PULMONARY HYPERTENSION PRESENTING WITH SCLERODERMA SINE SCLERODERMA IN A CHILD

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Case History

- A 4 year old girl, previously healthy.
- Family history:

  Parents – Yemenite origin, healthy

  3 cases of obstructive cardiomyopathy on the father's side.
- Presented with:

  Raynaud's phenomenon since January 2011

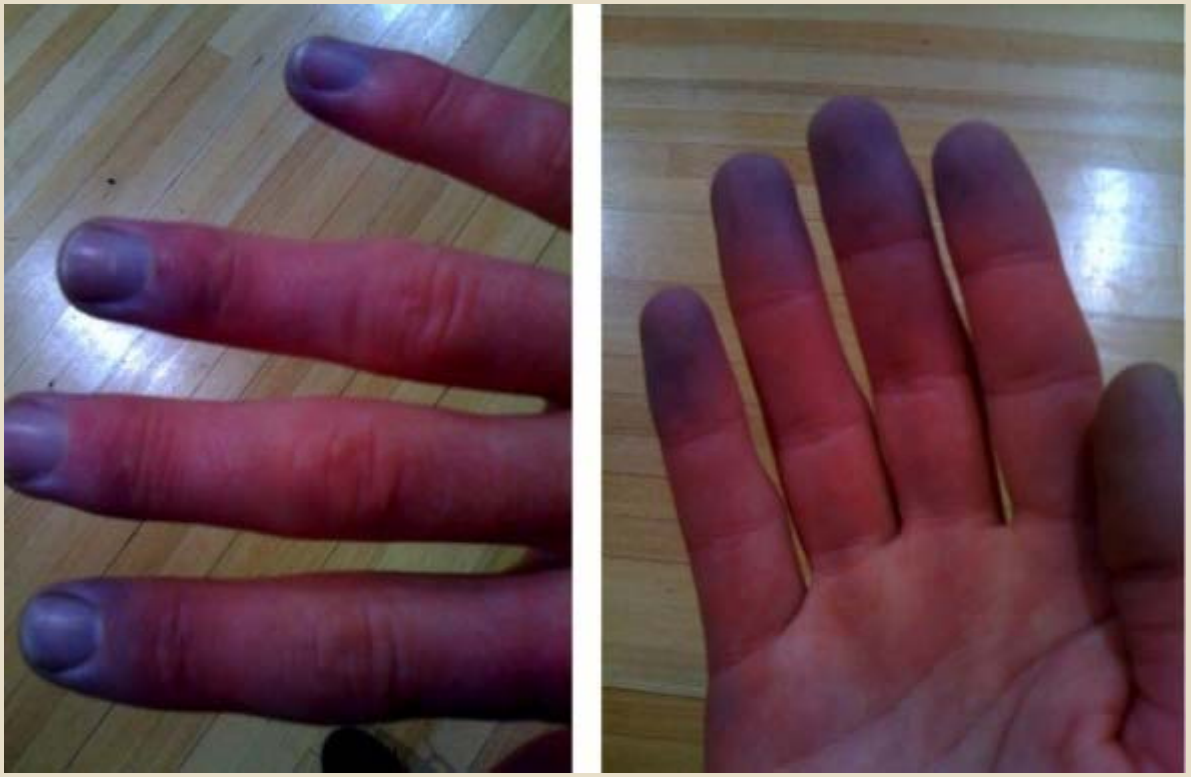
  Weight loss

  Exertional dyspnea

  No skin changes

  No dysphagia

Raynaud's phenomenon

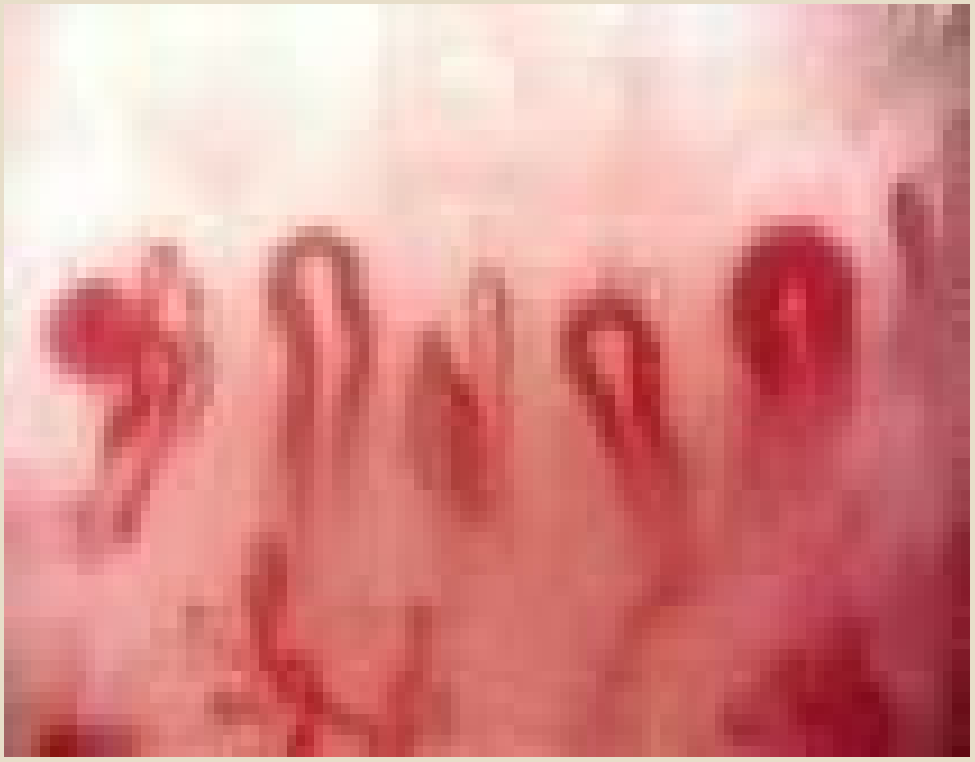


Physical examination

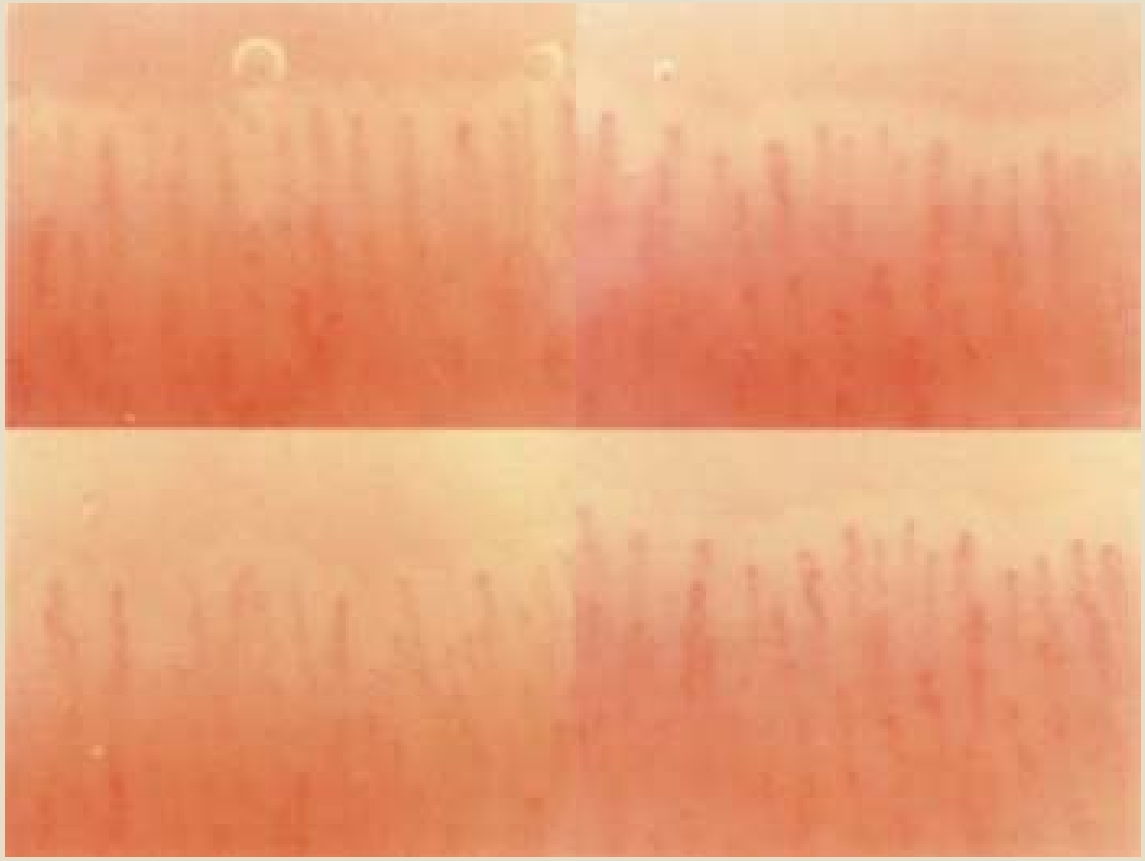
- Weight – 10th percentile; Height – 50th percentile
- No dyspnea; O2 saturation 100%
- Pulse rate 80/minute; BP – 110/70
- Skin – **digital infarcts of fingertips**; no additional skin changes: no tightness acrosclerosis.

