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# Pulmonary hypertension in adolescents with sickle cell disease

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**PULMONARY HYPERTENSION IN ADOLESCENTS WITH SICKLE CELL  
DISEASE**

by

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B.A., Boston University, 2012

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**PULMONARY HYPERTENSION IN ADOLESCENTS WITH SICKLE CELL  
DISEASE**

**KATHERINE AKINYEMI**

**ABSTRACT**

Sickle cell disease consists of a group of disorders that have a similar mutation in at least one of the beta-globin chains of hemoglobin. This results in a change of the hemoglobin to sickle shaped cells when in the deoxygenated state. It is these sickled cells that lead to the symptoms and complications characteristic of sickle cell disease, including vaso-occlusion. The recurrence of sickling and polymerization in the blood vessels throughout the body ultimately results in tissue and organ damage that increases the mortality of patients.

Pulmonary hypertension is the increase in blood pressure in the pulmonary vasculature causing less blood to reach the lungs. The right side of the heart has to pump harder to compensate for this, which can ultimately lead to right heart failure. With vaso-occlusion being the major complication in sickle cell disease and affecting many tissues and organs like the lungs, pulmonary hypertension has become a major risk factor in these patients, especially in children. Most research has been with adults so the seriousness of this condition is still being discovered in children.

This review will cover the important aspects of both sickle cell disease and pulmonary hypertension then discuss how pulmonary hypertension has become a significant risk factor for death in those with sickle cell disease. From there the importance of this finding in children will be discussed and a plan for future endeavors will be proposed.

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## LIST OF ABBREVIATIONS

ACS.....	acute chest syndrome
CO.....	cardiac output
CSSCD.....	Cooperative Study of Sickle Cell Disease
GMP.....	guanosine monophosphate
HbA.....	adult hemoglobin
HbC.....	hemoglobin C mutation
HbCC.....	hemoglobin C disease
HbF.....	fetal hemoglobin
HbS.....	sickle cell hemoglobin S mutation
HbS $\beta^0$ .....	sickle- $\beta^0$ thalassemia mutation
HbS $\beta^+$ .....	sickle- $\beta^+$ thalassemia mutation
HbSC.....	sickle cell hemoglobin C mutation
ISC's.....	irreversible sickled cells
LAP.....	left arterial pressure
LDH.....	lactate dehydrogenase
mPAP.....	mean pulmonary arterial hypertension
NACSSG.....	National Acute Chest Syndrome Study Group
NT-proBNP.....	N-terminal pro-brain natriuretic peptide
PAH.....	pulmonary arterial hypertension
PSR.....	proliferative sickle retinopathy

PVR.....pulmonary vascular resistance  
RHC.....right heart catheterization  
S<sub>O</sub><sub>Arab</sub>.....sickle cell-hemoglobin 0 Arab disease  
SCD .....Sickle Cell disease  
TRV.....tricuspid regurgitant velocity  
VCAM-1 ..... vascular cell adhesion molecule-1  
WHO.....World Health Organization

## **SICKLE CELL DISEASE**

### **What is Sickle Cell Disease?**

Sickle cell disease (SCD) refers to a group of disorders with autosomal recessive inheritance that are caused by abnormal hemoglobin (Genetics, 2002). Hemoglobin contains two alpha-globin subunits and two beta-globin subunits and along with heme it forms the adult form of this protein in red blood cells that transports oxygen from the lungs to the tissues of the body (Benson & Therrell Jr, 2010).

### **History**

Dr. James Herrick first described the abnormal red blood cells of SCD in 1910. He studied the blood of a young man who was at a school in Chicago but was originally from Grenada, West Indies. Since little to no information was known about this condition yet Herrick was only able to give his details of the sickled cells shape without a diagnosis of the disorder causing them (Herrick, 2001).

In 1915 Dr. Victor Emmel studied the blood of a patient with sickle cell anemia by making blood preparations on slides sealed with petrolatum. He observed the transformation of his patient's normal red blood cells into the sickled cells characteristic of SCD. He also looked at the blood of his patient's healthy father and noticed that the father's blood also sickled but not to the same

extent as his patient, making this Emmel's first attempt to determine a form of inheritance (EMMEL VE, 1917).

Decades later in 1949 Dr. James Neel looked at patients with sickle cell anemia and their parents. This allowed him to differentiate between the heterozygous sickle cell trait population, consisting of those carrying the sickle gene but not manifesting any symptoms, and the homozygous sickle cell anemia trait, consisting of those who had the actual disorder (Neel, 1949).

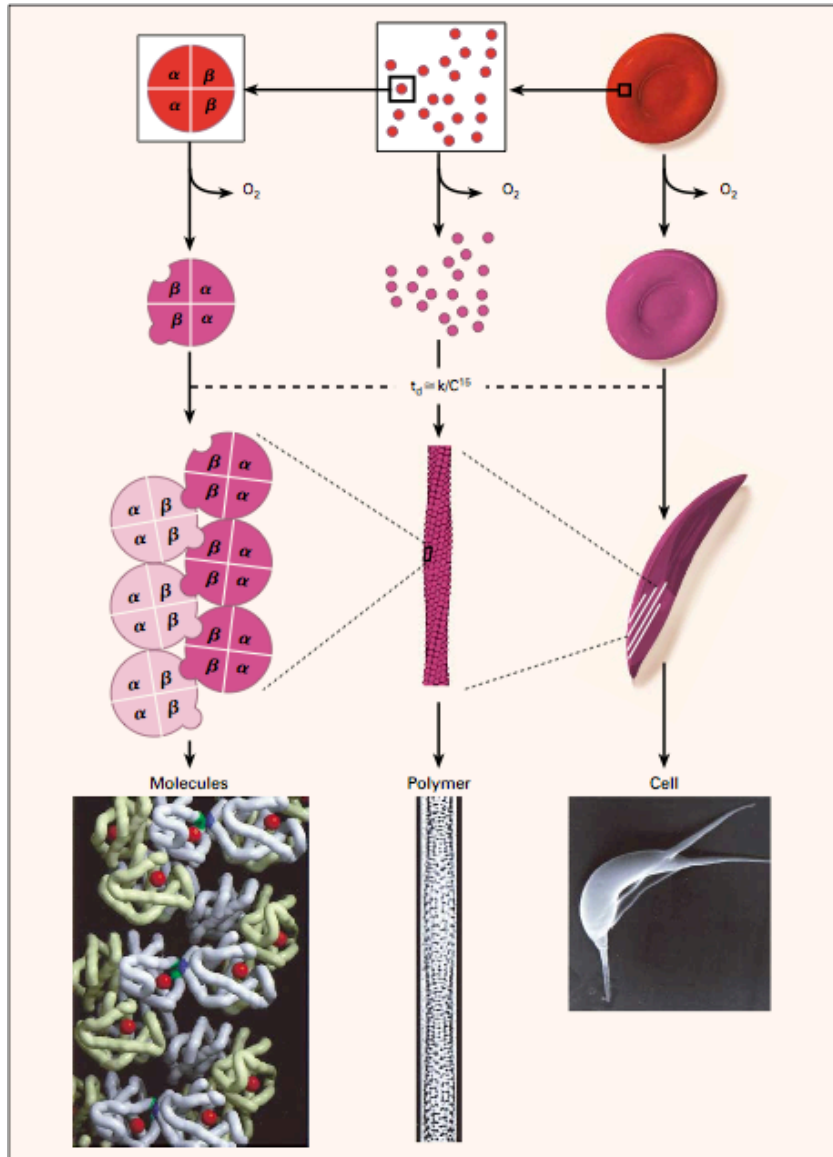
That same year Linus Pauling used gel electrophoresis to compare the hemoglobin of normal individuals, sickle cell anemia individuals, and sickle cell trait individuals. He observed that they all had different migratory patterns with the normal hemoglobin moving as a negative ion, the sickle cell anemia hemoglobin moving as a positive ion, and the sickle cell trait hemoglobin being a mixture of both the normal and sickle cell anemic patterns. This caused Pauling to suggest that there was a difference in the ionizable groups in the two hemoglobins and he hypothesized that the two conditions had different globins (Pauling, Itano, Singer, & Wells, 1949).

In 1957 Dr. Vernon Ingram compared the hemoglobin of normal individuals to those with sickle cell anemia using trypsin to digest the 2 proteins into peptides then using electrophoresis and chromatography to separate the peptides on paper. He noticed that there was a difference in only one peptide of the two hemoglobins which led him to discover that sickle cell hemoglobin was

caused by a single amino acid substitution of the normal hemoglobin (Hunt & Ingram, 1960).

### **Molecular Pathogenesis**

In SCD the abnormal hemoglobin results from a mutation in the beta-globin gene which is located on chromosome 11 (Fonseca, Souza, Salemi, Jardim, & Gualandro, 2012). In this point mutation there is a nucleotide change from thymine to adenine causing the sixth amino acid of the beta-globin chain, which was originally glutamic acid, to be replaced with valine. This new protein is now known as hemoglobin S (HbS). The replacement of the polar glutamic acid side chain with the non-polar valine side chain causes hydrophobic interactions between the beta subunits of adjacent hemoglobin molecules when they are in the deoxygenated state. These hydrophobic interactions cause polymerization of the HbS molecules which then cluster together in the red blood cells resulting in their distortion from normal biconcave discs to misshapen sickled cells (Figure 1) (Bunn, 1997). This sickling causes the red blood cells to lose their structural integrity and impedes blood flow through the vessels eventually leading to tissue and organ injury and resulting in the symptoms and complications associated with SCD (Caboot & Allen, 2013).



