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CASE REPORT
Congenital heart disease

Extracorporeal membrane oxygenation after prosthetic valve replacement in a child with neonatal Marfan syndrome: a case report

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Background Neonatal Marfan syndrome (nMFS), the most severe form of Marfan syndrome, is a rare condition that presents a clinical and treatment challenge. nMFS has high infant mortality related to progressive valvular dysfunction. Valve replacement in this setting improves long-term prognosis but carries high morbidity and mortality. Thus, sharing clinical experience in treating such patients is valuable.

Case summary A 2 year old with nMFS underwent tricuspid valve annuloplasty and prosthetic mitral valve replacement. Postoperative management was complicated by pulmonary hypertension, cardiogenic shock, and arrythmias. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) helped overcome these challenges but posed a high risk for prosthetic valve thrombosis (PVT). Despite decompression of the left atrium (LA) with an LA vent, the left ventricle (LV) was distended because of aortic regurgitation and no native cardiac output. We lowered the ECMO flow under echocardiographic guidance; used inodilators and pacing to encourage transmitral flow and reduce LV afterload. The patient completed a successful 6-day ECMO run with good end-organ perfusion. At last follow up, she was 6 years old, enjoying school, home-ventilated through the tracheostomy, and mobilizing with walking aids/wheelchair.

Discussion Valve replacement can improve life quality and expectancy for patients with nMFS. Lowering ECMO flow under echocardiography guidance till the aortic valve is seen to open; coupled with inodilators, pacing and adequate anticoagulation can be a safe way to deliver VA-ECMO for cardiogenic shock after prosthetic valve replacement. Further research is needed to show if this strategy prevents prosthetic valve thrombosis and provides sufficient haemodynamic support and myocardial rest.

Keywords Extracorporeal membrane oxygenation • Neonatal Marfan syndrome • Prosthetic valve replacement • Prosthetic valve thrombosis • Case report

ESC Curriculum 4.9 Multivalvular disease • 4.10 Prosthetic valves • 7.3 Critically ill cardiac patient • 7.5 Cardiac surgery • 9.6 Pulmonary hypertension

Learning points

- Prosthetic valve replacement (PVR) can improve quality of life and life expectancy in children with neonatal Marfan syndrome (nMFS).
- Venoarterial extracorporeal membrane oxygenation (VA-ECMO) after PVR increases the risk of clotting the prosthetic valve if the increased afterload prevents the aortic valve from opening.
- Lowering ECMO flow under echocardiography guidance till the aortic valve is seen to open; coupled with inodilators, pacing and adequate anticoagulation can mitigate the risk of prosthetic valve thrombosis (PVT) and still deliver effective VA-ECMO for cardiogenic shock after PVR.

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Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with mutations in FBN1 gene on Chromosome 15 encoding the Fibrillin-1 protein.[1] Neonatal MFS (nMFS), the most severe form of MFS has *de novo* mutations in Exons 23–32 of the gene.[1] Clinically, nMFS differs in its earlier presentation in infancy, with severe cardiac and pulmonary manifestations, particularly mitral and tricuspid valve (MV and TV) regurgitation and pulmonary emphysema.[1] Medical treatment often fails to control heart failure (HF) symptoms.[2] The surgical treatment options include valve repair/replacement. Survival figures remain poor even after surgery.[3] Venoarterial extracorporeal membrane oxygenation (VA-ECMO) improves postoperative outcomes.[4] Currently, VA-ECMO is used at maximum 'full' flow[5] for cardiogenic shock after paediatric cardiac surgery to provide complete myocardial rest and effective organ perfusion. However, multiple adult case reports[6–9] demonstrate lethal obstructive prosthetic valve thrombosis (PVT) on maximum 'full' flow VA-ECMO after prosthetic valve replacement (PVR) with two observational studies[10,11] showing 10% incidence. The case reports[6–9] suggest lowering ECMO flow to mitigate PVT risk, but this approach may lead to insufficient haemodynamic support and myocardial strain.