Physical examination (cont)

- Heart and lungs normal.
- No hepatosplenomegaly.
- Joint examination – unremarkable.
- **Capillaroscopy** – **abnormal** capillary drop-out and tortuous dilated loops.



Normal Capillaroscopy



Laboratory results

- **ESR** – 10mm/h; **CRP** – 0.05mg/dl
- **CBC, muscle and liver enzymes** – WNL
- **ANA** >>1:160 – mixed pattern
- **Antitopoisomerase I** (anti-scl 70): 104 U/ml (0-15)
- Anti dsDNA; anti Ro, La, RNP, Sm, histone, centromere; RNA polymerase –

ALL NEGATIVE

Laboratory results (cont)

- Rheumatoid Factor – negative
- Antiphospholipid antibodies – negative
- Complement – normal
- Von Willebrand Factor – 181% (50-150)

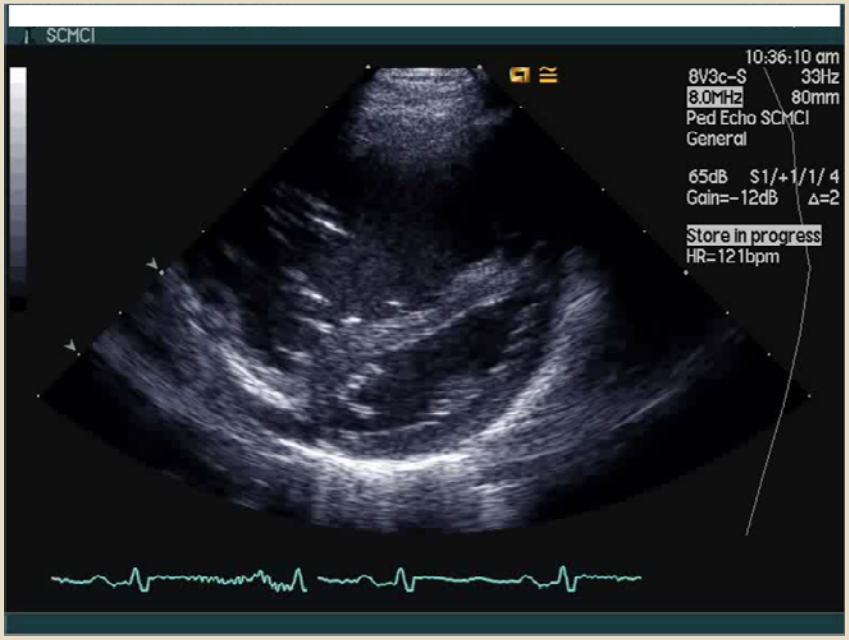
Electrocardiography

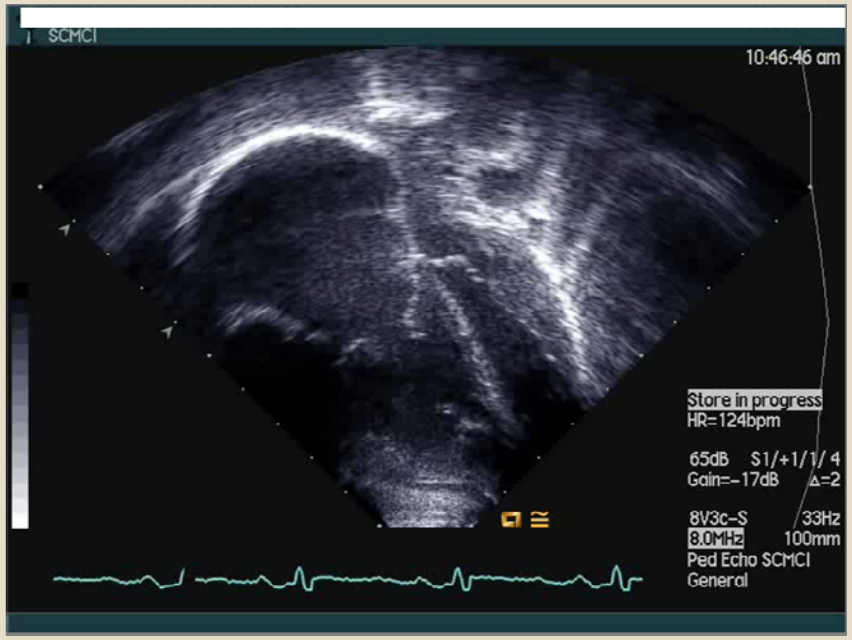
Sinus rhythm with right axis deviation and Rt ventricular hypertrophy.

Echocardiography

- Normal segmental anatomy.
- normal venous connections.
- Mild central TR with peak gradient of 70 mm Hg (BP 110/60) RV hypertrophied and moderately dilated. RA is mildly dilated. Mild to moderate RV dysfunction TAPSE- Tricuspid Annular Plane Systolic Excursion = 1.1 cm.
- The septum is flattened in systole and at the beginning of diastole, the LV tends to the left.
- Pulmonary arteries are enlarged with Doppler flow suggesting increased resistance.
- Trivial pulmonary regurgitation with peak early gradient around 34 mm Hg.

Echo- at presentation



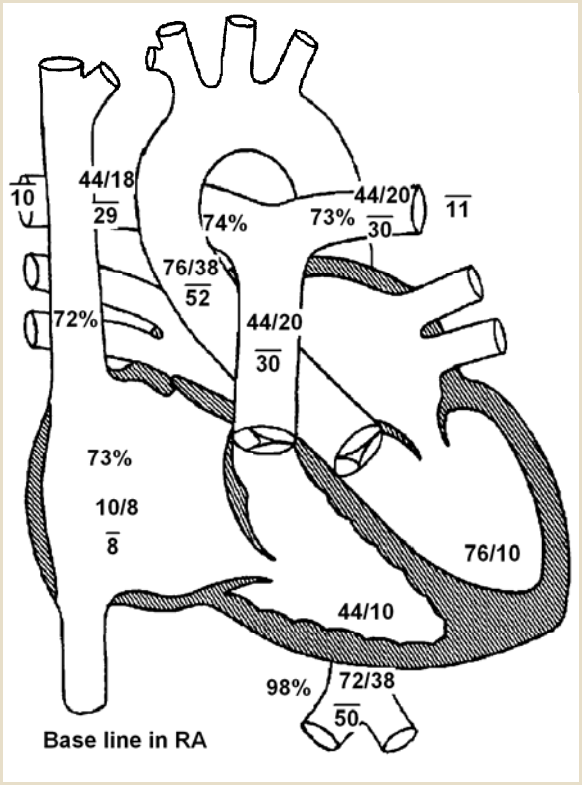


Pulmonary arterial Hypertension

- Standard diagnostic criteria for pulmonary hypertension include the presence of mean pulmonary artery pressure > 25 mm Hg with pulmonary artery wedge pressure < 15 mm Hg and pulmonary vascular resistance > 3 Wood units/m^2.

