UNIVERSITY of WASHINGTON

# Pulmonary Hypertension in Sickle Cell Disease

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Hematology Fellows Conference

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# Patient Presentation

- 28F with SCD, genotype SS.
- Presented to UWMC ER with 1 month progressive DOE and several days of chest pain
- Could climb 3 stairs at home before becoming dyspneic. SOB worse with lying flat.
  - Pain is different than vaso-occlusive crisis pain
  - No fevers, chills, cough
  - BP: 144/94

# Patient Presentation

- PMH:
  - Multiple vaso-occlusive pain crises over the past 8 months
  - Right atrial clot 11/12
  - Acute chest syndrome 8/12
  - CVA 6/12
  - Hypertension
- Medications:
  - Hydroxyurea, Folate, Warfarin, Amlodipine, Oxycontin, Vicodin

# Patient Presentation

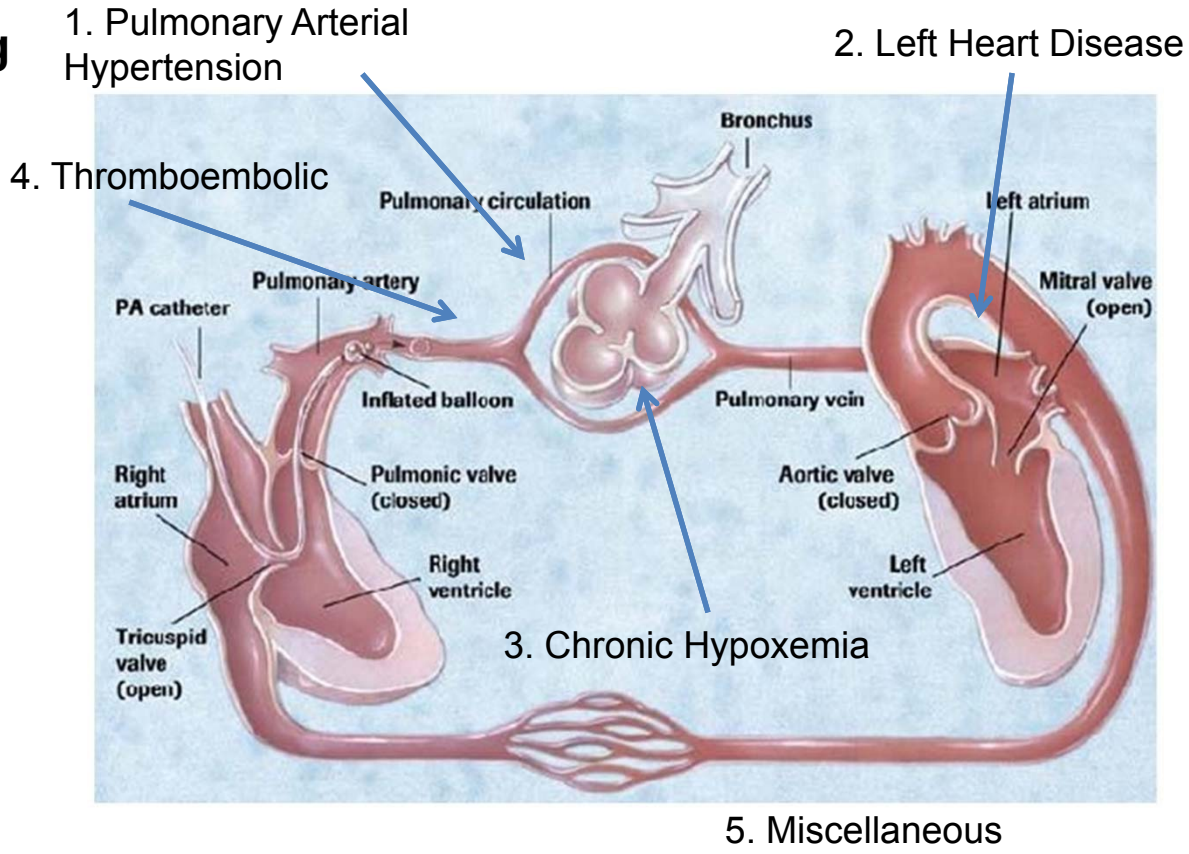
- CT Chest: diffuse, bilateral centrilobular ground-glass opacities, no focal consolidation, no PE. RV and pulmonary trunk enlargement.
- PFTs: no airflow obstruction, decreased FEV1 and FVC with preserved FEV1/FVC consistent with restrictive lung disease pattern (DLCO not measured)
- TTE (4m prior): TRV 3.6 m/s, PASP 57-62, and increased RV size with low normal RV function. LV function preserved at 55-60% with evidence of diastolic dysfunction.
- V/Q scan (5m prior): low probability of pulmonary emboli

