Conjunctival and pulmonary hemodynamic properties in sickle cell disease subjects with and without pulmonary hypertension

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Key Clinical Message
Conjunctival microvascular hemodynamic alterations were reported for the first time in sickle cell subjects with and without pulmonary hypertension. Assessment of the conjunctival microcirculation using noninvasive imaging may improve understanding of microvascular hemodynamic alterations that occur due to pulmonary hypertension in sickle cell disease.

Keywords
Conjunctiva, hemodynamics, microcirculation, pulmonary hypertension, sickle cell disease

Introduction
Pulmonary hypertension (PH) in adults with sickle cell disease (SCD) is associated with early mortality [1], and other complications, including renal insufficiency, leg ulcers, abnormal liver function, systemic hypertension, avascular necrosis, seizures, and cerebrovascular events [2]. Right heart catheterization (RHC) is the gold standard to confirm the diagnosis of PH and hemodynamic stratification to determine treatment and follow-up. Doppler echocardiography is also used to estimate cardiopulmonary hemodynamics. The hemodynamic characteristics of PH, particularly pulmonary artery pressure (PAP) [3], and tricuspid regurgitation velocity (TRV) [1], have been shown to be independent predictors of mortality in adults with SCD.

Since SCD is a systemic vascular disease [4], it is likely that SCD subjects with PH have alterations in microvascular hemodynamics in multiple organ systems. Previous studies have reported conjunctival microvascular hemodynamics in SCD subjects [5, 6]. However, to the best of our knowledge, there have been no studies evaluating conjunctival microcirculatory hemodynamics in SCD subjects with or without PH. In this study, we report the conjunctival and pulmonary hemodynamic properties in SCD subjects with and without PH.

Case Report
Prior to subject enrollment, the research study was explained to the subjects, and informed consents were obtained according to the tenets of the Declaration of Helsinki. Two SCD (SS genotype) subjects, one with and one without PH, participated in the study. Ten age-similar African-American subjects (age range: 32–68 years)
without SCD or history of cerebrovascular, hypertension or ocular diseases participated as healthy control subjects. Measurements in control subjects were obtained in our previously published studies [6, 7]. Systolic and diastolic blood pressures were measured three times at the time of conjunctival imaging, and the averaged values were reported.

Imaging of the conjunctival microcirculation was performed with our previously described and validated optical imaging system (EyeFlow™) [6–11]. Briefly, the imaging system comprised of a slit lamp biomicroscope and a digital charged-coupled device camera, was used to acquire image sequences of red blood cell movement within the conjunctiva microcirculation. Several image sequences were analyzed to provide the measures of diameter (D) and axial blood velocity (V) of conjunctival venules, as previously described [9]. Mean values of D and V were calculated from one randomly selected eye in each subject. Based on data in control subjects, 95% normal confidence intervals (CI) were calculated for conjunctival D and V.

In SCD subjects, data from RHC, Doppler echocardiography, and laboratory tests were obtained from medical records. Pulmonary hemodynamic data including systolic, diastolic, and mean PAP (sPAP, dPAP, mPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output were obtained from RHC, and TRV was documented from Doppler echocardiography. Diagnosis of PH was based on a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg [12]. TRV values greater than 3 m/sec were considered to be elevated [13]. Exercise capacity was assessed using a 6 minute walk distance (6MWD) test (normal range: 380–782 m) [14]. The SCD subject with PH was categorized according to the World Health Organization (WHO) clinical classification of PH [15].

Table 1 lists demographic and clinical characteristics of control and SCD subjects. Table 2 summarizes pulmonary hemodynamic properties of SCD subjects. In control subjects, the 95% CIs of mean conjunctival D and V were 17–23 μm (N = 10) and 0.39–0.59 mm/sec, respectively.

Case 1 was a 41-year-old male with SCD and controlled systemic hypertension, cholelithiasis, priapism, and acute chest syndrome during childhood. The subject was on hydroxyurea treatment, and had not received a blood transfusion within 2 months prior to conjunctival imaging. The ferritin level was 79 mg/dL, 2 months before conjunctival imaging. The echocardiography data obtained 40 days before conjunctival imaging demonstrated mild pulmonary valve stenosis, with right ventricle systolic pressure of 54 mm Hg. Since pulmonary stenosis may confound pulmonary artery hemodynamics, diagnostic RHC was performed for further evaluation of PH, which revealed a normal mPAP of 15 mm Hg. During the 2-month time interval between conjunctival imaging and RHC, the subject had two clinical visits, which indicated an unchanged clinical status and medication list.

