenital heart diseases. Among these cases, TGA combined with IAA is even more scarce, and only limited cases were reported. Patients in the single-stage repair of TGA and IAA that requires the aortic arch reconstruction combined with arterial switch operation have been reported to have high mortality. The rate of RV hypoplasia for TGA with AAO is higher than the isolated TGA. Therefore, primary biventricular repair of TGA associated with AAO and RV hypoplasia requires ECMO support due to high mortality and postoperative right ventricular failure.[22 25] TGA with aortic arch malformation had prolonged operation time, prolonged hypoperfusion time, difficult bleeding control and pulmonary hypertension.[26] With concomitant repair of AAO, surgery was performed with CPB using profound hypothermic selective cerebral perfusion, and usually was accompanied by lactate elevation. If patients require a high dose of inotropes to maintain the hemodynamic stability after surgery, the initiation of ECMO should be considered as soon as possible. It is difficult to maintain adequate ECMO flow due to massive bleeding after surgery, but the oxygen debt needs to be paid off with the augmented flow as soon as possible.

Late ASO repair is challenging. Over time, the left ventricle has less chance to function as a systemic ventricle of the whole body. ECMO support could be helpful to support left ventricle for adaptation to elevated afterload. The key point for the survival of this group of ECMO patients is whether left ventricle remodeling induced by low afterload causes intrinsic change in left ventricle myocardial properties. Some patients may need long-term ventricular support, while in these cases, switching ECMO into LVADs might be an option.[27]

In conclusion, ECMO could be an effective modality for cardiac failure as well as hypoxemia in pediatric patients with D-TGA before cardiac surgery. A promising ECMO weaning rate was obtained but the 30-day survival rate in this population was frustrating, mainly attributed to the original anatomy of coronary arteries and concomitant deformities. Of note, preoperative ECMO support is challenging in patients with D-TGA with intact ventricular septal defect and restrictive ASD. A thoughtful approach with regard to the mode of support, management of extracorporeal support, as well as the timing of the arterial switch operation may contribute to favorable outcome.

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Patient consent for publication The ethical standards of the institutional research committee granted permission to access and to analyze the data with a waiver of informed consent because this is a retrospective analysis of the collected data.

Ethics approval This study was approved by Zhejiang University School of Medicine Children's Hospital Committee on Clinical Investigation (No.2021-IRB-051).

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