ERJ Express. Published on July 20, 2011 as doi: 10.1183/09031936.00134410

PULMONARY HYPERTENSION DIAGNOSED BY RIGHT HEART CATHETERIZATION IN SICKLE CELL DISEASE

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Running title: Pulmonary hypertension in sickle cell disease

Background: Recent studies have recognized the importance of pulmonary hypertension (PH) in sickle cell disease (SCD). The aim of this study was to determine the prevalence and prognostic impact of PH and its features in patients with SCD.

Methods:80 patients with SCD underwent baseline clinical evaluation, laboratory testing, 6-minute walk test (6MWT) and echocardiography. Patients with peak tricuspid regurgitant jet velocity(TRV) ≥ 2.5 m/s were further evaluated through right heart catheterization (RHC) to assure the diagnosis of PH.

Results: Our study evidenced a 40% prevalence of patients with elevated TRV at echocardiogram. RHC (performed in 25/32 patients) confirmed PH in 10% (95% CI 3.4 to 16.5) of all patients, with a prevalence of post-capillary PH of 6.25% (95%CI 0.95 to 11.55) and pre-capillary PH of 3.75% (95%CI -0.4 to 7.9%). Patients with PH were older, had worse performance at 6MWT and more pronounced anemia, haemolysis and renal dysfunction. Survival was shorter in patients with PH.

Conclusions: Our study reinforced the use of echocardiogram as screening tool for PH in SCD but also the mandatory role of RHC for the proper diagnosis. Our findings confirmed the prognostic significance of PH in SCD as its association to pronounced hemolytic profile.

Keywords: pulmonary hypertension; sickle cell disease; hemodynamics; prevalence; right heart catheterization; survival.

INTRODUCTION

Sickle cell disease (SCD) encompasses a group of hereditary hemoglobinopathies resulting from inheritance of at least a mutant version of the β-globin gene (β^A) on chromosome 11, designated hemoglobin S (HbS).[1] In Hb S valine replaces glutamic acid in position 6 of the β-chain. This substitution leads to polymerization of hemoglobin when deoxygenated. [2]

In homozygous sickle cell anemia (SCA), both alleles of the β^S -globin are inherited. In addition to SCA, other major sickle genotypes resulting from co-inheritance of other β^Aglobin gene mutations or β-thalassemia mutations are recognized.[1] Individuals who have SCA are clinically indistinguishable from those who have $S\beta^0$ thalassemia and both are more severe than other sickle genotypes.[1] SCD is clinically characterized by the presence of chronic hemolytic anemia and by acute and chronic vaso-occlusion phenomena with cumulative and widespread organ damage. The World Health Organization (WHO) estimates there are around 275.000 births worldwide with SCD.[3]

Pulmonary hypertension (PH) associated to SCD was first described in 1936, by Yater e Hansmann[4] and corresponds to a frequent and serious complication, associated with increased morbidity and mortality. Traditionally, PH in SCD was considered to be a result of vaso-occlusive events, such as acute chest syndrome (ACS).[5,6] In the last few years, however, PH has been attributed to intravascular hemolysis and consequent deregulated nitric oxide (NO) metabolism.[7,8]

The early symptoms of PH are nonspecific and do not differ from those experienced by SCD patients without PH. [9] Previous studies suggested that the prevalence of PH in this disease is between 0 and 35%.[10-14] However, these

studies were limited by their retrospective data collection, patient selection and lack of right cardiac catheterization confirming the presence of PH and also differentiating pre and post capillary PH.

The aim of this study was to determine the prevalence and prognostic significance of PH in SCD patients.

METHODS

Population

In this cohort, we prospectively evaluated 80 consecutive adult patients (>18 years old) with SCD (subtypes SCA and $S\beta^0$thalassemia) followed at our university hospital. The diagnosis of SCD was based in hemoglobin electrophoresis and A2 hemoglobin level determination by chromatography. Patients had to be clinically stable, without history of ACS or blood transfusion in the last two weeks to be included. All patients provided written informed consent.

