Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
Α΄ Καρδιολογική Κλινική ΑΧΕΠΑ
Ιατρείο Πνευμονικής Υπέρτασης

Χρήστος Ν. Φελουκίδης

Ά Καρδιολογική Κλινική Α.Π.Θ.

3ο Πανελλήνιο Συνέδριο Πνευμονικής Υπέρτασης, Αθήνα, 7 Ιουνίου 2019

Conflicts of interest

- None

- Female
- DoB: 21 JAN 1976, 43yo

Background

- 2008
  - Thrombophilia (lupus anticoagulant)
  - Hypothyroidism
- 2010
  - Cutaneous lupus erythematosus
    - Put on hydroxychloroquine for 6m

Background

- 2015
  - Dyspnea in mild exertion
  - WHO FC II→III

  - Loud S2 (P2)
  - Normal breath sounds
  - BP: 135/75, 105 bpm, SATs: 98%

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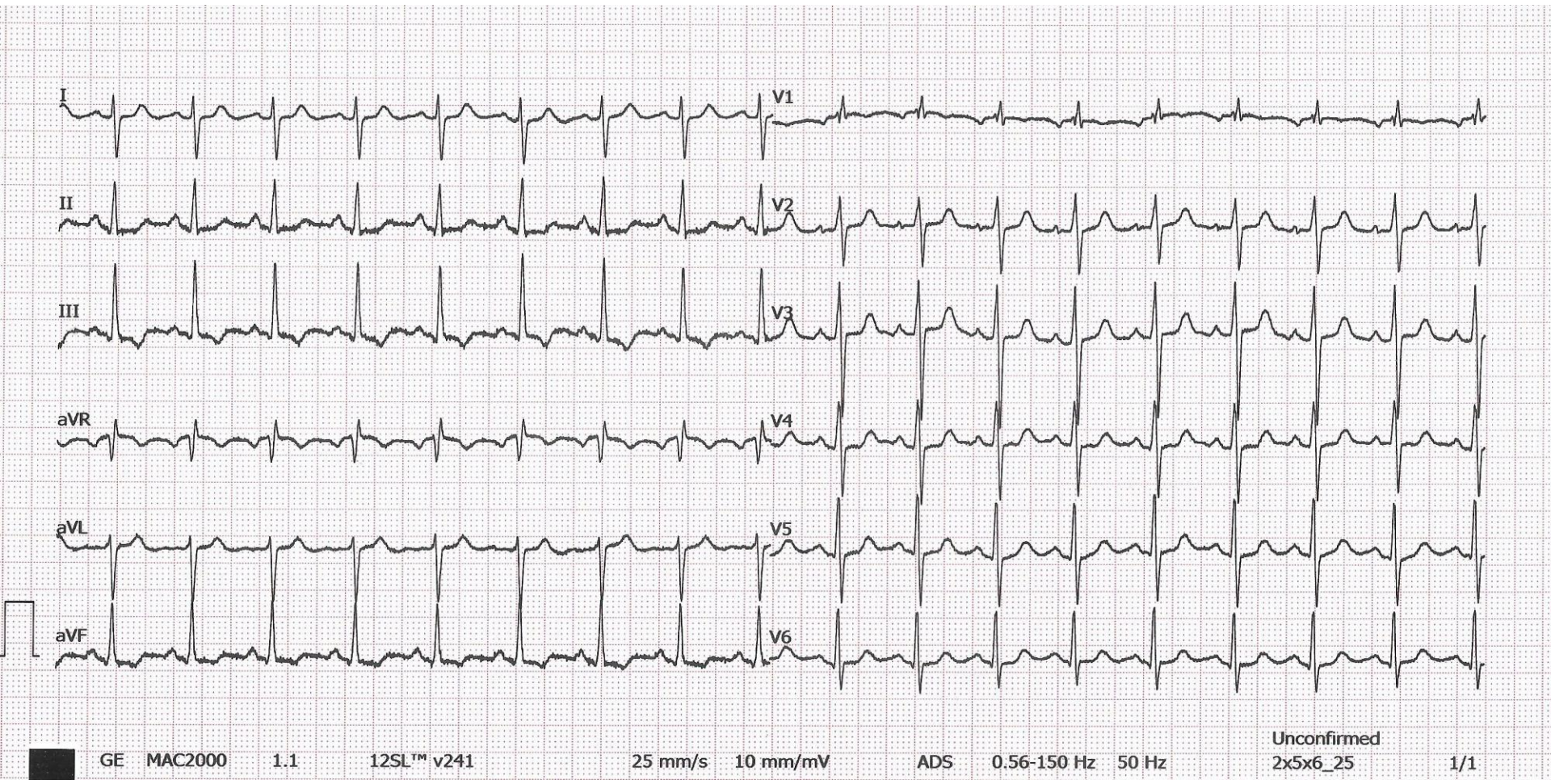
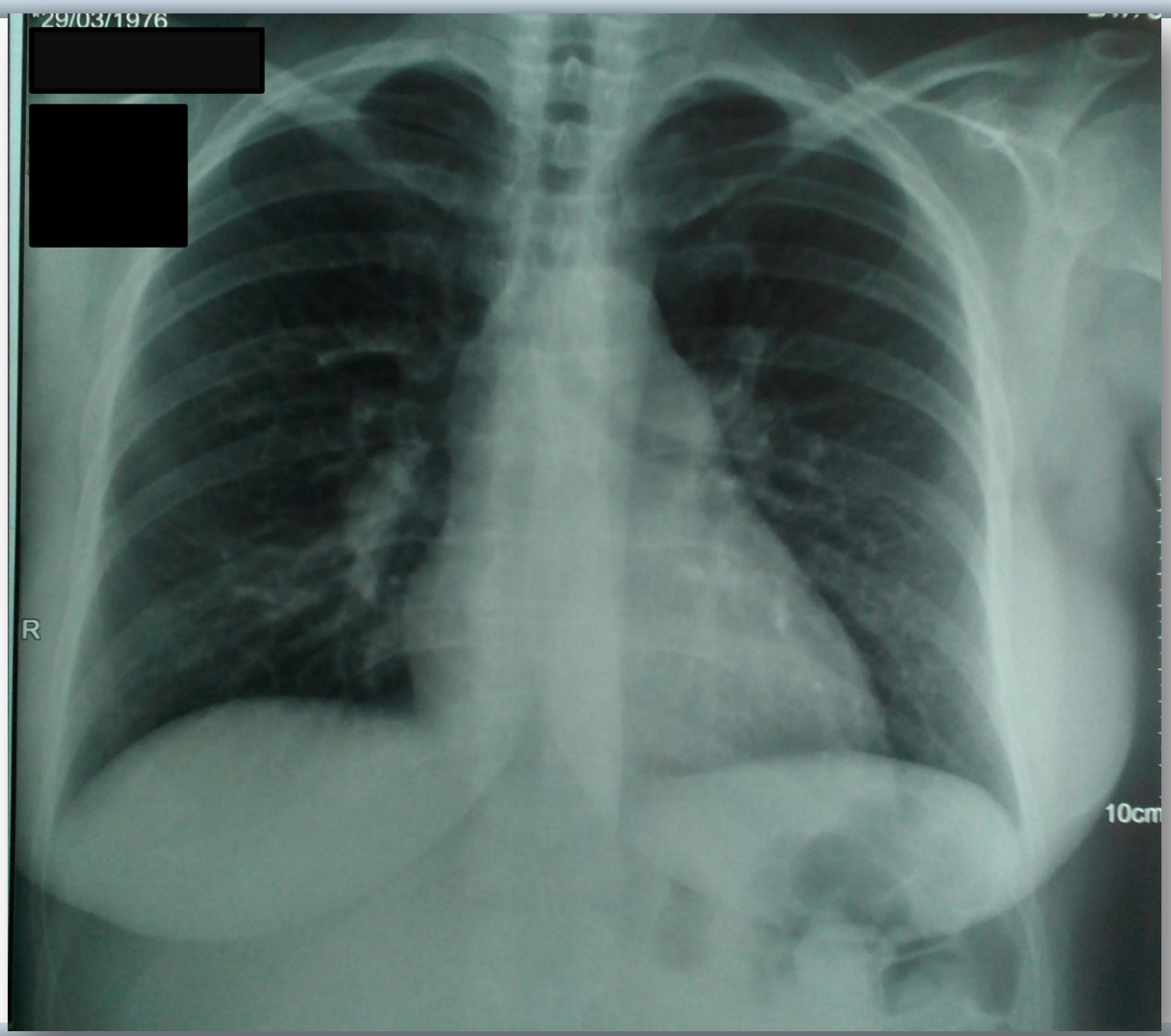


Chest x-ray



Blood tests

- Ht 46.9%, Hb 15.8mg/dl
- Fe= 30 μg/dl (NR 37-145μg/dl)
- ferritin= 118 ng/ml (NR 13-150ng/ml)

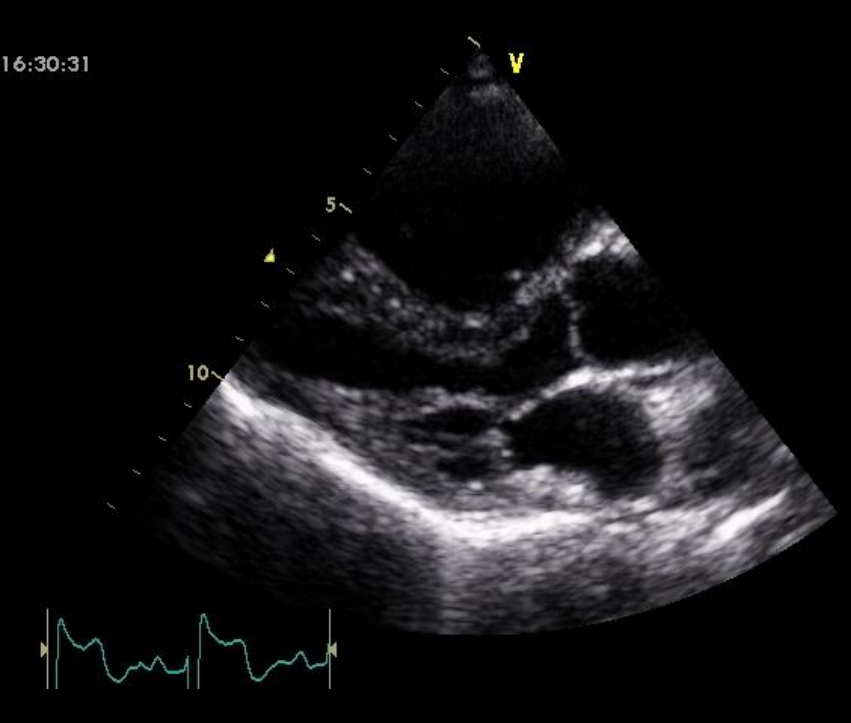
- SGOT= 43 U/lt, SGPT=37 U/lt, LDH= 236μU/lt
- Uric acid= 9.6 gr/dl
- TSH = 2.1 mU/L