We describe the case of an nMFS child undergoing PVR and the challenges in the immediate postoperative management including our experience of using low-flow ECMO to mitigate risk of PVT.

Timeline

Age	Events	Assessment and management
Birth	Facial dysmorphism noted (down-slanted palpebral fissures, high narrow palate, low set ears, micrognathia, and wide nasal bridge) and bilateral hindfoot deformity noted.	Karyotype normal. Molecular genetics sent. 3/6 systolic murmur in apical area and lower left sternal border found on clinical examination.
First 6 weeks	Diagnosed on cardiology review with • Mitral and Tricuspid valve prolapse with mild–moderate regurgitation • Moderate Aortic root dilatation, • Atrial septal defect (ASD)	Not in clinical HF; continues cardiology follow up. Reasonable weight gain following the 2.5th centile.
3 months	HF develops and progresses rapidly over the next few months. (repeated chest infections, irritability, feed intolerance, and failure to thrive)	Diuretics and captopril started.
6 months	Genetic confirmation of nMFS	Type 1 fibrillinopathy [heterozygous for FBN1 mutation in Exon 26 (c.3143T > C)] confirmed.
8 months	HF is refractory to medical treatment. Pulmonary hypertension develops—persistent desaturations. Sildenafil and home oxygen started.	Computed tomography (CT) chest shows pulmonary emphysema and kyphoscoliosis
8.5 months	Paediatric intensive care unit (PICU) admission after viral lower respiratory tract infection—ventilated—inability to wean and extubate. Multidisciplinary team (MDT) discuss risks-benefits of surgical valve repair/replacement.	Echocardiography shows poor contractility, dilated RV, moderate-to-severe MV and TV regurgitation, pulmonary hypertension on Milrinone, Sildenafil, Furosemide, Spironolactone, Atenolol, and Losartan.
9 months	MDT agree surgical valve repair will improve quality of life. Tracheostomy done to optimise pre-operative state and prepare for long term ventilatory support.	Neurology and genetic opinion: No structural abnormality in the brain. Respiratory opinion: Pulmonary emphysema not severe enough to contraindicate surgery.
10 months	First surgery: Tricuspid valve repair (leaflet repair with partial annuloplasty), mitral valve repair (anterior leaflet chordae shortening and posterior partial annuloplasty); ASD closure.	Good postoperative recovery.
Up to 28 months	Improved quality of life: weight gain and reduced chest infections. Tracheostomy decannulated briefly.	Residual TR and MR persist (see Supplementary material online, *Figures S1* and *S2*, *Videos S1* and *S2*)
30 months	PICU admission for worsening cardiac failure (*Figure 1A*). Tracheostomy re-inserted for respiratory support.	Echocardiography shows severe MR and TR with moderate aortic root dilatation. Levosimendan tried unsuccessfully.
32 months	Second surgery: Tricuspid valve repair and 33 mm St Jude's prosthetic mitral valve replacement.	Postoperative cardiogenic shock, pulmonary hypertension, and arrythmias develop. 'Full-flow' (150 ml/kg/min) VA-ECMO with left atrial (LA) venting started 12 h postoperatively. LA decompressed but Left ventricle (LV) distended with no native cardiac output. High risk of intracardiac thrombosis. ECMO flow reduced under echocardiography guidance with inodilators, pacing and anticoagulation till the aortic valve seen to open and LV seen to empty. Lactate clearance and organ perfusion maintained. Successfully decannulated from ECMO after 6 days. Chest closed on Day 9 PICU discharge on Day 20
Age 6 years	Last follow up	Enjoys school, tracheostomy home ventilated, mobilises with walking aids and wheelchair.

Case summary

A Caucasian female born at 37 + 3 weeks gestation in good condition after induction of labour for oligohydramnios and intrauterine growth restriction (birth weight 2.335 kg) was noted to have facial dysmorphism and bilateral hindfoot deformity. Over time, she developed hypotonia, arachnodactyly, plagiocephaly, and kyphoscoliosis. She was the first child of nonconsanguineous parents with no family history of Marfan syndrome. At 6 months of age, molecular genetics confirmed neonatal Marfan Syndrome (nMFS) [Type 1 fibrillinopathy, heterozygous for FBN1 mutation in Exon 26 (c.3143T > C)].