Cardiac catheterization 1

- Performed under general anesthesia.
- First evaluation on room air.

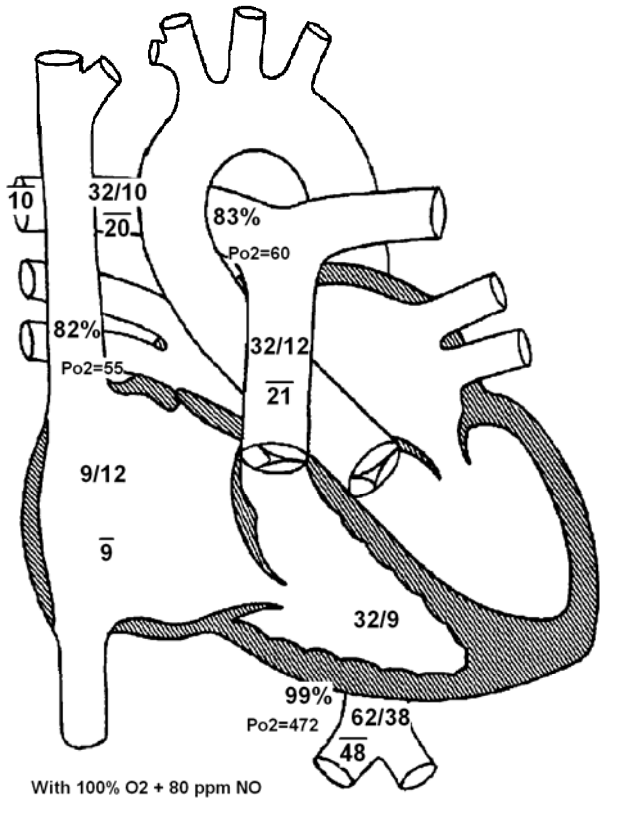


Rest

Qp = 2.38 L/min (3.78 L/min/m²)
Qs = 2.38 L/min (3.78 L/min/m²)
Rp = 8.40 units (5.29 units x m²)
Rs = 17.65 units (11.12 units x m²)
Qp/Qs = 1.00 : 1 | Rp/Rs = 0.48

Cardiac catheterization 1

- Second evaluation on 100 O2 with addition of 80 ppm NO.



NO + 100% O2
Qp = 2.42 L/min (3.84 L/min/m²)
Qs = 2.42 L/min (3.84 L/min/m²)
Rp = 4.55 units (2.86 units x m²)
Rs = 16.12 units (10.15 units x m²)
Qp/Qs = 1.00 : 1 | Rp/Rs = 0.28

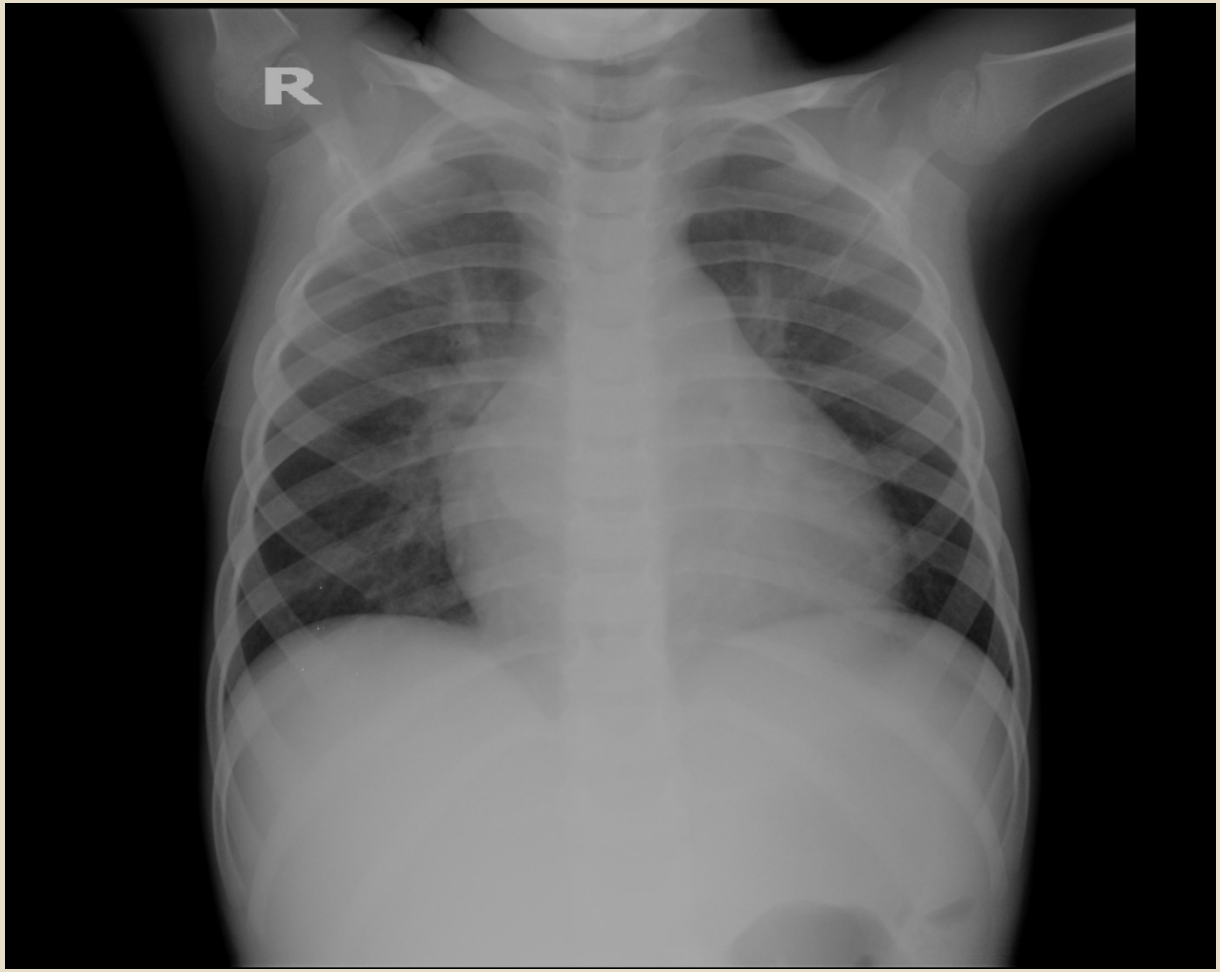
Cardiac catheterization-summary

- No cardiac disease was found (without shunt) and moderate PHT with 2/3 systemic pressure and PVR of 5.5 Wood units/m^2 was demonstrated with reactivity to oxygen and NO.
- Angiography –the PA's branch size was found normal with normal arborization in both lungs. Unobstructed pulmonary veins flow to LA without shunt to RA.
- LV function normal with normal left sided arch with no abnormal vessels.

