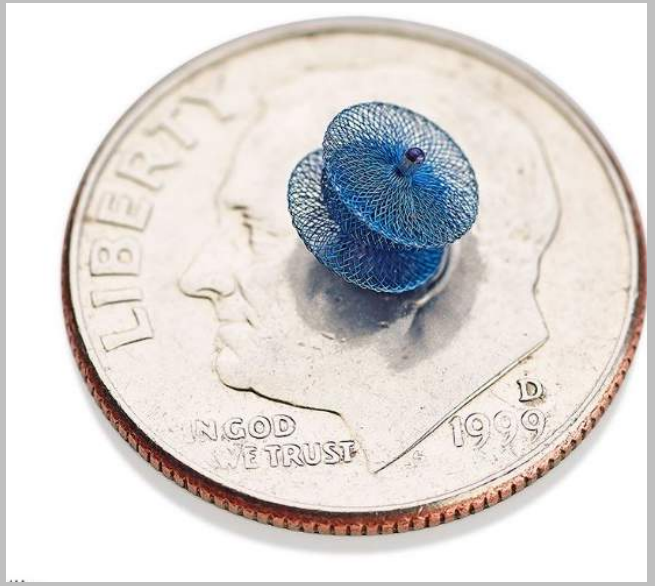
Treatment of Patent Ductus Arteriosus in Premature infants

Francisco J. Díaz Sotomayor, MD
Assistant Professor
Department of Pediatrics
UPR- School of Medicine
Interventional Pediatric Cardiology
Pediatric Critical Care Medicine

Nothing to disclose

Outline

- Introduction
- Current Management Recommendations
- Piccolo Data that obtained FDA approval
  - And got us interested
- Our experience in the CCPRC

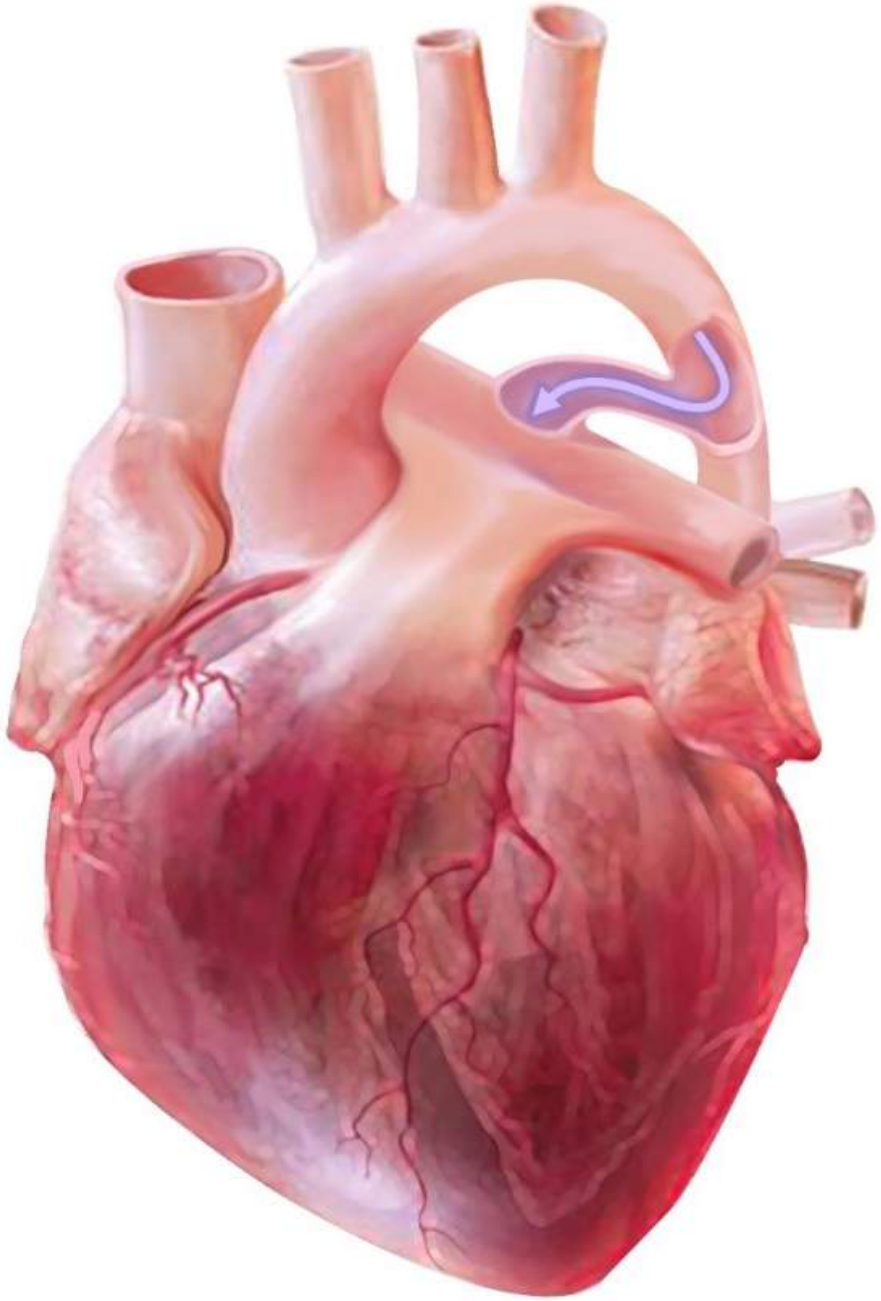


Prematurity

PREMATURE INFANTS ARE AT AN INCREASED RISK FOR COMPLICATIONS IN THE PRESENCE OF A PERSISTENT LARGE PATENT DUCTUS ARTERIOSUS (PDA)

OVER PERFUSION OF LUNGS AND UNDER PERFUSION OF SYSTEMIC CIRCULATION IS ASSOCIATED WITH:

- **BRONCHOPULMONARY DYSPLASIA (BPD)**
- **PULMONARY HYPERTENSION**
- **NECROTIZING ENTEROCOLITIS (NEC)**
- **INTRAVENTRICULAR HEMORRHAGE (IVH)**
- **RETINOPATHY OF PREMATURITY**
- **RENAL IMPAIRMENT**



Gillam-Krakauer et al. NeoReviews 19, no. 7 (2018): e394-e402
Chaudhary, N., et al. J Neonatal Biol 5, no. 238 (2016): 2167-0897

PEDIATRICS®

STATE-OF-THE-ART REVIEW ARTICLE|
NOVEMBER 01 2020

Patent Ductus Arteriosus of the Preterm Infant

Shannon E.G. Hamrick, MD; Hannes Sallmon, MD; Allison T. Rose, MD; Diego Porras, MD; Elaine L. Shelton, PhD; Jeff Reese, MD; Georg Hansmann, MD, PhD

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Determinants of Risk for Preterm Infants with an hsPDA

Pediatrics. 2020;146(5). doi:10.1542/peds.2020-1209

Lower Risk	Determinants of Risk (hsPDA)	Higher Risk
No	Tachycardia	Yes
No	Tachypnea	Yes
No need for respiratory support of oxygen, stable Spo_2 and Pao_2	Respiratory support	Need for invasive or non-invasive respiratory support Worsening respiratory situation (eg, increasing flow and F_{IO2} on HFNC; increasing PEEP, PIP and F_{IO2} on CPAP; NIV; MV) and frequent desaturations
Abdomen soft, not distended	Abdominal signs and symptoms	
Not present	Signs of organ dysfunction	Abdominal distension, residual feeding volume (other pre-NEC signs)
• LA only mildly dilated: LA/Ao ≤ 1.2 (PLAX) • Normal LV size • Normal systolic LV function (LVEF ≥ 55%) • Ductal Diameter ≤ 1mm (at narrowest ID) • PDA Vmax ≥ 3 m/s (CW Doppler) • Ductal systolic and diastolic left-to-right flow ≥ 2 m/s (continuous) usually indicates narrowing (closing) PDA • Normal mean and diastolic PA flow • ACA RI ≤ 0.75 • No (or only early) diastolic retrograde DAO flow	Echocardiography Doppler sonography (cerebral, abdominal)	• Severe LA dilation: LA/Ao ≥ 1.4 (PLAX) • Severe LV dilation (4C view, PSAX) • Systolic LV dysfunction (LVEF < 50%) • Ductal diameter ≥ 2 to 3 mm (at narrowest ID) or ductal diameter greater than or equal to MPA diameter • PDA Vmax ≤ 2m/s (W, unrestrictive) • Ductal left-to-right diastolic flow ≥ 0.5 m/s • Highly elevated mean + diastolic PA flow • Severe PA dilation (eg, LPA > AAO) • ACA RI ≥ 0.9 • Holodiastolic retrograde DAO flow (steal)

Pharmacologic Treatment Strategies for PDA in the Preterm Infant

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

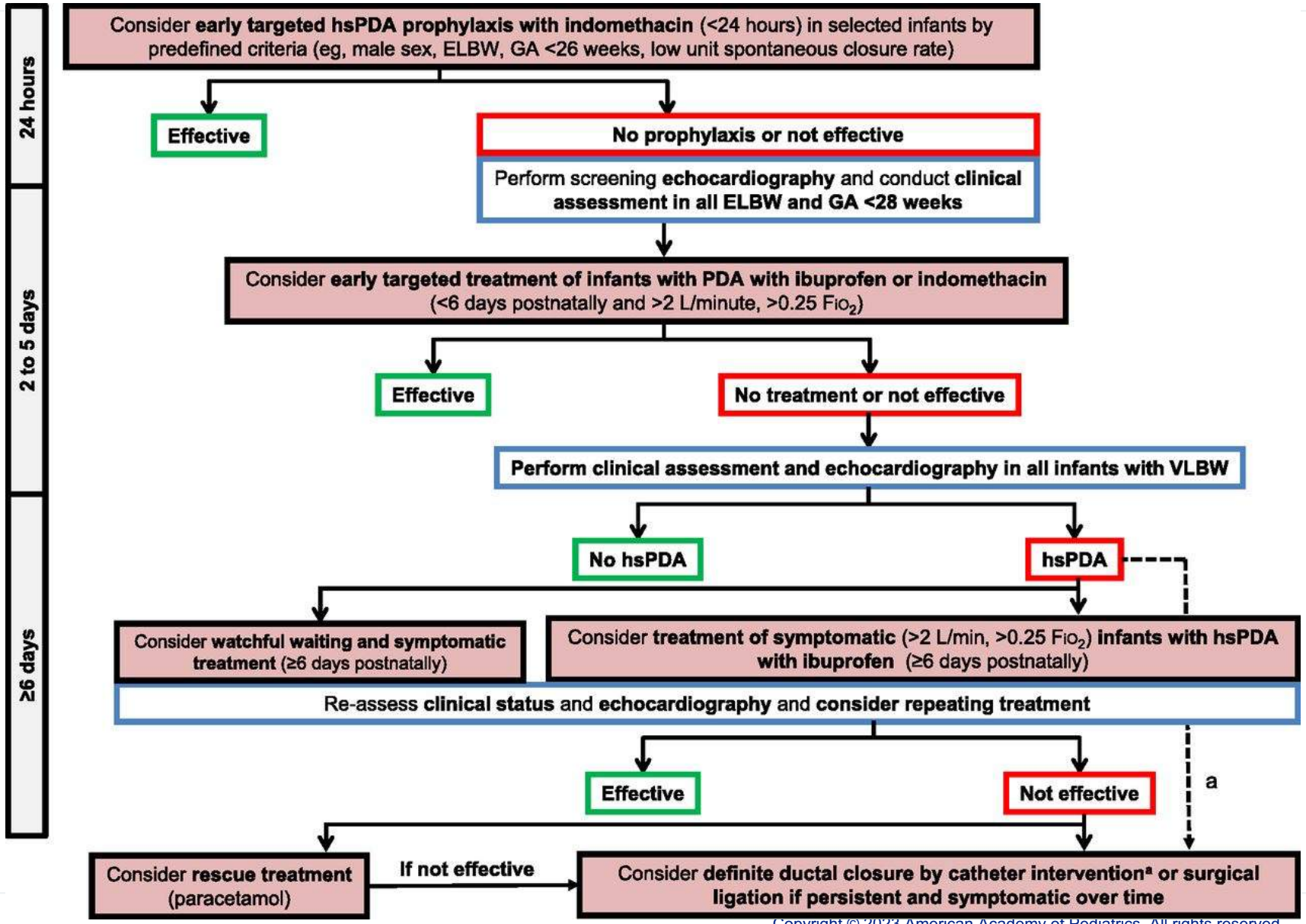
Pediatrics. 2020;146(5). doi:10.1542/peds.2020-1209