She had a cardiology review for a 3/6 systolic murmur in the apical region aged 6 weeks and was diagnosed with MV prolapse, dysplastic TV, secundum ASD, and aortic root dilatation on echocardiography. By 3 months, she developed manifestations of cardiac failure (feed intolerance, irritability, repeated chest infections, and failure to thrive; 2.5th centile weight) which progressed rapidly despite maximal medical treatment with diuretics and captopril. Aged 8 months, she was started on sildenafil and home oxygen for pulmonary hypertension. CT chest showed pulmonary emphysema not severe enough to contraindicate surgery. Neuroimaging showed no structural abnormality of the brain. The MDT agreed surgical valve repair would improve her quality of life. She underwent tracheostomy aged 9 months following prolonged ventilation after a viral respiratory illness. A TV and MV repair with ASD closure was performed aged 10 months (see Supplementary material online, *Figures S1* and *S2 and Videos S1* and *S2*). Intraoperatively, her lungs were seen to be emphysematous. Despite residual valvular regurgitation post repair, her cardiac failure symptoms improved providing good growth and neurodevelopment for 1 year. But, by age 2 years, she was in debilitating cardiac failure again (*Figure 1A*).

The multidisciplinary team and parents agreed to undertake a second valve repair/replacement. At age 32 months, a technically challenging TV annuloplasty and MV replacement with a 33 mm St Jude prosthetic valve were performed with a long cardiopulmonary bypass time (338 min). The patient was weaned from bypass on inotropic support (noradrenaline 0.08 μg/kg/min, adrenaline 0.06 μg/kg/min, milrinone 0.5 μg/kg/min). Immediate postoperative echocardiography showed satisfactory repair with biventricular systolic dysfunction. The patient returned to intensive care ventilated with an open chest.

Over the next few hours, cardiogenic shock worsened. Postoperative chest radiography (*Figure 1B*) showed cardiomegaly with a collapsed left lung and right pulmonary emphysema. Repeat echocardiography showed pulmonary hypertension with worsening tricuspid regurgitation (*Figure 2A*). The pulmonary artery pressure reduced after starting inhaled nitric oxide (*Figure 2B*). However, the

