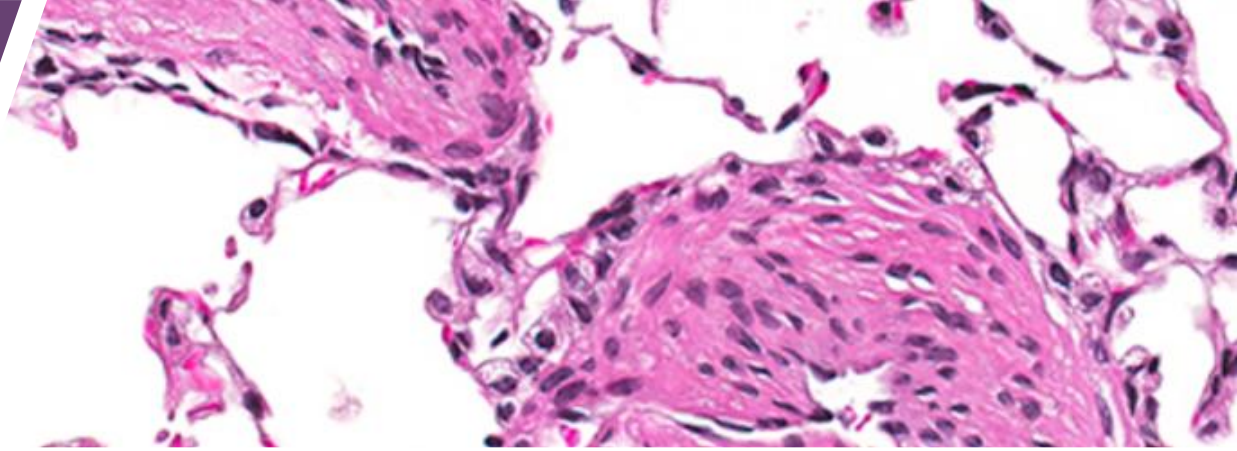

Užití sildenafilu k léčbě plicní hypertenze u dětí

Tomáš Juřenčák
P. Vít, J. Navrátil
Dětská kardiologie, Pediatrická klinika, FN Brno

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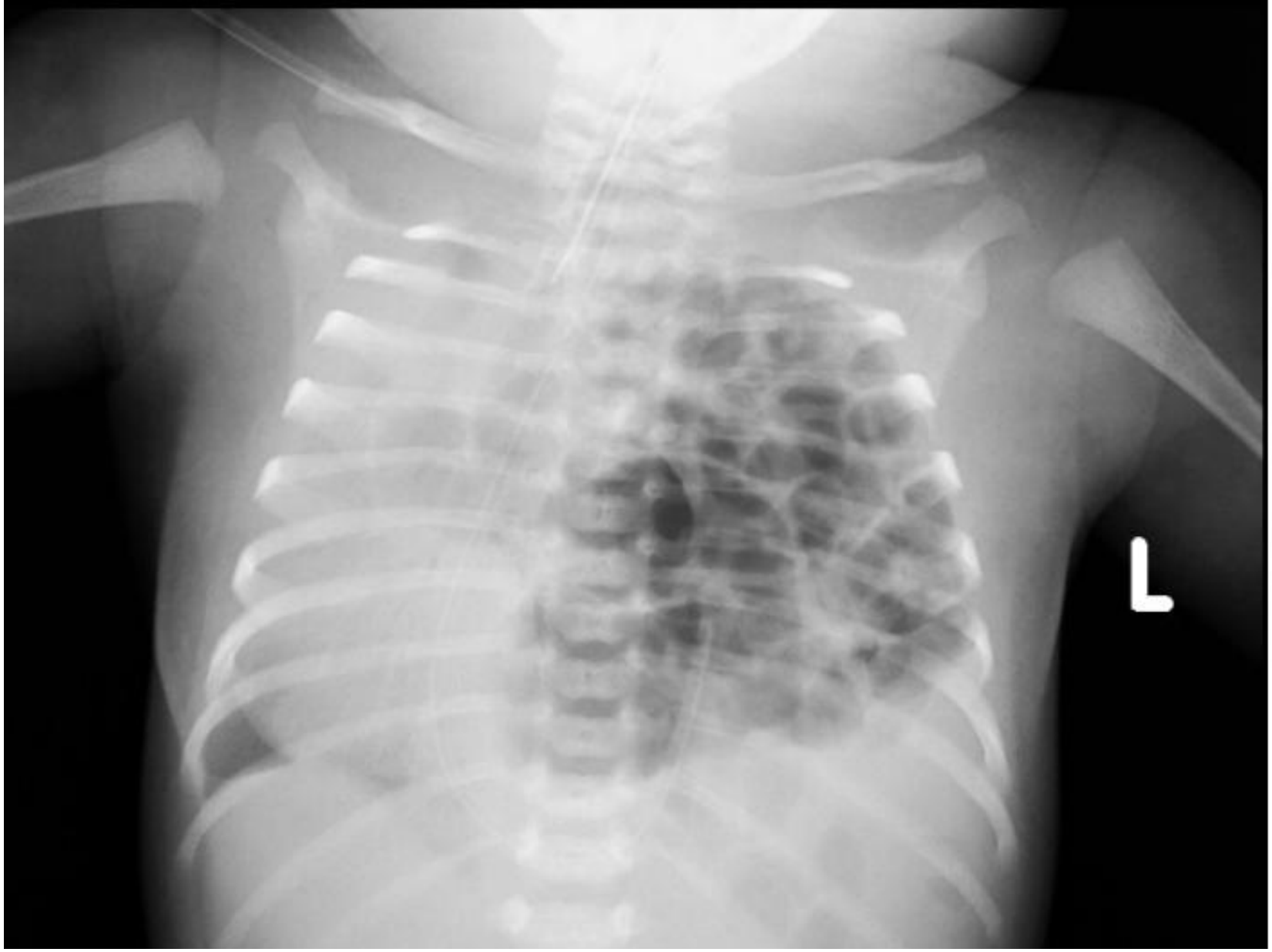
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

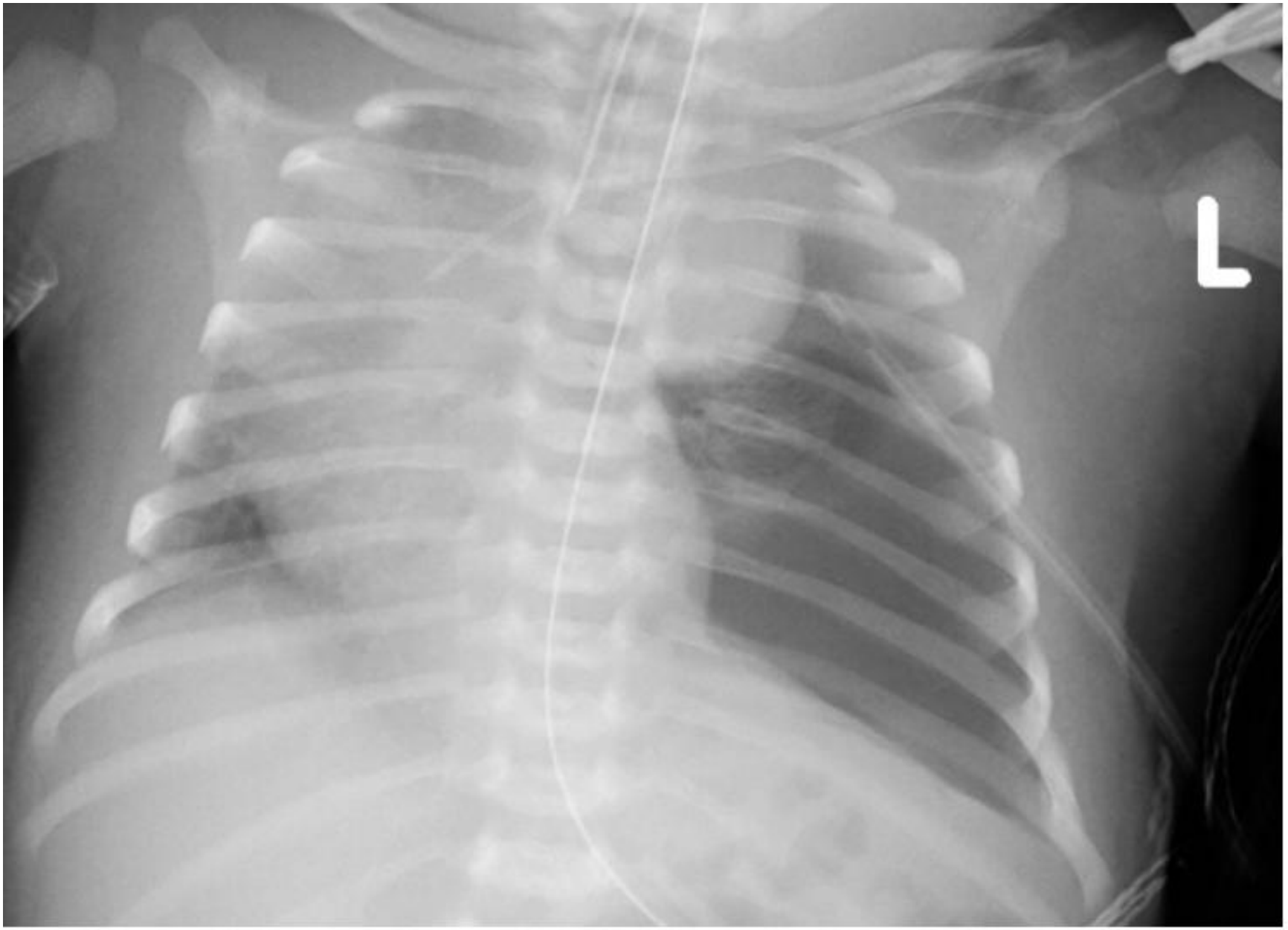
3.7 Developmental lung diseases

Plicní hypertenze následkem vrozené brániční kýly

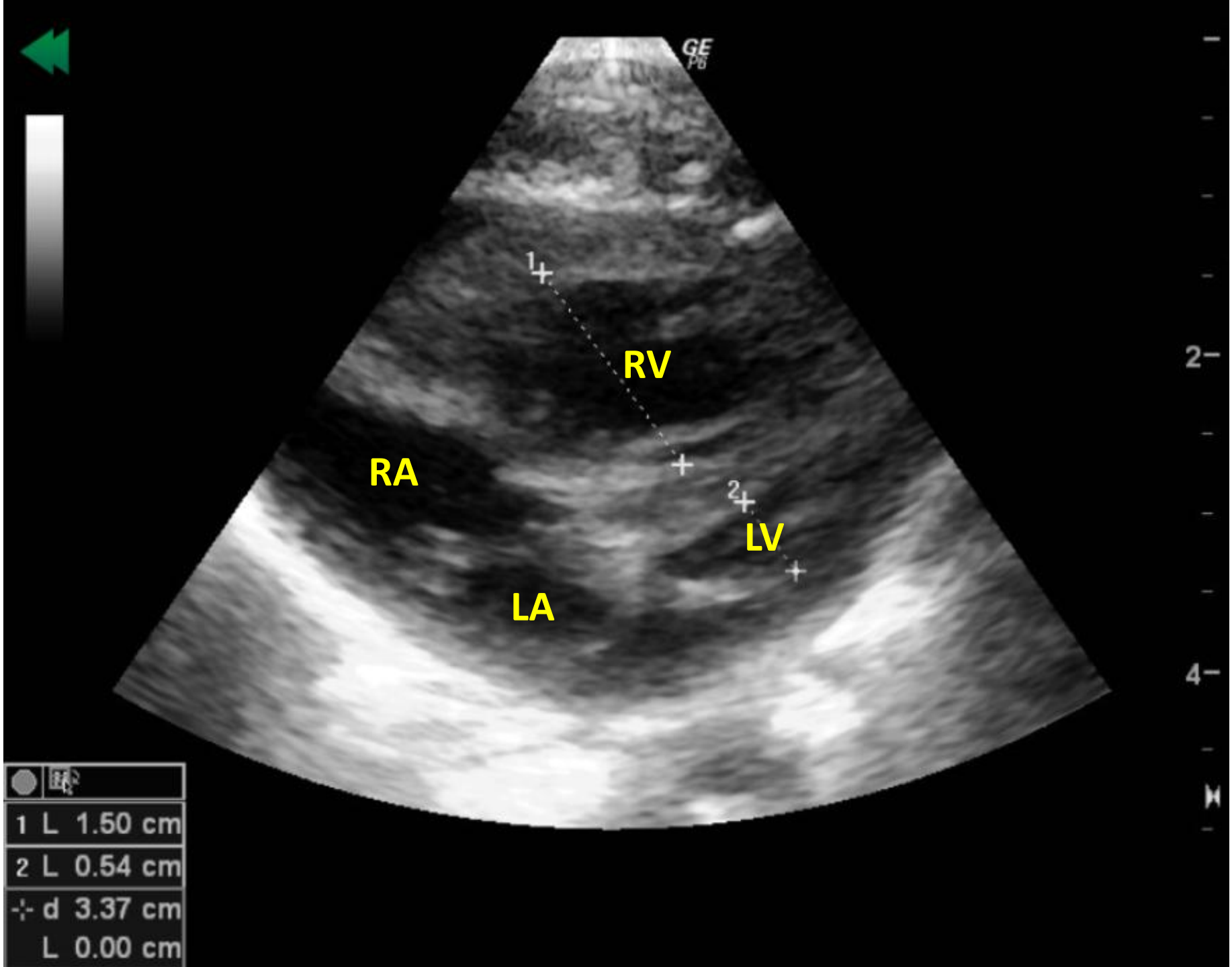
- prenatální nález levostranné brániční kýly
- 39. týden gravidity, plánovaný porod S.C.
- 4300 g, 50 cm