### Figure 1: Polymerization of Deoxygenated Red Blood Cells

This figure shows the change from oxygenated red blood cells (red) to deoxygenated red blood cells (pink). The left side of the figure illustrates the hydrophobic interactions between the beta subunits of adjacent hemoglobin molecules depicted as projections and indentations in the cartoon and as blue and green sites on the grey beta subunits in the high-resolution model. The middle diagram shows the 14-strand fiber resulting from polymerization. The right side of the figure shows how the polymerization deforms the red blood cell into a sickle shape portrayed in a cartoon as well as in a scanning electron micrograph. Figure taken from (Bunn, 1997).

## DISORDERS OF SICKLE CELL DISEASE

Those with SCD have at least one copy of the HbS mutation while the other beta-globin subunit of their hemoglobin can include a number of different mutations resulting in a large number of different genotypes. The most common genotype of SCD is when both beta-globin subunits contain HbS. This genotype is called sickle cell anemia and is the most severe variant out of all of the SCD disorders resulting in an overall lower survival rate by about 20 years. Three other common disorders of SCD are sickle cell hemoglobin C (HbSC), sickle- $\beta^0$  thalassemia (HbS $\beta^0$ ), and sickle- $\beta^+$  thalassemia (HbS $\beta^+$ ) (Steinberg, 2009).

Sickle hemoglobin C (HbSC) is the second most frequent SCD disorder and results from the hemoglobin C (HbC) mutation. In the second beta globin chain the glutamic acid in the normal adult hemoglobin is replaced with lysine (Hannemann et al., 2011) and the resulting genotype contains 50% HbS and 50% HbC (Lionnet et al., 2012). This disorder is generally less severe than HbSS and the complications associated with this condition present later in life compared to HbSS individuals. The presence of HbC in red blood cells increases the activity of the potassium-chloride cotransporter leading to the loss of both potassium and water from the cells and resulting in cell dehydration. This increases the concentration of hemoglobin in the red blood cells which enhances the sickling and polymerization of HbS (Nagel, Fabry, & Steinberg, 2003). The shape of HbSC cells also differ from those of HbSS cells with HbSC cells being

more folded than sickled, which is similar to the cells of HbC homozygotes (HbCC) (Lawrence, Fabry, & Nagel, 1991).

The two other less common disorders involve mutations in the beta thalassemia gene. In sickle- $\beta^0$  thalassemia (HbS $\beta^0$ ), the beta globin chain is not produced so there is no normal hemoglobin present. In sickle- $\beta^+$  thalassemia (HbS $\beta^+$ ), the beta globin chain is produced in reduced levels so small amounts of normal hemoglobin are present. With no production of HbA in HbS $\beta^0$  the symptoms and complications of this condition most resemble those of HbSS with both disorders being generally severe while HbS $\beta^+$  and HbSC have a less severe course of action (Serjeant, 2013).

In the Cooperative Study of Sickle Cell Disease (CSSCD), the largest study looking at both children and adults with SCD, individuals with HbSS and HbS $\beta^0$  had more bouts of pain and severe anemia compared to patients with HbSC and HbS $\beta^+$  (Platt et al., 1991). HbSS and HbS $\beta^0$  individuals also had more episodes of the pulmonary complication, acute chest syndrome (Castro et al., 1994). One exception to the degree of severity seen in these four disorders of SCD is the higher prevalence of proliferative sickle retinopathy (PSR), which is the blockage of vessels and thus lack of oxygen leading to the peripheral retina (Goldberg, 1977), seen in HbSC and HbS $\beta^+$  individuals compared to HbSS and HbS $\beta^0$  individuals (Serjeant, 2013). The exact reason for this is unknown but in HbSC it has been hypothesized that the cause of PSR is due to the higher hemoglobin concentration making the blood thicker (Steinberg, 2008). It has also

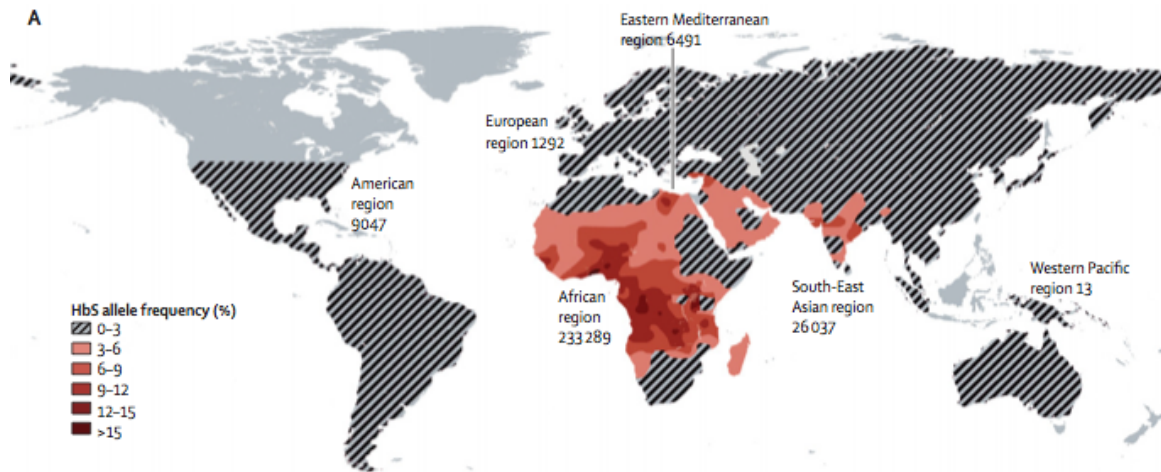
been hypothesized that the occurrence of PSR in HbSS is lower because the circulation to the retina becomes dysfunctional early on so the lesions characteristic of this complication are prevented from forming while the retinal circulation in HbSC is maintained allowing for the development of the lesions (Nagel et al., 2003).

### **Populations Affected by Sickle Cell Disease**

Sickle cell disease mainly affects individuals of African, Hispanic, and Mediterranean origin as well as those from India and Saudi Arabia. According to the World Health Organization, about 275,000 SCD births occur every year in the world (World Health Assembly, 2006). Figure 2 shows the distribution of the HbS allele in the world. Individuals in sub-Saharan Africa are the most affected by SCD with more than 250,000 newborns with sickle cell anemia being born every year (Serjeant, 2013). These numbers have been hard to estimate because in many of these countries where SCD is thought to be most prevalent there are no universal newborn screening programs to allow for early diagnosis.

Consequently, many children die from complications before being diagnosed or do not receive treatment early enough causing an underestimation of SCD individuals (Tshilolo et al., 2008).

In the United States SCD affects 1 in 365 African-Americans and 1 in 16,305 Hispanic Americans (Hamideh & Alvarez, 2013). It has been estimated that there are 72,000-98,000 individuals with SCD in the U.S. (Hassell, 2010).



**Figure 2: Prevalence of HbS Allele Worldwide**

This figure shows the regions with HbS affected individuals. Also shown are the estimates of individuals affected by the 4 most common disorders of SCD every year in each region. Figure taken from (D. C. Rees, Williams, & Gladwin, 2010).

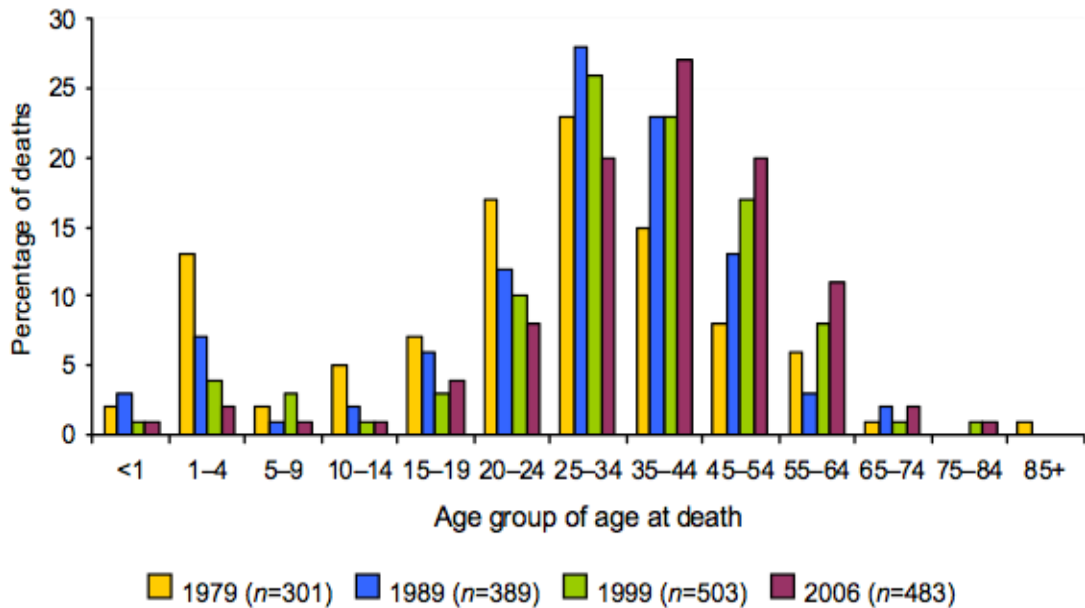
**Diagnosis**

The diagnosis of SCD in the United States is done through universal newborn screening. Within the first few months of birth the blood of infants is tested, most frequently by isoelectric focusing, which is a type of electrophoresis that separates hemoglobin on a gel (McGann, Nero, & Ware, 2013). Newborn screening was first suggested in the 1980’s after a trial looking at oral penicillin as a preventive measurement was shown to decrease the occurrence of pneumococcal sepsis during childhood. The early detection of children with sickle cell anemia allowed researchers to administer the pneumococcal vaccine sooner resulting in significant drop in death due to infection (Gaston et al., 1986).