	Drug of choice	Dosing	Comments	Pros	Cons
Targeted prophylaxis	Indomethacin	3 x 0.1 mg/kg per dose IV every 12 h	Do not start treatment within the first 6 h of life. It is not recommended to use ibuprofen IV in the first 24 h of life –increased risks for renal failure, GI hemorrhage, and possibly PPHN	Prevention of IVH (prophylaxis); risk reduction of pulmonary hemorrhage; association with beneficial neurodevelopmental outcome in boys	Unnecessary treatment of many infants without an hsPDA
Early Targeted Treatment of infants with hsPDA < 6 days	Indomethacin	1 x 0.2 mg/kg per dose IV, followed by 2 x 0.1 mg/kg per dose every 12 h	It is not recommended to use ibuprofen IV in the first 24 h of life –increased risks for renal failure, GI hemorrhage, and possibly PPHN	Risk reduction of pulmonary hemorrhage; possible risk reduction of in-hospital mortality	Unnecessary treatment of some infants who have a small PDA that is hemodynamically not significant; unclear effects on outcome
	Ibuprofen	10 mg/kg per dose PO or IV, followed by 5 mg/kg at 24 and 48 h of start			
Treatment in symptomatic infants hsPDA > 6 days	Ibuprofen	10 mg/kg per dose PO or IV, followed by 5 mg/kg at 24 and 48 h of start	Higher doses might be considered	Treatment only ion infants with hsPDA	No evidence for beneficial long-term outcome if administered late (>6–14 d); might still be associated with adverse outcome (eg, BPD) due to a longer duration of a significant shunt
Rescue Treatment	Paracetamol	15 mg/kg per dose PO or IV every 6 h for 3-7 days	Might be attempted in selected infants after failed standard COX inhibitor treatment; can also be applied earlier if contraindications for standard COX inhibitor use are present	Might prevent the use of more invasive measures, such as ligation or catheter intervention; no known renal or gastrointestinal side effects	Unclear effect on neurodevelopmental outcome

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Suggested Treatment Algorithm

Pediatrics. 2020;146(5). doi:10.1542/peds.2020-1209



Surgical Ligation of the DA
Very effective but…

- The PDA ligation rate in a US cohort of infants between 23-30 weeks of GA decreased from 8.4% in 2006 to 2.9 % in 2015.

- Bixler GM, Powers GC, Clark RH, Walker MW, Tolia VN. Changes in the diagnosis and management of patent ductus arteriosus from 2006 to 2015 in United States neonatal intensive care units. *J Pediatr.* 2017;189:105–112

- Prophylactic and early ligation are no longer indicated

- Mosalli R, Alfaleh K. Prophylactic surgical ligation of patent ductus arteriosus for prevention of mortality and morbidity in extremely low birth weight infants. *Cochrane Database Syst Rev.* 2008;(1):CD006181

- Major complications after surgical ligation include post ligation syndrome, AKI, vocal cord paralysis, prolonged Mech. Vent. and BPD.

- Foster M, Mallett LH, Govande V, et al. Short-term complications associated with surgical ligation of patent ductus arteriosus in ELBW infants: a 25-year cohort study [published online ahead of print November 4, 2019]. *Am J Perinatol*. doi:10.1055/s-0039-1698459

- Teixeira LS, Shivananda SP, Stephens D, Van Arsdell G, McNamara PJ. Postoperative cardiorespiratory instability following ligation of the preterm ductus arteriosus is related to early need for intervention*. J Perinatol*. 2008;28(12):803–81

- Aygün A, Poryo M, Wagenpfeil G, et al. Birth weight, Apgar scores and gentamicin were associated with acute kidney injuries in VLBW neonates requiring treatment for patent ductus arteriosus*. Acta Paediatr.* 2019;108(4): 645–65

- Henry BM, Hsieh WC, Sanna B, Vikse J, Taterra D, Tomaszewski KA. Incidence, risk factors, and comorbidities of vocal cord paralysis after surgical closure of a patent ductus arteriosus: a meta-analysis*. Pediatr Cardiol*. 2019;40(1): 116–12

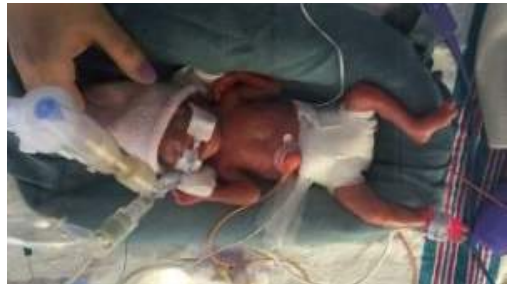
Treatment Options for Premature Infants with PDAs

TRANSCATHETER CLOSURE IS LESS INVASIVE THAN SURGERY AND MORE EFFECTIVE THAN MEDICAL THERAPY

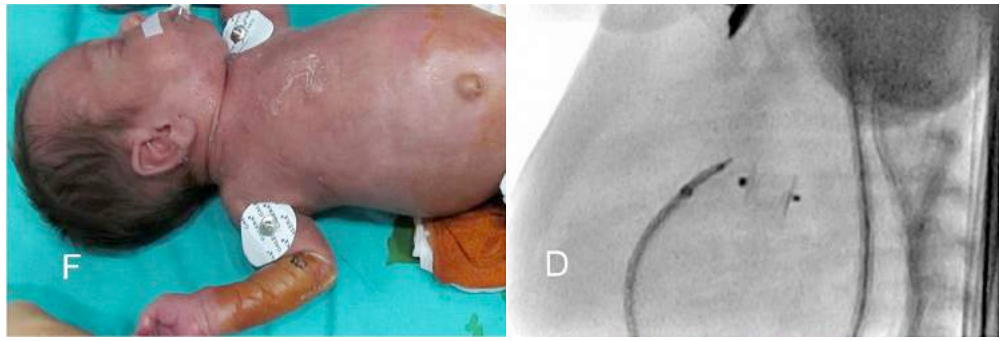
Medical Therapy

Surgical Ligation

Observation



Transcatheter Closure



Chaudhary, N., et al. J Neonatal Biol 5, no. 238 (2016): 2167-0897

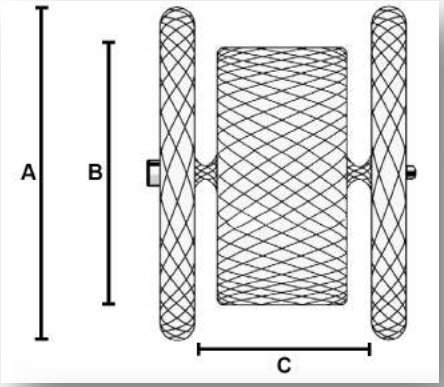
Jain, Amish, et al. *JAMA pediatrics* 169, no. 9 (2015): 863-872.

Van Overmeire et al. New England Journal of Medicine 343, no. 10 (2000): 674-681.

Ashrafi, Amir H. et al. Current opinion in cardiology 34, no. 1 (2019): 41-45.

Amplatzer Piccolo™ Occluder

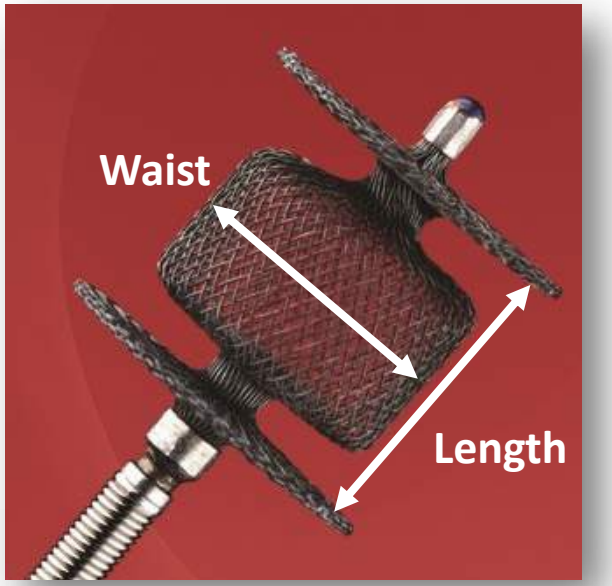
IDEAL FOR THE PREMATURE INFANT



A. Retention disc diameter
B. Waist diameter
C. Length between retention discs

REF	A ⟷ mm (in)	B ⟷ mm (in)	C ⟷ mm (in)
9-PDAP-03-02-L	4.00 (0.157)	3.00 (0.118)	2.00 (0.079)
9-PDAP-03-04-L	4.00 (0.157)	3.00 (0.118)	4.00 (0.157)
9-PDAP-03-06-L	4.00 (0.157)	3.00 (0.118)	6.00 (0.236)
9-PDAP-04-02-L	5.25 (0.207)	4.00 (0.157)	2.00 (0.079)
9-PDAP-04-04-L	5.25 (0.207)	4.00 (0.157)	4.00 (0.157)
9-PDAP-04-06-L	5.25 (0.207)	4.00 (0.157)	6.00 (0.236)
9-PDAP-05-02-L	6.50 (0.256)	5.00 (0.197)	2.00 (0.079)
9-PDAP-05-04-L	6.50 (0.256)	5.00 (0.197)	4.00 (0.157)
9-PDAP-05-06-L	6.50 (0.256)	5.00 (0.197)	6.00 (0.236)

Note: Length is measured from inside proximal disc to inside distal disc



Nine sizes:

- 3 waist diameters: 3, 4, 5 mm
- 3 waist lengths: 2, 4, 6 mm
- 3 disc sizes: 4, 5.25, 6.5 mm
- Sizing is noted as:
  9-PDAP-(waist)-(length)

Amplatzer Piccolo™ Occluder IDE & CAP Studies

OBJECTIVE

- To characterize the safety and effectiveness of the Amplatzer Piccolo Occluder to close the ductus arteriosus in subjects with a PDA.