# Patient outcome (hospital course)

- Treated initially with ABX, IVF, oxygen, and pain control
- On D3, patient went into acute respiratory failure requiring intubation. HbS = 42%.
- Underwent RBC exchange that night with improvement in her respiratory status and was subsequently extubated on D4 and transferred to the floor
- On D7, patient noted to be tachycardic in the evening. No change in dyspnea.
- Several hours later, patient found unresponsive and pulseless. CPR attempted and unsuccessful.

# Pulmonary Hypertension

- **PH: mean pulmonary artery systolic pressure > 25mmHg at rest *on right heart catheterization***
- On TTE, a TRV of 2.5-2.8 m/s is suggestive and ≥ 2.8 m/s is highly indicative of pulmonary hypertension
- ***Right heart catheterization is necessary* to confirm diagnosis, identify mechanism, and perform vasoreactivity testing to guide therapy**




Nef et al. Heart 2010

# Classification of Pulmonary Hypertension

**1. Pulmonary arterial hypertension**

- **Idiopathic PAH**
- **Heritable**
  - **BMPR2**
  - **ALK1, endoglin**
  - **unknown**
- **Drugs and toxins induced**
- **Associated with:**
  - Connective tissue diseases
  - HIV infection
  - Portal hypertension
  - systemic to pulmonary shunts
  - Schistosomiasis
  - Chronic haemolytic anaemia

**1'Pulm. veno- occlusive disease (PVO) and/or pulmonary capillary haemangiomatosis (PCH)**

**2. Pulmonary hypertension due to left heart disease**

- **Systolic dysfunction**
- **Diastolic dysfunction**
- **Valvular disease**

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

- **Chronic obstructive pulmonary disease**
- **Interstitial lung disease**
- **Sleep-disordered breathing**
- **Chronic exposure to high altitude**
- **Broncho pulmonary dysplasia (BPD)**
- **Developmental abnormalities**

**4. Chronic thromboembolic pulmonary hypertension (CTEPH)**

**5. Pulmonary Hypertension with unclear and/or mulifactorial mechanisms**

- **Haematologic disorders**
  *myeloproliferative disorders; splenectomy*
- **Systemic disorders**
  *Vasculitis sarcoidosis, pulmonary Langerhans cell histiocytosis LAM, neurofibromatosis.*
- **Metabolic disorders**
  *Glycogen storage disease, Gaucher disease, thyroid disorders*
- **Congenital heart disease**
  *other than systemic to pulmonary shunt*
- **Others**: *obstruction by tumours, fibrosingmediastinitis, chronic renal failure on dialysis*

**Figure 1** Updated clinical classification of pulmonary hypertension according to the proposals of the 4th World Symposium on Pulmonary Hypertension held in Dana Point 2008.