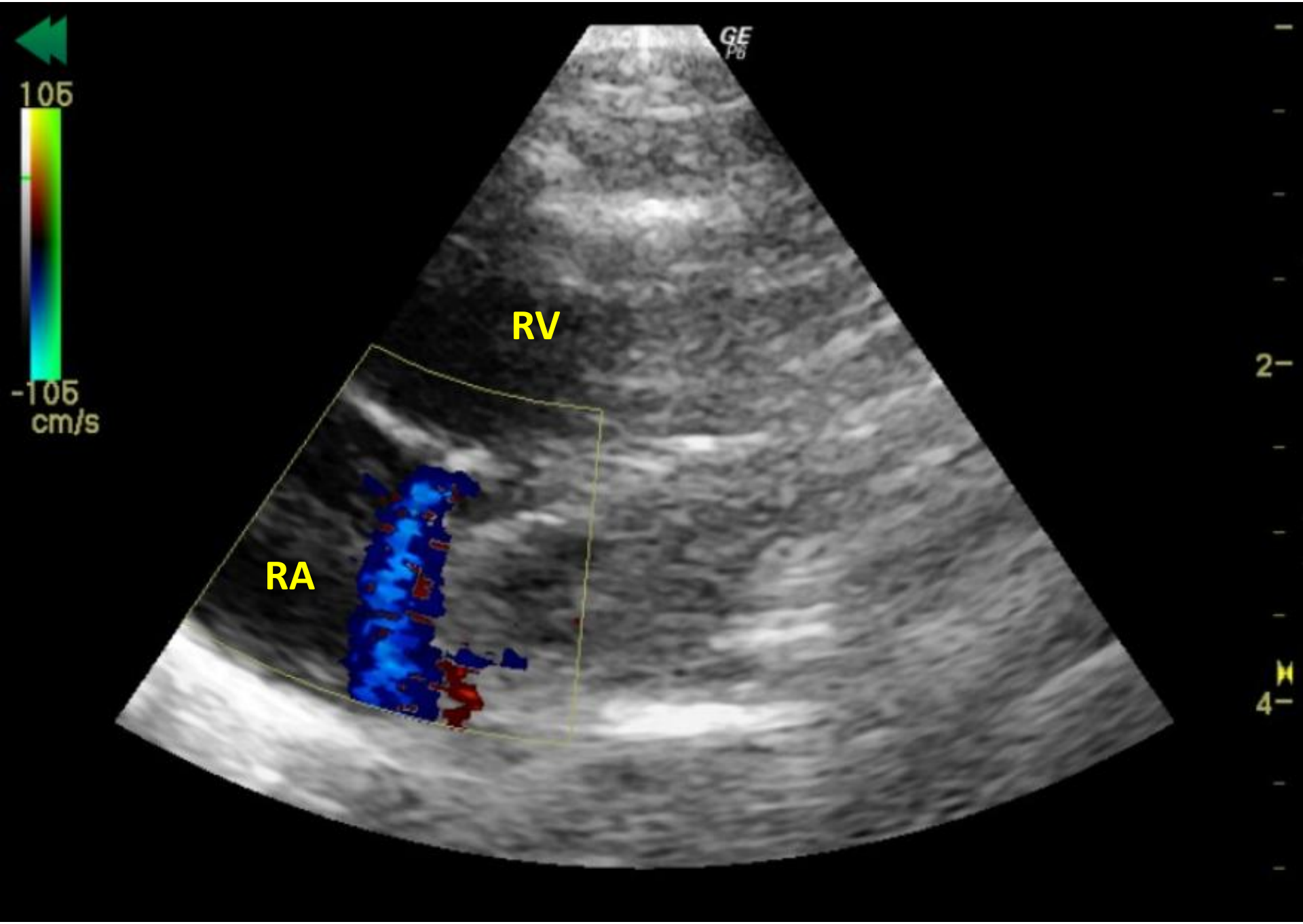


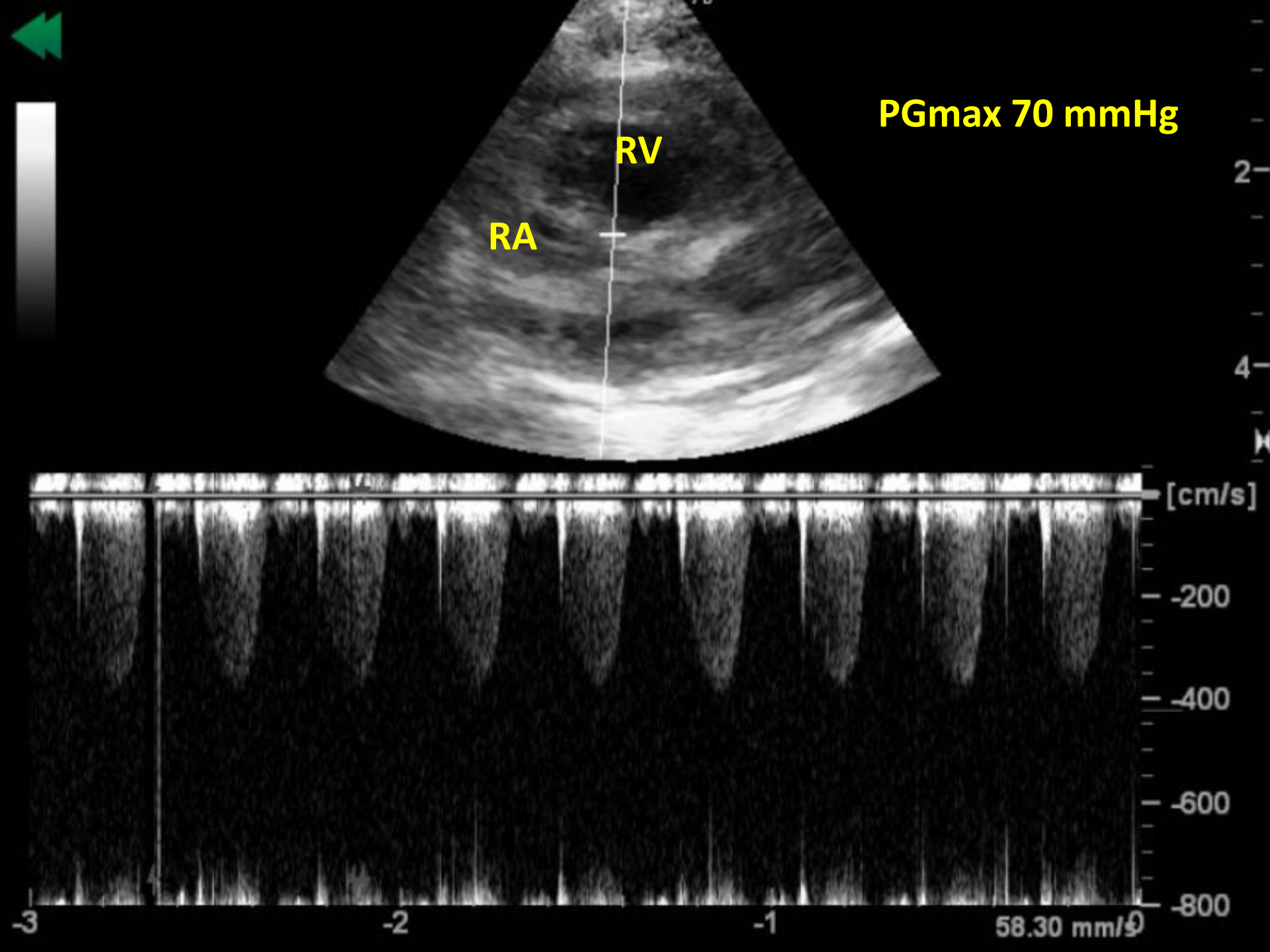
střevní kličky v levé hemithoraxu
přesun středočárových struktur doprava
plicní parenchym patrný jen vpravo bazálně laterálně

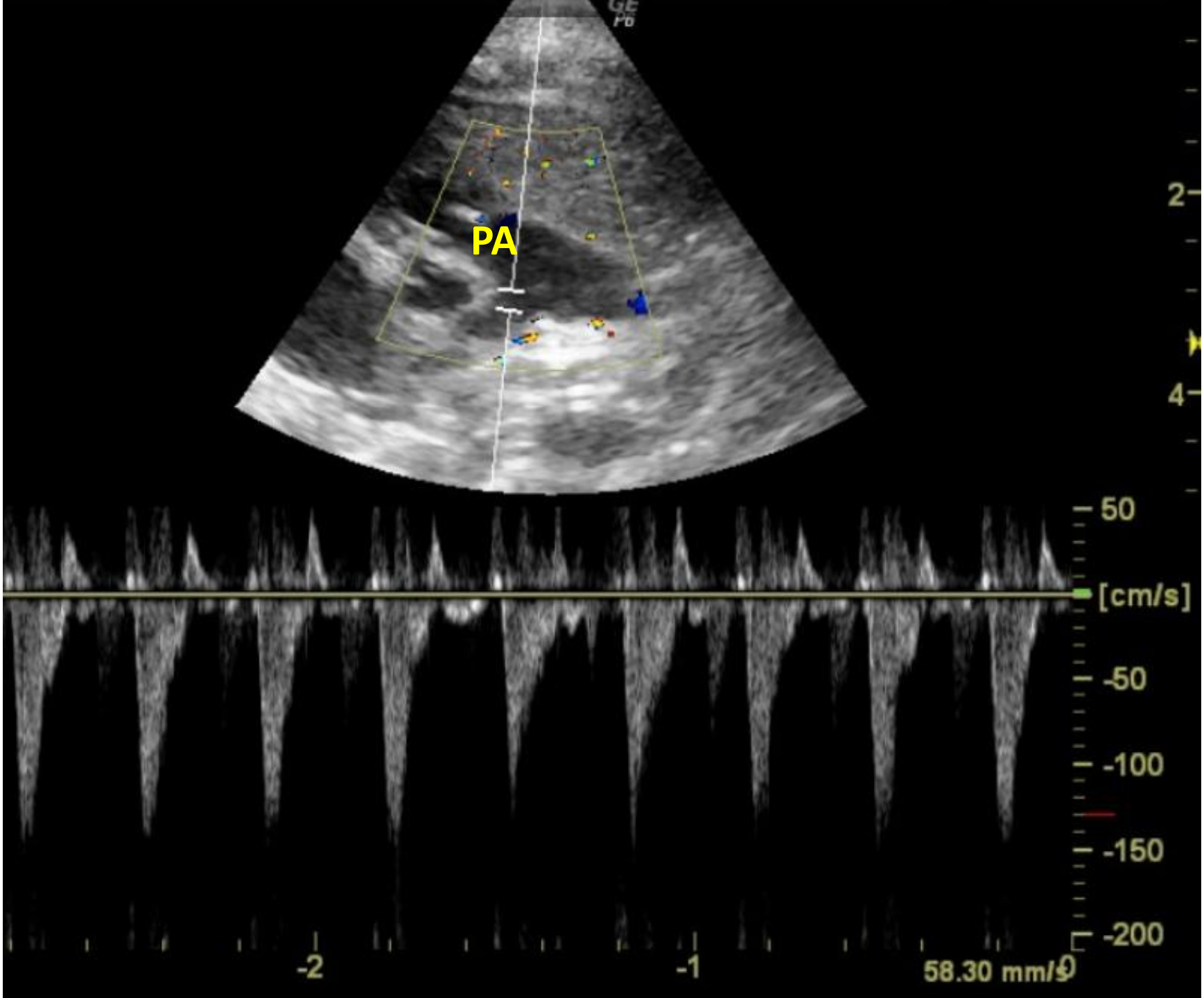


pooperační snímek, pneumothorax vlevo,
levá plíce hypoplastická/zkolabovaná centrálně,
posun struktur doprava