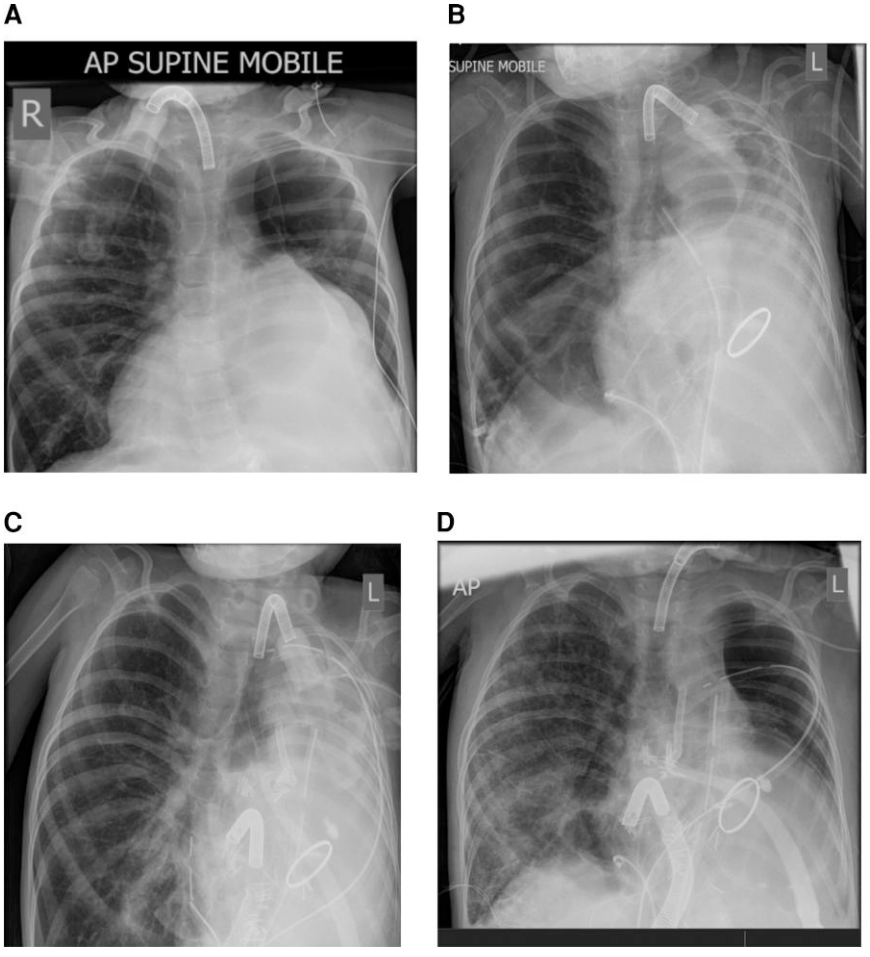

Figure 1 CXR before (*A*) and after (*B*) prosthetic valve replacement; after extracorporeal membrane oxygenation cannulation (*C*) and prior to decannulation on Day 6 of extracorporeal membrane oxygenation (*D*).