STUDY DESIGN

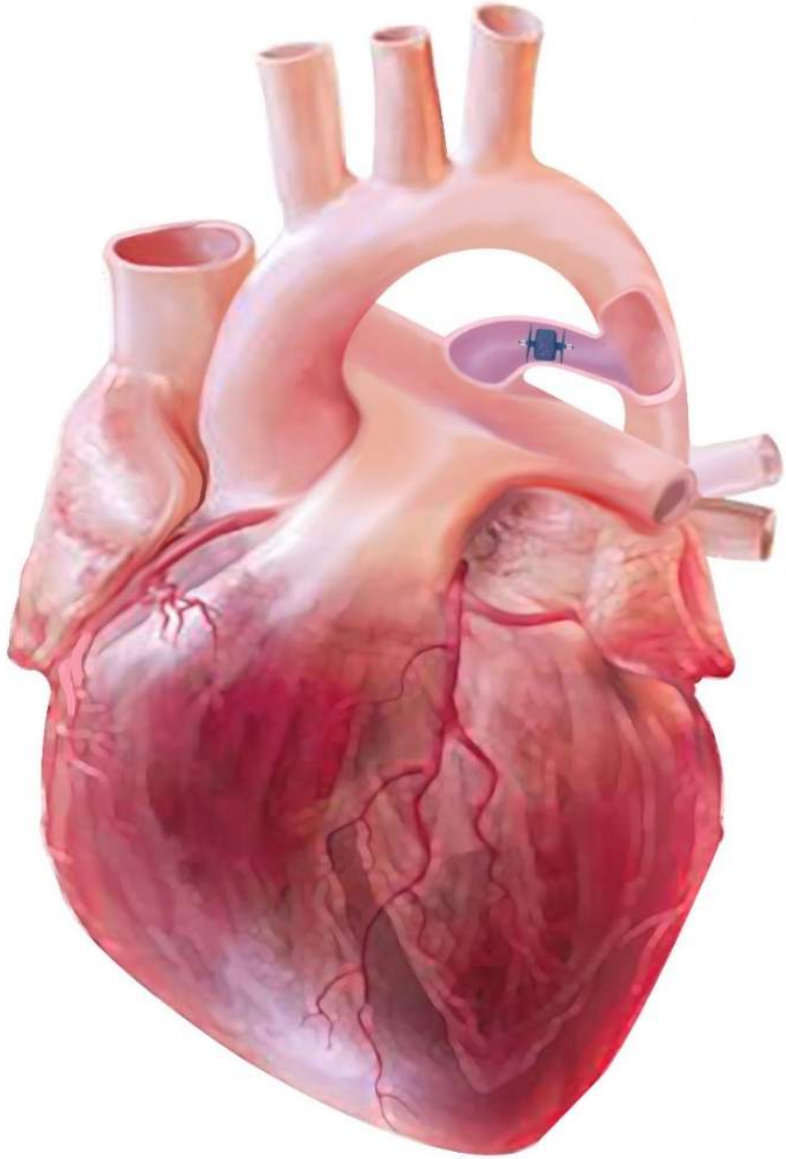
- Single arm, prospective, multicenter, non-randomized
- Independent Clinical Events Committee (CEC) and Echo Core Laboratory

SAMPLE SIZE

- IDE Study: 50 patients (18 subjects ≤ 2kg enrolled)
- CAP Study: 150 patients (82 subjects ≤ 2kg enrolled)

FOLLOW-UP

- Baseline, procedure, post-procedure, 30-days, 6-months, 1-year, 2-year, and 3 -years



Amplatzer Piccolo™ Occluder IDE Study

INCLUSION CRITERIA

- PDA diameter ≤ 4 mm
- PDA length ≥ 3 mm

KEY EXCLUSION CRITERIA

- Procedure weight < 700 gm
- Age at implant < 3 days
- Aortic coarctation or PA stenosis
- Cardiac output dependent on right to left shunt
- Intra-cardiac thrombus
- Active infection

PRIMARY SAFETY ENDPOINT:
Rate of major complications through 180 days post-implant

PRIMARY EFFICACY ENDPOINT:
Rate of effective PDA closure (Grade 0/1) at 6-months post-implant determined by TTE – core lab

SECONDARY ENDPOINT:
Rate of significant aortic or pulmonary obstruction through
6-months post-implant

Device Sizing for Premature Infants (≤ 2kg)

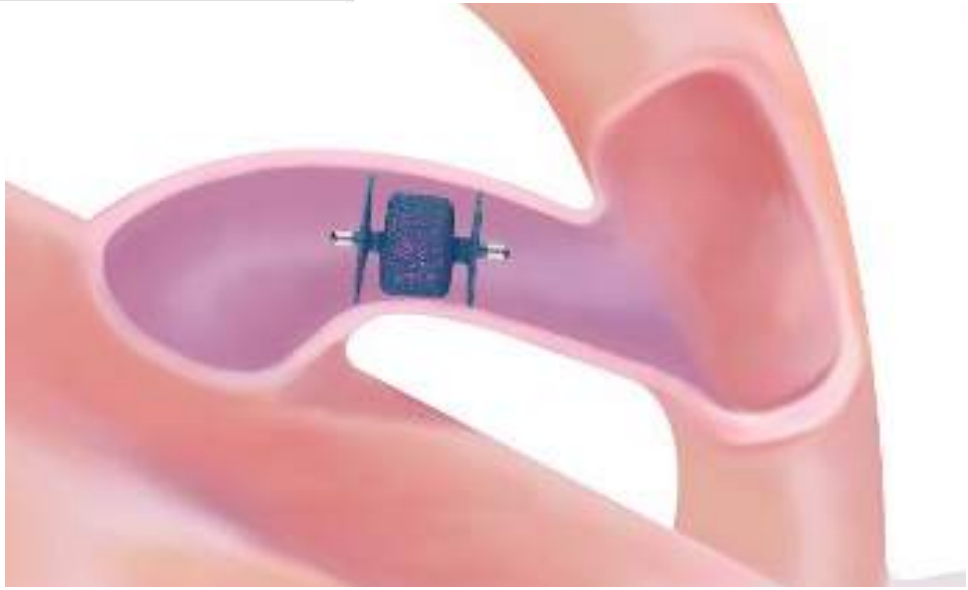
UNDER-SIZING MAY CAUSE DEVICE EMBOLIZATION

D mm (in)	E mm (in)	
	3–12 (0.118–0.472)	≥12.1 (≥0.476)
≤1.7 (≤0.067)	9-PDAP-03-02-L	9-PDAP-03-04-L
1.8–3.2 (0.071–0.126)	9-PDAP-04-02-L	9-PDAP-04-04-L
3.3–4 (0.130–0.157)	9-PDAP-05-02-L	9-PDAP-05-04-L

Device Waist Diameter (mm)	Device Disc Diameter (mm)
3.0	4.0
4.0	5.25
5.0	6.5

KEY GUIDELINES

- Avoid arterial access
- Transvenous approach
- Angio used as road map
- Real-time trans-thoracic echo
- Oversizing to achieve adequate device compression



Amplatzer Piccolo™ Occluder Study Results

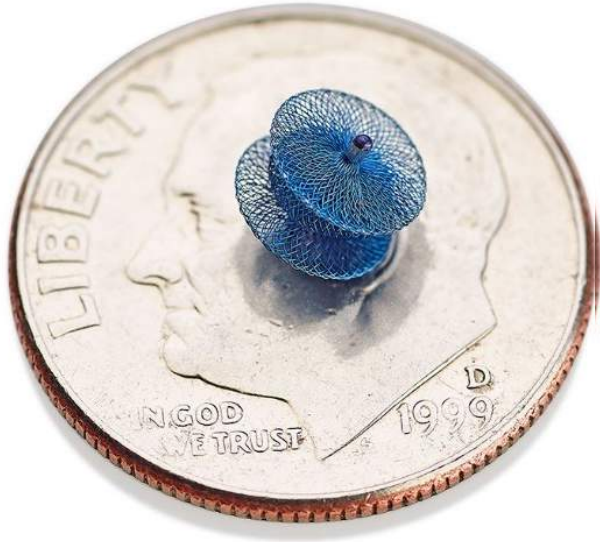
IDE TIMELINE (N=50 with 18 subjects ≤ 2 kg):

- First Enrollment: June 5th, 2017
- Last Enrollment: January 25th, 2018

CAP TIMELINE (N=150 with 82 subjects ≤ 2 kg)

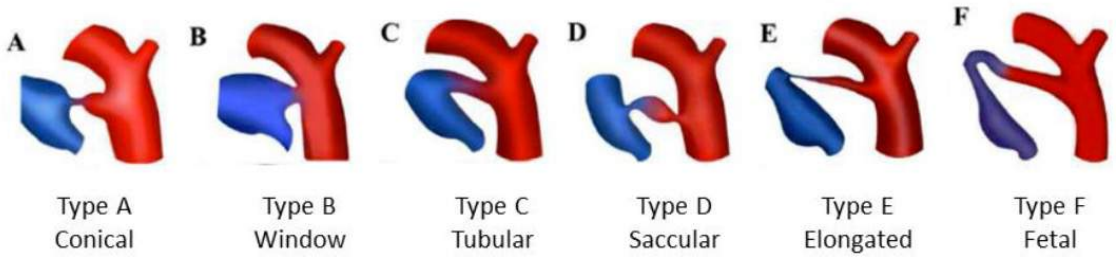
- First Enrollment: March 26th, 2018
- Last Enrollment: February 1st, 2019

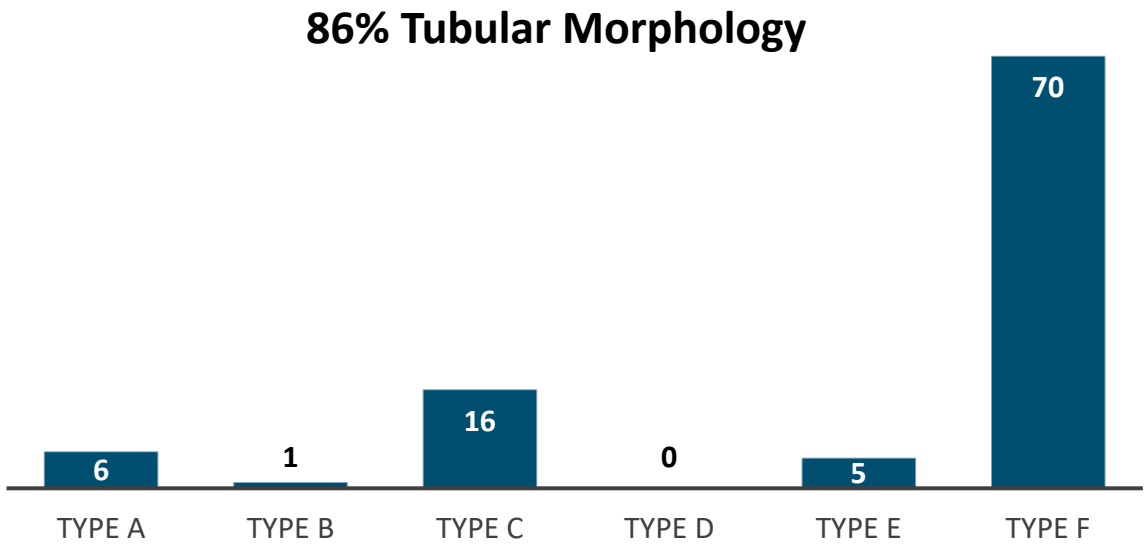
TOTAL = 200 patients including 100 patients ≤ 2 kg



PDA Morphology for ≤2 kg Cohort (n=100)

AMPLATZER PICCOLO™ OCCLUDER STUDY





Data cutoff April 17, 2019

*1 PDA type was “unknown” and 1 was “other – complex and tortous”

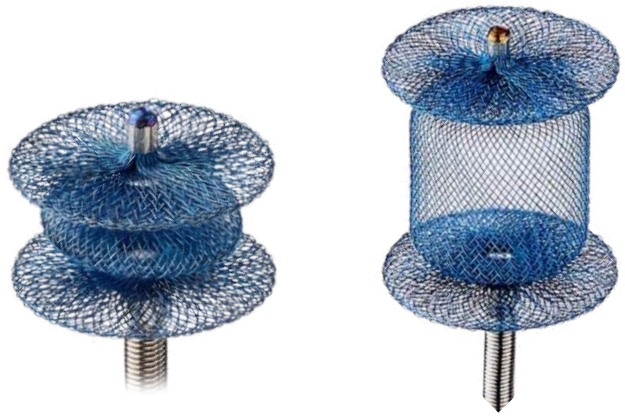
Procedural Success

AMPLATZER PICCOLO™ OCCLUDER STUDY

Clinical Outcome	≤ 2kg	> 2 kg	Total
Successful Implant	99% (99/100)	92% (92/100)	95.5% (191/200)
Intra-Procedural Embolization*	2% (2/100)	3% (3/100)	2.5% (5/200)
Post-Procedural Embolization/Migration**	1% (1/100)	1% (1/100)	1% (2/200)