Although the benefit of newborn screening was shown and this form of diagnosis strongly recommended by the National Institutes of Health at their 1987 Consensus Development Conference on Newborn Screening for Sickle Cell Disease and other Hemoglobinopathies, (National Institutes of Health, 1987) it was not until 2006 that newborn screening occurred throughout the entire United States (McGann et al., 2013).

### **Survival and Mortality**

Survival in those with SCD has come a long way in the past few decades. In the Dallas Newborn Cohort, survival at the age of 18 was 93.9% in HbSS and HbS $\beta^0$  and 98.4% in HbSC and HbS $\beta^+$  patients in 2010 compared to 85.6% and 97.4% respectively in 2004. These increases in survival are due to many factors including newborn screening and the decrease in age at which vaccinations are given (Quinn, Rogers, McCavit, & Buchanan, 2010). Figure 3 shows a significant decrease in death for the 1-4 age group resulting from these factors. The figure also shows that there was a shift in death age in adults from the 20-24 and 25-34 age groups to the 35-44 and 45-54 age groups. Although more patients are surviving past adolescence there is still the issue of complications that occur in adulthood. These individuals are now surviving into their thirties (Hassell, 2010) and higher but they still have a shorter lifespan by about 30 years when compared to the general population (Hamideh & Alvarez, 2013).



**Figure 3: Age at Death by Age Group**

This figure shows the number of sickle cell disease deaths for each age group during 4 specific years. Figure taken from (Hassell, 2010)

In a study looking at mortality of SCD in the U.S. from 1999-2009 the mortality rate of males was 35-44 years while in females it was 45-54 years (Hamideh & Alvarez, 2013). Many deaths have unexplained causes but a few studies noted some trends. In the Dallas Newborn Cohort patients were at the highest risk of death during their transition from pediatric to adult care (Quinn et al., 2010). Cardiovascular and pulmonary conditions were other common causes of death. These included acute chest syndrome, pulmonary hypertension, and congestive heart failure (Hamideh & Alvarez, 2013).

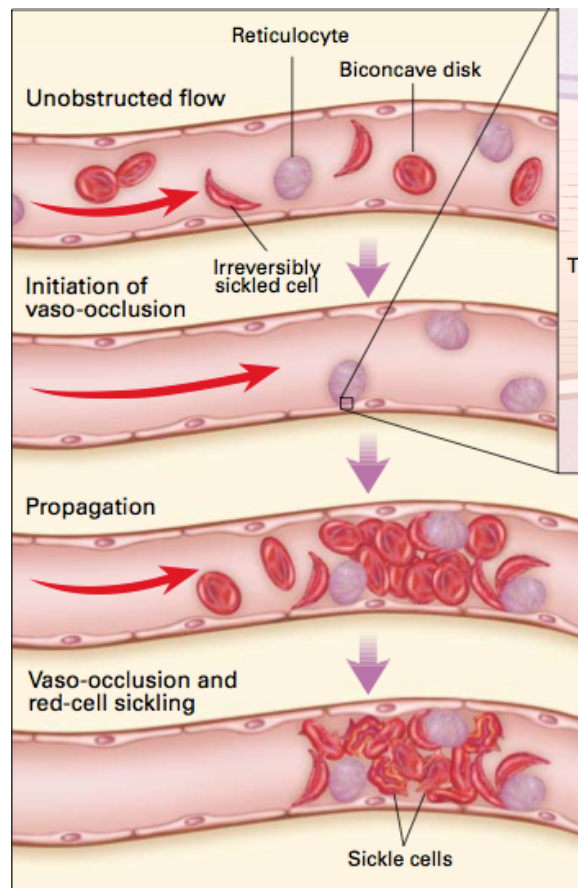
## **General Complications**

### **Pain Crises**

Pain crises is the number one symptom of SCD resulting in 95% of hospital admissions (Ballas & Lusardi, 2005). Patients most commonly feel this pain in their hands, feet, back, stomach, chest, or head (Platt et al., 1991). It is caused by the blockage of the smaller vessels by red and white blood cells resulting in blood flow interference and thus a reduction in the transportation of oxygen to the organs and tissues of the body (Gladwin & Vichinsky, 2008). This obstruction of blood flow is what is known as vaso-occlusion.

In the microcirculation, blood flow on the arteriolar side is much faster than on the venular side so as soon as the sickled red blood cells cross the capillaries and enter the venules they are travelling at a lower velocity until they reach the larger veins (Lipowsky, Kovalcheck, & Zweifach, 1978). Not only does this give the sickled cells ample time to start adhering to the endothelium of the vessels, it has also been shown that these cells are the most adherent in these post capillary venules unlike in the arterioles where the fast speed of blood flow prevents cell attachment (Lipowsky et al., 1978). The red blood cells have been categorized based on their density, which is determined by hemoglobin concentration. The increased density of these cells is due to cell dehydration caused by the increased activity of certain transporters that lead to removal of water from the cells (Joiner, 1993). From least to most dense there are reticulocytes, which are the immature red blood cells, discocytes, which are

young red blood cells, dense discocytes, and irreversible sickled cells (ISC's). In the post capillary venules it is the least dense cells, the reticulocytes and discocytes, that adhere to the endothelium preventing the passage of the most dense cells, the dense discocytes and ISC's, resulting in the blockage of the vessels (Figure 4) (Kaul, Fabry, & Nagel, 1989).



**Figure 4: The Manifestation of Vaso-Occlusion**

Shown is the two-step process that results in vaso-occlusion. During the first initiation step, reticulocytes, one of the least dense cells, adhere to the endothelium. This leads to the second propagation step, where irreversibly sickled cells and discocytes, labeled here as biconcave discs, are unable to get past the attached reticulocytes and so begin to pile up behind them resulting in the blockage that is characteristic of vaso-occlusion. With red blood cells being held up in these vessels they start to take their sickled form. Figure taken from (Hebbel, 2000).

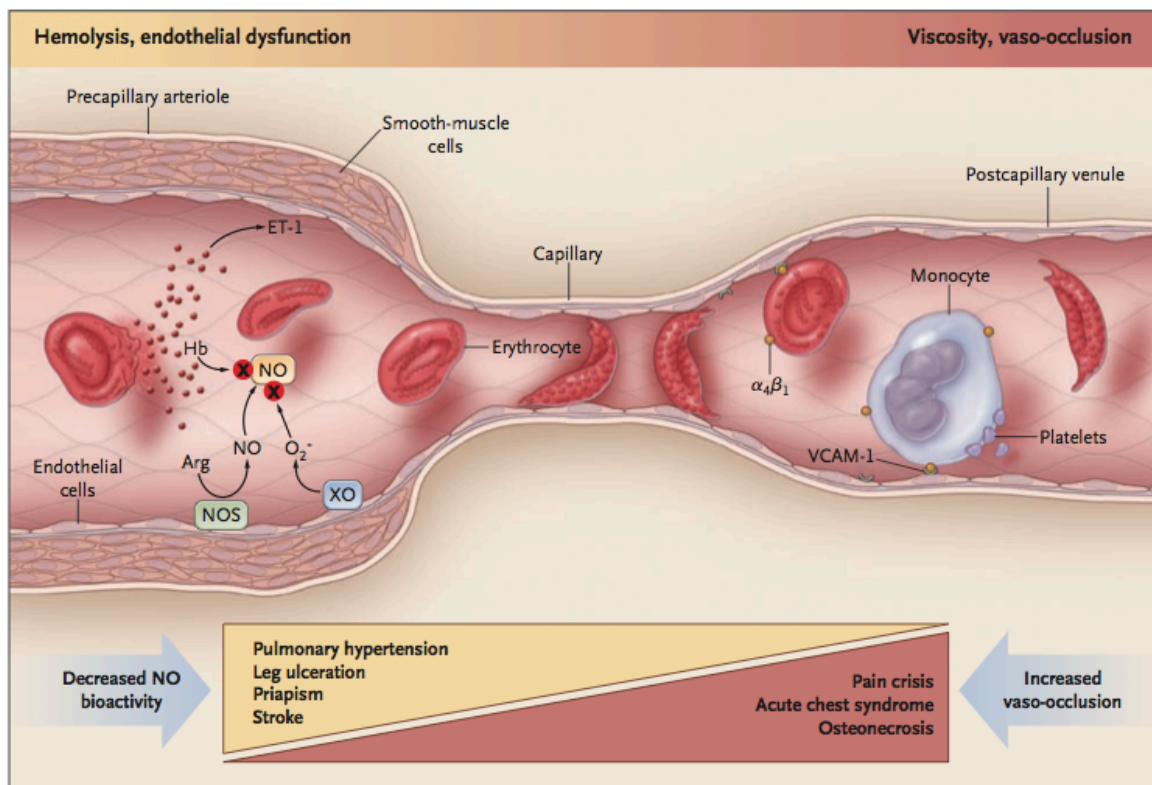
With this adhesiveness to the endothelium, blood flow through the veins is reduced further causing red blood cells to spend more time than usual in the deoxygenated state. This allows more cells to sickle and polymerize causing additional adherence to the endothelium and more blood flow obstruction (Ferrone, 2004). It is this blockage of the vessels that causes what is known as an acute painful episode (Hebbel, 2000)

The reduced blood flow caused by vaso-occlusion leads to organ and tissue damage. Further damage results from reperfusion injury, repeated cycles of ischemia and reperfusion, leading to inflammation (Hebbel, Osarogiagbon, & Kaul, 2004). When blood flow is inhibited it causes ischemia meaning oxygen is not reaching the tissues. This is remedied through reperfusion, where the tissues become re-oxygenated. This re-introduction of oxygen is the main cause of reperfusion injury (Carden & Granger, 2000). This process causes the production of reactive oxygen species and the expression of inflammatory mediators all leading to inflammation and vasculopathy (Hebbel et al., 2004).

