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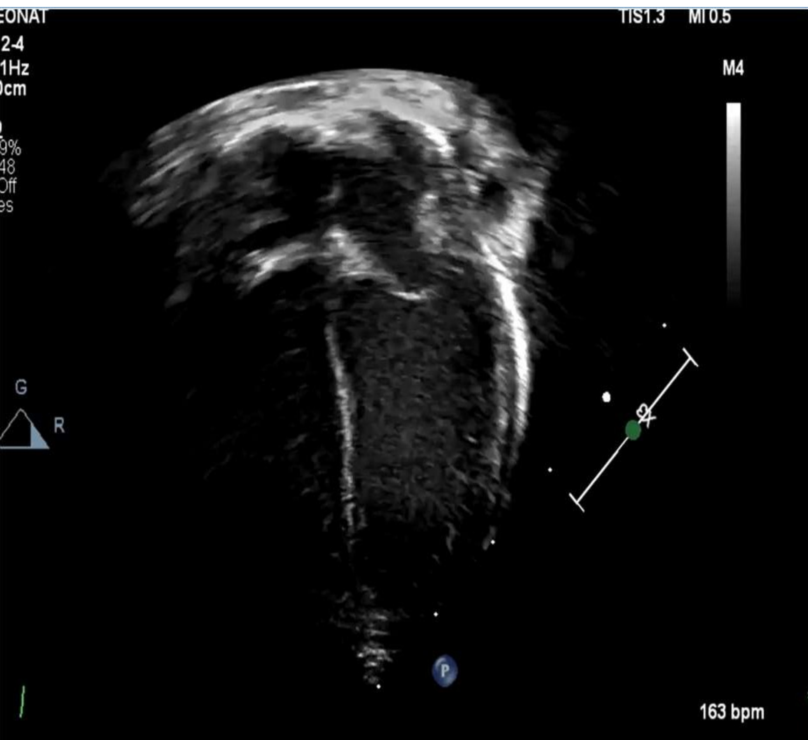

The phenotype of cardiovascular disease in Congenital Diaphragmatic Hernia

November 30, 2022

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I CONGRESSO INTERNACIONAL DE NEONATOLOGIA DO DF

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

Disclosure / Acknowledgements

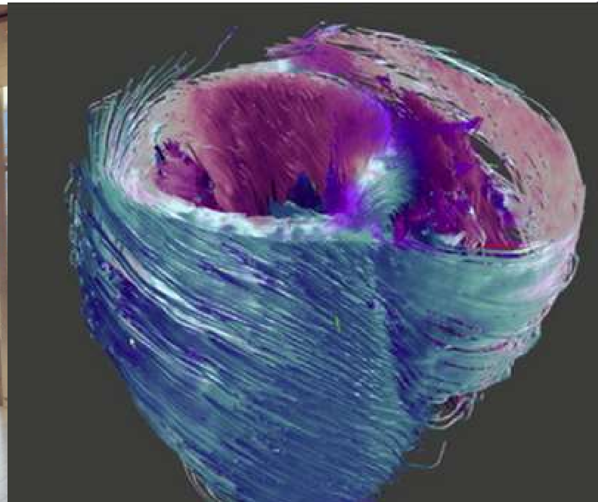
- No Disclosures relative to the content of this presentation

- This presentation will involve comments or discussion of unapproved or off-label, experimental or investigational use of iNO, inotropic, PGE or pulmonary vasodilators in CDH

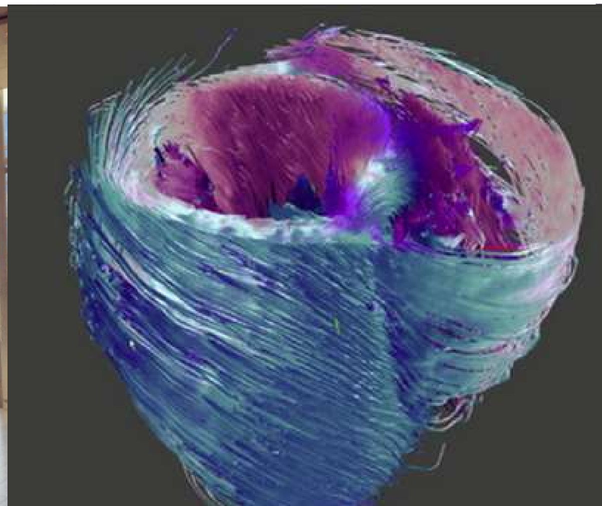
- *Agradeço à comissão organizadora por me convidar para esta magnífica conferência e para o seu extraordinário país, para a sua magnífica capital. É uma grande honra.*

Plan of the presentation

- CDH review - guidelines
- Cardiac function review
- 4 Cases: acute PH, LV dysfunction, mixed biventricular dysfunction
- Summary
- Questions

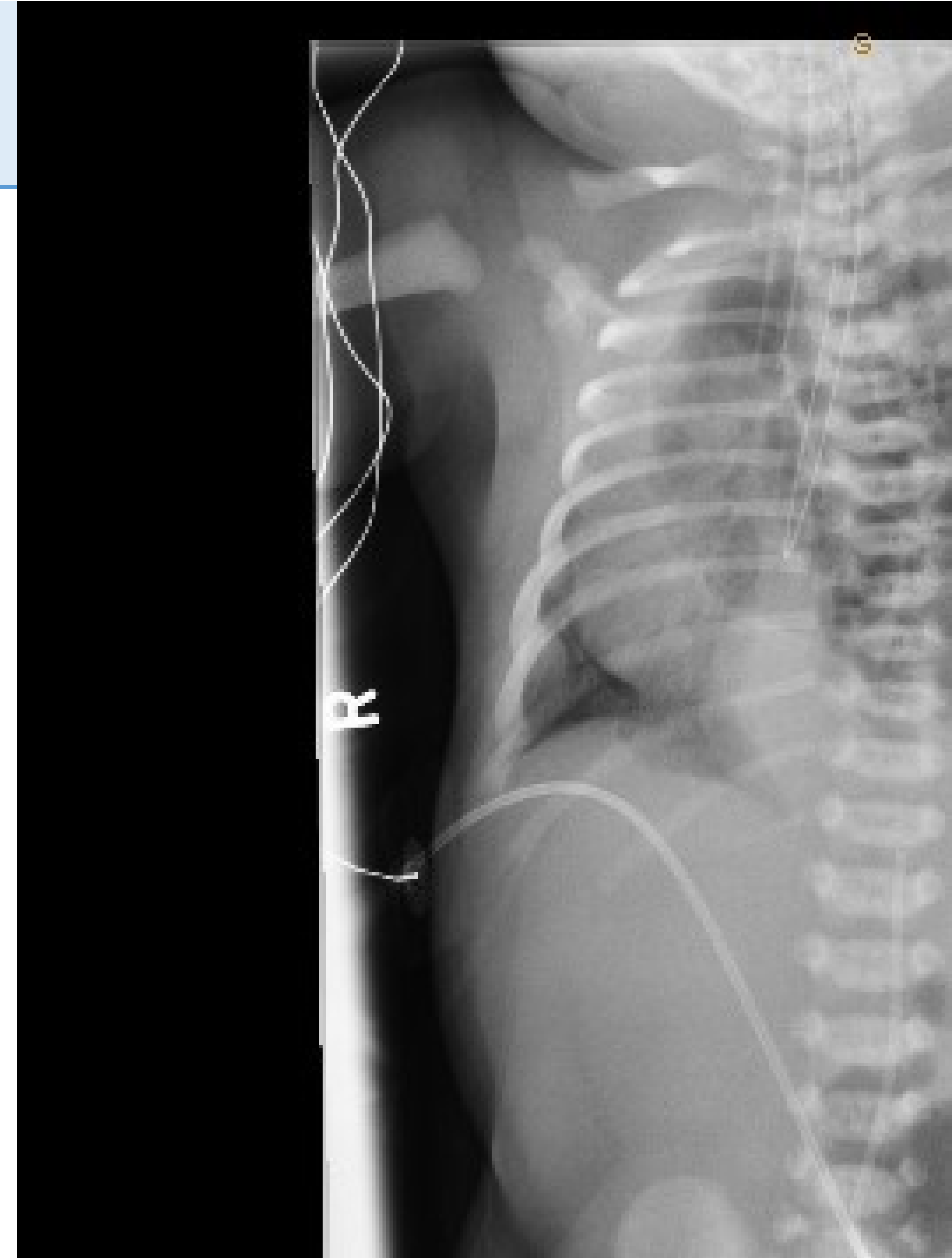


Congenital Diaphragmatic Hernia



Congenital Diaphragmatic Hernia

- 2.6/10,000 total births and increasing over time.
  - Thoracic organ compression by herniated viscera: contribution to pulmonary hypoplasia, abnormal pulmonary vasculature, and cardiac under-development
- Anomalies **in both lungs**, not only ipsilateral
  - Pathophysiology: abnormal mesenchymal cells function or migration – abnormal diaphragmatic and thoracic organs development.



Congenital Diaphragmatic Hernia

- 25-45% of mortality – majority in first post-natal week
  - Mostly hypoxic respiratory failure, cardiac dysfunction, pulmonary hypertension

- Key point: **Inotropic / cardiovascular management improve the care of CDH infants only in the context of excellent respiratory / airway care.**
  - Protocolized respiratory management
    - Avoid baro/volu/atelecta-trauma
  - Adequate secretion management
  - Avoid excessive oxygen supplementation. Adjust as per the preductal

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The Canadian CDH Collaborative

The Application:

"This app provides a point-of-care resource for evidence-based and consensus-driven national guidelines for the health surveillance and care of patients with congenital diaphragmatic hernia (CDH). The guidelines cover all aspects of care beginning at prenatal diagnosis through to hospital discharge and post-discharge surveillance. The guidelines are intended for any stakeholder involved in the care of CDH patients, including but not limited to specialty and primary medical care providers, allied health professionals, and families. The app is organized into distinct sections that correspond to the phase of care. Each phase of care provides recommendations that indicate their level of evidence and the strength of expert consensus. Each recommendation is also accompanied by a brief description of the evidence behind the formulation of the recommendation as well as a list of supportive references. The ultimate goal for the dissemination of the guidelines is to improve the quality of health care delivery for CDH patients by providing optimal performance benchmarks and removing unwanted variations in care. The app not only provides access to the guidelines, but also additional resources that may be beneficial to teams caring for CDH patients. They include (a) a link to the full, unabridged recommendations that provides more in-depth discussions of supporting evidence; (b) a daily intensive care rounding checklist designed specifically for CDH patients; (c) a guideline compliance tool that allows individual hospital centres to track their adherence to the guidelines as part of a continuous quality improvement initiative; and (d) two calculators that facilitate

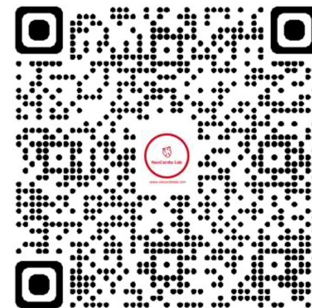
Download the application on Google Android or Apple App Store

GUIDELINE CPD

Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline

The Canadian Congenital Diaphragmatic Hernia Collaborative*

Update coming in 2023



Congenital Diaphragmatic Hernia Guidelines

- T-piece resuscitation post-intubation in the delivery room (max 25 cmH20)
  - Many centers use 100% in delivery room.
  - We locally use Canadian Pediatric Society NRP guidelines – Start with 21% and titrate.
- NasoGastric tube to decompress stomach
- pCO2: 45-60, pH: 7.25-7.40 (aim permissive hypercapnia to avoid pulmonary injury)
- Preductal sat 85% (no titration based on post-ductal).
  - 1st hour: may accept preductal 80% and above
  - ”gentle ventilation”.
  - HFOV second intention if PIP > 25
    - Avoid high MAP on HFOV
- Some ”light” analgesia / sedation
  - We use fentanyl 0.5 mcg/kg/hr IV to 1 mcg/kg/hr. Titrate.
  - If you do not need it – stop it (21%, minimal settings).

Ventilation
Newborns with CDH and immediate respiratory distress should be preferentially intubated at birth. Bag-valve-mask ventilation should be avoided.
Sedation should be provided to all mechanically ventilated newborns with CDH. Deep sedation and neuromuscular blockade should be provided selectively to those with greater ventilation or oxygen requirements.
A T-piece should be used with the ventilator to avoid a peak inspiratory pressure > 25 cm H_2O.
An arterial pCO_2 between 45 and 60 mm Hg and a pH between 7.25 and 7.40 should be targeted in all newborns with CDH.
Supplemental oxygen should be titrated to achieve a preductal saturation of at least 85%, but not > 95%.
Gentle, intermittent mandatory ventilation should be the initial ventilation mode for newborns with CDH who require respiratory support. High-frequency oscillatory ventilation or high-frequency jet ventilation should be used when the peak inspiratory pressure required to control hypercapnia using intermittent mandatory ventilation exceeds 25 cm H_2O.

Congenital Diaphragmatic Hernia Guidelines

- Monitor hemodynamic – perfusion
  - Refill, lactate, urine, BP, heart rate
- Judicious use of fluid (if concern of fluid depletion – avoid volume overload/edema)
  - Avoid excessive fluid intake
- ECHO to guide management if Hypoxic Resp failure and/or hemodynamic instability – to evaluate anatomy if no fetal ECHO
  - Targeted, focused.
  - Should wait 24 hours if stable to avoid disturbing
- My tips:
  - Avoid excessive manipulation, avoid too many people
  - Most experience personnel to care for these newborns
  - Multi-Disciplinary management
  - Silent room, calm, dark. Presence of parents. Avoid too many skin breaks (UAL / radial arterial line may be helpful).

Hemodynamic support
Treatment of poor perfusion (capillary refill > 3 s, lactate > 3 mmol/L, urine output < 1 mL/kg/h) and blood pressure below norms for age should include: • judicious administration of crystalloid, generally not exceeding 20 mL/kg; • inotropic agents such as dopamine or epinephrine; and • hydrocortisone. If poor perfusion continues, assessment of cardiac function (i.e., echocardiogram, central venous saturation) should be performed
Echocardiography
Two standardized echocardiograms, one within 48 h of birth and one at 2–3 w of life, are needed to assess pulmonary vascular resistance, as well as left ventricular and right ventricular function. Additional studies may be conducted as clinically indicated.
Management of pulmonary hypertension
iNO is indicated for confirmed suprasystemic pulmonary arterial hypertension without left ventricular dysfunction, provided lung recruitment is adequate. In the absence of clinical or echocardiographic response, iNO should be stopped.
Sildenafil should be considered in patients with refractory pulmonary hypertension (i.e., unresponsive to iNO) or as an adjunct when weaning iNO.
Milrinone should be used to treat cardiac dysfunction, particularly if it is associated with pulmonary hypertension.
Prostaglandin E_1 can be used to maintain ductus arteriosus patency and reduce right ventricular afterload in patients with pulmonary hypertension with right ventricular failure, or in the presence of a closing ductus.
Extracorporeal life support
The possibility of extracorporeal life support should be discussed during prenatal counselling for CDH, and should disclose that available evidence does not suggest a survival benefit to its use.

Congenital Diaphragmatic Hernia Guidelines

- Management of PH / inotropy:
  - iNO +/- Sildenafil
    - Sildenafil if no iNO available or as bridge if difficult to wean with rebound
  - Milrinone if BP adequate (cause hypotension) and urine output (renally cleared)
  - PGE – if restrictive ductus and PH/RV dysfunction or poor LV function
  - Epinephrine
    - Low-dose Dopamine (I prefer Epi)
  - Dobutamine (beware of tachycardia – filling)
  - Some centers use Norepi/Vasopressin
    - Not a lot of data.

- ECMO
  - Hypoxic Resp Failure despite targeted management
  - With protocolized management – multi-disciplinary care
    - No ECMO at our institution for CDH since 2015 (2 CDH with FETO)
    - Only 1 mortality in delivery room due to palliative care management for bilateral CDH with no residual lung on fetal MRI.

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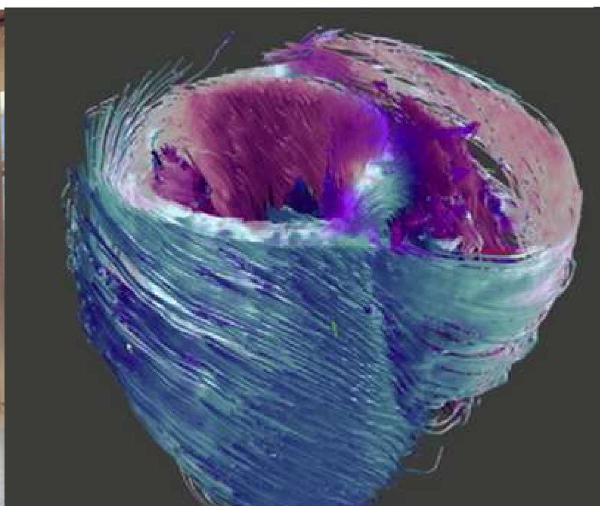
Congenital Diaphragmatic Hernia Guidelines

- Operation:
  - Decision of timing with surgery
  - We operate these infants in our unit, in their room, with Anesthesia and NICU working hand in hand during the operation
  - We operate according to CDH guidelines – usually around 3-5 days of life (sometimes more…)

Surgery
The following physiologic criteria should be met before surgery: • urine output > 1 mL/kg/h • $FiO_2 < 0.5$ • preductal oxygen saturation between 85% and 95% • normal mean arterial pressure for gestational age • lactate < 3 mmol/L • estimated pulmonary artery pressures less than systemic pressure. Failure to meet these criteria within 2 w should prompt consideration of either attempted repair or a palliative approach.

Basic in cardiac function

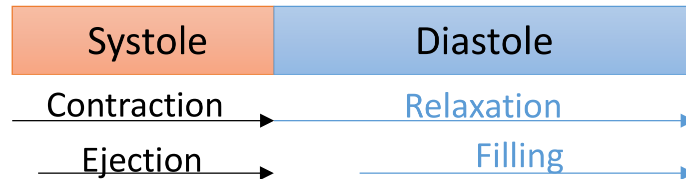


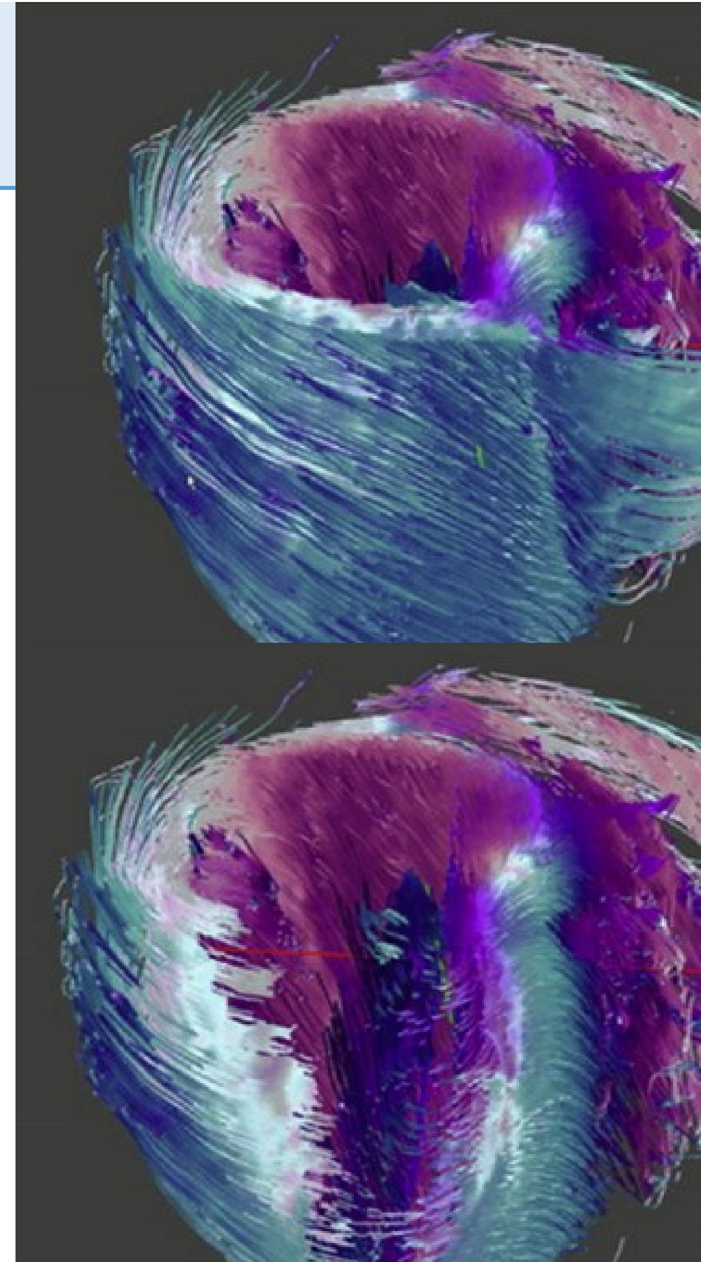
Cardiac function

Filling (diastole) to contraction-ejection (systole)

- Depend on architecture of ventricles
- Depend on preload (filling)/afterload/contractility
- Cross-talk between RV-LV
  - Ventricles dance together – fall together
- Activation by conducting system
  - Arrhythmia can cause problem.
  - Tachycardia – problem with filling (beware of inotropes)

Results in "2 phases" of cardiac cycle





Zhukov L, Barr AH. Proceedings of 14th IEEE Visualization Conference (VIS'03). 2003;597-602.
Klabude RE; http://www.cvphysiology.com/

Anatomic consideration

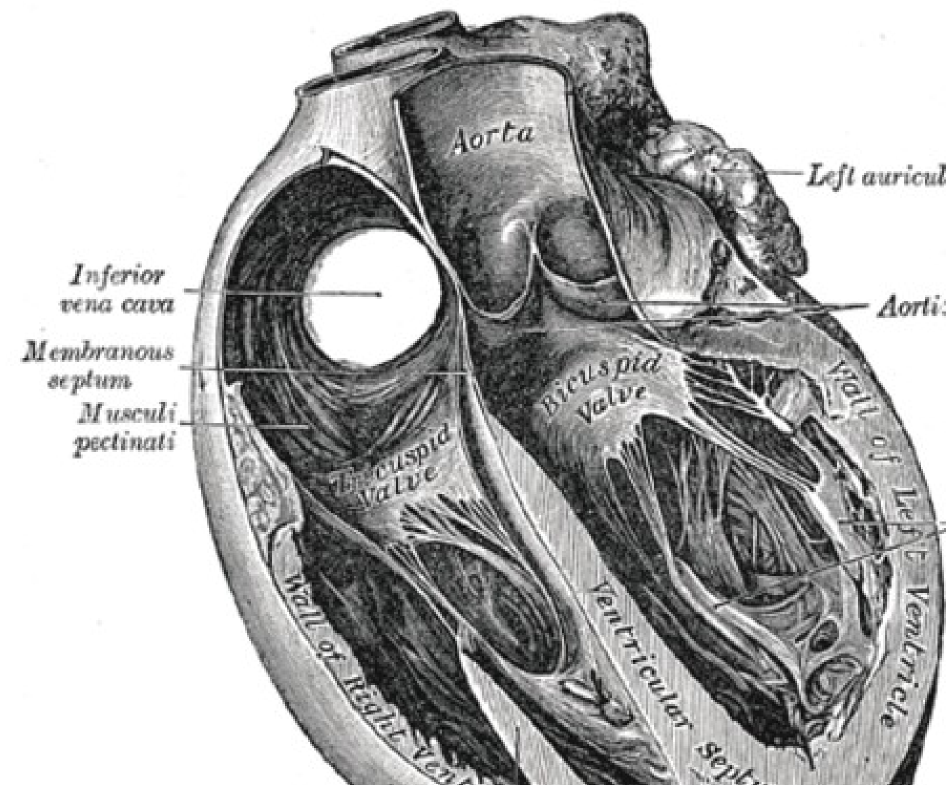
- LV: ellipsoidal / bullet-shape in normal configuration and post-natal physiology with low PVR and higher SVR

- RV: Triangular when viewed from side and crescent when viewed in cross section
  - RV becomes inefficient when septum does not contract towards it (septal distortion).

- Inter-ventricular septum has fibers shared between each ventricles

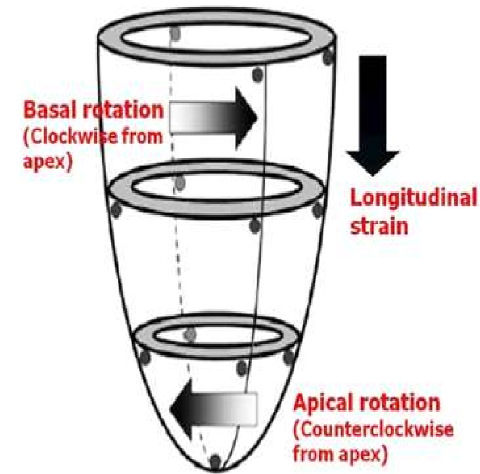
Ventricles

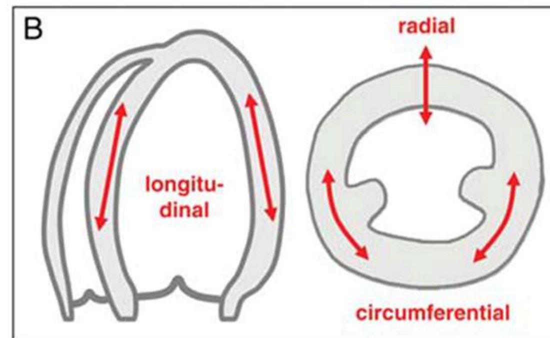
Anterior view



LV Cardiac function

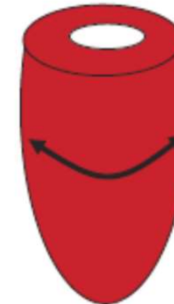
- LV contracts mostly circumferentially and with torsion
- Minor longitudinal contribution
- Wall gets “thicker” during contraction
- Septal configuration anomaly = loose contraction efficiency?