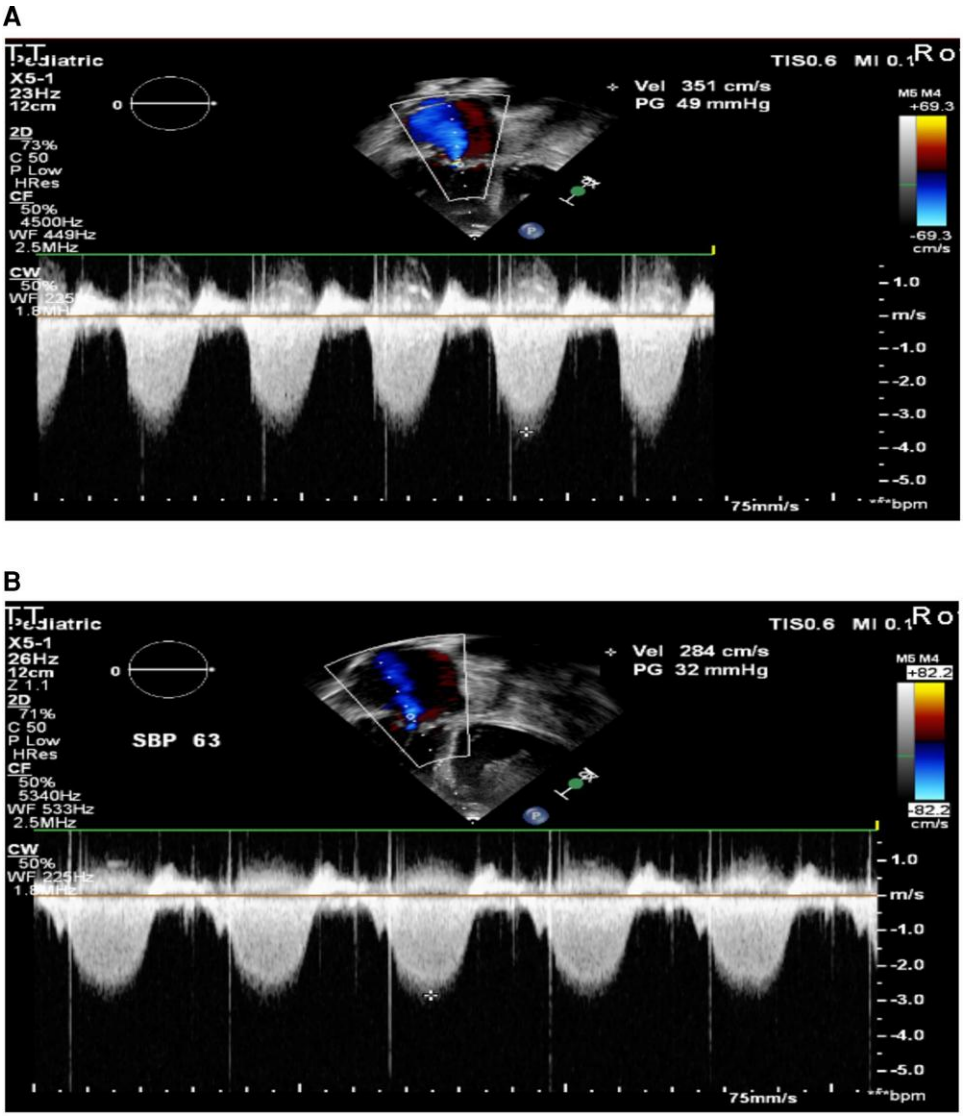

Figure 2 Postoperative echocardiographic image (apical four chamber view) showing pulmonary hypertension before starting inhaled nitric oxide (*A*) and reduced pulmonary hypertension after starting inhaled nitric oxide (*B*). iNO, inhaled nitric oxide.

patient continued to be acidotic with a low mean arterial pressure (40 mmHg), low cerebral near infrared spectroscopy (NIRS; 30–40%), low superior vena cava oxygen ($SVCO_2$) saturation (50%) and high arterial lactate (3–6 mmol/L). The central venous pressure was 10–14 mmHg, and the left atrium (LA) was dilated on echocardiography. During the first 12 h postoperatively, 100 mL/kg fluid and blood product resuscitation had been given, and the vasopressor requirement progressively increased. Steroids and calcium infusion were started. Further deterioration occurred, with frequent atrial ectopic beats and runs of wide complex ventricular tachycardia.

At this point, 12 h postoperatively, VA-ECMO was initiated. The patient was cannulated centrally (22 Fr drainage cannula in right atrium; 12 Fr return cannula in aortic arch), and a LA vent was inserted to decompress the enlarged LA, which was causing arrythmias, left bronchial compression, and pulmonary hypertension.

Our primary goal was to achieve organ perfusion and myocardial rest. We started with 'full' ECMO flow at 150 mL/kg/min and stopped the vasopressors. On echocardiography (Supplementary material online, *Video 1*), poor LV contractility and minimal MV and aortic valve movement were visualized. The LA vent allowed very little transmitral flow. However, constant aortic regurgitation with no native cardiac output increased LV end-diastolic volume. The lack of MV movement and blood stagnating in the LV risked developing a clot. Heparin dosing was optimized, aiming for higher anticoagulation targets. Continuous renal replacement therapy was started to manage fluid overload.

Bedside echocardiography was used to reduce ECMO flow from 150 to 120 mL/kg/min (80% of full flow). Milrinone (0.5 μg/kg/min), adrenaline (0.05 μg/kg/min), and sodium nitroprusside (3 ng/kg/min) were used together as inodilators. The LV ejection was confirmed with pulsatility on the arterial trace. The heart rate was slow sinus at 60–80 beats/min. Pacing in the AAI mode was started at 110 beats/min, which increased transmitral flow. Aortic regurgitation reduced, with good MV and aortic valve movement on echocardiography (see Supplementary material online, *Videos 2a* and *2b*, *Video S3*).

We accepted a lower mean blood pressure (40-45 mmHg) but monitored end-organ perfusion carefully to ensure lowering flow did not compromise haemodynamic support. Cerebral NIRS and $SVCO_2$ improved, and the lactate normalized in 6 h. The patient was successfully decannulated from VA-ECMO after 6 days. Her chest was closed on Day 9, and she was discharged from the ICU on Day 20. At last follow up, the patient was 6 years old, enjoying school, home-ventilated through the tracheostomy, and mobilizing with walking aids/wheelchair.