*All successfully retrieved

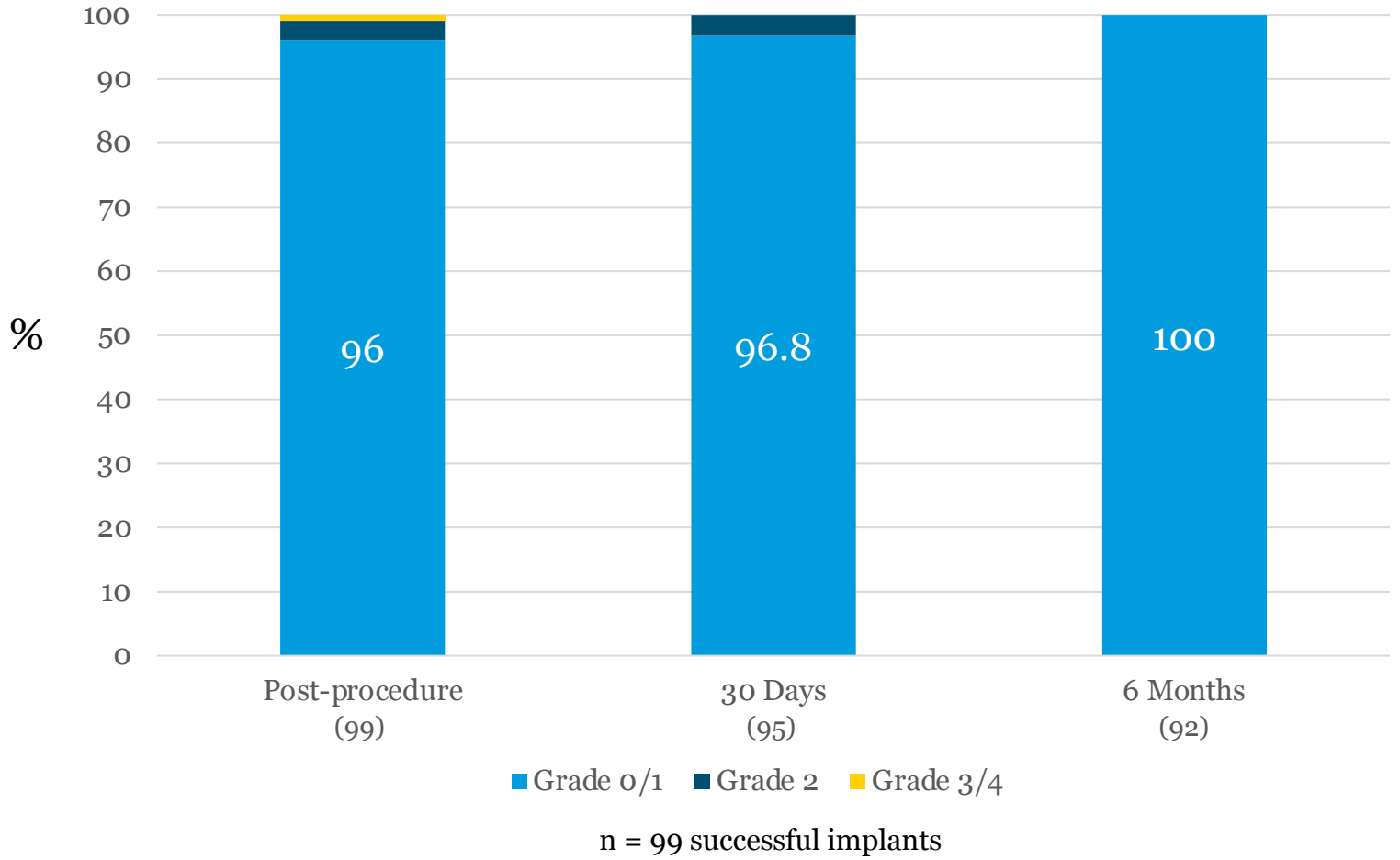
**Elective removal



Data cutoff August 19, 2019

Site Reported Residual Shunt for ≤ 2 kg Cohort

AMPLATZER PICCOLO™ OCCLUDER STUDY



n = 99 successful implants

Data cutoff August 19, 2019

Summary & Conclusions

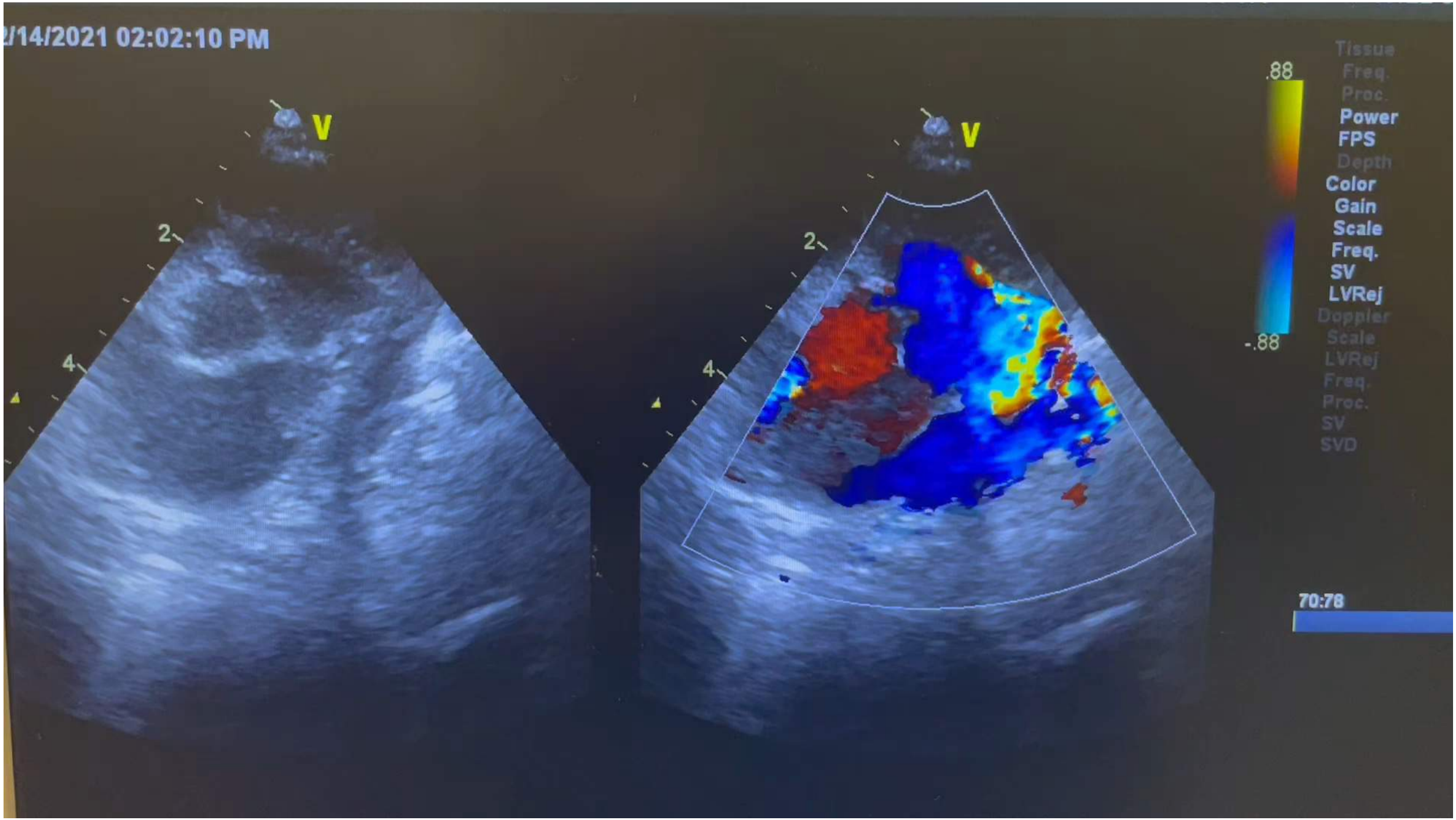
- The results of this study support the safety and effectiveness of the Amplatzer Piccolo™ Occluder.
  - Implant success rate: 95.5% (99% ≤ 2 kg, 92% > 2 kg)
  - Post procedure closure rate: 95.8%
  - Site reported 6-month closure rate: 99.4%
  - Device embolization/migration rate: 3.5%
  - Vascular access site complication rate: 1%
  - Tricuspid regurgitation rate: 2.5%
  - 6-month survival: 97%
- Transcatheter PDA closure with the Piccolo Occluder is a safe and effective non-surgical option for mechanical closure of the PDA.