RV
RA
LV
LA
1 L 1.50 cm
2 L 0.54 cm
d 3.37 cm
L 0.00 cm


106
-106
cm/s
RV
RA
2
4


PGmax 70 mmHg
RV
RA
2
4
[cm/s]
-200
-400
-600
-800
-3
-2
-1
0
58.30 mm/s

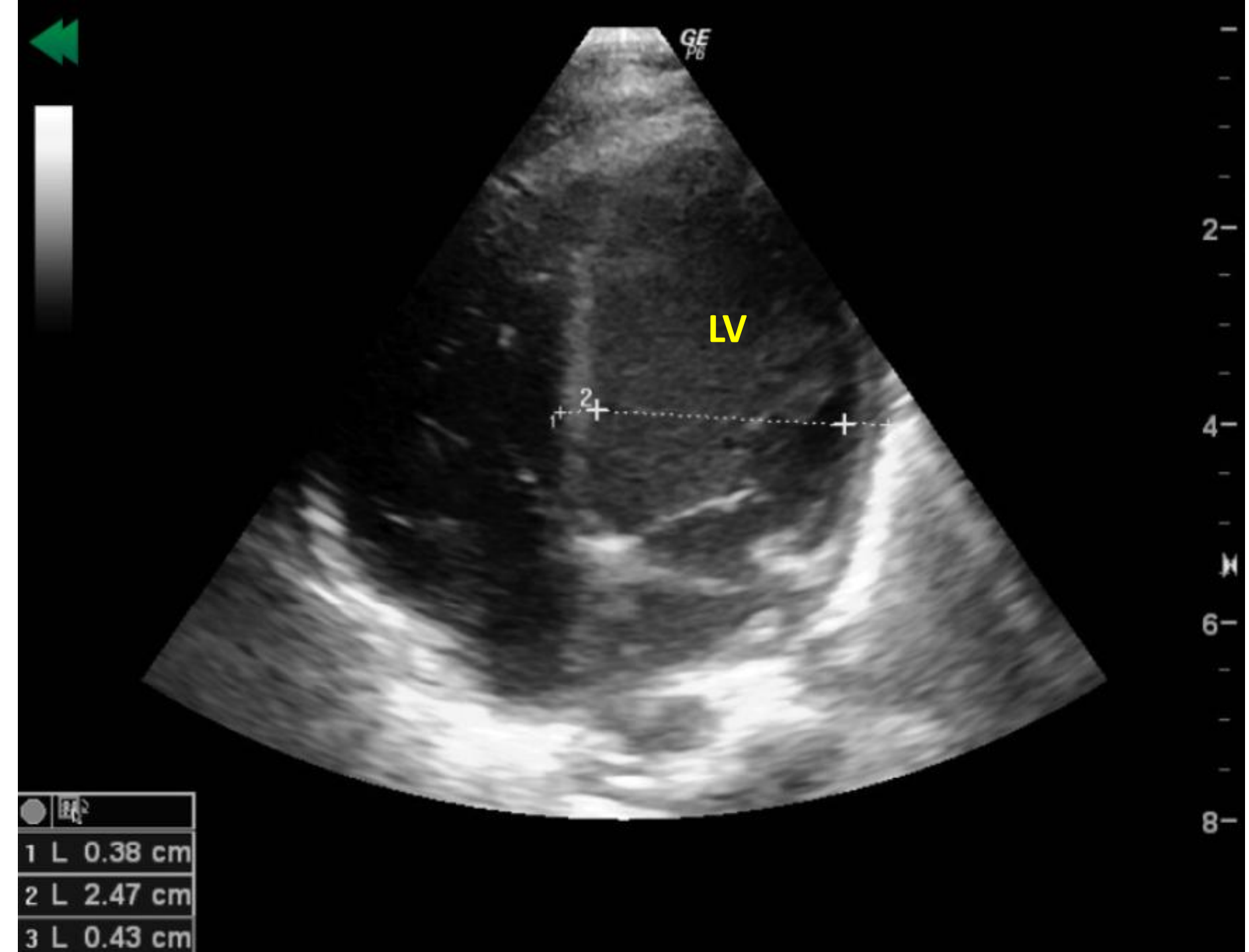

PA
2
4
50
[cm/s]
-50
-100
-150
-200
-2
-1
0
58.30 mm/s

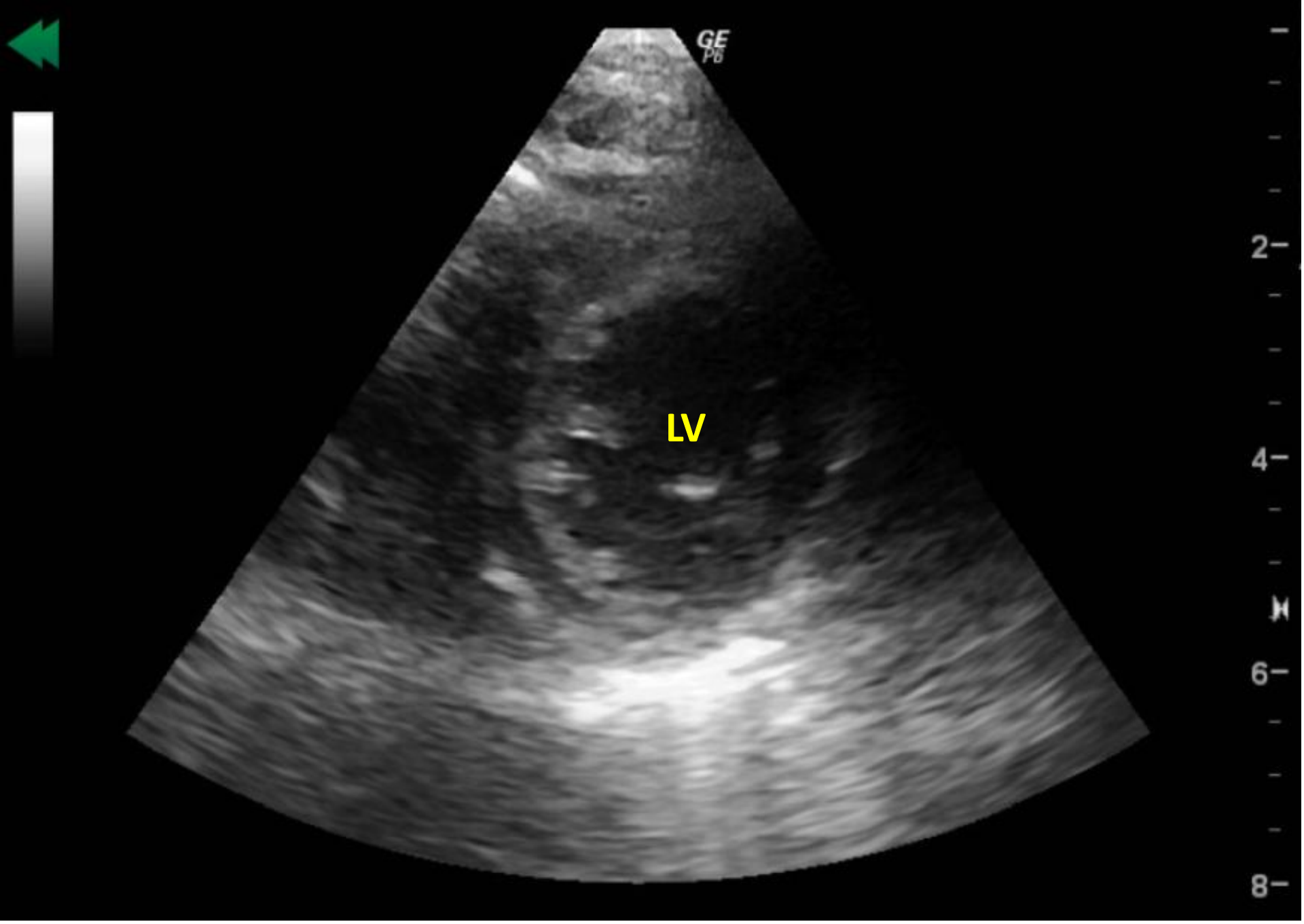
3.7 Developmental lung diseases

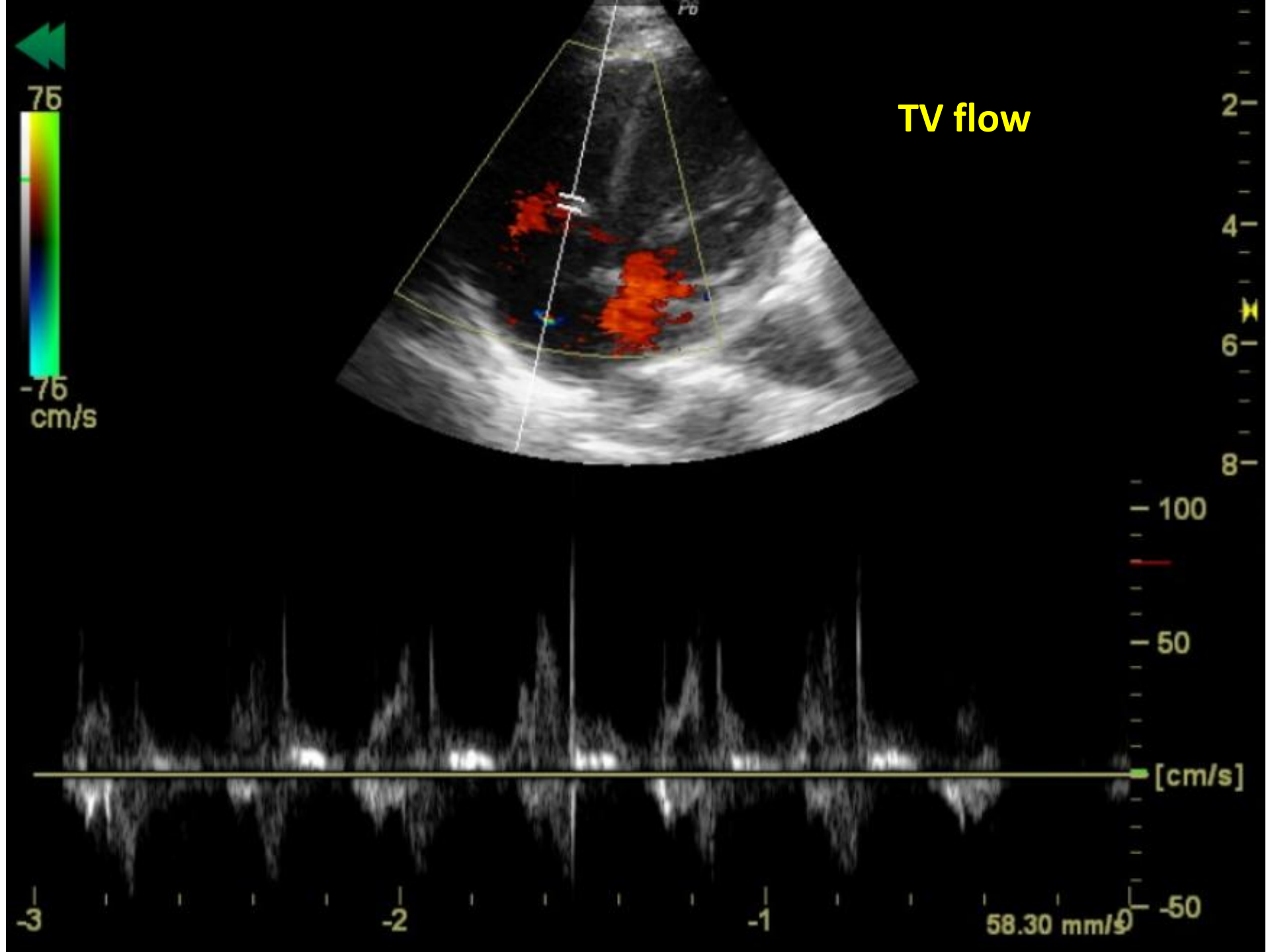
Plicní hypertenze následkem vrozené bráničí kýly

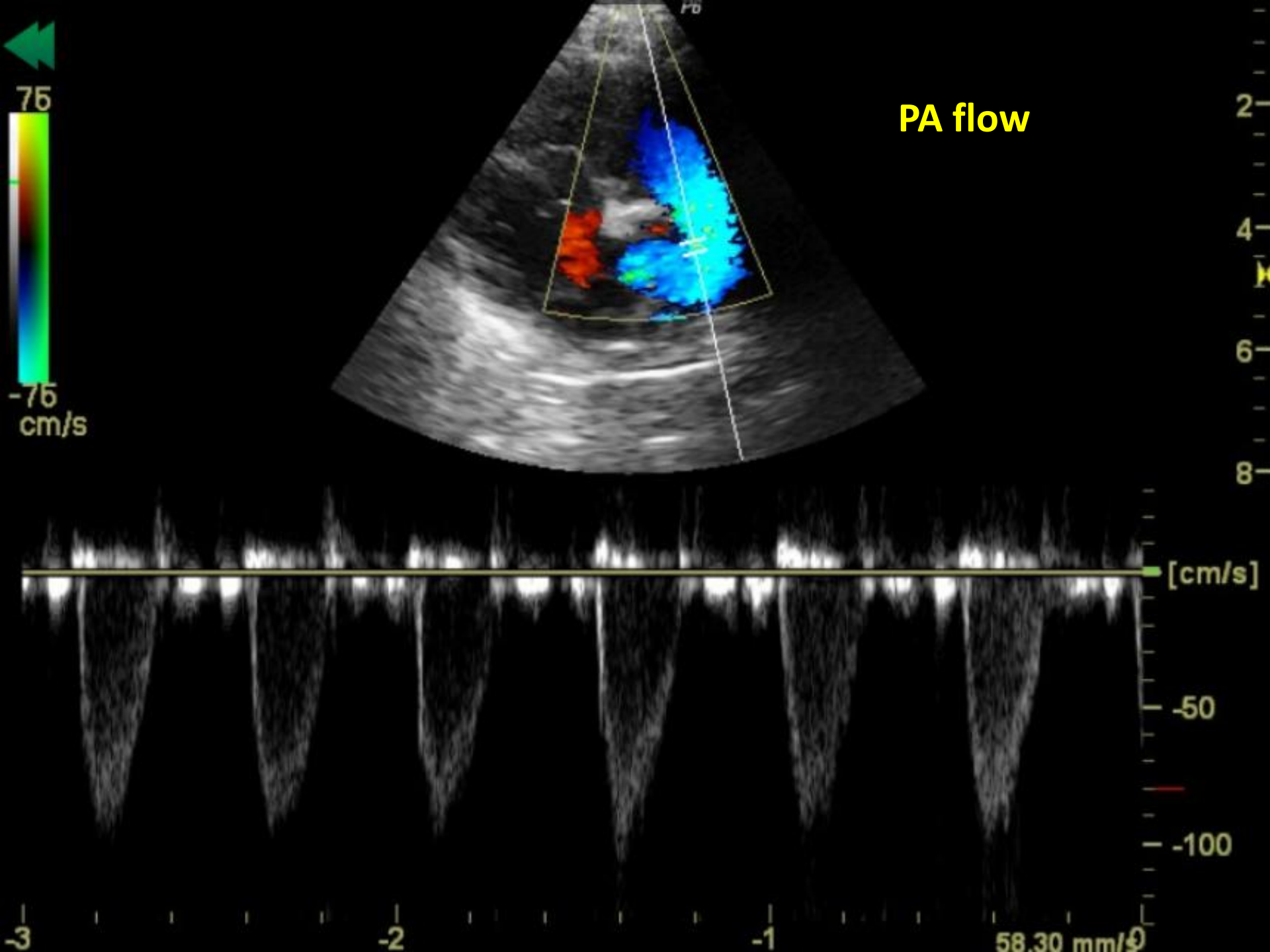
- komplexní intenzivní péče, operace
  UPV s aplikací NO (oxid dusnatý)

