ORIGINAL RESEARCH

Real-time Echocardiography-guided Weaning of Veno-arterial Extracorporeal Membrane Oxygenation in Neonates

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Abstract

Objective: The objective of the study is to evaluate the utility of real-time echocardiography (RTE) to provide objective hemodynamic guidance during decannulation of neonates from extracorporeal membrane oxygenation (ECMO).

Design: Retrospective case series.

Patients: Neonates with respiratory and circulatory failure who underwent venoarterial ECMO (VA-ECMO).

Interventions: Use of RTE to assess cardiac function, pulmonary hypertension (PH), and readiness for decannulation from ECMO.

Outcome measures: Data abstracted included clinical parameters, RTE data, and management decisions during weaning from VA-ECMO.

Results: We used RTE during weaning in 12 of 33 patients between 2016 and 2019. Findings prompted inotrope titration in 10 (83%) patients and volume resuscitation in 10 patients. PH was present in 12 (100%) patients and prompted initiation of prostaglandin infusion (in 3 (25%) patients. Ten of 12 patients were successfully weaned off; in 2, RTE was instrumental in halting decannulation.

Conclusions: RTE may serve as a valuable tool in clinical decision-making while weaning neonates from VA-ECMO and providing data to choose appropriate support for successful decannulation.

Keywords: Echocardiography, Weaning from extracorporeal membrane oxygenation, Veno-arterial extracorporeal membrane oxygenation.

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Introduction

Extracorporeal membrane oxygenation (ECMO) can be life-saving for patients with cardiorespiratory failure.[1] Historically, ECMO was primarily used during respiratory failure in neonates with meconium aspiration syndrome (MAS).[2] Neonatal respiratory failure is the most common indication for extracorporeal life support (ELSO), with over 30,000 neonatal runs listed in the ELSO database.[3] With advancements in medical management and mechanical ventilator support, in conjunction with innovative therapies such as inhaled nitric oxide, neonatal ECMO is now a relatively rare occurrence that is mainly used in patients with congenital diaphragmatic hernia (CDH) with pulmonary hypoplasia and pulmonary hypertension (PH).[4] Initiation of venoarterial (VA)-ECMO improves hypoxemic respiratory failure in these newborns with life-threatening persistent PH and supports end-organ perfusion and allows right ventricle (RV) unloading until pulmonary vascular resistance (PVR) decreases to allow for improvement in ventricular function. Since the successful treatment of Esperanza in 1975, there is remarkable consensus in initiating ECMO in neonates.[5] However, decannulation and assessing readiness to come off ECMO is still very subjective and not consensus or evidence-based. In neonates, accurately assessing time needed to allow for resolution of right heart failure and improvement in PVR can be challenging. Currently, there are limited data to guide clinicians in developing evidence-based protocols to decide when and how to wean neonates off VA-ECMO.[6–9] Successful weaning from ECMO depends on several clinical, hemodynamic, and echocardiographic variables.[10] Given that the most common current indication for VA-ECMO in neonates is severe PH in the setting of CDH, echocardiographic assessment of ventricular interaction, function, ductal patency, shunt directionality, and volume status offers the promise of real-time information to help clinicians decide whether a neonate is ready for VA-ECMO to be discontinued and to direct the support the patient needs for successful decannulation.[11,12] While real-time echocardiography (RTE) is commonly used in the management of pediatric and adult patients on ECMO, it has yet to become a common standard practice in neonatal intensive care units (NICUs).

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In this retrospective descriptive study, we share our center's initial experience in using echocardiography to assess cardiac function, intravascular volume status, and titrate vasoactive medications for decannulation from mechanical circulatory support in neonates with hypoxemic respiratory failure undergoing VA-ECMO. We hypothesized that RTE provided useful objective real-time information in determining readiness for decannulation from VA-ECMO.

Materials and Methods

Study Design

We conducted a retrospective observational study of all neonates admitted to our NICU from January 2016 to December 2019 undergoing VA-ECMO and in whom echocardiography was used when weaning from ECMO. The study was performed under a study protocol approved by the Institutional Review Board of Baylor College of Medicine and affiliated hospitals (no H-27591).

Patient Selection

All patients who underwent VA-ECMO in our NICU during the above-mentioned period were identified by our institutional ELSO data abstractor. Determination of use of echocardiography during weaning from ECMO was made by review of notes documented in the medical record during the weaning process.