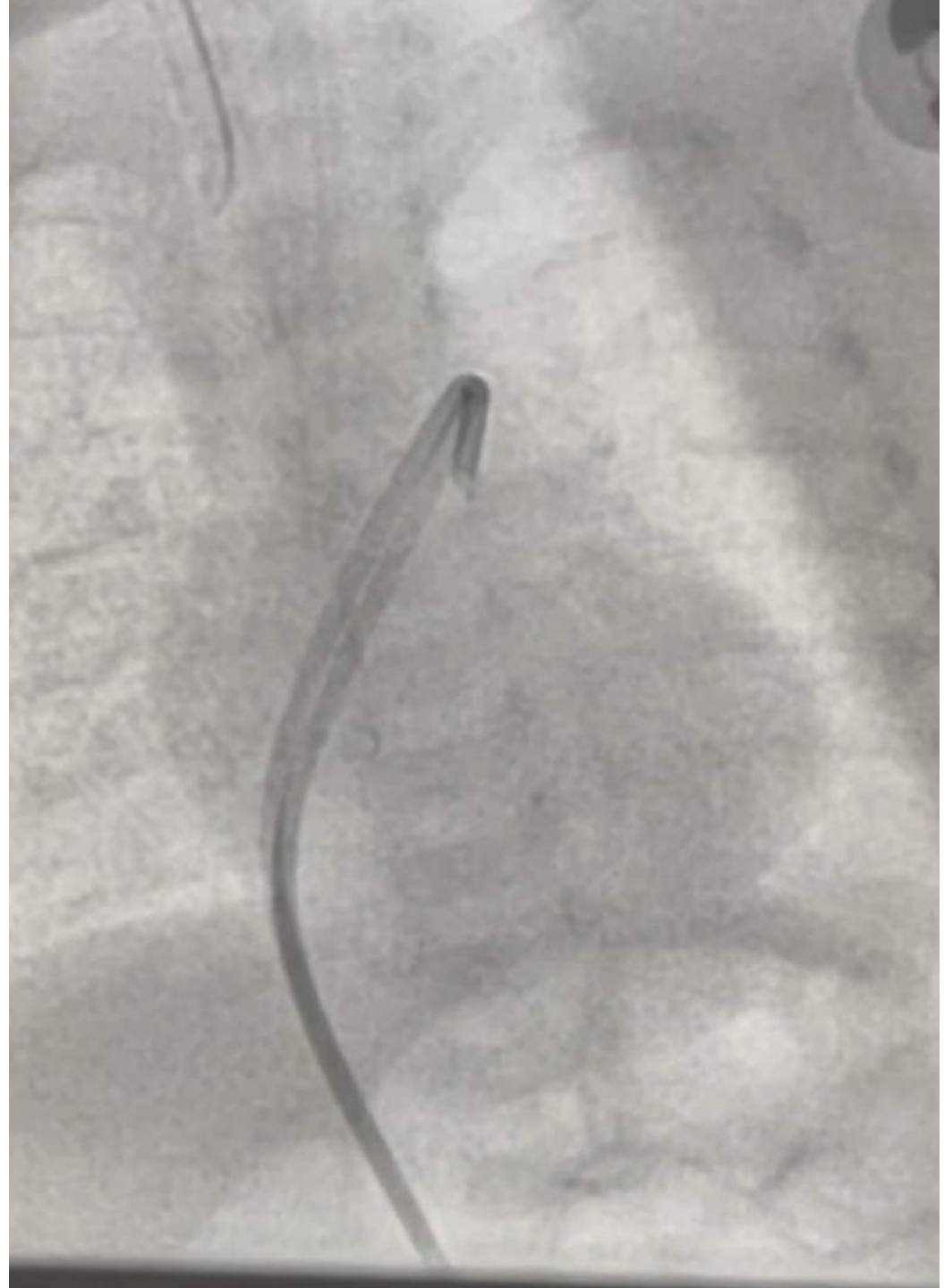
The CCPRC Experience

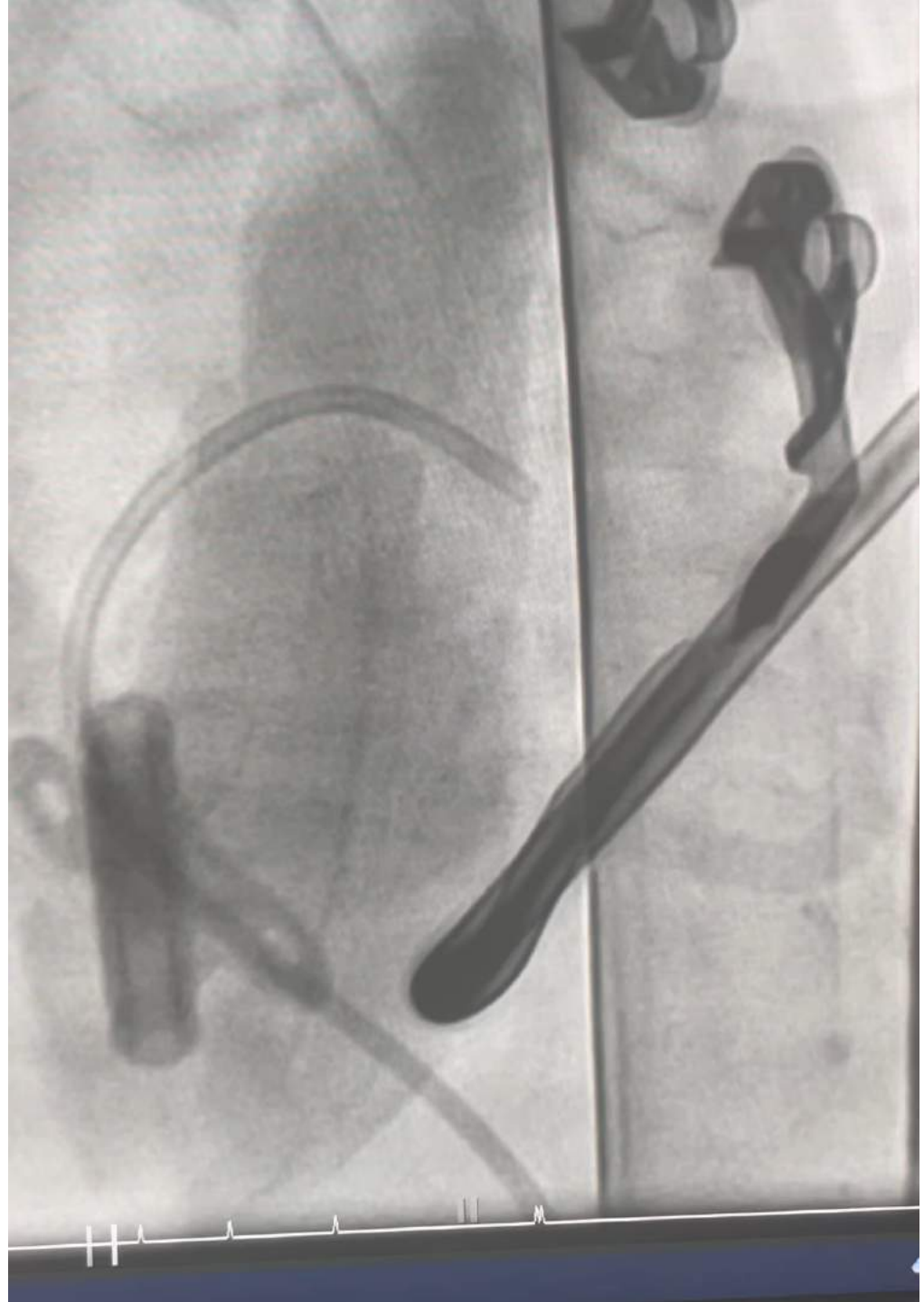
Date	Age	Weight
8/16/21	1 month 26 days	840 gms
10/4/21	3 months	1.5 Kg
11/4/21	19 days	2.1 Kg
11/8/21	1 month	1.4 Kg
12/3/21	23 days	970 gms
12/3/21	1 month	1.5 Kg
12/14/21	3 months	1.9 Kg
7/22/22	2 months	2.5 Kg
11/8/22	1month	1.2 Kg
11/15/22	21 days	1 Kg
12/20/22	5 months	3 Kg
01/13/23	2 months	1.8 Kg
01/31/23	1 month	2.7 Kg

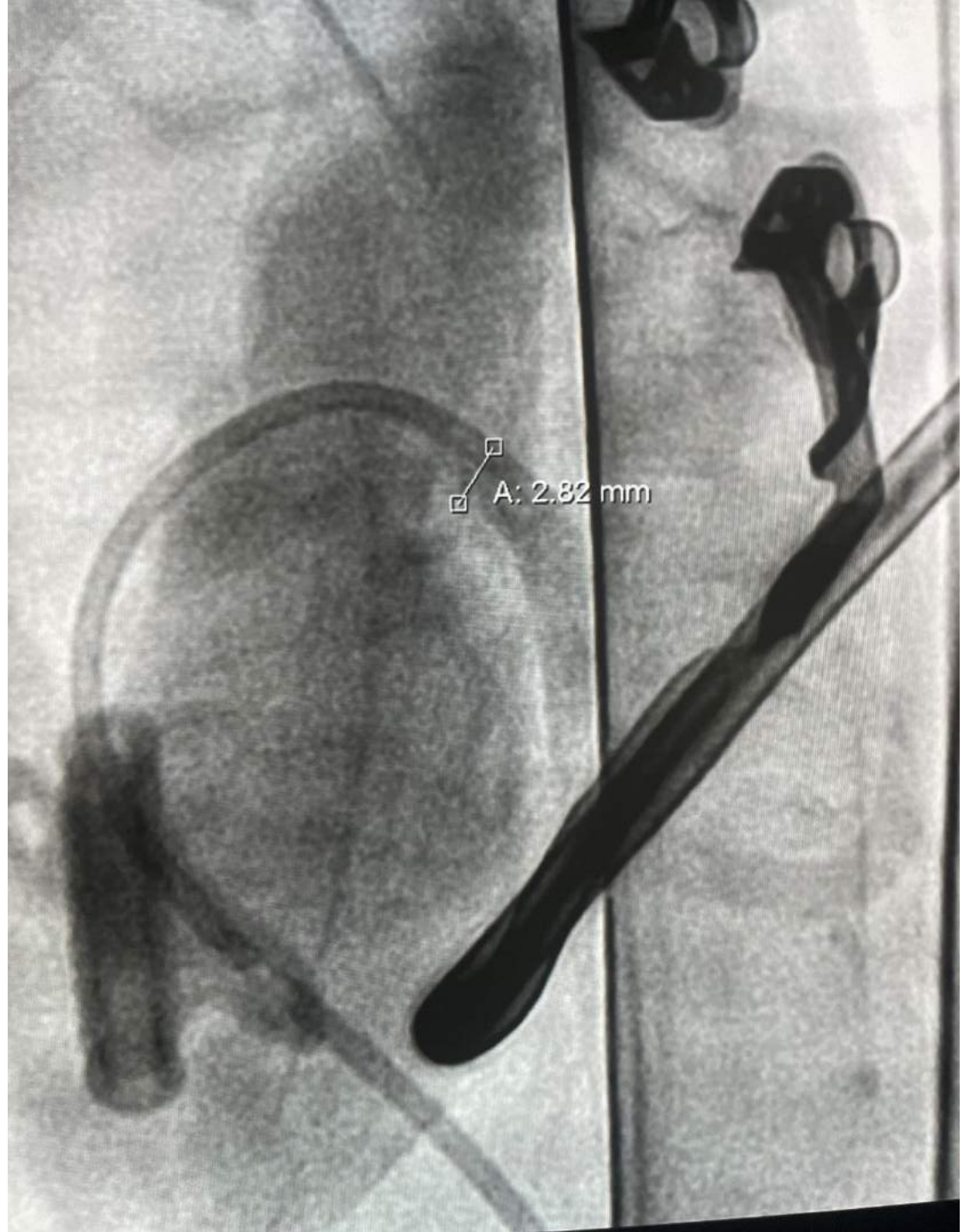
Tiny Baby with PDA

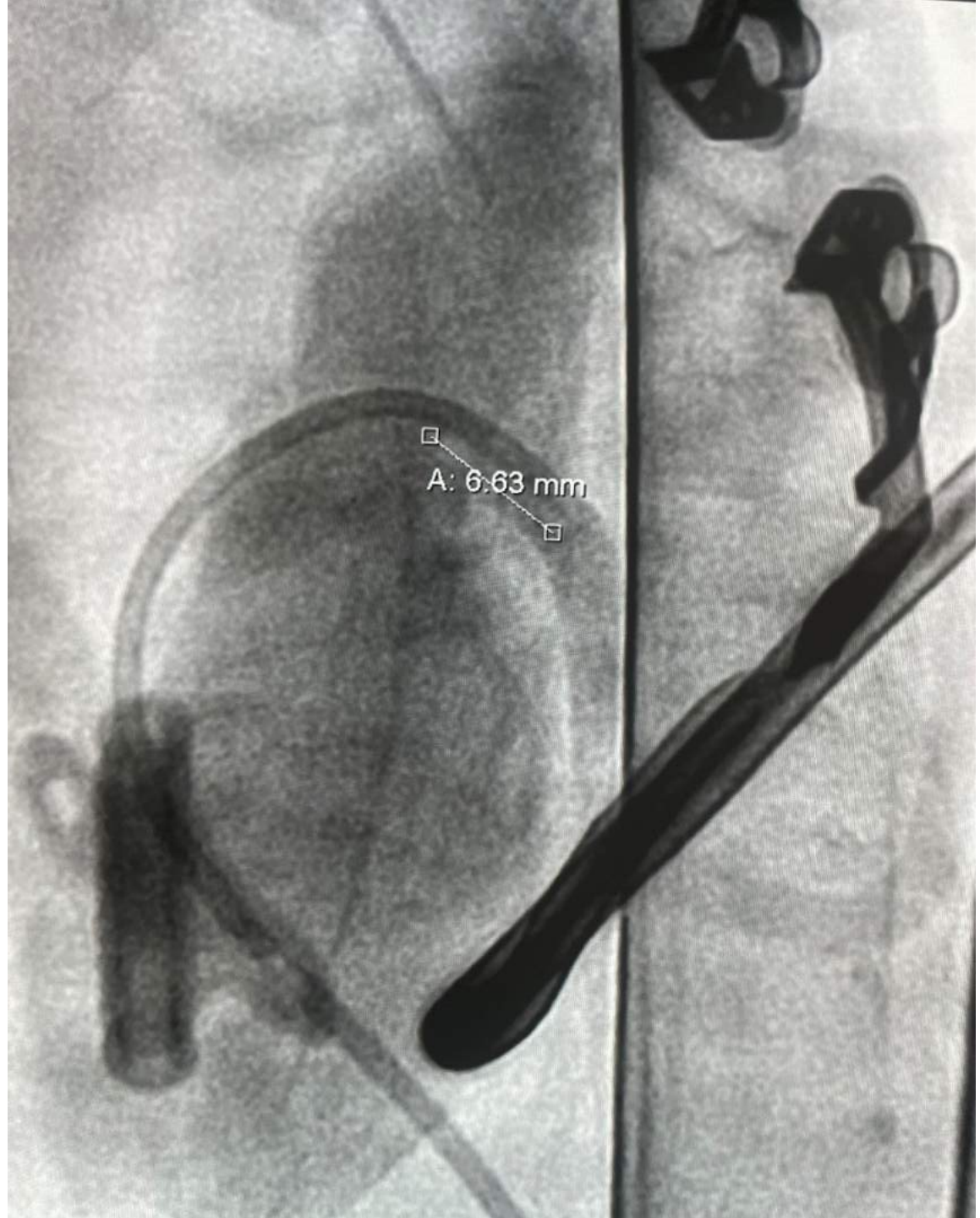
- 23 days old girl, Twin 2
- PreTAGA 26 weeks of GA
- Current weight 0.97 Kg
- Large PDA with LV dilation

