Clinical Case Reports

Open Access

CASE REPORT

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

Ali Kord Valeshabad[1], Justin Wanek[1], Robert E. Molokie[2,3,4], Roberto F. Machado[5], Victor R. Gordeuk[2] & Mahnaz Shahidi[1]

[1]Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois
[2]Department of Medicine, Division of Hematology/Oncology, University of Illinois at Chicago, Chicago, Illinois
[3]Department of Biopharmaceutical Sciences, University of Illinois at Chicago, Chicago, Illinois
[4]Jesse Brown VA Medical Center, Chicago, Illinois
[5]Department of Medicine, Section of Pulmonary and Critical Care, University of Illinois at Chicago, Chicago, Illinois

Correspondence
Mahnaz Shahidi, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, 1855 West Taylor Street, Chicago, Illinois 60612.
Tel: 312 413 7364; Fax: 312 413 7366;
E-mail: mahnshah@uic.edu

Funding Information
NIH grant EY001792, a Senior Scientific Investigator (MS) award and an unrestricted departmental award from Research to Prevent Blindness.

Received: 20 May 2015; Revised: 20 August 2015; Accepted: 8 October 2015

Clinical Case Reports **2015; 3(12): 1038–1041**

doi: 10.1002/ccr3.439

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. Table 3 reports conjunctival hemodynamic properties of control and 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. Mean conjunctival D and V measurements were 19 ± 4 μm ($N = 16$ venules) and 0.52 ± 0.22 mm/sec, respectively. Both conjunctival D and V measurements were within the normal 95% CIs based on data in control subjects.

Case 2 was a 50-year-old male with SCD and past medical history of PH, controlled systemic hypertension and

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.

Variables	SCD Case 1 (Without PH)	SCD Case 2 (With PH)	Healthy Controls ($N = 10$)
Age (years)	41	50	46 ± 11
SBP (mm Hg)	140	122	124 ± 11
DBP (mm Hg)	66	58	78 ± 5
Hematocrit (%)	29.9	25.6	–

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

Variables	SCD Case 1 (Without PH)	SCD Case 2 (With PH)
sPAP (mm Hg)	23	52
dPAP (mm Hg)	11	26
mPAP (mm Hg)	15	35
PCWP (mm Hg)	15	23
Cardiac output (L/min)	7.8	9.6
TRV (m/sec)	2.40	3.63

sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; TRV, tricuspid regurgitation velocity.

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.

Variables	SCD Case 1 (Without PH)	SCD Case 2 (With PH)	Healthy Controls ($N = 10$)
Conjunctival diameter (μm)	19 ± 4	17 ± 4	17–23
Conjunctival velocity (mm/sec)	0.52 ± 0.22	0.19 ± 0.04	0.39–0.59

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 noncontact 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.

References

1. Gladwin, M. T., R. J. Barst, J. S. Gibbs, M. Hildesheim, V. Sachdev, M. Nouraie, et al. 2014. Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. PLoS One 9:e99489.
2. De Castro, L. M., J. C. Jonassaint, F. L. Graham, A. Ashley-Koch, and M. J. Telen. 2008. Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. Am. J. Hematol. 83:19–25.