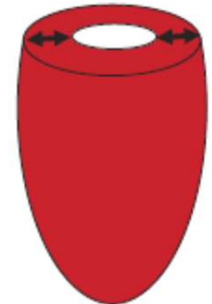


Longitudinal shortening
Endocardial + epicardial fibers

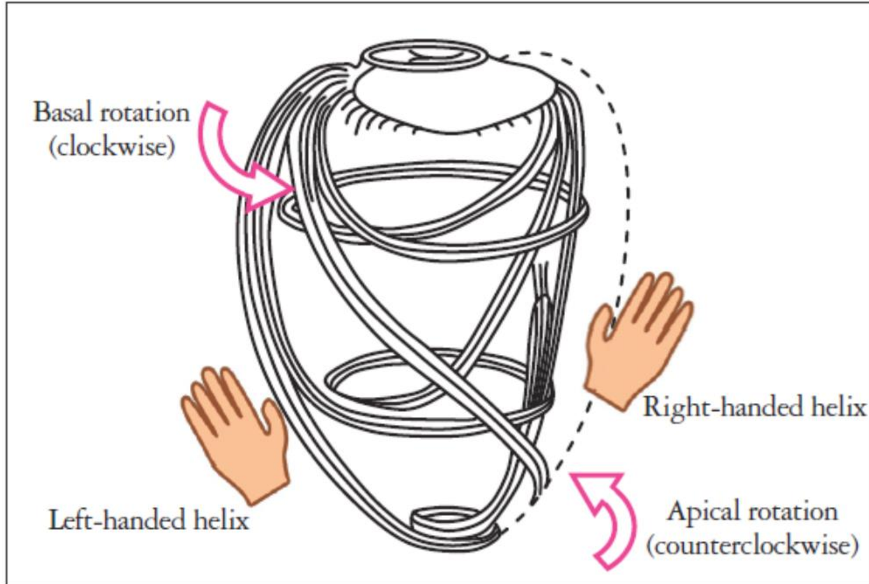
Circumferential motion
Circumferential fibers
Oblique/spiraling of fibers

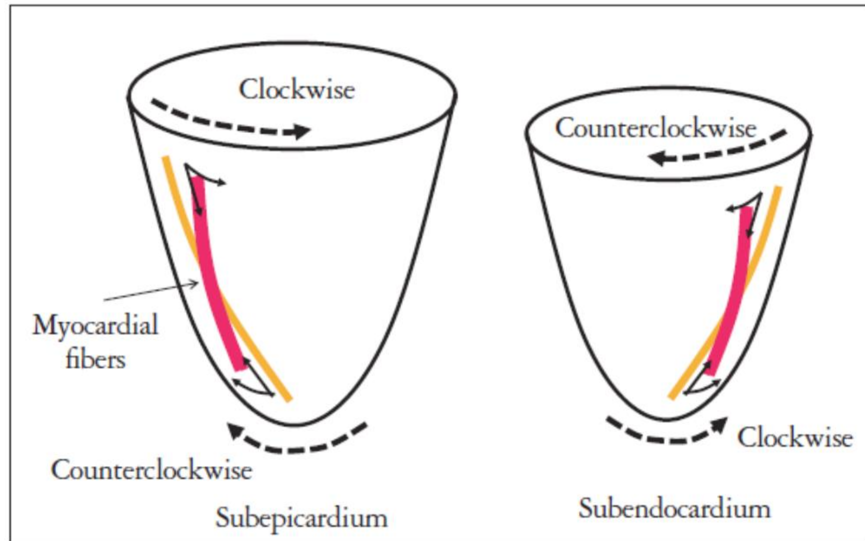


Radial thickening
Circumferential fibers

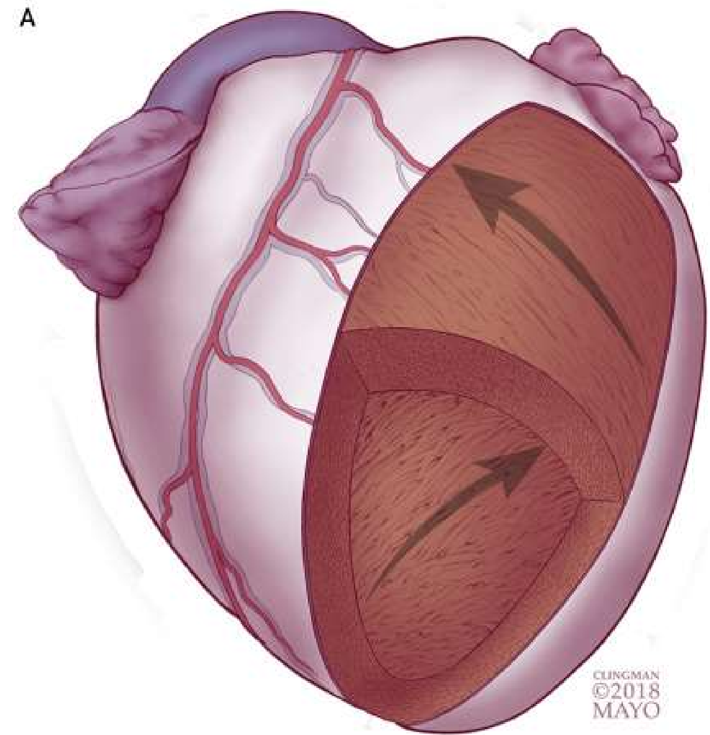


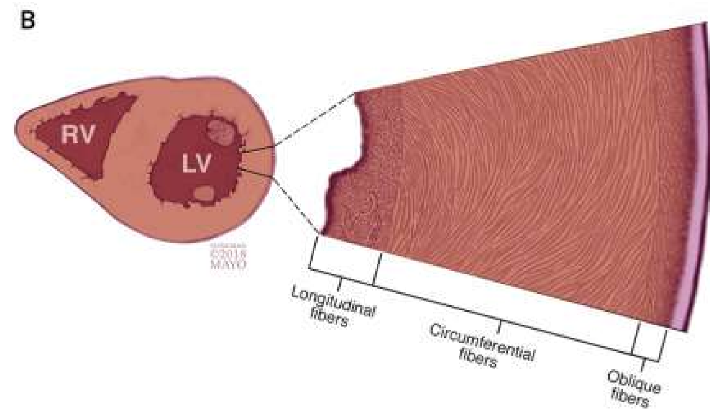
Indian heart journal 65 (2013) 117e123
Lai, W. W., Mertens, L. L., Cohen, M. S., & Geva, T. (2015). Echocardiography in pediatric and congenital heart disease: from fetus to adult. John Wiley & Sons.
Journal of Cardiovascular Magnetic Resonance, 2011
J Am Soc Echocardiogr 2012;25:543-52.
J Am Soc Echocardiogr 2011;24:277-313



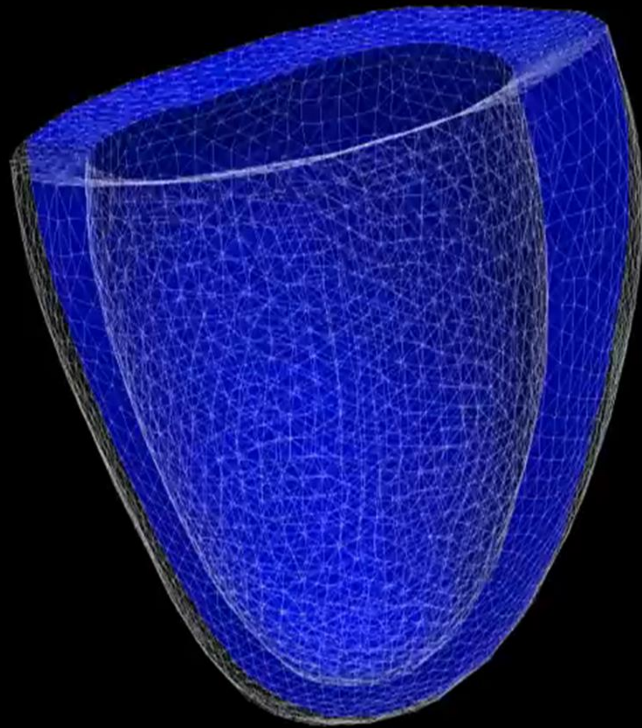


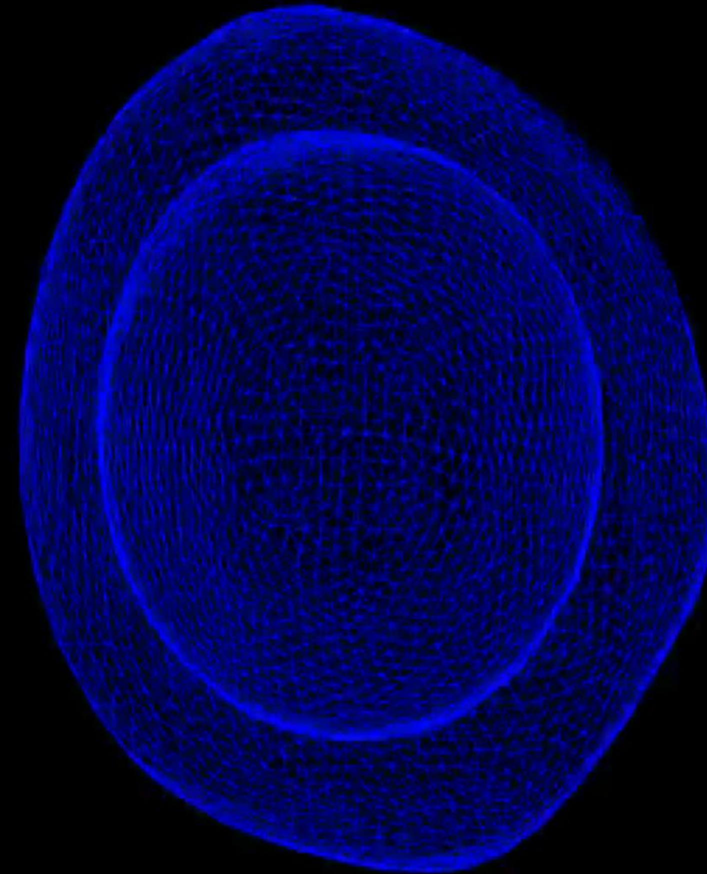
Nakatani S, 2011; Journal of Cardiovascular Ultrasound 19 (1-6)





Mayo Clin Proc. 2019;94(1):125-138





Displacement (cm)

simone.rossi@epfl.ch

LifeV (lifev.org)

Simone Rossi – Computational Cardiac Electromechanics: Left Ventricle - https://www.youtube.com/watch?v=FeGTS0iakkM

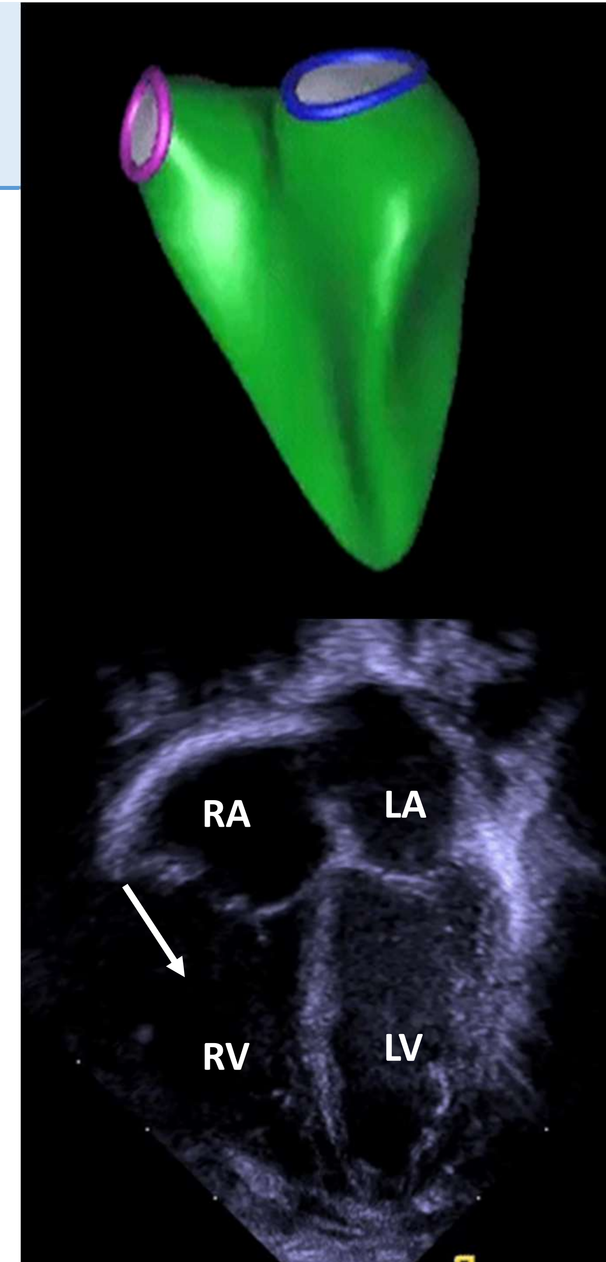
Right Ventricle

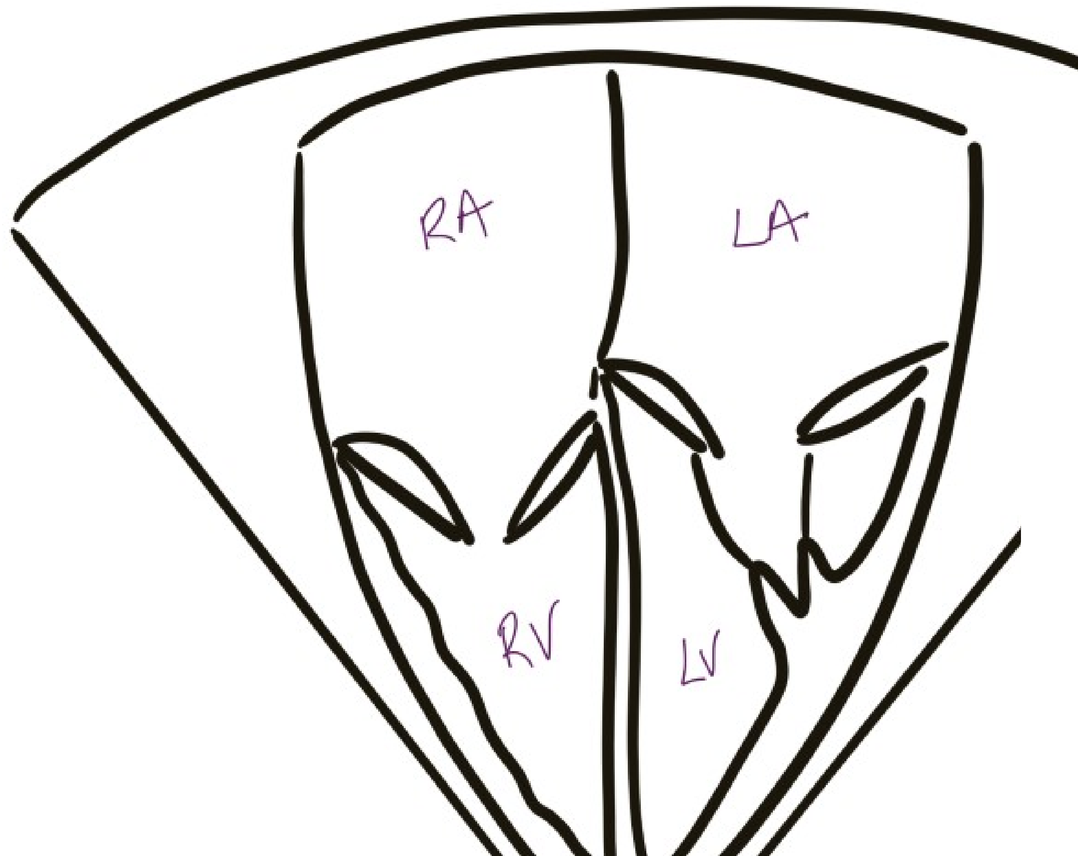
RV contracts **<u>longitudinally (below motion)</u>**

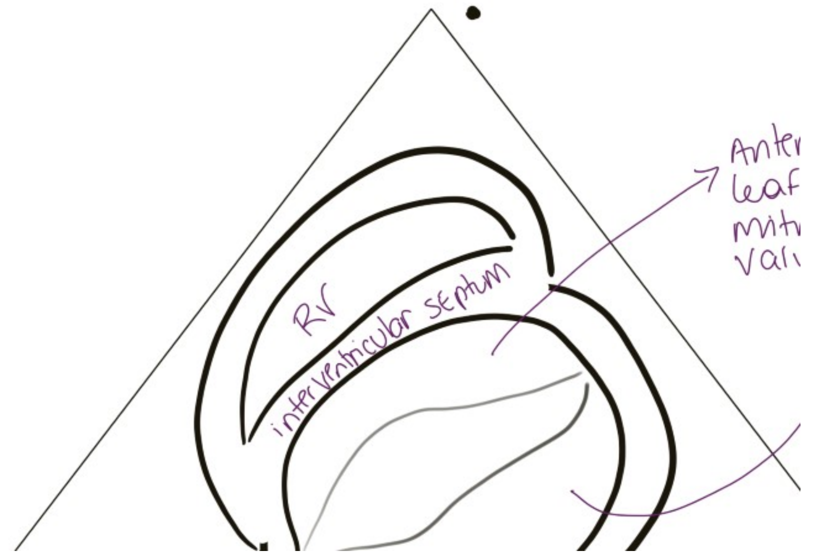
- Peristaltic motion from inflow (tricuspid valve) to RVOT (pulmonary valve)
- IV septum bulging in RV cavity
- Free wall going towards IVS

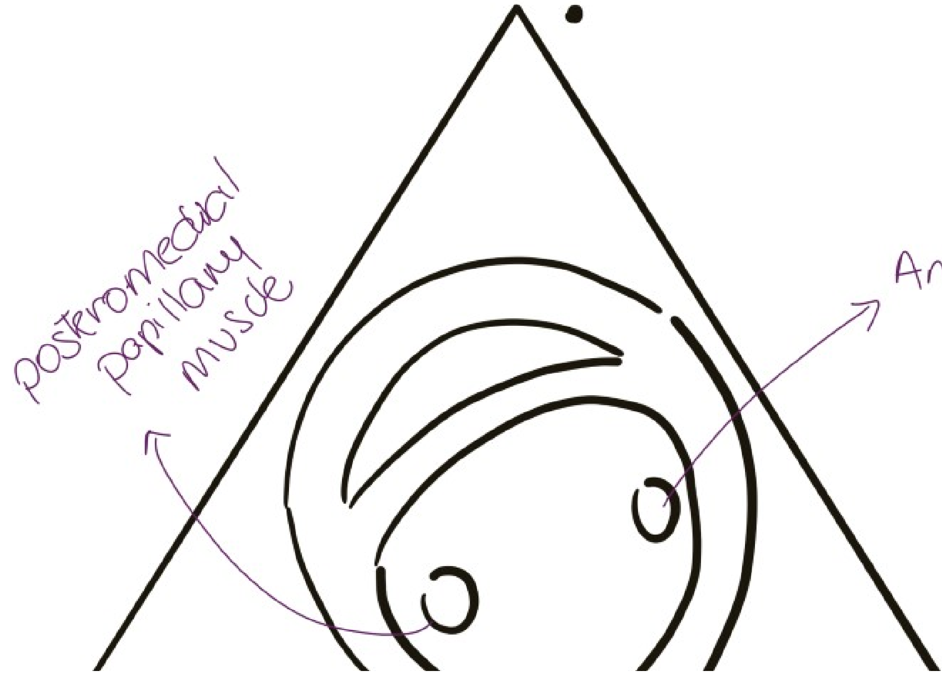
RV function by ECHO

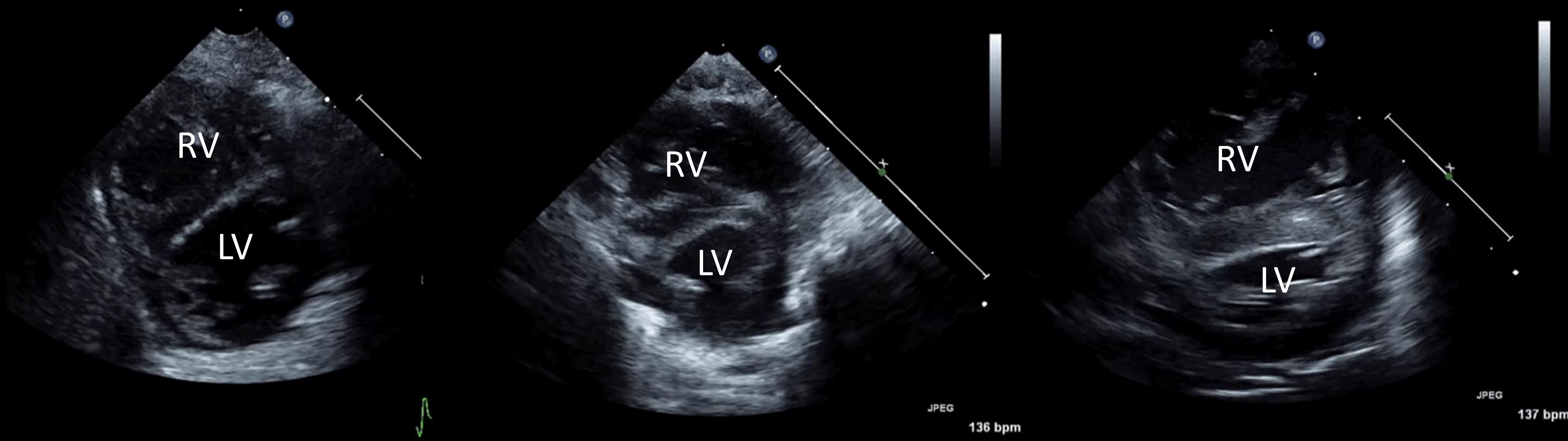
- TAPSE: Tricuspid Annular Plane Systole Excursion
  - Longitudinal movement as it plunges in RV cavity
- FAC: Fractional area change
  - FAC = (EDA – ESA) / (EDA) in Apical 4 or 3 Chamber view




RA
LA
RV
LV


RV
interventricular septum


posteromedial
papillary
muscle



Increasing RV afterload

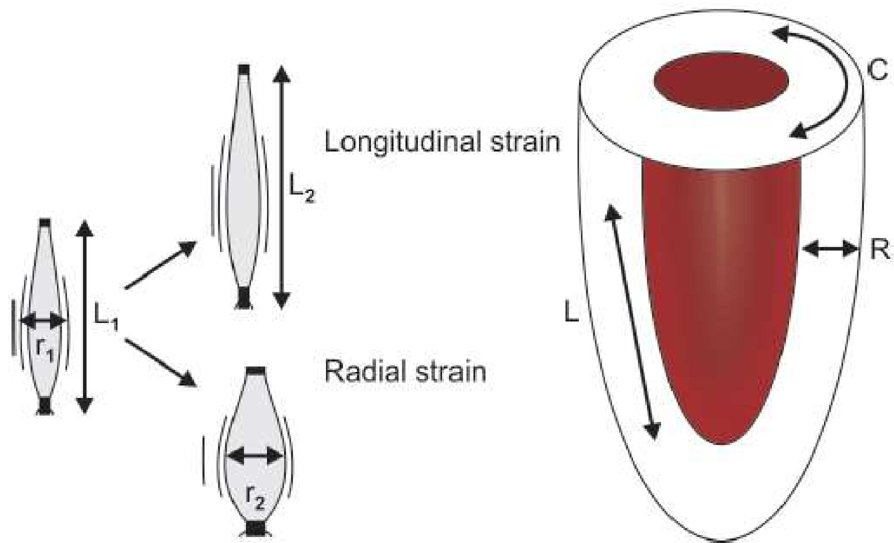
RV-LV cross-talk: RV function and LV function are inter-linked

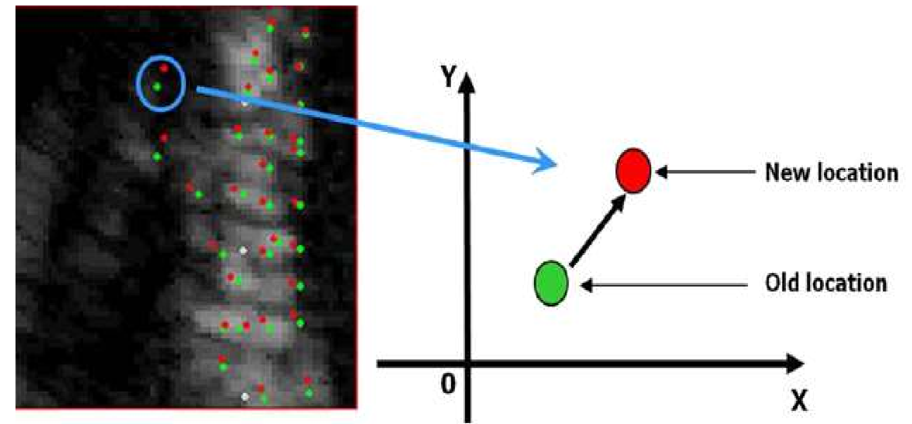
Strain by STE

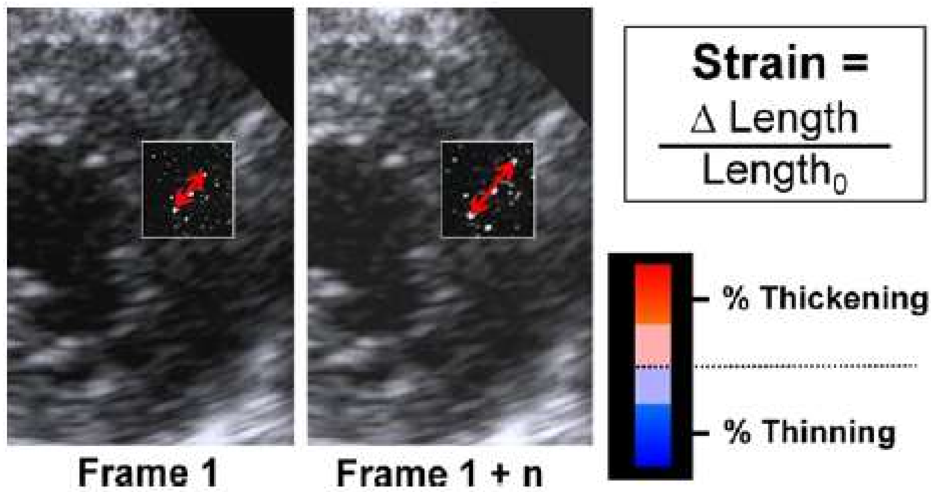
- Speckles (echodensities) form the ECHO images
  - Tracked on a frame by frame to measure magnitude (or percentage) of deformation
  - Speckle Tracking Echocardiography (STE)