Nef et al. Heart 2010

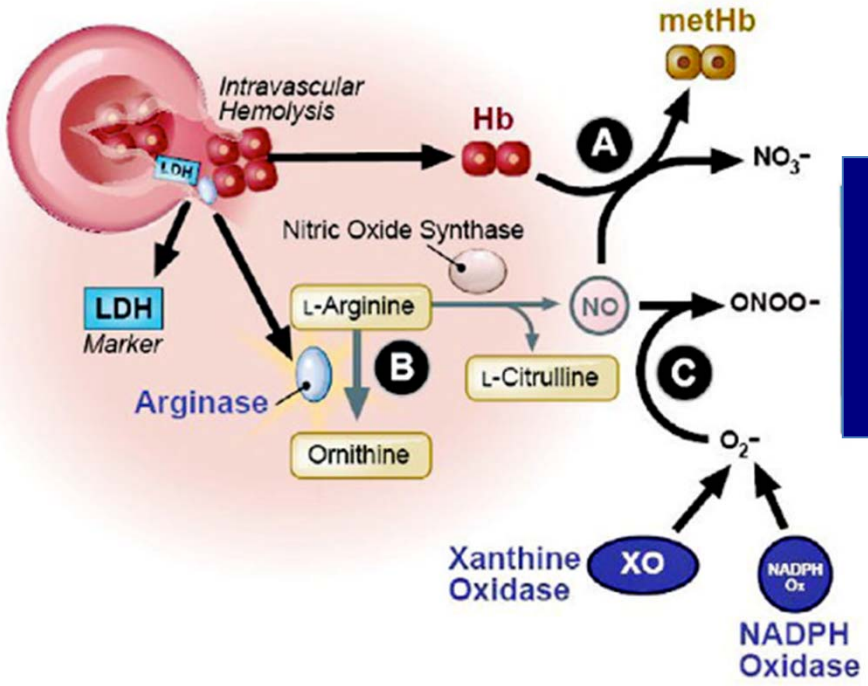
# Pulmonary Hypertension Classification and Sickle Cell Disease

| Group and Typical Hemodynamic Features | Examples of Associated Conditions | Aspects of Sickle Cell Disease Potentially Related to PH |
|---|---|---|
| 1 - Idiopathic pulmonary artery hypertension (PAH), including pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis<br>mPAP ↑ (often 50-60 mmHg)<br>PVR ↑<br>PCWP normal (<15 mmHg)<br>CO normal or low | •Heritable<br>•Drugs and toxins induced<br>•Associated with<br>- Connective tissue diseases<br>- HIV Infection<br>- Portal Hypertension<br>- System to pulmonary shunts<br>- Schistosomiasis<br>- Chronic hemolytic anemia | Vasculopathy (remodeling)<br>Hemolysis<br>Limited NO Bioavailability |
| 2 - PH due to left heart disease<br>mPAP ↑<br>PVR normal<br>PCWP ↑<br>CO normal or low | •Systolic dysfunction<br>•Diastolic dysfunction<br>•Valvular disease | Chronic anemia with left ventricular hypertrophy/dysfunction |
| 3 - PH due to lung disease and/or hypoxia<br>mPAP ↑ (often 25-40 mmHg) | •Chronic obstructive pulmonary disease<br>•Interstitial lung disease<br>•Sleep-disordered breathing<br>•Chronic exposure to high altitude | Parenchymal pulmonary changes (fibrosis, infarction) |
| 4 - Chronic thromboembolic PH (CTEPH) | | Pulmonary embolism<br>Coagulation activation |
| 5 - PH with unclear and/or multifactorial mechanisms | •Hematologic disorders e.g.<br>- Myeloproliferative disorders<br>- Splenectomy<br>•Systemic disorders e.g.<br>- Vasculitis<br>- Sarcoidosis<br>•Metabolic disorders e.g. Gaucher's<br>•Congenital heart disease<br>•Chronic renal failure on dialysis | Auto- or surgical splenectomy<br>End-stage renal disease |

mPAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; PCWP=pulmonary capillary wedge pressure; CO=cardiac output