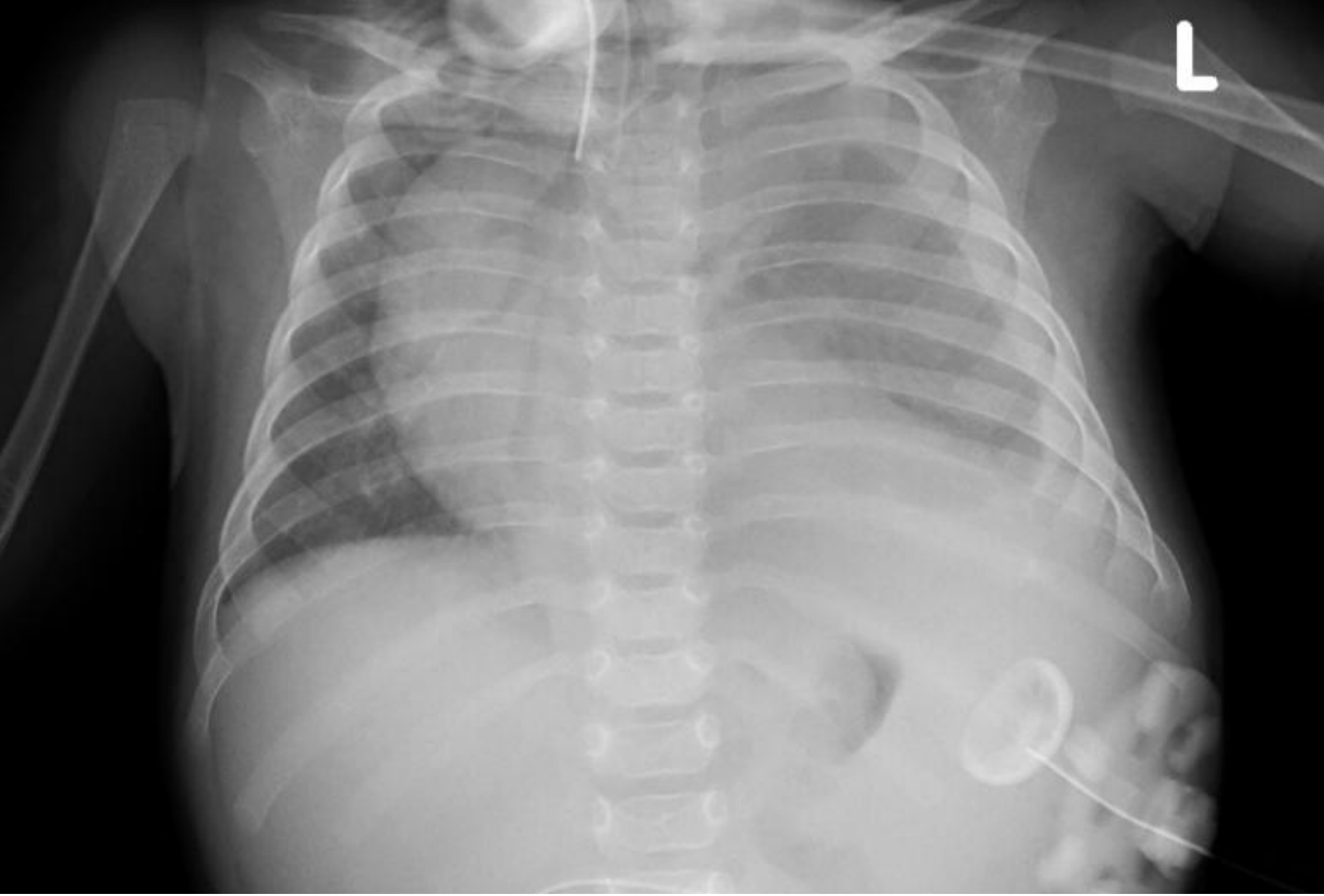
- sildenafil zaveden 49. den života
- maximální dávka 3 mg/kg/d
- za 28 dnů vymizení plicní hypertenze
- nezaznamenány klinicky významné či pozorovatelné nežádoucí účinky


GE
LV
2
2
4
6
8
1 L 0.38 cm
2 L 2.47 cm
3 L 0.43 cm


GE
LV
2
4
6
8


TV flow
75
-75
cm/s
2
4
6
8
100
50
[cm/s]
-50
-3
-2
-1
0
58.30 mm/s


PA flow
75
-75
cm/s
2
4
6
8
[cm/s]
-50
-100
-3
-2
-1
0
58.30 mm/s



levé plicní křídlo hypoplastické,
vzdušný plicní parenchym jen ve středním a částečně horním plicním poli

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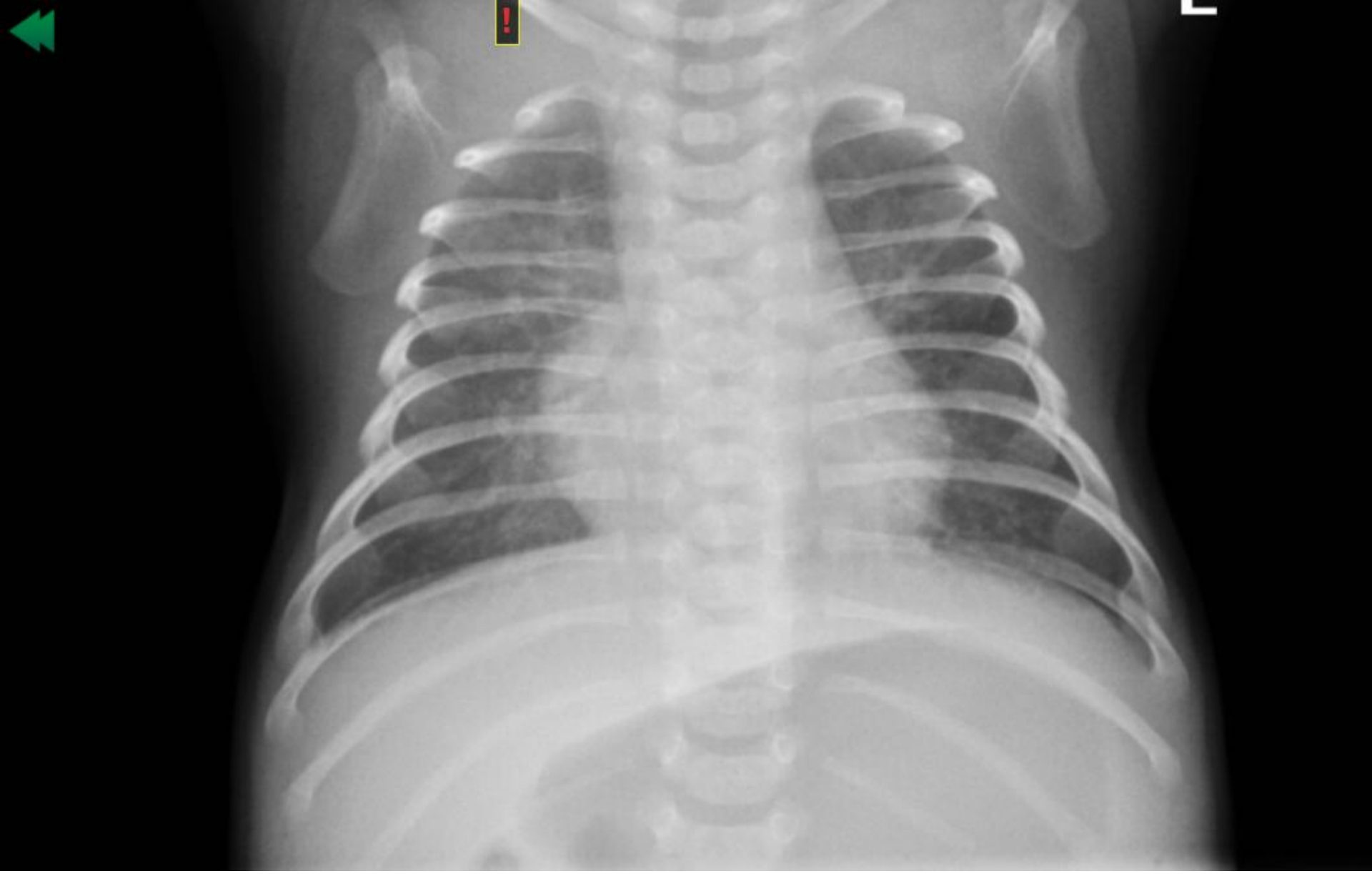
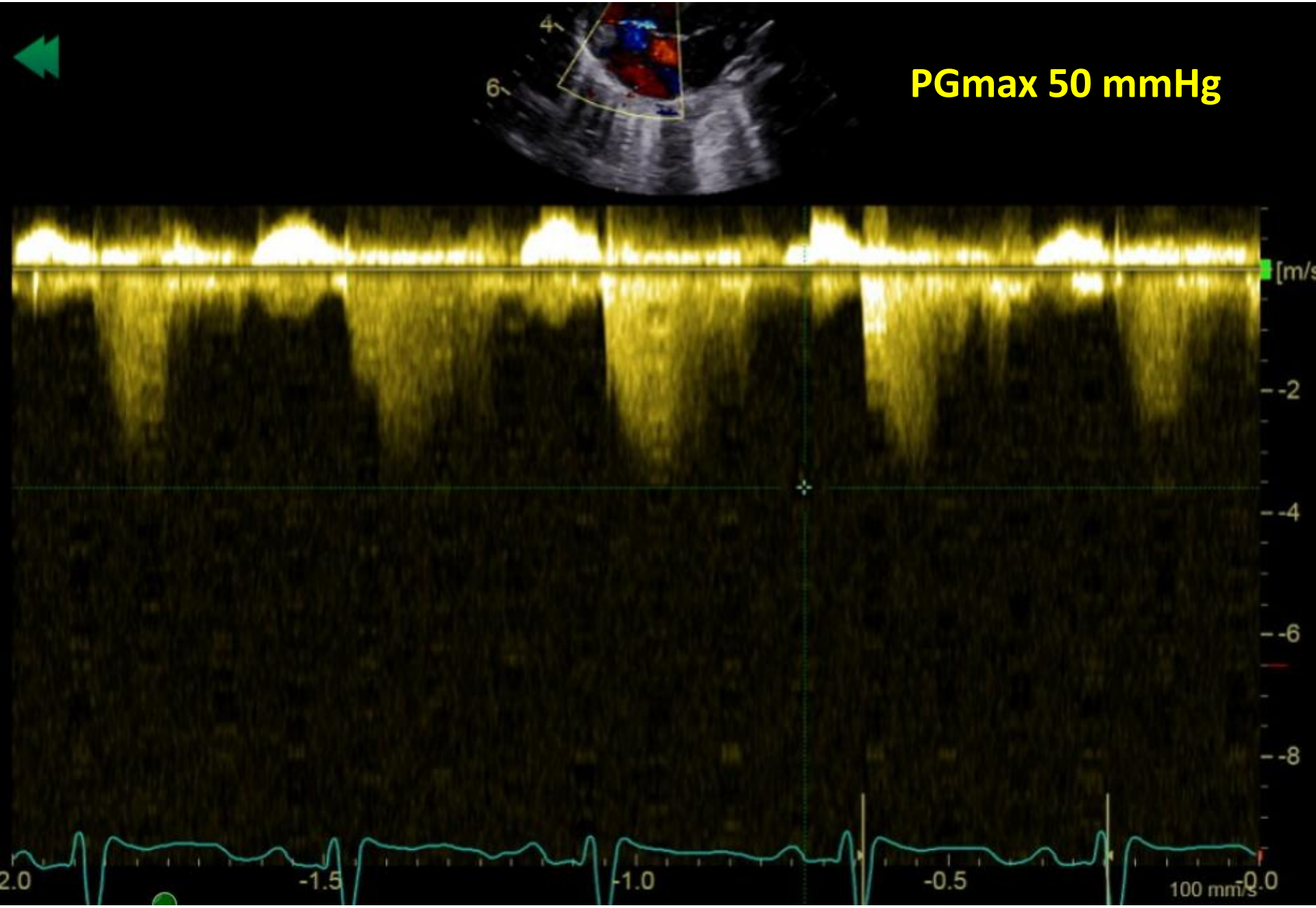
3.5 Alveolar hypoventilation disorders