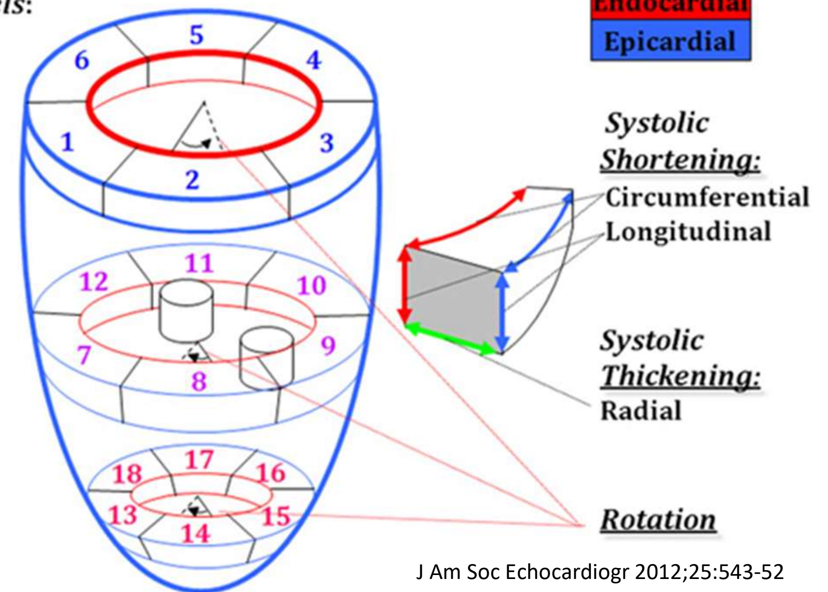
- Strain is absolute percentage of deformation of each segment and overall ventricle

- STE allows for:
  - Segmental analysis
  - Rate of myocardial expansion (diastole)
  - Circumferential, radial and rotational assessment of LV



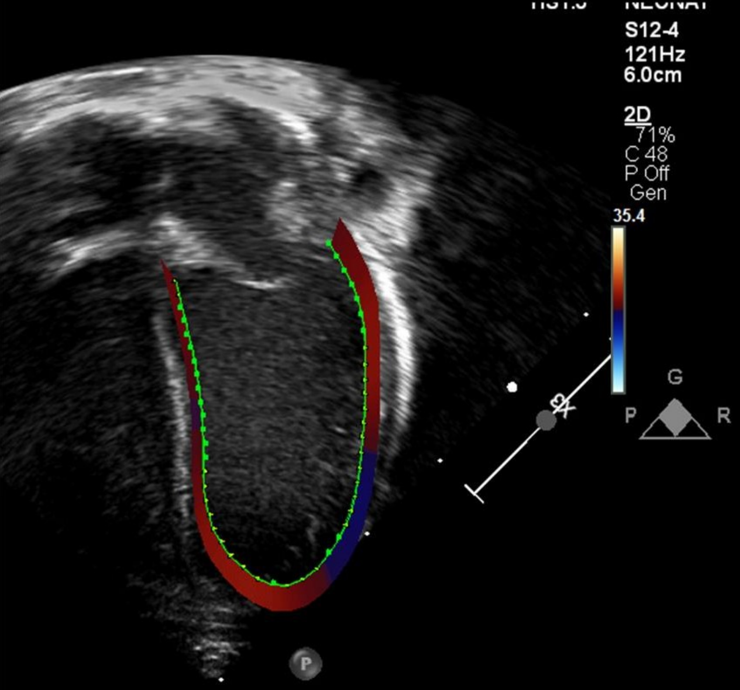


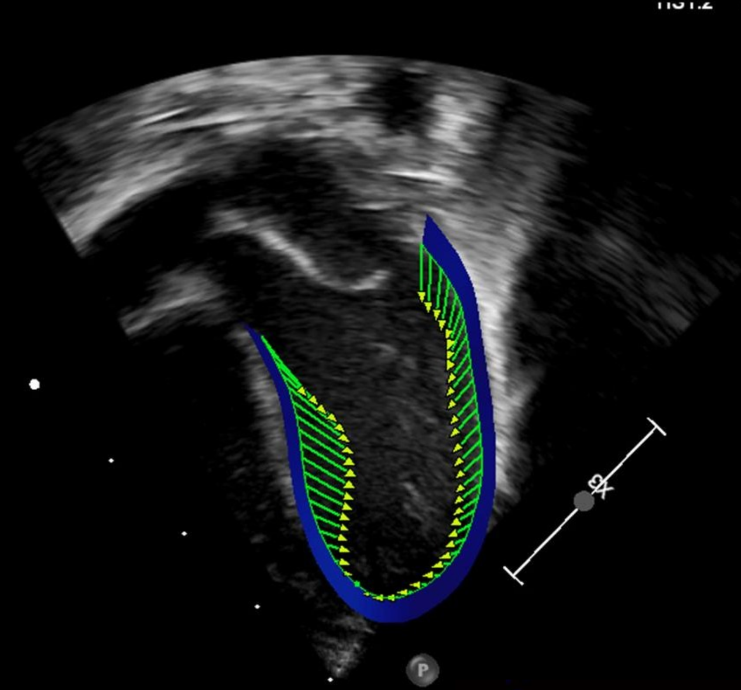


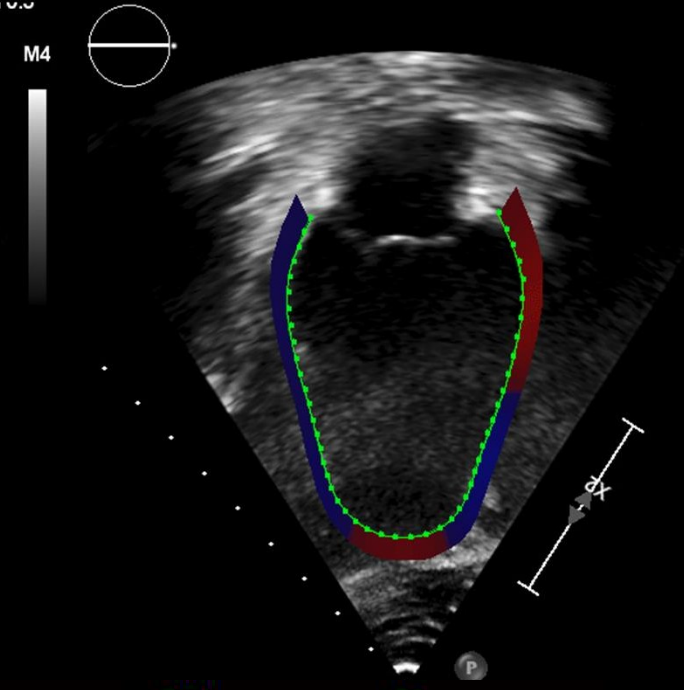


Bansal M, Kasliwal RR. Indian heart journal 65 (2013) 117e123
Garg, Kapur. Strain and Strain Rate imaging. Cardiological Society of India Cardiology Update 2014, pp.310-321

J Am Soc Echocardiogr 2012;25:543-52

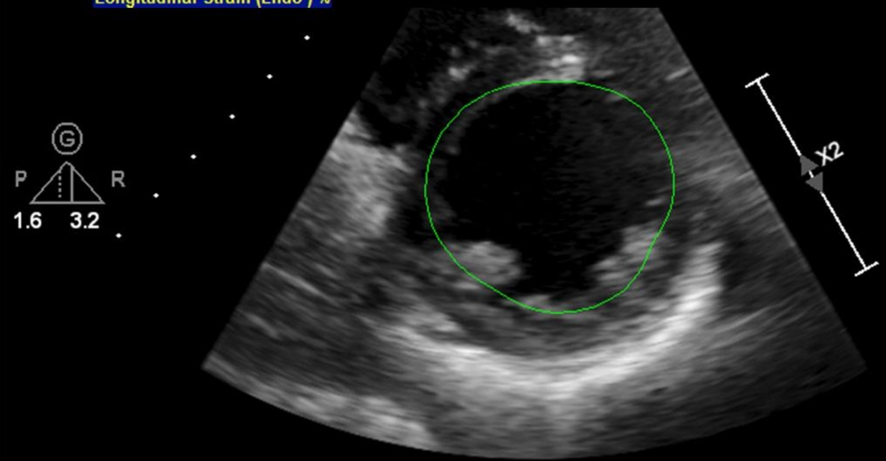






Longitudinal Strain (Endo) %

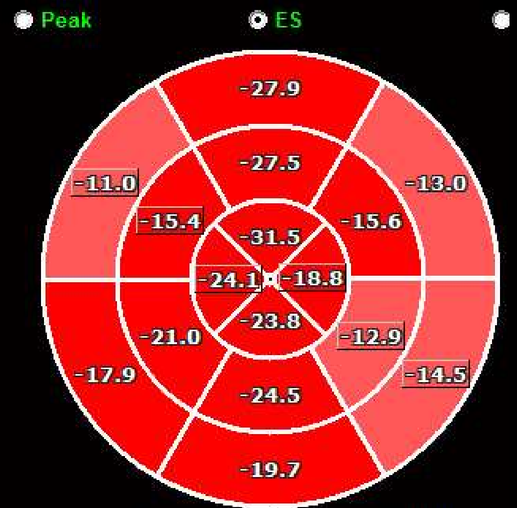
Longitudinal Strain (Endo) %



Average

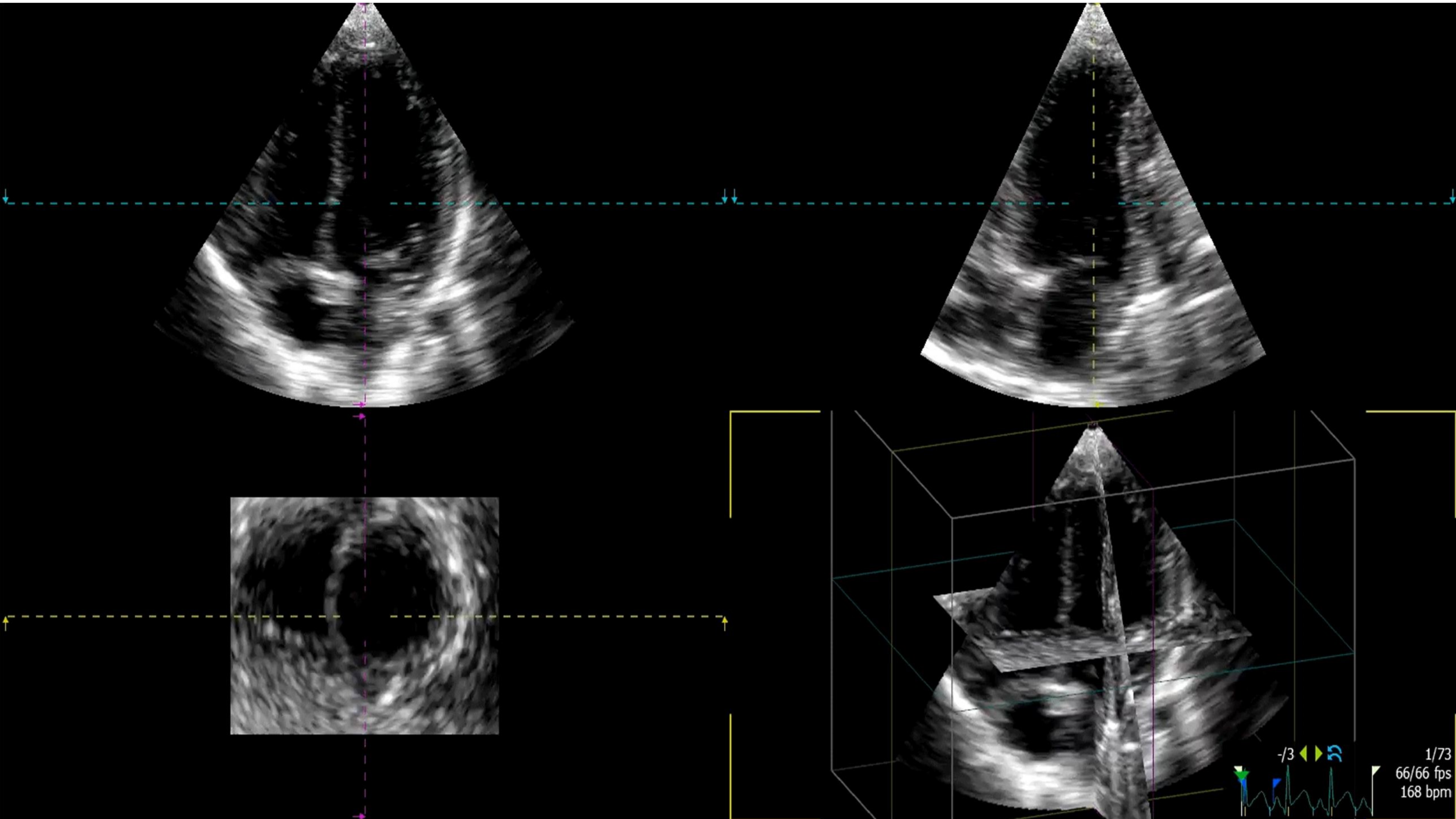
EndoGLS	-20.13	%
EF	49.40	%
EDV	8.32	ml
ESV	4.21	ml
ESL	2.60	cm
ESDbas	1.41	cm
EDL	3.22	cm
EDDbas	1.67	cm
SD-LS-Syst.	6.1	%

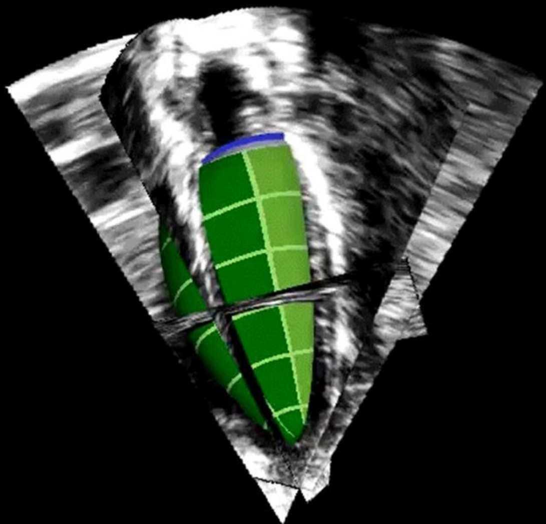
Syst. Endo Longitudinal Strain%



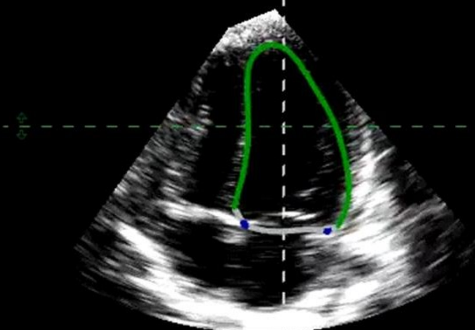
55 bpm

-20 20 %

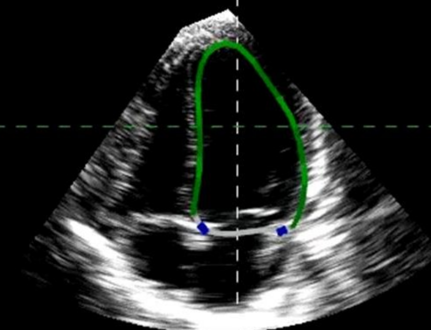

-/3
1/73
66/66 fps
168 bpm



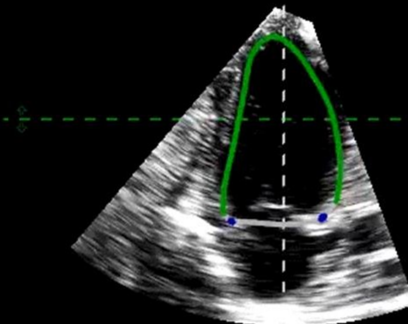
Global LV
EDV: 7.1 ml
ESV: 3.8 ml
SV: 3.3 ml
EF: 46.3 %
Mass: --.--
GLS: -17.3 %
GCS: -19.1 %



