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Echocardiography evaluation of neonatal vein of Galen aneurysmal malformation

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Original Article

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Abstract

Background: In neonatal vein of Galen aneurysmal malformation, vein of Galen aneurysmal malformation echocardiography remains the mainstay for early detection and explains various haemodynamic changes occurring due to a large systemic arterio-venous shunt. However, there is limited evidence of echocardiography in risk stratifying neonatal vein of Galen aneurysmal malformation vein of Galen aneurysmal malformation. The objective of this study was to identify echocardiographic parameters that could be associated with major outcomes and guide timing of neuro-intervention. *Methods:* In this retrospective chart review, infants < 28 days of age with the diagnosis of vein of Galen aneurysmal malformation vein of Galen aneurysmal malformation were included. Demographic, clinical, and echocardiographic parameters were compared in neonates who survived or died with neonatal presentation. A risk algorithm model based on key echocardiographic parameters was developed to determine those who are at risk of early death. *Results:* Of the 19 neonates included, with median birth weight 3.1 kg (IQR 2.58–3.36), nine (47%) neonates died at median age of 5 days (IQR 4–17). All neonates showed retrograde diastolic flow at the level of descending aorta by colour Doppler on the first post-natal echocardiogram at median age of 2 days (IQR 1–5.5). An aortic antegrade-to-retrograde velocity time integral ratio of < 1.5 and supra-systemic pulmonary artery pressure had 100% positive predictive value of death ($p = 0.029$), whereas aortic antegrade-to-retrograde velocity time integral ratio of > 1.5 and sub-systemic pulmonary artery pressure had 100% positive predictive value of survival ($p = 0.029$). *Conclusion:* Combination of aorta antegrade-to-retrograde velocity time integral ratio and degree of pulmonary hypertension on the first post-natal echocardiogram may help stratify the severity of disease and guide optimal timing for neuro-intervention for neonatal vein of Galen aneurysmal malformation.

Despite prenatal and early post-natal diagnosis of vein of Galen aneurysmal malformation, neonates continue to have poor outcomes in the current era.[1] Neonates with vein of Galen aneurysmal malformation are at risk of developing high output cardiac failure and pulmonary hypertension soon after birth.[2,3] The severity of heart failure depends on the amount of systemic "steal" into the low resistance cerebral circuit creating a state of decreased systemic cardiac output and increased pulmonary blood flow. Neonates, especially those presenting early on, are at an elevated risk of mortality and poor neurological and cardiovascular outcomes. Some neonates require early neuro-intervention to control heart failure and prevent multi-organ failure, while others can be medically managed until 4–6 months of age when elective neuro-intervention is performed to reduce procedural risk.

Echocardiography is the primary imaging modality to evaluate the cardiac effects of vein of Galen aneurysmal malformation. Previous studies have elucidated echocardiographic parameters that may help determine the severity of vein of Galen aneurysmal malformation at birth such as antegrade-to-retrograde velocity time integral ratio in the descending aorta by spectral Doppler, superior caval vein flow, and pulmonary hypertension index.[4–6] There is interest in using specific echocardiogram parameters to determine severity and identify the need for early intervention and predict the outcomes of this rare malformation; however, it is unclear if a single echocardiogram parameter can be used to predict outcomes in these patients. The primary objective of this study is to describe echocardiographic parameters in neonates with vein of Galen aneurysmal malformation and assess their association with major outcome measures in this high-risk population.

Methods

Study design

We performed a retrospective chart review of all patients with the diagnosis of vein of Galen aneurysmal malformation at Children's Medical Center, Dallas after obtaining approval from