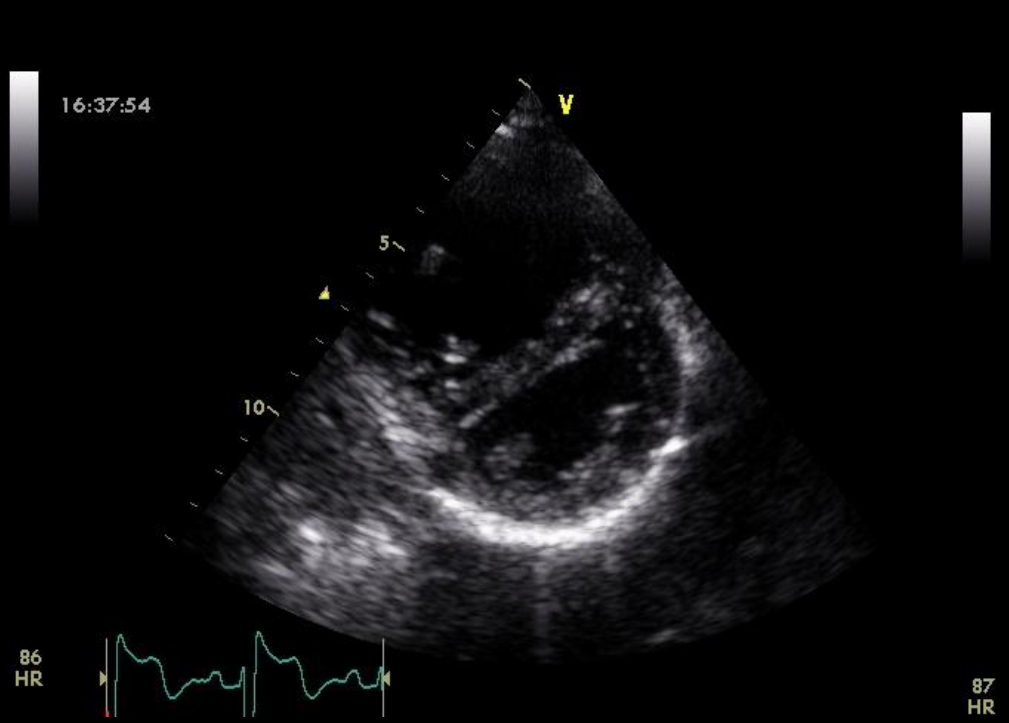
- **NTproBNP= 2263 pg/ml**

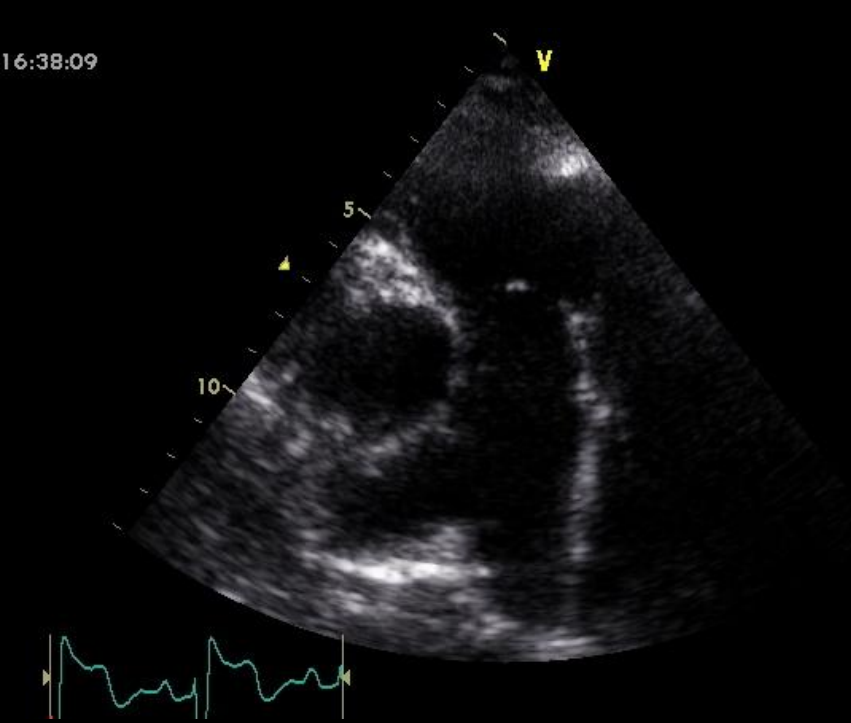
Blood tests

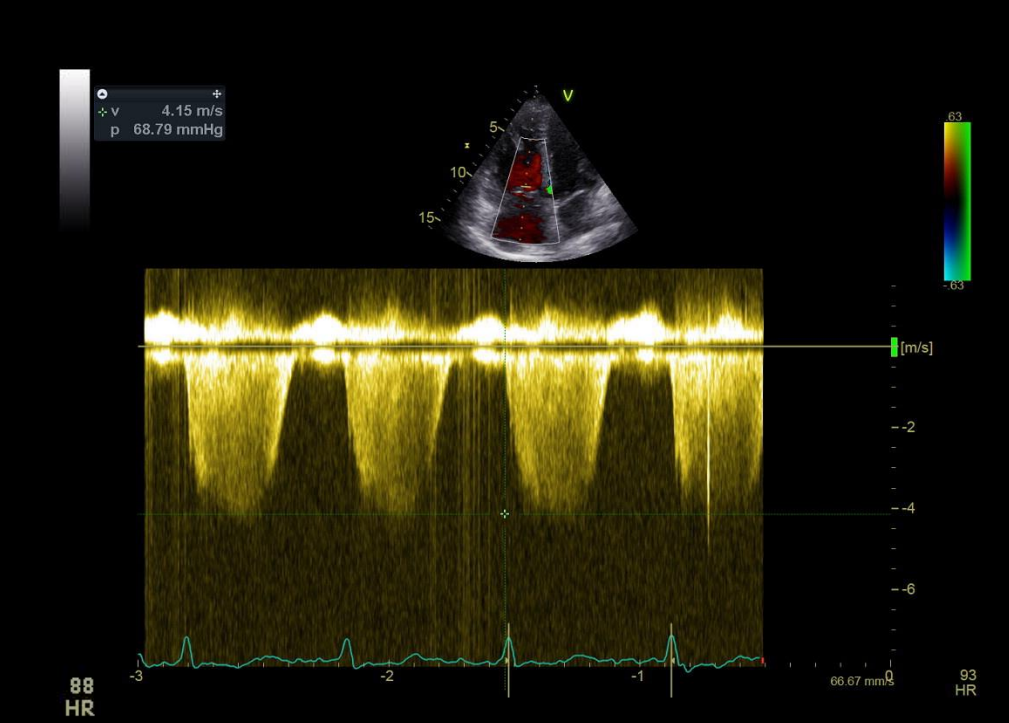
- Immunology tests:
  - ANA 1/640
  - IgG Anti-cardiolipin antibodies 25.5mplU/ml (+)
  - IgM Anti-cardiolipin antibodies 12.5mplU/ml (+)
  - anti-ENA screen>100U/ml (+)

	Pre	Post
SpO_2	98	93
HR	107	128
Dyspnoe	0	3
Fatigue	0	2
Total distance: 387m		

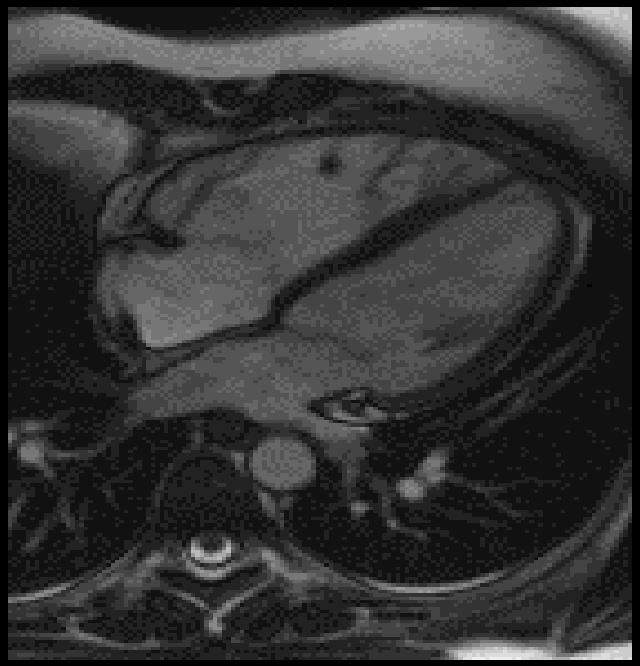

16:30:31
V
5
10

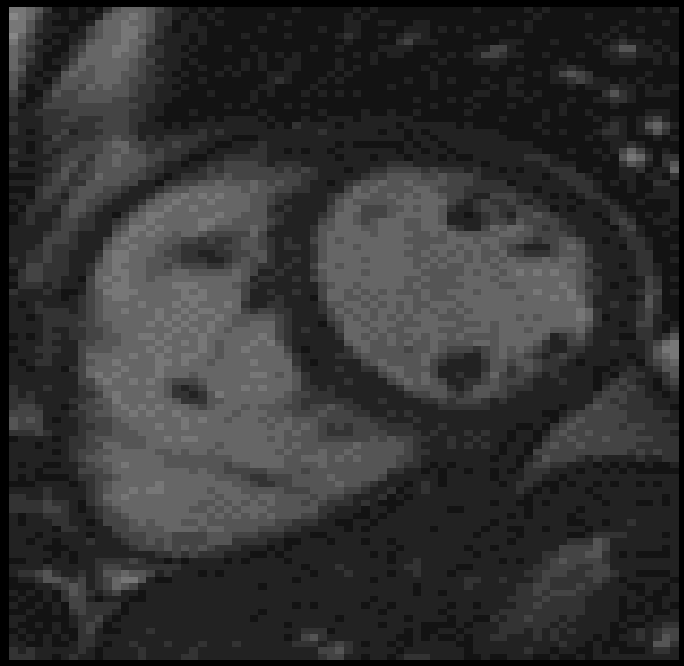

16:37:54
V
5
10
86
HR
87
HR


16:38:09
V
5
10


v 4.15 m/s
p 68.79 mmHg
V
5
10
15
63
-63
[m/s]
-2
-4
-6
-3
-2
-1
0
66.67 mm/s
88
HR
93
HR