### **Hemolysis**

Hemolysis is the breakdown of red blood cells with the release of its components into the plasma. This breakdown is a result of sickle cell polymerization which makes the red cell membrane unstable and prone to premature rupture (Reiter et al., 2002). With SCD red blood cells are breaking down faster than they are being produced by the bone marrow resulting in lower concentrations of hemoglobin in the body. This causes anemia, which has its

own number of symptoms associated with it. Hemolysis, like vaso-occlusion, also leads to the dysfunction of endothelial cells, which occurs through the removal of nitric oxide by the hemoglobin released into the blood (Figure 5)(D. C. Rees et al., 2010).



**Figure 5: Mechanism of Hemolysis and Vaso-Occlusion**

Shown is a schematic of hemolysis and endothelial dysfunction. Figure taken from (Rees et al., 2010).

Nitric oxide is produced by endothelial cells and is released into smooth muscle cells and blood vessels where it causes vasodilation among its other functions (Moncada & Higgs, 1993). When nitric oxide encounters oxygenated hemoglobin in the blood it is broken down into methemoglobin and nitrate ions. This reaction is normally limited because the red cell membrane acts as a barrier between nitric oxide and hemoglobin. Also, since oxygenated hemoglobin is present on the arterial side of the circulation, the rapid flow of plasma along the endothelium acts as another barrier separating the nitric oxide in the endothelium from the red blood cells passing by in the blood vessels (Schechter & Gladwin, 2003).

During hemolysis hemoglobin is released into the plasma which removes both the red cell membrane barrier and the plasma barrier allowing nitric oxide to now interact with the hemoglobin and be converted into methemoglobin and nitrate (Schechter & Gladwin, 2003). This removal of nitric oxide prevents it from having its vasodilation effect on the vasculature. Arginase is also released during hemolysis and acts by decreasing the levels of arginine, the substrate required for the synthesis of nitric oxide, resulting in even less nitric oxide being available (Gladwin & Vichinsky, 2008).

Another function of nitric oxide is the inhibition of leukocyte adhesion to the endothelium of post-capillary venules (Kubes, Suzuki, & Granger, 1991). In SCD there is no inhibition because hemolysis removes nitric oxide so the activation of the endothelium results in the increased adherence of lymphocytes,

monocytes, and granulocytes through the expression of leukocyte adhesion molecules like VCAM-1 (vascular cell adhesion molecule-1) and E-selectin. It is this expression that causes the adherence of reticulocytes to the endothelium seen in vaso-occlusion (De Caterina et al., 1995).

**Table 1: Major complications of Sickle Cell Disease**

Table lists the most common complications of SCD that occur as a result of vaso-occlusion and hemolysis. Figure taken from (Steinberg, 1999).

TYPE OF COMPLICATION	FEATURES
<b>Vaso-occlusive complications</b>	
Painful episodes	In more than 70 percent of patients; very frequent in some, rare in others
Stroke	In about 10 percent of patients in childhood; "silent" central nervous system damage with cognitive impairment in 5 to 9 times as many patients
Acute chest syndrome	In 40 percent of all patients; more common in children; more severe in adults
Priapism	In 10 to 40 percent of men; severe cases cause erectile dysfunction
Liver disease	In <2 percent of patients; many causes (e.g., iron overload, hepatitis B or C)
Splenic sequestration	In children <6 yr old; often preceded by infection
Spontaneous abortion	In about 6 percent of pregnant women with sickle cell anemia; much less frequent in sickle cell-hemoglobin C disease
Leg ulcers	In about 20 percent of adults with sickle cell anemia; rare in sickle cell-hemoglobin C disease
Osteonecrosis	In 10 to 50 percent of adults with sickle cell anemia and sickle cell-hemoglobin C disease
Proliferative retinopathy	Rare in sickle cell anemia; in 50 percent of adults with sickle cell-hemoglobin C disease
Renal insufficiency	In 5 to 20 percent of adults; severe anemia often present
<b>Complications of hemolysis</b>	
Anemia	Hematocrit values of 15 to 30 percent in sickle cell anemia; higher values in sickle cell-hemoglobin C disease
Cholelithiasis	Present in most adults; often asymptomatic
Acute aplastic episodes	Due to parvovirus B19 infection; appears with rapidly occurring, severe anemia
<b>Infectious complications</b>	
<i>Streptococcus pneumoniae</i> sepsis	In 10 percent of children <5 yr old with sickle cell anemia
Osteomyelitis	Due to salmonella and <i>Staphylococcus aureus</i>
<i>Escherichia coli</i> sepsis	In adults, initiated by urinary tract infection

## **Pulmonary Complications**

### **Acute Chest Syndrome**

Acute chest syndrome (ACS) is the leading cause of death in SCD individuals and the second most common cause of hospitalization (Raphael, Kavanagh, Wang, Mueller, & Zuckerman, 2011). It has been defined as a density in the lung as seen on a chest x-ray. This pulmonary infiltrate in the alveolar spaces of the lungs usually involves at least one complete segment of a lung and presents with a number of symptoms including fever, chest pain, rapid breathing, wheezing, and/or cough (Vichinsky et al., 2000).

### **Epidemiology**

ACS occurs more in HbSS and HbS $\beta^0$  compared to HbSC and HbS $\beta^+$  individuals with HbSS patients having the highest incidence overall (Castro et al., 1994). Although common in adults ACS is more prevalent in children, with those between the ages of two and four having the highest incidence (Ballas et al., 2010).

### **Clinic Presentation**

The clinical features of ACS differ between children and adults with children presenting more with wheezing, cough and fever while adults present with pain in their extremities and shortness of breath (Vichinsky et al., 1997). The Cooperative Study of Sickle Cell Disease showed that about 50% of patients diagnosed with ACS are already in the hospital for other complications with pain

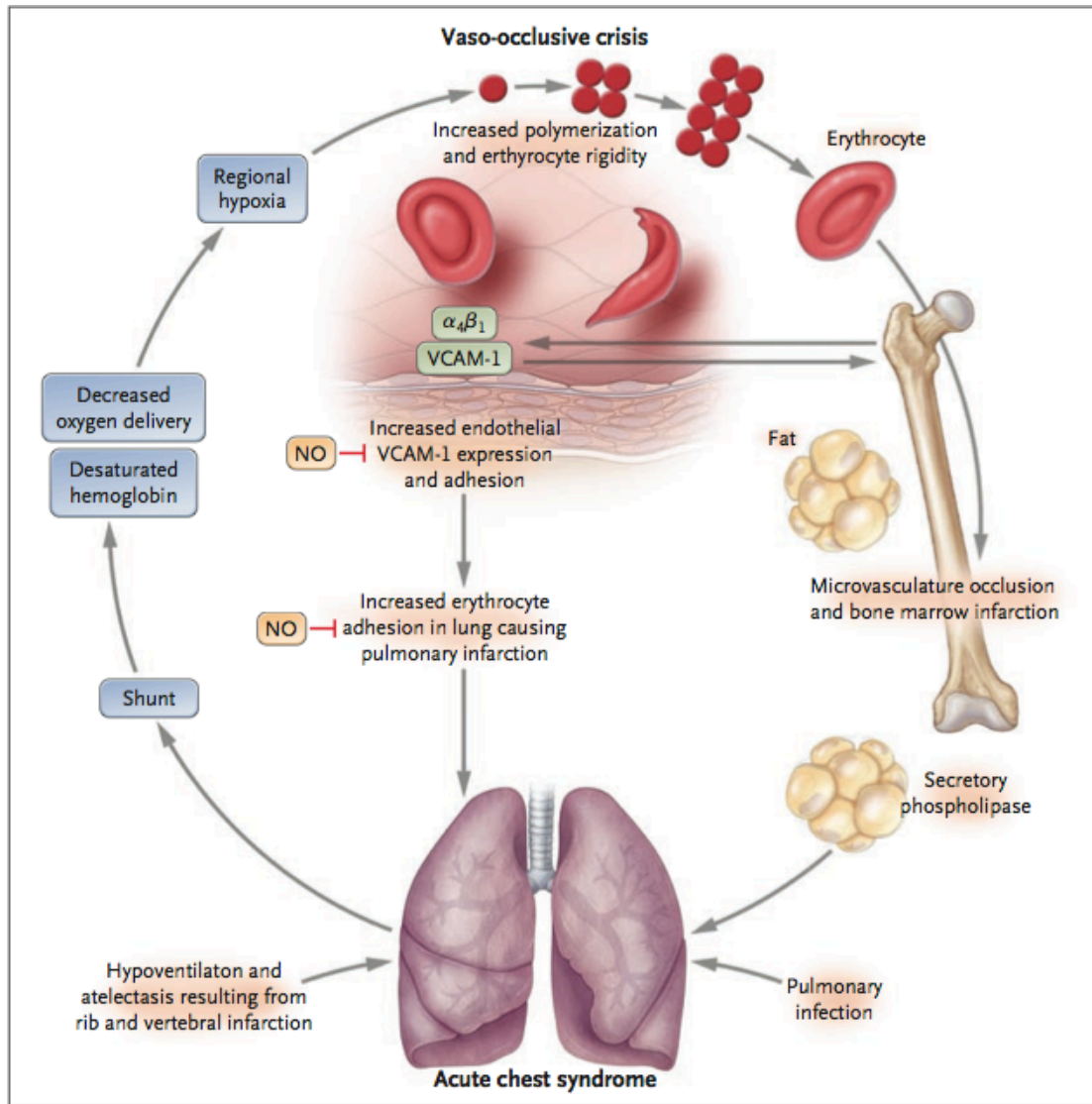
crises being the most common reason. In adults it usually takes 24 to 72 hours after the start of a pain crises to develop ACS with some signs of this development being a sudden drop in hemoglobin levels, an increase in hemolysis markers, and a decrease in platelet count (Gladwin & Vichinsky, 2008).

