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Case Report

Use of Low-Molecular-Weight Heparin for Right Atrial Thrombus Following Extracorporeal Membrane Oxygenation in Neonates after Surgical Repair of Congenital Diaphragmatic Hernia: A Case Report and Review of the Literature

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Abstract

Some critically ill neonates with congenital diaphragmatic hernia (CDH) require extracorporeal membrane oxygenation (ECMO) during the perioperative period. Neonates on ECMO face a significantly increased risk of thrombotic events. Thrombosis management varies across centers and may include anticoagulation, thrombolysis, or thrombectomy. We present our experience using low molecular weight heparin (LMWH) to treat a right atrial thrombus (RAT) following ECMO in a neonate with CDH.

Keywords

low molecular weight heparin; congenital diaphragmatic hernia; neonates; extracorporeal membrane oxygenation; right atrial thrombus

Introduction

Congenital diaphragmatic hernia (CDH) is a rare congenital anomaly characterized by diaphragmatic hypoplasia and abdominal organs herniating into the thoracic cavity. The prevalence of CDH is approximately 2.3 per 10,000 live births [1]. In some cases, critically ill neonates require emergency surgery and extracorporeal membrane oxygenation (ECMO) support due to cardiopulmonary insufficiency and circulatory failure. While ECMO can be lifesaving for neonates with severe CDH, its associated complications substantially reduce survival rates [2]. Dalton *et al.* [3] reported a 60% incidence of thrombus formation in neonates with CDH undergoing ECMO (n = 159). Treatment options for intracardiac thrombi in neonates include observation, anticoagulation, thrombolysis, and thrombectomy, with the choice of treatment tailored to the patient's specific conditions [4]. We report the case of a neonate with severe CDH who developed a right atrial thrombus (RAT) post-ECMO, which completely resolved after seven days of anticoagulant treatment with low-molecular-weight heparin (LMWH).

Case Report

A male neonate was delivered by cesarean section at 38 + 1 weeks, weighing 3.605 kg, with Apgar scores of 9 at 1 minute and 10 at 5 minutes. Prenatal ultrasound revealed CDH with a lung-to-head ratio of 2.4. Shortly after birth, the neonate experienced shortness of breath and required oxygen via a nasal catheter. Owing to worsening respiratory distress, he was intubated and placed on mechanical ventilation in synchronized intermittent mandatory ventilation (SIMV) mode with a respiratory rate (RR) of 35 breaths/min, peak inspiratory pressure (PIP) of 18 cm H_2O, positive end-expiratory pressure (PEEP) of 4 cm H_2O, and an inspiratory time (Ti) of 0.4 seconds. He was then transferred to our neonatal intensive care unit (NICU). A thoracic ultrasound confirmed a left-sided CDH with a defect measuring 3.5 × 4.1 cm, which allowed herniation of the gastric cavity, intestinal canal, and spleen into the thoracic cavity. Transthoracic echocardiography (TTE) revealed a ductus arteriosus of 0.5 cm with a right-to-left shunt, a pulmonary artery pressure of 70 mmHg, and a left ventricular ejection fraction (LVEF) of 65%. An electrocardiogram (ECG) indicated a first-degree atrioventricular block. The patient underwent successful repair of the left diaphragmatic hernia on the first day after birth.

Two hours post-surgery, the patient exhibited a sudden decrease in heart rate to 70–85 bpm, accompanied by a second- to third-degree atrioventricular block on the ECG. TTE revealed a left ventricular EF of 45% and an estimated pulmonary artery pressure of 58 mmHg. The patient subsequently developed ventricular fibrillation and required resuscitation with bedside defibrillation at 7 joules. Managing the patient's condition was challenging due to severe pulmonary hypertension and severe cardiac arrhythmias, making the restoration of sinus rhythm and the sta-

Table 1. Changes in the values of various coagulation tests following UFH dose adjustment during ECMO.