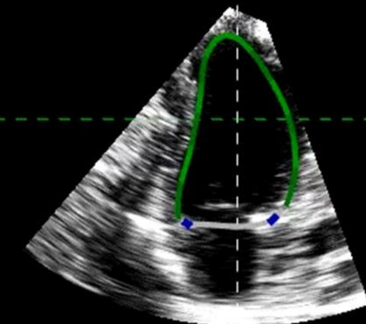
4Ch (LV)
3/73



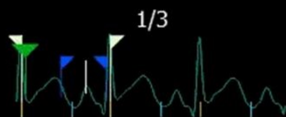
4Ch (LV) End-Diastole
26/73



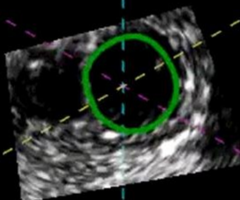
2Ch (LV)
3/73



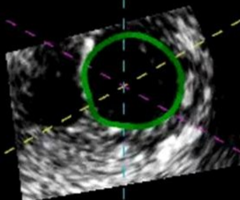
2Ch (LV) End-Diastole
26/73



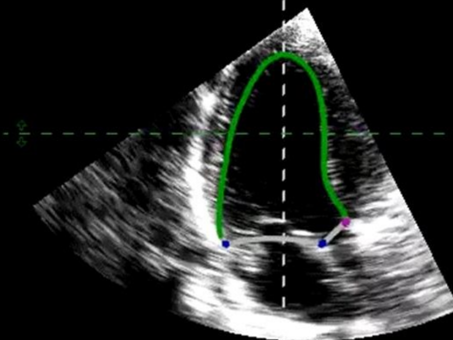
1/3
3/73
168 bpm
100 %



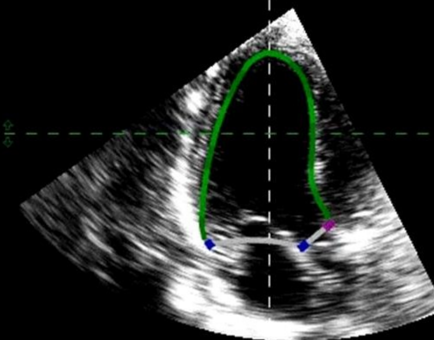
SAX (medial)
3/73



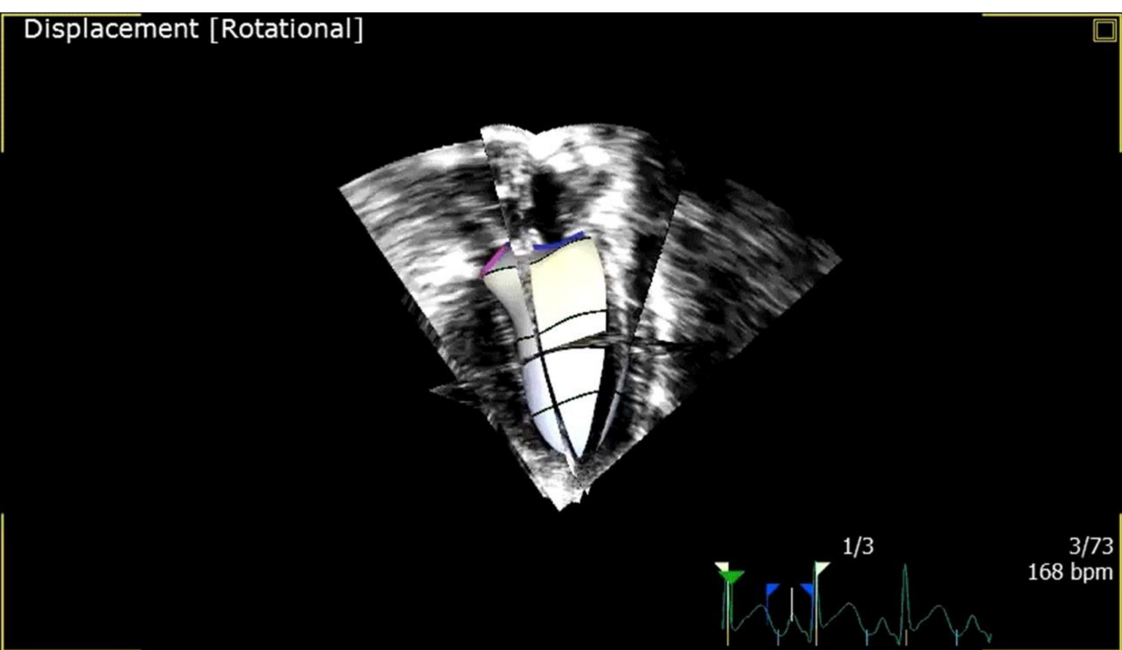
SAX (medial) End-Diastole
26/73

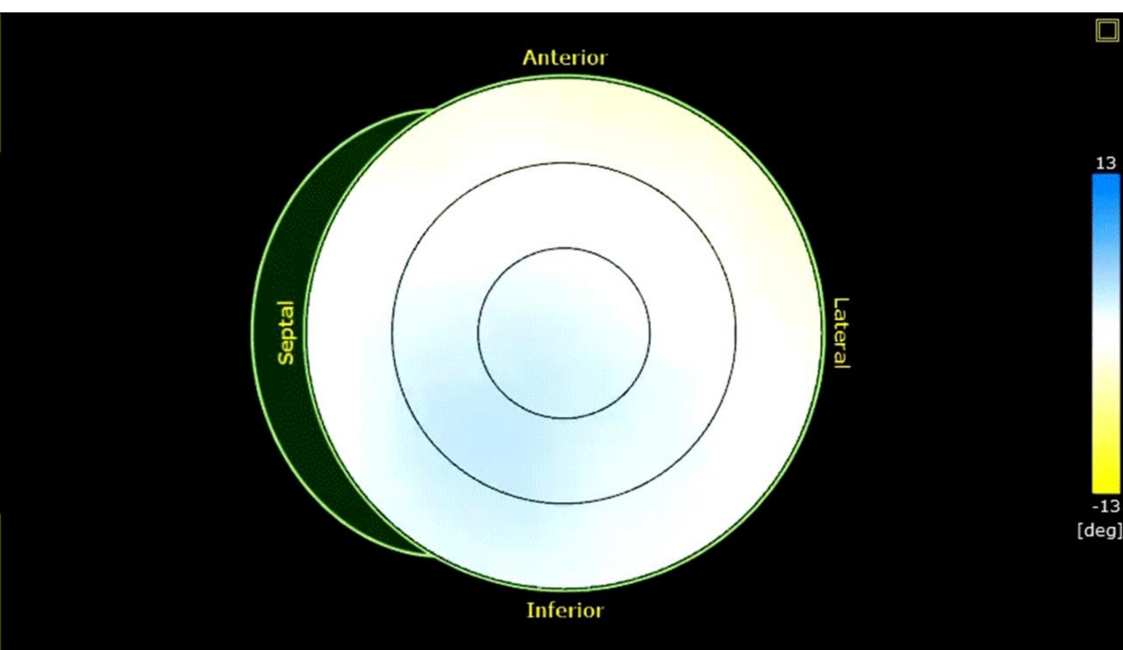


3Ch (LV)
3/73



3Ch (LV) End-Diastole
26/73





Global LV | T2P | Peak | ES

EDV: 7.1 ml

ESV: 3.8 ml

SV: 3.3 ml

EF: 46.3 %

Mass: --.--

SDI: 6.4 %

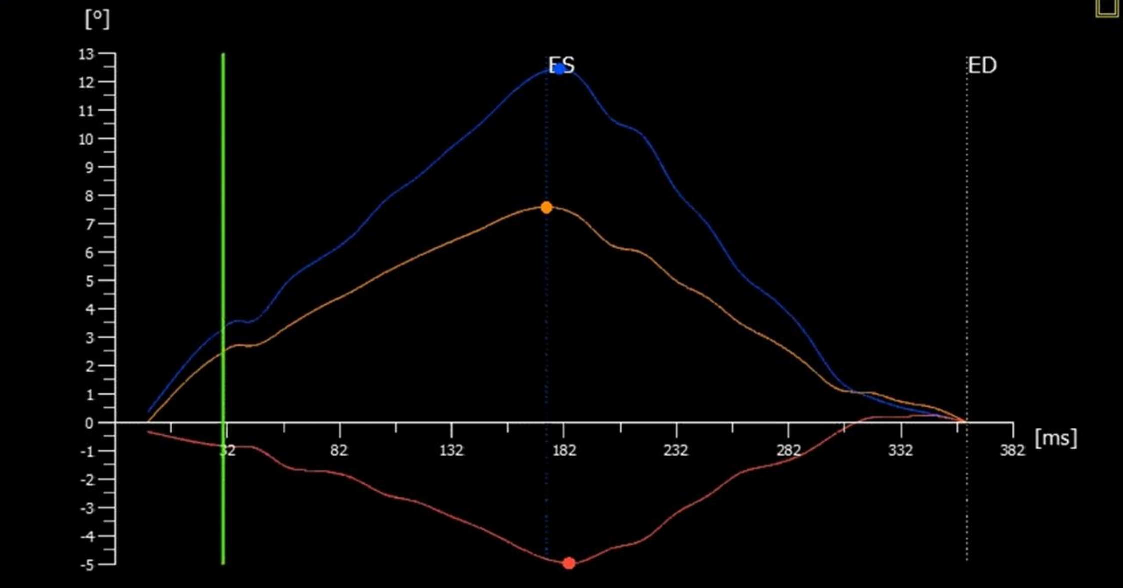
GLS: -17.3 %

GCS: -19.1 %

Twist: 12.5 °

Torsion: 3.6 °/cm

Length (ED): 34.3 mm

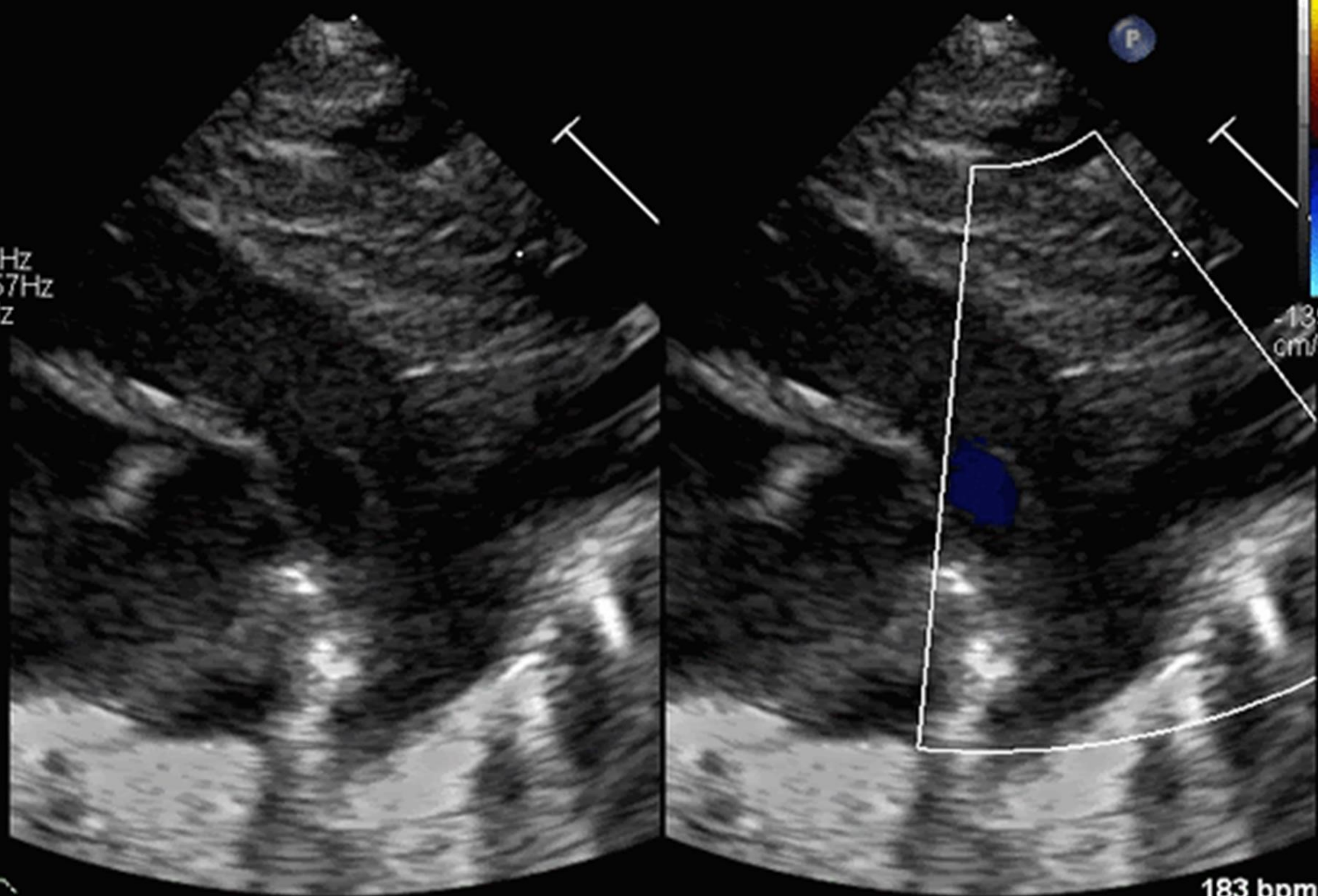


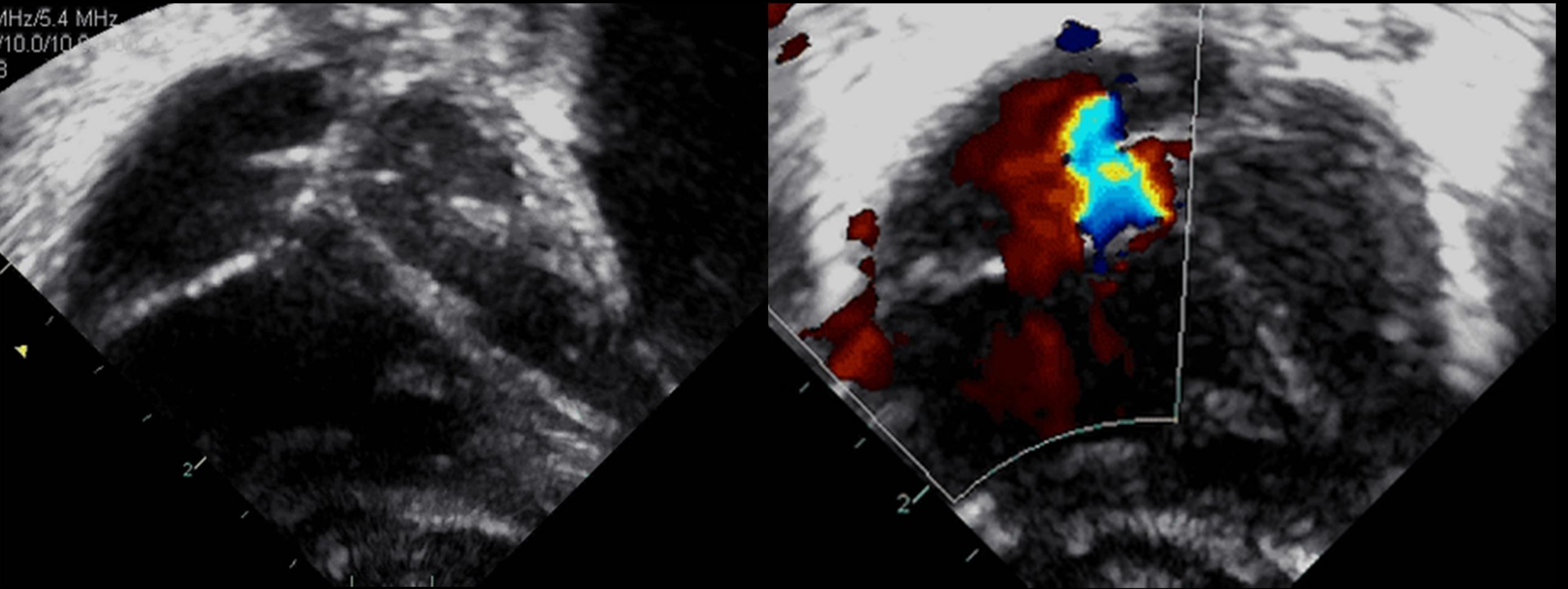
Case 1

Case 1

www.NeoCardioLab.com
@CardioNeo (Twitter)

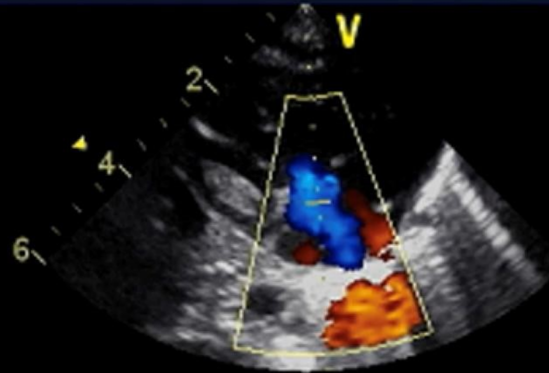
- Left-side CDH newborn boy
- Hypoxic respiratory failure with 100% FiO_2
- CO_2 58, pH 7.28
- Pre-ductal saturation of 84% and post-ductal saturation of 52%
- HFOV M16
- sBP 58, mBP 40
- ECHO requested


NEONAT20Beats
TIS0.8
MI 0.6
S12-4
35Hz
3.0cm
2D
68%
C 48
P Off
Res
CF
65%
16200Hz
WF1457Hz
4.5MHz
M4
139
P
183 bpm


MHz/5.4 MHz

1 TR Vmax	5.65 m/s
TR maxPG	127.55 mmHg

Power: 0 dB
FPS: 40.7/81.3



CTO

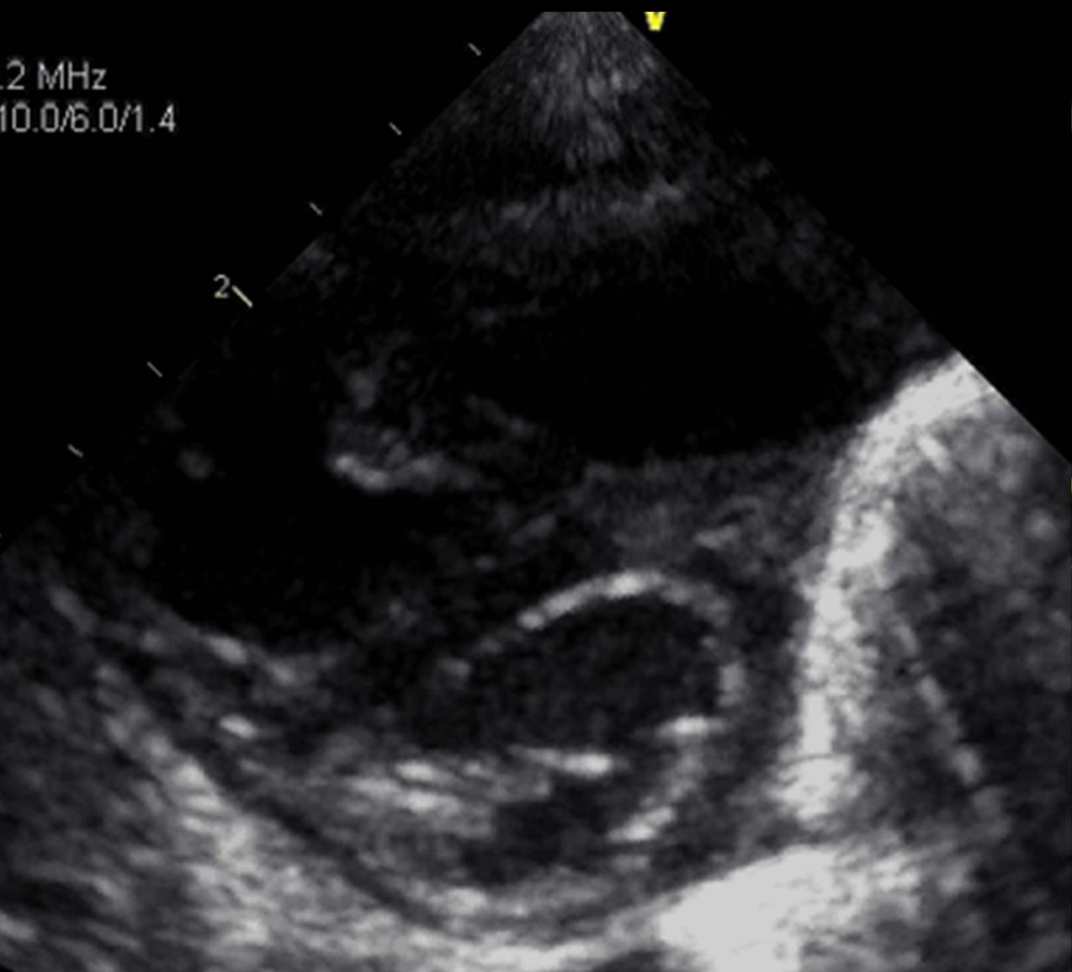
2
[m/s]
-2
-4
-6
-8

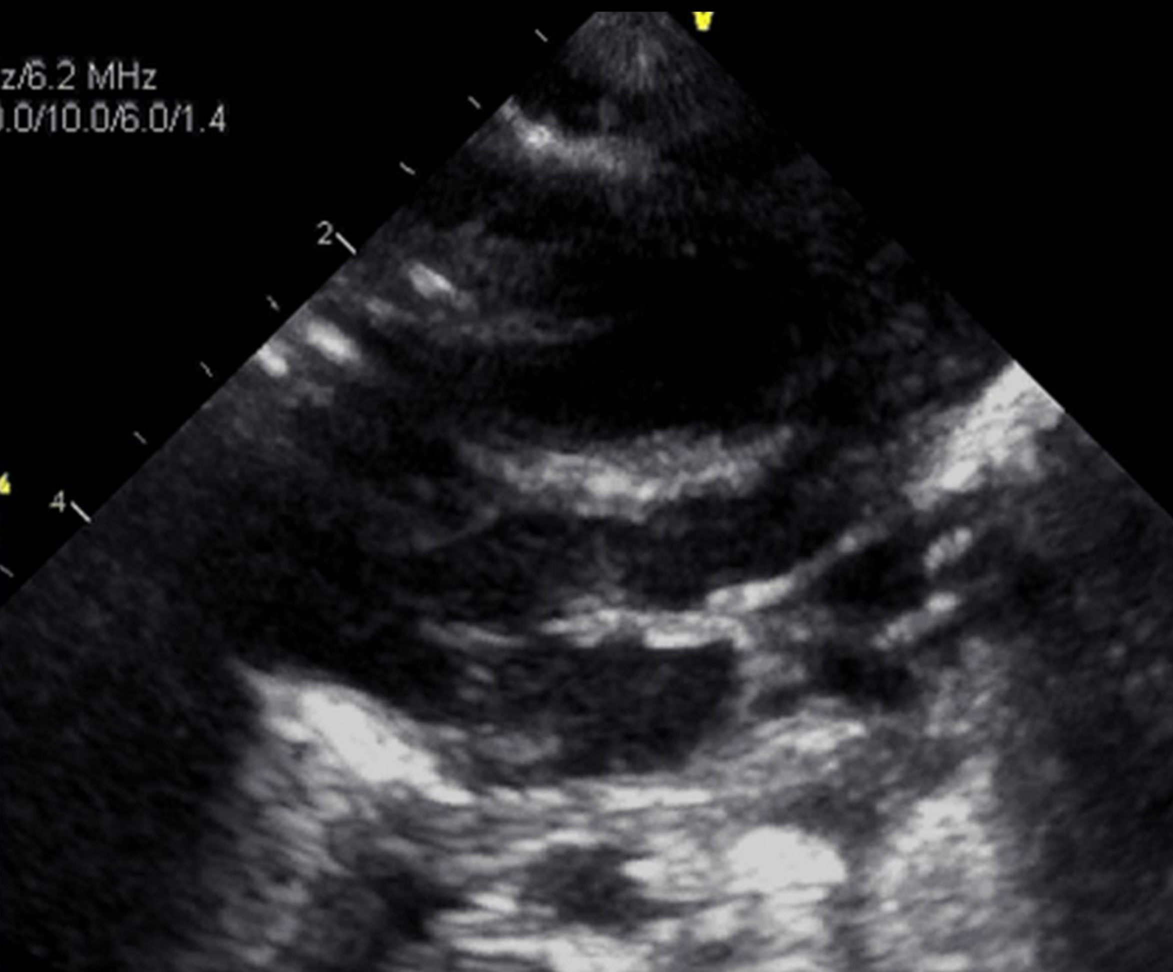
-3 -2 -1 0

66.67 mm/s

Image Time:1:29:12 PM
Image Date: 9/10/2021

HR


.2 MHz
10.0/6.0/1.4
2

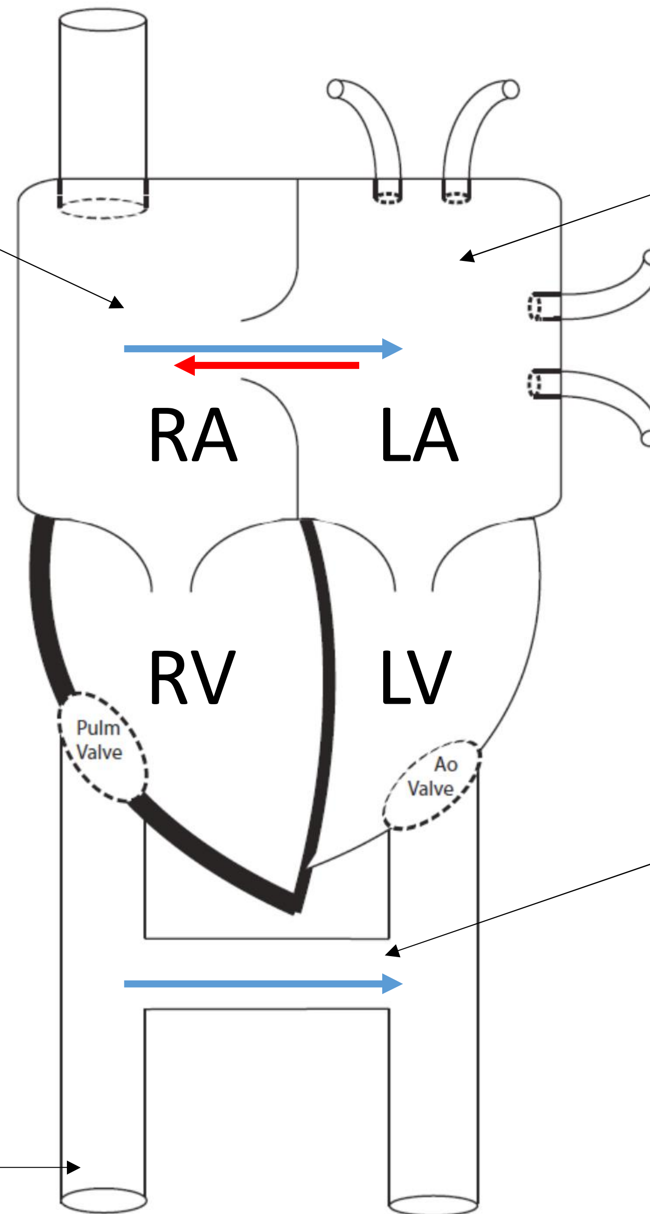

z/6.2 MHz
.0/10.0/6.0/1.4
2
4

Case 1

www.NeoCardioLab.com
@CardioNeo (Twitter)

- PFO found to be bidirectional, mostly right to left
- RV dilated, compressing the LV
- Right to left large ductus
- Predominant picture: **acute PH with RV failure**

High RV afterload leads to RV failure. Diastolic dysfunction leads to Right Atrial Hypertension; Leads to R to L shunt at atrial level (deO2 blood entering systemic circulation) – **leads to preductal low PaO2 and desaturation.** Maintains output



Low pulmonary vascular flow leads to decreased left atrial filling and left ventricular preload (RA pressure > LA pressure; R to L atrial shunt)

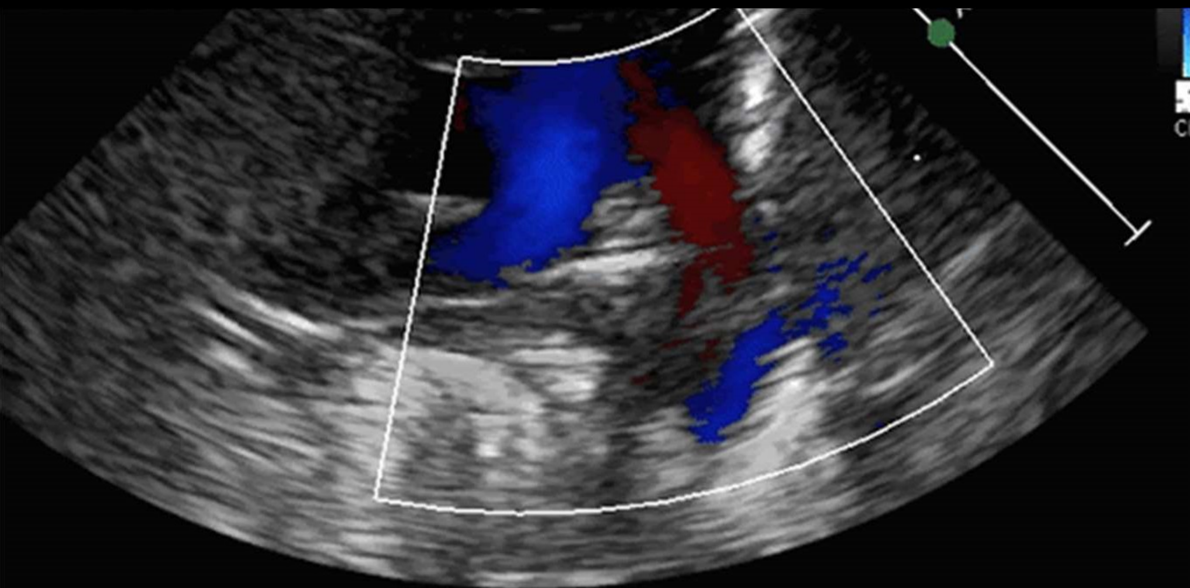
Decreased LV filling may lead to decrease LV output and systemic hypotension. Ductus can shunt right to left if still open

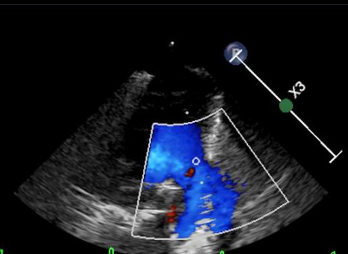
CDH: pulmonary hypoplasia with disturbed transition to extra-uterine life can lead to persistent high pulmonary vascular resistances (as well as decreased vascular area)

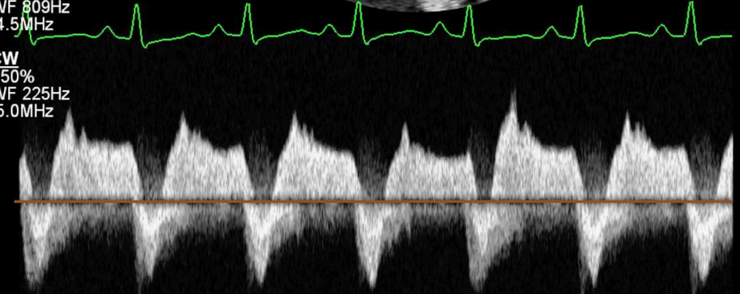
Case 1

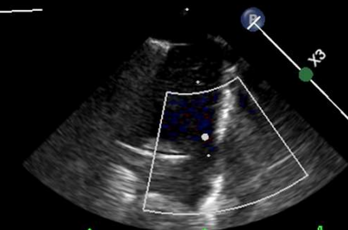
www.NeoCardioLab.com
@CardioNeo (Twitter)

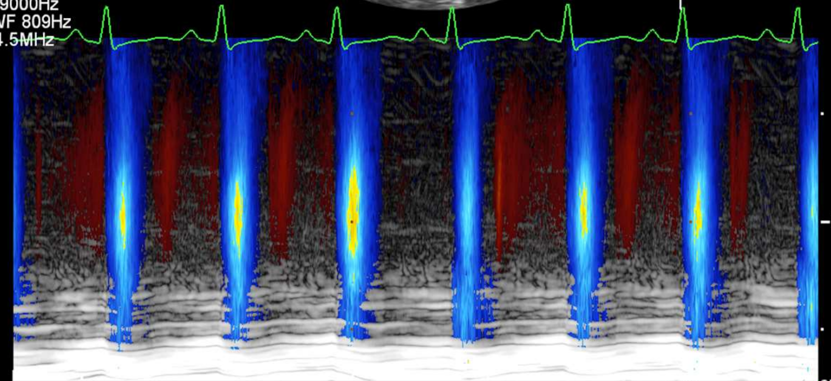
- Patient started on sedation (fentanyl 1 mcg/kg/hr)
- iNO started at 20 ppm + hydrocortisone 1 mg/kg q8hr
- Saturation dramatically increased in pre- and post-ductal, FiO2 progressively decreased to 30%
- ECHO repeated before repair at DOL 5…




NEONAT20Beats
TIS0.3 MI 0.0
S12-4
37Hz
3.0cm
2D
61%
C 48
P Off
Res
CF
65%
9000Hz
WF 809Hz
4.5MHz
M4 M4
+77.0
-77.0
cm/s


CW
50%
WF 225Hz
5.0MHz
160
80
cm/s
-80


NEONAT20Beats
TIS0.4 MI 0.5
S12-4
10Hz
3.0cm
2D / MM
66% 65%
C 48
P Off
Res
on ino
CF
65%
9000Hz
WF 809Hz
4.5MHz
M4 M4
+77.0
-77.0
cm/s


2
100mm/s

Management of isolated acute PH

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

- Ensure appropriate ventilation, but avoid hypocapnia (cerebral vasoconstriction) – aim permissive hypercapnia in CDH for lung protection
- Sedation/Analgesia may be considered to avoid reactive increase in PVR
- Oxygen administered to aim adequate pre-ductal saturation (85%)
- **iNO** studied in RCT for PPHN in the term and near-term newborns (but, in CDH… no improvement)
- Hydrocortisone normalizes PDE-5 activity in pulmonary artery smooth muscle cells from lambs with PPHN