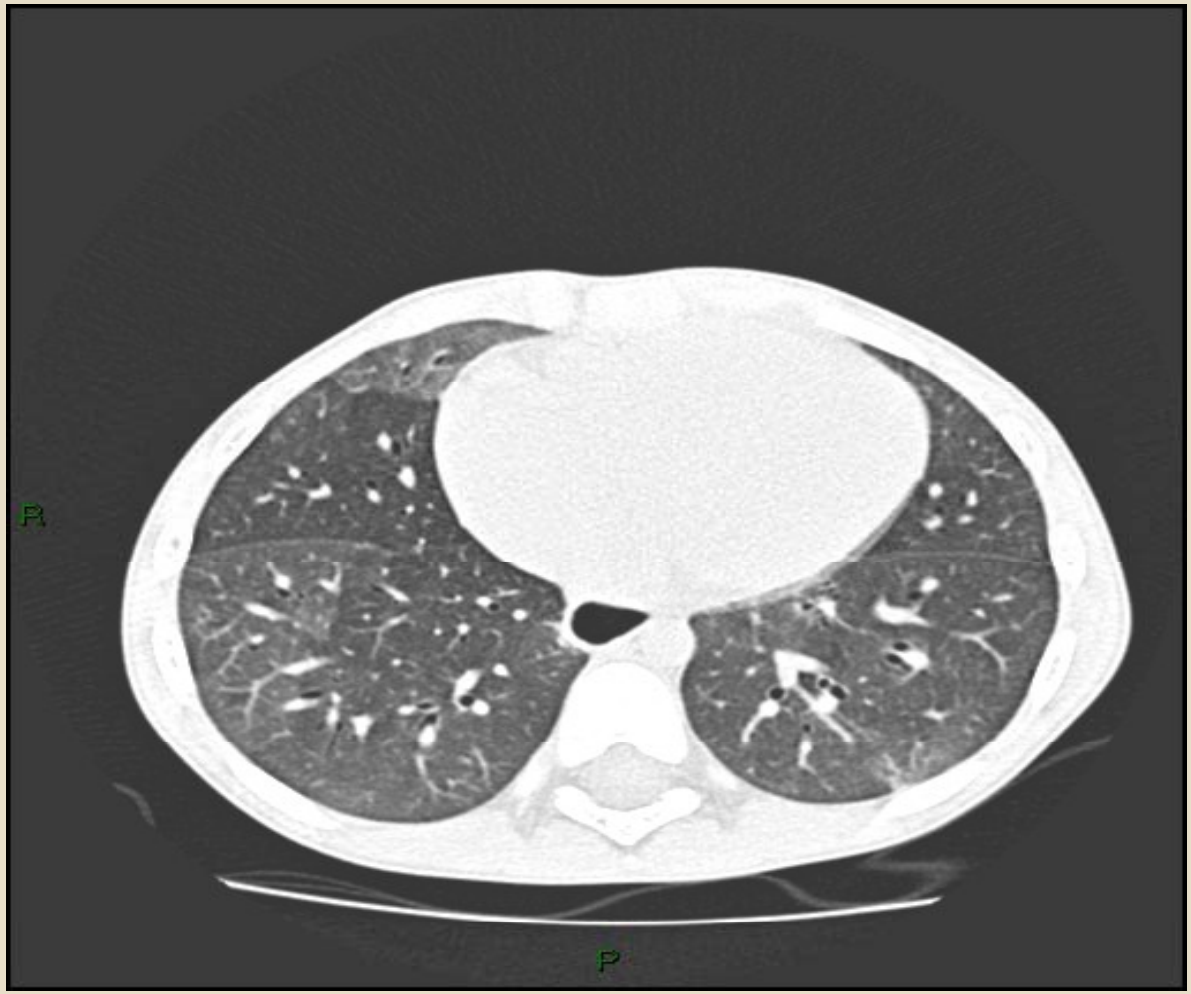
imaging

- *Chest x-ray* – bilateral central infiltrates and enlarged heart shadow.
- *High- resolution computed tomography*- Cardiomegaly was due to the enlarged right-side. No pericardial effusion. Congestion in the IVC and hepatic veins. Lung tissue with matte glass and mosaic diffusion shape were found in both lungs without pleural effusion.

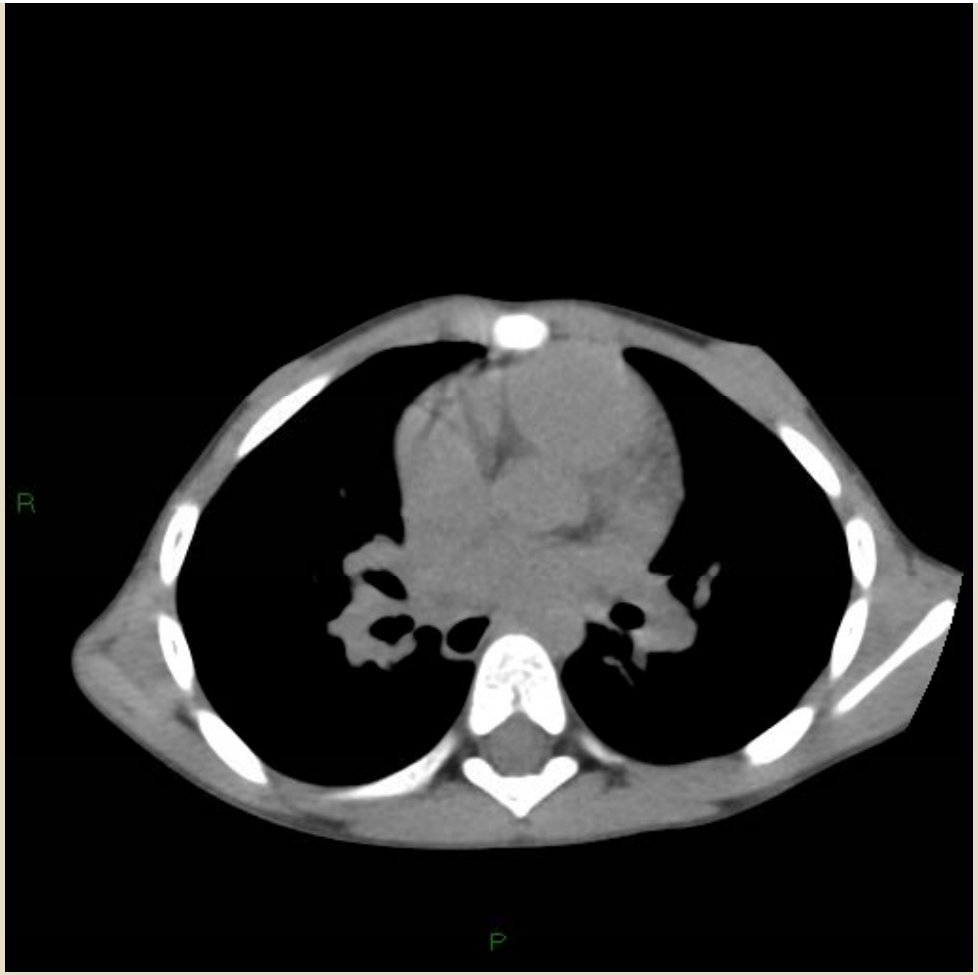
Chest X-ray



High- resolution computed tomography- CT



High- resolution computed tomography- CT



- ***Pulmonary function tests*** – inconclusive
- ***Radiological studies of the gastrointestinal tract*** – normal

In summary

A 4 year old girl with:

- Raynaud's phenomenon.
- Pulmonary arterial hypertension.
- Interstitial lung disease.
- Positive serology:

  ANA ↑↑

  Antitopoisomerase I (anti-scl 70) ↑↑
- No other symptoms or signs of scleroderma

↓

Scleroderma sine scleroderma

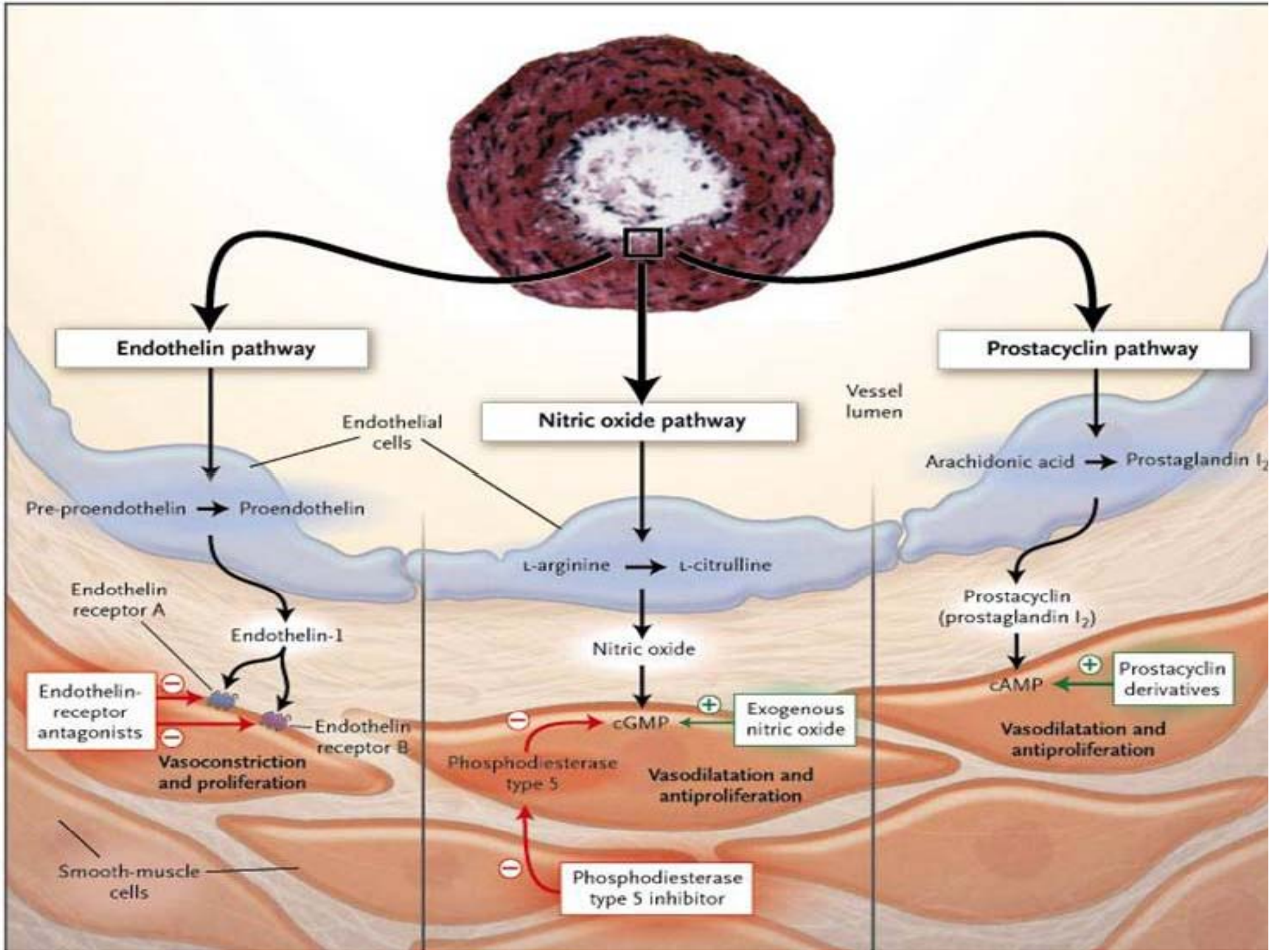
- scleroderma sine scleroderma -

  This form of scleroderma is unique in patients that have any of the characteristic features of internal organ involvement WITHOUT having detectable skin features.

  Scleroderma sine scleroderma is extremely rare.

Treatment

- IV Cyclophosphamide 500 – 750mg/m^2/month x 6 months.
- Bosentan – 31.5mg/d (dose increase to twice daily)
- Sildenafil – 25mg x 4/ d
- Calcium + Vit D
- Resprim
- Immunizations: Prevenar, Pneumovax, Influenza


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Arachidonic acid → Prostaglandin I2
Pre-proendothelin → Proendothelin
L-arginine → L-citrulline
Endothelin receptor A
Endothelin-1
Prostacyclin (prostaglandin I2)
Nitric oxide
Endothelin-receptor antagonists
Endothelin receptor B
cAMP
Prostacyclin derivatives
Exogenous nitric oxide
cGMP
Vasoconstriction and proliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

Course

6 months after presentation:

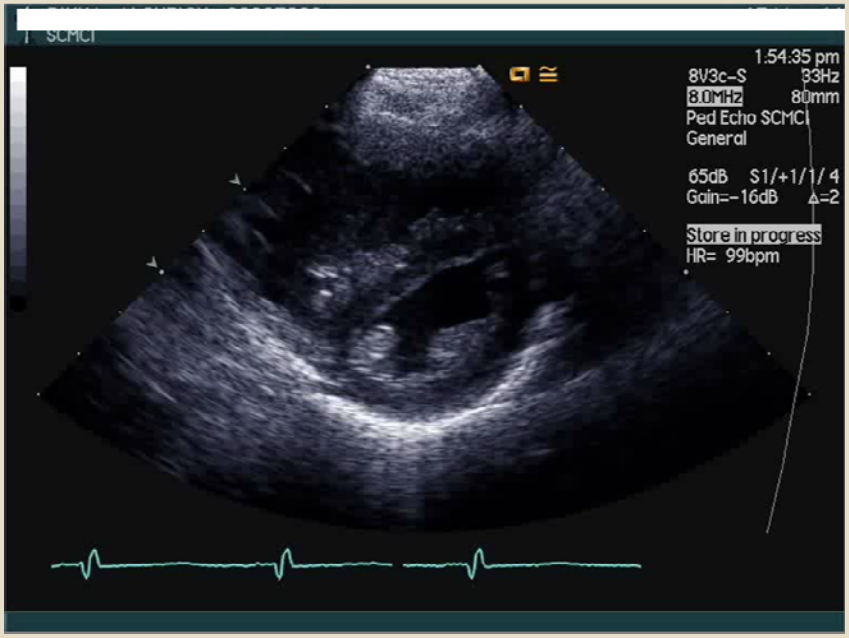
- Weight gain (1kg)
- Raynaud's phenomenon – resolved
- Fingertips – healed
- 6 minute walk – no change
- Von Willebrand Factor – decreased (181%→104)
- Improved ventricular function on echocardiogram

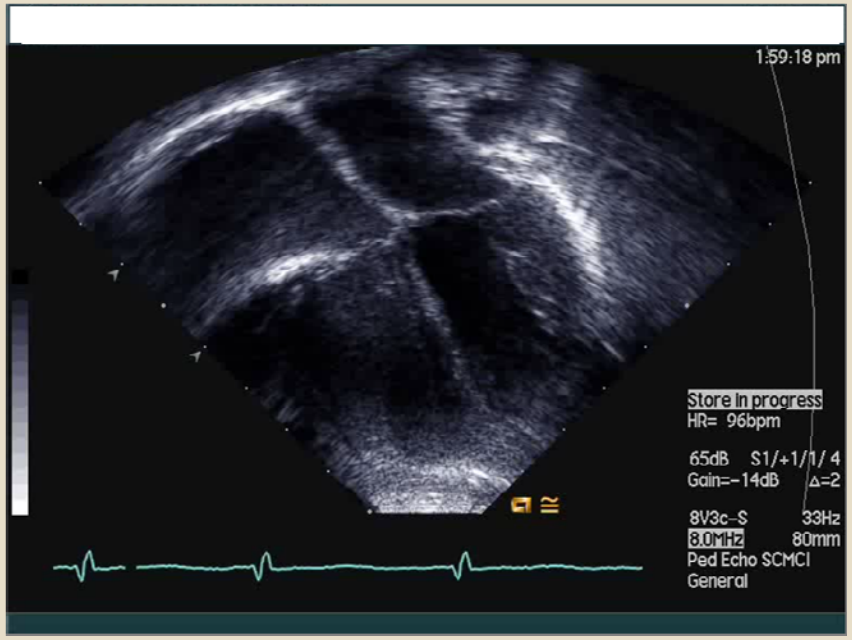
Cardiac follow up

- normal heart function. RV is less dilated; TR with peak gradient of 70 mm Hg. Partial flattening of septum throughout systole.