Hassell ASH Handbook 2011

# Pathophysiology of PAH in SCD: Hemolysis associated?




Decreased Nitric Oxide Bio-availability

- **Impaired vasodilation**
- **Increased vaso-constriction**
- **Hyperplasia/Proliferation**
- **Increased platelet activation**
- **Increased adhesion molecules**
- **Uncoupled NOS**

Kato, G.J., et. al. Blood Reviews 2007

# Left Ventricular Dysfunction and PH in SCD

- Chronic anemia creates a hyperdynamic state with an elevated cardiac output -> LV remodeling and diastolic dysfunction

- These findings are associated with a relative systemic hypertension and increased TRV

# Left Ventricular Dysfunction and PH in SCD

- Increased mortality was independent of, but additive to TRV
- Patients with diastolic dysfunction had a statistically significant higher SBP (137 mmHg vs 119 mmHg)

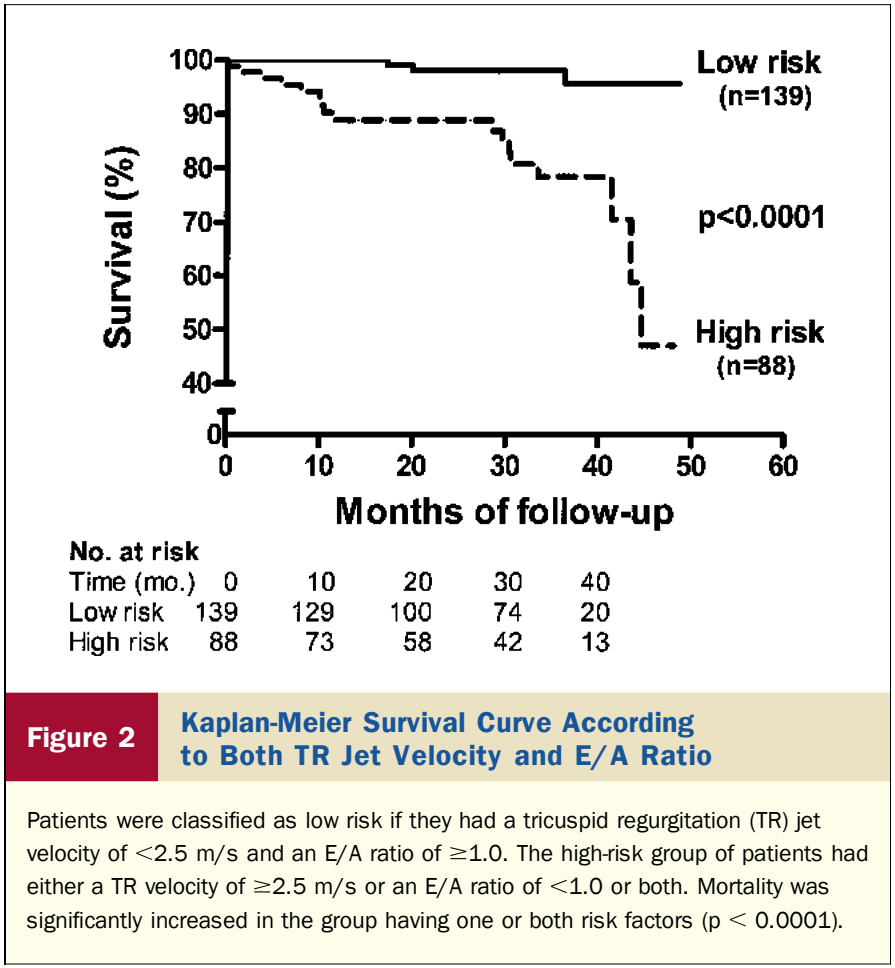



**Figure 2** **Kaplan-Meier Survival Curve According to Both TR Jet Velocity and E/A Ratio**

Patients were classified as low risk if they had a tricuspid regurgitation (TR) jet velocity of <2.5 m/s and an E/A ratio of ≥1.0. The high-risk group of patients had either a TR velocity of ≥2.5 m/s or an E/A ratio of <1.0 or both. Mortality was significantly increased in the group having one or both risk factors ($p < 0.0001$).