Clinical and laboratorial evaluation

All patients underwent baseline clinical evaluation, hematological testing, including complete blood count, reticulocyte count, hemoglobin electrophoresis, fetal hemoglobin level determination and also biochemical testing to evaluate the hemolytic profile. History of acute chest syndrome was assessed in medical records. The serum levels of inflammatory markers as well as liver and renal function were also determined. At the same day, all patients performed a 6-minute walk test (6MWT), as previously described.[15]

Echocardiographic studies

Doppler echocardiography was performed by the same cardiologist, blinded to all other patient data except to the diagnosis of sickle cell disease. The two-dimensional echocardiographic images were obtained using an Acuson ultrasound system (Sequoia 512, Montain View, CA). Cardiac measurements were performed according to the guidelines of the American Society of

Echocardiography [16]. Tricuspid regurgitation was assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views. Continuous-wave Doppler sampling of the peak regurgitant jet velocity (TRV) was used to estimate the right-ventricular-to-right-atrial systolic pressure gradient using the modified Bernouille equation (4 X $[TRV]^2$). The presence of valvular heart disease or left ventricular systolic dysfunction was considered as an exclusion criterion.

Invasive hemodynamic evaluation

Patients with TRV ≥ 2.5 m/s were submitted to right heart catheterization (RHC). A 7F flow-directed pulmonary artery catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was introduced in all patients. Cardiac output (CO) was measured by the standard thermodilution technique. We defined as pulmonary hypertension (PH), the presence of mean pulmonary artery pressure (mPAP) equal or greater than 25 mmHg; further classification into pre or post-capillary pulmonary hypertension was based on the level of the pulmonary artery occlusion pressure (PAOP); PH patients with PAOP ≤ 15 mmHg were classified as having pre-capillary pulmonary hypertension. All patients presenting PH at the right heart catheterization were evaluated for the presence of chronic thromboembolic disease by means of pulmonary V/Q scan.

Statistical analysis

Continuous data are expressed as mean±SD. Qualitative data are expressed as proportions with 95% confidence interval (95%CI) and were

compared using Fisher's exact test. All continuous variables were compared using unpaired t-test. Laboratorial measurements were log–transformed in order to reduce the influence of data distribution. A p value of less than 0.05 was considered significant. Survival during time was estimated using the Kaplan-Meier method. The log-rank test was used for curve comparison.

RESULTS

Eighty patients were included in the study (61.2% females) with mean age of 33.3 (10.1) years. Median follow-up time was of 31.9 months (3.3-34.6). An interpretable TRV was obtained in all patients and ranged between 0.79 and 4.17 m/s. In 32 patients (40% (95%CI 29.2 to 54.7%)), TRV was greater than 2.5 m/s, suggesting the presence of elevated pulmonary arterial systolic pressure (SPAP). Clinical, hematological, biochemical and echocardiographic characteristics of all patients are presented in table 1. Patients with TRV≥2.5 m/s presented more pronounced anemia, more hemolysis (mirrored by increased values of LDH and AST), higher levels of uric acid, γ-glutamiltransferase, blood urea nitrogen and creatinine.

Among 32 patients referred to right heart catheterization, 26 (81.2%) underwent the procedure. Four patients did not perform the exam for social or clinical reasons. Two patients refused the procedure. Hemodynamic data are showed in table 2.

The SPAP estimated through echocardiogram and measured at the RHC were well correlated (r=0.77, p=<0.001); however, invasive measurement confirmed the presence of elevated pulmonary artery pressure in only 8 of the 26 patients submitted to the procedure, corresponding to 10% of the total sample (95%CI from 3.4 to 16.5%). From these, 5 patients (6.2% - 95%CI from 0.9 to 11.5%) presented a PAOP > 15 mmHg, thus being classified as post-capillary hypertension; the remaining 3 patients were classified as having pre-capillary (arterial) pulmonary hypertension (3.7% - CI 95% 0.4 to 7.9%). Patients' distribution according to the echocardiographic and invasive hemodynamic characteristics is presented in figure 1.