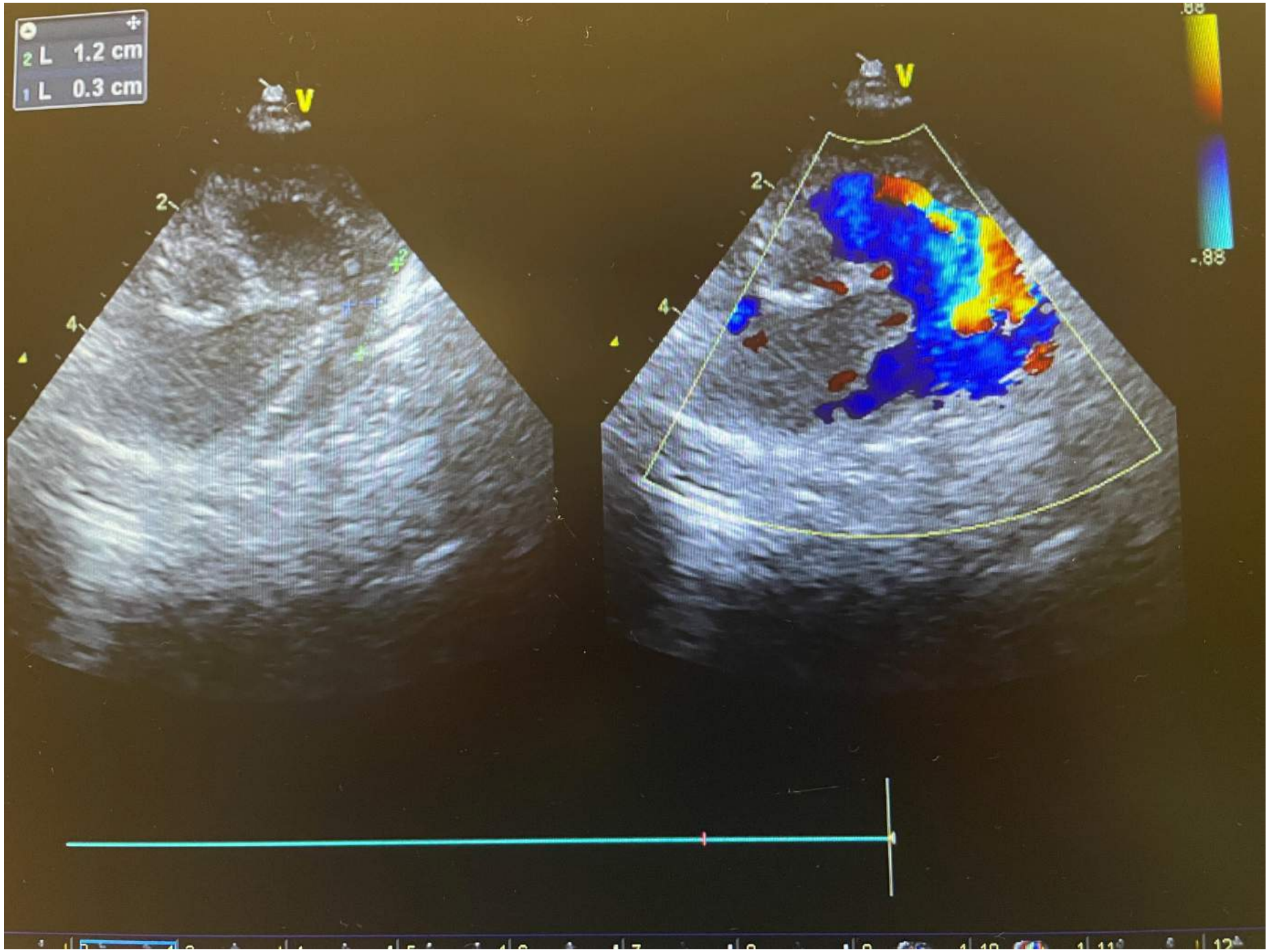

/14/2021 02:02:10 PM
V
2
4
V
2
4
.88
-.88
Tissue
Freq.
Proc.
Power
FPS
Depth
Color
Gain
Scale
Freq.
SV
LVRej
Doppler
Scale
LVRej
Freq.
Proc.
SV
SVD
70:78