Measured Outcomes

Maternal and Neonatal Birth Data

Data abstracted included maternal age, type of delivery, infant's gestation and weight at birth, and Apgar scores. All data are presented as mean (+ SD) or (min, max) as appropriate.

ECMO and Vasoactive Support Data

Details abstracted included the diagnosis necessitating ECMO, the day of life of initiation and duration of ECMO. Additionally, we reviewed the types of vasoactive medications used during the ECMO weaning. Specific inotrope or volume resuscitation titration in response to real-time echocardiographic observations was recorded.

Echocardiographic Data

All infants had either a prenatal echo or routine postnatal echocardiographic evaluation prior to placement on ECMO to exclude any complex congenital heart disease. Ventricular volumetric analyses, great artery measurements, and atrio-ventricular valves (A-V) competency were determined using standard echo views. Comprehensive assessment of left ventricle (LV) function was assessed by measuring fractional shortening (FS) and ejection fraction (EF); RV function was assessed in a qualitative manner and interpreted using the American Society of Echocardiography guidelines as normal values for FS and EF in infants and children have been established.[12] In our cohort, a modified pediatric protocol was used at the bedside to subjectively assess RV and LV systolic and diastolic function, tricuspid regurgitation (TR) jet, septal configuration, pulmonary valve regurgitant velocity, and shunt direction across the patent ductus arteriosus (PDA), atrial septal defect, and ventricular septal defect.[11] Because of the volume-unloading that occurs with VA-ECMO and the increased left ventricular afterload induced by the ECMO circuit, there are certain inherent limitations in judging function while on ECMO.[13] In order to address these limitations, we obtained a baseline echo on full flow. We then weaned the flow in a stepwise manner under continuous echo monitoring. Inotropic and pulmonary vasodilator therapy were titrated as indicated in order to allow for more accurate determinations of true cardiac function to be ascertained.

Results

Patient Demographics

During the study period, 39 infants underwent cannulation for ECMO; of the 33 treated with VA-ECMO, 12 had echocardiography utilized during weaning from ECMO at the clinician's discretion. Of the 21 patients who did not get RTE-guided weaning, most were decannulated prior to instituting the RTE protocol. Only 53% of infants were successfully weaned in the non-RTE cohort. Notably, 10 of 21 non-RTE patients underwent withdrawal of life-sustaining therapy due to complications such as bleeding or a life-limiting diagnosis such as alveolar capillary dysplasia or pulmonary hypoplasia secondary to bilateral renal agenesis. Median duration of ECMO for the 11 non-RTE patients compared with the 12 patients who underwent RTE-guided weaning was 327 (82, 554) vs 138 (82, 486) hours (min-max), $p = 0.27$. Duration of ECMO in hours is depicted in Figure 1. Maternal data and infant birth information are shown in Table 1.

Process of Weaning

Candidacy for discontinuing ECMO support was discussed daily in a multidisciplinary bedside meeting, including representatives from neonatology, surgery, PH, ELSO specialists, and transfusion medicine. Fluid balance, arterial blood gas (ABG), and pump mixed venous saturation were monitored. Decreases in requirement for vasoactive medications, pump flow, circuit FiO_2 requirement and sweep gas requirement were evaluated to assess readiness to be decannulated. Once the patient was deemed potentially ready for decannulation, a 30-minute "trial-off" was conducted using the following procedure. A baseline ABG was obtained and ventilator settings adjusted to optimize lung recruitment. Next, ECMO flow was decreased by approximately 10 mL/kg/minute every 10–15 minutes from our usual flow of 100–50 mL/kg/minute. At this flow rate, an ABG was obtained along with baseline evaluation of echo parameters. Ventilator settings