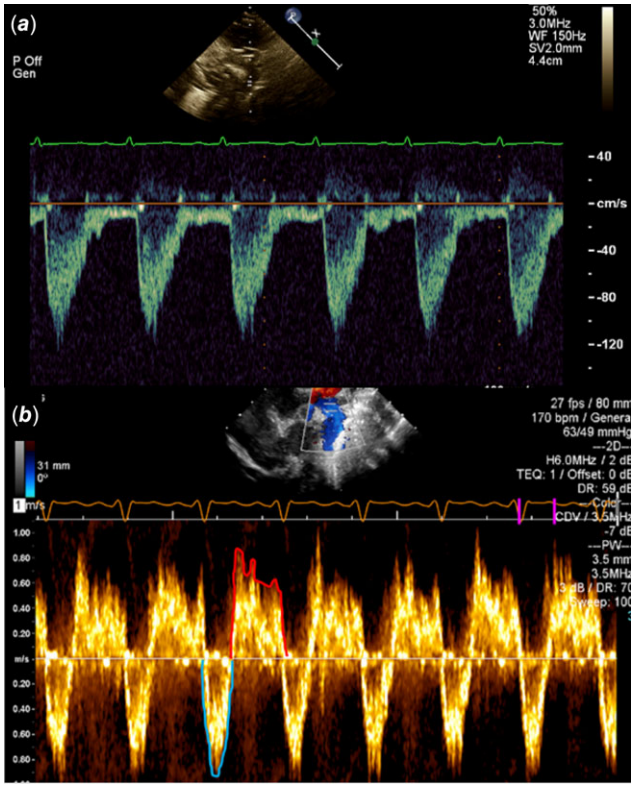

Figure 1. ***a***: normal pulse wave doppler of the transverse aorta with antegrade blood flow in systole and no retrograde diastolic flow. ***b***: pulse wave doppler of the transverse aorta in neonatal vein of Galen aneurysmal malformation demonstrating significant diastolic flow reversal (red) with antegrade: retrograde VTI ratio of < 1 in this patient.

internal review board (Institutional Review Board study number STU-2021-0845) between January 2007 and March 2022. Neonates less than 28 days old at the time of diagnosis and requiring hospitalisation, medical, and/or surgical interventions were included. Infants in whom the diagnosis was made beyond 28 days of age and those who did not have an echocardiogram at our institution prior to their first intervention were excluded from the study. In addition, patients who had inadequate information regarding survival at one year of age, either due to transfer to another centre or inadequate data in our system, were excluded. The demographic, clinical, and brain MRI data were obtained from patients' medical records.

Echocardiography

We assessed echocardiographic parameters that were previously reported to have an association with disease severity in patients with vein of Galen aneurysmal malformation. These echocardiogram measurements include ratio of antegrade-to-retrograde velocity time integral based on spectral Doppler at the level of descending thoracic aorta (Fig. 1),[4] superior caval vein two dimensional and Doppler measurements in subcostal views to calculate superior caval vein flow,[5] degree of pulmonary hypertension (based on tricuspid valve regurgitation peak gradient, interventricular septal configuration/motion, and patent ductus arteriosus direction of flow), as well as subjective assessment of right and left ventricle systolic function. Superior caval vein flow was calculated using the previously published formula: superior caval vein cross-sectional area x velocity time integral x heart rate/body weight (kg).[7] Patients were categorised as supra-systemic pulmonary artery pressure or sub-systemic pulmonary artery pressure by ratio of tricuspid regurgitation peak gradient to systemic systolic blood pressure. If the tricuspid regurgitation was inadequate for right ventricle pressure estimate, then secondary signs like patent ductus arteriosus direction of flow and septal position were used. Most of the information was obtained from the echocardiogram reports. If the reports were lacking these measurements, PD, MC, and CR obtained this data from source images without prior knowledge of their outcomes. Images were reviewed on Syngo Dynamics workstations (Siemens Medical Solutions, Ann Arbor, MI, United States of America)

Clinical management

The medical management of the neonates with vein of Galen aneurysmal malformation was at the discretion of the medical team in combination with the procedural team. In 2020, a multi-disciplinary team was formed including members from Neonatology, Neurosurgery, Cardiology, Aneasthesia, and Neurology. This group created an algorithm to guide medical and procedural management of these patients based on the most up-to-date literature on this lesion.[8] Since the creation, the primary team was able to consult the members of the multi-disciplinary team to help guide decision-making. The decision to perform a neuro-intervention was at the discretion of the medical team and the proceduralist. Some of the patients in our study had an intervention performed by a paediatric interventional radiologist while others had intervention performed by a paediatric neurosurgeon with specialised training in interventional neuroradiology.

Data analysis

Clinical and echocardiographic parameters were compared between infants who died versus survived at their last follow-up. As the data were not normalised, continuous variables were expressed as median (interquartile range) and categorical variables were expressed as number (percentage). Categorical variables were analysed using the Fisher exact test, and nonparametric continuous variables were analysed using the Mann–Whitney U-test. Based on previously published echocardiographic cut-offs that elucidated the severity of neonatal vein of Galen aneurysmal malformation, binary analysis was performed using odds ratio for determining post-test probability of death and survival in our population.