Days during ECMO (d)	1					2				3		
UFH dose (U/kg/h)	14.8	14.8	8.7	8.7	8.7	14.8	14.8	8.7	8.7	6.0	6.0	6.0
ACT (s)	262.0	248.0	238.0	204.0	175.0	168.0	192.0	245.0	225.0	196.0	186.0	175.0
APTT (s)	>180.0	175.0	>180.0	>180.0	68.9	50.0	78.0	79.8	83.0	92.0	68.7	60.3
D-dimer levels (ug/mL)	0.2	0.3	3.5	9.4	14.2	12.7	20.3	17.0	16.7	20.0	19.0	16.7
FIB (g/L)	0.8	0.9	0.8	2.0	2.3	2.0	1.4	1.0	0.8	0.6	0.6	0.6
FDP (ug/mL)	0.8	0.5	12.6	38.1	56.0	42.4	61.5	44.4	51.6	81.4	60.4	70.4

ECMO, extracorporeal membrane oxygenation; UFH dose, unfractionated heparin dose; ACT, activated clotting time; APTT, active partial thromboplastin time; FIB, fibrinogen; FDP, fibrinogen degradation products.

UFH continuous intravenous pumping. Coagulation tests measurement per 6 hours.

bilization of hemodynamics difficult. Blood gas analysis revealed a pH of 7.423, a PaO_2 of 38.5 mmHg, a $PaCO_2$ of 69.2 mmHg, and a lactate level of 2.9 mmol/L. Given the severity of the patient's condition, ECMO was initiated with an oxygen index (OI) of 47. An 8 Fr arterial cannula was inserted into the right common carotid artery at a depth of 3 cm, and a 10 Fr venous cannula was placed in the right internal jugular vein at a depth of 7 cm. TTE and bedside chest X-ray confirmed correct cannula positioning. The ECMO circuit employed consisted of a ROTAFLOW Centrifugal Pump (Maquet Cardiopulmonary GmbH; Lot Number: 3000248858; Kehler Strasse, Rastatt, Germany) and a Medos hilite LT Oxygenator (Medos Medizintechnik AG; Lot Number: 190516M779; Xenios AG, Heilbronn, Germany). It was prepared with 150 mL of a compound electrolyte solution and operated with a flow fluctuation of 0.45 L/min and a centrifugal pump rotation speed of 2280 rpm. The initial unfractionated heparin (UFH) dose target was set at 15 U/kg/h, adjusted based on activated clotting time (ACT) and active partial thromboplastin time (APTT) values. Coagulation tests were conducted every 6 hours, aiming for an ACT of 180–220 seconds and an APTT of 60–80 seconds (Table 1).

At the sixtieth hour of ECMO, the heart rate stabilized within the range of 120–130 bpm, and no further arrhythmias occurred. The patient's blood pressure fluctuated between 89–95/51–59 mmHg. Blood gas analysis revealed a pH of 7.469, a PaO_2 of 165 mmHg, a $PaCO_2$ of 43.7 mmHg, and a lactate level of 1.7 mmol/L. TTE revealed that the pulmonary artery pressure had decreased to 40 mmHg, with an LVEF of 56%. ECMO was terminated at the sixty-second hour after its initiation, and cervical vessel reconstruction was conducted. Subsequent TTE imaging revealed a right atrial thrombus (RAT) measuring approximately 0.5 cm × 0.4 cm (Fig. 1). As a result, LMWH was initiated for anticoagulation at an initial dose of 1 mg/kg every 12 hours subcutaneously. Anti-factor X activated (Xa) levels were monitored daily to maintain a target range of 0.5–1.0 U/mL, with LMWH doses adjusted based on anti-factor Xa levels measured 4–6 hours postdosing (Table 2). Follow-up TTE assessments were regularly performed to monitor thrombotic resolution and check for intracranial hemorrhage. By the fifth day of anticoagulant treatment, TTE revealed significant dissolution of the atrial thrombus to approximately 0.2 cm × 0.2 cm (Fig. 2). By the seventh day, the RAT had completely resolved (Fig. 3). The LMWH dose was subsequently adjusted to 0.5–1.0 mg/kg every 12 hours, with anti-factor Xa levels maintained within the range of 0.1–0.3 U/mL. After discharge, the patient was prescribed oral aspirin at a dosage of 3 mg/kg/day and underwent regular monitoring of coagulation function. There were no complications, such as thrombus recurrence or bleeding at the 3-month follow-up.