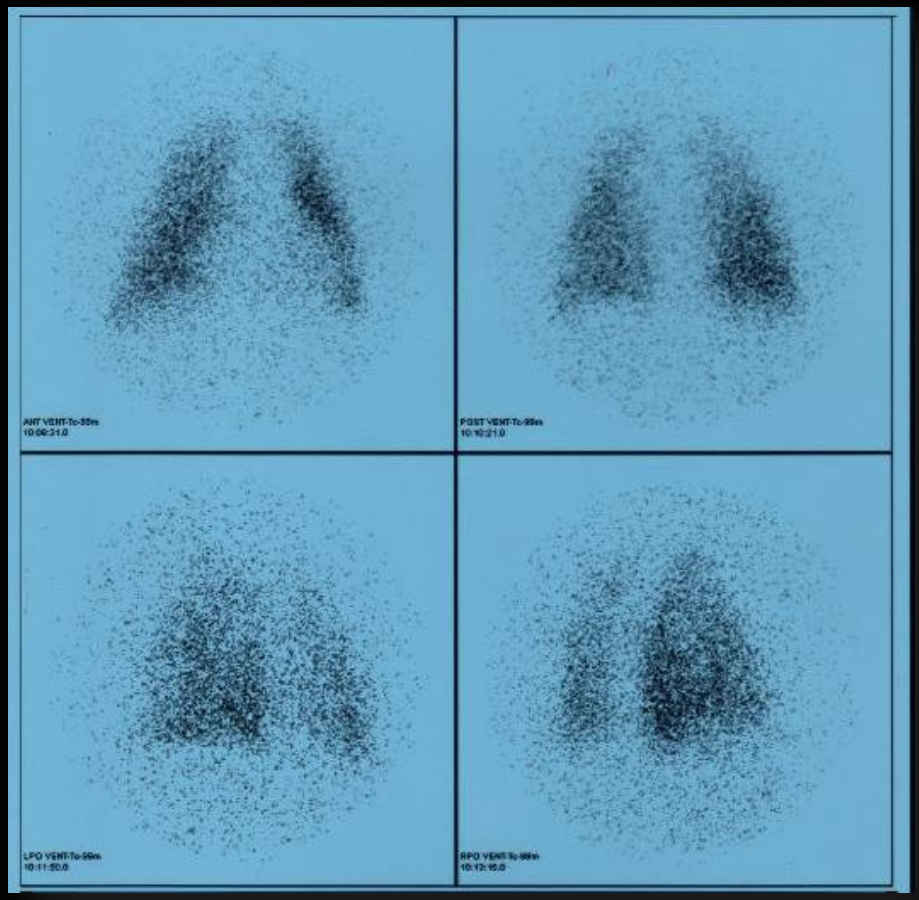
CMR

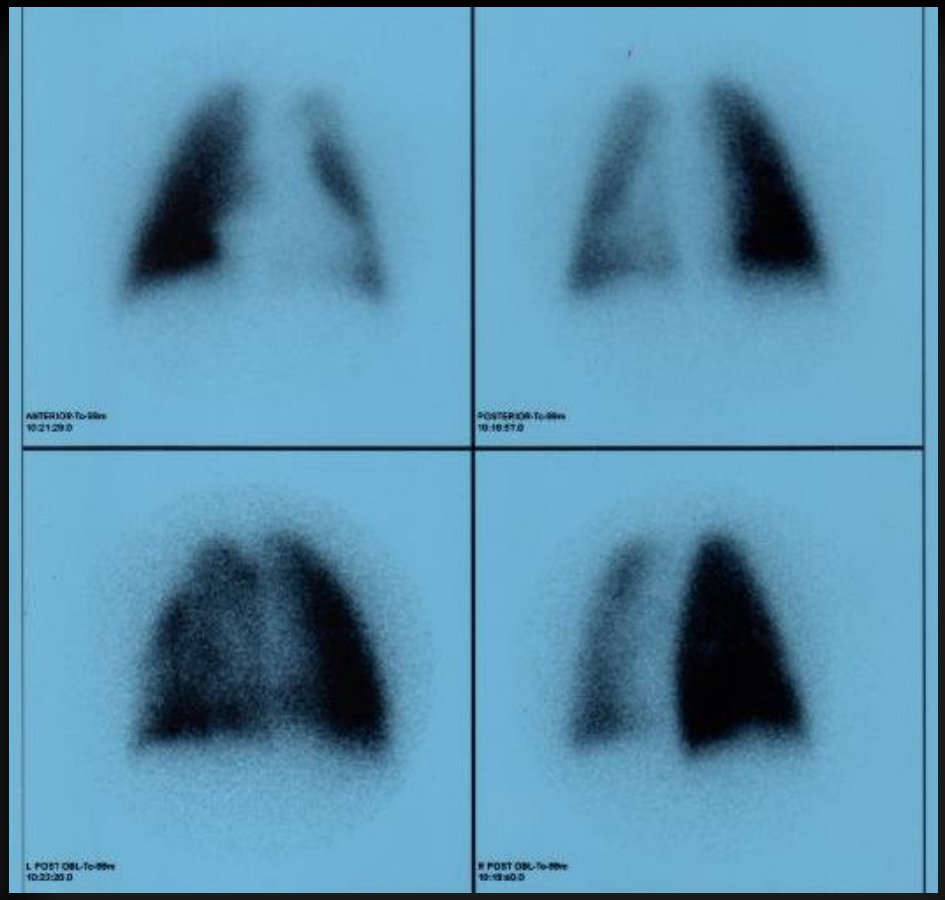




- **LFTs**
  - FEV1 (%pred) 93%
  - FVC (%pred) 100%
  - DLCO (%pred) 60%

V/Q scan





Blood tests

- Ht 46.9%, Hb 15.8mg/dl
- R 37-
- /ml Hp
- SGPT=37
- U/lt
- Uric acid= 9.6 gr/dl
- proBNP= 2263 pg/ml

Reumatologists' consultancy → **SEL**

- Immunology tests:
  - ABA 1/640
  - IgG καρδιολιπίνης 25.5mplU/ml (+)
  - IgM καρδιολιπίνης 12.5mplU/ml (+)
  - ENA scr >100U/ml (+)
- LFTs
  - FEV1 (%pred) 93%
  - FVC (%pred) 100%
  - DLCO (%pred) 60%

RHC

Hb: 15.8 g/dl, HR: 101/min BSA: 1.86m^2	Baseline	
	Pressure (mmHg)	SAT (%)
RA	9	
RV	101/3	
PA	103/37/m60	**70**
PAWP	10	
PVR (Wood)	6.9	
PVRi (Woodxm^2)	13	
CO (L/min)	7.2	
CI (L/min/m^2)	3.8	

Comprehensive clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension

1.1 Idiopathic

1.2 Heritable
- 1.2.1 BMPR2 mutation
- 1.2.2 Other mutations

1.3 Drugs and toxins induced

1.4 Associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 human immunodeficiency virus (HIV) infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease (Table 5)
- 1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1′.1 Idiopathic

1′.2 Heritable
- 1′.2.1 EIF2AK4 mutation
- 1′.2.2 Other mutations

1′.3 Drugs, toxins and radiation induced

1′.4 Associated with:
- 1′.4.1 Connective tissue disease
- 1′.4.2 HIV infection

1″. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction

2.2 Left ventricular diastolic dysfunction

2.3 Valvular disease

2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension

4.2 Other pulmonary artery obstructions
- 4.2.1 Angiosarcoma
- 4.2.2 Other intravascular tumors
- 4.2.3 Arteritis
- 4.2.4 Congenital pulmonary arteries stenoses
- 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy

5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Treatment

- Ambrisentan 10mg OD
- Tadalafil 40mg OD
- Hydroxychloroquine 200mg BiD (plaquenil)
- Methylprednisolone 16mg BiD (progressive tampering)
- Thyrohormone 0.1μg OD

Follow Up

	Baseline		6 months FU	
	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)
Hb (mg/dl)	15.8		11.2	
RA	9		5	
RV	101/3		74/2	
mPAP	103/37/m60	70	64/23/m**41**	84
PAWP	10		9	
PVR (Wood)	6.9		3.3	
PVRi (Wxm^2)	13		6.2	
CO (L/min)	7.2		11.3	
CI	3.8		6	
6MWD (m)	387		**612**	
NT-proBNP	2263		**75**	