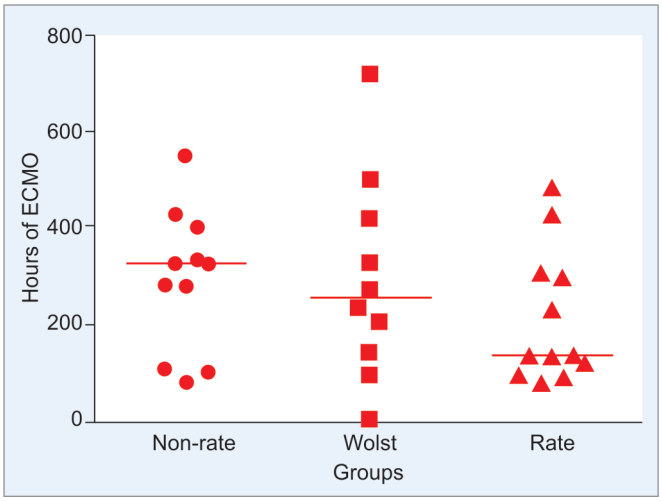

Fig. 1: ECMO duration comparison between the three groups. Median values: Non-RTE (327), RTE (138), $p = 0.27$

Table 1: Patient characteristics

Characteristics	
N	12
Maternal age at delivery (years)	28.3 (7.5, 17–42)
Type of Delivery	
Vaginal	4
CS	8
Elective CS	5
Emergency CS	3
Apgar at 1 minute	5 (1–9)
Apgar at 5 minutes	7 (3–9)
Diagnosis	
CDH*	7
Left CDH	5
Right CDH	2
Other	5
MAS	1
Hydrops	2
HIE/PH/IDDM	1
CPAM	1
Race	
African American	1
Asian	2
Hispanic	1
Caucasian	8
Gestational age in weeks	37.2 (1.6, 33–39)
Birth weight (kg)	3.37 (0.7)
Male	8
Female	4

Data reported as mean (SD, range) and absolute numbers. *All CDH repairs were done on ECMO. CPAM, congenital pulmonary airway malformations; HIE: HIE, hypoxic ischemic encephalopathy; IDDM, infant of a diabetic mother

Table 2.1: Echocardiographic findings

PH*	12 of 12	
Decreased preload	6 of 12	
Decreased LV contractility	2 of 12	
Decreased RV contractility	4 of 12	One patient with weaning halt
Decreased BiV contractility	1 of 12	One patient with weaning halt
Shunt R–L	3 of 12	
Shunt L–R	5 of 12	
Bidirectional Shunt	4 of 12	
PDA Patency	9 of 12	
Echo-guided decannulation completed	10 of 12	
Echo-guided decannulation halted	2 of 12	

*PH based on TR jet, septal position, shunt across PDA/ASD

Table 2.2: RTE-guided interventions

Medication		*Dose Range*
Epinephrine		
Infusing prior	7 of 12	0.02–0.12mcg/kg/minute
Initiated during	2 of 12	0.02–0.04 mcg/kg/minute
Dopamine		
Infusing prior	3 of 12	5–15 mcg/kg/minute
Initiated during	4 of 12	5 mcg/kg/minute
Vasopressin		
Infusing prior	4 of 12	0.01–0.06 u/kg/hour
Initiated during	4 of 12	0.02 µ/kg/hour
Milrinone		
Infusing prior	2 of 12	0.250–0.500 mcg/kg/minute
Initiated during	1 of 12	0.375 mcg/kg/minute
PGE		
Infusing prior	7 of 12	0.0125–0.025 mcg/kg/minute
Initiated during	3 of 12	0.025 mcg/kg/minute
iNO	12 of 12	20 PPM
Sildenafil	12 of 12	1–4 mg/kg/day

and FiO_2 were titrated to target PO_2 and PCO_2. An attending neonatologist, cardiologist or pediatric PH consultant was at bedside to assess the real-time ECHO changes and to assist with management. After approximately 10 minutes of flow at 50 mL/kg/minute flow, another ABG with lactate was obtained. If clinical, echo parameters and ABG were reassuring, the ECMO circuit was clamped. During the 30-minute clamp time, vital signs were monitored continually, echo assessment was performed every 10 minutes or sooner if vital signs changed, and ABGs with lactate were obtained every 10 minutes.