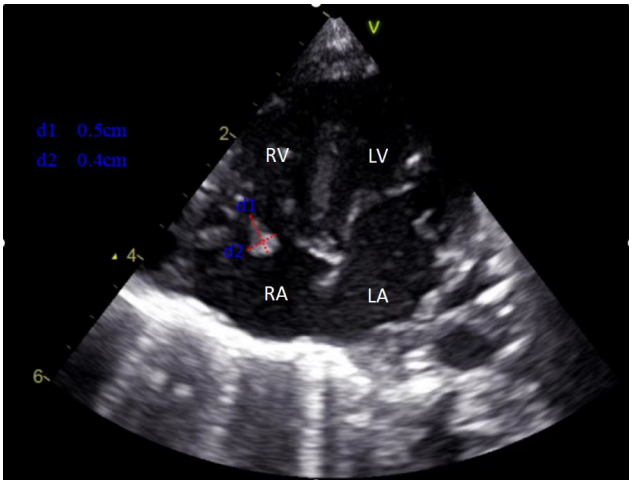

Fig. 1. Echocardiography image. Transthoracic echocardiography (TTE) revealed a right atrial thrombus (RAT) measuring approximately 0.5 cm × 0.4 cm. RA, right atrium; RV, right ventricle; LV, left ventricle; and LA, left atrium; d1, long diameter; d2, cross diameter.

Discussion

The ECG before the operation indicated a first-degree atrioventricular block. We suspected that the heart rapidly shifted to the left thoracic cavity after the operation, resulting in aggravated arrhythmia. Owing to cardiac insuffi-

Table 2. Changes in the values of various coagulation tests following low molecular heparin dose adjustment.

Days after ECMO (d)	1		2		3		4		5		6		7		8		9	
LMWH dose (mg/Kg/12 h)	1.00	1.00	1.00	1.00	1.25	1.25	1.25	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.00	1.00	0.50	0.50
Anti-factor Xa levels (U/mL)	3.60	3.70	3.90	3.90	4.20	4.50	5.60	5.20	5.40	4.80	4.70	4.90	4.90	4.30	3.80	3.10	1.70	1.40
APTT (s)	51.20	76.40	70.50	53.00	73.90	58.50	68.9	89.00	95.00	80.00	68.70	69.90	76.30	77.20	95.60	80.00	53.00	44.00
D-dimer levels (ug/mL)	1.73	1.68	2.03	2.50	2.68	1.72	1.33	1.44	1.42	1.75	1.39	1.05	0.65	0.42	0.52	0.67	0.68	1.16
FIB (g/L)	2.73	2.66	2.17	2.06	2.62	2.69	2.92	2.38	1.88	1.63	1.51	1.52	1.60	1.52	1.55	1.53	1.35	1.24
FDP (ug/mL)	7.71	4.68	4.19	6.03	7.35	3.87	4.19	3.47	5.43	6.81	3.39	2.88	1.37	0.55	1.51	1.90	2.25	2.84

ECMO, extracorporeal membrane oxygenation; LMWH dose, low molecular heparin dose; Xa, X activated; APTT, active partial thromboplastin time; FIB, fibrinogen; FDP, fibrinogen degradation products. Administered subcutaneous LMWH every 12 hours. Coagulation tests measurement 4–6 hours after dosing.

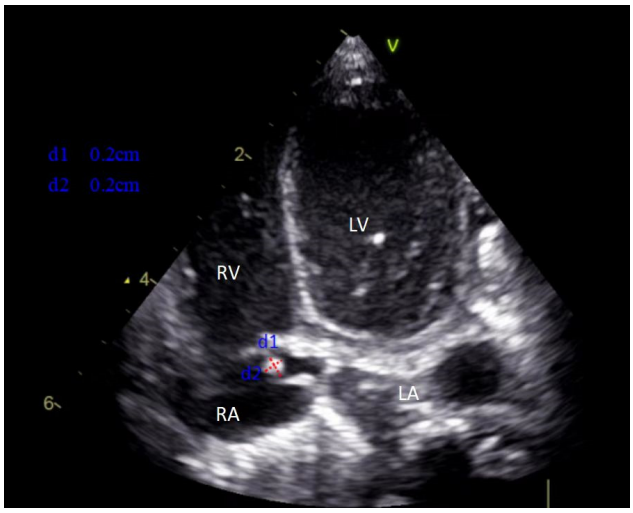

Fig. 2. Echocardiography image. TTE revealed that RAT dissolved to approximately 0.2 cm × 0.2 cm.