## **Etiology**

Figure 6 shows how three major triggers associated with vaso-occlusion produce the cycle of ACS that can lead to lung injury and tissue death. In a study done by the National Acute Chest Syndrome Study Group (NACSSG) looking at 538 patients with SCD, a specific cause of an ACS episode was determined in only 38% of patients (Vichinsky et al., 2000). Three major causes of ACS are pulmonary infection, lung obstruction by bone marrow fat, and accumulation of sickled red blood cells in the pulmonary vasculature (Gladwin & Vichinsky, 2008). Of these three causes pulmonary infection is the most common with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* being the most prevalent pathogens. In the NACSSG study pulmonary infection was the most common cause of ACS in children less than nine years of age (35%). The prevalence in children 10 to 19 years of age was 22% and in adults older than 20 years of age it was 26% (Vichinsky et al., 2000).

Lung obstruction by bone marrow fat is due to pain crises specifically in the pelvis and femur. Fluid accumulation and obstruction of the bone marrow leads to necrosis causing its contents to be released into the blood which then reach the lungs resulting in inflammation, hypoxia, and pulmonary hypertension

(Gladwin & Rodgers, 2000). The third major cause of ACS is the accumulation of sickled red blood cells. The red cells that enter the lungs are already in the deoxygenated state and with hypoxia due to other complications like vaso-occlusion there is increased HbS polymerization and thus sickling. This causes the adhesion of sickled cells to the endothelium of the pulmonary vessels resulting in blockages that ultimately lead to ACS and the death of lung tissue (Figure 6) (Graham, 2004).



**Figure 6: Process of Acute Chest Syndrome**

The three major triggers associated with vaso-occlusion produce the cycle of ACS that can lead to lung injury and tissue death. Figure from (Gladwin & Vichinsky, 2008).

## **Treatments**

The treatment of SCD depends on the severity of an individual's condition. Most therapy is supportive, helping one deal with the pain and the complications associated with SCD, but they do not help treat the long term effects SCD has on the organs and tissues of the body (Sheth, Licursi, & Bhatia, 2013). The two forms of treatment commonly used to manage SCD are blood transfusion and hydroxyurea therapy.

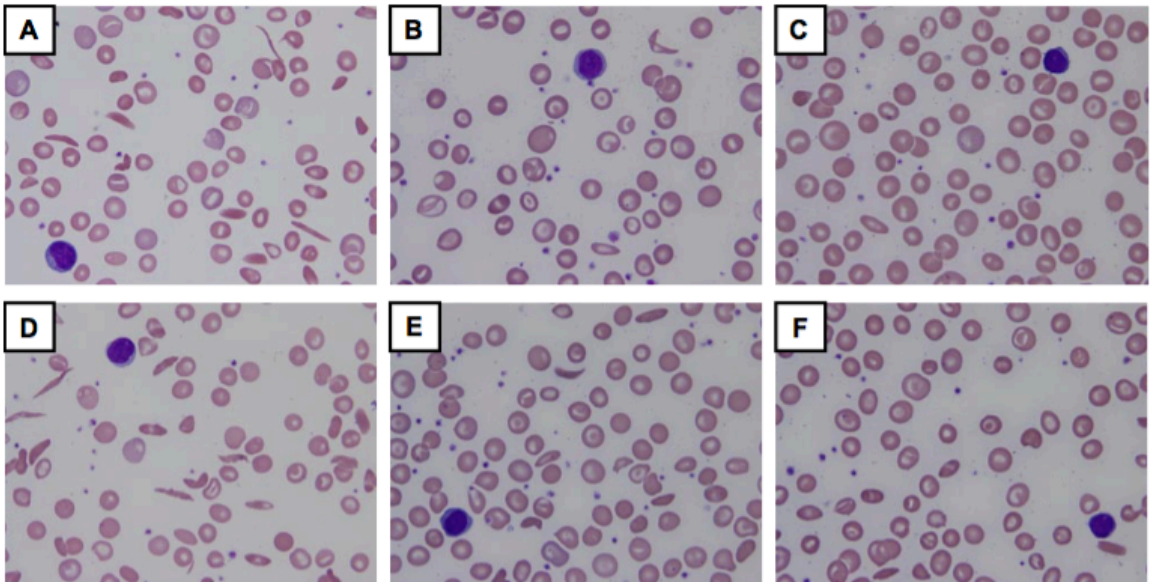
Red blood cell transfusion was one of the earliest forms of therapy used in treating SCD. It works by increasing one's hematocrit levels so that their blood is better able to carry oxygen to the tissues. In SCD patients this increase dilutes the blood so that the percentage of HbS is lower, resulting in less sickling and thus less SCD symptoms like anemia and vaso-occlusion (Wayne, Kevy, & Nathan, 1993). There are three types of transfusions used based the severity of one's symptoms.

Simple transfusion is used when a patient needs to increase the amount of oxygen getting to their tissue. The downside of this is the possible increase in the blood's viscosity due to the increase in hematocrit, which can actually make it harder for oxygen to reach the tissues and result in pain crises. Chronic transfusion is used to lower the amount of HbS and increase the amount of normal adult hemoglobin HbA. Long term use has been shown to lead to complications so this type of transfusion is used only in specific situations like cerebrovascular disease (Russell et al., 1984). Exchange transfusion is used to

either prevent or help treat complications of SCD that are detrimental to the organs (Wayne et al., 1993).

Hydroxyurea was originally used in the 1980's as a chemotherapeutic agent but is now one of the most important drugs used in treating SCD because of its ability to increase fetal hemoglobin (HbF) (A. L. Rees, 2015). It works by preventing the aggregation of HbS molecules in the blood, decreasing the sickling of red blood cells and resulting in less painful episodes as well as the need for transfusions as seen in the BABY HUG trial (Wang et al., 2011). This drug was originally used only in adults and is approved by the FDA for only adults but is increasingly being used in children with positive results.

Because the symptoms of SCD are so variable individuals use different dosages of hydroxyurea and have different HbF responses. Figure 7 shows the comparison of 2 children with HbSS who received hydroxyurea. Both children were given increased doses until they reached their maximum tolerated dose. Although they both had different HbF responses they still showed improvement in their bloodwork over time (Ware, 2010).



**Figure 7: Morphologic Changes During Increased Hydroxyurea Dosage**  
 Shown are the differences in HbF response between two children when given increased doses of hydroxyurea. (A-C) show the change of the child with a high HbF response and (D-F) show the child with a low HbF response. They both show an increase in hemoglobin and volume of red blood cells as well as a decrease in sickled cells, white blood cells, and neutrophils. Figure taken from (Ware, 2010).

## PULMONARY ARTERIAL HYPERTENSION

### History

Before the 1950's not much was known about pulmonary hypertension due to the lack of techniques used to study the heart and lungs. In 1940 Cournand and Richards developed the technique of cardiac catheterization after seeing German physician Werner Forssmann perform it on himself in 1929 (Cournand et al., 1945). These two physicians first studied this technique on

different animals and then used it on humans. The use of right heart catheterization allowed physicians to take blood samples, measure blood pressure in various parts of the heart, and measure gas concentrations in the blood.

In 1951 Dresdale who had worked under Cournand and Richards, looked at pulmonary hypertension in a mother and her two children. He was unable to determine the cause of their condition giving it the name primary pulmonary hypertension, which is today known as idiopathic pulmonary hypertension (Dresdale, Schultz, & Michtom, 1951). In 1958 Heath and Edwards looked at the structural changes in the pulmonary arteries in patients with pulmonary hypertension associated with congenital septal defects of the heart. With this information they categorized these changes into six grades (Heath & Edwards, 1958). In 1970 Wagenvoort and Wagenvoort gave a full description of primary pulmonary hypertension by looking at 156 patients in Europe (Wagenvoort & Wagenvoort, 1970).

In 1973 the WHO held its first meeting in Geneva, Switzerland where pulmonary hypertension was classified into two groups, pulmonary and secondary pulmonary hypertension (WHO Meeting on Primary Pulmonary Hypertension, Hatano, & Strasser, 1975).

