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### • Why does "emotional stress" promote sickle vaso-occlusive crisis?



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Sickle cell patients are hemolyzing all the time. But what triggers the transition from steady state to crisis?

Our patients tell us that stress, cold, and pain itself can trigger VOC.

I believe them, but what is the mechanism?





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### Decrease in Perfusion Promotes Microvascular Occlusion



Recruitment of many "vaso-occlusive vessels" results in regional obstruction of perfusion, pain, organ damage, loss of organ function, and premature death.

After Eaton- Hofrichter, Blood 1976





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The goal was to produce transient hypoxia similar to what normally happens during sleep

**Hypoxic Exposure Protocol:** breathed room air for at least 5 minutes until stable  $\rightarrow$  A valve was manually switched to breath 100% N<sub>2</sub> for 5 breaths and then returned to room air.





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Sangkatumvong S, et al, 2011, Am.J.Resp.Crit.Care.Med 184(4): 474-481

### Transient hypoxia causes parasympathetic withdrawal in SCD subjects



SCD patients have significant loss of the parasympathetic component of their autonomic nervous system balance upon transient exposure to hypoxia.

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SCD individuals have a hypersensitive autonomic nervous system

### Sighs in SCD subjects more likely to induce drops in perfusion



Sangkatumvong S, et al, 2011, Am.J.Resp.Crit.Care.Med 184(4): 474-481



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### **Could Pain Trigger Vasoconstriction** and Promote Vaso-occlusion?









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### Fear of Pain as well as Pain Induces a Decrease in Microvascular Perfusion



# SCD individuals have different response to pain than non-SCD



SCD subjects have increased neural responsiveness

SCD subjects vaso constricted faster in response to pain.

SCD subjects had stronger vasoconstriction reactivity to pain than non-SCD



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Maha Khaleel Payal Shah Saranya Veluswamy



Shah et al, 2019 Haematologica



Temperature( C)

# Repeated stimuli cause progressive decrease in perfusion





Saranya Veluswamy



So, pain, stress, anxiety, cold exposure all cause vasoconstriction and decreased perfusion and based on the basic SCD model, should cause sickle vaso-occlusion.

Is there any evidence that vasoconstriction / decreased prefusion predicts or promotes vasoocclusive crisis in individuals with sickle cell disease?





### The magnitude of vasoconstriction (M<sub>vasoc</sub>) during sleep predicts future VOC pain rate



Vasoconstriction patterns are obtained from the photoplethysmogram (PPG) signal which comes from a standard pulse oximetry sensor. This signal is recorded during sleep studies but not part of standard analysis.

Chalacheva, Ji, Rosen, DeBaun, Khoo, Coates, 2021 AJH 96(1): 60



# The magnitude of vasoconstriction (M<sub>vasoc</sub>) during sleep predicts future VOC pain rate



Nocturnal peripheral vasoconstriction predicts the frequency of severe acute pain episodes in children with sickle cell disease

Patjanaporn Chalacheva<sup>1</sup> | Yunhua Ji<sup>2</sup> | Carol L. Rosen<sup>3</sup> | Michael R. DeBaun<sup>4</sup> | Michael C. K. Khoo<sup>2</sup> | Thomas D. Coates<sup>5</sup> Am J Hematol 2021, 96(1):60-68

Parameter (n=212)	Estimate	P-value
M <sub>vasoc</sub>	3.29	0.0050
Age	3.17	<0.0001
Hgb	2.47	0.0196

Sleep disordered breathing does not predict acute severe pain	Arousal index (AI)	0.69	0.318
Shaina M. Willen <sup>1</sup> I Mark Rodeghier <sup>2</sup>   Carol L. Rosen <sup>3</sup>   Michael R. DeBaun <sup>1</sup> <i>Am J <u>Hematol</u></i> 2018 93(4): 478-485	Apnea hypopnea index (AHI)	-0.15	0.679
	Periodic Limb movement (PLM)	0.02	0.084



Sleep disordered breathing indices (AHI, AI, PLMS) predict the magnitude of nocturnal vasoconstriction (M<sub>vasoc</sub>)





Vasoconstriction propensity and associated decrease in microvascular prefusion plays a significant role in the pathophysiology of sickle vaso occlusion and likelihood of vaso occlusive crisis.

The vasoconstriction derived from a photoplethysmography (PPG) signal primarily reflects sympathetic nervous system (SNS) activity.

We suspect that the average SNS activity detected by PPG over time is an objective and quantifiable measure of "stress" that may be useful to predict and monitor certain types of human disease outcomes.





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Conclusion: We should listen to our patients and their mothers.





## **Team Effort**

- CHLA SCD Research
- Thomas Coates
- Obdulio Carreras
- Chris Denton
- Jon Detterich
- Roberta Kato
- Maha Khaleel
- Honglei Liu
- Ajay Perumbeti
- Mammen Puliyel
- Payal Shah\*
- Nathan Smith
- Richard Sposto
- Sylvie Suriany
- Saranya Veluswamy
- Sally Ward
- John Wood
- Sickle cell families<sup>\*</sup>

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- Patjanaporn Chalacheva\*
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- John Sunwoo
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- Lonnie Zeltzer
- Ravi Bhatt
- Sarah Martin
- Laura Seidman
- Jennie Tsao

- UCI Pain program
- Kalpna Gupta
- Sarah Martin
- <u>Vanderbilt</u>
- Michael DeBaun
- <u>Case Western</u>
- Carol Rosen

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### **Quaerite Veritatem:**

Seek the Truth

### (And stay as far away as possible from those who think they have found it ...)



### Thank you for your attention