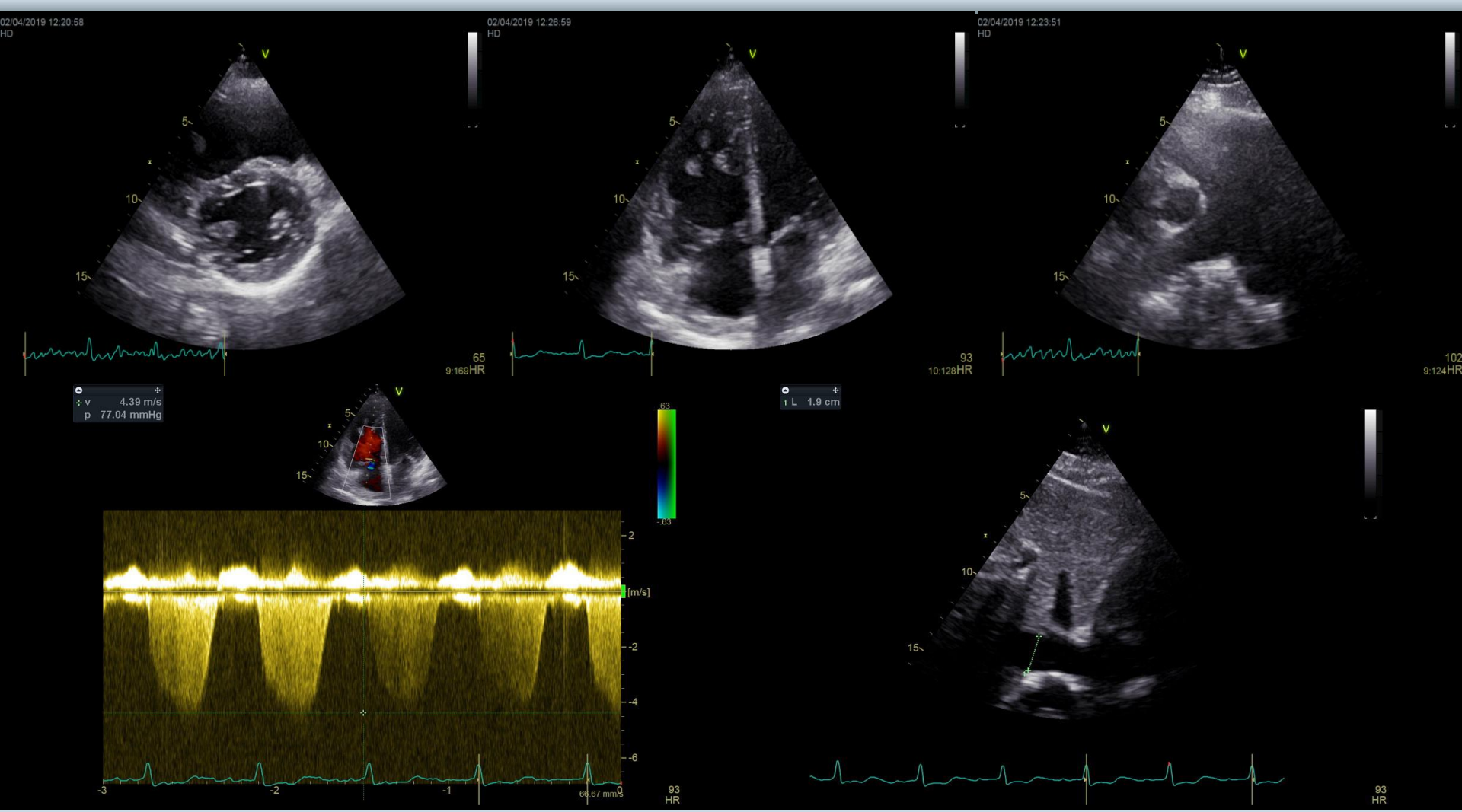
Follow Up

	Baseline		6 months FU		24 months FU	
	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)
Hb (mg/dl)	15.8		11.2		11.8	
RA	9		5		8	
RV	101/3		74/2		67/7	
mPAP	103/37/m60	70	64/23/m41	84	69/26/m46	82
PAWP	10		9		11	
PVR (Wood)	6.9		3.3		3.5	
PVRi (Wxm^2)	13		6.2		6.7	
CO (L/min)	7.2		11.3		9.3	
CI	3.8		6		4.89	
6MWD (m)	387		612		600	
NT-proBNP	2263		75		44	

04/2019

- Dyspnoe in mild exertion since 2m
- WHO FC III
- Hb 7.1mg/dl
  - menorrhagia
  - Received 3 RCC

ECHO – 04/19


02/04/2019 12:20:58
HD
02/04/2019 12:26:59
HD
02/04/2019 12:23:51
HD
v 4.39 m/s
p 77.04 mmHg
L 1.9 cm
[m/s]
65
9:169HR
93
10:128HR
102
9:124HR
93
HR
93
HR

4/2018 **RHC**

	48 months FU (04/19)	
	Pressure (mmHg)	SAT (%)
Hb (mg/dl)	10.5	
RA	10	
RV	79/0	
mPAP	75/37/m53	85
PAWP	8	
PVR (Wood)	3.2	
PVRi (Wxm^2)	6.2	
CO (L/min)	13.8	
CI	7	
6MWD (m)	600	
NT-proBNP	83	

5/2018 **RHC**

	48 months FU (04/19)	
	Pressure (mmHg)	SAT (%)
Hb (mg/dl)	10.5	
RA	10	
RV	79/0	
mPAP	75/37/m53	85
PAWP	8	
PVR (Wood)	3.2	
PVRi (Wxm^2)	6.2	
CO (L/min)	13.8	
CI	7	
6MWD (m)	600	
NT-proBNP	83	

5/2018 **RHC**

	48 months FU (04/19)	
	Pressure (mmHg)	SAT (%)
Hb (mg/dl)	10.5	
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PAWP	8	
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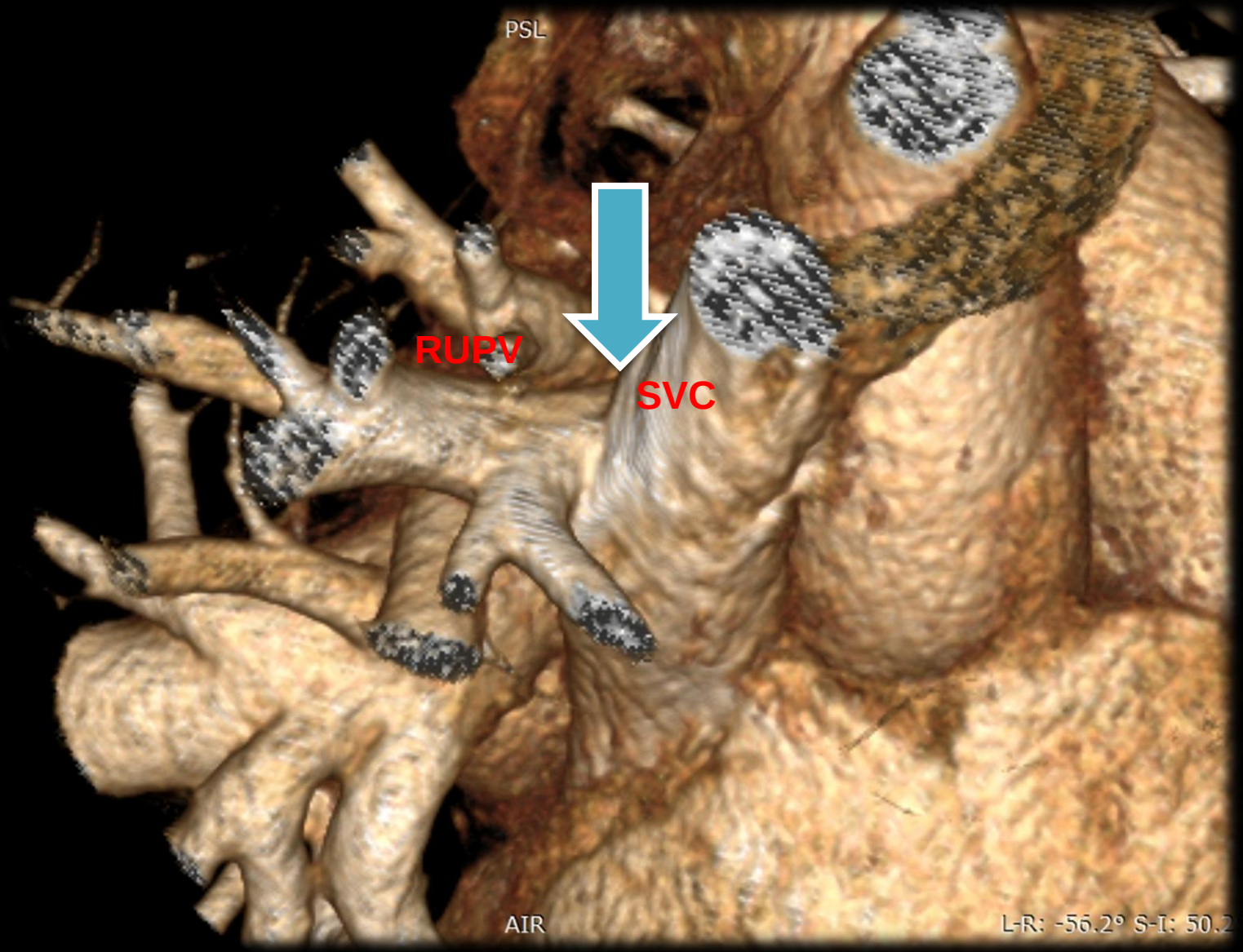
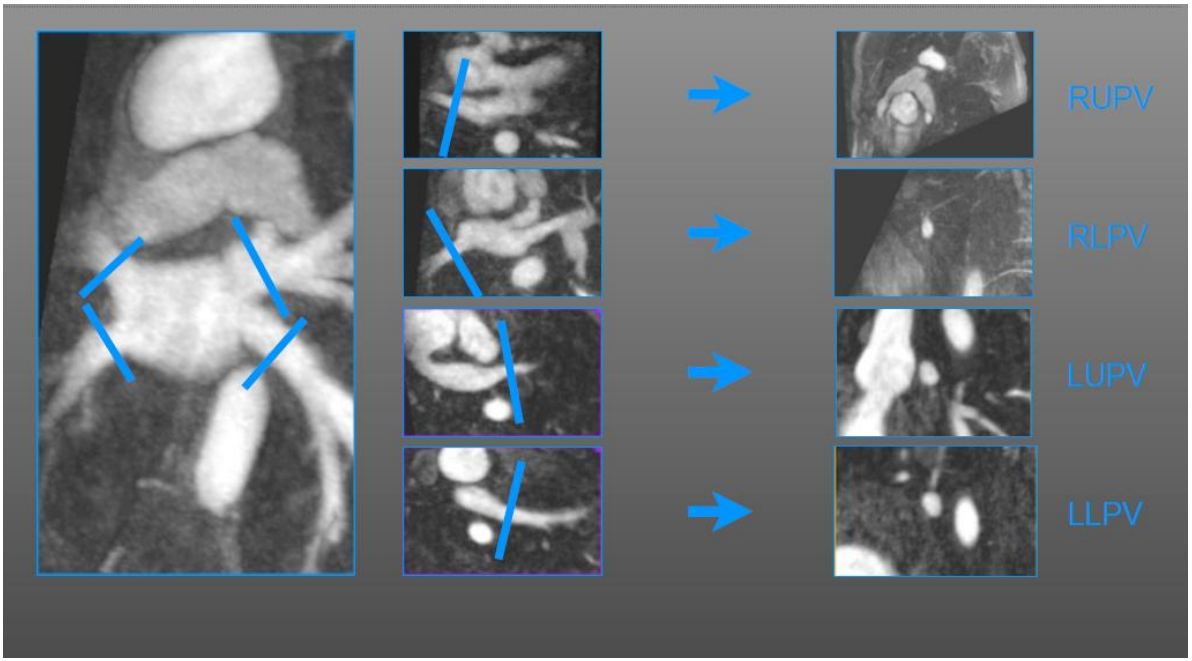
PVRi (Wxm^2)	6.2	
CO (L/min)	13.8	
CI	7	
6MWD (m)	600	
NT-proBNP	83	

RHCs

	Baseline		6 months FU		24 months FU		48 months FU (05/19)	
	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)
Hb (mg/dl)	15.8		11.2		11.8		10.5	
RA	9		5		8		10	
RV	101/3		74/2		67/7		79/0	
mPAP	103/37/m60	70	64/23/m41	84	69/26/m46	82	75/37/m53	85
PAWP	10		9		11		8	
PVR (Wood)	6.9		3.3		3.5		3.2	
PVRi (Wxm^2)	13		6.2		6.7		6.2	
CO (L/min)	7.2		11.3		9.3		13.8	
CI	3.8		6		4.89		7	
6MWD (m)	387		612		600		600	
NT-proBNP	2263		75		44		83	