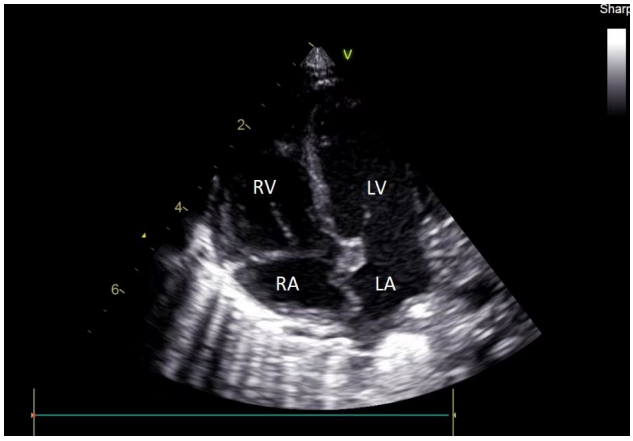

Fig. 3. Echocardiography image. TTE revealed that the RAT had completely resolved.

ciency resulting from electrophysiological disorders, persistent pulmonary hypertension of the newborn (PPHN), and congenital cardiac malformations, this patient required ECMO support. Heparin exerts an anticoagulant effect by binding to antithrombin III (AT-III) and increasing its activity. The level of AT-III is relatively low in infants 6 months old and younger, and AT-III deficiency may occur as the duration of ECMO assistance increases. In addition, the low ECMO flow rate, the turbulence and stasis around the intubation site, and the endothelial damage to the right atrium caused by internal jugular vein cannulation contributed to the formation of a RAT in this patient.

RAT is a recognized complication associated with indwelling central venous catheters in neonates and children [4]. Owing to their fragile vascular structures, neonates typically require veno-arterial (V-A) ECMO, which increases the risk of RAT formation. This condition often arises from low ECMO flow rates, turbulence, and stasis around the cannula, as well as endothelial damage in the right atrium due to internal jugular vein cannulation. Marsh *et al.* [5] reported that the RAT developed in two out of three neonates, necessitating a central venous catheter post-ECMO. Similarly, Riccabona *et al.* [6] reported a high incidence of thrombotic events (20%) in 30 children with ECMO. Given its prevalence yet frequent underdiagnosis, RAT formation after ECMO is a significant concern. We advocate for the routine implementation of prophylactic anticoagulants and daily TTE for neonates after ECMO to mitigate the risks of RAT formation and prevent severe thrombotic complications.

Among neonatal thromboses, those involving the central venous line (specifically in the right atrium or superior vena cava) have the highest mortality rate because of the risk of thrombus dissemination to the lungs, potentially leading to pulmonary embolism [7]. Timely treatment is the key to preventing the progression of thrombi, which can result in limb ischemia, cerebral embolism, pulmonary embolism, and other severe complications. Surgical removal of a thrombus in neonates poses significant challenges, as the procedure's success is constrained by the small size of their blood vessels and the clinical instability associated with neonatal thrombosis [8]. Thrombolytic therapy, although effective for clearing large vessel occlusions that cause significant organ or limb damage, is seldom administered to neonates because of its bleeding risks and its propensity to decrease physiological levels of fibrinogen in neonates [9]. Anticoagulant therapy is the pre-

ferred treatment for a RAT unless there are contraindications. The standard treatment duration is three months, although it may be shortened if the thrombus resolves and if the patient remains asymptomatic [10]. Effective management of RATs in neonates requires a tailored treatment strategy, taking into account the specific conditions of each patient.