Results

Of 31 patients with the diagnosis of vein of Galen aneurysmal malformation in our system, 19 patients met the inclusion and exclusion criteria. The median birth weight was 3.1 kg (IQR 2.58–3.36) with 10 (53%) males and 9 (47%) females. Seven neonates were diagnosed prenatally. In the remaining 12, the median age of diagnosis was 2 days (IQR 1–3.5). Of the 14 who were diagnosed post-natally, all neonates presented with symptoms of congestive heart failure or persistent pulmonary hypertension.

Echocardiography

The median age of first post-natal echocardiogram was 2 days (IQR 1–5.5). All neonates had some retrograde diastolic flow at the level of descending aorta noted by colour Doppler. Spectral Doppler for calculation of antegrade-to-retrograde velocity time integral ratio

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Table 1. Demographic characteristics and echocardiographic parameters.

	Total (n = 19) Median (IQR) Number [percentage]	Died (n = 9) Median (IQR) Number [percentage]	Survived (n = 10) Median (IQR) Number [percentage]	*p* value
Demographics				
Age at diagnosis (days)	1 (0–1)	1 (0–1)	1 (0–2)	0.77
Birth weight (Kg)	3.1 (2.6–3.4)	3.17 (3.015–3.36)	2.8 (2.54–3.13)	0.238
Gestational age (weeks)	38 (37–39)	38 (37–39)	38 (37–39)	1
Male	10 [53%]	6 [67%]	4 [40%]	0.37
Intervention performed	13 [68%]	5 [56%]	8 [80%]	0.35
Age of first intervention (days)	7 (3–11)	4 (3–7)	10 (4.75–38)	0.42
Prenatal diagnosis	7 (37%)	3 (33%)	4 (40%)	1
Clinical parameters				
Need for mechanical support	13 [68%]	9 [100%]	4 [40%]	0.01
Need for inotropic support	9 [47%]	6 [66.7%]	3 [30%]	0.18
Multi-organ dysfunction	11 [58%]	8 [89%]	3 [30%]	0.02
Echocardiographic parameters				
Age at first echocardiogram (days)	2 (1–5.5)	2 (1–3)	4.5 (1–9)	0.19
Aorta Antegrade: retrograde VTI ratio	1.05 (0.91–2)	1.04 (0.91–1.31)	1.96 (0.85–2.65)	0.23
RV pressure percent of systemic pressure (%)	86 (69–102)	100 (81–114)	83 (65–88)	0.11
SVC flow (ml/kg/min)	515 (380–591)	486 (422–591)	520 (361–581)	0.96
Ventricular dysfunction	6 [32%]	4 [44%]	2 [20%]	0.35
Binary analysis				
VTI<1.5	11 (58%)	8 (89%)	3 (30%)	0.049
Supra-systemic PA pressure	7 (37%)	6 (66.7%)	1 (10%)	0.019
SVC flow>400 (ml/kg/min)	11 (58%)	6 (66.7%)	5 (50%)	1

PA = pulmonary artery; RV = right ventricle; SCV = superior caval vein; VTI = velocity time integral (on spectral Doppler).

was available in 17 patients, and superior caval vein spectral Doppler for calculation of superior caval vein flow was available in 16 patients. The median antegrade-to-retrograde velocity time integral ratio in the descending aorta by spectral Doppler was 1.05 (0.91–2). The patent ductus arteriosus was entirely shunting right to left in 11 (59%) patients, bidirectional in 3 (15%), entirely left to right in 1 (5%) and not evident in the remaining 4 (21%) patients at the time of first echocardiogram. The right ventricle was significantly dilated (≥ moderate) in 15 (79%) patients, and ventricular dysfunction was present in 6 (32%) patients. There were no differences in the echocardiographic parameters between those with prenatal vs. post-natal diagnosis. In 3 (16%) patients, the superior caval vein was over-riding the atrial septum with a sinus venosus type of atrial septal defect. Of them, one was also diagnosed with concomitant coarctation of aorta. In addition, two patients were noted to have a muscular ventricular septal defect that were present on their last follow-up at 2 months and 15 months of age, respectively. The rest of the echocardiographic measurements are listed in Table 1.