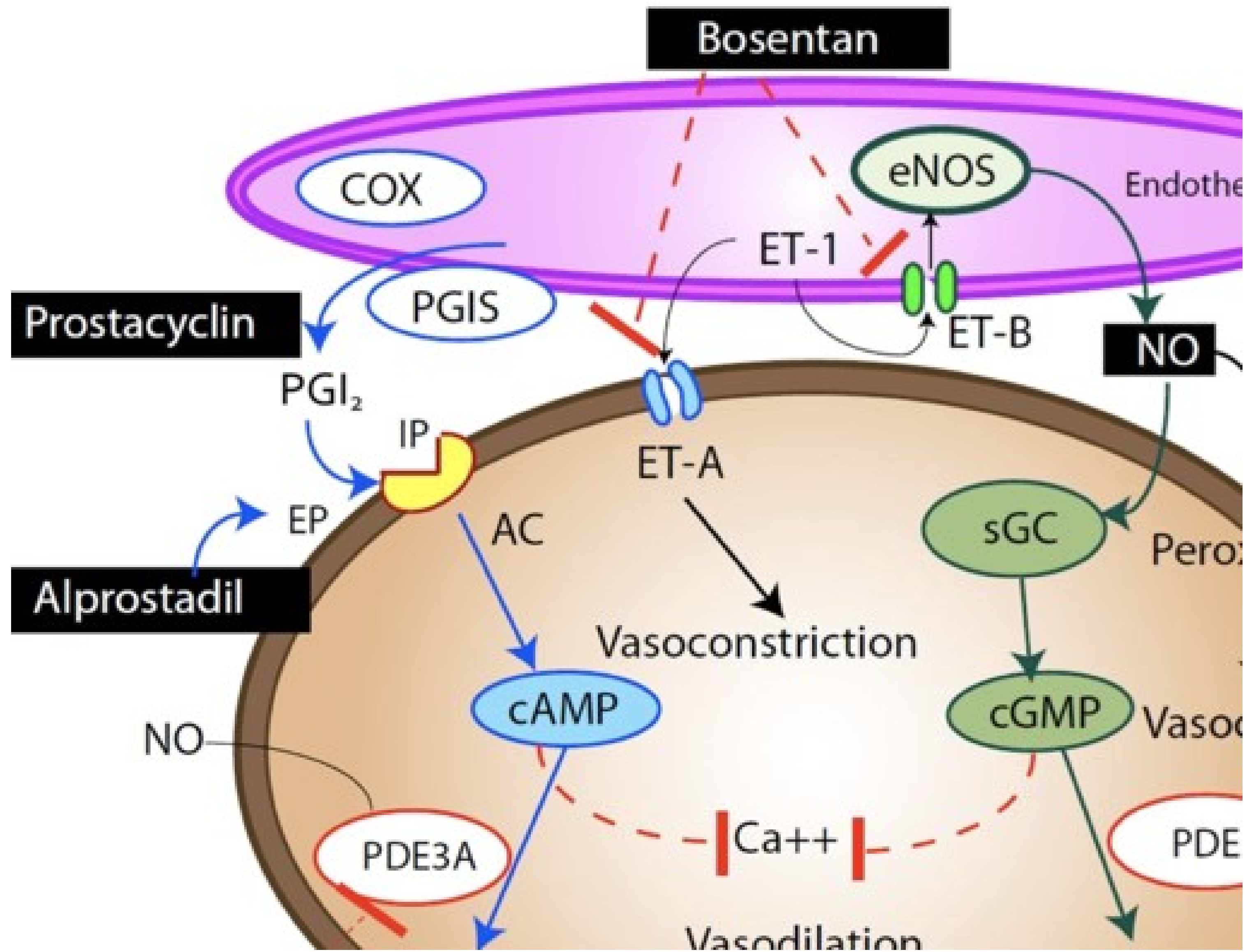
AHA/ATS Guideline

Pediatric Pulmonary Hypertension

Guidelines From the American Heart Association and American Thoracic Society

PPHN:

- iNO indicated to reduce ECMO need ($OI > 25$)
- Adequate lung recruitment
- Some may benefit from PGE if RV failure to unload RV and sustain systemic output (no RCT)



Satyan Lakshminrusimha and Martin Keszler NeoReviews December 2015, 16 (12) e680-e692; DOI: https://doi.org/10.1542/neo.16-12-e680

Nitric oxide for respiratory failure in infants born at or near term (Review)

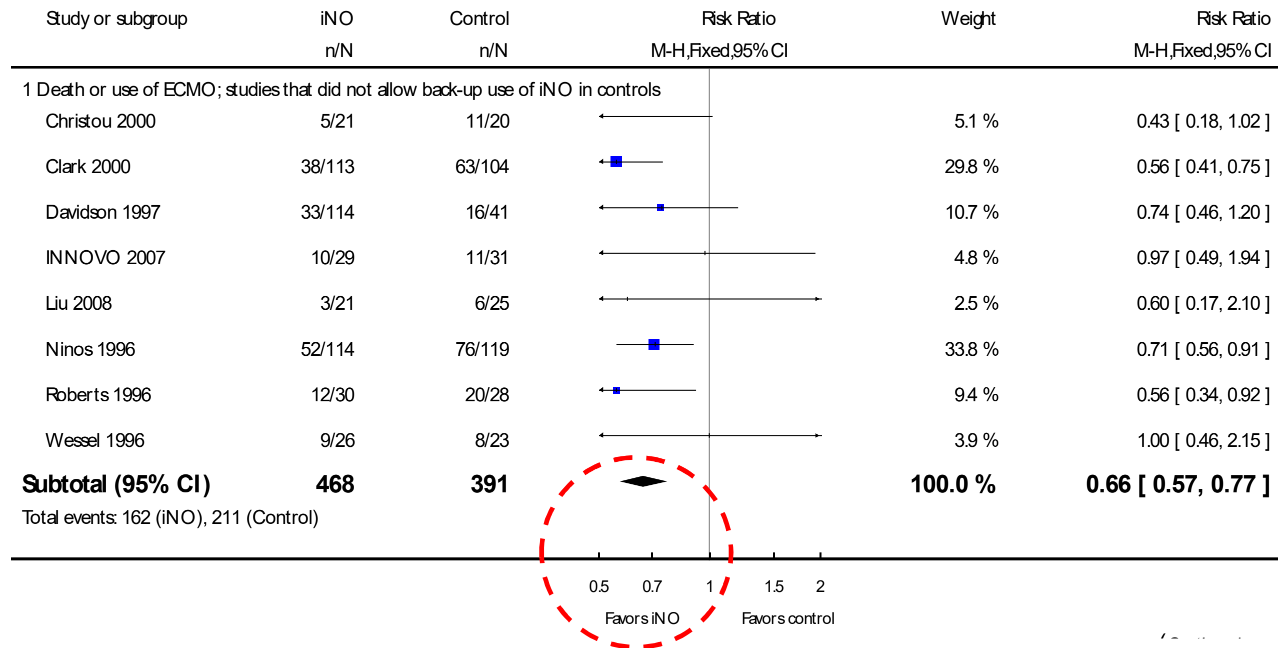
Barrington KJ, Finer N, Pennaforte T, Altit G

Analysis 1.1. Comparison 1 Inhaled NO versus control, Outcome 1 Death or use of ECMO.

Review: Nitric oxide for respiratory failure in infants born at or near term

Comparison: 1 Inhaled NO versus control

Outcome: 1 Death or use of ECMO



Study or subgroup	iNO n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Death or use of ECMO; studies that did not allow back-up use of iNO in controls					
Christou 2000	5/21	11/20		5.1 %	0.43 [0.18, 1.02]
Clark 2000	38/113	63/104		29.8 %	0.56 [0.41, 0.75]
Davidson 1997	33/114	16/41		10.7 %	0.74 [0.46, 1.20]
INNOVO 2007	10/29	11/31		4.8 %	0.97 [0.49, 1.94]
Liu 2008	3/21	6/25		2.5 %	0.60 [0.17, 2.10]
Ninos 1996	52/114	76/119		33.8 %	0.71 [0.56, 0.91]
Roberts 1996	12/30	20/28		9.4 %	0.56 [0.34, 0.92]
Wessel 1996	9/26	8/23		3.9 %	1.00 [0.46, 2.15]
Subtotal (95% CI)	**468**	**391**		**100.0 %**	**0.66 [0.57, 0.77]**
Total events: 162 (iNO), 211 (Control)					

Nitric oxide for respiratory failure in infants born at or near term (Review)

Barrington KJ, Finer N, Pennaforte T, Altit G

Study or subgroup	iNO n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi^2 = 5.56, df = 7 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 5.24 (P < 0.00001)					
2 Death or use of ECMO; studies that allowed back-up use of iNO in controls					
Mercier 1998	5/55	4/52		100.0 %	1.18 [0.34, 4.16]
Subtotal (95% CI)	**55**	**52**		**100.0 %**	**1.18 [0.34, 4.16]**
Total events: 5 (iNO), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.79)					
3 Death or use of ECMO; infants with diaphragmatic hernia					
Clark 2000	12/13	17/18		39.7 %	0.98 [0.81, 1.19]
Ninos 1997	24/25	23/28		60.3 %	1.17 [0.97, 1.41]
Subtotal (95% CI)	**38**	**46**		**100.0 %**	**1.09 [0.95, 1.26]**
Total events: 36 (iNO), 40 (Control)					
Heterogeneity: Chi^2 = 1.77, df = 1 (P = 0.18); I^2 =43%					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Chi^2 = 22.65, df = 2 (P = 0.00), I^2 =91%					

0.5 0.7 1 1.5 2

Favors iNO Favors control

The incidence of death or requirement for ECMO was 40/46 control infants and 36/38 infants with iNO (RR 1.09, 95% CI 0.95 to 1.26; two studies, 84 infants; RD 0.08, 95%

JAMA Pediatrics | Original Investigation

Evaluation of Variability in Inhaled Nitric Oxide Use and Pulmonary Hypertension in Patients With Congenital Diaphragmatic Hernia

Luke R. Putnam, MD, MS; Kuojen Tsao, MD; Francesco Morini, MD; Pamela A. Lally, MD; Charles C. Miller, PhD;
Kevin P. Lally, MD, MS; Matthew T. Harting, MD, MS; for the Congenital Diaphragmatic Hernia Study Group

Drugs R D (2014) 14:215–219
DOI 10.1007/s40268-014-0063-7

CURRENT OPINION

Initial Oxygenation Response to Inhaled Nitric Oxide Predicts Improved Outcome in Congenital Diaphragmatic Hernia

Sibel Tiryaki · Coskun Ozcan · Ata Erdener

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

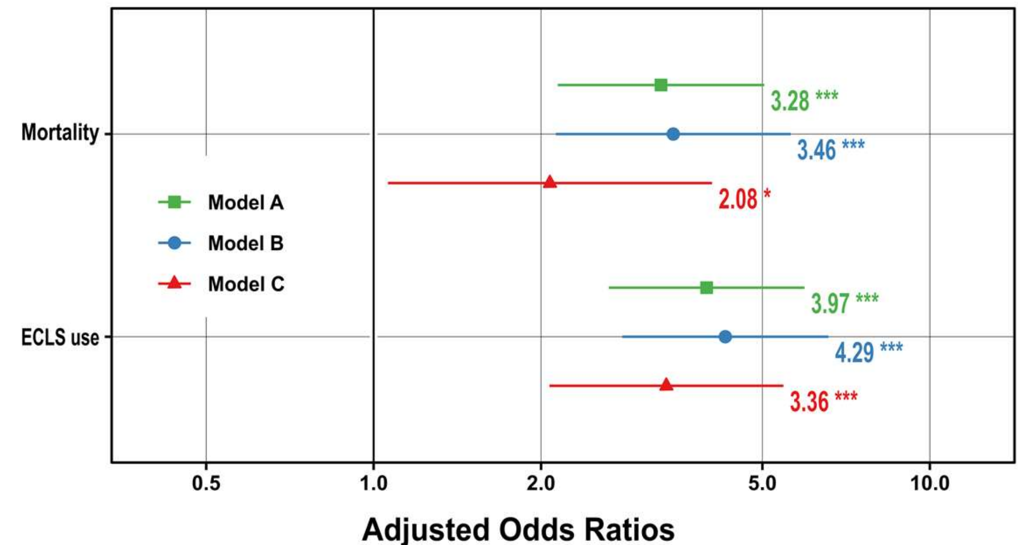
Inhaled Nitric Oxide Is Associated with Improved Oxygenation in a Subpopulation of Infants with Congenital Diaphragmatic Hernia and Pulmonary Hypertension

Kendall M. Lawrence, MD[1], Stylianos Monos, BA[1], Samantha Adams, BS, MS[1], Lisa Herkert, MSN, CRNP[1], William H. Peranteau, MD[1,2], David A. Munson, MD[3], Rachel K. Hopper, MD[4], Catherine M. Avitabile, MD[2,3], Natalie E. Rintoul, MD[2,3], and Holly L. Hedrick, MD[1,2]

iNO in CDH – the controversy continues

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill
Montreal Children's Hospital
McGill University Health Centre

- iNO has not been associated with improved outcomes in RCT including CDH newborns.
- Poster at PAS 2022 by Stanford group using the CDH registry
  - 1777 patients in CDH study group with echo in first 2 days of life
  - No improvement even in isolated RV dysfunction
  - Early iNO use associated with increased mortality and ECLS use even when adjusting:
    - A) echo characteristics (PH, function, shunt pattern), B)+ neonatal characteristics and defect side C) + size and repair



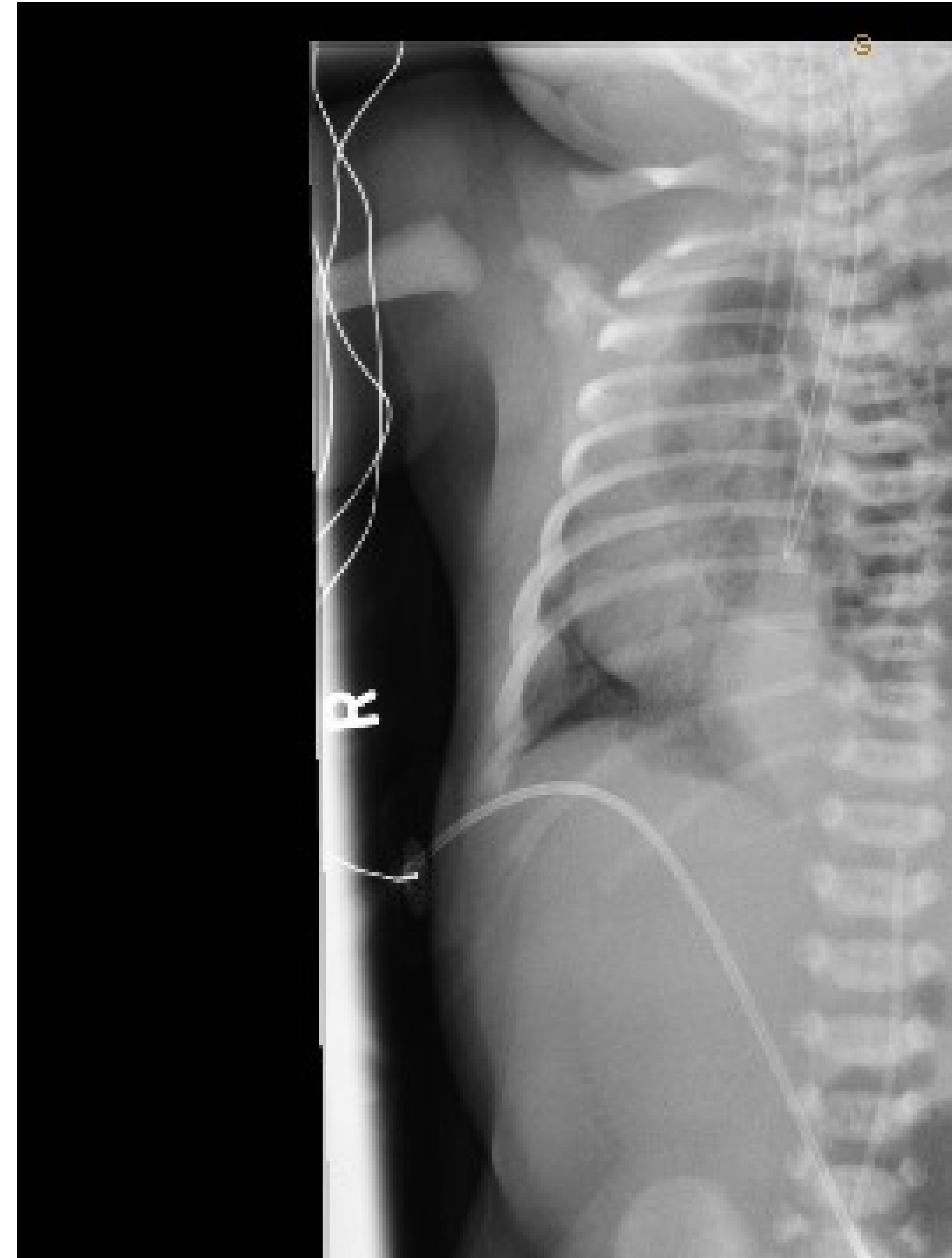
Stanford Children's Health | Lucile Packard Children's Hospital Stanford

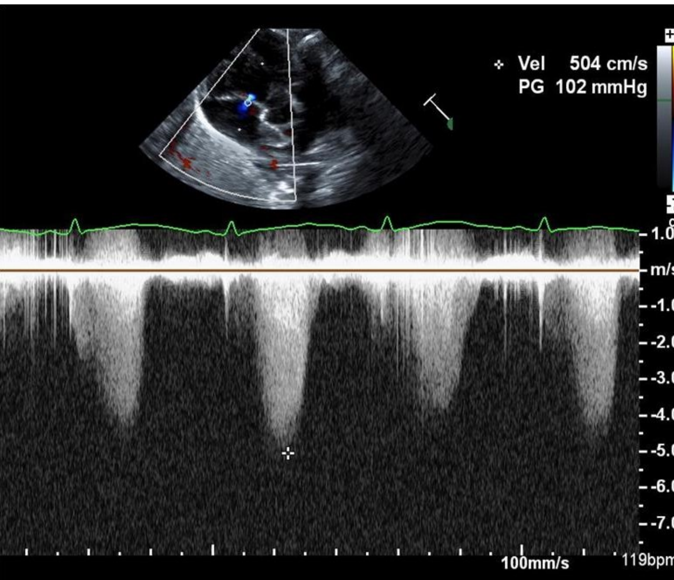
Noh C et al, for the CDH study group, PAS abstract, unpublished data

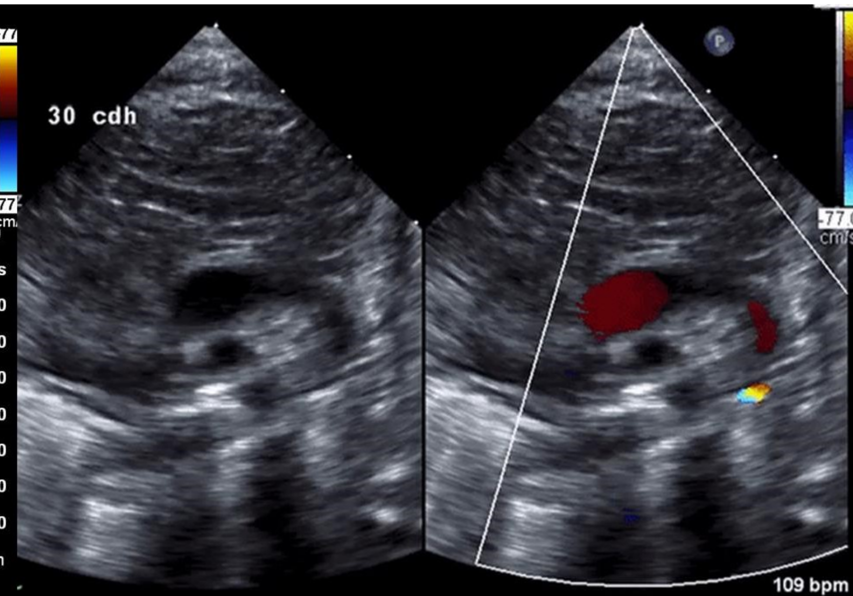
Case 2

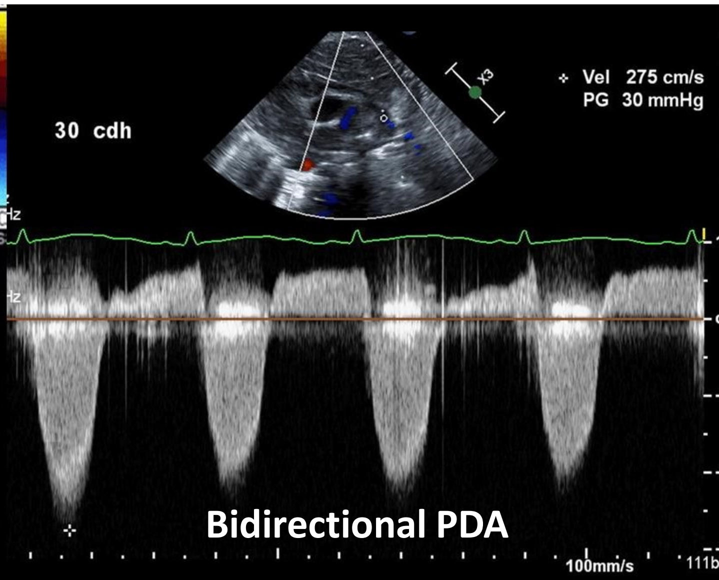
Case Presentation

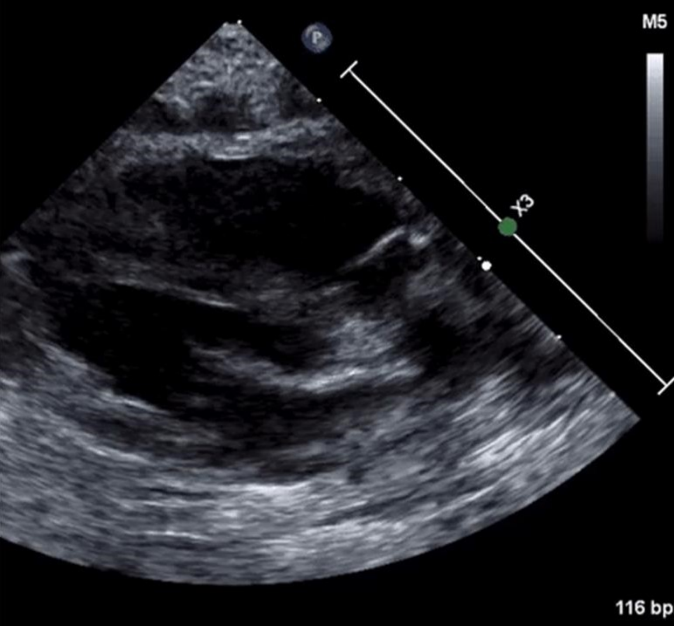
- Lt. sided CDH. Born at 38 wks.
- Post-natal, MAP 15, FiO2 80% with PaO2 35 (OI: 35)
- Pre-ductal saturation 89, post-ductal of 56%
- mBP (via UAL): 32

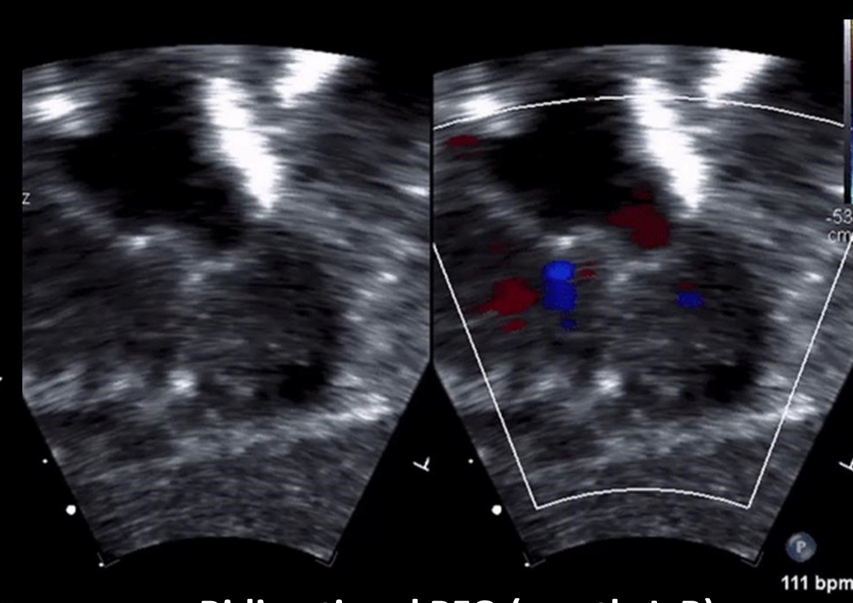


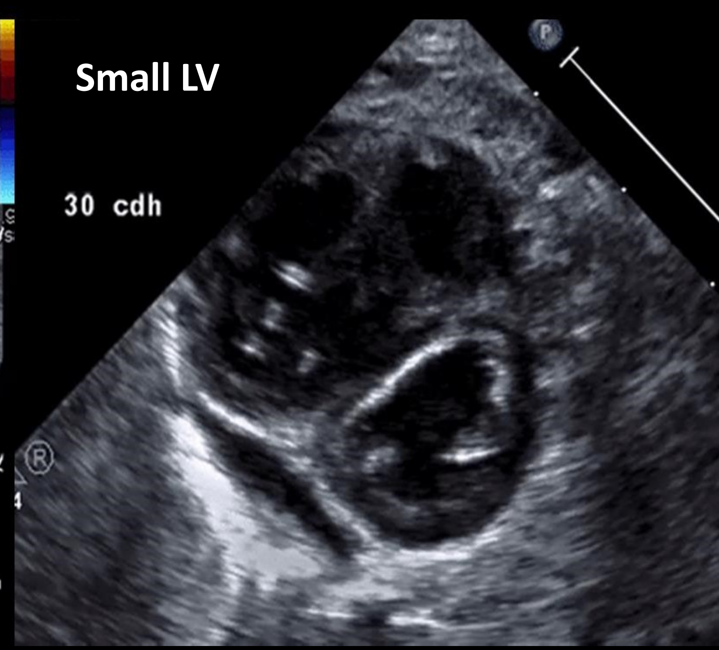

Vel 504 cm/s
PG 102 mmHg
m/s
100mm/s
119bpm


30 cdh
109 bpm


30 cdh
Vel 275 cm/s
PG 30 mmHg
Bidirectional PDA
100mm/s

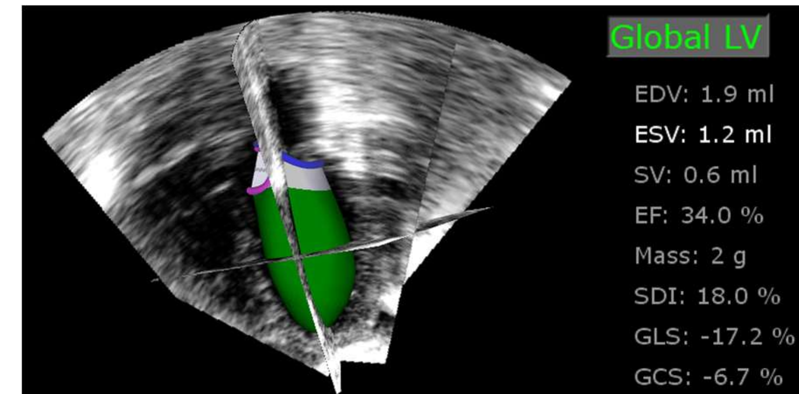

M5
116 bpm


111 bpm
Bidirectional PFO (mostly L-R)