## **Pathogenesis**

Pulmonary arterial hypertension (PAH) is high blood pressure in the arteries of the lungs [CITE]. It mostly affects the small arteries of the lungs which are called the resistance arteries (McLaughlin et al., 2009). These arteries carry blood from the heart to the lungs and control their flow. In this disorder the resistance arteries become constricted so that less blood is flowing through them and thus reduced blood is reaching the lungs (Chaudry et al., 2011). This causes an increase in the resistance of the arteries and in order to overcome this there has to be an increase in pressure so that enough blood still reaches the lungs. This is done by the right side of the heart, specifically the right ventricle. With the right side of the heart having to work much harder to pump blood through the resistance arteries it eventually becomes weakened and results in right heart failure (McLaughlin et al., 2009).

In normal vessels there is a balance between cell proliferation and apoptosis so that the vascular luminal cross-section doesn't change allowing blood to flow through the vessels at a constant rate. In PAH there is an increase in the protein thromboxane A2 in the smooth muscle cells of the resistance arteries and a decrease in prostacyclin production. Thromboxane A2 is a hormone known for being a vasoconstrictor and it also causes cell growth and promotes blood clotting. Prostacyclin is a compound that causes vasodilation. So with the vasoconstriction and cell proliferation caused by thromboxane A2 and the inhibition of vasodilation normally caused by prostacyclin there is an overall

decrease in the diameter of the arteries. Endothelin-1 is another protein that is increased in PAH and with its vasoconstriction and cell proliferation properties it also contributes to the narrowed vessels resulting in the need for higher pressures (McLaughlin et al., 2009).

## **Diagnosis**

The diagnosis of PAH is determined by looking at certain measurements using Doppler echocardiography and right heart catheterization. It has been shown that right heart catheterization is more accurate than Doppler echocardiography and should be used for the confirmation of PAH (McLaughlin et al., 2009). Doppler echocardiography is less invasive as it is a type of ultrasound of the heart showing the movement of blood. It is used on patients who are suspected of having PAH and it can be used to determine mean pulmonary arterial pressure (mPAP), left arterial pressure (LAP), and cardiac output (CO) all of which are done by measuring tricuspid regurgitant velocity (TRV). These measurements also allow for the calculation of pulmonary vascular resistance (PVR) (D'Alto et al., 2013). Right heart catheterization is more invasive allowing for a more accurate measurement of the pressures in the pulmonary arteries. In this procedure a catheter is put into the right side of the heart and then into the pulmonary artery [CITE]. Measurements of cardiac output, pulmonary capillary wedge pressure, and mPAP (McLaughlin et al., 2009).

With the use of both of these procedures it has been determined that PAH is confirmed in individuals having a mPAP  $\geq$  25 mmHg, pulmonary capillary wedge pressure  $\leq$  15 mmHg, and a PVR  $>$  3 Wood units (Chin & Rubin, 2008). The measurement of TRV done during Doppler echocardiography is used to determine the suspicion of PAH in an individual. More testing is done in those who have a TRV  $>$  2.5 m/sec which corresponds to a mPAP of 30 mmHg (Dahoui et al., 2010)

### **Classifications**

Pulmonary hypertension used to be categorized into two groups, primary and secondary pulmonary hypertension but in 1998 the second World Symposium took place in France and pulmonary hypertension was classified as having 5 major categories which have been modified over the years (Table 2). Group 1 is labeled as pulmonary arterial hypertension and involves conditions where pulmonary hypertension is concentrated in the pulmonary arteries. In this group idiopathic and hereditary PAH occur more in females compared to males (Thenappan, Shah, Rich, & Gomberg-Maitland, 2007). A major cause of heritable PAH seems to be a mutation in the bone morphogenetic protein receptor type 2, which is found in 80% of cases. Drugs and toxins like appetite suppressants and stimulating medications have also been found to cause PAH. Among the conditions associated with PAH connective tissue disease is the most severe

while portal hypertension and congenital heart disease are the least severe. (Chin & Rubin, 2008).

Group 2 involves pulmonary hypertension with left heart disease also known as pulmonary venous hypertension. Group 3 is associated with lung disease and/or hypoxemia. Within this group pulmonary hypertension is a frequent complication with these conditions and although not extremely severe individuals do have low survival rates. Group 4 is chronic thromboembolic pulmonary hypertension caused by blockage of pulmonary vessels that have not been cleared and resulting in right ventricle dysfunction. Group 5 is pulmonary hypertension with uncertain multifactorial mechanisms and is where sickle cell disorder is classified (Chin & Rubin, 2008) (Simonneau et al., 2013).

## Table 2: Pulmonary Hypertension Classifications.

Shown are the 5 current major categories of pulmonary hypertension. Table taken from (Simonneau et al., 2013).

1. Pulmonary arterial hypertension
  - 1.1 Idiopathic PAH
  - 1.2 Heritable PAH
    - 1.2.1 BMPR2
    - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
    - 1.2.3 Unknown
  - 1.3 Drug and toxin induced
  - 1.4 Associated with:
    - 1.4.1 Connective tissue disease
    - 1.4.2 HIV infection
    - 1.4.3 Portal hypertension
    - 1.4.4 Congenital heart diseases
    - 1.4.5 Schistosomiasis
- 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
- 1''. **Persistent pulmonary hypertension of the newborn (PPHN)**
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**
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
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
  - 5.1 Hematologic disorders: **chronic hemolytic anemia**, 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: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

The WHO has also classified pulmonary hypertension into 4 functional categories used to assign disease severity. Functional class I describes individuals with no symptoms of pulmonary hypertension during rest, normal activities, or exercise. Functional class II individuals show no symptoms at rest but have a little trouble with normal activities and exercise. Functional class III individuals may be fine at rest but any type of activity will cause symptoms including shortness of breath and chest pain. Functional class IV is the most severe with individuals showing symptoms at rest. They have difficulty with any type of basic activity and show signs of right heart failure (WHO Meeting on Primary Pulmonary Hypertension, 1975).

### **Right Heart Failure**

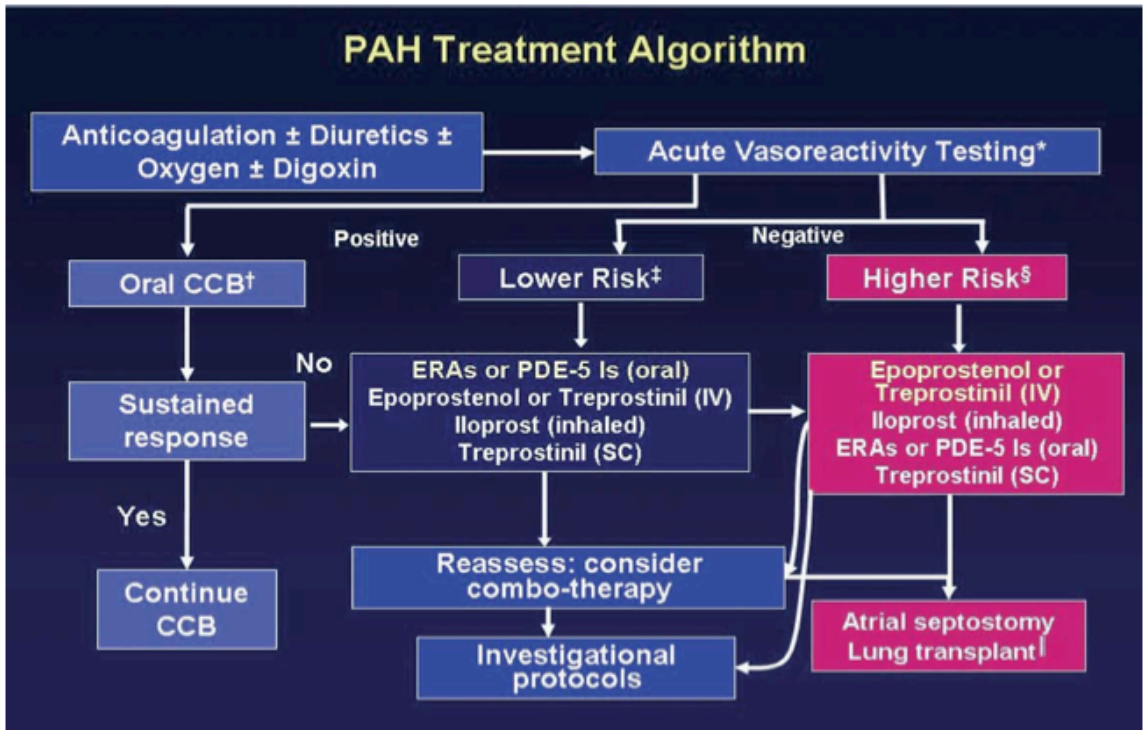
Right heart failure is the main cause of death in individuals with PAH (D'Alonzo et al., 1991). Many factors play a role in this condition and a lot is still unknown but it all starts with the dysfunction of the right ventricle. When the resistance in the pulmonary arteries first increases less blood is able to flow through these vessels, resulting in increased amount of blood left in the right ventricle. The right ventricle then compensates for this increased afterload by increasing its contractility, which over time leads to right ventricle hypertrophy where the cardiac muscle of this chamber becomes thickened as a result of working harder than normal. In a study looking at 578 patients belonging to Group 1 of the World Health Organization (WHO) classification, 55% of patients

had right ventricular hypertrophy and 22% had right atrial enlargement (Thenappan et al., 2007).