The comparison between patients with true PH (n=8) and the remaining patients from our cohort (n=66) revealed a significant difference in age, distance walked at 6MWT, presence of proteinuria, platelets count and BUN, LDH, uric acid, γ-glutamyltransferase and hemoglobin levels (table 3). Although the number of patients in each subgroup precludes further evaluation, no significant difference was found in the comparison of the clinical and hemodynamic variables between patients with pre and post capillary PH, except for the PAOP (data not shown). Noteworthy is the fact that all confirmed PAH patients presented PVR levels higher than 2.5 Woods. Chronic thromboembolic disease was excluded in all patients by means of pulmonary V/Q scan.

During the follow-up period 7 patients died (table 4), two in the group TRV < 2.5 m/s and 5 in the group TRV ≥ 2.5 m/s. In the later group, three patients had been submitted to right heart catheterization, two presenting as post-capillary PH and the other one presenting as pre-capillary PH. Although there was a trend toward a survival difference between the two groups classified according to the presence of a TRV ≥ 2.5 m/s, it did not quite reach statistical significance (p=0.07). Patients with PH confirmed by right heart catheterization presented worse survival as compared to the remaining patients, regardless their measured TRV (p=0.0005).

DISCUSSION

Our study was the first prospective study to estimate the prevalence and prognostic significance of pulmonary hypertension in SCD patients based on right heart catheterization. Our results indicated that SCD patients with pulmonary hypertension present worse clinical, laboratorial and functional profile associated to worse prognosis.

Clinical and echocardiographic characteristics of our population are similar to other previously described.[10,11,13-15] Approximately 40% of our patients presented TRV ≥ 2.5 m/s and this subgroup presented more anemia, hemolysis and renal dysfunction when compared to the group with normal TRV. Similarly to literature, there is no difference between the two groups according HbF level, vaso-occlusive episodes and acute chest syndrome.

This specific subgroup of patients has been previously described as presenting higher mortality. These results have been ascribed to increased prevalence of PH in this population. [7,8,13] Nevertheless, the presence of PH was solely addressed by echocardiogram in these previous studies. Our findings raised the speculation that the higher mortality associated to the presence of TRV≥2.5m/s may not be totally related to the presence of pulmonary hypertension but may also be associated to other pathophysiological phenomena of SCD.

Furthermore, invasive hemodynamics revealed a higher prevalence of a post-capillary component (PAOP >15mmHg) in the subgroup of patients with true pulmonary hypertension, indicating a possible underlying left ventricular dysfunction.

Castro et al., in 2003, also reported a large proportion of patients (50%) with high PAOP (> 15 mmHg), despite the normal ejection fraction in echocardiogram.[17] Anthi et al., in 2007, found a prevalence of 46.2% of venous (post-capillary) hypertension among patients with SCD and PH.[18] In a recent study, using only echocardiogram, Sachdev et al. reported a prevalence of 10-11% of left heart disease in SCD patients with pulmonary hypertension. [19] Although the increased PAOP was once attributed to an "inversed" Bernheim effect [17](left ventricular filling inhibition by paradoxical ventricular septal motion), the most probable explanation is an underlying diastolic dysfunction. Diastolic dysfunction is well described in SCD and is imputed to microvascular occlusion, iron overload and chronic high output. [19]

Consequently, our findings reinforced the multifactorial mechanisms that may be related to the development of PH in SCD patients. Among those multiple mechanisms, hemolysis, asplenic status, thrombosis and left heart disease (with diastolic component) may share a role in vascular damage. The implication of our findings are particularly important if specific therapeutical approach for the management of pulmonary hypertension is considered, since treatments for pre and post capillary pulmonary hypertension may be considerably different. The clinical results of controlled trials of endothelin receptor antagonists use in heart failure have been disappointing so far, despite their proven efficacy in pulmonary arterial hypertension. [20,21]

Moreover, several considerations on the pathophysiology of PH in the SCD have emphasized only the role of hemolysis and pulmonary vasoconstriction in the genesis of this complication. Our study, in fact, found a very similar pattern as observed in other studies. Although questioned,[22] there

is evidence of the role of hemolysis in pathogenesis of PH in SCD. Our study also confirms the impact of PH on the mortality of SCD patients.