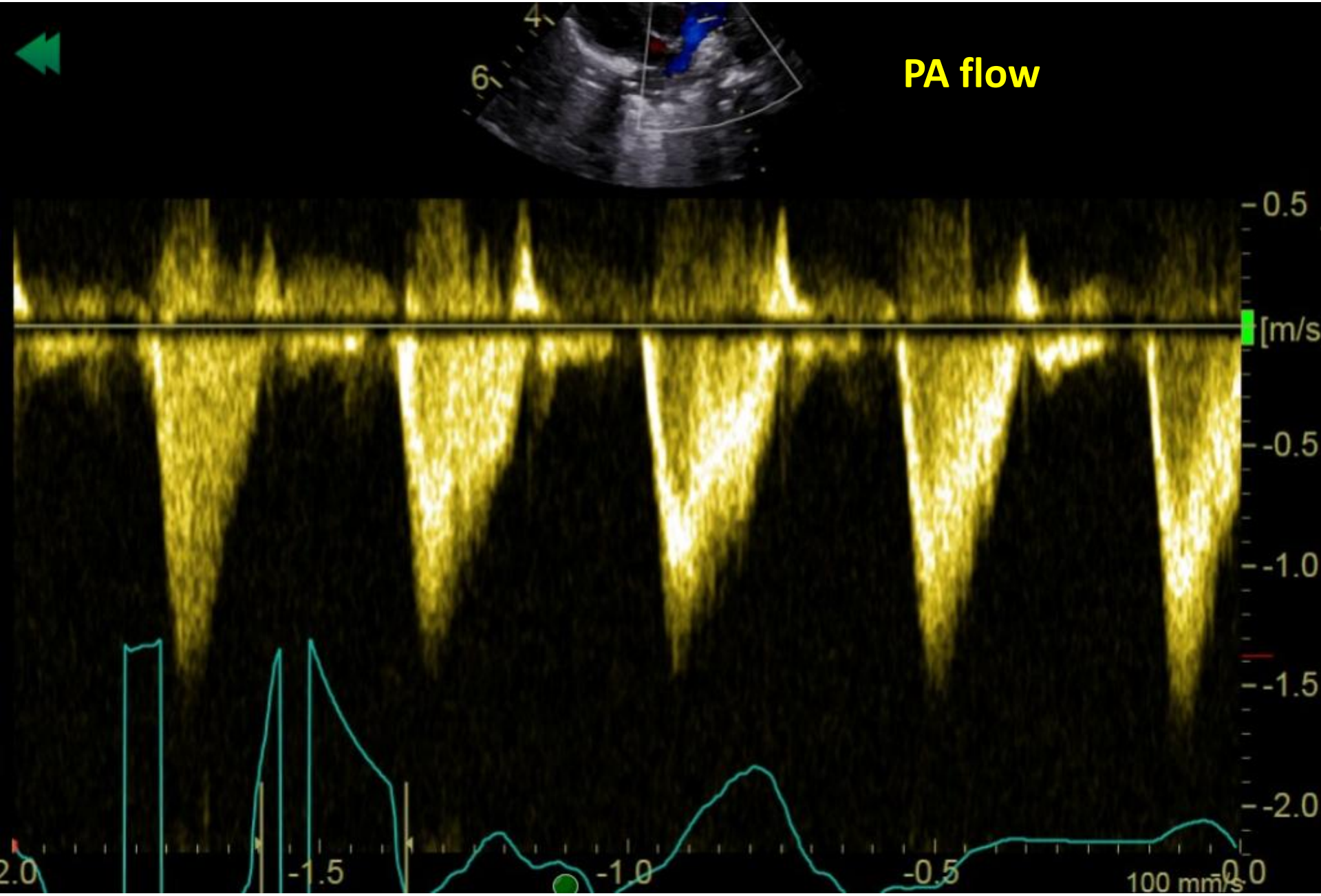
Plicní hypertenze u pacienta s Downovým syndromem

- lehká prematurita, 34. t.g.,
- hypotrofie pod 3. perc.,
- porodní míry 1050 g, 40 cm
- morbus Down – chronická hypoventilace následkem obstrukce horních cest dýchacích



oboustranně centrálně zmnožená bronchovaskulární kresba
plicní parenchym bez jednoznačných infiltrací, bez ložisek
hyperplazie thymu

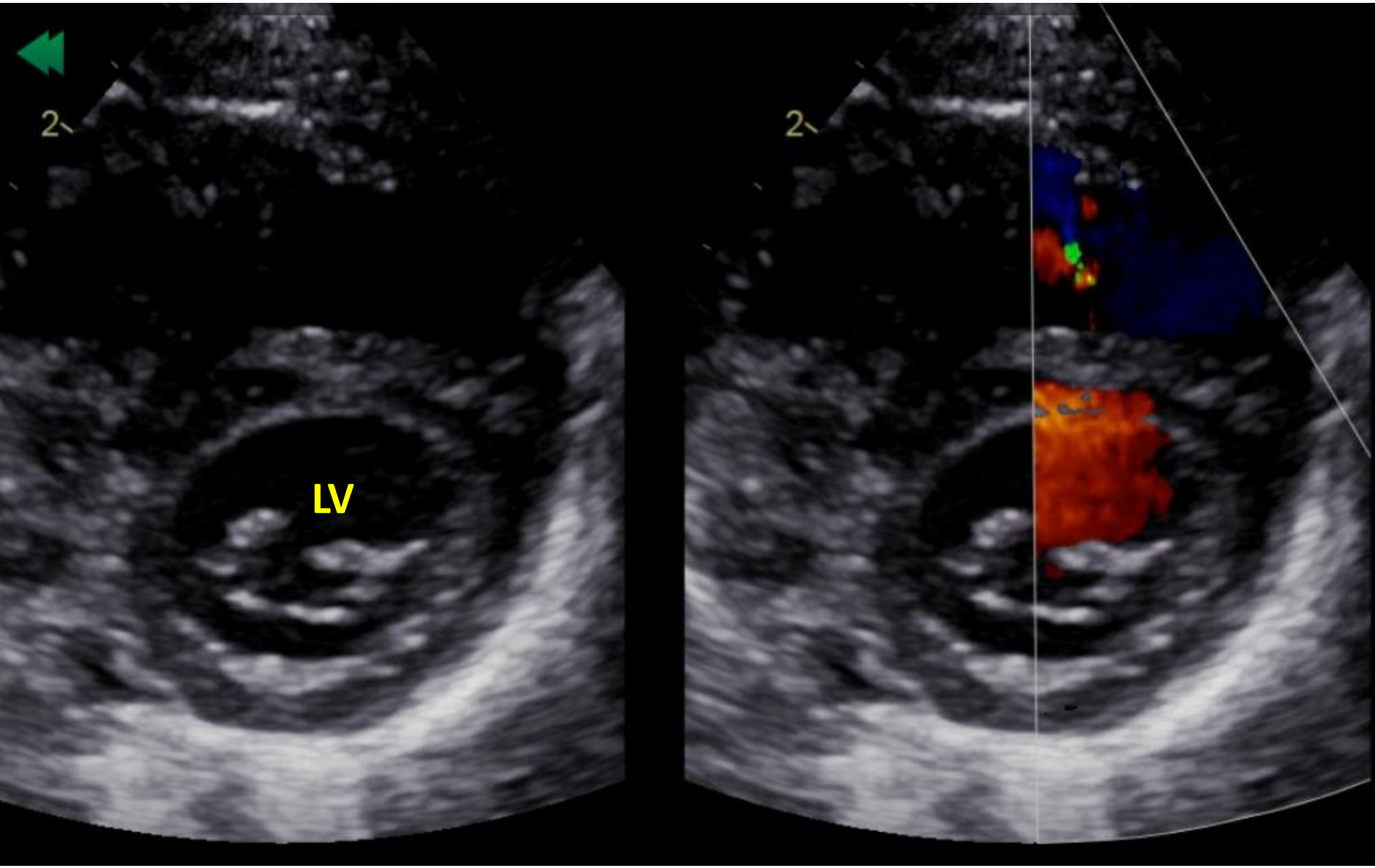

PGmax 50 mmHg
4
6
[m/s
-2
-4
-6
-8
2.0
-1.5
-1.0
-0.5
-0.0
100 mm/s

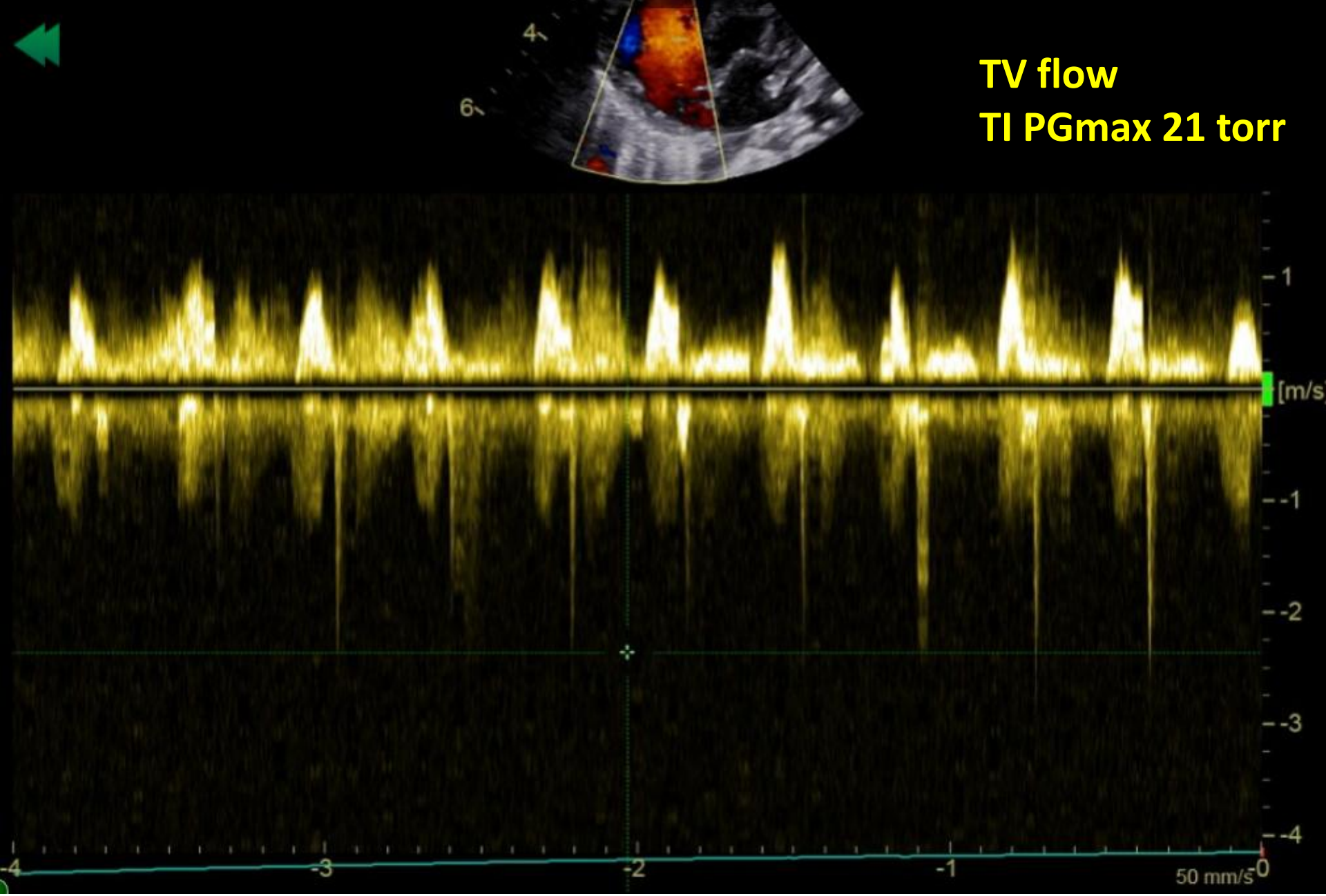

PA flow
4
6
0.5
[m/s]
-0.5
-1.0
-1.5
-2.0
2.0
-1.5
-1.0
-0.5
0.0
100 mm/s

3.5 Alveolar hypoventilation disorders

Plicní hypertenze u pacienta s Downovým syndromem

- terapie zavedena v 6 týdnech věku
- oxygenoterapie kyslíkovými brýlemi
- sildenafil max. dávka 2,5 mg/kg/d
- za 16 dnů vymizení plicní hypertenze
- projevy respirační infekce jako možné nežádoucí účinky léčby