PSL
RUPV
SVC
AIR
L-R: -56.2° S-I: 50.2



RUPV

↓

SVC

↓

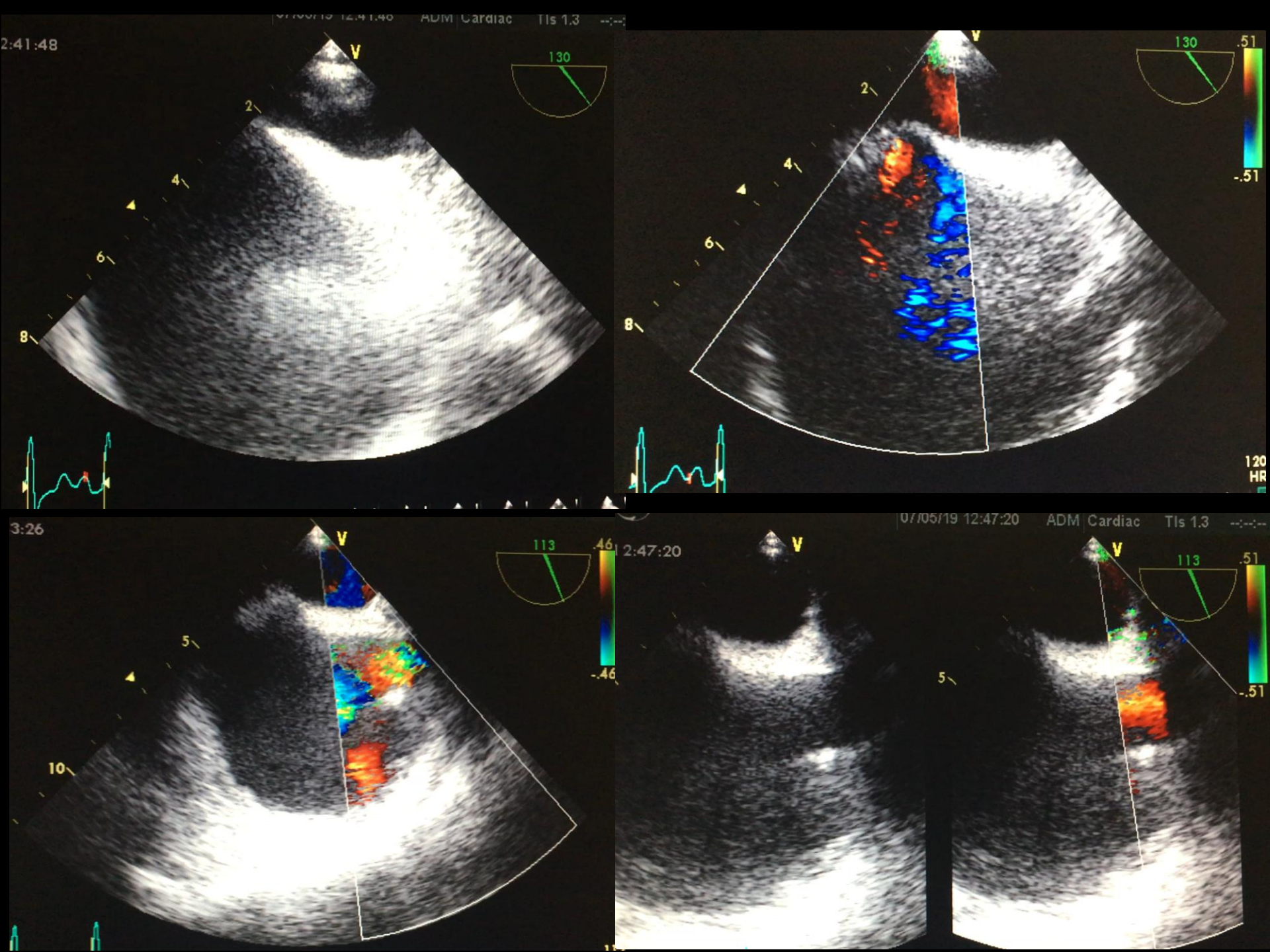
RA

↓

L->R shunt

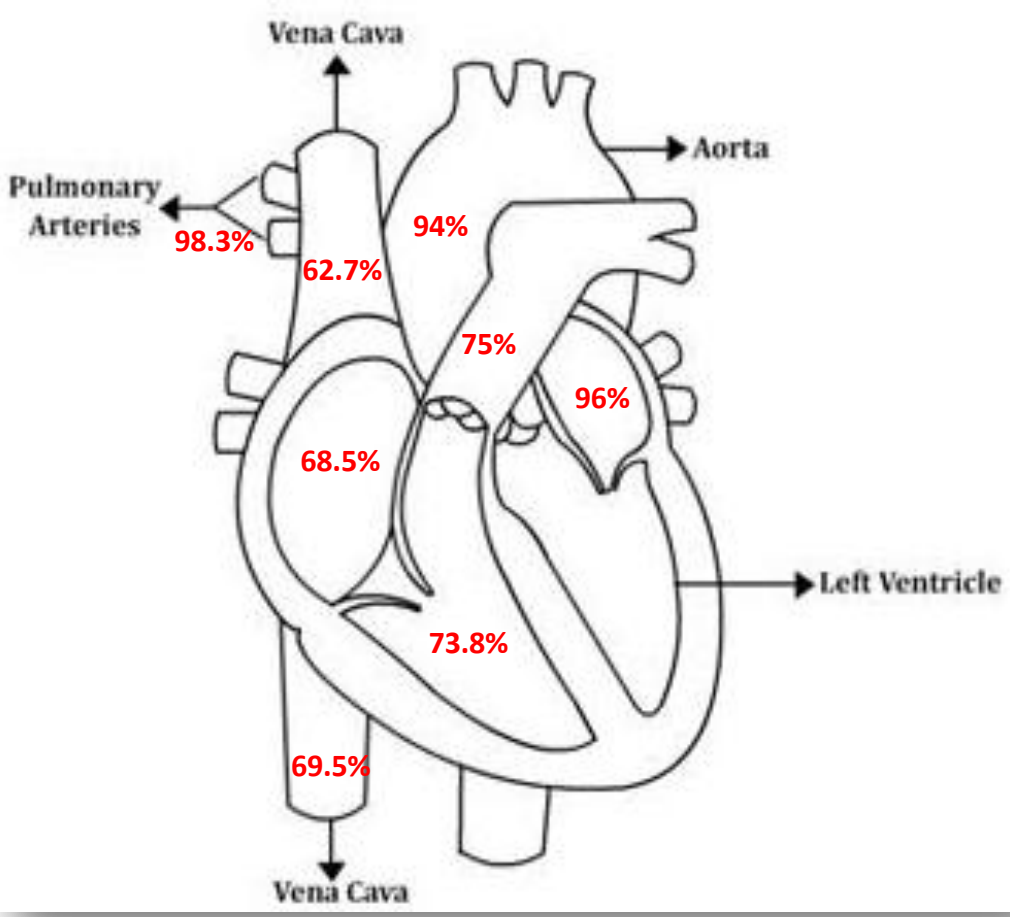
RHCs

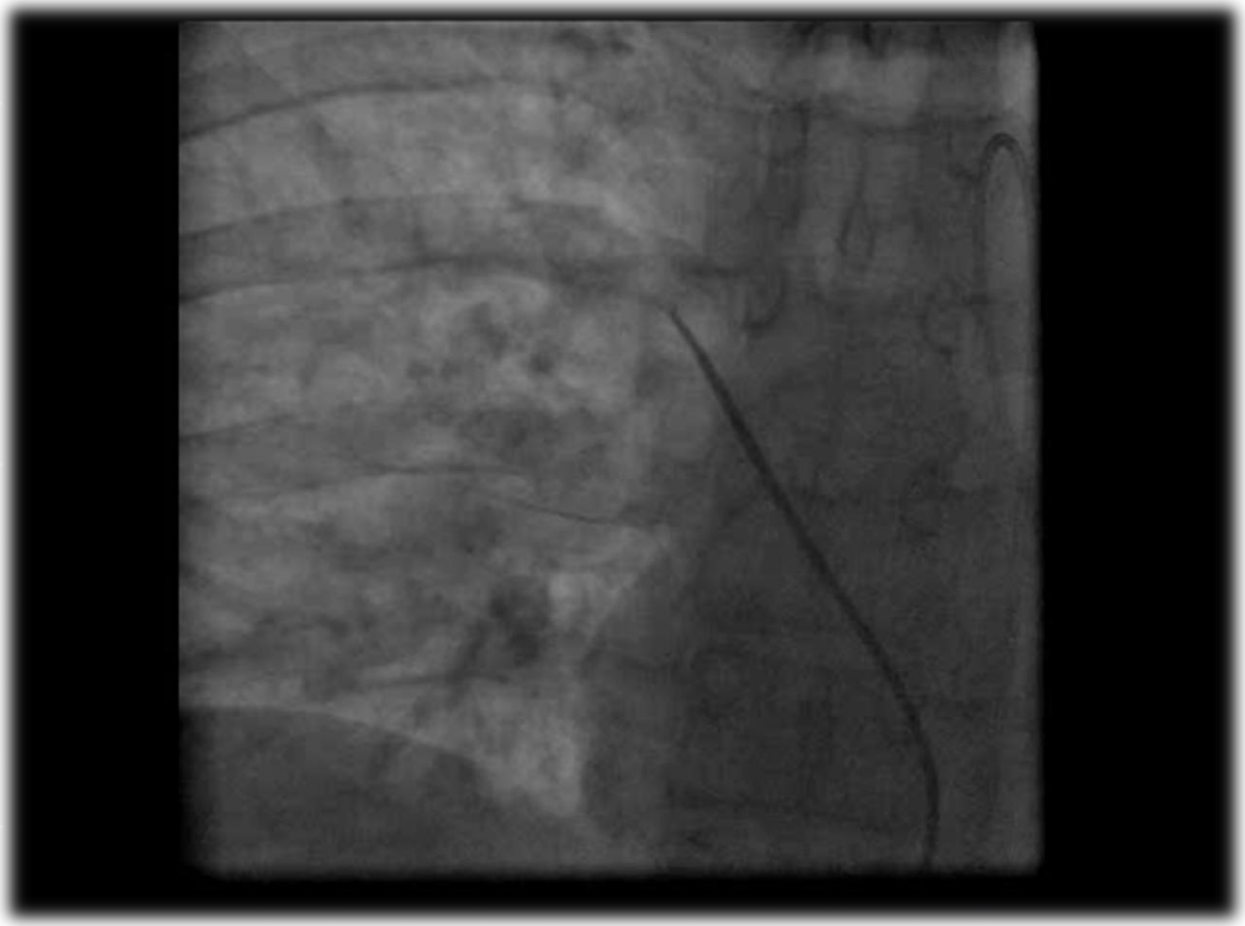
	Baseline		6 months FU		24 months FU		48 months FU (05/19)	
	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)	Pressure (mmHg)	SAT (%)
Hb (mg/dl)	15.8		11.2		11.8		10.5	
RA	9		5		8		10	
RV	101/3		74/2		67/7		79/0	
mPAP	103/37/m60	70	64/23/m41	84	69/26/m46	82	75/37/m53	85
PAWP	10		9		11		8	
PVR (Wood)	6.9		3.3		3.5		3.2	
PVRi (Wxm^2)	13		6.2		6.7		6.2	
CO (L/min)	7.2		11.3		9.3		13.8	
CI	3.8		6		4.89		7	
6MWD (m)	387		612		600		600	
NT-proBNP	2263		75		44		83	