Nonetheless, it is relevant to consider other factors. The hemodynamic profile has some patterns already described in the literature.[17,23] The values of pulmonary vascular resistance (PVR) are markedly low, if compared to other populations of PH patients. [24] The mean value of PVR in this group is 2.3 woods and the highest PVR was 5.1 woods. In the group without PH the mean value of PVR was 0.78 woods, sharply lower than the usual reference value of 1.7 Woods. [25] These findings are attributable to the lower viscosity and the decreased vascular resistance in response to high cardiac output secondary to the regimen of chronic anemia .[17,26]

When individuals with PH are compared to the remaining patients, differences in clinical, hematological, biochemical and functional characteristics become more evident. It is noteworthy the elevation of uric acid (512 ± 78 mmol/L vs 306 ±99 mmol/L, $p < 0.0001$) and fall of platelets (284± 129 x 10^9/L vs 422 ± 122 x 10^9/L, p 0.0015) seen in the PH group.

High levels of uric acid have been observed in patients with other forms of PH and were assigned to the depletion of adenosine triphosphate (ATP) in the tissues and worsening of oxidative metabolism.[27] Hyperuricemia also occurs in hemolytic disease as a consequence of the increased production of uric acid after the recycling of purines. Associated renal dysfunction may also be related to increased uric acid level. [28]

The decrease on platelets counts was not expected in a context of an inflammatory disease and the presence of hyposplenism. It is not possible; however, to exclude that lower platelets counts could be associated with the

presence of hepatitis C or older age, as already described in SCD .[29,30] Although our study evidenced older age in this subgroup of patients, no association with hepatitis C could be noted.

Survival was significantly lower in the group with PH confirmed by right heart catheterization, regardless the hemodynamic pattern (pre or post-capillary). This finding is particularly relevant and raises the importance of the appropriate diagnosis of PH in this particular subgroup of patients.

Our study has some limitations that need to be accounted. The monocentric design and small sample size should be taken into consideration when extrapolating our results. To allow a better scrutinization of our results, 95%CI were included. Moreover, not all patients selected for completion of catheterization could be subjected to the procedure. Even under these limitations, to our knowledge, our study presented the largest proportion of individuals evaluated by invasive hemodynamic assessment.

We conclude that pulmonary hypertension is a significant complication SCD with direct prognostic implication. Our study reinforces the use of echocardiogram as a screening tool for PH in SCD patients and also the mandatory role of RHC for the proper diagnosis. The higher prevalence of post-capillary PH associated to SCD strengthens not only the multifactorial pathways that may be involved with this particular clinical condition but also the need for appropriate hemodynamic characterization before any attempt for specific therapeutical approach targeting PH management.

Disclosure

None of the authors declares any potential conflict of interest

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Table 1 –SCD patients characteristics according to the TRV

