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Targeted neonatal echocardiography-guided therapy pre-embolisation for congenital hepatic vascular malformation: inhaled nitric oxide to prevent paradoxical embolisation to the systemic circulation

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Abstract

Arteriovenous malformations may present with significant haemodynamic compromise in the neonatal period, typically with high output cardiac failure that may be accompanied by hypoxia and right ventricular dysfunction. Targeted neonatal echocardiography performed by trained neonatologists provides an enhanced physiology-based approach that can guide treatment and minimise complications. We present a case of a large hepatic vascular malformation whose therapy was guided by targeted neonatal echocardiography to prevent paradoxical embolisation of procedural glue to the systemic circulation.

Neonatal hepatic arteriovenous malformations are rare, associated with significant haemodynamic derangements and have high mortality.[1] The increase in pulmonary blood flow in the fetus induces pulmonary hypertension through remodelling of the vascular bed.[2] Management of hypoxic respiratory failure and cardiac dysfunction may be challenging given the complexity of potential contributors to the clinical phenotype and the presence of physiological considerations that are infrequent in "typical" transitional acute pulmonary hypertension. The presence of refractory cardiovascular dysfunction usually dictates the timing for intervention,[1,3] which is typically staged endovascular embolisation at specialised referral centres.[1,3]

A standardised approach to postnatal stabilisation and medical management prior to embolisation is not established, given the rarity of these cases.[4] Furthermore, the procedure itself also carries the risk of complications and may cause further haemodynamic alterations such as glue embolisation to other tissues, usually the lungs, with associated worsening of hypoxic respiratory failure due to ventilation/perfusion mismatch[5,6] has been reported. Particularly in the neonatal period, when the intra- and extra-cardiac shunts are often patent, there is also a risk of paradoxical embolisation to the systemic circulation.[7] Cardiovascular management within specialised centres with access to neonatologists with formal training in targeted neonatal echocardiography (TnECHO) may enhance the precision of care. We present a case of a neonate with a large hepatic arteriovenous malformation, highlight relevant physiological insights gained from comprehensive targeted neonatal echo assessment, and discuss how these data led to an enhanced approach to patient care.

Case

A male infant was born at 38-week gestation following an uncomplicated pregnancy with a birth weight of 3.39 kg. Antenatal evaluation demonstrated a structurally and functionally normal heart with cardiomegaly, and several hepatic arteriovenous malformations without evidence of hydrops fetalis. After uncomplicated delivery, the baby was admitted to the neonatal intensive care unit with mild tachypnoea and low-flow oxygen requirement. His neurological exam was within normal limits. Abdominal ultrasound showed multiple hepatic arteriovenous malformations distributed across all lobes of the liver, which was confirmed by abdominal magnetic resonance imaging. On postnatal day 1 TnECHO evaluation, performed by a haemodynamic consultant, demonstrated a dilated right ventricle and atrium with pulmonary hypertension and predominant right-to-left ductal and atrial shunts (Table 1). Right ventricular (RV) function, as assessed by tricuspid annular planar systolic excursion (TAPSE), and right ventricular area change which quantify longitudinal systolic performance were normal. Due to progressive respiratory distress requiring intubation, embolisation was planned on postnatal day 6. Due to the risk of procedural glue embolisation across atrial shunt to the systemic circulation and brain, empiric pulmonary vasodilator therapy was initiated to lower pulmonary

Table 1. Serial targeted neonatal echocardiography before and after embolisation

	Pre-embolisation		Post-embolisation	
Age (days)	1	6	7	8
Time (hours)			1 hour	24 hours
BP (mmHg)	65/40	70/45	60/45	70/50
FiO2	23%	21%	40%	40%
Adjunct therapies	None	iNO	iNO	Milrinone
TnECHO evaluation				
RVSp	80 mmHg + RAp	55 mmHg + RAp	92 mmHg + RAp	70 mmHg + RAp
IVS motion	Flat in end-systole	Flat in end-systole	Flat in end-systole	Flat in end-systole
TAPSE (mm)	8.1	9.1	6.8	9.3
RV-FAC (3Ch) (%)	32	36	25	38
RVO (ml/kg/min)	170	280	145	175
LV EF* (%)	68	72	45	68
LVs (cm/second)	6.8	6.4	2.3	5.2
LV global strain** (%)	−14.6	−15.2	−5.5	−17.4
LVO (ml/kg/minute)	225	255	168	190
IVRT (ms)	40	42	74	47
E:A ratio	0.76	0.83	Fused	0.81
PDA shunt	Bidirectional 80% R-L	Bidirectional 80% L-R	Bidirectional 60% L-R	Bidirectional 50% L-R
ASD shunt	R-L	Bidirectional 95% L-R	Bidirectional 30% L-R	L-R