Sachdev et al J Am Coll Cardiol. 2007

# Pulmonary dysfunction and PH in SCD

- 310 adults with SCD evaluated
- 90% had abnormal PFTs, with the most common abnormality being a restrictive pattern with a decreased DLCO (74%)
- Given high prevalence of restrictive lung disease, routine pulse oximetry monitoring indicated with clinical visits

**TABLE 2. SUMMARY OF PULMONARY FUNCTION TEST RESULTS**

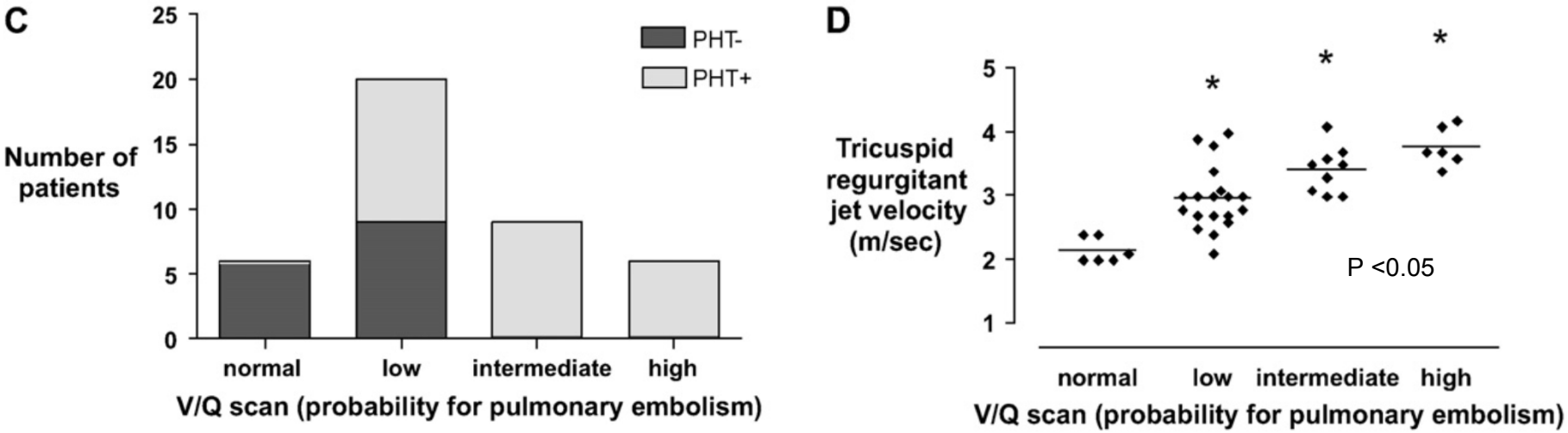
| | All Patients (*n* = *310*) |
|---|---|
| Summary of PFT results | |
| $FEV_1$ | |
| Median | 82.80 |
| Mean ± SD | 83.03 ± 16.06 |
| FVC | |
| Median | 83.62 |
| Mean ± SD | 84.37 ± 16.01 |
| $FEV_1$/FVC, % | |
| Median | 98.61 |
| Mean ± SD | 98.36 ± 9.15 |
| TLC | |
| Median | 69.79 |
| Mean ± SD | 70.20 ± 14.69 |
| RV | |
| Median | 78.04 |
| Mean ± SD | 88.60 ± 60.88 |
| $D_{LCO}$ | |
| Median | 53.74 |
| Mean ± SD | 56.57 ± 20.11 |
| Adjusted $D_{LCO}$* | |
| Median | 61.74 |
| Mean ± SD | 64.54 ± 19.93 |
| Subclassification based on PFTs | |
| Normal, n (%) | 31 (10) |
| Isolated low $D_{LCO}$, n (%) | 40 (13) |
| Mixed O/R, n (%) | 5 (2) |
| Obstructive, n (%) | 4 (1) |
| Restrictive, n (%) | 230 (74) |

*Definition of abbreviations*: $D_{LCO}$ = diffusion capacity for carbon monoxide; O/R = obstructive/restrictive; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity.