3. Mehari, A., S. Alam, X. Tian, M. J. Cuttica, C. F. Barnett, G. Miles, et al. 2013. Hemodynamic predictors of mortality in adults with sickle cell disease. Am. J. Respir. Crit. Care Med. 187:840–7.
4. Morris, C. R. 2011. Vascular risk assessment in patients with sickle cell disease. Haematologica 96:1–5.
5. Cheung, A. T., P. C. Chen, E. C. Larkin, P. L. Duong, S. Ramanujam, F. Tablin, et al. 2002. Microvascular abnormalities in sickle cell disease: a computer-assisted intravital microscopy study. Blood 99:3999–4005.
6. Wanek, J., B. Gaynes, J. I. Lim, R. Molokie, and M. Shahidi. 2013. Human bulbar conjunctival hemodynamics in hemoglobin SS and SC disease. Am. J. Hematol. 88:661–4.
7. Kord Valeshabad, A., J. Wanek, R. Zelkha, J. I. Lim, N. Camardo, B. Gaynes, et al. 2015. Conjunctival microvascular haemodynamics in sickle cell retinopathy. Acta Ophthalmol. 93:e275–80.
8. Kord Valeshabad, A., J. Wanek, F. Mukarram, R. Zelkha, F. D. Testai, and M. Shahidi. 2015. Feasibility of assessment of conjunctival microvascular hemodynamics in unilateral ischemic stroke. Microvasc. Res. 100:4–8.
9. Shahidi, M., J. Wanek, B. Gaynes, and T. Wu. 2010. Quantitative assessment of conjunctival microvascular circulation of the human eye. Microvasc. Res. 79:109–13.
10. Gaynes, B., P. Y. Teng, J. Wanek, and M. Shahidi. 2012. Feasibility of conjunctival hemodynamic measurements in rabbits: reproducibility, validity, and response to acute hypotension. Microcirculation 19:521–9.
11. Kord Valeshabad, A., J. Wanek, B. Gaynes, S. L. Saraf, R. E. Molokie, and M. Shahidi. 2015. Conjunctival microvascular hemodynamics and vaso-occlusive crisis in sickle cell disease. Clin. Hemorheol. Microcirc. [Epub ahead of print].
12. Badesch, D. B., H. C. Champion, M. A. Sanchez, M. M. Hoeper, J. E. Loyd, A. Manes, et al. 2009. Diagnosis and assessment of pulmonary arterial hypertension. J. Am. Coll. Cardiol. 54(1 Suppl):S55–66.
13. Upadhya, B., R. B. Stacey, W. Ntim, M. A. Knovich, and M. Pu. 2014. Echocardiography-derived tricuspid regurgitant jet velocity is an important marker for the progression of sickle-cell disease. Acta Haematol. 132:152–8.
14. Casanova, C., B. R. Celli, P. Barria, A. Casas, C. Cote, J. P. de Torres, et al. 2011. The 6-min walk distance in healthy subjects: reference standards from seven countries. Eur. Respir. J. 37:150–6.
15. Simonneau, G., I. M. Robbins, M. Beghetti, R. N. Channick, M. Delcroix, C. P. Denton, et al. 2009. Updated clinical classification of pulmonary hypertension. J. Am. Coll. Cardiol. 54(1 Suppl):S43–54.
16. Cheung, A. T., P. Harmatz, T. Wun, P. C. Chen, E. C. Larkin, R. J. Adams, et al. 2001. Correlation of abnormal intracranial vessel velocity, measured by transcranial Doppler ultrasonography, with abnormal conjunctival vessel velocity, measured by computer-assisted intravital microscopy, in sickle cell disease. Blood 97:3401–4.
17. Gutsaeva, D. R., P. Montero-Huerta, J. B. Parkerson, S. D. Yerigenahally, T. Ikuta, and C. A. Head. 2014. Molecular mechanisms underlying synergistic adhesion of sickle red blood cells by hypoxia and low nitric oxide bioavailability. Blood 123:1917–26.
18. Hsu, L. L., H. C. Champion, S. A. Campbell-Lee, T. J. Bivalacqua, E. A. Manci, B. A. Diwan, et al. 2007. Hemolysis in sickle cell mice causes pulmonary hypertension due to global impairment in nitric oxide bioavailability. Blood 109:3088–98.
19. Gladwin, M. T., and G. J. Kato. 2005. Cardiopulmonary complications of sickle cell disease: role of nitric oxide and hemolytic anemia. Hematology Am. Soc. Hematol. Educ. Program 2005:51–7.
20. Koutsiaris, A. G.. 2014. Correlation of axial blood velocity to venular and arteriolar diameter in the human eye in vivo. Clin. Hemorheol. Microcirc. [Epub ahead of print].
21. Koutsiaris, A. G., S. V. Tachmitzi, N. Batis, M. G. Kotoula, C. H. Karabatsas, E. Tsironi, et al. 2007. Volume flow and wall shear stress quantification in the human conjunctival capillaries and post-capillary venules in vivo. Biorheology 44:375–86.
22. Pegelow, C. H., L. Colangelo, M. Steinberg, E. C. Wright, J. Smith, G. Phillips, et al. 1997. Natural history of blood pressure in sickle cell disease: risks for stroke and death associated with relative hypertension in sickle cell anemia. Am. J. Med. 102:171–7.
23. Wright, J. T. Jr. 1988. Profile of systemic hypertension in black patients. Am. J. Cardiol. 61:41H–5H.
24. Statius van Eps, L. W., C. Pinedo-Veels, G. H. de Vries, and J. de Koning. 1970. Nature of concentrating defect in sickle-cell nephropathy. Microradioangiographic studies. Lancet 1:450–2.