2
LV
2


TV flow
TI PGmax 21 torr
4
6
1
[m/s]
-1
-2
-3
-4
-4
-3
-2
-1
0
50 mm/s

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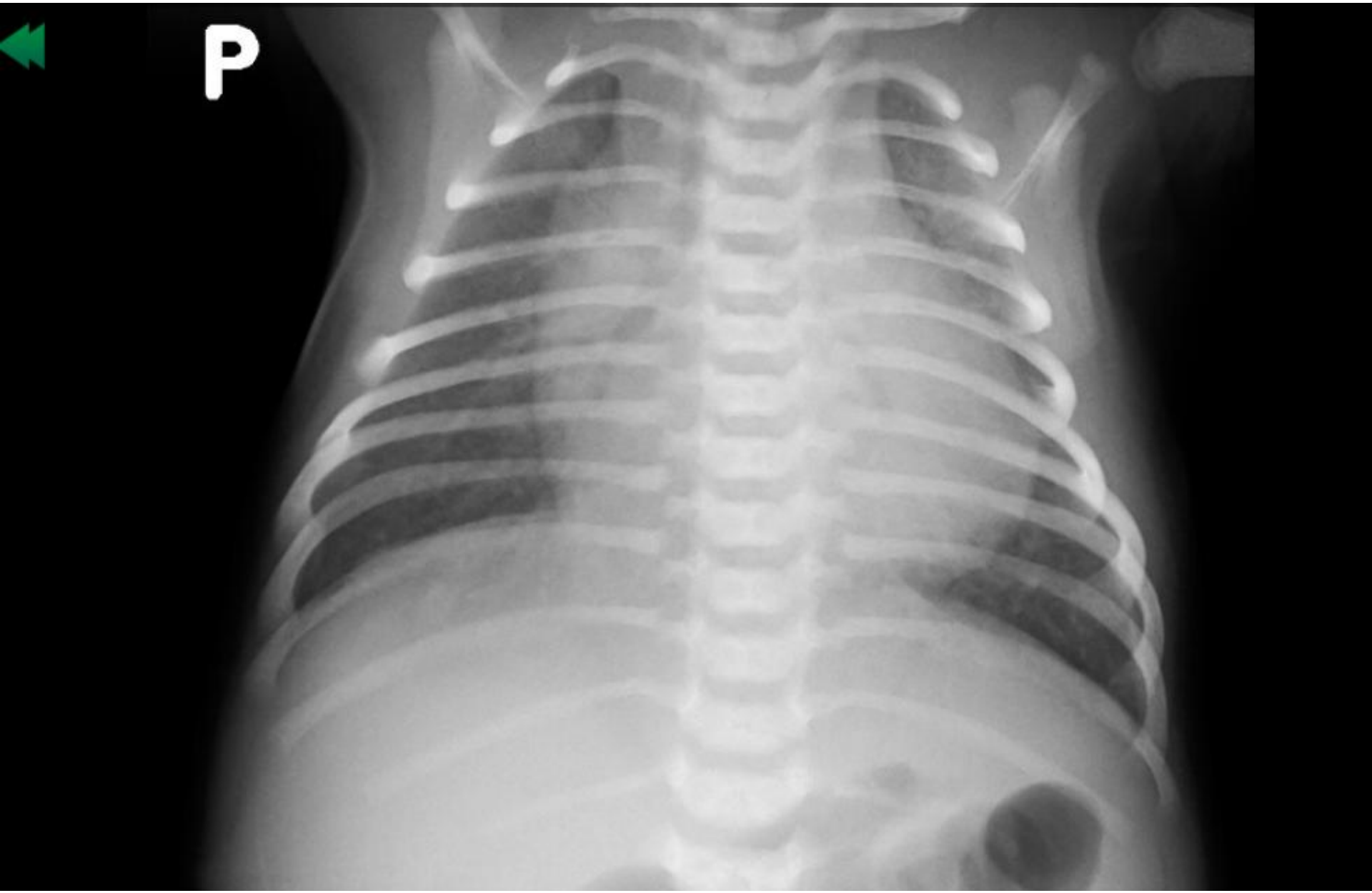
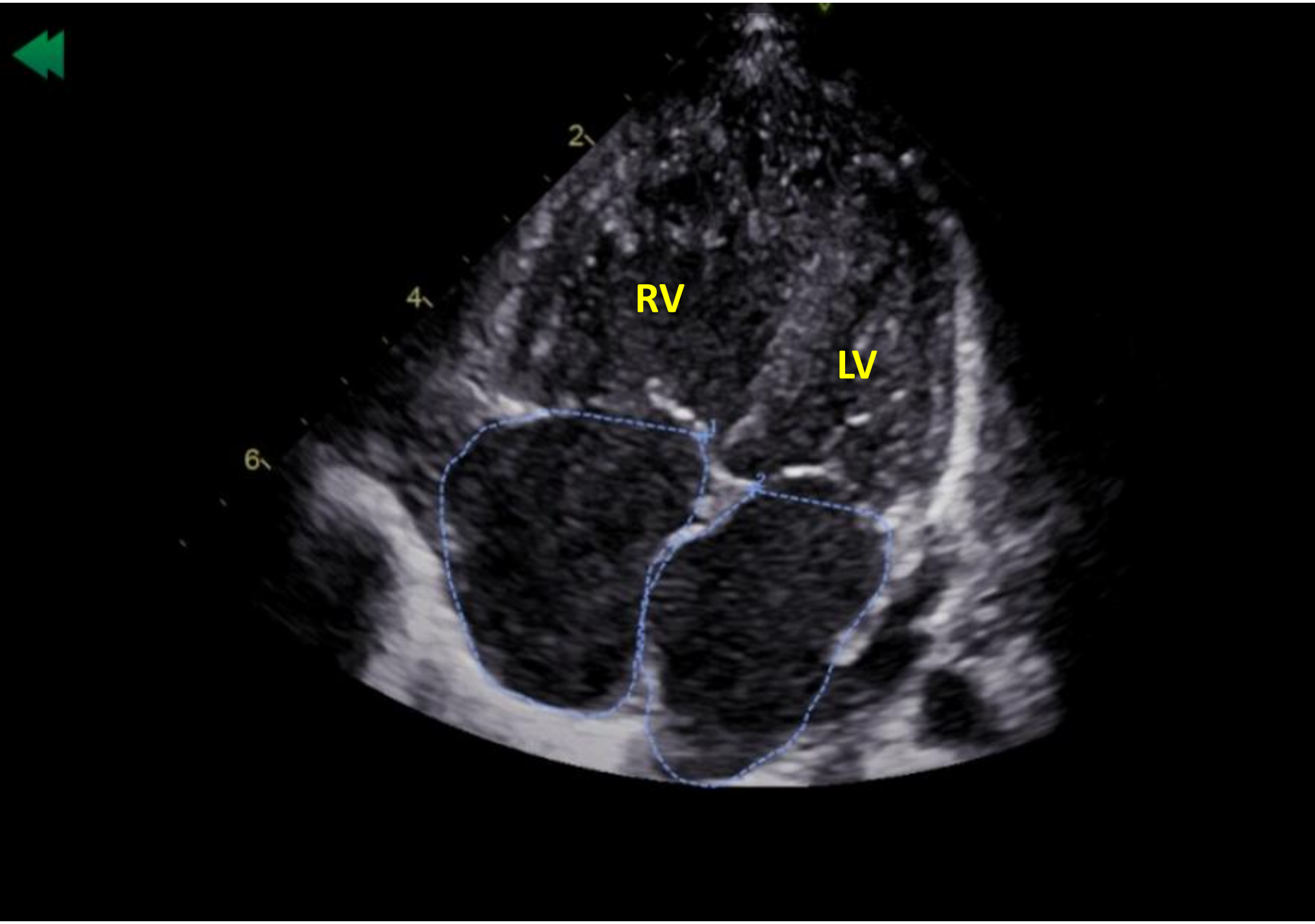
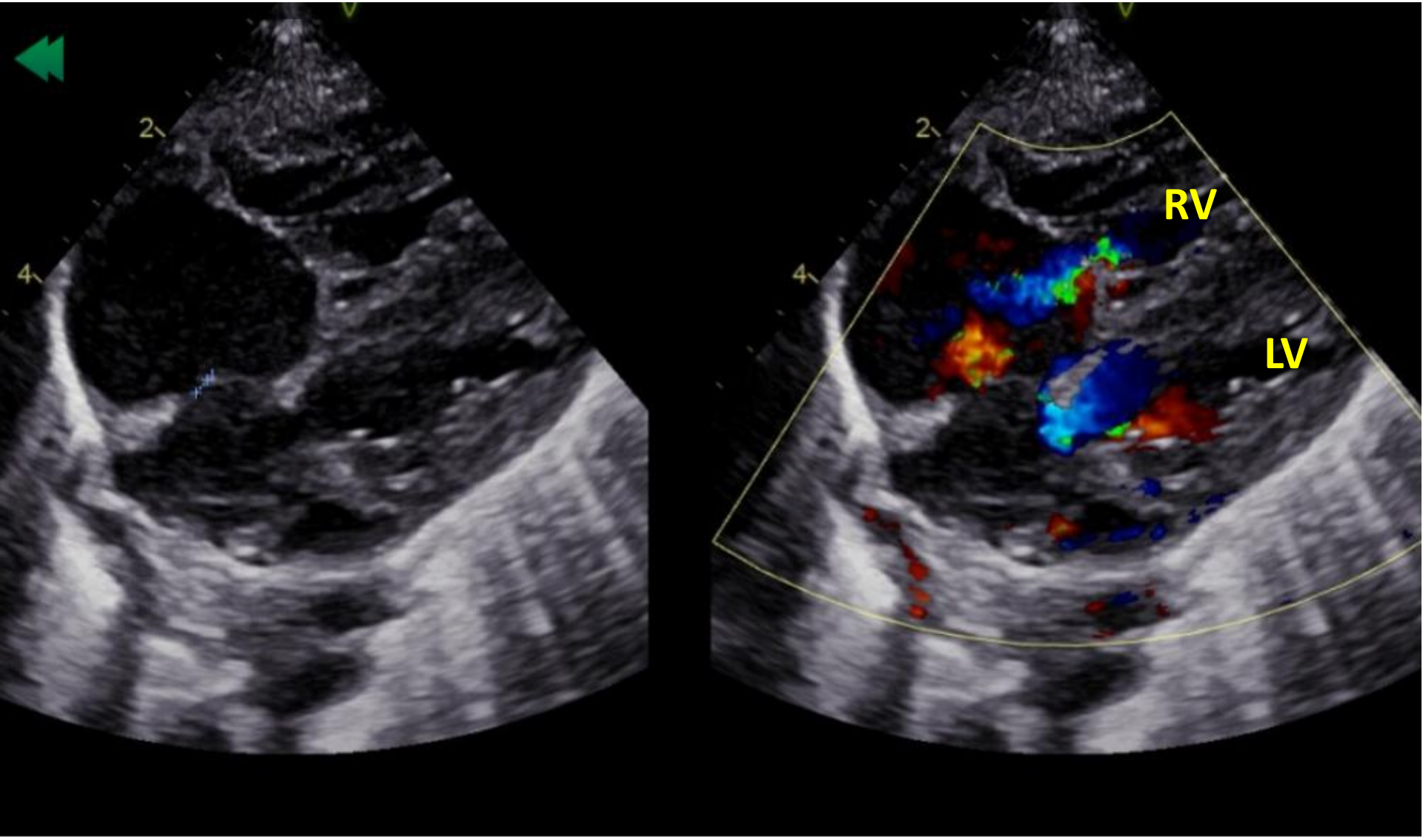
Perzistující plicní hypertenze novorozence

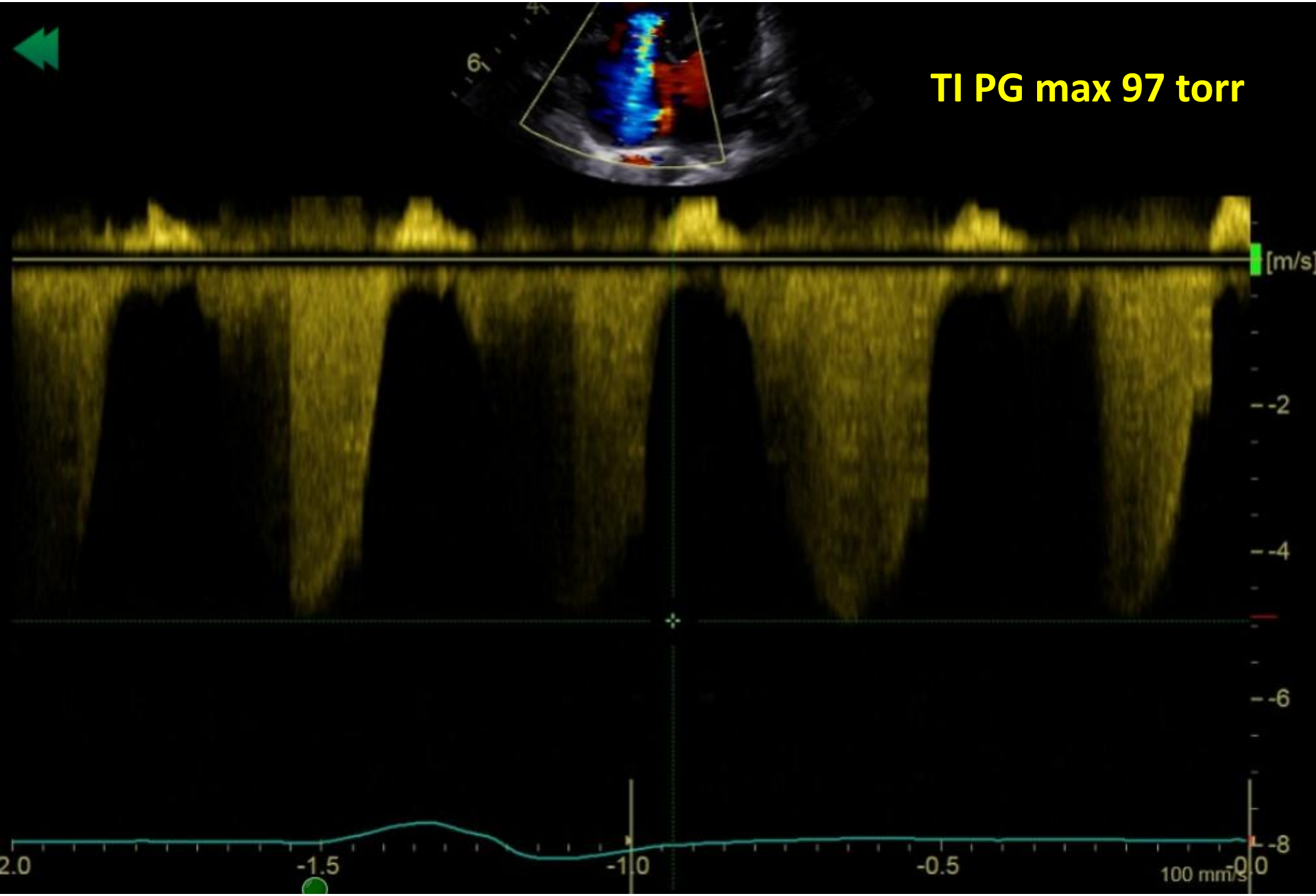
- těhotenství fyziologické, porod v termínu
- 3740g, 53cm
- infekce matky během porodu
- následně infekce novorozence
- vznik PPHN