Table 1. Demographic and clinical characteristics of healthy control subjects and sickle cell disease subjects with and without pulmonary hypertension (PH). Data in healthy control subjects were reported as mean ± standard deviation. Systolic (SBP) and diastolic (DBP) blood pressures were available in seven healthy control subjects.

Table 2. Pulmonary hemodynamic properties in sickle cell disease subjects with and without pulmonary hypertension (PH).

Table 3. Conjunctival hemodynamic properties in healthy control subjects and sickle cell disease subjects with and without pulmonary hypertension (PH). Data in healthy control subjects were reported as 95% confidence intervals.
diabetes, renal insufficiency, chronic leg ulcer, and gout. This subject was not receiving hydroxyurea treatment and did not have a blood transfusion within 2 months of conjunctival imaging. The ferritin level was not available within 2 months of imaging. The diagnosis of PH was documented by RHC and echocardiography. The echocardiography data obtained 11 months before conjunctival imaging showed an increased TRV of 3.63 m/sec. The initial 6MWD test performed 10 months before conjunctival imaging was 244 m and lower than normal. The oxygen saturation was measured to be 87% at rest and 88% during activity, and therefore the subject was prescribed supplemental oxygen of 2 L/min at rest and 3 L/min during activity. RHC revealed postcapillary PH with an elevated mPAP of 35 mm Hg and pulmonary capillary wedge pressure of 23 mm Hg. The subject was categorized as group 1 of the WHO clinical classification of PH (pulmonary arterial hypertension). During the 7-month time interval between conjunctival imaging and RHC, the subject had six follow-up clinical visits with one echocardiography which demonstrated persistent increase in TRV and PAP with negligible improvements in exercise capacity, and shortness of breath. Mean conjunctival D and V measurements were 17 ± 4 μm (N = 8 venules) and 0.19 ± 0.05 mm/sec, respectively. Conjunctival D was within the normal 95% CI in control subjects, while conjunctival V was lower than normal 95% CI limit.

Discussion

PH is a prognostic factor in SCD and is associated with early mortality [1] and other complications [2]. RHC is the gold standard for the diagnosis and monitoring of PH, but it is invasive and carries a small, but present risk of mortality and other complications. In contrast, conjunctival microvascular imaging is a noninvasive and non-contact technique to assess hemodynamic properties of the microcirculation. Conjunctival microvascular and hemodynamic abnormalities including abnormal vessel diameter, vessel tortuosity, microaneurysms, and decreased blood velocity have been documented in SCD subjects [5, 6]. Decreased conjunctival blood velocity has been associated with SCD complications such as stroke [16] and retinopathy [7]. In this study, we reported conjunctival blood velocity in two SCD subjects with and without PH.

The mean conjunctival V in the SCD subject with PH (case 2) was far below the lower limit of the 95% CI established in healthy control subjects, indicating the potential of conjunctival imaging to detect hemodynamic abnormalities in SCD subjects with PH. The exact mechanism of decreased conjunctival V in the SCD subject with PH is not clear. Although SCD is associated with microvascular hemodynamics abnormalities which vary based on pathophysiology of the disease complications, the substantially lower conjunctival V observed in case 2 is likely attributed to the combination of PH and SCD. One possible explanation could be higher microvascular network resistance due to increased adherence of red and white blood cells, and platelet to the endothelium and to each other resulting from hypoxia in the SCD subjects with PH [17]. Interestingly, the conjunctival D was within the normal range in the SCD subject with PH in this study despite lower than normal conjunctival V. This finding may suggest a diminished vasodilatory response to hypoxia in this SCD subject due to vasculopathy [18], increased consumption of nitric oxide, or decreased activity of soluble guanylate cyclase and other downstream messengers in vascular smooth muscle [19]. Future studies in a larger population are required to investigate the relationships between severity of PH and microvascular velocity in SCD subjects.

Conjunctival V measurements in healthy control subjects in this study were lower than values reported in previous studies [20, 21], which may be attributed to differences in ethnicity of the study populations and measurement techniques. Furthermore, decreased DBP in SCD subjects as compared to healthy control subjects is consistent with previous studies [22–24]. This may be attributed to a progressive renal tubular defect in SCD subjects, which begins in early childhood ages [23, 24]. However, the exact cause of hypotension in SCD subjects is still unclear.

Conclusions

Assessment of conjunctival microvascular hemodynamics may improve understanding of the pathophysiology of pulmonary hypertension in sickle cell disease.

Conflict of Interest

MS has a patent for the EyeFlow™ technology. All other authors declare that they have no conflicts of interest.

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