2:41:48
V
130
2
4
6
8
V
130
.51
-.51
2
4
6
8
120
HR
3:26
V
113
.46
-.46
5
10
2:47:20
V
07/05/19 12:47:20
ADM Cardiac
TIs 1.3
V
113
.51
-.51
5

RHC – indirect Fick – 04/2019

BSA: 1.94m^2	Hb: 9.6 g/dl, HR: 97/min	Pressures (mmHg)
RA		12
RV		100/19
PA		104/30/m58
LA		17
LV		127/17
Ao		125/87/m105
PVR (Wood)		5.1
PVRi (Woodxm^2)		9.9
SVRi / SVR		17.5/8.99
Qp (L/min) / CI p (L/min/m^2)		7.9/4.05
Qs (L/min) / CI s (L/min/m^2)		5.3/2.7
Qp/Qs		1.48
L→R shunt		2.88





So, who came first?

Comprehensive clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
  1.2.1 BMPR2 mutation
  1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
  1.4.1 Connective tissue disease
  1.4.2 human immunodeficiency virus (HIV) infection
  1.4.3 Portal hypertension
  1.4.4 Congenital heart disease (Table 5)
  1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1'.1 Idiopathic
1'.2 Heritable
  1'.2.1 EIF2AK4 mutation
  1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
  1'.4.1 Connective tissue disease
  1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
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3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
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3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
  4.2.1 Angiosarcoma
  4.2.2 Other intravascular tumors
  4.2.3 Arteritis
  4.2.4 Congenital pulmonary arteries stenoses
  4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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European Heart Journal 2016;37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1. Eisenmenger's syndrome

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.

2. PAH associated with prevalent systemic-to-pulmonary shunts

- Correctable[a]
- Non-correctable

Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3. PAH with small/coincidental[b] defects

Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.

4. PAH after defect correction

Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.

PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance.
[a]With surgery or intravascular percutaneous procedure.
[b]The size applies to adult patients. However, also in adults the simple diameter may be not sufficient for defining the haemodynamic relevance of the defect, and also the pressure gradient, the shunt size and direction, & the pulmonary to systemic flows ratio should be considered
(Web Table II on the web at; www.escardio.org/guidelines).

www.escardio.org

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Anatomical-pathophysiological

Classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

1. Type

1.1 Simple pre-tricuspid shunts

- 1.1.1 Atrial septal defect (ASD)
  - 1.1.1.1 Ostium secundum
  - 1.1.1.2 Sinus venous
  - 1.1.1.3 Ostium primum
- 1.1.2 Total or partial unobstructed anormalous pulmonary venous

1.2 Simple post-tricuspid shunts

- 1.2.1 Ventricular septal defect (VSD)
- 1.2.2 Patent ductus arteriosus

1.3 Combined shunts

Describe combination and define predominant defect

1.4 Complex congenital heart disease

- 1.4.1 Complete atrioventricular septal defect
- 1.4.2 Truncus arteriosus
- 1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
- 1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
- 1.4.5 Other

2. Dimension (specify for each defect if more than one congenital heart defect exists)

2.1 Haemodynamic (specify Qp/Qs)[a]

- 2.1.1 Restrictive (pressure gradient accross the defect)
- 2.1.2 Non-restrictive

2.2 Anatomic[b]

- 2.2.1 Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
- 2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)

3. Direction of shunt

3.1 Predominantly systemic-to-pulmonary

3.2 Predominantly pulmonary-to-systemic

3.3 Bidirectional

4. Associated cardiac and extracardiac abnormalities

5. Repair status

5.1 Unoperated

5.2 Palliated (specify type of operation/s, age at surgery)

5.3 Repaired (specify type of operation/s, age at surgery)

[a] Ratio of pulmonary (Qp) to systemic (Qs) blood flow.
[b] The size applies to adult patients.

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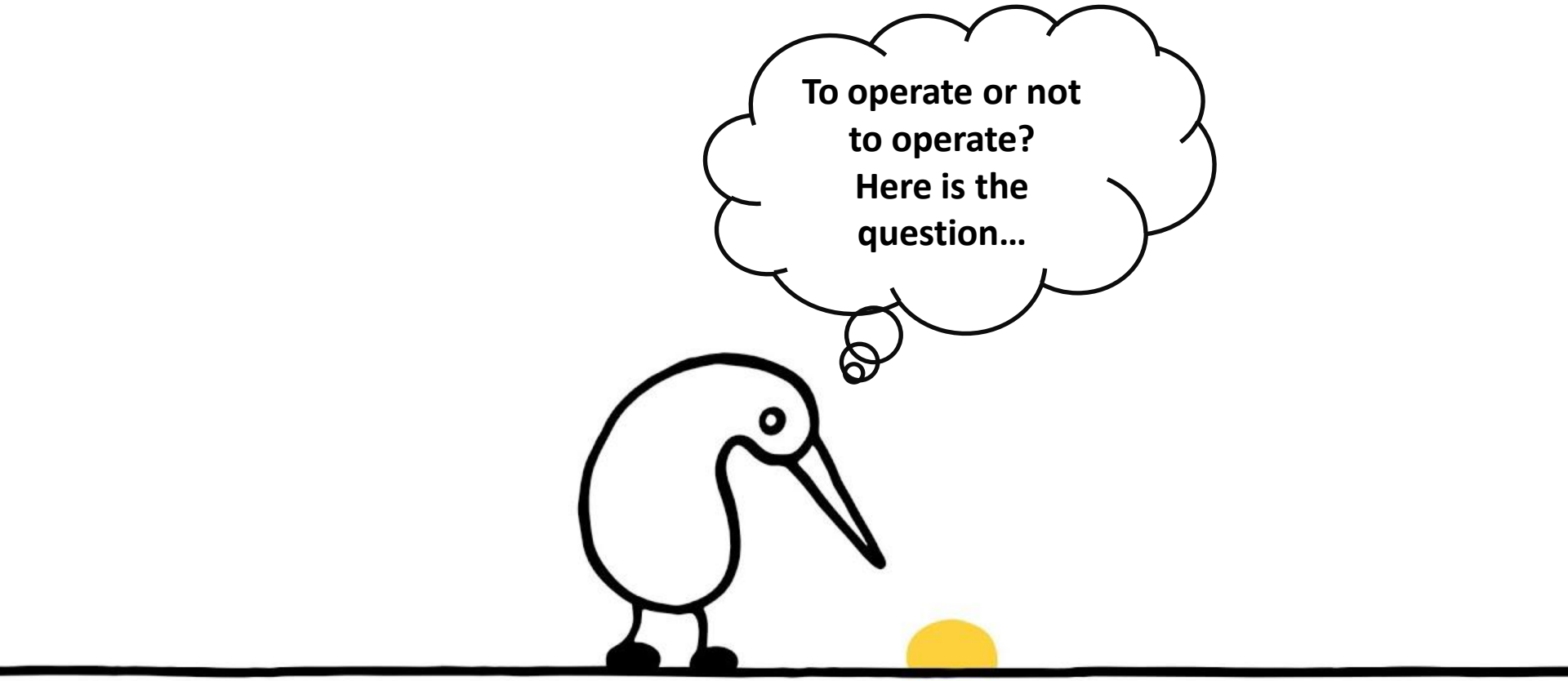
European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;


To operate or not
to operate?
Here is the
question…

Pulmonary arterial hypertension associated with adult congenital heart disease

Recommendations			Class	Level
PVRi (Wu · m²)	PVR (Wu)	Correctable[a]		
<4	<2.3	Yes	IIa	C
>8	>4.6	No	IIa	C
4-8	2.3-4.6	Individual patient evaluation in tertiairy centres	IIa	C

PVR = pulmonary vascular resistance.
PVRi = pulmonary vascular resistance inde.
WU = Wood units.
[a]With surgery or intravascular percutaneous procedure.

9.9	5.1

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European Respiratory Journal 2015 46: 903-975;

Indications for Intervention in Atrial Septal Defect

	Class[a]	Level[b]
• Patients with significant shunt (signs of RV volume overload) and PVR < 5 WU should undergo ASD closure regardless of symptoms.	I	B
• Device closure is the method of choice for secundum ASD closure when applicable.	I	C
• All ASDs regardless of size in patients with suspicion of paradoxical embolism (exclusion of other causes) should be considered for intervention.	IIa	C
• Patients with PVR ≥ 5 WU but < 2/3 SVR or PAP < 2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targered PAH therapy) and evidence of net L-R shunt (Qp:Qs > 1.5) may be considered for intervention.	IIb	C
• ASD closure must be avoided in patients with Eisenmenger physiology.	III	C