Outcomes

Of the 19 patients, 9 (47.4%) died at median age of 5 days (IQR 4–17). The median age of the remaining 10 (53%) patients at their last follow-up was 465 days (IQR 130–1613). There was no significant difference in the echocardiographic parameters between patients who survived versus died (Table 1). Of the patients with early mortality, patent ductus arteriosus was entirely shunting right to left in 8 (89%) and bidirectional in 1 (11%). In those who survived, the ductus arteriosus was not identified/closed in 4 (40%), shunting bidirectional in 2 (20%), and shunting right to left in 3 (30%) and left to right in 1 (10%). In terms of clinical status, need for mechanical ventilation, need for inotropic support and multi-organ dysfunction were associated with early mortality compared to survival (Table 1). Using binary cut-off values based on prior reported literature, the combination of both the aortic antegrade-to-retrograde velocity time integral ratio and degree of pulmonary hypertension was helpful in predicting death and survival. In neonates with an aortic antegrade-to-retrograde velocity time integral ratio of < 1.5 and supra-systemic pulmonary artery pressure, the positive predictive value of death was 100% (p = 0.029) whereas in those with aortic antegrade-to-retrograde velocity time integral ratio of > 1.5 and sub-systemic pulmonary artery pressure, the positive predictive value of survival was 100% (p = 0.029) (Fig. 2).

A total of 13 (68%) patients underwent neuro-interventions in the form of coil embolisation (n = 10) or glue embolisation (n = 3) of major vascular structure feeding the vein of Galen aneurysmal

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(a) Aorta A:R VTI ratio <1.5		
	Died	Alive
Present	8	3
Absent	1	5
p = 0.0498 Predicting death: PPV 73%, NPV 83%		

(b) Suprasystemic PA pressure		
	Died	Alive
Present	6	1
Absent	3	9
p = 0.0198 Predicting death: PPV 86%, NPV 75%		

(c) SVC flow > 400 ml/kg/min		
	Died	Alive
Present	6	5
Absent	2	3
p = 1.0		

(d) Aorta A:R VTI ratio <1.5 AND supra-systemic PA pressure		
	Died	Alive
Present	5	0
Absent	4	8
p = 0.029 Meeting both criteria predicting death: PPV 100%, NPV 67%		

(e) Aorta A:R VTI ratio >1.5 AND sub-systemic PA pressure		
	Died	Alive
Present	0	4
Absent	9	4
p = 0.029 Meeting both criteria predicting survival: PPV 100%, NPV 69%		

Figure 2. Binary analysis of the study cases in 2 x 2 tables set up demonstrates post-test probability of death versus survival based on echocardiographic parameters. Aortic antegrade-to-retrograde velocity time integral ratio: aorta A:R VTI; NPV = negative predictive value; pulmonary artery = pulmonary artery; SCV = superior caval vein; PPV = positive predictive value.

malformation. Among those who underwent neuro-interventions, 7 (54%) had intervention under seven days of age. The median age (IQR) of neuro-intervention was 7 (3–11) days. In the two patients who had intervention outside of the neonatal period (208 days and 107 days), both had antegrade-to-retrograde velocity time integral ratio > 2.5, while one had supra-systemic pulmonary artery pressure and one had sub-systemic pulmonary artery pressure. Post-intervention complications including intracranial haemorrhage, stroke, coil embolisation, seizures, or hydrocephalus were noted in a total of 6 (46%) neonates. Of the patients that died, five underwent either partial or complete embolisation, and two died due to worsening intracranial haemorrhage after neuro-intervention and medical care were subsequently withdrawn.

Of the six neonates that did not undergo neuro-intervention, two had significant comorbidities in the form of craniofacial and airway abnormalities that died before neuro-intervention could be performed. One patient was made "do not resuscitate" due to parental request and had extensive intracranial haemorrhage pre-intervention. One patient had significant left-sided holo-hemispheric ischaemic stroke on MRI head with diffuse cortical laminar necrosis and atrophy of the brainstem where neuro-intervention was not offered. The remaining two patients survived without the need for neuro-intervention.

Discussion

This retrospective study was undertaken to evaluate the ability of echocardiographic parameters to predict outcomes in neonates with vein of Galen aneurysmal malformation. The mortality of neonatal vein of Galen aneurysmal malformation remains high in the current era despite higher rates of fetal diagnosis and advance in neonatal neuro-interventions and neonatal ICU. The mortality of neonatal vein of Galen aneurysmal malformation in our study was 47%, similar to other reported series.[1,6,9] In agreement with previously published studies, we were able to demonstrate a difference in survival with an antegrade-to-retrograde velocity time integral ratio < 1.5 and supra-systemic pulmonary artery pressure.[4] Additionally, the combination of aortic antegrade-to-retrograde velocity time integral ratio and pulmonary hypertension improved the accuracy in predicting death and survival in our cohort.

