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TRV: A Physiological Biomarker in Sickle Cell Disease

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Clinical and translational research makes the biggest leaps in human disease when effective biomarkers are developed and put into play. Effective biomarkers are often convenient surrogate markers of clinical outcomes that dramatically speed up the development of clinically useful interventions. They also often point to new mechanistic pathways that open up opportunities for new intervention strategies. The biomarkers may be biochemical, physiological, imaging, or any other reproducible indicator. Familiar examples of effective biomarkers that guide clinical management resulting in improved clinical outcomes include blood pressure, serum cholesterol, or tumor size from radiographic imaging.

In sickle cell disease (SCD), the first truly successful biomarker was fetal hemoglobin [1]. Natural history epidemiological investigation demonstrated that patients with higher levels suffer fewer clinical complications of SCD. Bench investigations showed that fetal hemoglobin inhibited polymerization of sickle hemoglobin. Intervention with hydroxyurea raises fetal hemoglobin levels, and improves clinical outcomes. Hydroxyurea is now an approved, standard of care drug in sickle cell disease, and indications for its prescription continue to expand.

The second truly successful biomarker in SCD is a physiological biomarker: transcranial Doppler (TCD) velocity of blood flow in the cerebral arteries [2]. TCD velocity predicts risk of stroke in children with SCD. Therapeutic intervention with monthly transfusion of red blood cells lowers the TCD velocity, and markedly reduces the incidence of first stroke. Three very important lessons emerged from TCD research. Successful application of TCD: (1) occurred despite lack of consensus over the precise physiological mechanism of TCD velocity; (2) occurred despite known limitations in its specificity; (3) required highly standardized TCD measurement conditions and specific technician training.

In this issue, Forrest and colleagues at Yale University show that tricuspid regurgitant velocity (TRV) measured during Doppler echocardiography in children with SCD is a biomarker that associates with proteinuria, a sign of renal disease. In order to put this observation in perspective, it is helpful to trace the findings that establish TRV as a physiological biomarker in SCD.

Elevated TRV predicts mortality in adults with SCD more strongly than any other marker. A longstanding marker of pulmonary hypertension in the echocardiography world, TRV was first introduced as a biomarker in SCD research by Sutton and colleagues in 1994 in a retrospective study [3]. Gladwin and colleagues in 2004 published a prospective cross-sectional screening study of adults with SCD that showed that a TRV of two standard deviations above the mean (≥2.5 m/s) was prevalent (32%), and predicted about a ten-fold risk for early mortality [4], findings confirmed by Ataga and colleagues [5]. Both Gladwin

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and Ataga attributed the findings to pulmonary hypertension, correct in principle. However, since the consensus clinical definition of pulmonary hypertension uses a threshold for diagnosis of mean pulmonary artery pressure three standard deviations above the mean (25 mmHg) by right heart catheterization, these differences in definitions have led to confusion and debate [6]. Nevertheless, TRV is emerging as a robust physiological biomarker of clinical outcome in SCD.

TRV in SCD adults reproducibly correlates with several important clinical outcomes. Several studies confirm that elevated TRV in SCD adults is associated with important clinical outcomes: pulmonary hypertension [7–9], proteinuria [10,11], leg ulcers [4,7,12–15], decreased exercise capacity [8,16], and early death [4,5]. TRV is one of several longstanding noninvasive modalities for estimating pulmonary artery pressure in the fields of echocardiography and pulmonary hypertension. This same association has been documented by right heart catheterization studies in SCD [8]. In adults, TRV ≥2.5 m/s has a positive predictive value for pulmonary hypertension of only 25% [7], although our group has found that a TRV of three standard deviations above the mean (≥3 m/s) has a 77% positive predictive value (Mehari et al., manuscript submitted), respectable yields for a screening test. TRV can be a useful screening tool in adults with SCD, especially if coupled with a six minute walk distance less than 500m [16,17].

To put these numbers in context, TCD velocity is highly useful and now constitutes standard of care despite an estimated positive predictive value of only 36% [18]. Like TCD, (1) there is lack of consensus over the precise physiological mechanism of TCD velocity [6]; (2) there are limitations in its specificity; (3) highly standardized measurement conditions are required to minimize variability [19].

It would be ideal to identify subjects at high risk to target preventative strategies. Elevated TRV is detectable in childhood [20], decades before the typical age at which pulmonary hypertension becomes clinically symptomatic [21]. Elevated TRV in children with SCD is associated with many of the same clinical features found in SCD adults with elevated TRV: higher systolic blood pressure, lower hemoglobin, higher serum levels of bilirubin and lactate dehydrogenase [20]. SCD children with elevated TRV show a greater decline in systemic arterial oxygen saturation during exercise than children without a TRV elevation [22]. Although it is not immediately associated with decreased exercise capacity as it is in adults with SCD, elevated TRV in children with SCD predicts future loss of exercise capacity [23].

Forrest et al. in this issue add another piece to this picture, showing that abnormal TRV in children with SCD is associated with proteinuria, a form of end organ disease seen also in SCD adults with high TRV [10,11]. It appears at this point that childhood echocardiography screening might be identifying an early stage of elevated TRV, but only long term longitudinal cohort studies will give the definitive answer. These children over years or decades may be at risk to develop loss of exercise capacity and potentially clinically significant pulmonary hypertension. An evidence-based medicine report commissioned by the American Thoracic Society has submitted a recommendation that children over the age of 8 years with SCD should be screened by TRV measurement, acknowledged by the panel to be a weak recommendation based on only moderate evidence (Klings, et al., manuscript submitted). More research is needed in order to provide better evidence regarding screening guidelines in children with SCD.