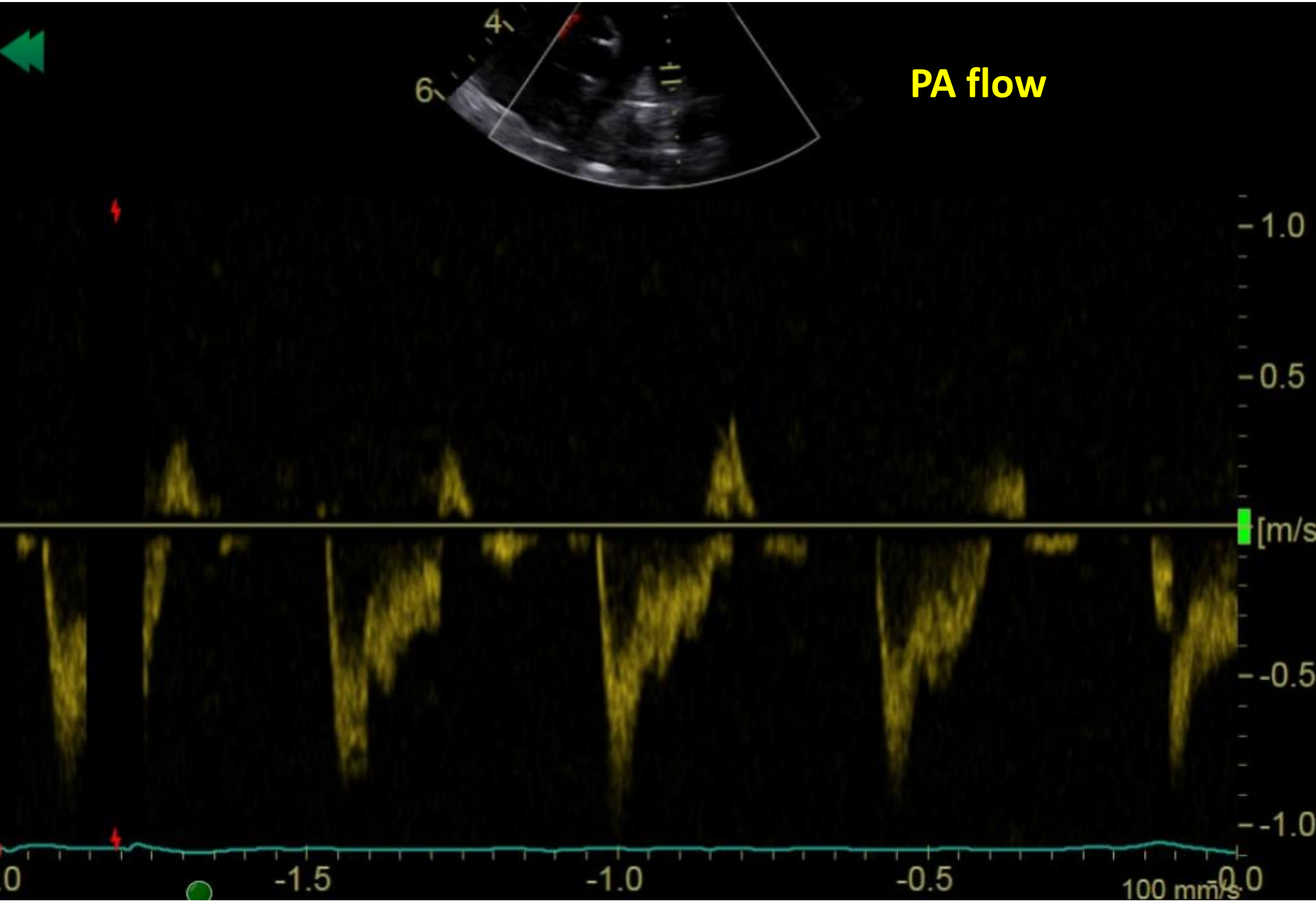


Rozšířený kulovitý srdeční stín s prominencí pravostranných srdečních oddílů.
Susp. infiltrace plicního parenchymu vlevo ve středním plicním poli