These two parameters represent the main physiologic consequences of vein of Galen aneurysmal malformation which result in the critical illness. The antegrade-to-retrograde velocity time integral ratio quantifies the amount of systemic steal that is being re-routed through the low resistance malformation. Though these patients have high output heart failure, most of the cardiac output does not reach the end organs because of the systemic steal which ultimately can result in multi-organ dysfunction from inadequate perfusion. The degree of pulmonary hypertension is related to the obligatory increased pulmonary blood flow that occurs both in utero and post-natally that results in right heart failure.[9–11] By capturing these two physiologic problems and quantifying them with these echocardiographic measurements, we may be able to better predict which neonates will have more significant disease.

Using the combination of these two values may be helpful to the medical team in determining the ideal timing of neuro-intervention. Patients with an aortic antegrade-to-retrograde velocity time integral of < 1.5 and supra-systemic pulmonary artery pressure on their first echo may be more likely to have severe disease whereas those with an aorta antegrade-to-retrograde velocity time integral ratio of > 1.5 and sub-systemic pulmonary artery pressure are more likely to have less severe disease. Based on our results, we recommend using the following algorithm for determining timing of intervention (Fig 3). Aortic antegrade-to-retrograde velocity time integral < 1.5 with supra-systemic pulmonary artery pressure on the first echocardiogram is an indication for urgent intervention as long as there are no contraindications to embolisation. Aortic antegrade-to-retrograde velocity time integral > 1.5 and sub-systemic pressure are an indication for medical management, with close monitoring of worsening signs of systemic steal and pulmonary hypertension. Decision for neuro-intervention in vein of Galen aneurysmal malformation varies among centres but largely depends on the

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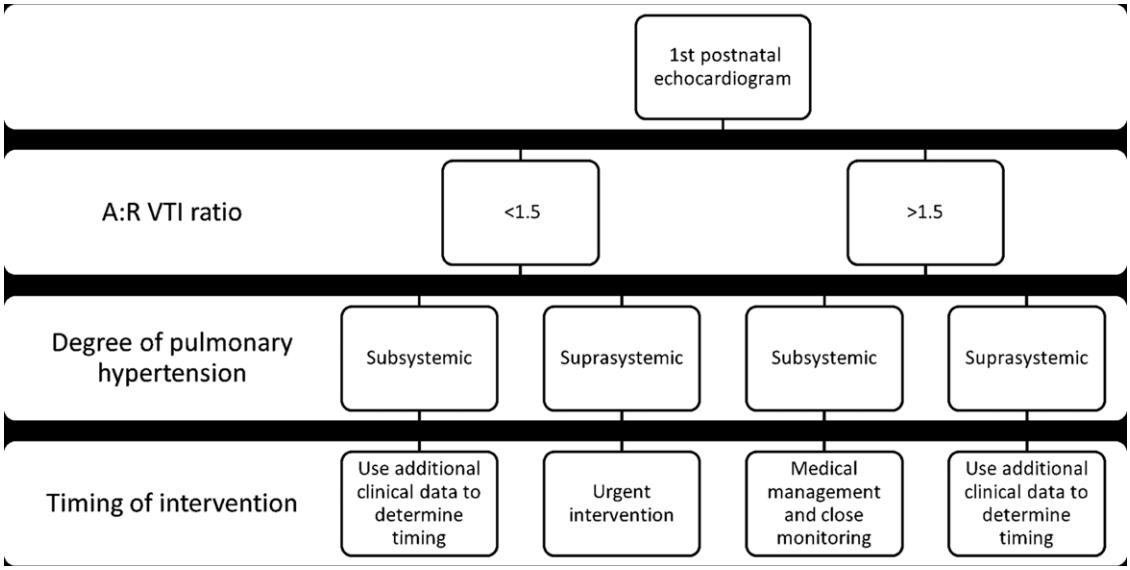

Figure 3. Proposed algorithm for management of neonatal vein of Galen malformation at our institution based on study findings.

severity of haemodynamic compromise as well as pre-interventional brain malformation such as connection of the vein of Galen aneurysmal malformation to deep venous drainage, concomitant brain injury and hydrocephalus.[12,13] As this is a rare condition, there are no large, randomised studies that guide appropriate timing of neuro-intervention. Further research is needed to identify the impact and complications of neuro-intervention on neurological outcomes.