	Baseline data (n=80)	TRV<2.5 m/s (n=48)	TRV≥2.5 m/s (n=32)	p value*
Age (years)	33 ± 10	30 ± 8	38 ± 11	0.001
Female sex (%)	61.2	68.7	50	0.07
Body mass index	20.6 ± 2.6	21.1 ± 2.8	20 ± 2.3	0.6
Left ventricle ejection fraction (%)	64 ± 7	64 ± 7	64 ± 6	0.67
6MWT(meters)	499 ± 141	515 ± 148	475 ± 131	0.004
O_2 saturation (%)	92 ± 13	93 ± 15	90 ± 6	0.38
Clinical history				
Hydroxyurea use (%)	13.7	18.7	6.2	0.102
Priapism (%)	70.9	62.5	80	0.18
Hepatitis C (%)	27.5	16.6	34.3	0.04
Leg ulcer (%)	30	12.5	50	0.001
Proteinuria (%)	36.2	25	40.6	0.06
Deep venous thrombosis (%)	10	4.1	18.7	0.07
Ischemic Stroke (%)	13.7	14.6	12.5	0.53
Acute chest syndrome (%)	13.7	18.8	6.3	0.18
Hematological findings				
Hemoglobin (g/L)	82 ± 12.9	86.7 ± 16.1	75.5 ± 12.1	<0.001
Reticulocytes(%)	11.2 ± 5.43	10.9 ± 5.33	11.8 ± 5.65	0.51
Leucocytes (x109/L)	11.4 ± 3.4	11 ± 3.5	12.1 ± 3.2	0.11
Platelets ($x10^9$/L)	407 ± 124	427 ± 121	378 ± 126	0.082
Fetal hemoglobin (%)	7.4 ± 5.41	8.29 ± 5.78	6.22 ± 4.64	0.15
Lactate dehydrogenase (U/L)	1116 ± 553	909 ± 445	1427 ± 561	<0.001
Uric Acid (mmol/L)	332.5 ± 125	290 ± 100	390 ± 112	0.001
Aspartate aminotransferase (U/L)	48.8 ± 20.7	42.6 ± 17.6	54.9 ± 22.6	0.007
γ-glutamyltransferase (U/L)	89.7 ± 62.3	71 ± 64.5	120 ± 45.6	<0.001
Unconjugated bilirubin (µmol/L)	53.1 ± 50.44	53.35 ± 56.4	53.7 ± 41.9	0.211
C-reactive protein (ng/mL)	6.4 ± 7.7	5.3 ± 5.5	7.98 ± 9.92	0.36
Urea (mmol/L)	4.21 ± 2.9	3.5 ± 1.7	5.2 ± 3.7	0.006
Creatinine (µmol/L)	61.9 ± 29.2	56.4 ± 22.8	71.4 ± 36.2	0.027

Table 2 – Invasive Hemodynamic data, according to the presence of pulmonary hypertension

	Without PH (n=18)	PH (n=8)	p value
Age	35.3±11.6	45.6±10.7	0.04
PVR (Woods)	0.8±0.6	2.24±1.5	0.002
Cardiac index (L/min/m^2)	5±1.36	4.9±1.7	0.85
PAOP (mmHg)	13.3±2	16±5.7	0.07
SPAP	28.5 ± 4.5	48,1 ± 13.3	<0.001
mPAP	18.7± 2.8	33.1±8.9	<0.001
6MWT	511±78.9	460±152	0.25

SPAP – systolic pulmonary artery pressure; mPAP – mean pulmonary artery pressure; PAOP -pulmonary artery occlusion pressure ; 6MWT – six-minute walk test

Table 3 –SCD patients characteristics according to the right heart catheterization

	TRV <2.5 m/s plus TRV≥2.5 m/s *and* mPAP<25 mmHg (n=66)	mPAP≥25 mmHg (n=8)	p value*
Age (years)	31.3 ± 11.6	45.6 ± 11	0.04
Female sex (%)	64.6	37.5	0.3
Body mass index	20.8±2.65	20.1±2.8	0.5
Left ventricle ejection fraction (%)	64.2 ± 7.1	62.5 ± 6	0.53
6MWT(meters)	53 ± 71	460 ± 152	0.02
O_2 saturation (%)	92.1 ± 6.12	87.5 ± 7.41	0.77
Clinical history			
Hydroxyurea use (%)	15.4	12.5	0.4
Priapism (%)	62.5	80	0.47