* Adjusted for hemoglobin concentration.

Klings et al Am J Resp Crit Care Med 2006

# Thromboembolic Disease and PH in SCD

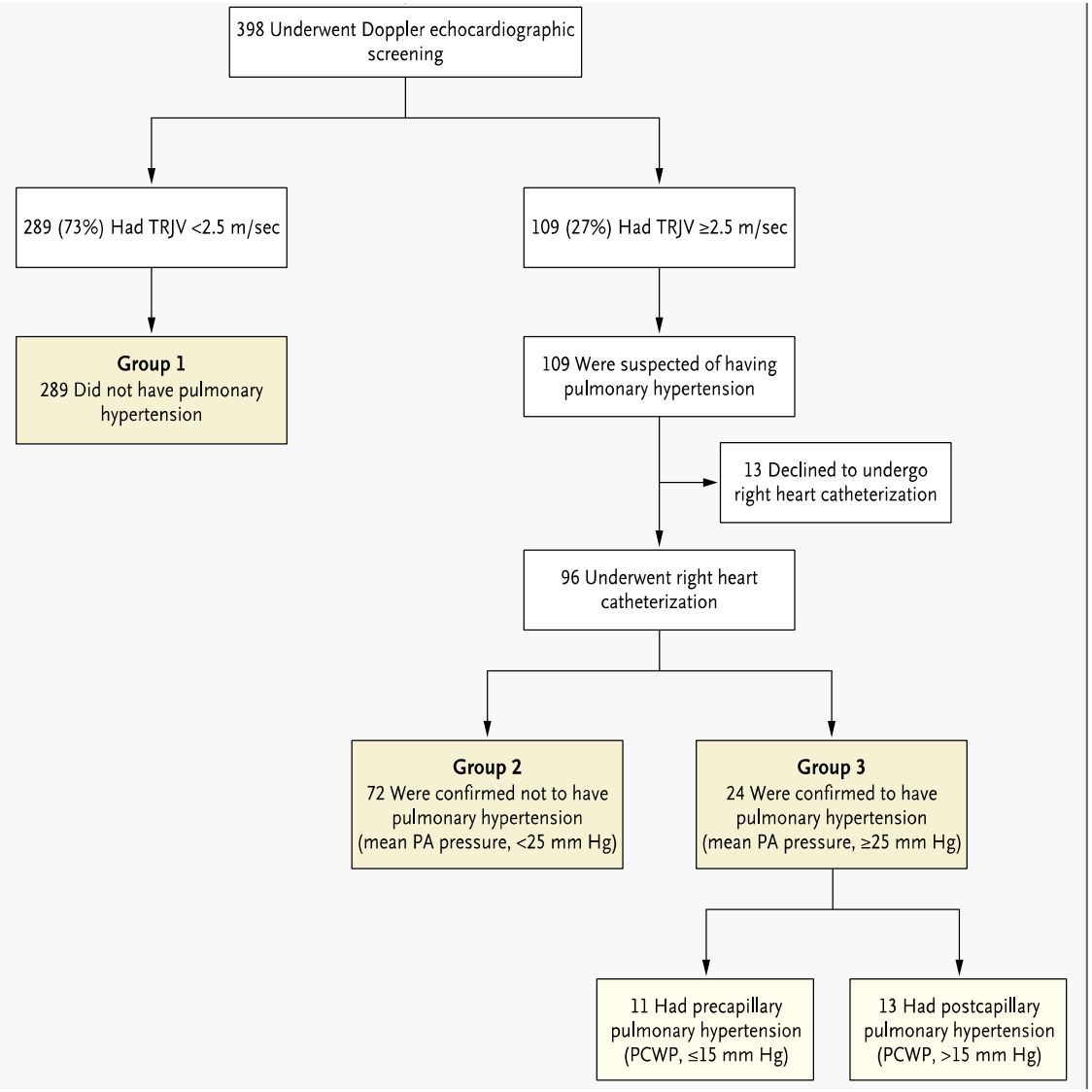



V/Q scans are more sensitive for detecting chronic thromboembolic events than CT scans