This increase in size of the heart chambers is due to an increased afterload. Because of the higher resistance in the pulmonary arteries less blood is flowing through from the heart to the lungs so there is more blood left over in the right ventricle causing the right side to increase its size to compensate for the extra volume of blood (McLaughlin et al., 2009). As the increased pulmonary resistance persists the right ventricle becomes less able to compensate leading to dilation of the ventricular walls and no further increase in contractility. This causes less blood to flow through the pulmonary vessels and into the left side of the heart resulting in a lower cardiac output that can ultimately lead to right heart failure (Noordegraaf & Galiè, 2011).

## **Treatments**

The treatment of pulmonary hypertension depends on the severity of the disease. The earlier one is diagnosed the better the results of treatment. There are two types of treatment, primary and advanced. Primary therapy is used at the beginning stages of pulmonary hypertension and focuses on treating the causes of the pulmonary hypertension. Advanced therapy is used with severe disease and focuses on treating the actual pulmonary hypertension. Figure 7 shows the process used when treating pulmonary hypertension (McLaughlin et al., 2009).



**Figure 8: Procedure Used To Treat Pulmonary Hypertension.**

Shown are the primary and advanced treatments of pulmonary hypertension. Primary treatments include anticoagulants, diuretics, oxygen, and digoxin. Advanced treatments depend on acute vasoreactivity testing and include calcium channel blockers (CCBs) for a positive response and endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and prostanoids for a negative response. Figure taken from (McLaughlin et al., 2009)

Primary treatment can be used on individuals with pulmonary hypertension in any of the five WHO groups. It includes anticoagulants, diuretics, oxygen, and digoxin (Figure 7). Warfarin is the anticoagulant commonly used and it works by preventing the formation of blood clots that would otherwise block blood flow in the vessels. This is most beneficial for idiopathic PAH and group 4 PH individuals who are prone to thrombosis. Diuretics are used to reduce fluid build up caused by the increased afterload that occurs in right heart failure (Chin

& Rubin, 2008). Desaturation occurs with vasoconstriction of the pulmonary arteries due to hypoxemia resulting from low cardiac output (Humbert, Sitbon, & Simonneau, 2004). This is treated with supplemental oxygen, which keeps an individual's oxygen saturation above 90% (McLaughlin & McGoon, 2006). The use of digoxin still needs to be investigated further but so far it has been shown to help the heart pump more blood thus increasing its cardiac output which is useful in individuals with right heart failure (McLaughlin et al., 2009).

Advanced Therapy in WHO groups 2-5 has not been researched as much as group 1, specifically idiopathic PH so the following treatments are based on studies done with group 1 PAH. Treatment starts with acute vasoreactivity testing, which is done during right heart catheterization and is a sign of how well an individual will respond to calcium channel blockers. The patient is given either inhaled nitric oxide, intravenous prostacyclin, or intravenous adenosine, which are all vasodilators (Humbert et al., 2004). A positive response is indicated by a mPAP that falls by at least 10 mmHg and is less than or equal to 40 mmHg with no decrease in cardiac output (McLaughlin et al., 2009). Less than 10% of individuals with idiopathic PAH have a positive vasoreactivity test (Sitbon et al., 2005). The most common calcium channel blockers are nifedipine, diltiazem, and amlodipine and the choice of which one to use is determined by the individual's baseline heart rate (Galiè et al., 2009). Patients taking these drugs must be followed closely because only half of them continue to respond long term (sustained response) (Chin & Rubin, 2008). Also a lack of improvement into

WHO functional class I or II indicates that this treatment won't work long term so other forms of therapy should be considered (McLaughlin et al., 2009).

Patients with a negative acute vasoreactivity response are then classified as being high risk or low risk. One's risk level is determined by a combination of factors including signs of right heart failure, severity of symptoms, and WHO functional class (McLaughlin et al., 2009). Regardless the risk level the three types of treatment given are endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostanoids. The endothelin receptor antagonists used are bosentan, ambrisentan and sitaxsentan. They act by inhibiting endothelin-1, which is a vasoconstrictor of the vessels (Chin & Rubin, 2008). The phosphodiesterase type-5 inhibitors, sildenafil and tadalafil, act by preventing the fast breakdown of cyclic GMP by phosphodiesterases therefore resulting in vasodilation by nitric oxide (McLaughlin et al., 2009). The prostanoids are epoprostenol, treprostinil, and iloprost. They are synthetic prostacyclin and act by inducing vasodilation and inhibiting platelet aggregation (Galiè et al., 2009). Epoprostenol has a very short half life so it must be given through a continuous pump while treprostinil and iloprost are longer acting (Chin & Rubin, 2008).

Some patients continue to get worse while being treated with one of the above-mentioned medications or their condition is too severe to be treated with just one drug (monotherapy) so they require combination therapy. This involves the use of more than one drug taken at the same time and seems to be safe and effective. The best combination of drugs has not yet been determined so the

choice of therapy should be based on each individual's characteristics (Buckley, Staib, & Wicks, 2013).

Lastly if medical therapy is unsuccessful in improving conditions the last consideration is lung transplantation and atrial septostomy. Lung transplantation can be a single or double transplantation and has been shown to improve quality of life. Atrial septostomy is when a shunt is created between the left and right heart atria decreasing the pressure on the right side of the heart (McLaughlin et al., 2009).

## **PULMONARY ARTERIAL HYPERTENSION IN SICKLE CELL DISEASE**

### **Prevalence and Mortality**

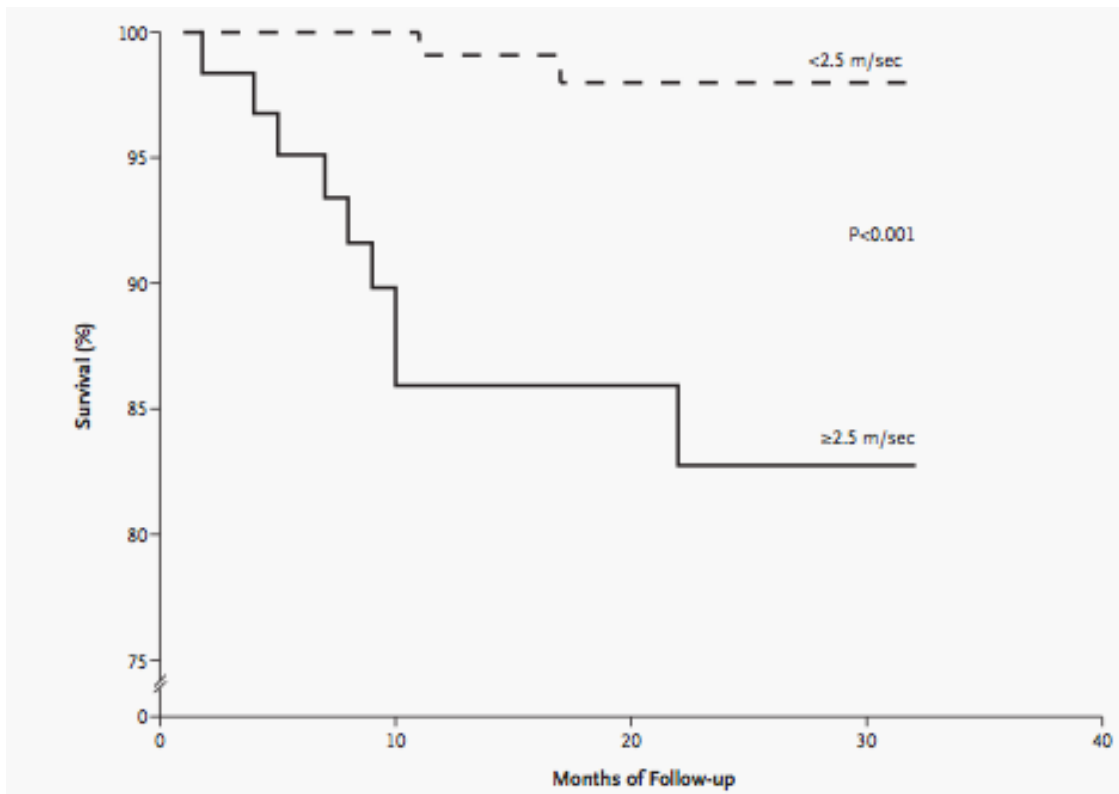
The prevalence of adults with sickle cell disease associated with pulmonary hypertension differs between studies and countries. Most researchers have used Doppler echocardiography to diagnose pulmonary hypertension, looking for a TRV of 2.5 m/sec or greater. One study in the United States found pulmonary hypertension in 36% of patients with HbSS and HbS $\beta^0$  and in 25% of patients with HbSC, HbS $\beta^+$ , and in the less common sickle cell-hemoglobin O Arab disease (SO<sub>Arab</sub>) (De Castro, Jonassaint, Graham, Ashley-Koch, & Telen, 2008). A study in Saudi Arabia found 37.1% of SCD adults to have pulmonary hypertension (Al-Khoufi, 2013). In children in the U.S. 30% with SCD had and elevated mPAP (Pashankar, Carbonella, Bazy-Asaad, & Friedman, 2008) while

44% of children in London with HbSS and 6% with HbSC had pulmonary hypertension.

Other studies have used both echocardiography and right heart catheterization to look at pulmonary hypertension. In France 27% of adults with SCD had a TRV of at least 2.5 m/sec but on RHC the prevalence decreased to 6% (Parent et al., 2011). In Brazil 40% of adults had pulmonary hypertension on echocardiography but only 10% were confirmed on RHC (Fonseca et al., 2012). Because echocardiography can inaccurately estimate the prevalence of pulmonary hypertension through imprecise measurement of mPAP it is now mostly used as a screening tool to see which patients are at risk of having pulmonary hypertension (McGoon et al., 2004).