While UFH has been extensively used to prevent and treat thrombosis in neonates, it is increasingly being replaced by LMWH because of its several advantages. LMWH offers predictable efficacy, requires less laboratory monitoring, and presents a lower risk of bleeding. Because it is suitable for subcutaneous administration, LMWH is particularly advantageous for neonates with poor venous access. A prospective cohort study involving 173 children, one-third of whom were under three months of age, revealed the efficacy of LMWH in treating thrombosis and preventing thromboembolic events in high-risk children [11]. In this study, thrombus resolution was achieved in 94% of those receiving therapeutic doses of LMWH. Among those receiving prophylactic LMWH, 96% remained asymptomatic for new or recurrent thromboembolic events. A systematic review including 1329 children, most of whom were younger than three months, reported that when therapeutic doses of LMWH were used, the recurrence rate of thrombosis was 3.2%, the regression rate was 60%, and the bleeding rate was 1.8% [12]. In children receiving preventive doses, the incidence of thrombosis was 2.2%, and major bleeding complications were rare, at only 0.6% [12]. Thus, LMWH is considered both safe and effective for anticoagulation treatment and prevention in neonates.

Anticoagulant treatment monitoring is crucial during ECMO. Since a single monitoring approach cannot precisely reflect the anticoagulation and coagulation status, ACT, APTT, and anti-Xa are commonly combined for assessment [13]. A coagulation test is conducted every 4–6 hours, with the target values being 180–220 seconds for ACT, 60–80 seconds for APTT, and 0.3–0.7 U/mL for the anti-Xa level. If monitoring reveals that ACT and APTT are below the target range along with signs of thrombosis such as abnormal vascular ultrasound or limb ischemia, increasing the dose of anticoagulants should be considered. If the risk of bleeding, such as bleeding tendency or active bleeding, increases and if the coagulation index exceeds the target range, the dose of anticoagulants should be reduced. When the heparin dosage exceeds 30 U/kg/h and the AT-III is less than 50%, plasma transfusion is necessary. When the platelet count decreases significantly and heparin-induced thrombocytopenia (HIT) is suspected, the anticoagulant drug, such as argatroban, should be changed, and the dose should be adjusted based on the new drug's properties and the patient's response [14]. During the adjustment of the treatment plan, the patient's symptoms, signs, and relevant examination indicators should be closely monitored to prevent thrombosis and minimize bleeding complications effectively.

The recommended initial dose of LMWH for treating RATs in children is 1.5 mg/kg every 12 hours, with dose adjustments based on anti-factor Xa levels measured 4–6 hours after administration, with a target range of 0.5–1.0 U/mL [11]. Neonates, particularly preterm ones, require higher and more prolonged doses of LMWH to reach therapeutic anti-factor Xa levels owing to their low antithrombin levels and rapid clearance [15]. A systematic review of 1112 children revealed that the mean therapeutic LMWH dose was 2.1 mg/kg twice daily for preterm neonates, 1.7 mg/kg for term neonates, and 1.2 mg/kg for children aged 1–6 years [12]. Monitoring children closely during treatment is crucial. Dose adjustment should be precise according to the situation to ensure safety and efficacy. Additionally, continuous research and practice are needed to optimize the LMWH treatment protocol for children with RATs.

Conclusions

ECMO is recognized as a significant risk factor for RATs in neonates who have undergone surgical repair for CDH. Consequently, we advocate for routine prophylactic anticoagulant therapy and daily TTE after ECMO to monitor and manage this risk. The use of LMWH has proven to be both safe and effective in treating RATs in neonates. The dosage of anticoagulants should be adjusted based on the patient's symptoms, signs and related examination indicators to prevent thrombosis effectively and minimize bleeding complications.

Availability of Data and Materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contributions

JJH, JXH, and QC designed the study, performed the statistical analysis, participated in the operation, and drafted the manuscript. ZYG, HC, and SMH collected the clinical data. All authors have made a great contribution to the editing of the manuscript. All authors are fully involved in the work, the content of the appropriate part of the public responsibility, and agree to be responsible for all aspects of the work, to ensure that the problems associated with its accuracy or completeness.

Ethics Approval and Consent to Participate

The present study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Fujian Children's Hospital (2023ETKLRK10012). The data are anonymous, and the requirement for informed consent was therefore waived.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.7811.

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