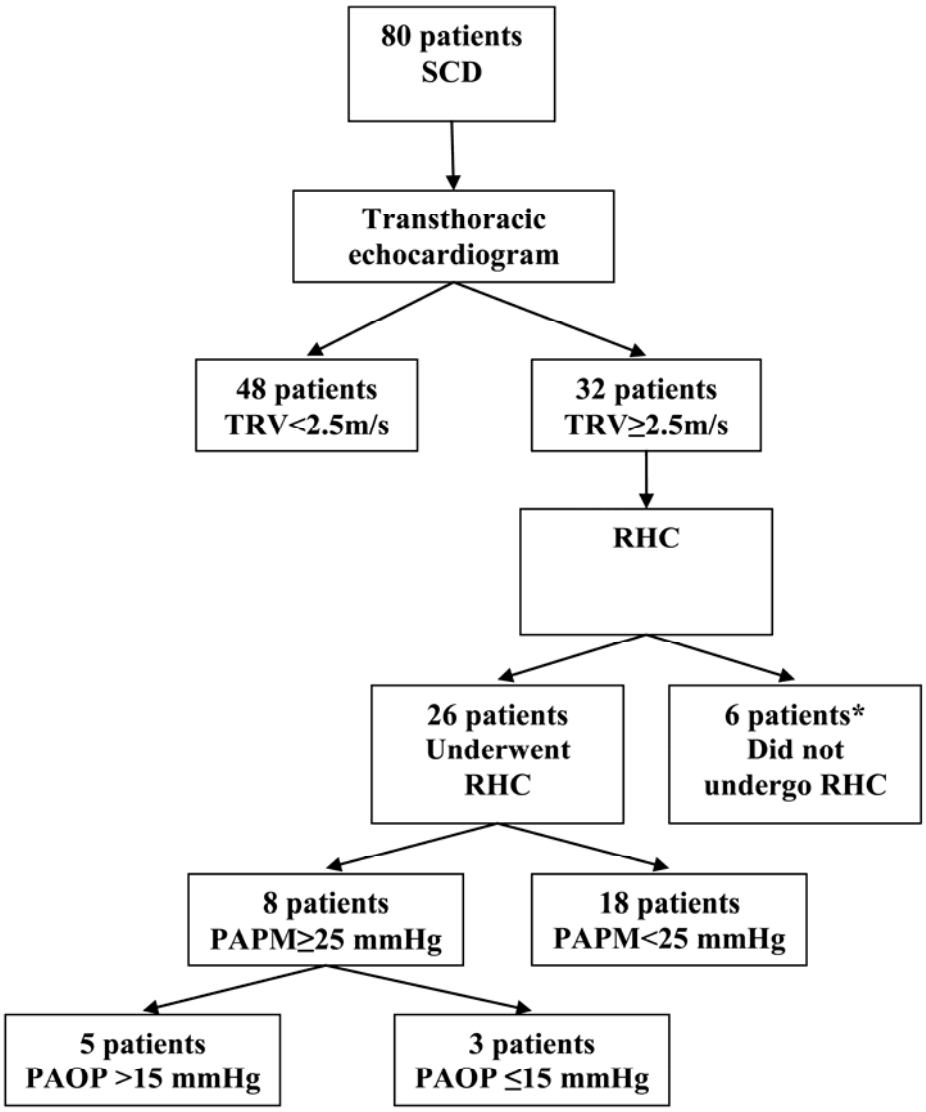
Hepatitis C (%)	24.6	25	0.33
Leg ulcer (%)	23.1	37.5	0.41
Proteinúria (%)	30.7	87.5	0.02
Deep venous thrombosis (%)	7.7	37.5	0.04
Ischemic Stroke (%)	15.4	0	0.22
Acute chest syndrome (%)	16.6	12.5	0.62
Hematological findings			
Hemoglobin (g/L)	84.4 ± 12	73 ± 10.2	0,01
Leukocytes(x10^9/L)	11±3.4	12.1±4.27	0.58
Reticulocytes(%)	11 ± 5.3	13.5 ± 6.5	0.23
Platelets (x10^9/L)	420 ± 122	308 ± 137	0.02
Fetal hemoglobin (%)	7.8 ± 5.7	6.21 ± 3.44	0.9
Lactate dehydrogenase (U/L)	1041 ± 535	1596 ± 424	0.006
Uric Acid (mmol/L)	282.5 ± 109	516 ± 81.5	<0.001
Aspartate aminotransferase (U/L)	46.3 ± 18.8	61.2 ± 25.5	0.04
γ-glutamyltransferase (U/L)	82.2 ± 61.7	135 ± 64.3	0.34
Unconjugated bilirubin (µmol/L)	55.7±28	72.84±65	0.22
C-reactive protein (ng/mL)	5.28±5.5	6.36±4	0.61
Urea (mmol/L)	7.74 ± 3,57	18.6 ± 11.5	<0.001
Creatinine (µmol/L)	56.6 ± 21.1	99 ± 45.9	<0.001