Patients with both pulmonary hypertension and sickle cell disease have higher hemodynamic measurements compared to SCD individuals without pulmonary hypertension. Although these values are not as high as in individuals with just idiopathic pulmonary hypertension the association between these 2 conditions results in a significant increase in mortality (Gladwin et al., 2004). Figure 8 shows the rise in mortality of SCD individuals with pulmonary hypertension in the months after diagnosis compared to SCD individuals without pulmonary hypertension. Their survival is inversely proportional to their tricuspid regurgitant jet velocity (TRV), which is used to estimate mean arterial pressure (mPAP). A TRV of less than 2.5 m/sec corresponds to a normal mPAP while a TRV of 2.5 m/sec or greater corresponds to a high mPAP. Those with an

increasing mPAP show a continual increase in mortality rate as time goes on (Gladwin et al., 2004).



**Figure 9: Estimated Survival of SCD Individuals With and Without Pulmonary Hypertension**

This figure compares survival rate of sickle cell disease individuals without diagnosed pulmonary hypertension (dashed line) and those with diagnosed pulmonary hypertension (solid line). Figure taken from (Gladwin et al., 2004).

### Pathogenesis

The pathogenesis of pulmonary hypertension in sickle cell disease has not been fully established but there are many theories that have been studied. Three commonly proposed theories are decreased nitric oxide availability due to

hemolysis, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, and lactate dehydrogenase (LDH) as a biomarker. As previously mentioned in process of hemolysis, the breakdown of red blood cells in SCD patients causes a decrease in NO levels because released hemoglobin binds with nitric oxide and released arginase increases its levels in the plasma shifting its metabolism from producing arginine to producing ornithine thus decreasing the amount of arginine that can be used to make NO (Gladwin & Vichinsky, 2008). One study found that increased levels of arginase in the plasma correlated with patients who had pulmonary hypertension and the lower the levels of arginine in a patient's plasma the more severe their pulmonary hypertension. So the endothelial dysfunction due to low levels of NO and the increased amount of ornithine due to higher levels of arginase in the plasma are thought to contribute to the pathogenesis of pulmonary hypertension (Morris CR, Kato GJ, Poljakovic M, & et al, 2005).

Another study looked at N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients from both the National Institute of Health's Pulmonary Hypertension Screening Study and the Multicenter Study of Hydroxyurea in Sickle Cell Anemia Patients' Follow-up Study. Researchers found that high NT-proBNP levels were due to right ventricular dysfunction, which leads to pulmonary hypertension. It was also shown that these biomarkers levels were also correlated with tricuspid regurgitant jet velocity whose measurement is a sign of possible pulmonary hypertension. Lastly an association between LDH and hemolysis was found in studies of both adults and children. In one study of adult

SCD patients LDH was found to be associated with several sign of hemolysis including low levels of hemoglobin and high levels of plasma arginase (Kato et al., 2006). In a study with children, although LDH wasn't being studied as a biomarker for hemolysis it was found to be the strongly correlated with an increased TRV which correlated with signs of hemolysis (Liem, Young, & Thompson, 2007). When LDH was correlated directly to hemolysis in the study it was found to only explain 30% of the elevated TRV suggesting that there are possibly more than just one cause of pulmonary hypertension in the pediatric population. One suggested theory is hemolytic anemia causing the release of plasma free hemoglobin, which reacts with nitric oxide decreasing its bioavailability. Arginase present in the red cells also reduces the bioavailability of nitric oxide and together.

### **FUTURE ENDEAVORS.**

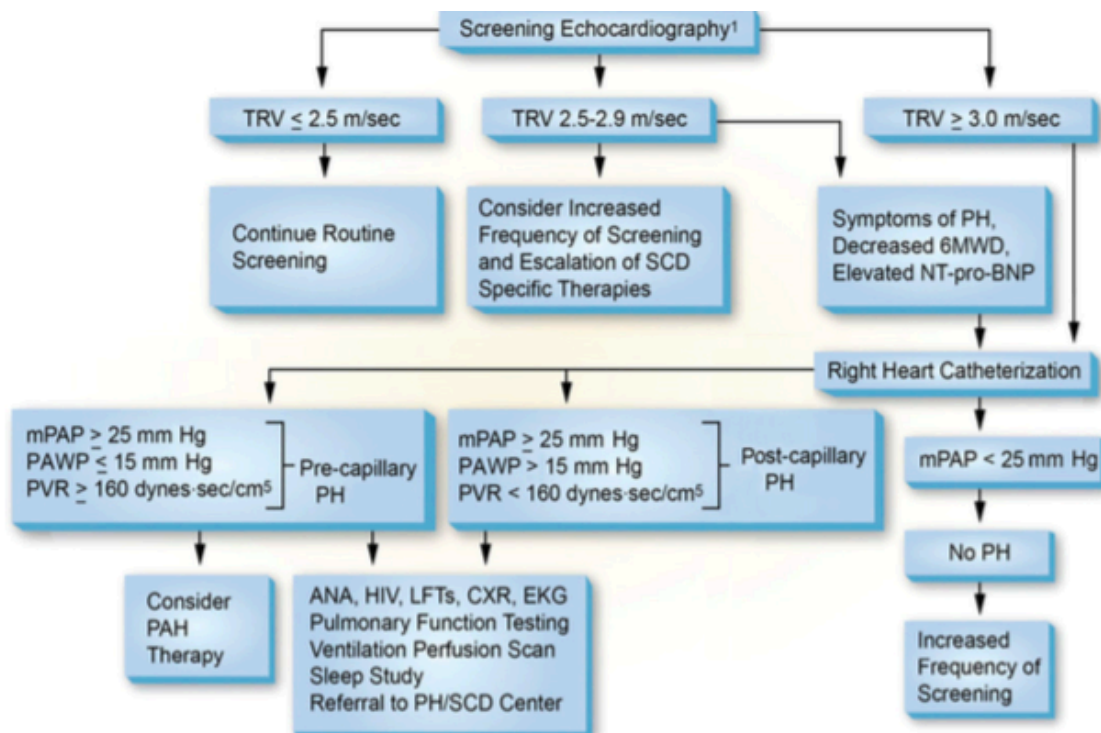
The study of pulmonary hypertension in children with sickle cell disease has only recently come to be researched; thus there are many unknowns. The biggest hindrance in the development of defined management of pulmonary hypertension in this population is the unknown cause of the disease itself.. As previously mentioned there are several proposed theories currently being studied and it looks like there will probably be more than just one cause suggesting the need for more than just one form of treatment. Right now the research indicates that the next step should be performing more longitudinal studies with a high

number of subjects who are just children and young adults. Once more clinical trials on this age population are completed and the specific causes of pulmonary hypertension are determined, a specific treatment plan can be put into place and patients, both children and adult SCD patients, can begin to avoid the increased mortality associated with having pulmonary hypertension.

In the meantime, as more data is being attained about this condition in both children and young adults, there are actions that can be taken right now to help the pediatric population. Studies looking at the differences between children and adults have shown that an elevated TRV, which seems to be a prominent marker for pulmonary hypertension, does not have the same detrimental effects in children as it does in adults (Hagar, Michlitsch, Gardner, Vichinsky, & Morris, 2008). This suggests that early intervention at a young age could either help prevent development of pulmonary hypertension or help reverse the effects of newly diagnosed pulmonary hypertension.

Based on what is known today the TRV measurement is currently the best way to screen for possible pulmonary hypertension so children should be continuously tested so that pulmonary hypertension can be detected early and the appropriate measures can be taken to avoid further complications. Figure 9 is a proposed algorithm for the testing of pulmonary hypertension. Doppler echocardiography should be the first screening tool to assess TRV measurements since it is not an invasive procedure. Those with a low TRV are at the lowest risk of developing PH but should still continue to get screened on a

regular basis. Those with acute TRV levels should frequently get screened and a treatment plan should be put in place to help lower their TRV levels so that they can avoid developing the symptoms of PH that will lead them to having to undergo right heart catheterization. Those with a high TRV should immediately be tested using the more invasive right heart catheterization to confirm if they truly have PH and if so what type. This will help determine the form of treatment needed.



**Figure 10: A Suggested Process of Assessing Pulmonary Hypertension in those with Sickle Cell Disease**

Shown is a proposed mechanism for the continual testing of pulmonary hypertension depending on one's TRV levels based non-invasive Doppler echocardiography. Figure taken from (Klings et al., 2014)

In conclusion, there are still many questions to be answered about pulmonary hypertension in the young SCD population and more longitudinal studies are needed to determine the specific causes of PH and the best way to treat it. Early intervention for all children and young adults with SCD to avoid future complications is the best plan. There need to be more centers with physicians who are fluent in this condition so that children are being fully monitored and treated. This is the best way to keep a patient's condition under control and help prevent pulmonary hypertension as well as other complications associated with SCD.

Specific areas that should be studied more in the near future include specific treatment plans in this pediatric population as well as elevated TRV measurements and its effects on mortality risk. Once the direct association of TRV with pulmonary hypertension and its effects on children is determined it will become easier to come up with a management plan that will decrease the complications associated with pulmonary hypertension and hopefully substantially decrease mortality risk.

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## VITA