Discussion

Refractory cardiac failure results in morbidity and early death in nMFS. In a large series[2] of 60 patients, 89% died by age 2 years. Early valve repair/replacement improves both life expectancy and quality.[1,2] The choice between valve repair and replacement remains controversial.[3] The authors of the largest published case series[3] of six patients with nMFS undergoing mitral valve surgery believe the underlying degenerative process in nMFS makes it unlikely repair will last long-term and advocate PV replacement, especially in younger patients. We opted for repair first because of her young age and to avoid the anticoagulation commitment.

Prosthetic valve replacement in young children carries high mortality; upto 42% in patients ≤2 years old compared with 6% in older patients in one single-centre study.[12] But ECMO can improve postoperative survival with one study[13] demonstrating 78% survival among patients started on ECMO after mitral repair/replacement. A large single-centre study[14] of 54 patients undergoing PVR shows 10% need ECMO postoperatively.

Venoarterial ECMO is reported to increase the risk of PVT[6–11] in adults. There are no reports of PVT in children on ECMO.[13,14] More recently, an observational study[15] of PVR in 29 children (median age 19 months; 2002–20) found only one patient needed ECMO. They reported an overall 10.3% (3 of 29 patients) risk of early PVT but it is unclear if the one ECMO patient developed PVT.

Evidence in favour of the low-flow ECMO strategy is limited and weak. We found only one single-centre retrospective observational study[11] supporting lowering ECMO flow in which 9/90 adults (10%) with PVR on VA-ECMO developed PVT with 56% mortality. Central cannulation [odds ratio (OR) 5.53; 95% confidence interval (CI) 1.24–38.78] and higher ECMO flow (OR 2.18; 95% CI 1.11–4.67) were associated with thrombosis in univariate analysis, but only central cannulation showed significant association on multivariable analysis. The authors explained higher ECMO flow reduces transprosthetic intracardiac flow and recommended lower flow (60–80% of total cardiac output) and inotrope use to maintain ventricular ejection. We found one adult case report describing PVT despite using low-flow ECMO.[8]

Previous reports[6–9] also recommend LV decompression devices to prevent blood stasis and thrombosis. A paediatric review[5] on ECMO for cardiogenic shock similarly emphasizes importance of LV decompression strategies if full-flow ECMO prevents aortic valve opening. It does not specifically describe lowering the ECMO flow with inodilators as a strategy. However, the review authors accept there is currently no consensus on the optimal method for LV decompression in younger paediatric patients.

The most common LV decompression technique in paediatric ECMO is LA venting,[5] which reduces transmitral flow and can be counterproductive in preventing PVT.[11] Its use in this situation is only justified if LA decompression itself is advantageous as it was in our patient. Other surgical/transcutaneous LV decompression methods such as a heart pump (Impella), intra-aortic balloon pump, and LV apical vent are not often used in younger paediatric patients and carry significant risks.[5] In addition, none of these devices improve transmitral flow as needed to prevent PVT. Our strategy of lowering ECMO flow, using inodilators, and pacing achieved both goals—increasing transmitral flow and decompressing the LV.

Conclusion

Valve surgery can improve life quality and expectancy for patients with nMFS. Lowering ECMO flow under echocardiography guidance till the aortic valve is seen to open; coupled with inodilators, pacing and adequate anticoagulation can be a safe way to deliver VA-ECMO for cardiogenic shock after PVR. Further research is needed to show if this strategy prevents PVT while providing sufficient haemodynamic support and myocardial rest.

Lead author biography

Toranj Wadia is a UK Paediatric intensive care fellow with a specialist interest in cardiac intensive care and paediatric ECMO. She has 10 years of paediatric intensive care experience in the UK and India.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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To the patient and her family.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: Consent was obtained from the patient's mother as the patient is an underage child for publication of all clinical information including sharing of videos and images related to the management of this case. The authors have adhered to publication ethics as set out by the Committee on Publication Ethics (COPE) and ICMJE recommendations for reporting about patients.

