

Longitudinal Characterization of Hemodynamic Changes with Multimodal Optical Techniques in Patients with Sickle Cell Disease Treated with Mitapivat

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Background

- There is an unmet need for robust, point-of-care technologies that can assess tissue hemodynamics influenced by treatments for sickle cell disease (SCD)
- Mitapivat, an oral pyruvate kinase activator, has been shown to improve red blood cell metabolism and anemia in patients with SCD [1,2]
- Optical technologies are an attractive, non-invasive candidate for assessing tissue hemodynamics at the bedside

Goal: Evaluate the sensitivity of optical hemodynamic assessments to changes associated with mitapivat over the course of a year

Methods

- Participants (n = 15) were enrolled in a longitudinal study of mitapivat, at the NIH in collaboration with NHLBI (Clinicaltrials.gov, NCT04610866). Nine with baseline data were evaluated
- Time-domain near infrared spectroscopy (TD-NIRS) measures attenuation and delay of an incident light pulse to recover **quantitative hemoglobin concentration** and **tissue oxygen saturation (StO₂)**, the ratio of oxyhemoglobin (O₂Hb) to total hemoglobin (tHb) [3]

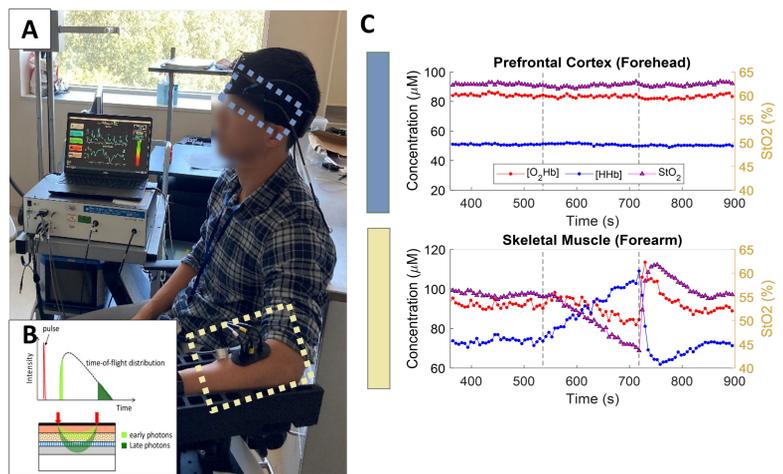


Figure 1: **Optical hemodynamic assessment on a healthy volunteer** A) Photograph of healthy volunteer with optical probes measuring hemodynamics in the forehead and forearm B) Schematic of the travel path of photons entering tissue for TD-NIRS C) Hemodynamic data acquired from the NIRS probes in the forehead (blue) and forearm (yellow) during a brachial cuff occlusion. Red represents oxyhemoglobin concentration (O₂Hb), blue represents deoxyhemoglobin (Hb), and pink represents tissue oxygen saturation (StO₂)

- Additional hemodynamic measures can be derived such as cerebral blood volume (CBV), oxygen extraction fraction (OEF), and optical hyperemic response Δ[O₂Hb]

$$CBV = \frac{[tHb] * MW_{Hb}}{Hb_{blood} * D_{bt}} \quad OEF = \frac{S_aO_2 - S_tO_2}{\beta * S_aO_2} \quad \Delta O_2Hb = [O_2Hb]_{peak} - [O_2Hb]_{occlusion\ end}$$

Results

- Measurements acquired at baseline before starting mitapivat and for seven additional visits during the first year
- Resting baseline measurements and brachial cuff occlusion performed to acquire optical measures of tissue composition and vascular reactivity
- Study patients exhibited **increased blood hemoglobin** and a **reduction of hemolytic markers (i.e. LDH, bilirubin)**

Acute Hemodynamic Changes

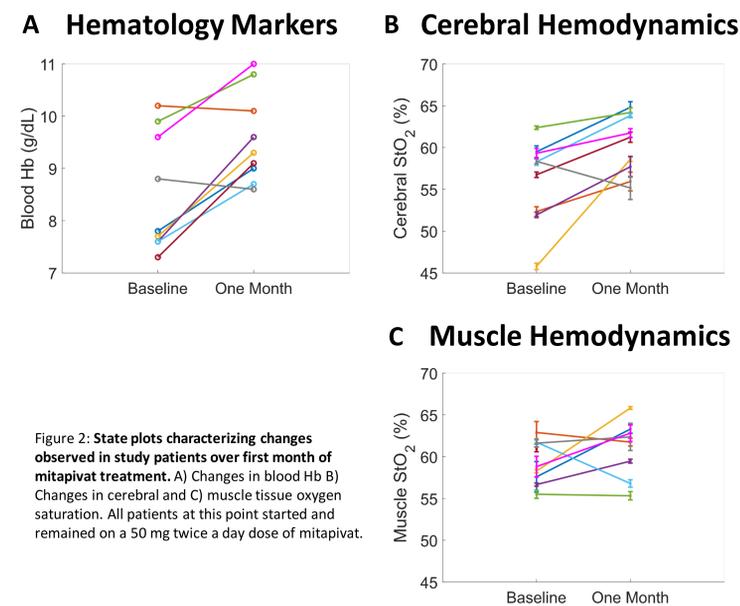


Figure 2: **State plots characterizing changes observed in study patients over first month of mitapivat treatment.** A) Changes in blood Hb B) Changes in cerebral and C) muscle tissue oxygen saturation. All patients at this point started and remained on a 50 mg twice a day dose of mitapivat.