Abbreviations: 2Ch: 2-chamber; 3Ch: 3-chamber; 4Ch: 4-chamber; ASD: atrial septal defect; BP: blood pressure; EF: ejection fraction; FiO2: fraction of inspired oxygen; iNO: inhaled nitric oxide; IVS: interventricular septum; LVO: left ventricular output; PDA: patent ductus arteriosus; RAp: right atrial pressure; R-L: right to left; L-R: left to right; RV-FAC (3Ch): right ventricular fractional are change in three-chamber view; RVO: right ventricular output; RVSp: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; TnECHO: targeted neonatal echocardiography
*Summation of LV 4Ch and 2Ch views
**Summation of global strain from LV 4Ch, 2Ch, and 3Ch views

vascular resistance and right heart pressures and minimise right-to-left transatrial shunting. Inhaled nitric oxide was initiated at 20 ppm and serial echoes were performed until, after 6 hours, exclusively left-to-right transatrial flow was detected. Partial embolisation with n-butyl-2-cyanoacrylate glue was completed by interventional radiology (Fig 1a). Following the procedure, the infant had escalating oxygen requirement (21–40%) and TnECHO (1 hour) demonstrated systemic pulmonary hypertension, RV systolic dysfunction with both left ventricular (LV) systolic and diastolic dysfunction. Transductal/atrial flow was bidirectional but predominantly left to right. Chest radiograph showed bilateral evidence of pulmonary glue embolism. Inhaled nitric oxide was weaned off due to the severity of LV systolic (low ejection fraction, global strain, and peak systolic s' wave) and diastolic dysfunction (prolonged isovolumic relaxation time, a wave reversal in the right upper pulmonary vein). Milrinone at 0.33 mcg/kg/minute was started to support myocardial function in the setting of increased LV afterload. Echo on the following day revealed normal biventricular systolic function and bidirectional shunts (Table 1). Due to persistent respiratory disease and pulmonary hypertension, he underwent two other partial embolisations on days 18 and 56 for which he was managed similarly, with pre-embolisation nitric oxide and milrinone. After the second procedure, he developed worsening in oxygenation (21–50%) and echocardiography confirmed severe pulmonary hypertension (right ventricular systolic pressure of 100 mmHg). Chest computed tomography was consistent with multiple subsegmental emboli of procedural glue bilaterally (Fig 1b). He improved in the subsequent days and was successfully weaned off nitric oxide. Brain magnetic resonance imaging on day 34 showed a small focus of diffusion restriction within the left centrum semiovale representing a tiny focus of acute ischaemia. The infant was extubated to non-invasive ventilation on day 58, milrinone was discontinued on day 59 and he was discharged from the neonatal intensive care unit on day 75.

Discussion

Arteriovenous malformations, significant enough to cause haemodynamic manifestations in the newborn period, are rare. The transitional period is characterised by significant changes in the systemic and pulmonary vascular resistance, shunt flow, and heart function. The normal postnatal adaptative process may be compromised in the presence of pathophysiological changes related to arteriovenous malformations with consequent poor tissue oxygen delivery. In particular, fetal volume overload in utero affects cardiomyocyte structure which can predispose particularly to right ventricular dysfunction. Pulmonary overcirculation during fetal life causes flow-induced pulmonary hypertension via remodelling, augmented response to pulmonary vasoconstricting stimuli, and impairment of endothelium-dependent relaxation.[2] Several types of arteriovenous malformations have been associated with a transitional circulation phenotype[4] in which hypoxic respiratory failure and impaired right ventricular performance are the predominant manifestations. This case highlights the dynamic nature of

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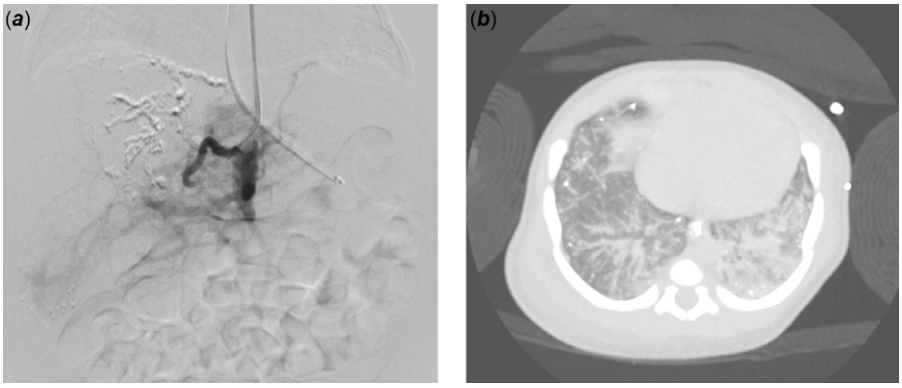