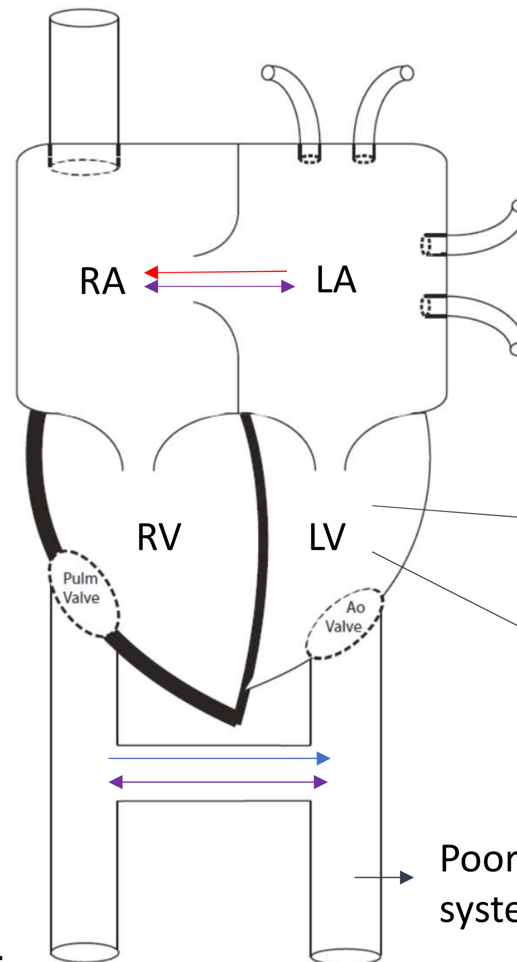

Small LV
30 cdh

Summary of ECHO

- Bidirectional PDA with R-L gradient in systole of 30 mmHg.
- PFO bidirectional, mostly left to right.
- TR 102 mmHg with SBP at 59 mmHg, Suprasystemic PA pressure.
- Mild RA and RV dilatation. RV dysfunction by TAPSE - 5.6 mm.
- Estimated LV end diastolic **volume Z-score -3.5** by 3D
- **Predominant picture: small LV/dysfunction with altered output + PH**
- **Started on PGE 0.01 mcg/kg/min + Milrinone**



RV facing high afterload IVS become dyskinetic, bow into LV cavity, impeding RV-LV function; and decreasing LV pre-load



EDP of LV increases, potential for LA hypertension and post-cap PH; PFO is L-R or Bidirectional

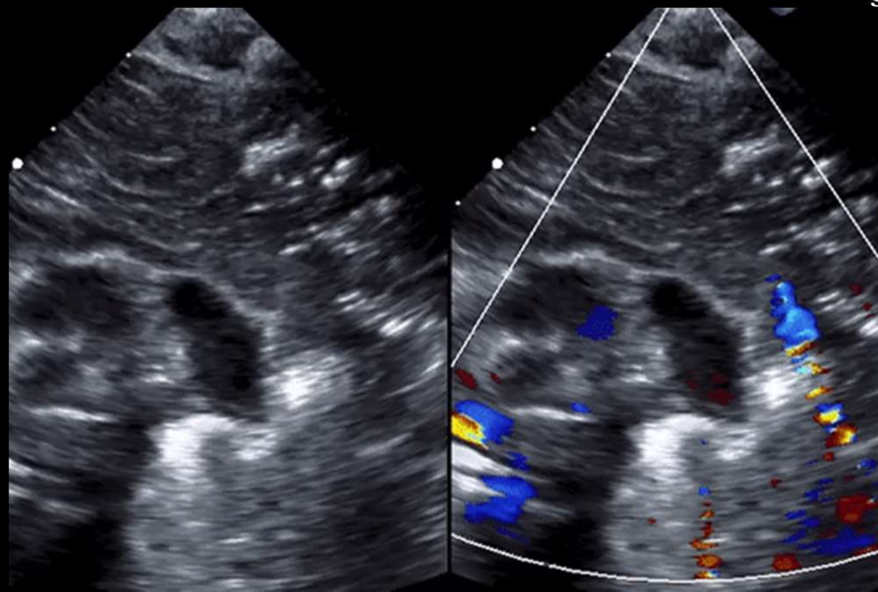
Relative LV hypoplasia

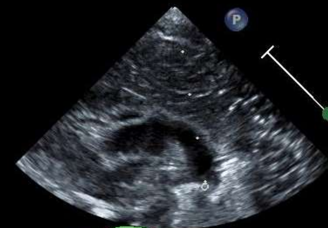
Decreased LV performance

R-L or Bidirectional PDA: Potentially contributing to the systemic flow

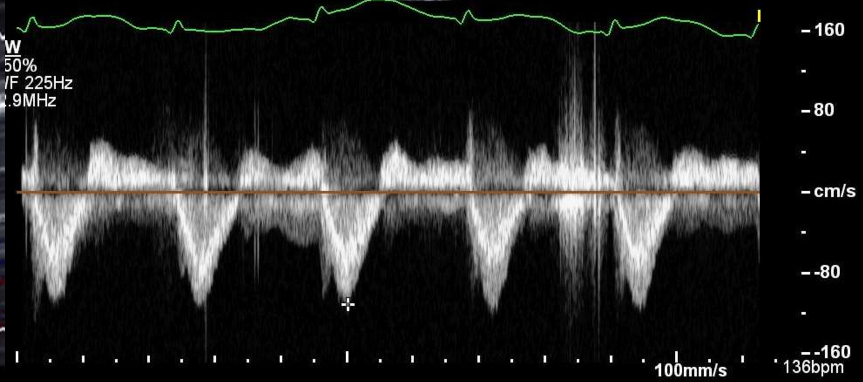
- iNO may create a steal
- **PDA may be beneficial to unload RV and provide systemic output**

Poor LV output to systemic circulation





Vel 111 cm/s
PG 5 mmHg



LV in CDH

- CDH newborns often present with signs of PH and respiratory failure
- Increasing reports of LV hypoplasia in CDH: autopsy, fetal and MRI studies
  - Mechanical compression during fetal growth
  - Primary mesenchymal defect resulting into left-sided anomalies
  - Abnormal streaming of fetal blood flow preferentially filling the RV

- Kohl T et al. Ultrasound Obstet Gynecol. 2010 Aug;36(2):259.
- Siebert JR et al. J Pediatr Surg. 1984 Oct;19(5):567-71.
- Crawford DR et al. Br J Obstet Gynaecol. 1989 - Jun;96(6):705-10.
- Sharland GK et al. Am J Obstet Gynecol. 1992 Jan;166(1 Pt 1):9-13.

LV in CDH

- Fetus with CDH (1,2):
  - Cardiac ventricular disproportion associated with post-natal mortality
- Newborns with CDH (3, 4):
  - Report of reduction in indexed LV mass
  - ECMO: lower indexed LV mass than those without ECMO
  - Confirmed in neonatal lambs model
- Adults with CDH (5):
  - Persistent abnormal cardiac function and decreased LV stroke volume by MRI

1: Crawford DR et al. Br J Obstet Gynaecol. 1989 - Jun;96(6):705-10.
2: Sharland GK et al. Am J Obstet Gynecol. 1992 Jan;166(1 Pt 1):9-13.
3: Schwarts SM et al. J Pediatr. 1994 Sep;125(3):447-51
4: Karamanoukian HL et al, J Pediatr Surg. 1995 Jul;30(7):925-8
5: Abolmaali N et al. Eur Radiol 20:1580–1589

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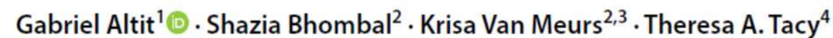
ORIGINAL ARTICLES

Ventricular Performance is Associated with Need for Extracorporeal Membrane Oxygenation in Newborns with Congenital Diaphragmatic Hernia

Gabriel Altit, MDCM, FRCPC, FAAP[1], Shazia Bhombal, MD, FAAP[1], Krisa Van Meurs, MD, FAAP[1,2], and Theresa A. Tacy, MD, FAAP[1]

ORIGINAL ARTICLE

Diminished Cardiac Performance and Left Ventricular Dimensions in Neonates with Congenital Diaphragmatic Hernia


Gabriel Altit[1] · Shazia Bhombal[2] · Krisa Van Meurs[2,3] · Theresa A. Tacy[4]

Received: 29 November 2017 / Accepted: 2 March 2018
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Table IV. Deformation measurements

	ECMO (n = 15)	Non-ECMO (n = 29)	*P* value
RV pGLS (%)	–5.2 (3.9)	–10.7 (5.0)	.001
RV pGLSR (1/s)	–0.68 (0.41)	–1.12 (0.33)	.0007
RV EDSR (1/s)	0.78 (0.43)	1.28 (0.57)	.007
LV pGLS (%)	–9.1 (4.9)	–14.9 (5.3)	.002
LV pGLSR (1/s)	1.10 (0.50)	1.46 (0.56)	.053
LV EDSR (1/s)	1.2 (0.5)	1.4 (0.7)	.43

All results are expressed as mean (SD).

Table V. Pulmonary pressure assessment by echocardiography

	ECMO (n = 15)	Non-ECMO (n = 29)	*P* value
Pulmonary/systemic ratio by PDA/TR (%)	103 (4)	103 (16)	1.00
TR or PDA available (%)	12 (80)	23 (79)	1.00
TR jet available (%)	8 (53.3)	20 (69)	.34
PDA available (%)	10 (66.7)	18 (62)	1.00
Right to left PDA (%)	2/10 (20)	2/18 (11)	.58
Bidirectional PDA (%)	8/10 (80)	13/18 (72)	.67
Flat or bowing SC in systole (%)	15 (100)	24 (83)	.15

PDA, patent ductus arteriosus; *SC*, septal curve; *TR*, tricuspid regurgitation.
All results are expressed as mean (SD).

Regional deformation comparisons

	CDH (*n* = 44)	Controls (*n* = 18)
LV-free wall LS	– 13.8 (6.8)	– 20.7 (5.3)
LV septal LS	– 11.9 (6.6)	– 20.97 (4.9)
RV septal LS	– 6.5 (5.7)	– 18.1 (5.7)
RV-free wall LS	– 9.8 (6.8)	– 21.3 (3.1)
p value: RV-IVS versus LV-IVS	0.0002*	0.14
p value: RV-IVS versus RV-free wall	0.02*	0.09
p value: LV-IVS versus LV-free wall	0.19	0.87
p value: RV-free wall versus LV-free wall	0.009*	0.73

LV in CDH – Numerous publication by the Glasgow group

Early Postnatal Ventricular Dysfunction Is Associated with Disease Severity in Patients with Congenital Diaphragmatic Hernia

Neil Patel, MD[1], Anna Claudia Massolo, MD[2], Anshuman Paria, MBBS[1], Emily J. Stenhouse, MBChB[3], Lindsey Hunter, MRCPCH[4], Emma Finlay, BSE[4], and Carl F. Davis, FRCS[5]

Ventricular Dysfunction, Interdependence, and Mechanical Dispersion in Newborn Infants with Congenital Diaphragmatic Hernia

Anna Claudia Massolo[a] Anshuman Paria[b] Lindsey Hunter[c] Emma Finlay[c] Carl F. Davis[d] Neil Patel[b]

Am J Respir Crit Care Med. 2019 Dec 15;200(12):1522-1530. doi: 10.1164/rccm.201904-0731OC.

Ventricular Dysfunction Is a Critical Determinant of Mortality in Congenital Diaphragmatic Hernia.

Patel N[1], Lally PA[2], Kipfmueller F[3], Massolo AC[4], Luco M[5], Van Meurs KP[6], Lally KP[2], Harting MT[2].

CDH - New paradigm – Addressing the LV?

Milrinone in congenital diaphragmatic hernia – a randomized pilot trial: study protocol, review of literature and survey of current practices

Satyan Lakshminrusimha[1], Martin Keszler[2], Haresh Kirpalani[3], Krisa Van Meurs[4], Patricia Chess[5], Namasivayam Ambalavanan[6], Bradley Yoder[7], Maria V. Fraga[3], Holly Hedrick[3], Kevin P. Lally[8], Leif Nelin[9], Michael Cotten[10], Jonathan Klein[11], Stephanie Guilford[1*], Ashley Williams[1], Aasma Chaudhary[3], Marie Gantz[12], Jenna Gabrio[12], Dhuly Chowdhury[12], Kristin Zaterka-Baxter[12], Abhik Das[12] and Rosemary D. Higgins[13]

The case of Milrinone

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

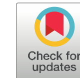
Montreal Children's Hospital
McGill University Health Centre

- PDE3 inhibitor → ↑ intra-cellular calcium.
- Theoretical effect: Inotropic, lusitropic (promotes filling), ↓ systemic and pulmonary vascular resistance → ↓ afterload in LV and/or RV dysfunction.
- Very limited neonatal data
- Renally excreted and can accumulate in blood, vasodilation and can induce distributive shock → refractory hypotension
- Can lead to V/Q mismatch

Dietrichs ES, Kondratiev T, Tveita T. Milrinone ameliorates cardiac mechanical dysfunction after hypothermia in an intact rat model. Cryobiology. 2014;69(3):361-6.
McNamara PJ, Laique F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. Journal of critical care. 2006;21(2):217-22.
Tveita T, Sieck GC. Effects of milrinone on left ventricular cardiac function during cooling in an intact animal model. Cryobiology. 2012;65(1):27-32.
Dietrichs ES, Kondratiev T, Tveita T. Milrinone ameliorates cardiac mechanical dysfunction after hypothermia in an intact rat model. Cryobiology. 2014;69(3):361-6.

PGE

Prostaglandin E1 in infants with congenital diaphragmatic hernia (CDH) and life-threatening pulmonary hypertension



Kévin Le Duc [a,*], Sébastien Mur [a], Dyuti Sharma [b], Estelle Aubry [b], Morgan Recher [c], Thameur Rakza [a], Laurent Storme [a], Center for Rare Disease «Congenital Diaphragmatic Hernia»

- PGE1 improved oxygenation and circulatory function in severe CDH and life-threatening PH.
- PGE1 may improve cardiorespiratory failure through reopening of the DA.
- CDH may have bi-ventricular dysfunction

Table 2
Fetal and neonatal characteristic of CDH patients treated with PGE_1 for a life-threatening PH (n = 18) and CDH patients treated with prophylactic PGE1 (n = 16).

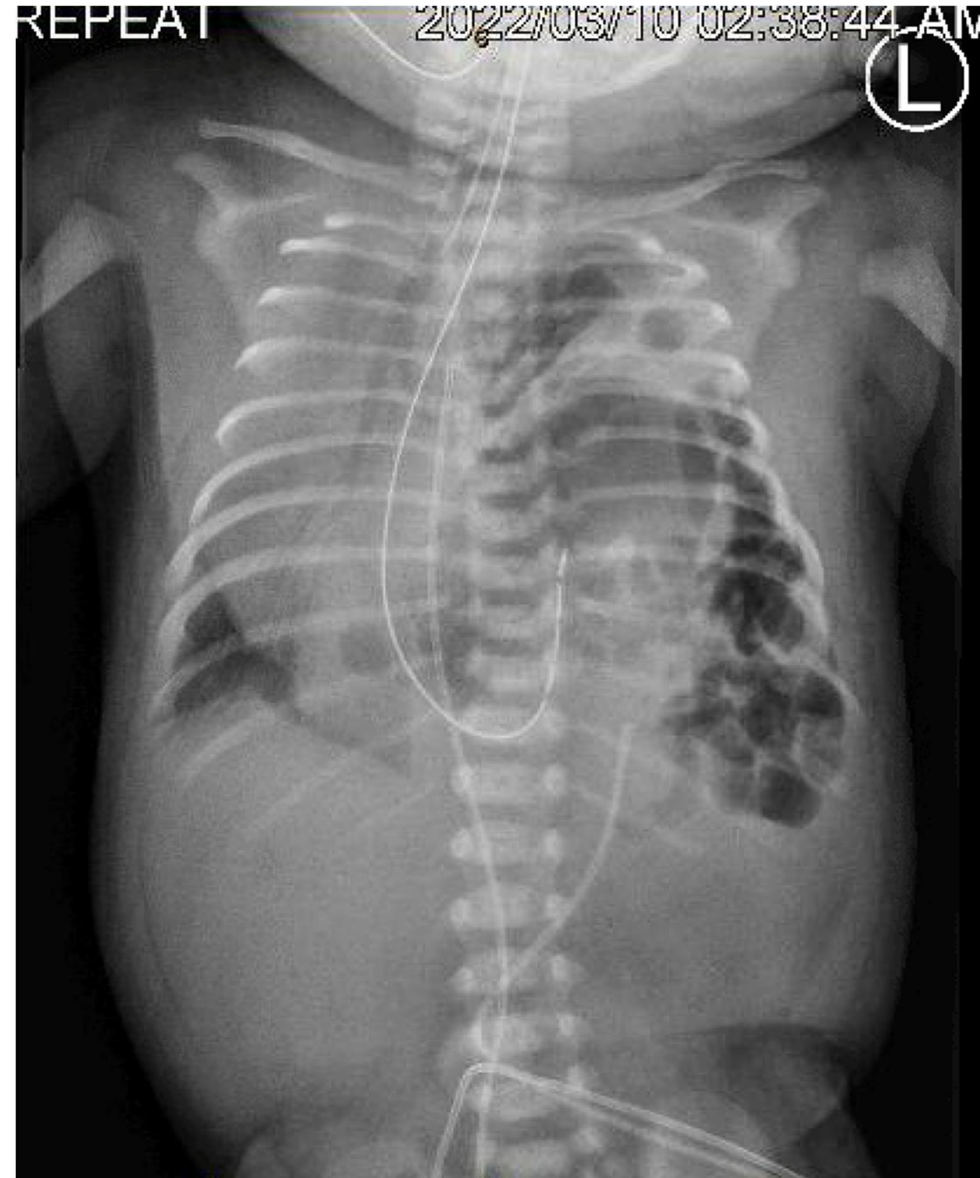
	PGE1 Rescue Treatment N = 18	Prophylactic PGE1 N = 16	P value
Prenatal diagnosis (%)	16 (89)	12 (75)	0.06
Left CDH (%)	13 (72)	13 (81)	1.0
LHR o/e	36 [35; 43]	38.5 [28.5; 65.4]	0.93
Fetal MRI %	32 [30; 35]	42 [28; 53]	0.12
Liver herniation (%)	13 (72)	7 (43)	0.74
Male sex (%)	8 (44)	7 (43)	0.75
Gestational age (weeks)	39 [38; 40]	39.9 [38.4; 41.3]	0.6
Birth weight (kg)	3.5 [3.0; 3.7]	3.2 [2.7; 3.5]	0.14
Inhaled NO	18 (100)	11 (68)	0.02
Age at CDH repair (days)	2 [1.3; 2.8]	1 [0; 2]	0.13
Duration of Mechanical Ventilation (h)	160 [128; 218]	120 [71; 168]	0.004*
Duration of Noninvasive Ventilation (days)	12 [6; 19]	3 [1; 4]	0.003*
Duration of O_2 supplementation (days)	45 [21; 94]	15 [7; 41]	0.05*
ECMO support (%)	0 (0)	1 (6)	1.0
NICU length of stay	65 [46; 109]	52 [36; 92]	0.38
Death	5 (27)	1 (6)	0.18

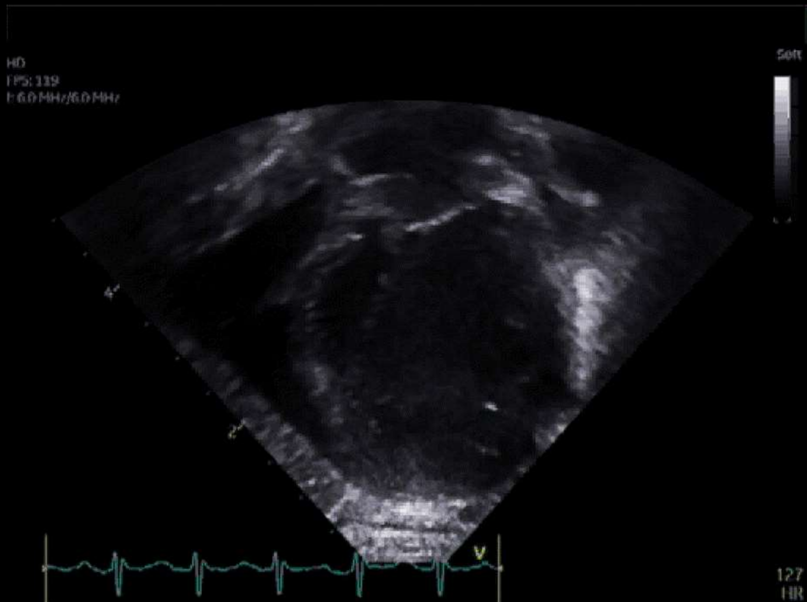
Categorical data expressed as n (%) and continuous data expressed as median and IQR. LHR, lung-to-head ration; o/e, observed/expected; NICU, neonatal intensive care unit; CDH, congenital diaphragmatic hernia.

* Significant difference accepted as p ≤ 0.05.

Case 3

- 38+5 weeks, male
- Prenatal diagnosis of L-CDH
- Liver, spleen in the chest
- 45 x 25/5
- Initially 50% FiO2 with pre-post differences (95% and 75%)
- Started by iNO by clinical team
- 57/41 BP by UAL
- Called for evaluation by ECHO

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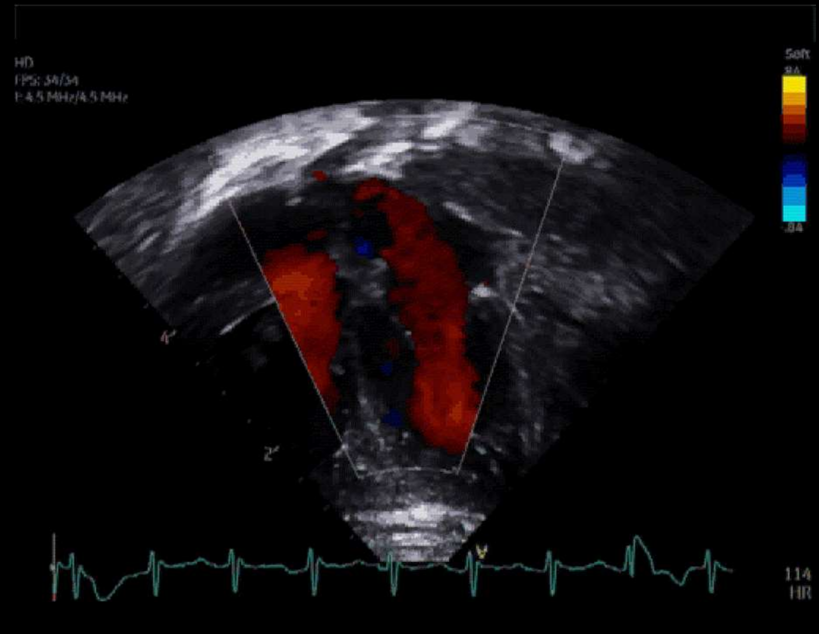
Soft
127
HR


HD
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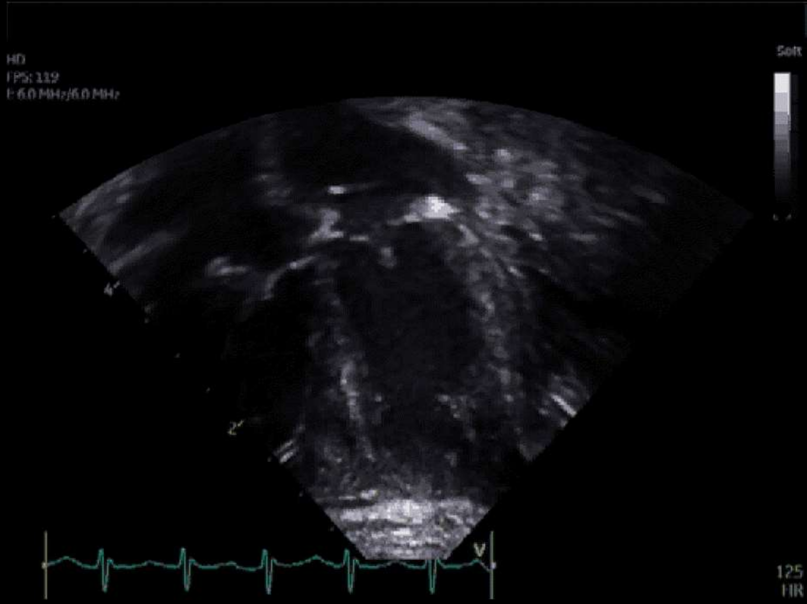
114
HR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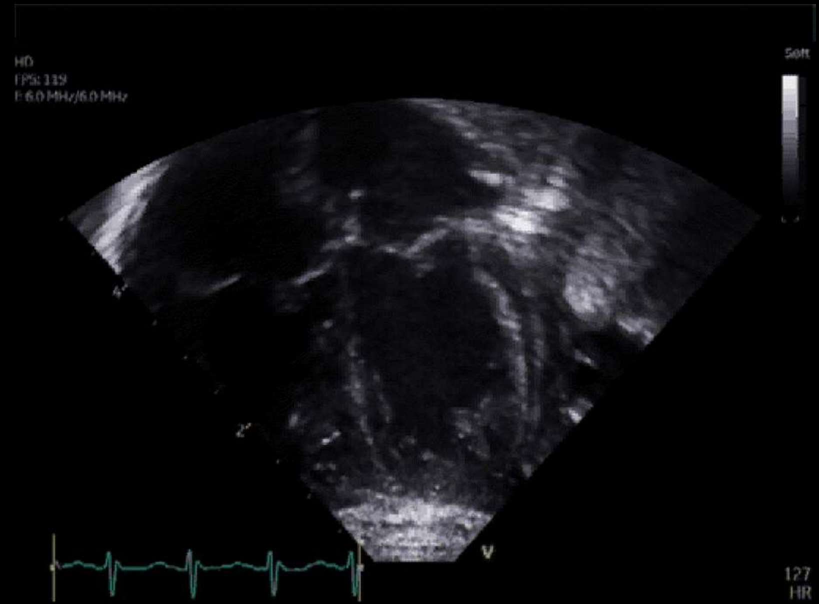
HR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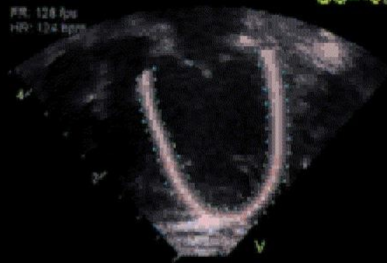
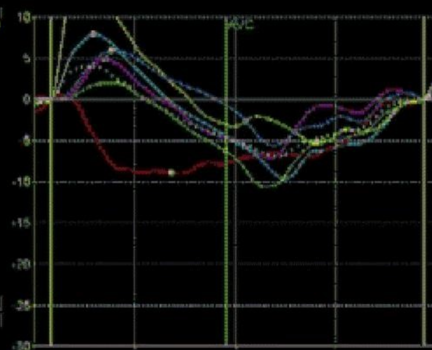
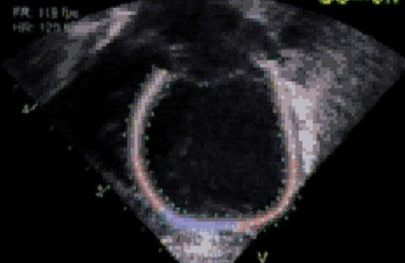
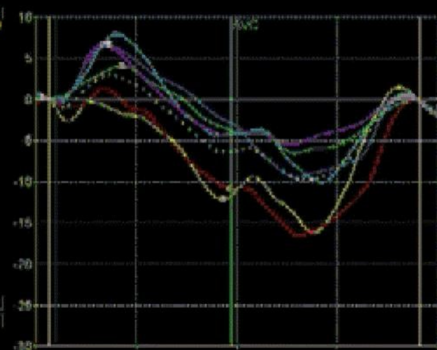
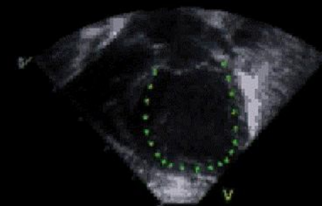
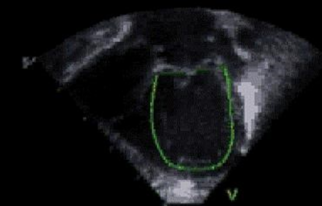
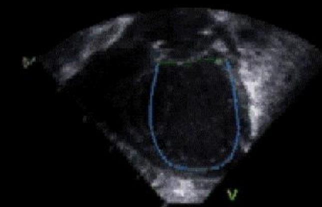
Soft
127
HR