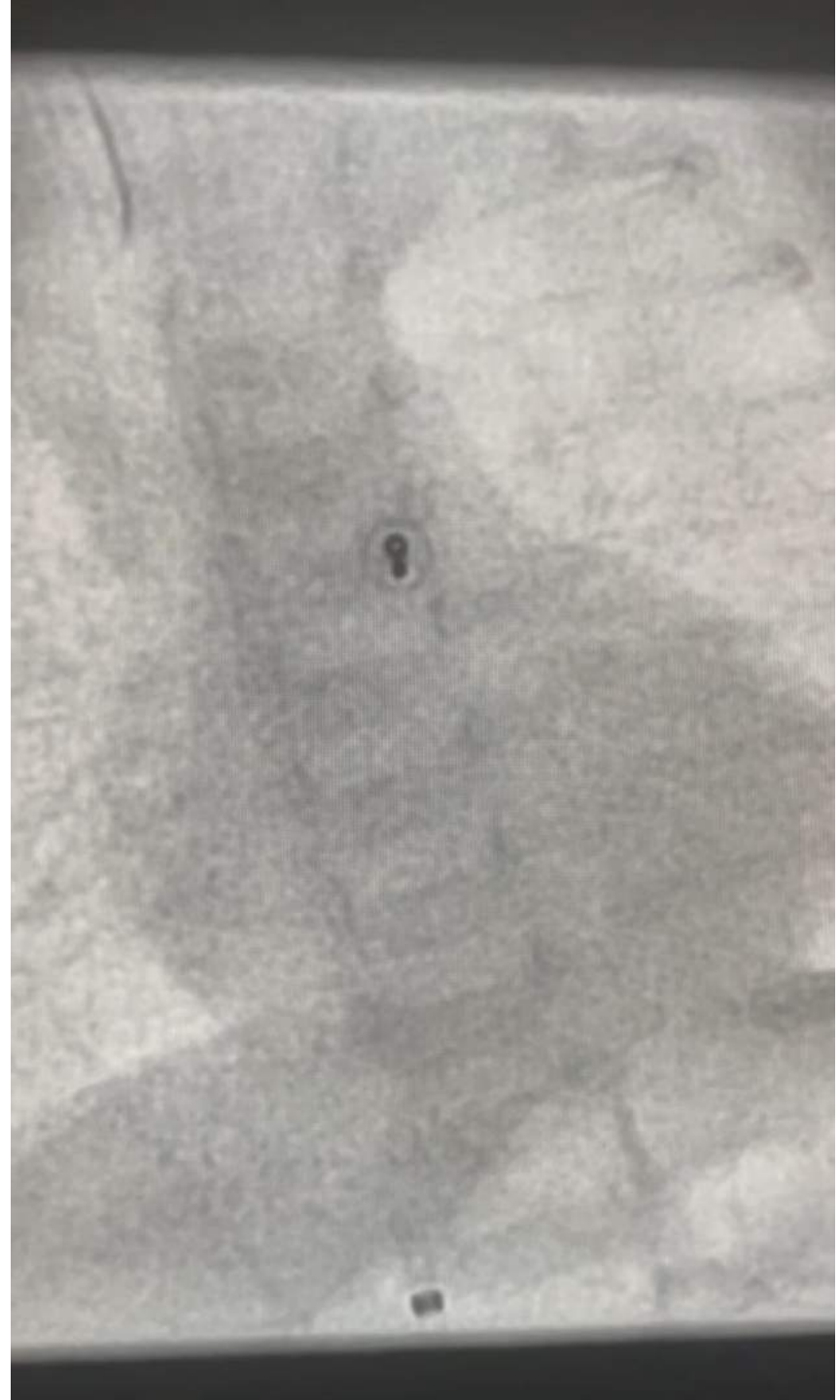


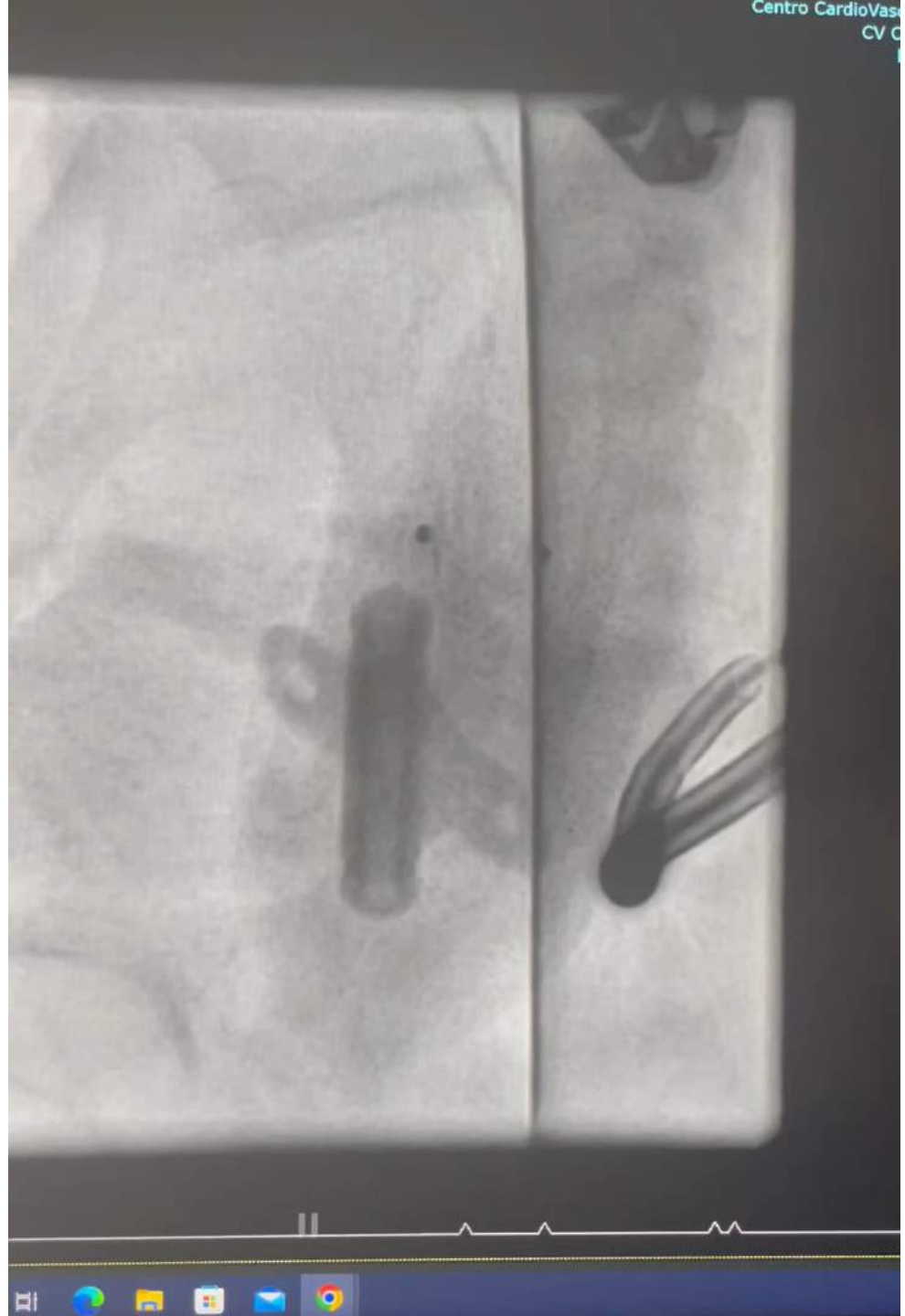


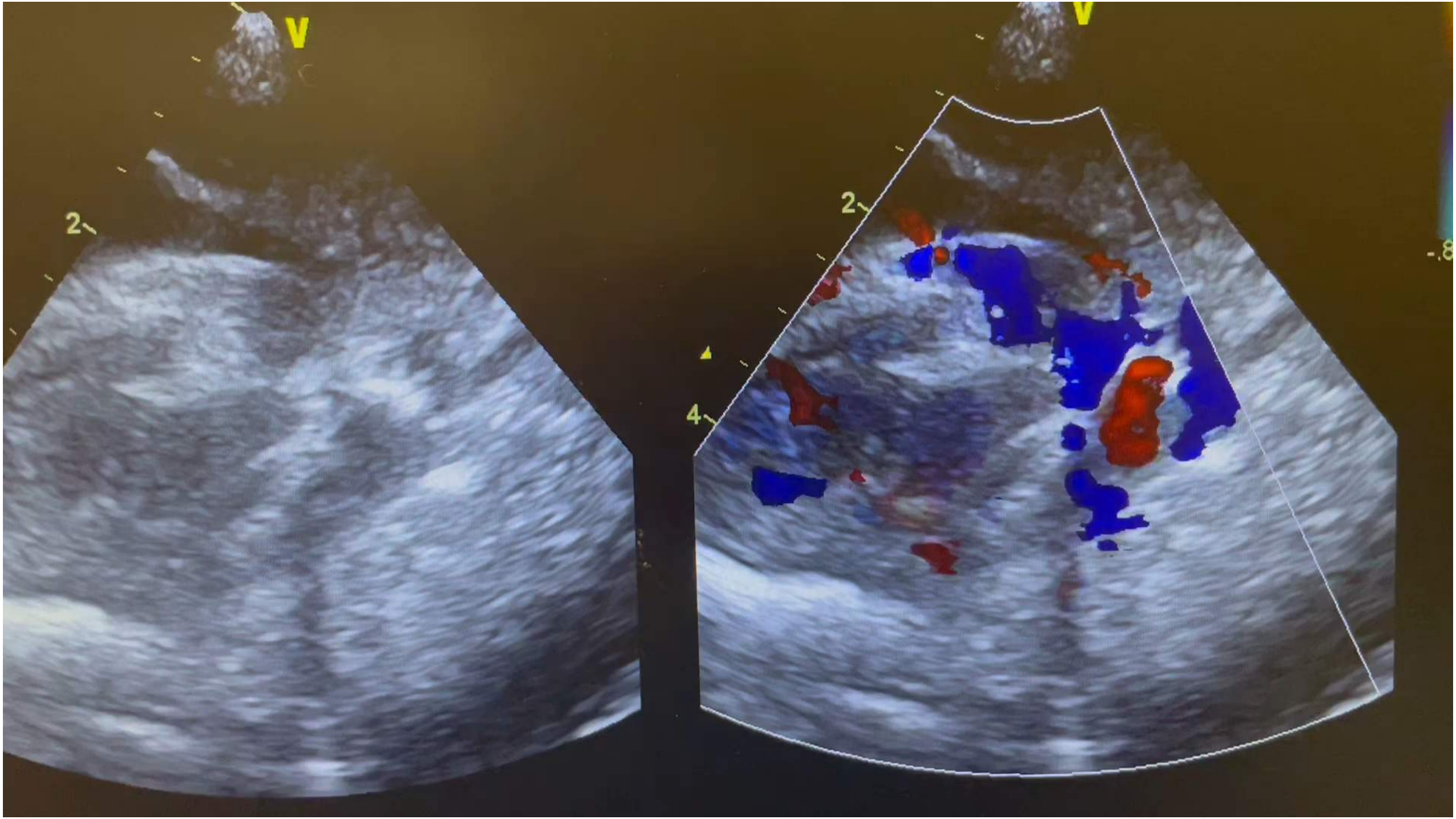

A: 2.82 mm

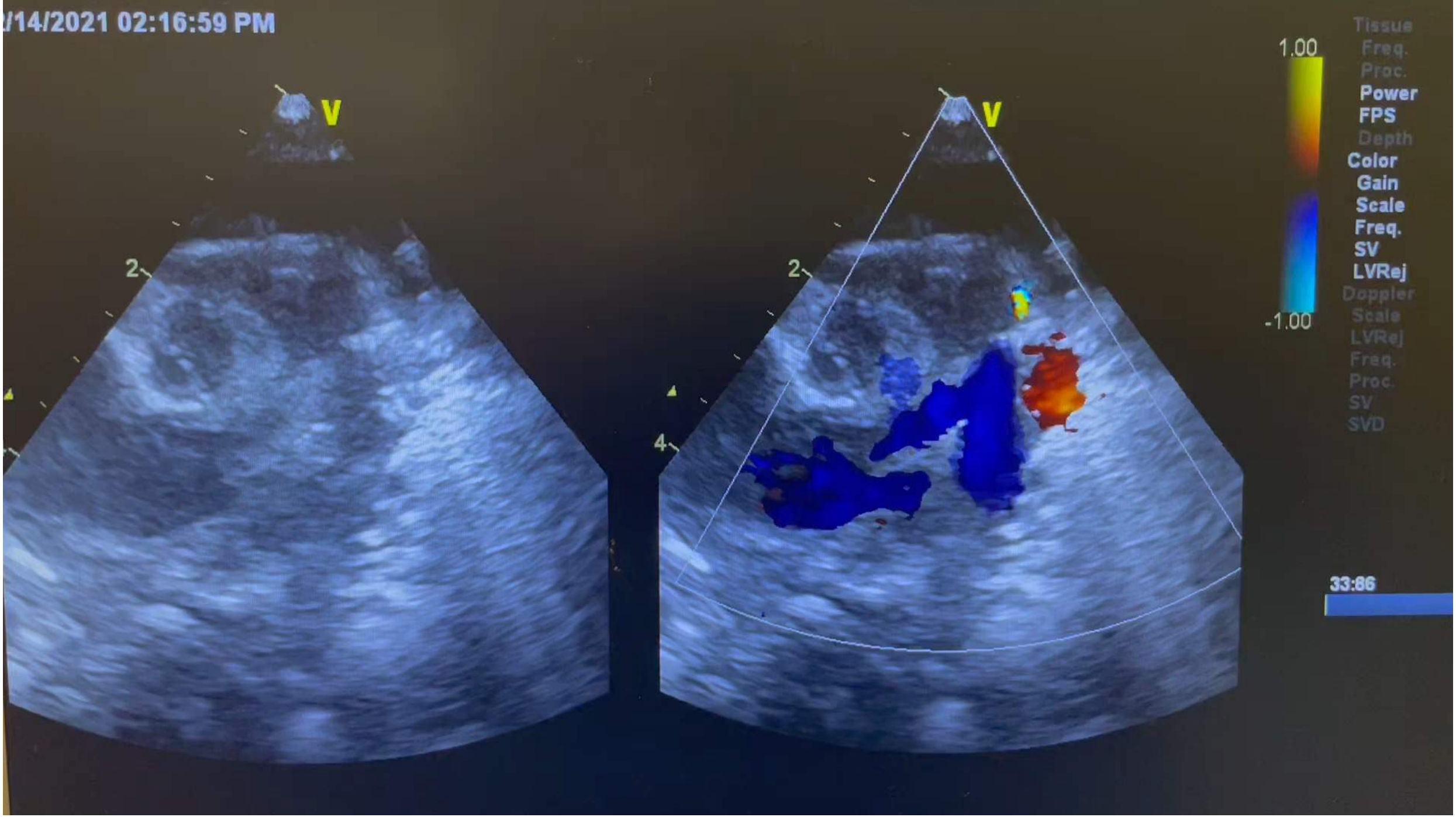

A: 6.63 mm

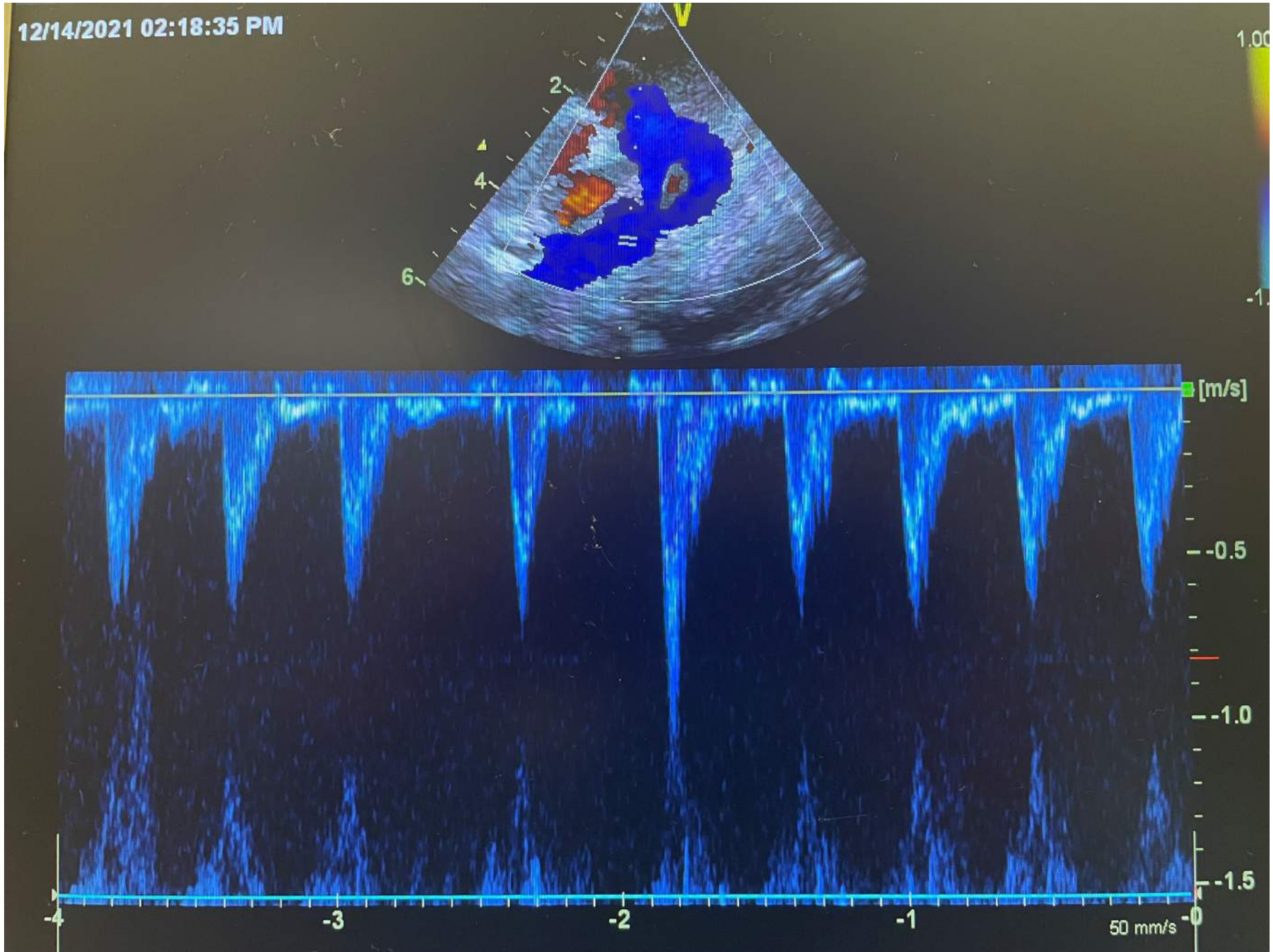

2 L 1.2 cm
1 L 0.3 cm
V
V
2
4
2
4
.88
-.88

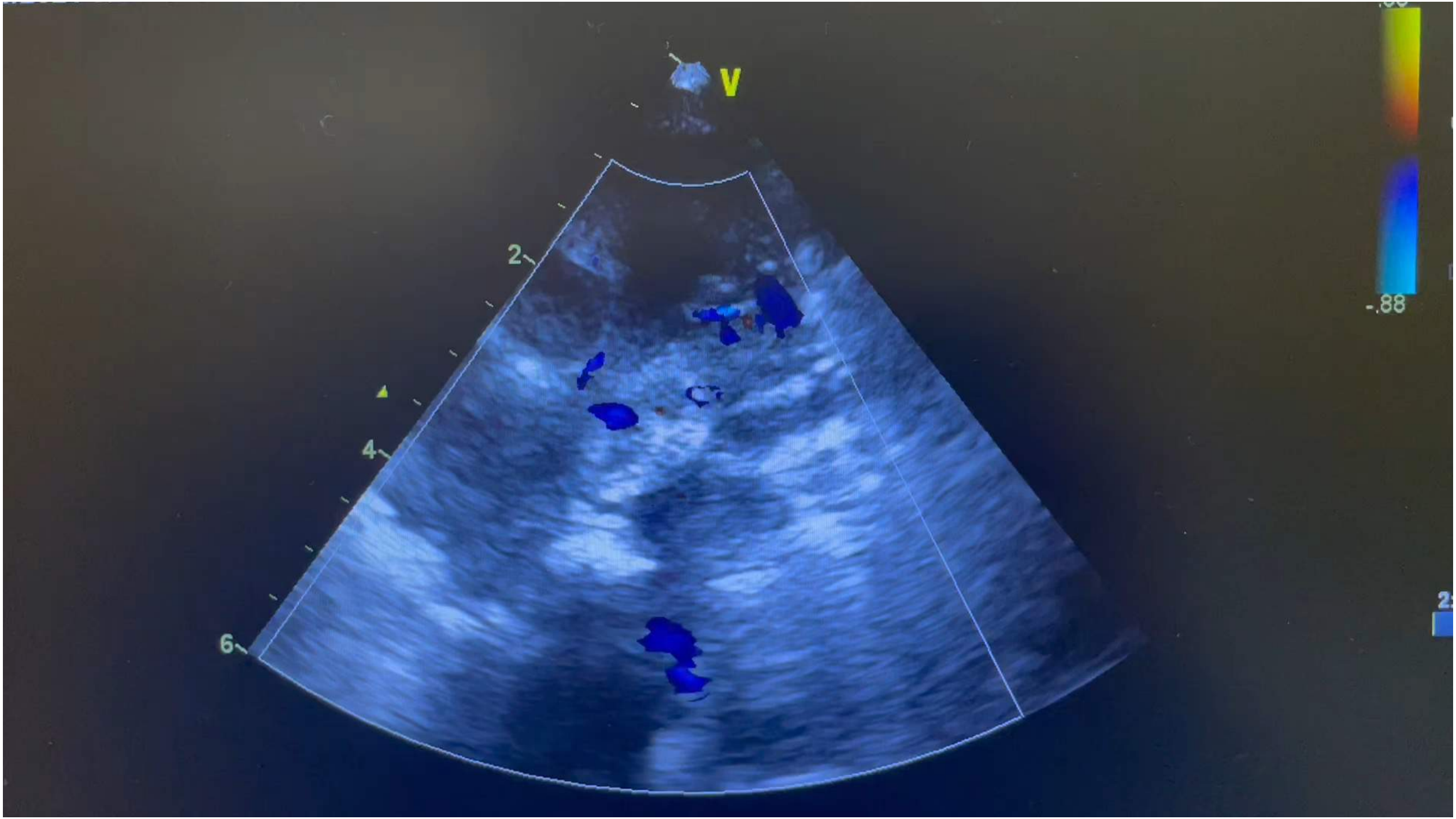


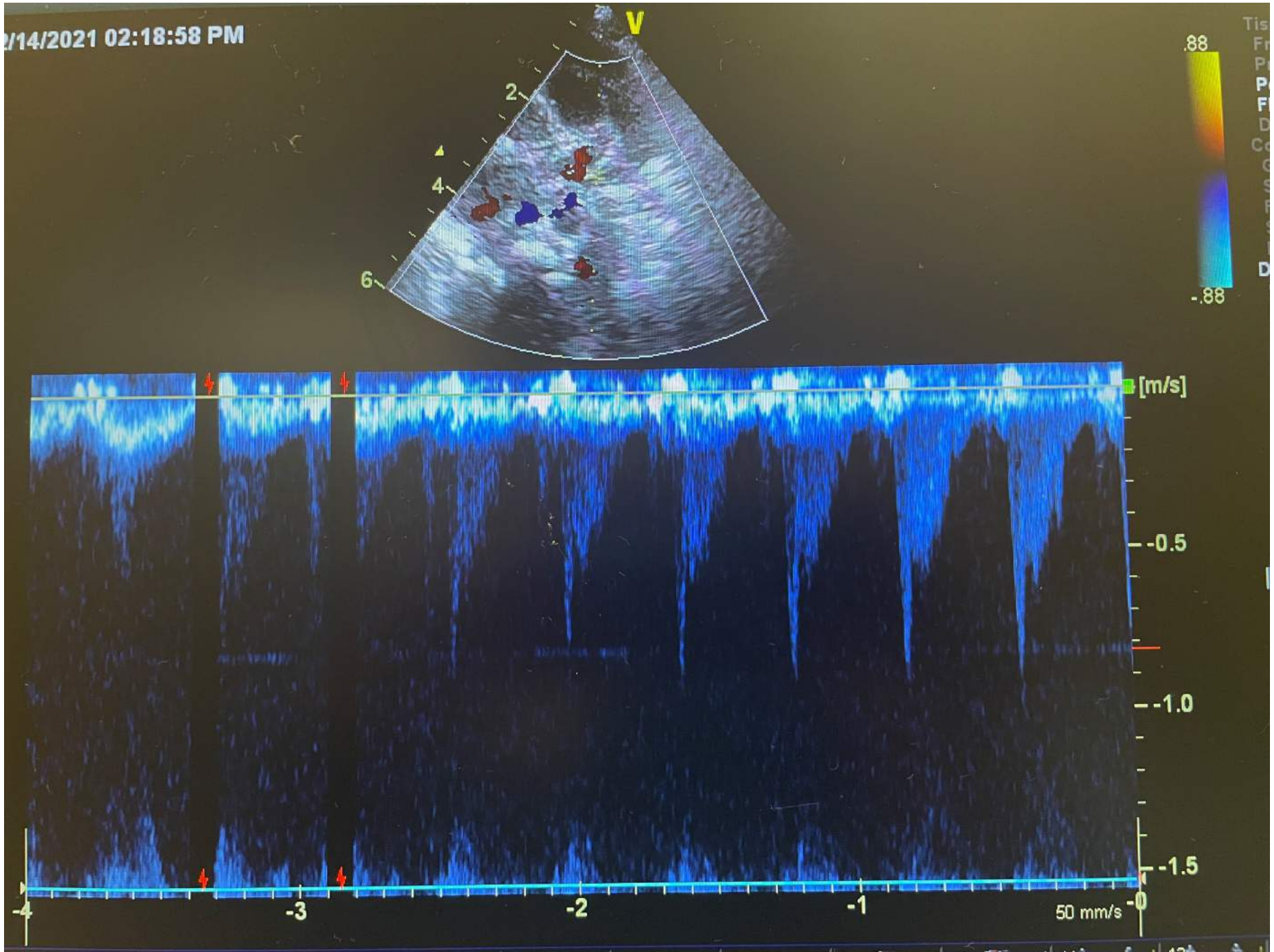

Centro CardioVas
CV C

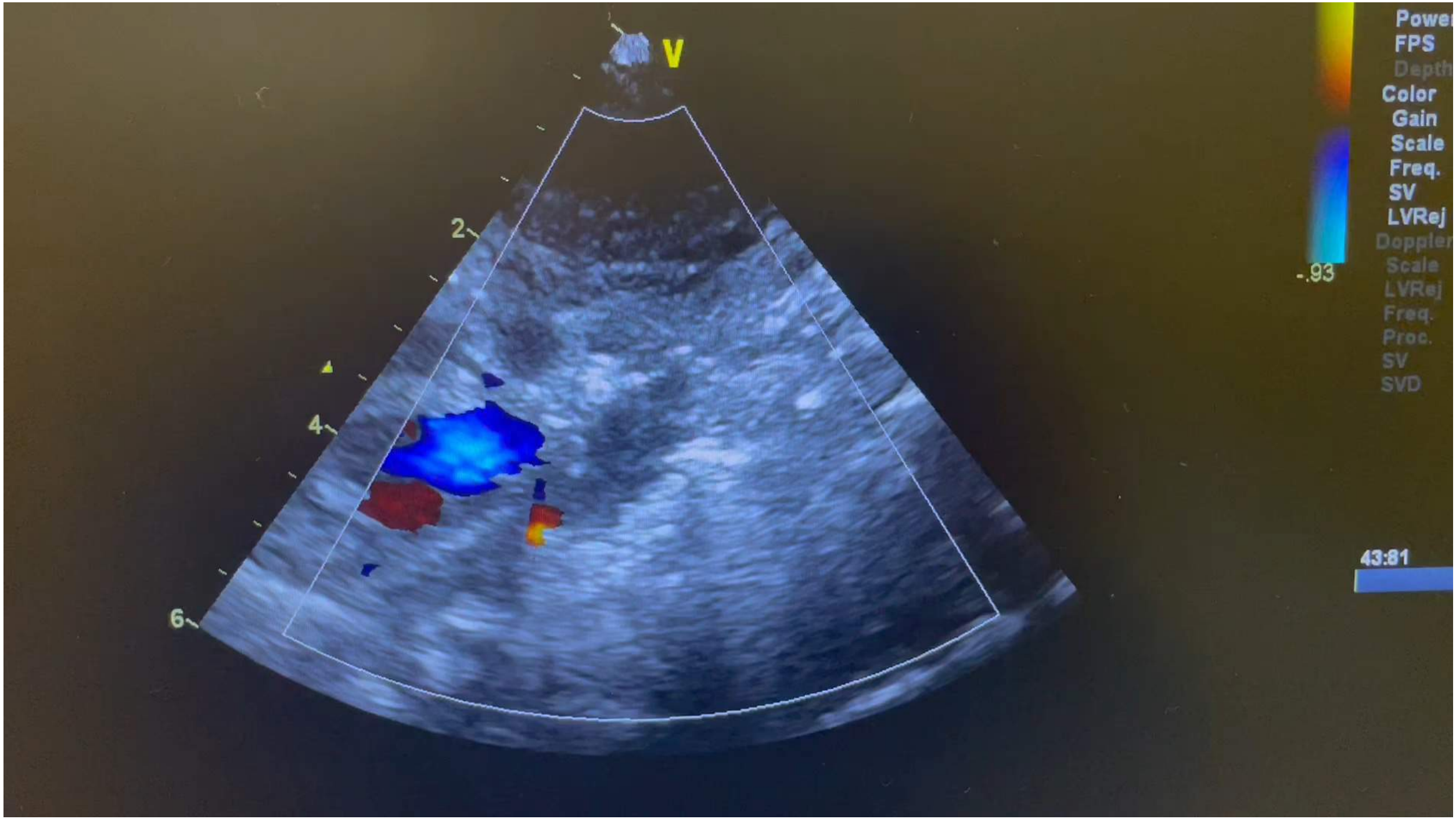



/14/2021 02:16:59 PM
V
2
V
2
4
1.00
-1.00
Tissue
Freq.
Proc.
Power
FPS
Depth
Color
Gain
Scale
Freq.
SV
LVRej
Doppler
Scale
LVRej
Freq.
Proc.
SV
SVD
33:86


12/14/2021 02:18:35 PM
2
4
6
[m/s]
-0.5
-1.0
-1.5
-4
-3
-2
-1
-0
50 mm/s


V
2
4
6
-.88


/14/2021 02:18:58 PM
V
2
4
6
.88
-.88
[m/s]
-0.5
-1.0
-1.5
-4
-3
-2
-1
0
50 mm/s


V
2
4
6
Power
FPS
Depth
Color
Gain
Scale
Freq.
SV
LVRej
-.93
Doppler
Scale
LVRej
Freq.
Proc.
SV
SVD
43:81

Final thoughts…

- The optimal management of the PDA in premature infants remains uncertain due to the lack of evidence for long term benefits and the complications of medical and surgical interventions.
- In recent years, devices to occlude the PDA of premature infants have become available and several trials have demonstrated successful and safe transcatheter PDA closure in this population.
- Whether catheter-based interventions will result in improved long-term outcomes remains to be seen.
- Careful study of the benefits of catheter-based interventions in this patients is needed.


GRACIAS