PVR 5.1 SVR 8.9
PAP 104 syst pres 125
Qp/Qs=1.48

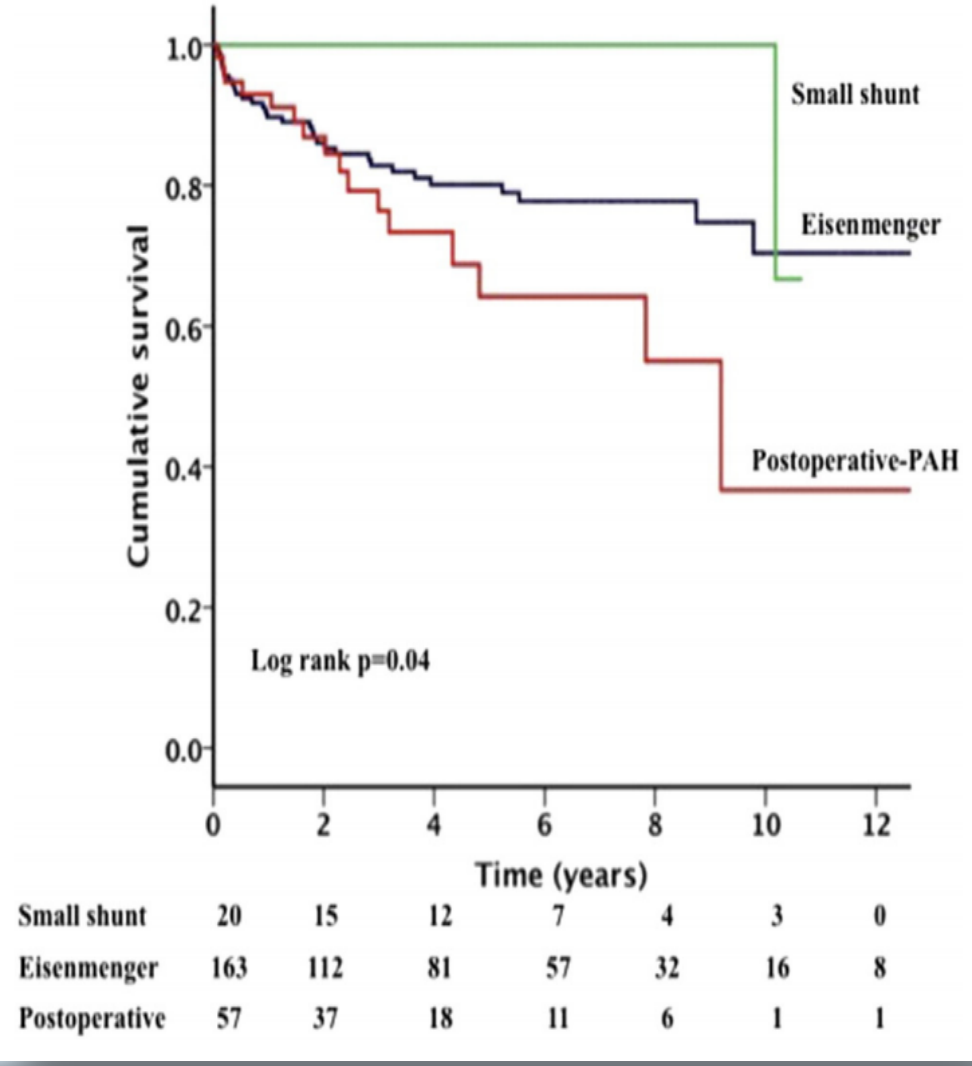
e.
shunt; PAH = pulmonary arterial hypertension;
ry vascular resistance; Qp:Qs = pulmonary to systemic flow ratio;
units.

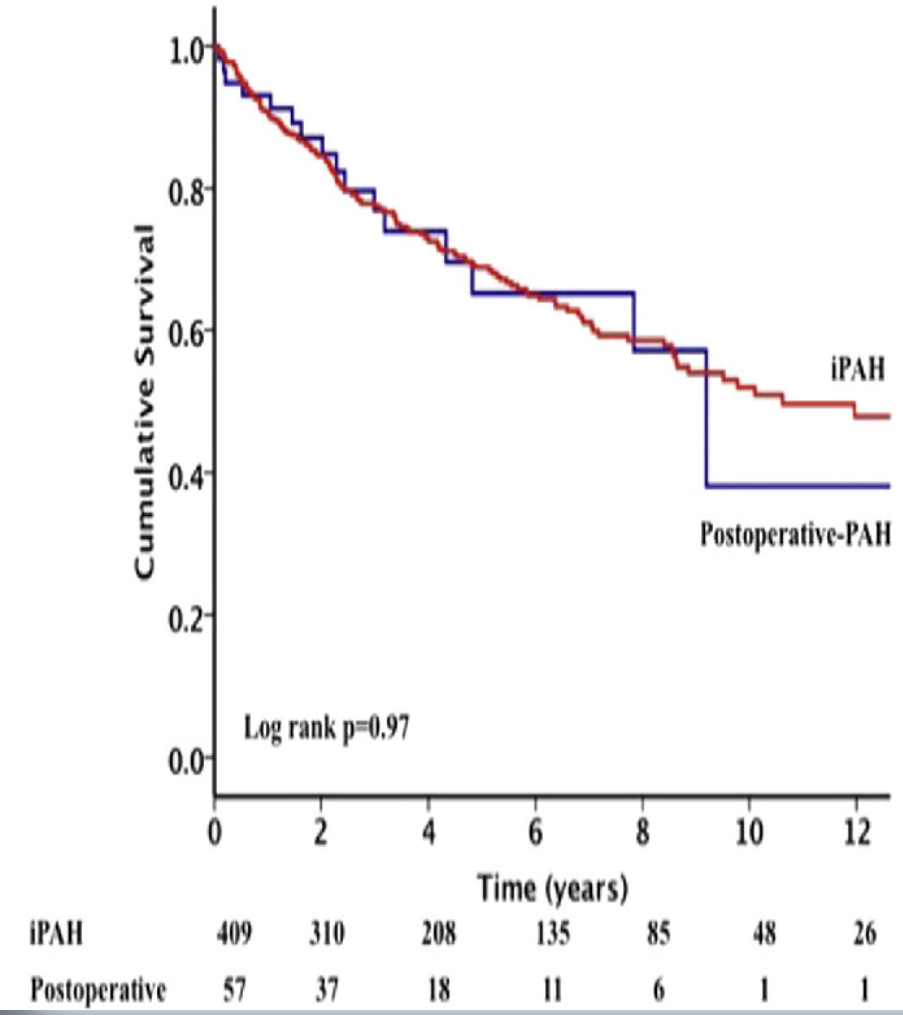
European Heart Journal 2010; doi:10.1093/eurhearj/ehq249

Anomalous Pulmonary Venous Connections

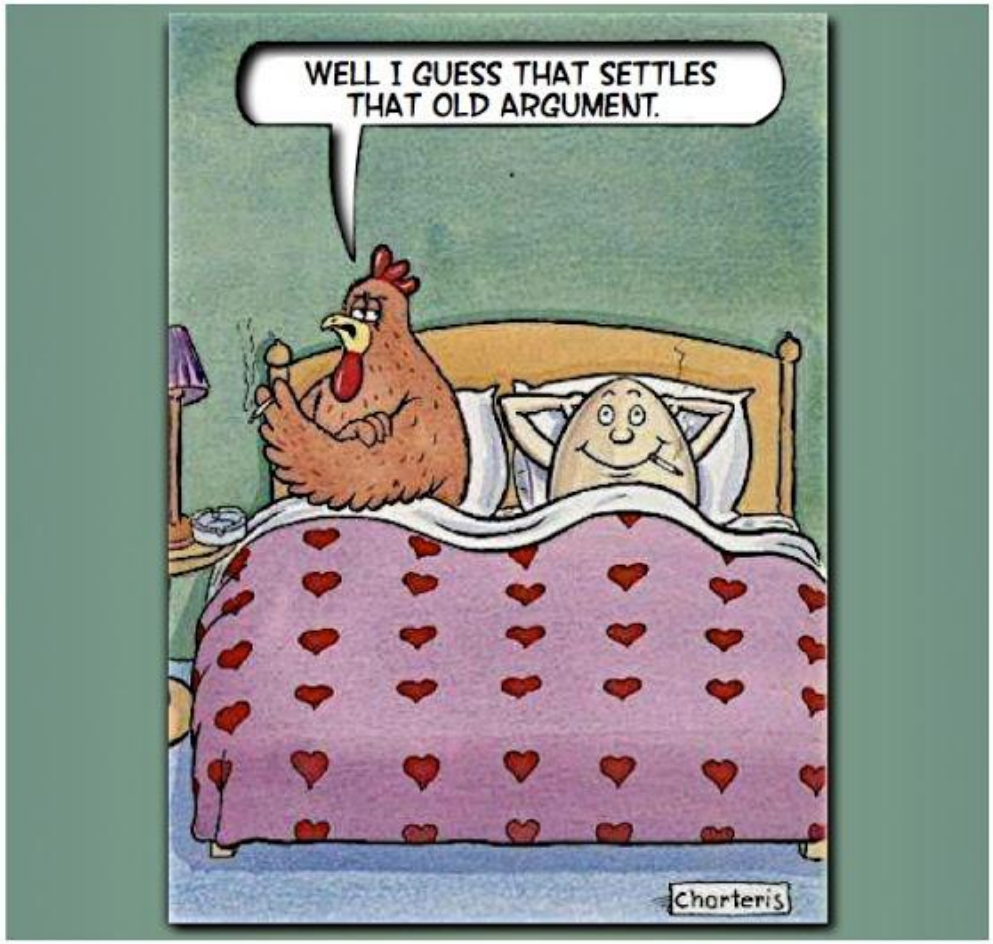
Therapeutic		
I	B-NR	Surgical repair is recommended for patients with partial anomalous pulmonary venous connection when functional capacity is impaired and RV enlargement is present, there is a net left-to-right shunt sufficiently large to cause physiological sequelae (e.g., Qp:Qs ≥1.5:1), PA systolic pressure is less than 50% systemic pressure and pulmonary vascular resistance is less than one third of systemic resistance.
I	B-NR	Repair of partial anomalous pulmonary venous connection is recommended at the time of closure of a sinus venosus defect or ASD.
I	B-NR	Repair of a scimitar vein is recommended in adults when functional capacity is impaired, evidence of RV volume overload is present, there is a net left-to-right shunt sufficiently large to cause physiological sequelae (e.g., Qp:Qs ≥1.5:1), PA systolic pressure is less than 50% systemic pressure and pulmonary vascular resistance is less than one third systemic.
IIa	B-NR	Surgery can be useful for right- or left-sided partial anomalous pulmonary venous connection in asymptomatic adults with RV volume overload, net left-to-right shunt sufficiently large to cause physiological sequelae (e.g., Qp:Qs ≥1.5:1), pulmonary pressures less than 50% systemic and pulmonary vascular resistance less than one third systemic.
IIa	B-NR	Surgery can be useful for repair of a scimitar vein in adults with evidence of RV volume overload, with Qp:Qs 1.5:1 or greater