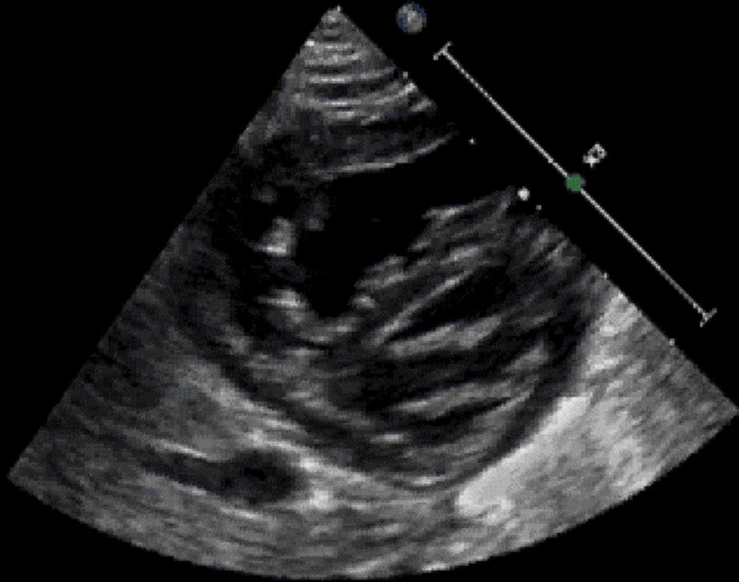




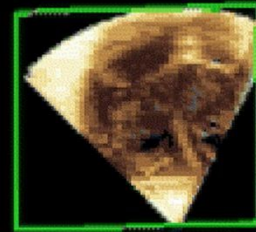


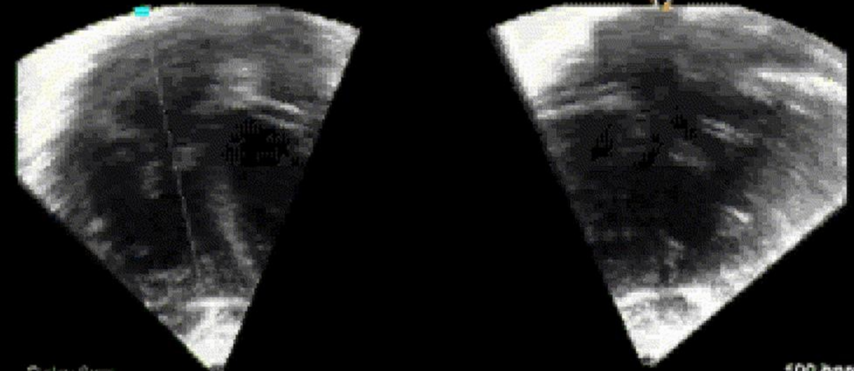
Case 3

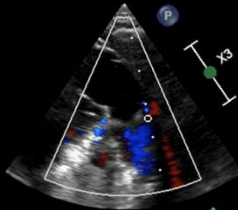
www.NeoCardioLab.com
@CardioNeo (Twitter)

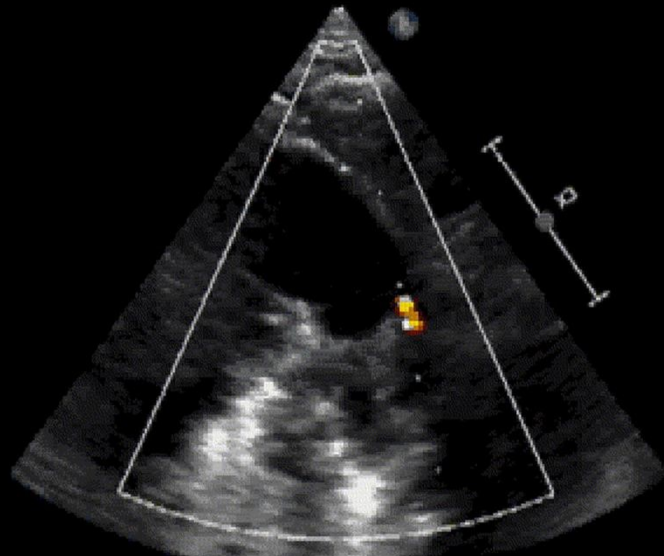
- Moderate-severe LV dysfunction
- Lactate adequate, urine output 2 mL/kg/hr
- iNO wean
- Decision to initiate Milrinone 0.5 mcg/kg/min considering the normal BP and urine output
- Hydrocortisone added at 1mg/kg IV q8hr
- ECHO repeated DOL3: mild to normal LV function, PDA small bidirectional (mostly Left to right)
- CDH repaired at DOL4.
- TnECHO repeated post-OR DOL6:

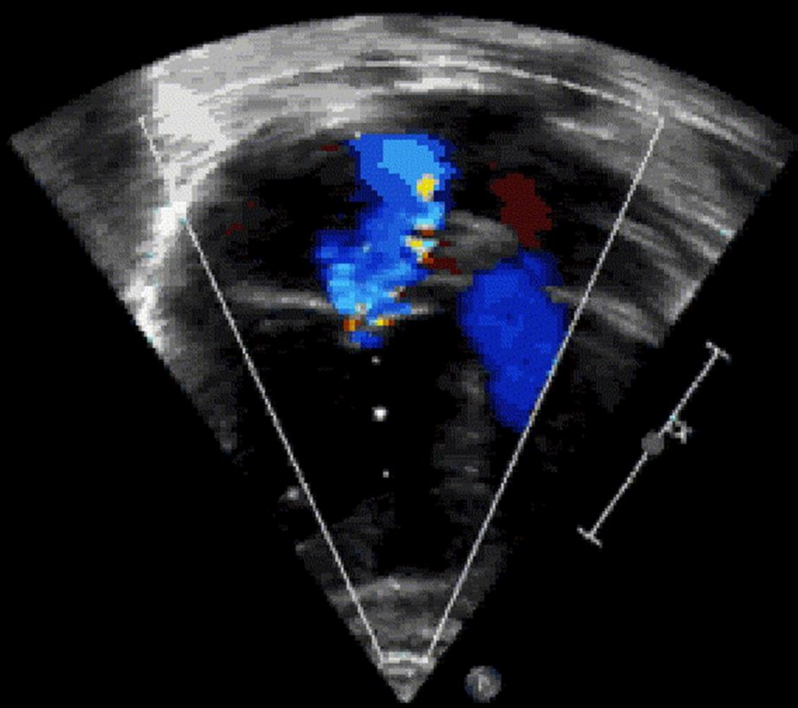

MUHC 20Beats
103 bpm


MUHC 3Beats
3D Beats 6Q
X7-2
Full Volume

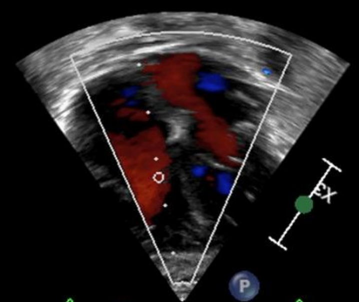

100 bpm


MUHC 20Beats
TIS0.5 MI 0.1
S8-3
24Hz
6.0cm
2D
70%
C 48
P Off
HRes
CF
40%
6600Hz
WF 659Hz
3.3MHz
CW
50%
WF 225Hz
2.9MHz
Vel 287 cm/s
PG 33 mmHg
M5 M4
+77.0
-77.0
cm/s
100
cm/s
-100
-200
-300
-400

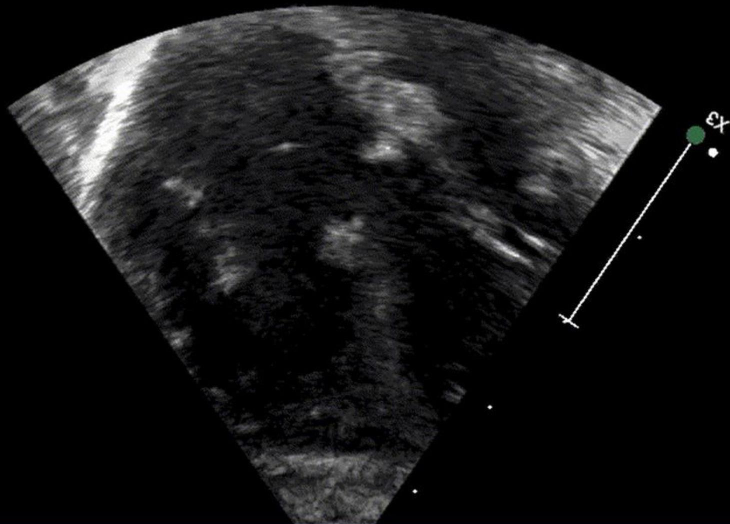




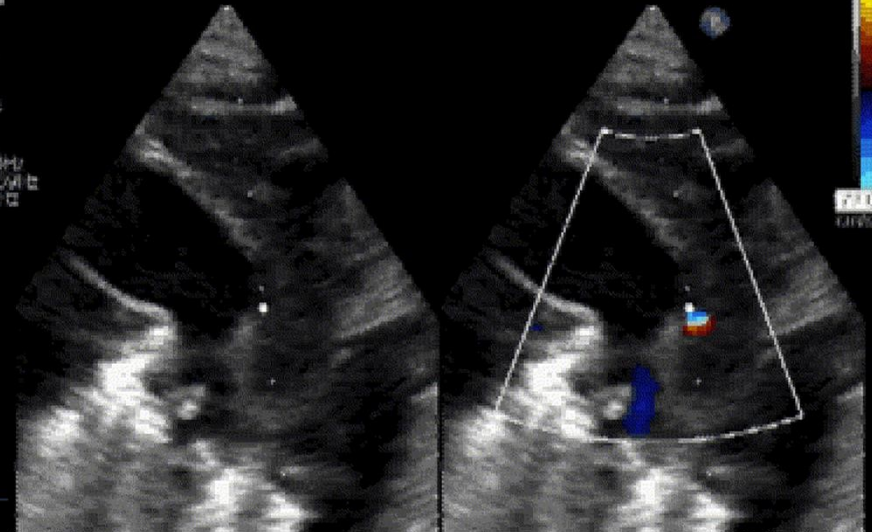
MUHC 20Beats
TIS1.4 MI 1.0
82 bpm



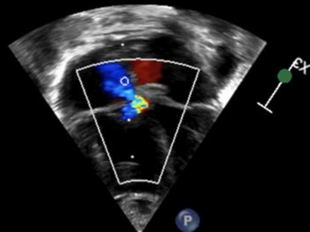
MUHC 20Beats
TIS0.4 MI 0.1
S8-3
24Hz
6.0cm
2D
70%
C 48
P Off
HRes
CF
40%
6600Hz
WF 659Hz
3.3MHz
CW
50%
WF 225Hz
2.9MHz
Vel 485 cm/s
PG 94 mmHg
m/s
-1.0
-2.0
-3.0
-4.0
-5.0
100mm/s



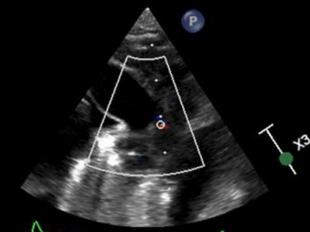
MUHC 20Beats
TIS1.3 MI 0.9
S8-3
144Hz
5.0cm
2D
68%
C 48
P Off
HRes
M5
G
P
R
3.2 6.4



MUHC 20Beats



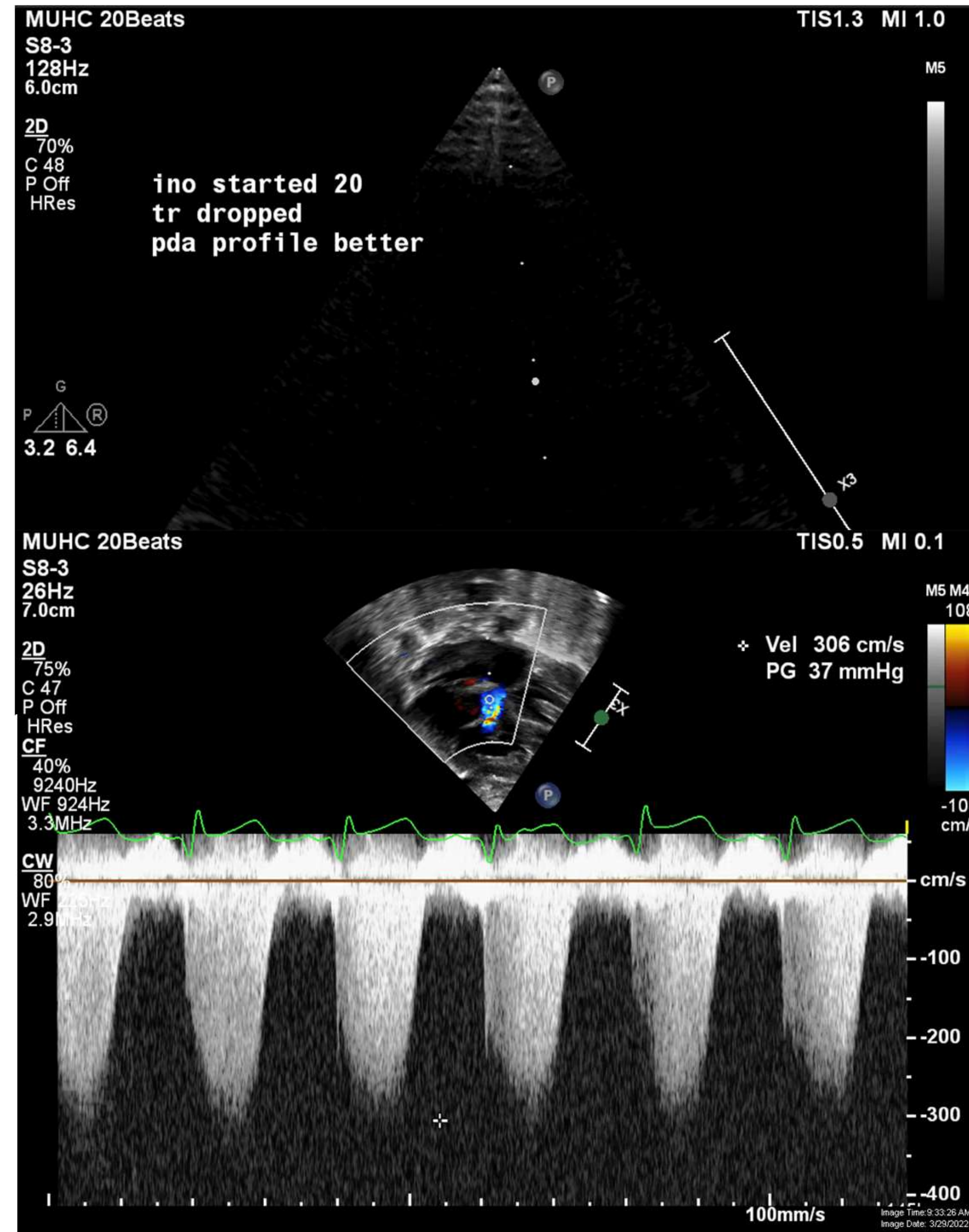
MUHC 20Beats
TIS0.5 MI 0.1
S8-3
26Hz
6.0cm
2D
70%
C 48
P Off
HRes
CF
40%
6600Hz
WF 659Hz
3.3MHz
CW
50%
WF 225Hz
2.9MHz
Vel 355 cm/s
PG 50 mmHg
M5 M4
-100
cm/s
--100
--200
--300
--400
100mm/s



MUHC 20Beats
TIS0.5 MI 0.1
S8-3
26Hz
6.0cm
2D
70%
C 48
P Off
HRes
CF
40%
6600Hz
WF 659Hz
3.3MHz
CW
50%
WF 225Hz
2.9MHz
M5 M4
+77.0
-77.0
cm/s
-300
-200
-100
cm/s
--100
--200
--300
100mm/s

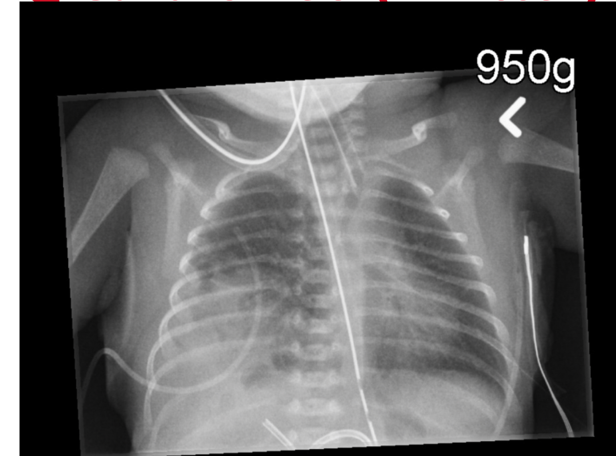
- Patient with response to iNO
- Mixed picture – biventricular function: initially LV dysfunction and eventually pulmonary reactive vascular disease
- Re-attempted iNO wean that failed similarly under echo guidance
- Transitioned to Sildenafil.

- Last ECHO: TR at 37, RV function and LV function normal by various metrics.

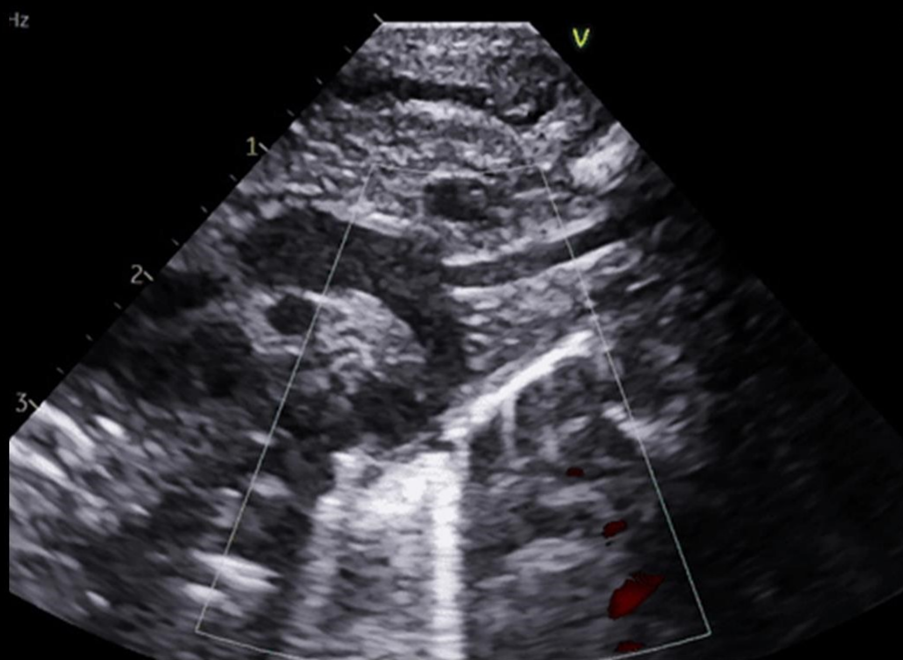


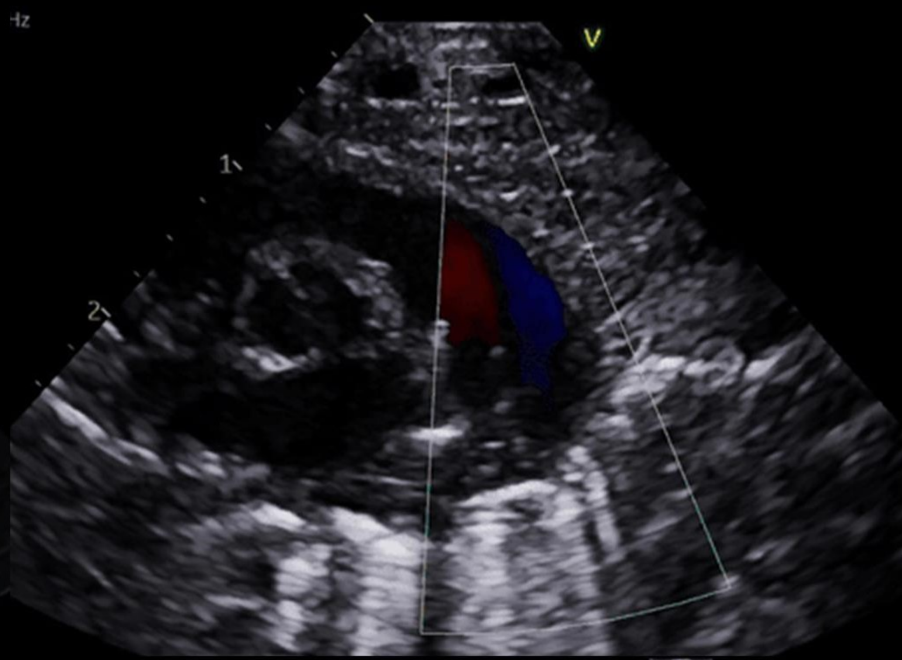
Case 4

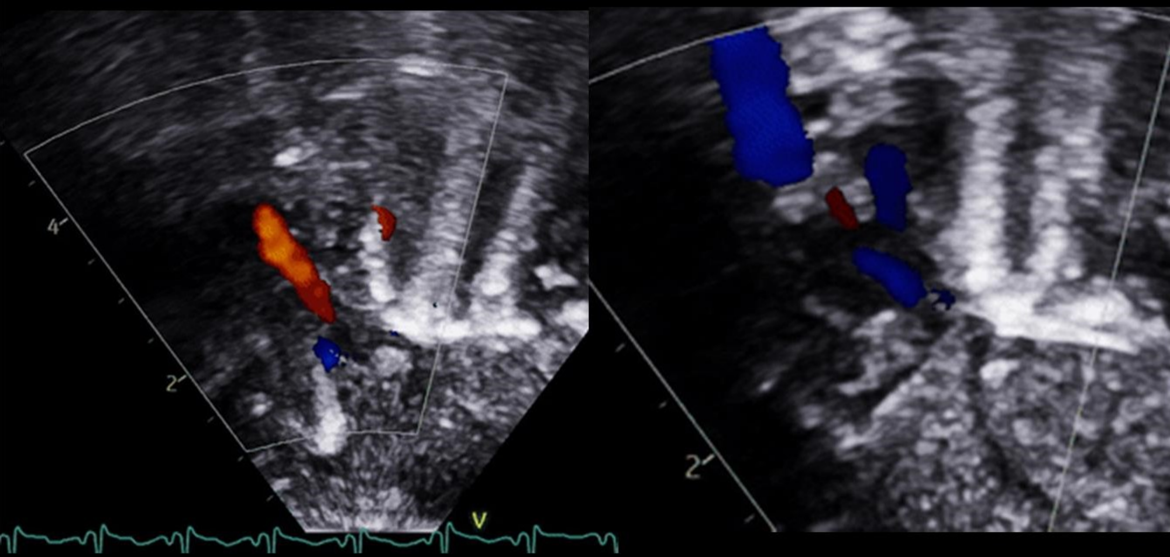
Case 4



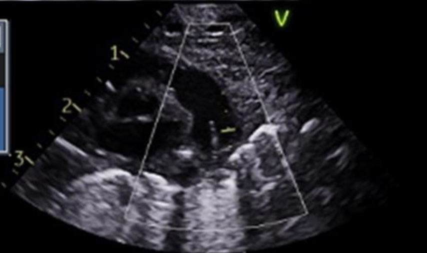
- 26+1 male, PPROM at 24 weeks
- Right sided CDH (not eventration) – post-natal diagnosis
  - Confirmed with ultrasound (later)
- BW: 900 grams
- Intubated in the delivery room
  - RDS / 100% FiO2, R-CDH noticed on first X-ray. Surfactant given.
- Initially ACVG (5mL/kg) - high PIP – Team decided: HFJV initially (30/11 x 360 – M 11).
- 100% FiO2, CO2 40-50s. Pre-Post differences, PaO2 in 30s.
- Bp 39/12 at 1st ECHO (day 1)