Anthi et al Am J Resp Crit Care Med 2007

# Prevalence of PH in SCD

- Previous studies had suggested a prevalence of PH of 30% based on echocardiographic findings of an elevated TRV[1]
- Prevalence based on right heart catheterization was 6%
- Positive Predictive Value 25%
- 13 patients had post-capillary PH and 11 had pre-capillary PH, suggesting that PH in the sickle cell disease population is multifactorial




[1]Gladwin et al. NEJM 2004
[2]Parent et al. NEJM 2011

# Additional diagnostics for evaluation of PH in SCD

- 6 Minute Walk Distance Test
  - Patients with RHC-proven PH had a shorter 6 minute walk distance (320m vs. 435m, p=0.002)[1]
  - Non-cardiopulmonary limitations such as avascular necrosis limits utility on some patients with SCD

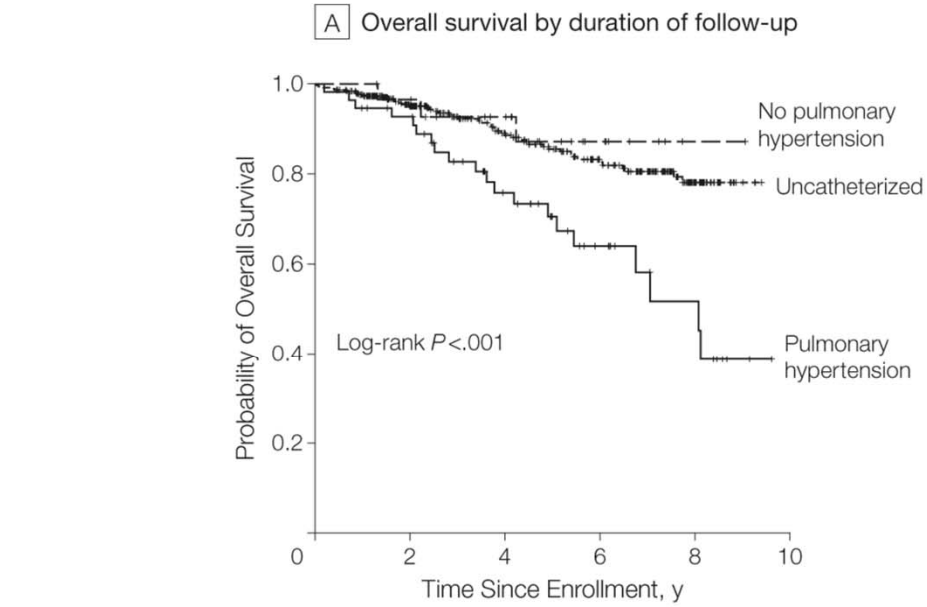
- Brain Natriuretic Peptide (NT-pro-BNP)
  - One study demonstrated a PPV of 78% when level ≥ 160 for when definition utilized for PH was TRV ≥ 2.5 m/s on echocardiography[2]
  - Never studied in RHC diagnosed pulmonary hypertension