Figure 1. (*a*) Intraprocedural image of n-butyl-2-cyanoacrylate glue embolisation in the hepatic arteriovenous malformation. (*b*) Chest tomography scan showing glue embolisation to pulmonary vessels.

cardiovascular physiology and adaptive heart function responses to embolisation of arteriovenous malformations and the merits of longitudinal TnECHO evaluation by trained haemodynamic specialists.

We have previously developed an algorithm for haemodynamic therapy-guided treatment of cerebral arteriovenous malformation based on phenotypic presentation and physiologic delineation.[8] In this case, the initial presentation of the infant was consistent with suprasystemic pulmonary hypertension. The need for embolisation of a large network of vessels is associated with a high risk for glue embolisation. These have been described in a variety of conditions,[5,9] including a neonate after embolisation for cerebral arteriovenous malformation.[6] In our case, the large right-to-left transatrial shunt presented a concerning risk of stroke due to paradoxical glue embolisation into the pre-ductal systemic circulation. Therefore, reversal of this shunt using nitric oxide enabled controlled embolisation with preferential delivery of embolised glue to the pulmonary vascular bed, rather than the cerebral circulation, thereby avoiding potential iatrogenic brain injury (Supplementary Fig 1). Access to longitudinal neonatologist performed TnECHO-enabled pre-procedural iNO testing to appraise the reversibility of the elevated pulmonary vascular resistance (PVR) and a minimum duration of iNO is needed to reach this goal. These assessments were not only frequent, but also at inconvenient times of the day. Furthermore, unique measurements that are not routinely done in anatomical cardiology scans aided in the decision-making and precision in regard to the assessment of ventricular outputs and objective measurements of right heart function.

Paradoxical embolism has been described in adults following other thromboembolic events, but also following embolisation procedures.[7,10] To our knowledge, this complication has not been described in neonates. Manipulation of PVR with inhaled nitric oxide pre-emptively, with documented TnECHO evidence of shunt reversal, may have mitigated the risk of a potentially catastrophic complication. The patient developed glue embolism but did not have clinical or radiological evidence of systemic or brain embolisation, supporting the success of this approach.

Continuation of nitric oxide between procedures was not advisable due to the risk of reducing the pulmonary pressure to subsystemic levels thereby encouraging left-to-right ductal and atrial shunt, and therefore, providing two additional sources of pulmonary over-circulation. The immediate fall in both RV and LV outputs is likely multifactorial due to the elimination of the hepatic arteriovenous malformation and the severity of biventricular dysfunction due to elevated pulmonary and systemic afterload. After the first two procedures, the infant developed clinical signs suggestive of pulmonary embolism with worsening hypoxia and RV dysfunction. This diagnosis was confirmed by the identification of multiple glue emboli on chest tomography scan and by worsening of pulmonary hypertension parameters and right ventricular dysfunction on echo. The nature of severe LV dysfunction may relate to increased LV afterload or ventricular interdependence secondary to afterload-related RV dysfunction due to pulmonary embolisation. Embolisation of glue into the coronary arteries is possible, although it would appear to be less likely in the absence of embolic damage to any other systemic organs. It is plausible that the biventricular dysfunction may also have related to transatrial glue embolisation into the coronary arteries, although there was no evidence of regional wall dysfunction. In the post-procedural phase, supportive treatment with milrinone was sufficient to ameliorate the worsening of pulmonary hypertension. Afterload reduction with milrinone was likely also beneficial to the LV following embolisation in order to support myocardial performance.[4]

Comprehensive evaluation by TnECHO aids in the characterisation of the underlying physiology, facilitates enhanced monitoring, and informs treatment choices. One important factor to be considered pre-procedure is the presence of intra- and extracardiac shunts and its directionality. The nuances presented in this case highlight the value of a dedicated team with neonatal haemodynamic expertise in a specialised centre in order to provide optimal care for neonates with similar conditions.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S104795112000373X

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. No research ethics board approval was required.

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