  LV filling normal.
- TAPSE > 1.55 cm -2 cm - RV function index (Tricuspid Annular Plane Systolic Excursion).
- 6 minute walk -500 meters with decrease in oxygen saturation to 84% and an increase in heart rate to 190. No change in blood pressure with improved oxygen saturation after a few seconds.

Echo- under treatment (1 month)





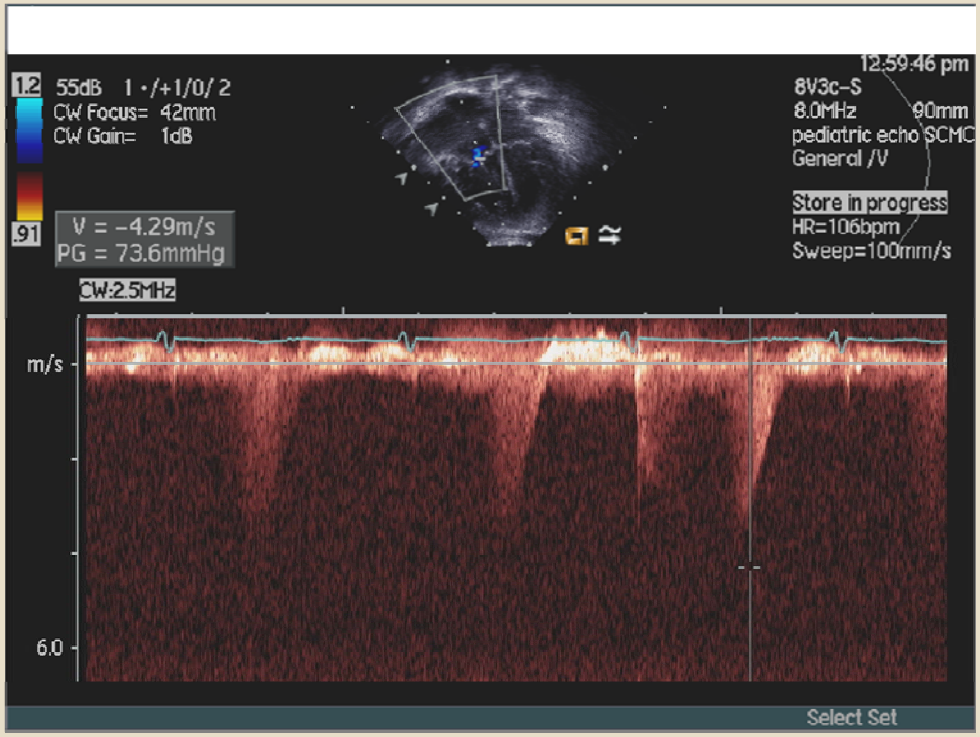
- However, no significant change of pulmonary pressure was found on the echo.
- High resolution CT -compared with the previous review findings show pulmonary deterioration. Interstitial lung disease with air trapping component and signs of pulmonary hypertension.

↓

Treatment change: to mycophenolate mofetil

- Two months ago she suffered from recurrent pre syncope and syncope.
- She was hospitalized and her physical exam was unchanged.
- The blood tests were normal including D-dimers and troponin level.
- Base line ECG –No change RVH with NSR.

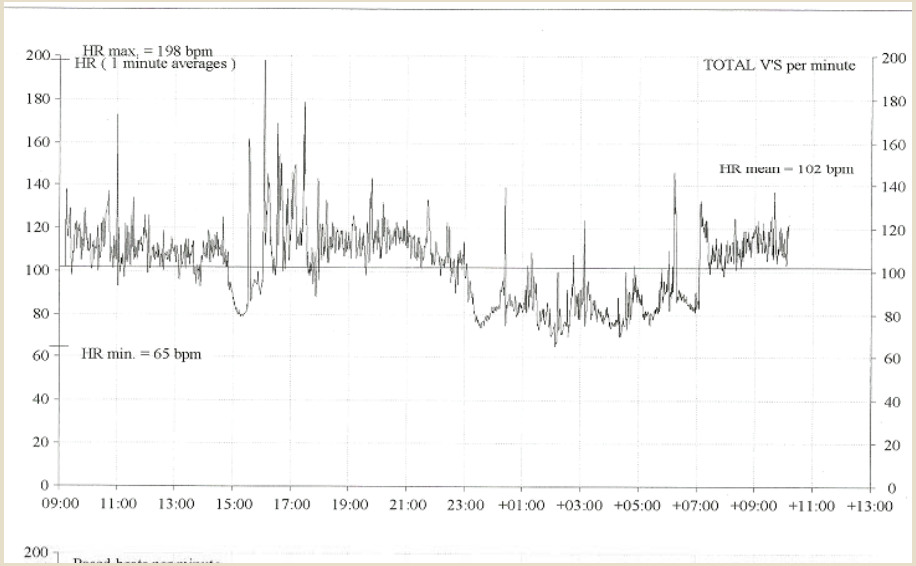
Echocardiogram



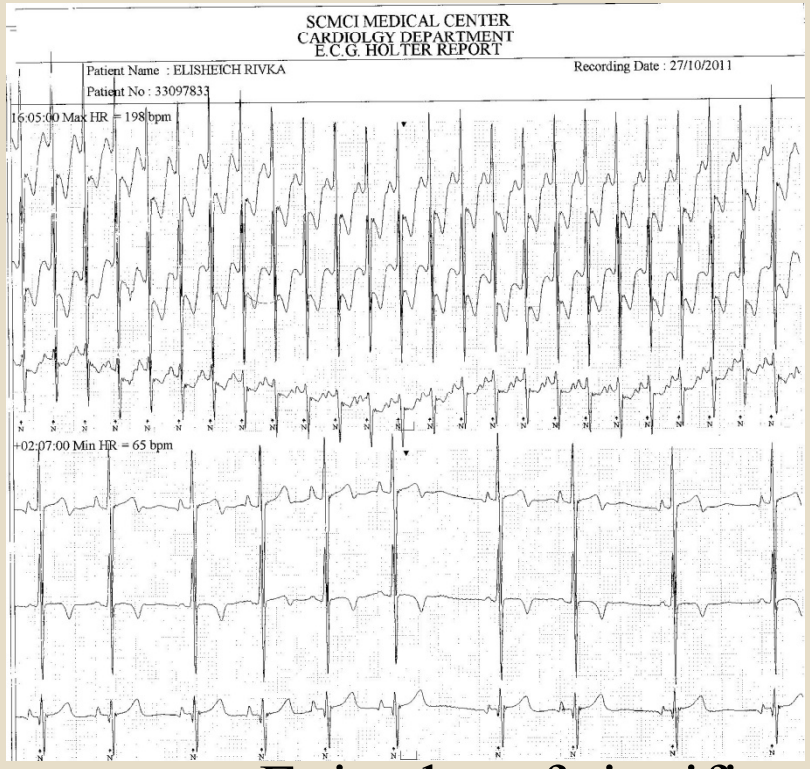
- TR velocity determined by the systolic pressure difference between RV and RA
- TR + RA = PA pressure (without any RVOT obstruction)
- Estimated RV pressure sub-systemic (80 Vs 100)