[1]Anthi et al Am J Resp Crit Care Med 2007
[2]Machado et al JAMA 2006

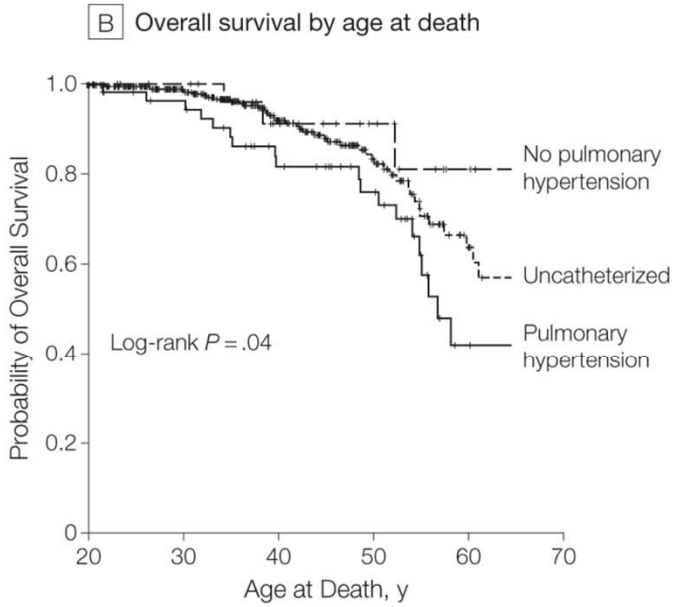
# Work-Up for Pulmonary Hypertension in SCD

- Echocardiography -> Right Heart Catheterization
- Pulmonary Function Tests with 6-minute walk test
- CT scan vs. V/Q scan
- Sleep Study (as clinically indicated)
- HIV, ANA, ANCA, RF, LFTs (as clinically indicated)

# Prognosis of Pulmonary Hypertension in SCD




| No. at risk | | | | | |
|---|---|---|---|---|---|
| No pulmonary hypertension | 29 | 25 | 20 | 8 | 1 |
| Uncatheterized | 381 | 284 | 187 | 128 | 37 |
| Pulmonary hypertension | 55 | 48 | 30 | 15 | 8 |




| No. at risk | | | | | |
|---|---|---|---|---|---|
| No pulmonary hypertension | 29 | 26 | 16 | 11 | 4 |
| Uncatheterized | 376 | 276 | 157 | 79 | 22 |
| Pulmonary hypertension | 55 | 48 | 35 | 26 | 6 |

Gladwin et al. JAMA 2012

# Treatment

- Hydroxyurea: Goal ANC 2.0 and Plts 80,000
- Exchange transfusions as necessary
- Treat conditions contributing to PH:
  - LV dysfunction: BP control
  - Chronic thromboembolism
  - Restrictive lung disease and hypoxemia
  - Asthma
  - OSA

# Treatment – PAH directed trials

- ASSET-1 and ASSET-2[1]
  - RCTs of bosentan (endothelial receptor antagonist) vs. placebo in PAH (ASSET-1) and post-capillary PH (ASSET-2)
  - Both closed early secondary to poor accrual
- Walk-PHaSST[2]
  - RCT of sildenafil (PDE-5 inhibitor) vs. placebo in any form of PH (based on TRV ≥ 2.7m/s and decreased 6MWD)
  - Study stopped early secondary to more serious adverse events in treatment group (46% vs. 22%), most frequently hospitalization for pain crisis
  - Analysis of available data did not demonstrate any observed improvement in primary efficacy measure of 6MWD in treatment gorup
- Arginine
  - 5 days of oral arginine decreased PASP on echo by 15.2%[3]
  - Follow-up longer duration studies have failed to show benefit in functional capacity and TRV

[1]Barst et al. Br J Haematol. 2010
[2]Machado et al. Blood 2011
[3]Morris et al. Am J Respir Crit Care Med 2003

# Conclusions

- Pulmonary hypertension in sickle cell disease is heterogeneous and the cause can be multifactorial
- Echocardiography has a high false positive rate and is not dependable for making a diagnosis of pulmonary hypertension
- All sickle cell disease patients should have a right heart catheterization to make definitive diagnosis
- TRV is an independent risk factor of increased mortality regardless of presence or absence of PH for unclear reasons
- Prognosis is poor and treatment should be directed at decreasing hemolysis and the underlying cause