Patient-specific Interventions

Guided by clinical vital sign changes and echo evaluation, vasoactive infusions were adjusted and/or volume boluses were administered (Tables 2.1 and 2.2). During the weaning process, based on biventricular function, we increased epinephrine dosage in 7 of 12 patients and initiated it in an additional 2 of 12 patients. Dopamine was initiated in 4 of 12 patients, but we did not increase it in 3 of 12 patients who were already on it prior to weaning as these patients were already at a maximum therapeutic dosage; instead, we switched over to epinephrine for its better inotropic effect. Evidence of persistent PH was noted in 12 of 12 patients. We initiated vasopressin in 4 of 12 patients and increased the dosage in an additional 4 of 12 patients based on ventricular septal bowing. In one patient with evidence of TR jet acceleration with change in RV volume, we initiated milrinone; 2 of 12 patients were on it at initiation of weaning. In patients with severe PH and depressed RV function, the ductus arteriosus was kept patent using prostaglandin (PGE) infusion as a "pop off" for the RV and to improve preload for the LV.[14] A PDA was present in 9 of 12 patients. PGE was initiated in 3 of 12 patients in addition to 7 of 12 patients who were on it prior to initiation of weaning. Observation of systemic hypotension with adequate ventricular function on RTE prompted volume resuscitation with fresh frozen plasma (FFP), packed red blood cells (PRBCs), cryoprecipitate, normal saline, albumin, and platelets. We used normal saline in 1 of 12 patients, PRBCs in 4 of 12 patients, cryoprecipitate in 1 out of 12 patients, and FFP in 3 of 12 patients. After completion of the weaning trial, the ECMO flow was returned to full flow and the

surgeons, family, and consultants were notified and the decision and timing for decannulation determined.

Patient Outcomes

Using RTE as part of our weaning process allowed us to identify 10 patients who were deemed to be clinically ready for discontinuation of ECMO support and decannulation. All 10 patients were successfully decannulated. In one patient, despite maximizing vasoactive support, severe RV dysfunction persisted and the trial-off was aborted after only 10 minutes of clamping. In another patient, a significant increase in the TR jet and right-to-left shunting across the PDA despite titration of milrinone and epinephrine infusions and prior optimization with sildenafil and iNO prompted us to halt the weaning attempt at 60 mL/kg flow.

Discussion

In this study, we report our center's initial experience using RTE to assess myocardial performance, interventricular interactions, severity of PH, and readiness for decannulation from mechanical circulatory support in neonates with hypoxemic respiratory failure and circulatory failure undergoing VA-ECMO. We found RTE allowed for assessment of biventricular function, septal configuration, ventricular interaction, intracardiac volume, and the presence and direction of intracardiac and ductal level shunts during different loading conditions. These findings in turn allowed us to intervene and tailor our management according to the infant's need. Although the number of patients in which RTE was used in this four-year period was relatively small, our cautious attempts to introduce and test the feasibility and utility of this imaging modality during decannulation yielded some valuable insights.

In our retrospective cohort, RTE was used to help guide changes in vasoactive infusions and/or volume boluses in response to hypotension observed during the trial off mechanical support in a substantial number of infants. Inadequate cardiac function prompted titration of vasoactive infusions, while determination of suboptimal intracardiac volume status prompted a volume bolus. Dopamine and epinephrine were the inotropic medications commonly used for systolic ventricular dysfunction. Milrinone was used for its inotropic, lusitropic functions.[14] If RV dysfunction was noted despite use of pulmonary vasodilators, PGE was used to keep the ductus open as a "pop off" to offload the RV. Vasopressin was used for its alpha-adrenergic property to increase the systemic vascular resistance (SVR) if there was echocardiographic evidence of the ventricular septum flattening or bowing into the LV due to increased right-sided pressures. Inhaled nitric oxide and sildenafil were used to decrease PVR. When volume expansion was deemed necessary, choice of volume expander was based on the hematocrit (Hct) and coagulation status in addition to hypotension. In instances where the Hct was less than our threshold of 40%, PRBCs were chosen as the preferred volume replacement and to increase oxygen-carrying capacity. Infusion of plasma and cryoprecipitate was initiated based on the most recent coagulation profile as appropriate. If fibrinogen levels were low, cryoprecipitate was chosen; if partial thromboplastin time was prolonged, FFP was chosen.