2
4
6
RV
LV

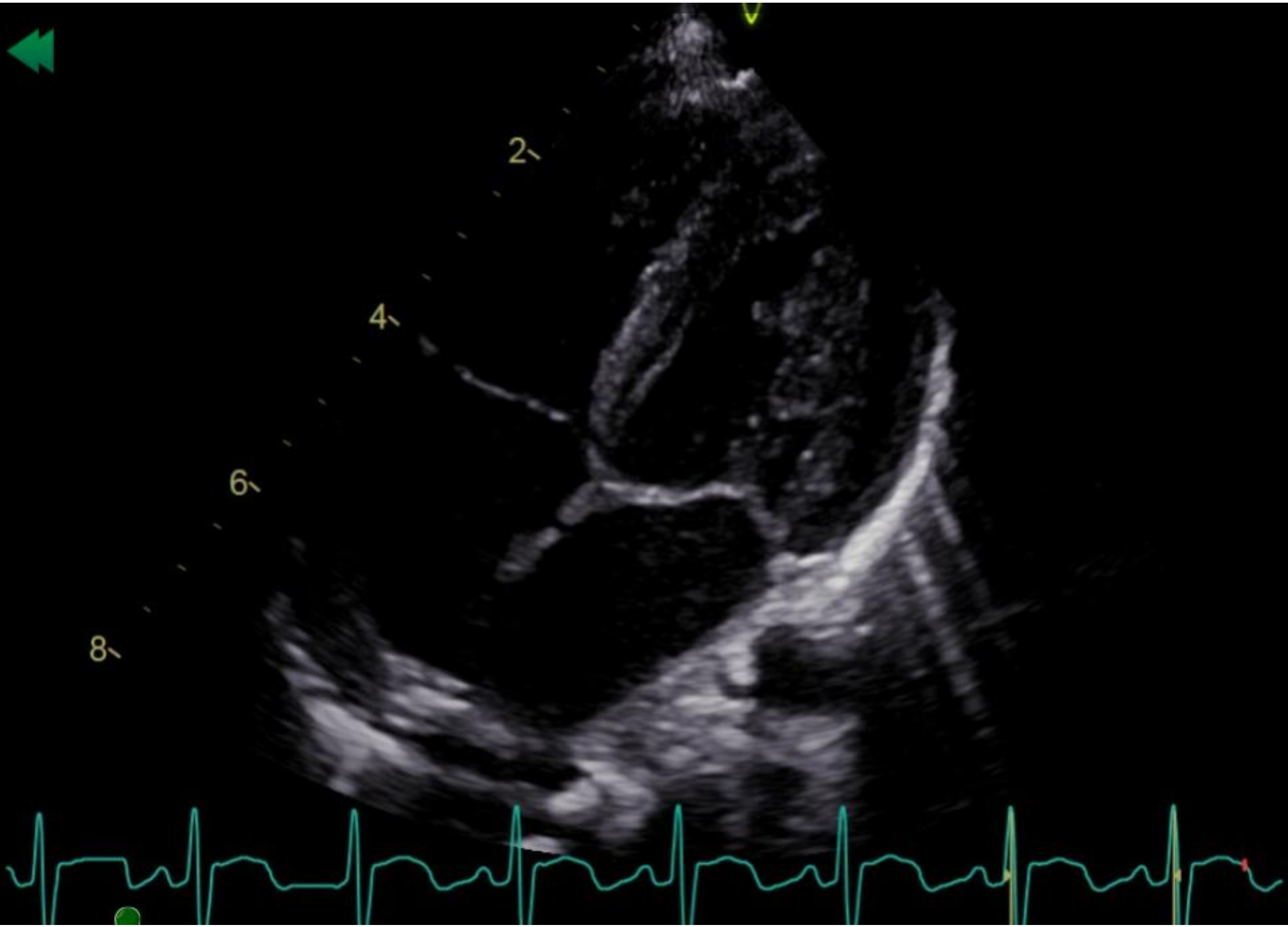

RV
LV

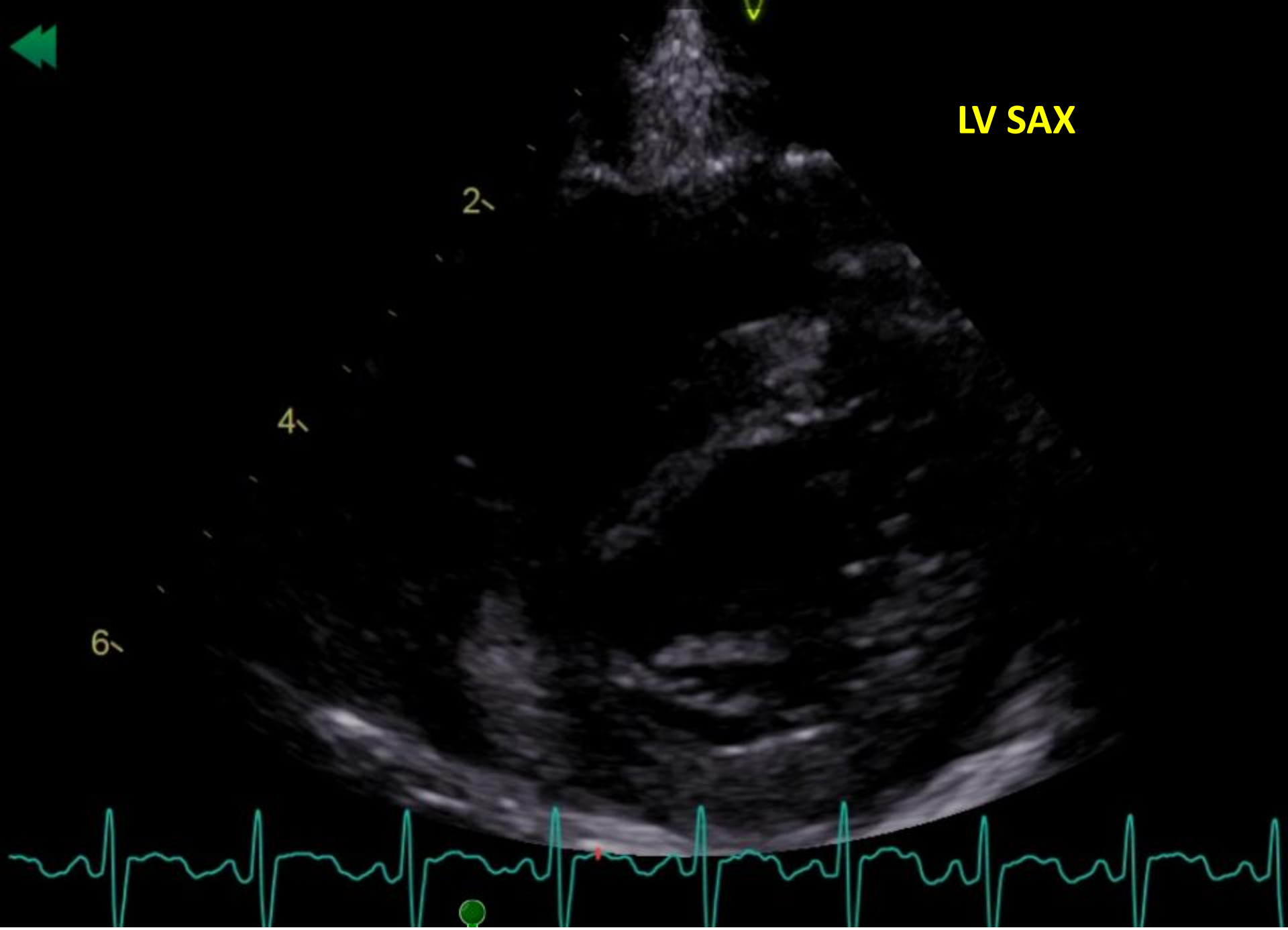

TI PG max 97 torr
[m/s]
-2
-4
-6
-8
2.0
-1.5
-1.0
-0.5
0.0
100 mm/s

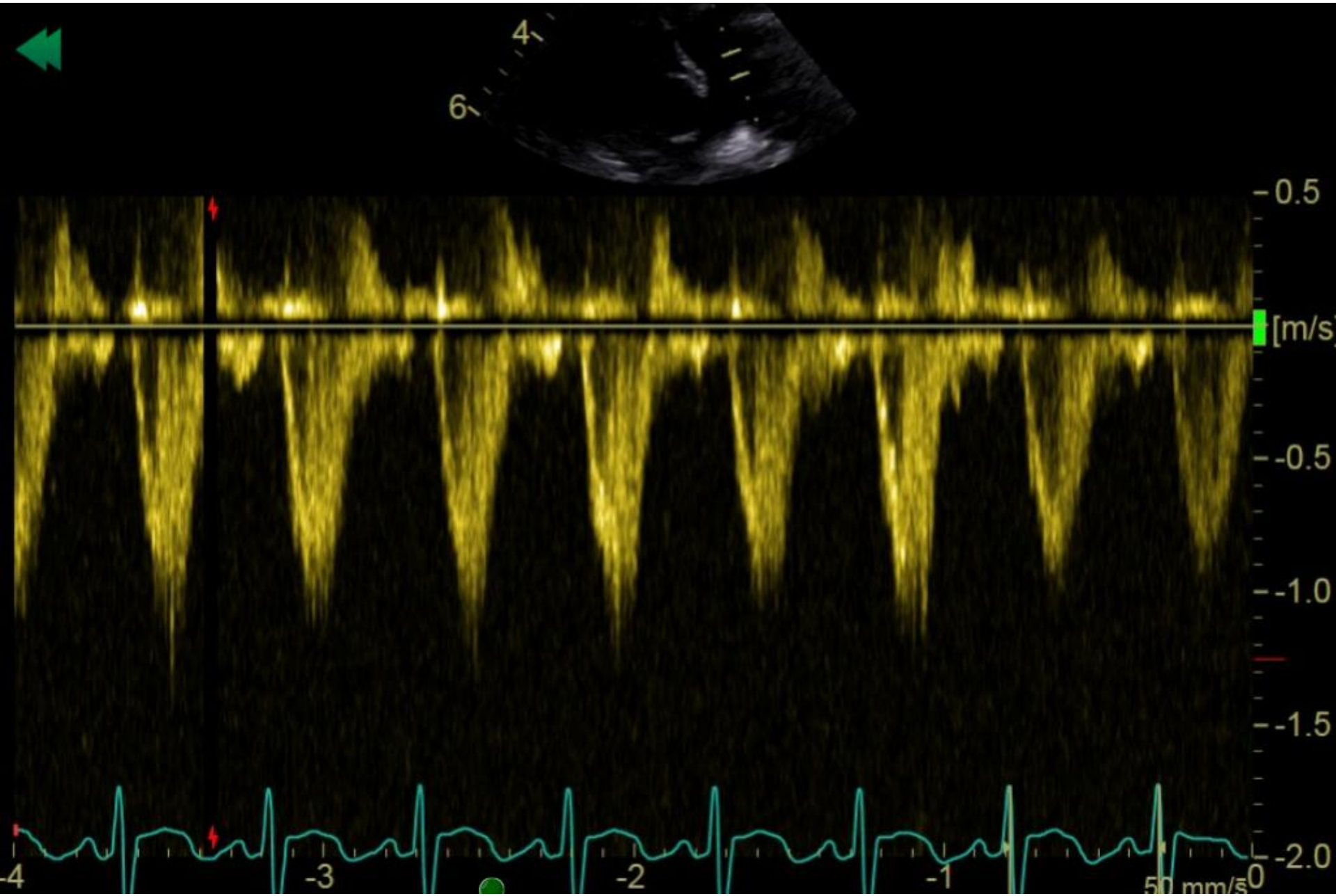

PA flow
4
6
1.0
0.5
[m/s
-0.5
-1.0
-1.5
-1.0
-0.5
0.0
100 mm/s

Perzistující plicní hypertenze novorozence

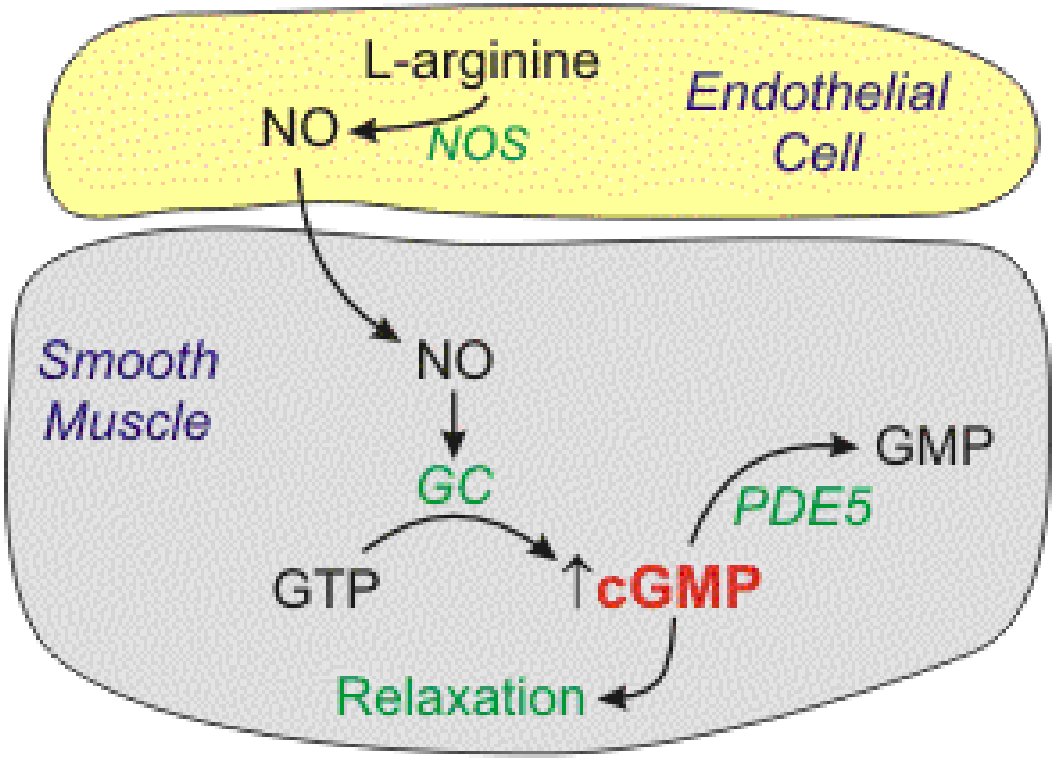
- sildenafil nasazen 8. den života
- max. dávka 3 mg/kg/d
- oxygenoterapie
- za 14 dnů vymizení plicní hypertenze
- nezaznamenány klinicky významné či pozorovatelné nežádoucí účinky


2
4
6
8


LV SAX
2
4
6


4
6
0.5
[m/s]
-0.5
-1.0
-1.5
-2.0
-4
-3
-2
-1
0
50 mm/s

Sildenafil
inhibitor fosfodiesterázy typu 5



Abbreviations: NO, nitric oxide; NOS, nitric oxide synthase; GC, guanylyl cyclase; PDE5, cGMP-dependent phosphodiesterase (type 5)

https://www.cvpharmacology.com/vasodilator/PDEI

Sildenafil je účinný v léčbě plicní hypertenze u dospělých

The NEW ENGLAND JOURNAL of MEDICINE

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Article Figures/Media

November 17, 2005
N Engl J Med 2005; 353:2148-2157
DOI: 10.1056/NEJMoa050010

40 References 1220 Citing Articles Letters

278 pac., sildenafil vs. placebo, signifikantní zlepšení 6-MWT, echo, WHO functional class, méně hospitalizací, bezpečný profil.

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Table 3. Incidence of Clinical Worsening and of the Most Frequent Adverse Events in the Placebo and Sildenafil Groups.*

Event	Placebo (N=70)	Sildenafil		
		20 mg (N=69)	40 mg (N=67)	80 mg (N=71)
	number (percent)			
Clinical worsening	7 (10)	3 (4)	2 (3)	5 (7)
Death	1 (1)	1 (1)	0	2 (3)
Hospitalization for pulmonary arterial hypertension	7 (10)	2 (3)	2 (3)	2 (3)
Initiation of prostacyclin	1 (1)	0	0	0
Initiation of bosentan	0	0	1 (1)	2 (3)
Adverse event†				
Headache	27 (39)	32 (46)	28 (42)	35 (49)
Flushing	3 (4)	7 (10)	6 (9)	11 (15)
Dyspepsia	5 (7)	9 (13)	6 (9)	9 (13)
Back pain	8 (11)	9 (13)	9 (13)	6 (8)
Diarrhea	4 (6)	6 (9)	8 (12)	7 (10)
Limb pain	4 (6)	5 (7)	10 (15)	6 (8)
Myalgia	3 (4)	5 (7)	4 (6)	10 (14)
Cough	4 (6)	5 (7)	3 (4)	6 (8)
Epistaxis	1 (1)	6 (9)	5 (7)	3 (4)
Pyrexia	2 (3)	4 (6)	2 (3)	7 (10)
Insomnia	1 (1)	5 (7)	4 (6)	3 (4)
Influenza	2 (3)	4 (6)	4 (6)	3 (4)
Visual disturbance	0	0	3 (4)	5 (7)
Gastritis	0	2 (3)	2 (3)	3 (4)

* The analysis included all patients who received study medication. Some patients had more than one event.
† Adverse events shown are those reported by 3 percent or more of patients and those reported more frequently with sildenafil than with placebo.

Sildenafil je účinný v léčbě plicní hypertenze i u dětí

rok	periodikum	název práce	pacienti	Dávka (mg/kg/d)	FU (m)
2014	Circulation	STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension.	220	0,7-6	36
2012	Circulation	A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension.	235	0,7-6	4

Sildenafil je účiný v léčbě plicní hypertenze i u dětí

rok	periodikum	název práce	pacienti	Dávka (mg/kg/d)	FU (m)
2009	Journal of Pediatrics	Effects of Long-term Sildenafil Treatment for Pulmonary Hypertension in Infants with Chronic Lung Disease	25	1,5-8	8
2007	Neonatology	Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension.	7	N/A	N/A
2005	Circulation	Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study.	14	1-4	12
2003	Circulation	Intravenous sildenafil is a potent pulmonary vasodilator in children with congenital heart disease.	12	1	N/A

Circulation. 2014 May 13;129(19):1914-23. doi: 10.1161/CIRCULATIONAHA.113.005698. Epub 2014 Mar 17.

STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension.

Barst RJ[1], Beghetti M, Pulido T, Layton G, Konourina I, Zhang M, Ivy DD; STARTS-2 Investigators.

rok	periodikum	název práce	pacienti	Dávka (mg/kg/d)	FU (m)
2014	Circulation	STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension.	220	0,7-6	36

Higher mortality in high dose group
37 deaths – all worse baseline characteristics

Přechodný zákaz užívání sildenafilu u dětí byl přehodnocen

Drug Safety and Availability
Drug Alerts and Statements
Medication Guides
Drug Safety Communications
Drug Shortages
Postmarket Drug Safety Information for Patients and Providers
Information by Drug Class

FDA Drug Safety Communication: FDA clarifies Warning about Pediatric Use of Revatio (sildenafil) for Pulmonary Arterial Hypertension

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En español

This information is in follow-up to the **FDA Drug Safety Communication** issued on August 30, 2012.

[03-31-2014] The U.S. Food and Drug Administration (FDA) is clarifying its previous recommendation related to prescribing Revatio (sildenafil) for children with pulmonary arterial hypertension (PAH). Revatio is FDA-approved

Nežádoucí účinky pozorované u dětí nejsou závažné

Table 2. Most frequent adverse effects to Sildenafil treatment, as seen in the STARTS 1 study.

Number	Adverse Effect	Patients Who Developed Adverse Reactions (n = 234)	Percentage
1	Upper respiratory tract infection	53	22.64%
2	Vomiting	45	19.23%
3	Headache	44	18.80%
4	Bronchitis	37	15.81%
5	Pyrexia	36	15.38%
6	Pharyngitis	31	13.24%
7	Cough	30	12.82%
8	Diarrhoea	27	11.53%
9	Nasopharyngitis	25	10.68%

Barst et al., Circulation 2012

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PEDIATRICS

ORIGINAL RESEARCH ARTICLE
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Reported sildenafil side effects in pediatric pulmonary hypertension patients

Stephanie L. Siehr, Elisa K. McCarthy, Michelle T. Ogawa and Jeffrey A. Feinstein*

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Table 2 | Incidence of reported side effects.

Category	Side effect	Incidence %
Gastrointestinal	Diarrhea	40
	Dyspepsia	35
Vascular	Flushing	41
	Headache	38
	Epistaxis	25
Neurologic	Myalgia	30
	Hyperactivity	26
	Pyrexia	24
	Insomnia	24
	Abnormal vision	9

European Heart Journal (2016) **37**, 67–119
doi:10.1093/eurheartj/ehv317

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Sildenafil has shown efficacy

approved in Europe for children 1–17 years of age

high doses should not be used in children (no more than 3 mg/kg/d)

Sildenafil a plicní hypertenze u dětí

- Plicní hypertenzi u dětí lze efektivně terapeuticky ovlivnit

- Při užívání po dobu 3 let a při užití dávek do 3 mg/kg/d je sildenafil účinný a bezpečný

Circulation. 2014 May 13;129(19):1914-23. doi: 10.1161/CIRCULATIONAHA.113.005698. Epub 2014 Mar 17.

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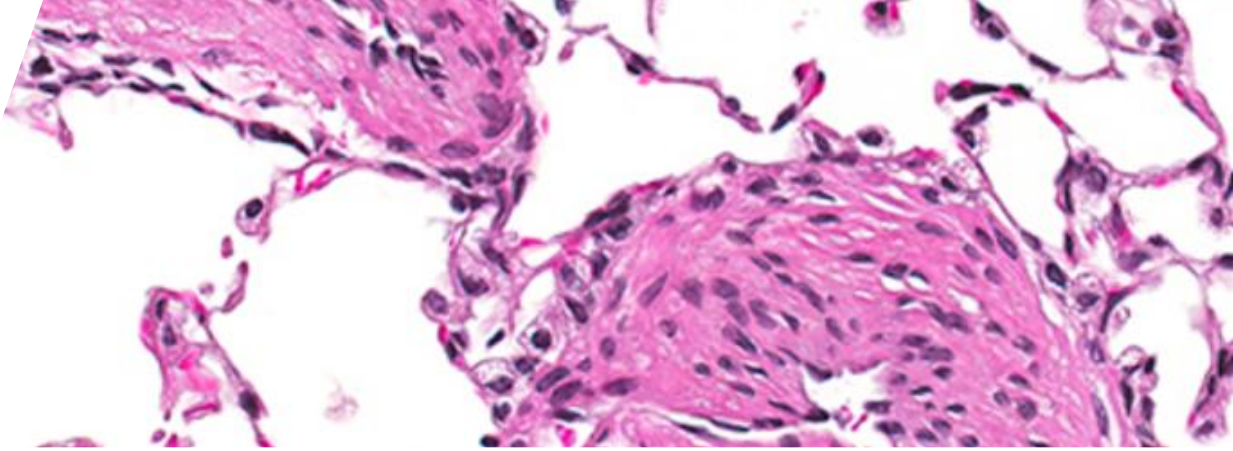

Děkuji za pozornost

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