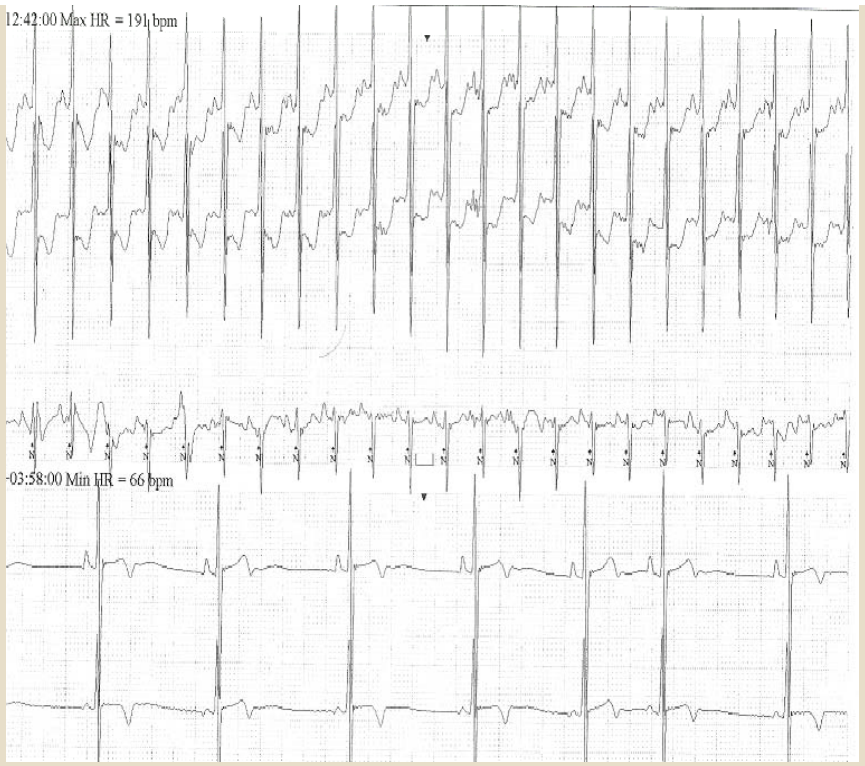
24h ECG recording (Holter)

- Performed in the hospital.
- Goal- to record heart rate during an episode.



24h ECG recording (Holter)

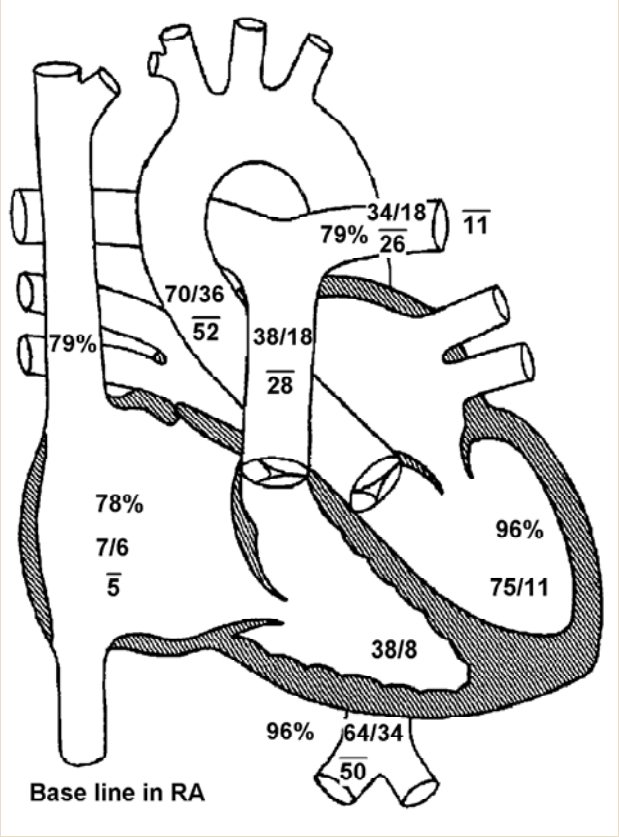




- Episodes of significant sinus tachycardia with sudden decrease in HR
- Most with ST depression and T wave inversion
- Ischemia??

Cardiac catheterization 2

- Performed under general anesthesia.
- First evaluation on room air.

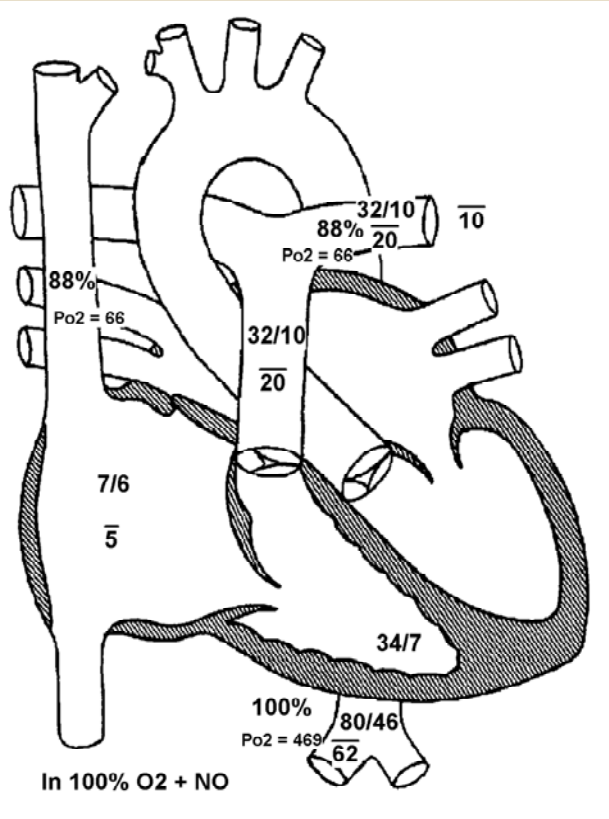


Base line in RA

Qp = 2.94 L/min (4.52 L/min/m²)
Qs = 2.94 L/min (4.52 L/min/m²)
Rp = 6.13 units (3.98 units x m²)
Rs = 14.98 units (9.73 units x m²)
Qp/Qs = 1.00 : 1 | Rp/Rs = 0.41

Cardiac catheterization 2

- Second evaluation on 100 O2 with addition of 80 ppm NO.