Table 4– Cause of death and patient characteristics

Patient	**Gender**	**Age**	**TRV**	**mPAP**	**PAOP**	**Cause of death**
SB 38	F	23	1.99	NA*	NA*	Cranial traumatism
EPP21	M	37	1.16	NA*	NA*	Spontaneous intracranial hemorrage
ESM 25	F	65	3.32	28	12	Chronic Renal Failure
ACAV 03***	F	36	3.9	NA*	NA*	Acute anemia, Pneumonia
JL 39	M	40	2.7	NA*	NA*	Hepatic failure
CAA 10	M	51	3.37	40	18	Right Ventricular Dysfunction , Pneumonia
LBM 45	M	58	4.17	43	8	Right Ventricular Dysfunction

NA* – Right heart catheterization was not performed; in this case, patients were included only in the survival analysis based on the results of the echocardiogram.
TRV – peak regurgitant jet velocity
mPAP – Mean pulmonary artery pressure
PAOP – pulmonary artery occlusion pressure

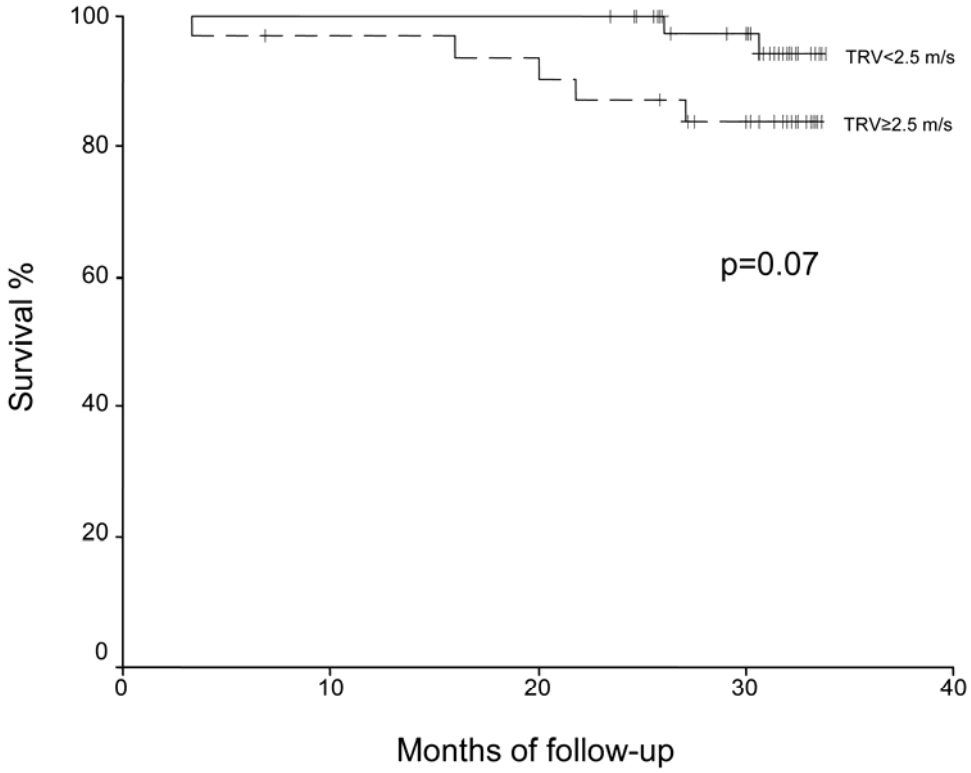
Figure 1



SCD – Sickle cell disease; TRV – Peak regurgitant jet velocity; RHC – right heart catheterization; mPAP – mean pulmonary artery pressure; PAOP – pulmonary artery occlusion pressure

* reasons for failure to perform RHC:
clinical reasons:- hyperhemolytic reaction (TRV=3.05m/s; Female; 28 years) , patient with alloimmunization and severe anemia in steady-state (TRV =3.9 m/s; Female; 36 years), and infection(TRV =2.61 m/s; Male; 21 years)
refusal – 2 patients (TRV =2.65 m/s; Female; 37 years), (TRV =2.7 m/s; Male; 40 years)
social problems- 1 patient(TRV =3.37 m/s; Male; 45 years)

Figure 2



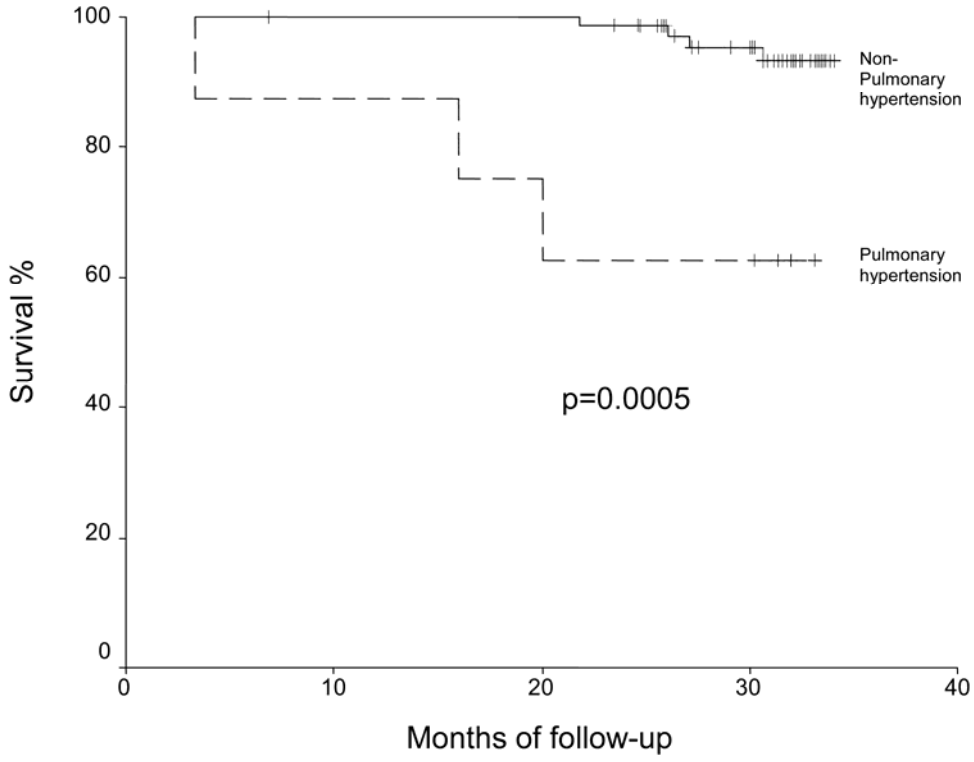


Figure 3