PVR 5.1 SVR 8.9
PAP 104 syst pres 125
Qp/Qs=1.48

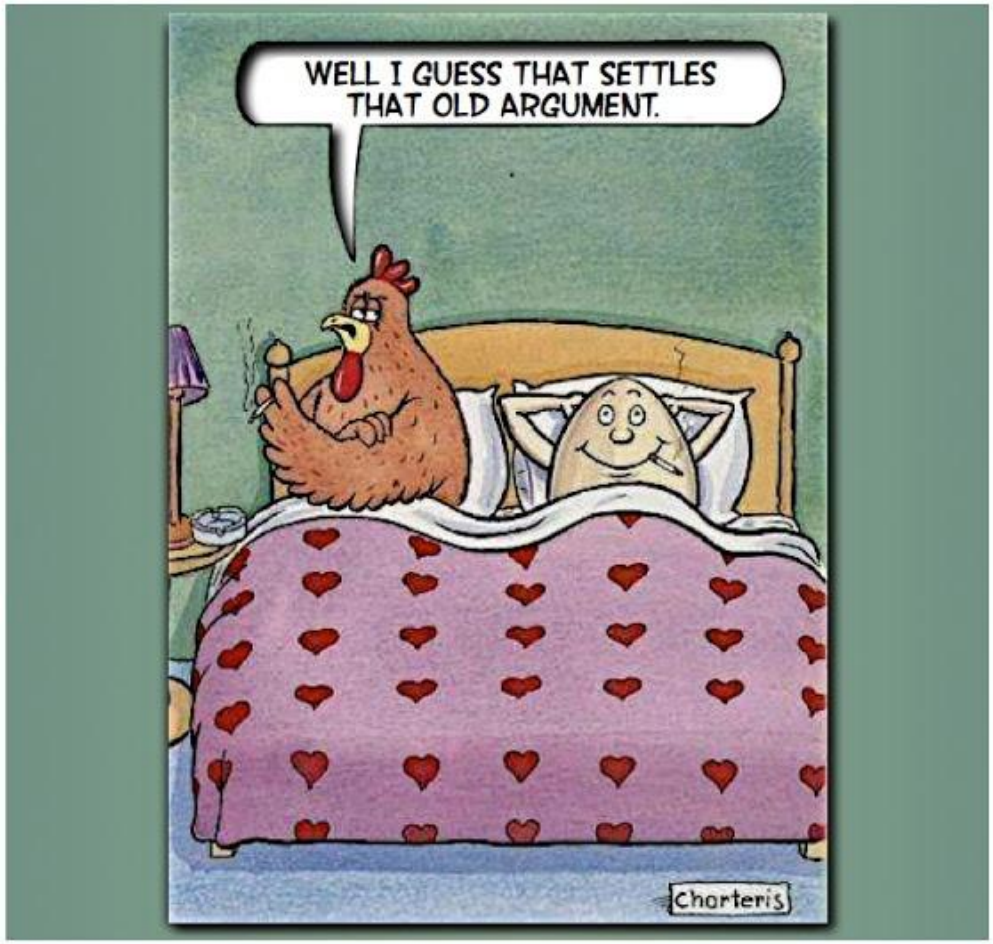

Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
Small shunt
Eisenmenger
Postoperative-PAH
Log rank p=0.04
0
2
4
6
8
10
12
Time (years)
Small shunt 20 15 12 7 4 3 0
Eisenmenger 163 112 81 57 32 16 8
Postoperative 57 37 18 11 6 1 1

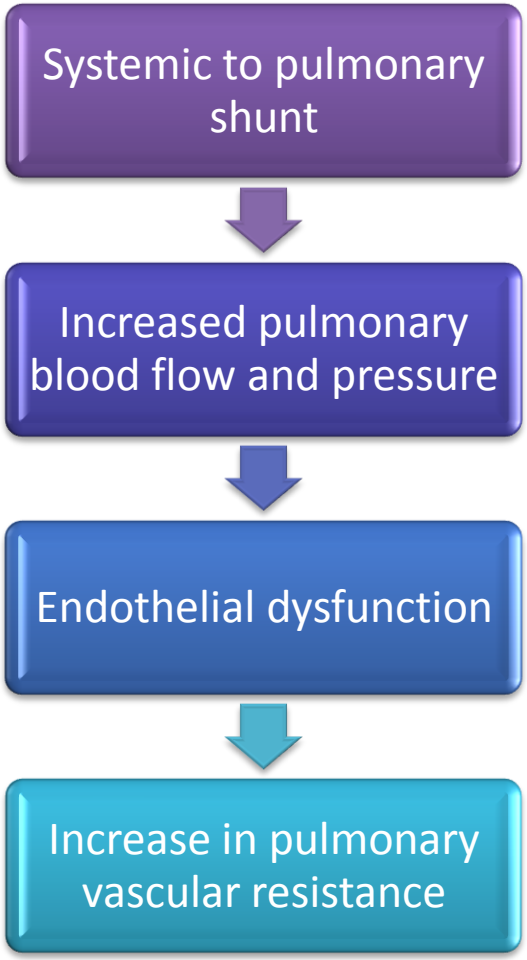

Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
iPAH
Postoperative-PAH
Log rank p=0.97
0
2
4
6
8
10
12
Time (years)
iPAH 409 310 208 135 85 48 26
Postoperative 57 37 18 11 6 1 1

Which came first?



Thank you for your attention!!!☺





Alonso-Gonzalez R et al, Int J Cardiol 2015
Galie N et al, Drugs 2008
Nashat H et al, J Thorac 2018

11/2017

Clinical worsening

WHO FC III

Ambrisentan 10

Tadalafil 20

Furosemide 20

Plaquenil

Azathioprine

Methylprednisolone

ASA 100

Levothyroxine

Hb 9.6
Fe 23 mcg/dl
Ferritin 15 ng/ml

NT-proBNP 83pg/ml

Ambrisentan 10

Tadalafil 20

Furosemide 20

Hydroxycloroquinine

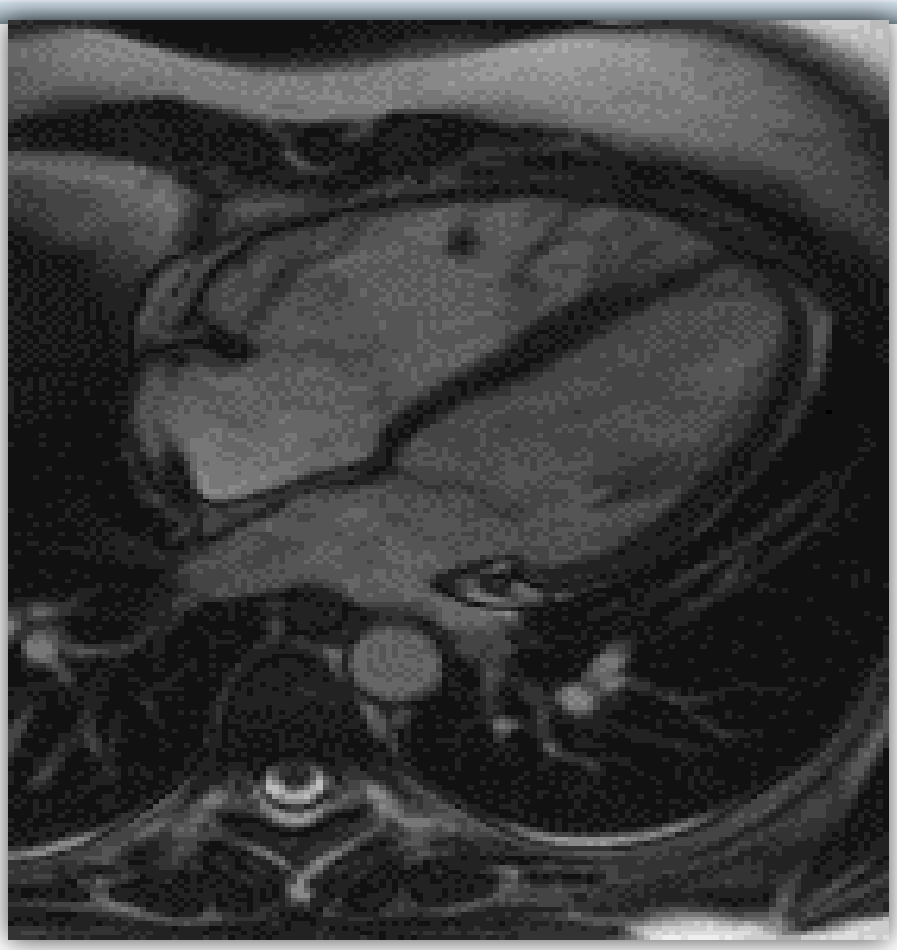
Azathioprine

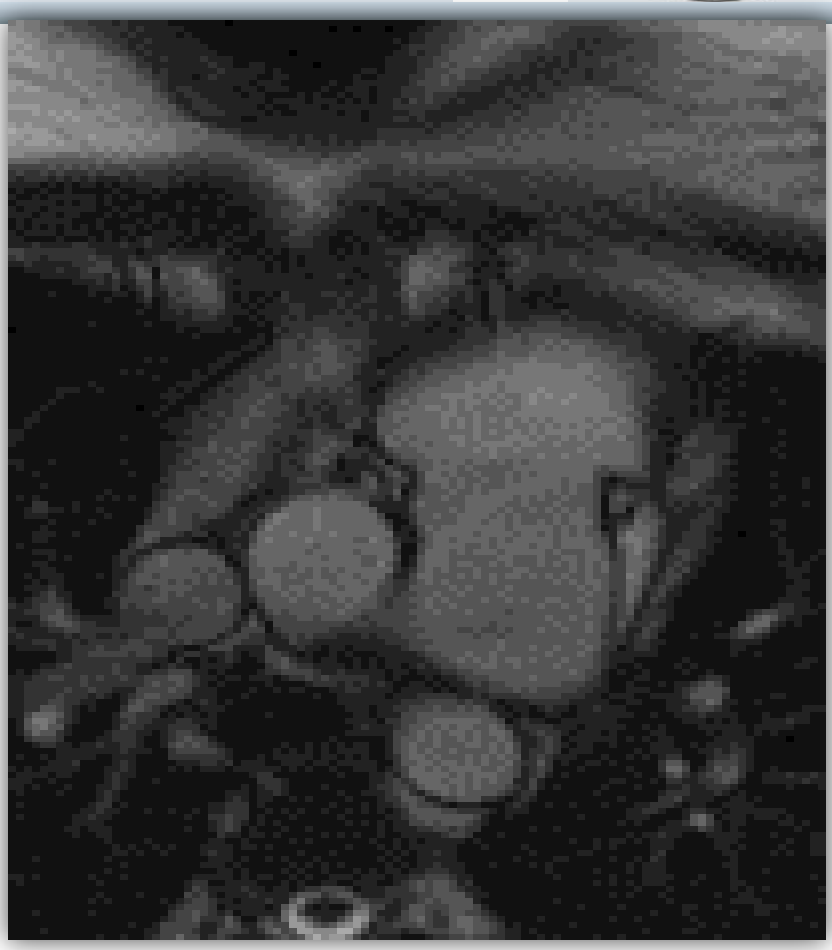
Methylprednisolone

ASA 100

Levothyroxine

Lets take a closer look…





And now, what?

THANK YOU FOR YOUR ATTENTION