- Over entire year, **mean brain StO₂ increased (+ 4.3%)** which mirrors mean increase in blood Hb (+ 1.3 g/dL)
- Reduced CBV (-1.4 mL/100g) and OEF (-4.5%) were also observed

Long Term Hemodynamic Changes

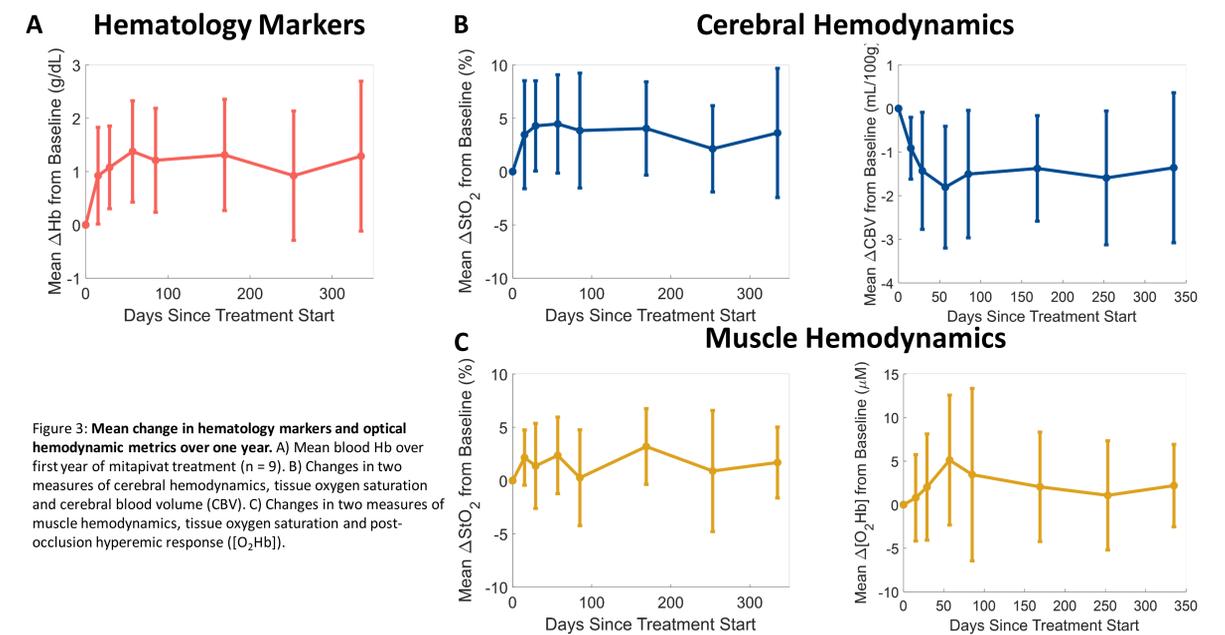


Figure 3: **Mean change in hematology markers and optical hemodynamic metrics over one year.** A) Mean blood Hb over first year of mitapivat treatment (n = 9). B) Changes in two measures of cerebral hemodynamics, tissue oxygen saturation and cerebral blood volume (CBV). C) Changes in two measures of muscle hemodynamics, tissue oxygen saturation and post-occlusion hyperemic response ([O₂Hb]).

	Metric	Net Change after One Year
Hematology Markers	Blood Hb (g/dL)	+ 1.3 ↑
	LDH (U/L)	- 139 ↓
Cerebral Hemodynamics	Cerebral StO ₂ (%)	+ 4.3 ↑
	CBV (mL/100g)	- 1.4 ↓
	OEF (%)	- 4.5 ↓
Muscle Hemodynamics	Muscle StO ₂ (%)	+ 1.7 ↑
	Δ[O ₂ Hb] (μM)	+ 2.2 ↑

Table 1: Summary of the mean net change in hematology markers and optical hemodynamic metrics over one year of treatment with Mitapivat

- Muscle hemodynamics also show slight change from baseline, but not as high in magnitude
- Decreased hemolysis and release of cell-free hemoglobin can reduce nitric oxide scavenging and improve endothelial function, leading to a potential improvement in hyperemic response

Conclusions

- Optical technologies could provide complementary microvascular information for monitoring SCD treatments
- Observed hemodynamic changes mirror trends observed in clinical biomarkers
- Integration of optical technologies that quantify flow will enable more comprehensive hemodynamic assessment

References

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