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References

1. Carande EJ, Bilton SJ, Adwani S. A case of neonatal Marfan syndrome: a management conundrum and the role of a multidisciplinary team. *Case Rep Pediatr* 2017;**2017**: 8952428.
2. Stheneur C, Faivre L, Collod-Béroud G, Gautier E, Binquet C, Bonithon-Kopp C, Claustres M, Child AH, Arbustini E, Adès LC, Francke U, Mayer K, Arslan-Kirchner M, De Paepe A, Chevallier B, Bonnet D, Jondeau G, Boileau C. Prognosis factors in probands with an FBN1 mutation diagnosed before the age of 1 year. *Pediatr Res* 2011;**69**: 265–270.
3. Kim ER, Kim WH, Choi ES, Cho S, Jang WS, Kim YJ. Surgical management of mitral regurgitation in patients with Marfan syndrome during infancy and early childhood. *Korean J Thorac Cardiovasc Surg* 2015;**48**:7–12.
4. Bhaskar P, Davila S, Hoskote A, Thiagarajan R. Use of ECMO for cardiogenic shock in pediatric population. *J Clin Med* 2021;**10**:1573.
5. Balasubramanian Sendhil K, Tiruvoipati R, Amin M, Aabideen KK, Peek GJ, Sosnowski AW, Firmin RK. Factors influencing the outcome of paediatric cardiac surgical patients during extracorporeal circulatory support. *J Cardiothorac Surg* 2007; **2-4**.

6. Kagiyama N, Okura H, Nezuo S, Kawamoto T, Murakami T, Hashimoto Y, Tanemoto K, Yoshida K. Two cases of acute bioprosthetic mitral valve thrombosis immediately after mitral valve replacement. *Circulation* 2014;**129**:e328–e330.
7. Challa A, Latona J, Fraser J, Spanevello M, Scalia G, Burstow D, Platts D. Mitral valve bioprosthesis and annuloplasty thrombosis during extracorporeal membrane oxygenation: case series. *Eur Heart J Case Rep* 2020;**4**:1–6.
8. Sandoval E, Ascaso M, Pereda D, Quintana E. Extracorporeal membrane oxygenation and mechanical valves: an unfriendly relationship. *J Thorac Cardiovasc Surg* 2018;**156**:103–105.
9. Martínez Monzonís A, Rial Munin M, Veiras del Río S, Lázare Iglesias H, Fernández AL. Acute bioprosthetic mitral valve thrombosis during venoarterial extracorporeal membrane oxygenation. *Rev Port Cir Cardiotorac Vasc* 2021;**26**:263–265.
10. Cevasco M, Saha A, Garan AR, Witer L, Sanchez J, Kurlansky P, *et al.* Incidence and outcomes of prosthetic valve thrombosis during extracorporeal membrane oxygenation support for postcardiotomy shock. *J Heart Lung Transplant* 2019; Volume 38, Issue 4, Supplement S423.
11. Melehy A, Sanchez J, Fried JA, Takeda K. Prosthetic valve thrombosis during extracorporeal life support for postcardiotomy shock. *Interact Cardiovasc Thorac Surg* 2020;**31**:573–575.
12. Beierlein W, Becker V, Yates R, Tsang V, Elliott M, de Leval M, van Doorn C. Long-term follow-up after mitral valve replacement in childhood: poor event-free survival in the young child. *Eur Cardio-Thorac Surg* 2007;**31**:860–865.
13. Chaturvedi RR, Macrae D, Brown KL, Schindler M, Smith EC, Davis KB, Cohen G, Tsang V, Elliott M, de Leval M, Gallivan S, Goldman AP. Cardiac ECMO for biventricular hearts after paediatric open heart surgery. *Heart* 2004;**90**:545–551.
14. Van Doorn C, Yates R, Tsang V, deLeval M, Elliott M. Mitral valve replacement in children: mortality, morbidity, and haemodynamic status up to medium term follow up. *Heart* 2000;**84**:636–664.
15. Elmahrouk Ahmed F, Mashali Mohamed H, Ismail Mohamed F, Arafat Amr A, Alamri Rawan M, Baho HA, Shihata MS, Jamjoom AA. Mitral valve replacement in infants and younger children. *Sci Rep* 2021;**11**:15239.