The echocardiogram is often the primary diagnostic, non-invasive tool that provides insights into the cardiovascular and haemodynamic condition in neonates with vein of Galen aneurysmal malformation. Thankavel and colleagues showed that neonates with A: R VTI of < 1.5 at the level of descending thoracic aorta were associated with developing significant haemodynamic instability and early mortality[4] which is consistent with our findings. The above-mentioned study was performed at our centre, and some of the patients may have overlapped as the time of reviewing patients was similar. However, 12 (63%) of patients included in the current study were after that publication. Our results are also consistent with other reports where degree of retrograde flow in the descending aorta is associated with mortality.[1,14] Degree of pulmonary hypertension has not consistently been associated with mortality,[1] though degree of pulmonary hypertension has been historically regarded as a sign of severe disease. Our study demonstrates an association between supra-systemic pulmonary artery pressure and mortality. Continuous right-to-left shunting across the patent ductus arteriosus results from systemic steal across the low resistance circuit of brain as well as from elevated pulmonary artery pressures.[15] Most of the neonates in our study who had early mortality were noted to have continuous right-to-left shunting across the patent ductus arteriosus, therefore, could also be a poor prognostic marker.

Superior caval vein flow has also been reported as a marker that can be used to predict outcomes in neonates with vein of Galen aneurysmal malformation. Physiologically, higher superior caval vein flow is a surrogate marker for increased blood flow through the malformation. Heuchan et al inferred that those with superior caval vein flow > 400 ml/kg/min had adverse outcomes (death and neurological damage).[5] In our study, increased superior caval vein flow of > 400 was found in majority of the neonates (15/19). However, there was no significant difference in the superior caval vein flow between those who survived versus died. The difference in our study may be related to the retrospective nature and that the components of the superior caval vein flow were not targeted specifically on these echocardiograms. In addition, differences in mortality amongst patients with similar echocardiographic parameters could stem from actual differences in the micro-architecture of the vein of Galen aneurysmal malformation. These include number and type of groups of arterial feeders, the presence of "pseudo feeders," and leptomeningeal collaterals, periventricular calcifications, venous congestion, and parenchymal changes have been associated with poor outcomes.[16–18] Therefore, combining echocardiogram with additional neuroimaging parameters could help prognosticate disease severity in these neonates. Future studies are necessary to evaluate these parameters together through a multi-disciplinary approach.

While this was not a primary objective of this study, we did identify several patients that had CHD in addition to vein of Galen aneurysmal malformation. McElhinney, et al. previously reported associated CHD, including sinus venosus atrial septal defects and coarctation of the aorta.[19] We had 3 (16%) patients with a right-sided superior caval vein over-riding the atrial septum with connection to the left atrium, which is a higher percentage than would be expected in the general population.[10] This anomaly is on the same spectrum as sinus venosus defects.[11] This association should be investigated further to determine any prognostic significance.

Limitations: The data are limited by a small number of patients with this rare disease and our findings should be validated in larger multi-centre studies. The assessment of antegrade-to-retrograde velocity time integral and superior caval vein flow was measured retrospectively in our study as this was not routinely reported in the result section of the report. However, the readers were blinded to the outcome while collecting the data on Syngo for accurate unbiased assessment of these values. Additionally, antegrade-to-retrograde velocity time integral ratio and superior caval vein flow could not be calculated in all patients as spectral Doppler of

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descending aorta and superior caval vein were not obtained for all patients. In addition, statistical differences among echocardiographic parameters in neonates who died versus survived could not be achieved due to preselection of an overall high-risk population.

Conclusion

In the current era, the mortality of neonatal vein of Galen aneurysmal malformation remains high. We postulate that using a combination of aorta antegrade-to-retrograde velocity time integral ratio and degree of pulmonary hypertension on the first post-natal echocardiogram can help stratify the severity of disease and predict risk of death in neonates with vein of Galen aneurysmal malformation. Hence, using these echocardiogram findings may help the medical team in determining optimal timing of neurointervention in this cohort.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123003402.

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Competing interests. None.

Ethical standard. Ethical approval was waived by the local Ethics Committee of University of Texas Southwestern Medical Center in view of the retrospective nature of the study, and all the procedures and tests performed were part of the routine care.

Author contribution. All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Pezad Doctor, Melinda J Cory, and Claudio Ramaciotti. The first draft of the manuscript was written by Pezad Doctor and Melinda J Cory, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Informed consent. The need for informed consent was waived for this study as none of the information or images reveal patient identity.

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