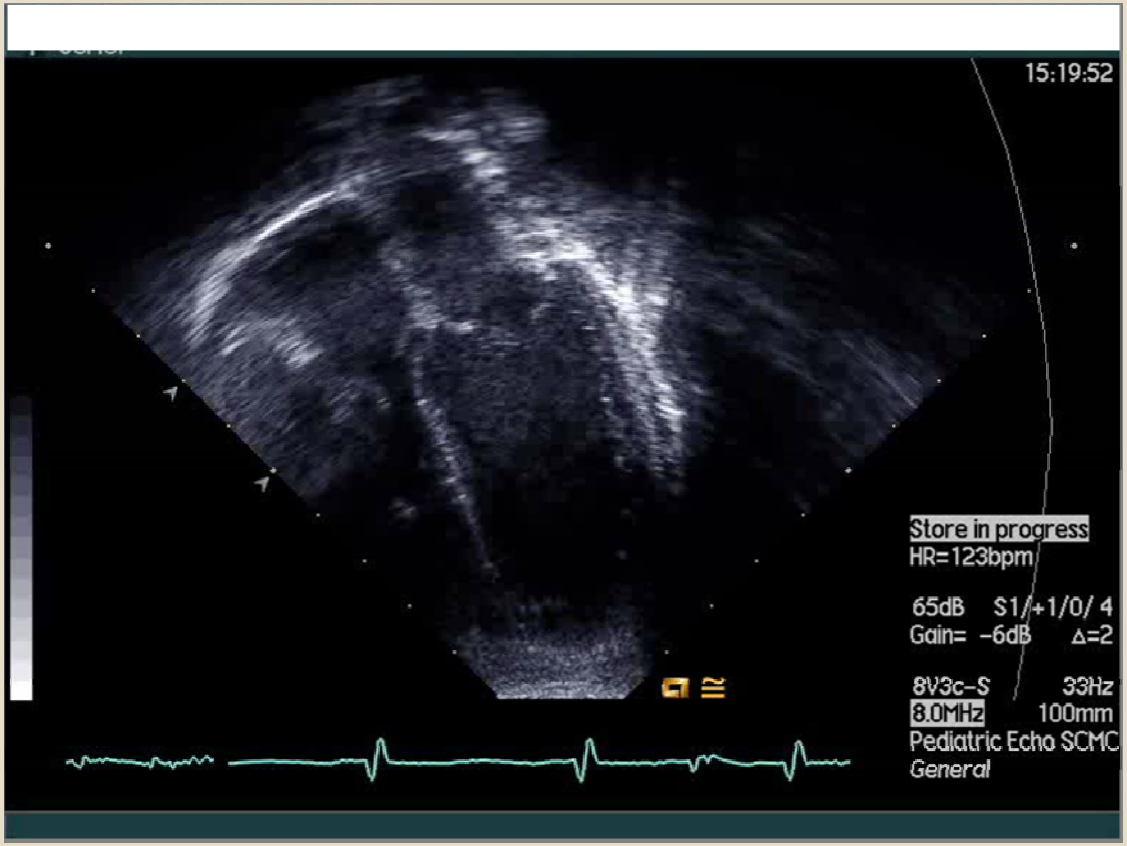


NO + 100% O2
Qp = 2.89 L/min (4.45 L/min/m²)
Qs = 2.89 L/min (4.45 L/min/m²)
Rp = 3.46 units (2.25 units x m²)
Rs = 19.70 units (12.80 units x m²)
Qp/Qs = 1.00 : 1 | Rp/Rs = 0.18

Catheterization – Summary

- Cardiac catheterization - no coronary disease found in angiography with improvement in PVR (4.5 →2.2 wu).
- Insertion of Hickman line (permanent catheter) for flolan treatment (Epoprostenol).

Echo under flolan treatment



- RV volume is closer to normal.
- RV function improved.
- TR jet less than 50 mmHg.

- Under treatment with Flolan- asymptomatic and without syncope.
- No ST depression on ECG monitoring (Holter) during tachycardia.
- 6 minute walk -550 meters with normal oxygen saturation (98%) and an increase in heart rate to 150.

Von Willebrand antigen (range: 50-150%)

Date	Result
11/4/2011	181
20/6/2011	140
21/7/2011	116
1/11/2011	111
18/12/2011	65

Treatment –summary

- SYR - Mycophenolate 400 mg x2/d
- PO BOSENTAN -Tracleer 31.25mg X2/d
- PO VIAGRA - Sildenafil 25mg X 4/d
- SYR RESPRIM -6 ml X 1/48h
- IV FLOLAN – Epoprostenol 20ng/kg/min
- SC CLEXAN -14 mg X1/D

diffuse cutaneous systemic sclerosis

- Chronic multisystem connective tissue disease. characterized by sclerodermatous skin changes and visceral involvement.
- **Annual incidence**: 0.45-1.9 cases/100,000 persons
- **Prevalence**: 24 cases/100,000
- **Onset in childhood – rare.**

Systemic sclerosis sine scleroderma

- Described in adults:

  Other than absence of skin thickening – no difference in internal organ involvement.
- **In children – only 1 case report**

  presented as nocturnal seizures and Raynaud's phenomenon.

  (Navon P, et al, Acta Paediatrica, 1993)

Systemic sclerosis sine scleroderma (cont)

- Pulmonary arterial hypertension presenting with systemic sclerosis sine scleroderma has been found in only 1 reported case in an adult.

  (Pauling JD, et al, Rheumatology Oxford, 2008)

  - **Not reported in children!**

Presenting signs and symptoms in children with systemic sclerosis

Signs - symptoms	Percent of patients (n = 164 patients)*
Skin tightening	84
Raynaud's phenomenon	72
Arthralgia	32
Muscle weakness and pain	17
Subcutaneous calcification	10
Dysphagia	16
Dyspnea	14

* Percentage calculated only on those series in which detailed information were provided.
Cumulative series from references Martini, G, et al. Arthritis Rheum 2003; Burge, SM, et al. JR Soc Med 1984; Larregue, M, et al. Ann Dermatol Venereol 1983; Su‡rez-Almazor, ME, et al. Arthritis Rheum 1985.

Laboratory tests in children with Systemic Sclerosis

- ANA 81-97%
- Anti-topoisomerase 28-34%
- Anti-centromere 7-8%

Cardiac involvement

- Cardiac fibrosis:

  conduction defect

  arrhythmias

  impaired ventricular function
- Cardiac Ischemia
- **Pulmonary HT**: myocardial damage, heart failure
- Severe cardiomyopathy
- Pericardial effusion

Pulmonary Involvement In Systemic Sclerosis

Two principal clinical manifestations:

- Interstitial lung disease in 40% of adult patients, rare in children.
- Pulmonary vascular disease leading to pulmonary arterial hypertension in 8-12% in adult patients <4% in children.

Vascular disease may occur with or without concurrent interstitial lung disease.

Pulmonary hypertension is an important cause of death in systemic sclerosis.

Pathogenesis of pulmonary hypertension in systemic sclerosis – related interstitial lung disease

Parenchymal fibrosis → destruction of pulmonary vasculature

Hypoxia – induced vascular remodeling

Diffuse fibroproliferative pulmonary vasculopathy (similar to isolated PAH)

Pulmonary hypertension treatment

- Endothelin – 1 receptor antagonists (Bosentan- tacleer)
- Phosphodieterase type 5 inhibitors (Sildenafil)
- Prostanoids (Epoprostenol, Iloprost)

Response to therapy – **suboptimal**

Interstitial lung disease (ILD)

- A leading cause of death.
- ILD alone – median survival: 5-8 years.
- ILD with pulmonary hypertension – survival significantly shortened.
- Therapy: Cyclophosphamide – drug of choice

  Role of: Mycophenolate mofetil
  Imatinib
  Rituximab
  (treatment success still questionable)

  Lung transplantation

Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease and the impact of pulmonary arterial hypertension therapies

Arthritis & Rheumatism, August 2011

Retrospective analysis of 70 systemic sclerosis patients with pulmonary hypertension complicating interstitial lung disease who received pulmonary arterial hypertension therapies:

After a mean ± SD of 7.7 ± 6.2 months of treatment:

no significant changes in functional class,
6 minute walk distance or hemodynamic parameters.

71% survived after 1 year.
39% survived after 2 years.
21% survived after 3 years.

- Is this the correct diagnosis ?
- Is the treatment provided for arterial pulmonary hypertension optimal ?
- Shall we alter the scleroderma treatment ?
- Is there another explanation for the occurrence of tachycardia and ST depression ?
- Due to the long waiting time for a lung transplant, when is the optimal time to be added to the transplant list?

- Thanks to:

P. Hashkes ,

E. birk ,

L. Arel ,

T. Dagan ,

D. Adam ,

מרפאת יתר לחץ ריאתי- "שניידר"

- כ 50 חולים
- יתר לחץ דם ראשוני-6 (1 נפטר ,2 לאחר השתלת ריאות)
- מחלת ריאות- 15 (alveolar proteinosis ,BPD) 2, נפטרו
- מחלת רקמת חיבור -3 (סקלרודרמה, MCTD,APLA) 2 נפטרו
- תסמונת אייזנמנגר - 5 (1 נפטר)

- 15 חולים עם מומי לב (*PDA, VSD, DILV, Shone complex, Truncus arteriosus, Mitral stenosis*).
- 3 לאחר תיקון מלא אך עם בעיה בכלי דם הריאתיים.
- 10 לאחר גלן או פונטן כושלים – זרימה פסיבית.