Children with SCD and elevated TRV may be an ideal group for randomized controlled trials to test possible strategies to prevent progression to high risk status in adulthood. Such trials might test hydroxyurea or other disease modifying strategies for this indication. Since

death with high TRV appears to occur mainly in adulthood, such trials would need to use a more immediate surrogate marker, such as exercise capacity, an endpoint accepted by the Food and Drug Administration for approval of pulmonary hypertension therapeutics. If and when an intervention in presymptomatic children with high TRV is found that prevents progression to adulthood pulmonary hypertension and death, TRV will have fully followed in the footsteps of TCD as a physiological biomarker of risk in children with SCD.

References

1. Akinsheye I, Alsultan A, Solovieff N, et al. Fetal hemoglobin in sickle cell anemia. Blood. 2011; 118(1):19–27. [PubMed: 21490337]
2. Adams RJ. Big strokes in small persons. Arch Neurol. 2007; 64(11):1567–1574. [PubMed: 17998439]
3. Sutton LL, Castro O, Cross DJ, et al. Pulmonary hypertension in sickle cell disease. AmJ Cardiol. 1994; 74(6):626–628. [PubMed: 8074054]
4. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. New Engl J Med. 2004; 350(9):886–895. [PubMed: 14985486]
5. Ataga KI, Moore CG, Jones S, et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. BrJ Haematol. 2006; 134(1):109–115. [PubMed: 16803576]
6. Bunn HF, Nathan DG, Dover GJ, et al. Pulmonary hypertension and nitric oxide depletion in sickle cell disease. Blood. 2010; 116(5):687–692. [PubMed: 20395414]
7. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med. 2011; 365(1):44–53. [PubMed: 21732836]
8. Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J RespirCrit Care Med. 2007; 175(12):1272–1279.
9. Fonseca GH, Souza R, Salemi VM, et al. Pulmonary hypertension diagnosed by right heart catheterization in sickle cell disease. Eur Respir J. in press.
10. De Castro LM, Jonassaint JC, Graham FL, et al. Pulmonary Hypertension in SS, SC and Sβ-Thalassemia: Prevalence, Associated Clinical Syndromes, and Mortality. Blood. 2004; 104(11): 462a. [PubMed: 15044250]
11. Ataga KI, Brittain JE, Jones SK, et al. Association of soluble fms-like tyrosine kinase-1 with pulmonary hypertension and haemolysis in sickle cell disease. Br J Haematol. 2011; 152(4):485–491. [PubMed: 21223248]
12. Akgul F, Yalcin F, Seyfeli E, et al. Pulmonary Hypertension in Sickle-Cell Disease: Comorbidities and Echocardiographic Findings. Acta Haematologia. 2007; 118(1):53–60.
13. Halabi-Tawil M, Lionnet F, Girot R, et al. Sickle cell leg ulcers: a frequently disabling complication and a marker of severity. Br J Dermatol. 2008; 158(2):339–344. [PubMed: 18047512]
14. Serarslan G, Akgul F, Babayigit C. High prevalence of pulmonary hypertension in homozygous sickle cell patients with leg ulceration. Clin Exp Hypertens. 2009; 31(1):44–48. [PubMed: 19172458]
15. Minniti CP, Taylor JGt, Hildesheim M, et al. Laboratory and echocardiography markers in sickle cell patients with leg ulcers. Am J Hematol. 2011; 86(8):705–708. [PubMed: 21630312]
16. Machado RF, Barst RJ, Yovetich NA, et al. Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. Blood. 2011; 118(4): 855–864. [PubMed: 21527519]
17. Machado RF, Martyr S, Kato GJ, et al. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. Br J Haematol. 2005; 130(3):445–453. [PubMed: 16042696]
18. Seibert JJ, Glasier CM, Kirby RS, et al. Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: an 8-year study. Pediatr Radiol. 1998; 28(3):138–142. [PubMed: 9561529]

19. Liem RI, Young LT, Lay AS, et al. Reproducibility of tricuspid regurgitant jet velocity measurements in children and young adults with sickle cell disease undergoing screening for pulmonary hypertension. Am J Hematol. 2010; 85(10):741–745. [PubMed: 20652966]

20. Kato GJ, Onyekwere OC, Gladwin MT. Pulmonary hypertension in sickle cell disease: relevance to children. Pediatr Hematol Oncol. 2007; 24(3):159–170. [PubMed: 17454785]

21. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. Blood. 2003; 101(4):1257–1261. [PubMed: 12393669]

22. Minniti CP, Sable C, Campbell A, et al. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. Haematologica. 2009; 94(3):340–347. [PubMed: 19211639]

23. Gordeuk VR, Minniti CP, Nouraie M, et al. Elevated tricuspid regurgitation velocity and decline in exercise capacity over 22 months of follow up in children and adolescents with sickle cell anemia. Haematologica. 2011; 96(1):33–40. [PubMed: 20884713]