Use of RTE during weaning from VA-ECMO in our retrospective cohort permitted a level of precision in management not available in earlier decades. This precision-based approach to volume resuscitation and inotrope titration not only aided in the successful weaning of 10 of 12 patients but also guided us to abort the weaning trial in 2 of the 12 patients; in one whom cardiac function was suboptimal and one in whom PH worsened despite above interventions. Specifically, in the latter two patients, RTE was a key factor in the decision to abort the weaning process. In the patient whose RV function did not improve despite aggressive titration of vasoactive medications, use of PGE infusion and milrinone, volume resuscitation would have been deleterious and could have precipitated acute cardiovascular collapse in the setting of biventricular failure. In another patient, an infant of a diabetic mother with significant septal hypertrophy, the diastolic dysfunction markedly deteriorated with volume repletion and there was evidence of left atrial hypertension and pulmonary venous congestion. RTE in this case allowed us to identify the futility of initiating inotropes, and recognize the need for additional time for ventricular rest before reattempting a weaning trial.

In our cohort, the main indication for VA-ECMO was PH and RV dysfunction. Assessing cardiac function, especially in the setting of PH, in neonates on VA-ECMO is challenging because of the changes in volume loading of the ventricles, lack of pulmonary blood flow, and alterations in systemic vascular resistance due to VA-ECMO and changes in PVR induced by ventilator management. Using echocardiography to estimate right ventricular performance is technically challenging due to its anatomical and functional distinctiveness.[15] The current adult guidelines for the echocardiographic quantification of RV function recommend using multiple indices to describe the RV in a thorough and comprehensive manner, such as RV index of myocardial performance, tricuspid annular plane systolic excursion, fractional area change, Doppler tissue imaging-derived tricuspid lateral annular systolic velocity (S'-wave), three-dimensional RVEF, RV longitudinal strain /strain rate by speckle-tracking echocardiography.[13] These indices are even more difficult to measure in critically ill neonates at risk for hemodynamic decompensation with prolonged interrogations. RTE during the weaning trial allowed us to evaluate whether the PH had resolved and the infant was hemodynamically ready for decannulation.

The RTE-weaning model provides clinicians real-time data to interpret changes in cardiac-loading conditions. Dynamic changes with stepwise decreases in circuit flow allowing the heart to fill and thus eject more affect the myocardial contractility and resistance to flow. Information regarding the ability of both LV and RV to adapt to these dynamic volume shifts and function optimally after a period of prolonged rest is readily available with RTE. RTE has the unique distinction of providing direct correlation of myocardial function during different loading conditions non-invasively to guide interventions with tailored vasoactive medications and timely decannulation. The goal of this review was to first address the binary question of whether RTE-provided data useful for weaning. Our results suggest that RTE is a valuable and feasible tool that can be easily incorporated into clinical practice to help clinicians decide which patients need intervention and whether they need volume versus inotropic support versus RV support. Additionally, RTE also provides information when the patients are not ready to come off ECMO support.

In summary, our results suggest that RTE serves as an objective diagnostic tool in weaning neonates from VA-ECMO while serving

as a guide toward optimizing medical interventions that may result in successful decannulation. Our retrospective review documents our attempts to bridge an important knowledge gap in understanding the process of physiological readiness for decannulation and utility of RTE to streamline the weaning from ECMO. This is the first article that exclusively studies the use of RTE during decannulation in neonatal ECMO.

What is Known?

- The leading indication for neonatal ECMO currently is hypoxic-respiratory failure due to PH in infants with congenital diaphragmatic hernia.
- Resolution of maladaptive PH, which usually wanes significantly in the first two weeks of life, signals an infant's readiness for discontinuation of ECMO support.
- There are no published guidelines advocating the routine use of echocardiography in determining a neonate's readiness to come off ECMO support.

What this Study Adds?

- Real-time echocardiography is a valuable tool to aid clinical decision-making while weaning neonates from VA-ECMO.
- Use of real-time echocardiography facilitates successful decannulation as it provides information regarding the need for fluid volume versus inotropic support.
- Use of real-time echocardiography during "clamp" trials permits rapid identification of neonates not ready for decannulation.

Competing Interests

None.

Author Contribution

SHG made substantive contributions to the conception, drafting, and design of this paper, reviewed and revised it critically for important intellectual content and approved the final manuscript.

AK, AV, RC, CC, and JGP made substantive contributions to the paper by performing the initial literature review of the subject matter, interpreting the patient data in light of the literature review, conceptualizing, designing and drafting the initial manuscript, and approving the final manuscript.

CJF conceptualized and designed the paper, supervised the work, critically reviewed and revised the manuscript for important intellectual content, and approved the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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