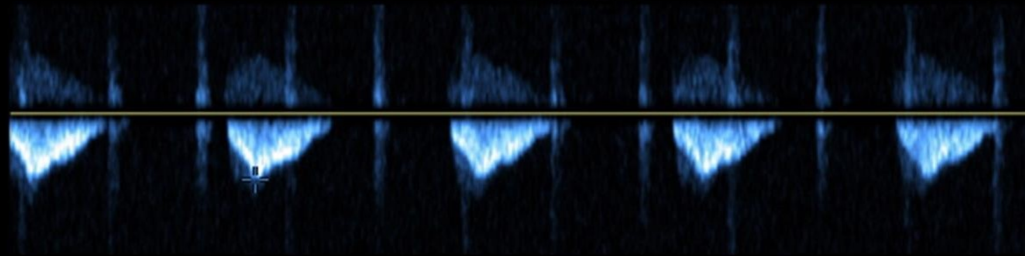


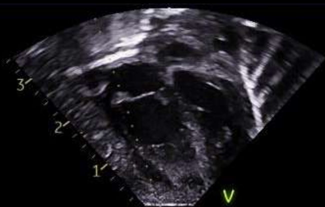


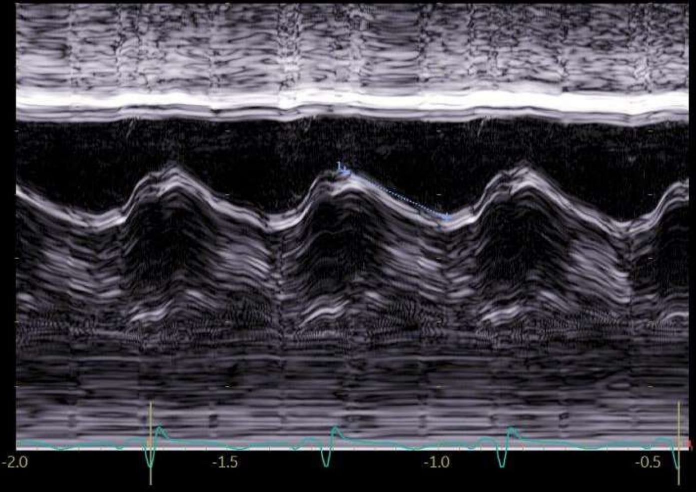


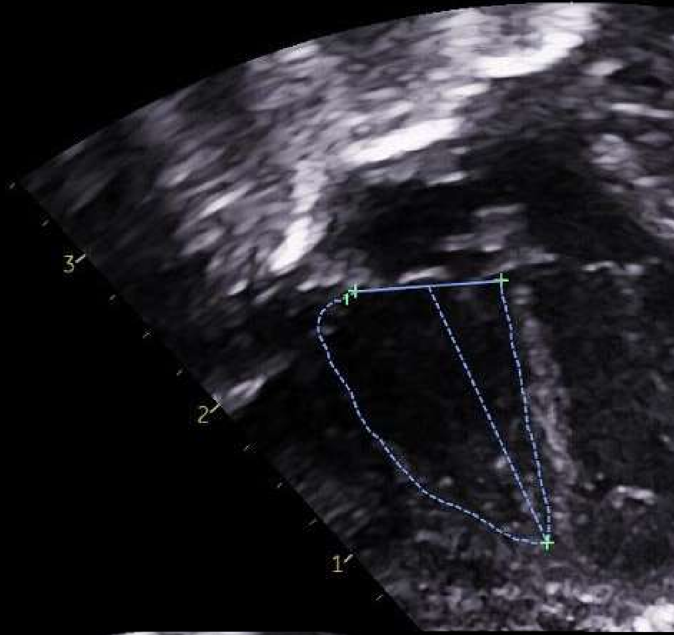
<temporary>
Velocity = 0.47 m/s
PG = 0.9 mmHg

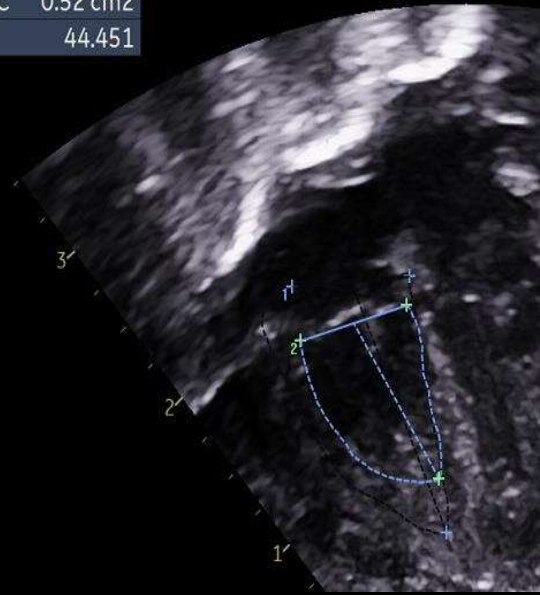


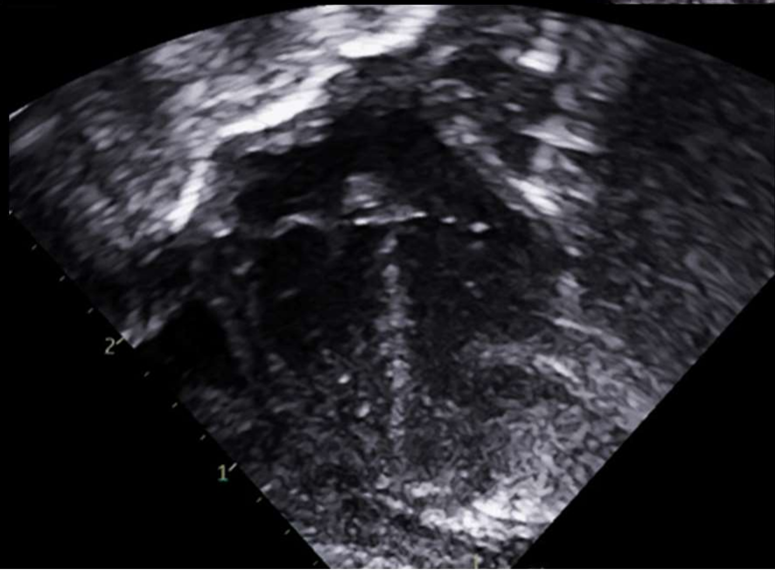




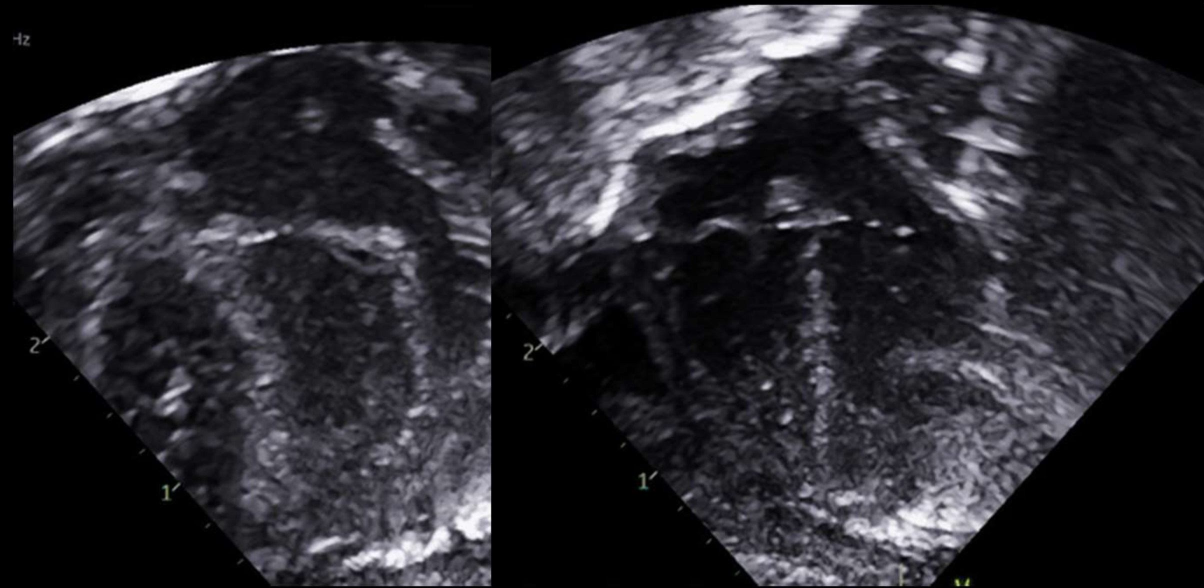

1 TAPSE 3.66 mm
f: 9.0 MHz
-2.0
-1.5
-1.0
-0.5

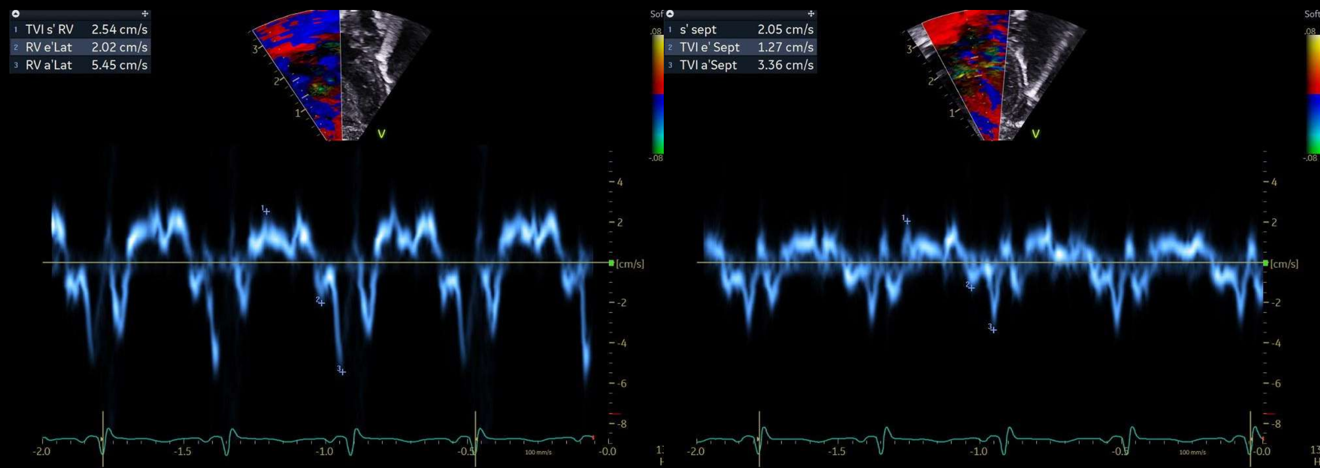

1 RVAd A4C 0.94 cm2
FPS: 116
f: 9.0 MHz


1 RVAd A4C 0.94 cm2
2 RVAs A4C 0.52 cm2
FAC 44.451

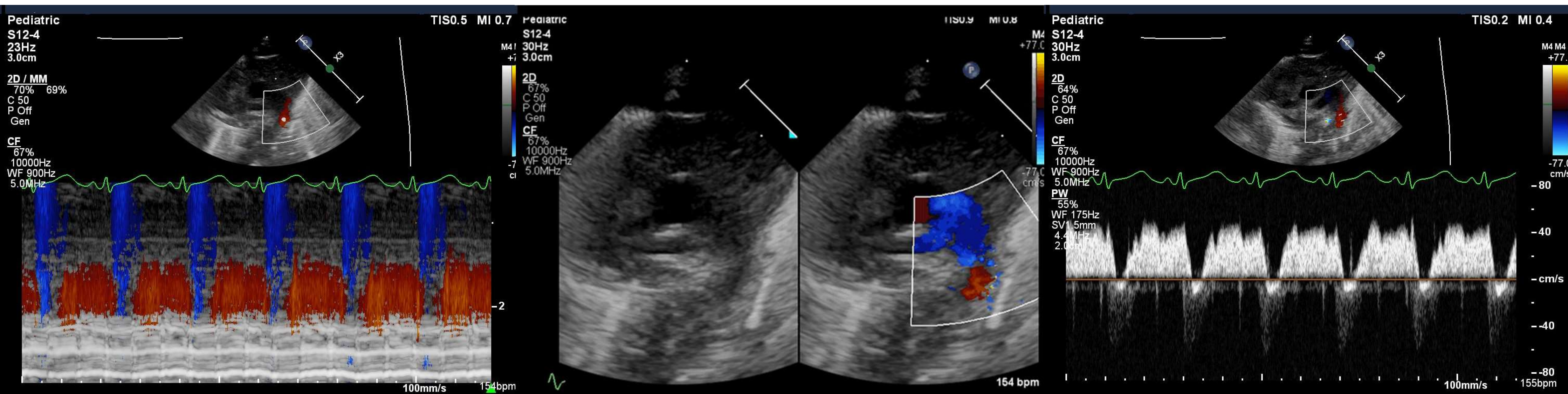


- EF by Simpson’s 55%
- RV-*S’* (TDI) - 2.5 (low)
- LV-*S’* (TDI) - 2.1 (normal range)

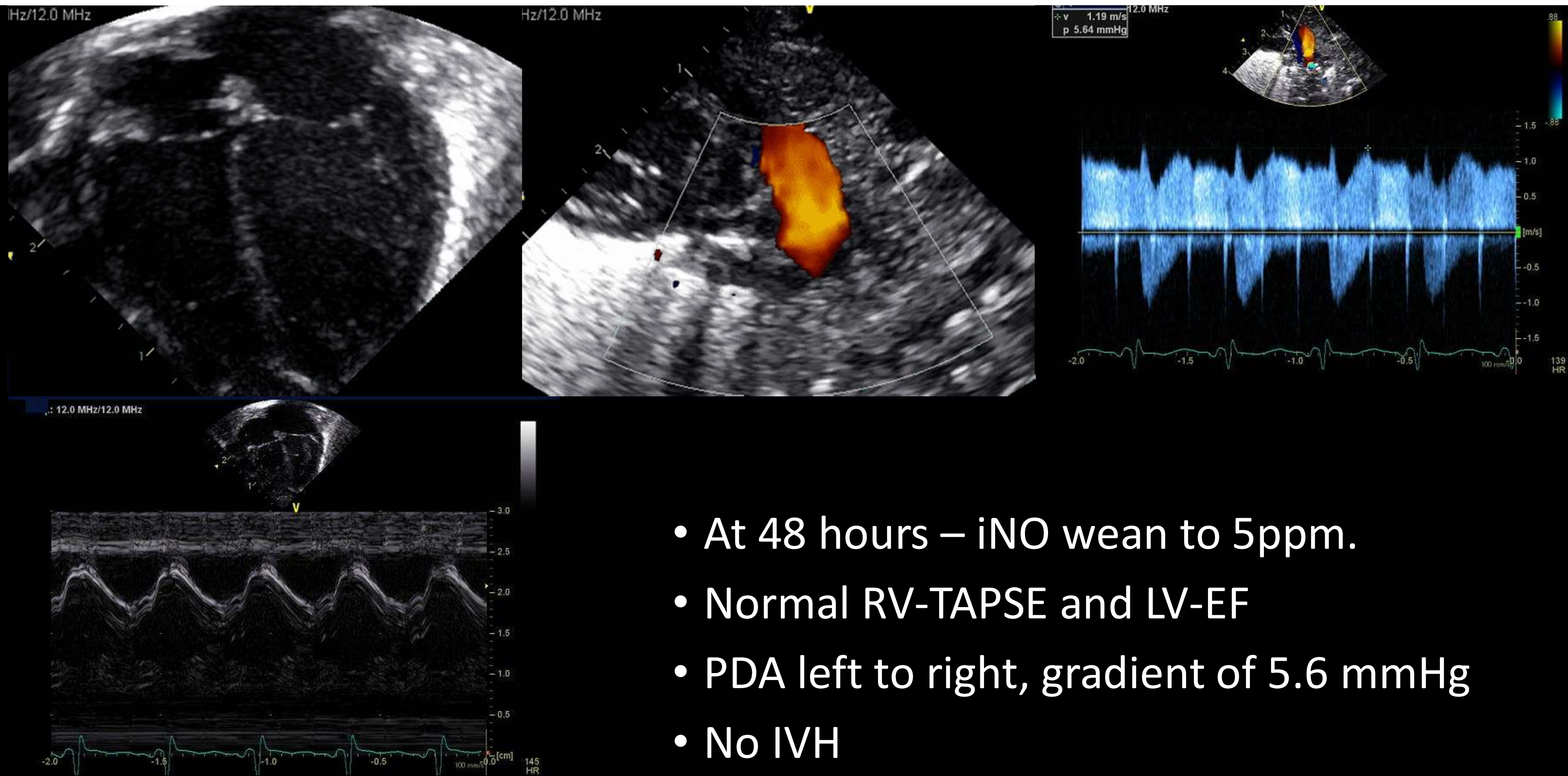




	Preterm cohort
	Day 1
Number of infants	66
Left ventricle free wall	
s`	2.8 (0.9)
e`	3.6 (1.4)
a`	4.0 (1.5)
e`/a`	0.95 (0.36)
E/e`	11 (4)
Septum	
s`	2.4 (0.6)
e`	2.8 (0.8)
a`	3.9 (1.1)
e`/a`	0.76 (0.21)
Right ventricle free wall	
s`	3.6 (0.9)
e`	3.9 (1.3)
a`	6.7 (1.8)
Left ventricle event times	
Heart rate	154 (14)
Isovolumic relaxation time	58 (13)
Isovolumic contraction time	56 (13)
Systolic time	147 (20)
Diastolic time	131 (22)
Myocardial performance index	0.80 (0.22)



- Afternoon after introduction of iNO 10 ppm
- PDA mostly left to right (R-L early in systole)


v 1.19 m/s
p 5.64 mmHg
• At 48 hours – iNO wean to 5ppm.
• Normal RV-TAPSE and LV-EF
• PDA left to right, gradient of 5.6 mmHg
• No IVH

Case 4

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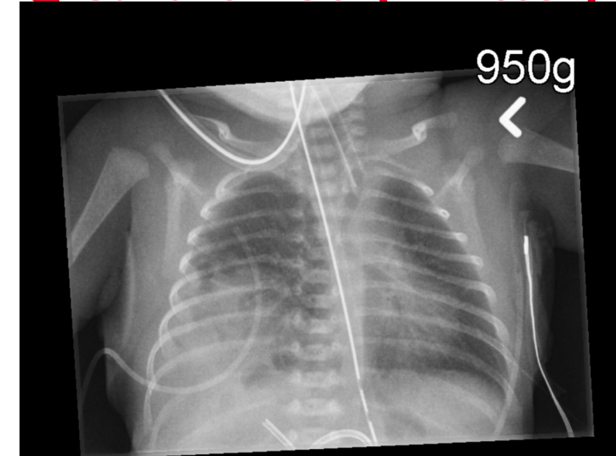


- Stayed only on iNO 4ppm until OR, NPO (OIT)
  - Minimal ventilation (CO_2 50-60)
  - CMV → HFOV due to evolving lung disease
  - Dexamethasone peri-operative
- Operated at 32 weeks corrected age
- Now corrected 36 weeks
  - Bubble CPAP +6 – FiO 24%
  - 7.37/50/28/3
  - Off iNO since November 4th
    - ECHO repeat: PDA closed, PFO left to right, No pulm hypertension

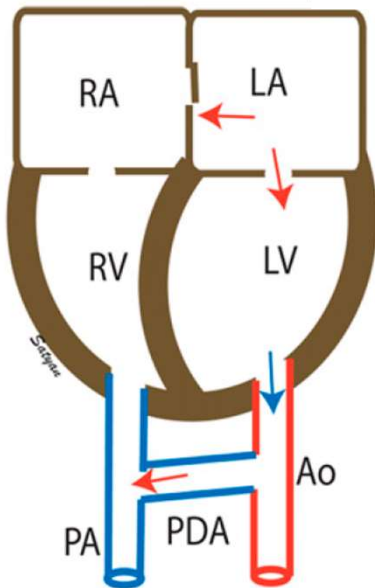
Summary

CDH Pathophysiology Review

by Dr Shazia Bhombal (Stanford University), drawings by Dr Satyan Lakshminrusimha (UC Davis)

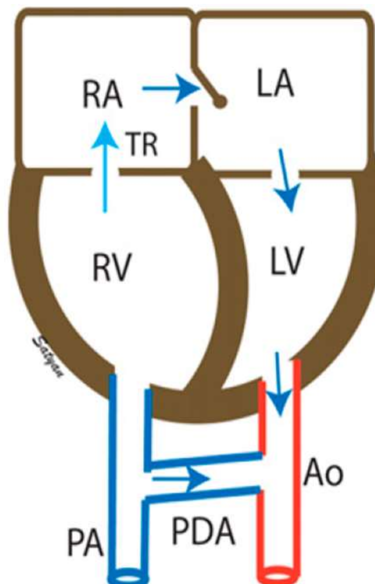
No/mild PH No cardiac dysfunction	PH No cardiac dysfunction/RV dysfunction	PH LV dysfunction/BiV dysfunction
	Pulmonary arterial Phenotype	Pulmonary venous Phenotype

#1



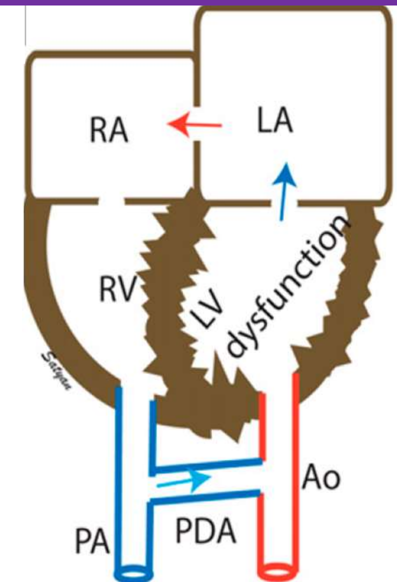
Left to Right atrial shunt
Left to Right PDA

#2



Right to left atrial shunt
Right to left PDA

#3



Left to right atrial shunt
Right to left PDA

CDH Management – Precision Medicine

Adapted from slide provided by Dr Shazia Bhombal (Stanford)

#1

Early Echocardiography → Assess for CHD

No or mild PH, normal function

Resp management, no additional support
Continue to monitor for clinical change and echo as needed

Moderate or severe PH

#3

Normal function

iNO
+/- Milrinone

#2

RV dysfunction +/- LV

iNO
Maintain ductus
Systolic and diastolic RV support

- Milrinone
- Epi
- Vasopressin
- ± Hydrocort
- ± Ductus

LV dysfunction/+/-RV

Systolic and diastolic LV support

- Milrinone
- Dobutamine
- Epi

± ductus for systemic flow
Avoid iNO
± Ductus
± Hydrocortisone

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

Conclusion

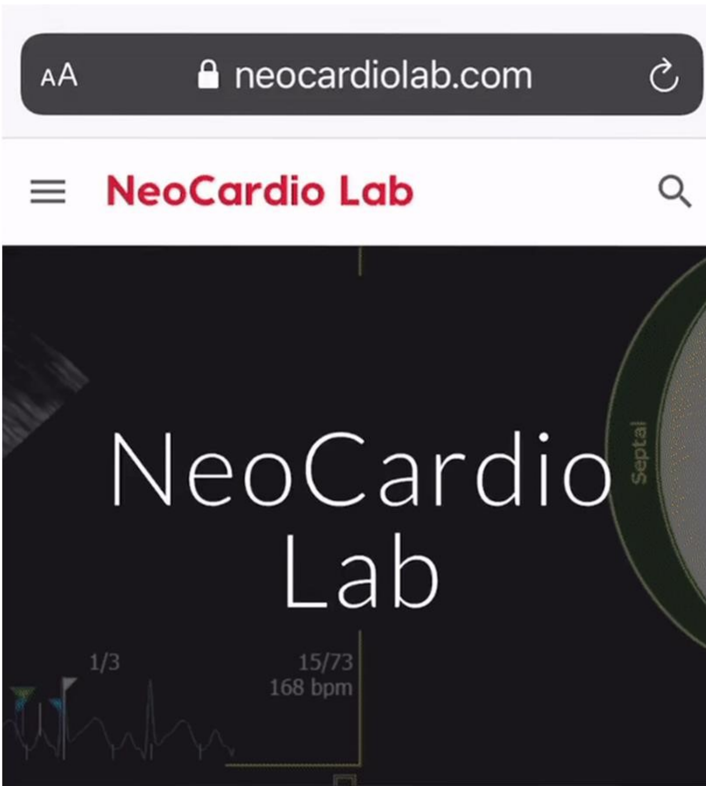
Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

- Less is often better for these infants
  - Judicious use of any cardiovascular strategy – stepwise
- Multi-disciplinary care – the ”devil is in the details”
- Respiratory care is extremely important – no heart can help a lung that is broken
- When needing cardiac support – target the underlying phenotype.
  - This phenotype may change in time.

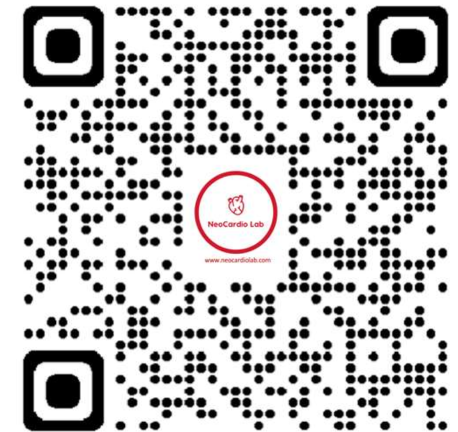
The story of Teo, Ode and Marko
L'histoire de Téo, Ode et Marko

The story of Noah, Alina and Armen
L'histoire de Noah, Alina et Armen



Questions? Comments?
Merci – Thank you - Obrigado

- **A special thanks to the organizing committee and to my mentor (Pr G. Sant'Anna)**
- Gabriel Altit – gabriel.altit@neocardiolab.com



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