Revisiting Arginine Therapy for Sickle Cell Acute Vasoocclusive Painful Crisis

Patients with sickle cell disease (SCD) suffer from episodic and recurrent painful episodes caused by microvascular vasoocclusive events that produce end-organ ischemia–reperfusion injury and infarction (1). These events are characterized by extreme bone pain and organ injury, including acute lung injury in a subset of patients. Mechanistically, vasoocclusive episode (VOE) events are associated with P-selectin and inflammasome-dependent inflammation, with intravascular adhesion of platelets, neutrophils, and erythrocytes in the endothelium (1). Interestingly, in addition to a central role of P-selectin expression in triggering platelet–neutrophil–erythrocyte aggregation, recent studies in mouse models suggest that both cytokine stimulation and exposure to oxyhemoglobin and heme, released intravascularly during hemolysis, can trigger platelet-inflammasome–dependent shedding of IL-1β and caspase-1–carrying platelet extracellular vesicles; these vesicles promote intrapulmonary adhesive events that arrest pulmonary blood flow (2). During VOE events, a subset of patients develop acute increases in pulmonary artery systolic pressure, estimated by the Doppler-echocardiographic tricuspid regurgitant jet velocity (TRV) (3). In a study of patients with severe acute chest syndrome (ACS), the TRV increased to 2.5–2.9 m/s in 23% of patients and to ⩾3 m/s in 37%, and right ventricular dysfunction occurred in 13%. Importantly, a TRV of ⩾3.0 m/s was associated with increased plasma brain natriuretic peptide, cardiac troponin release, requirement for invasive mechanical ventilation, and death (4). Despite an understanding of the important contribution of acute pulmonary hypertension during VOE events in patient risk assessment, no clear therapeutic options are available outside of rapid red blood cell exchange transfusion, which we believe should be considered in all patients with TRV of ⩾3.0 m/s and right ventricular dysfunction during hospitalization with VOE or ACS.

A recent study by Onalo and colleagues has revisited a role for L-arginine treatment during VOE events in a pediatric cohort with SCD. In this prospective, double-blind, randomized controlled trial, children aged 5–17 years who presented to the hospital with acute VOE events, with or without ACS, received oral L-arginine or placebo. They previously reported that children who received L-arginine experienced shorter time-to-event-resolution and duration of hospitalization, with no serious adverse events (5). In this issue of the *Journal*, Onalo and colleagues (pp. 70–80) describe additional cardiopulmonary benefits of L-arginine therapy in 47 children (6). Increased pulmonary artery systolic pressures, as estimated by TRV of ⩾2.5 m/s on echocardiogram, were present in 61% of children at presentation. Although both groups showed improvement in TRV and brain natriuretic peptide over the 5-day treatment period, the arginine group showed greater reduction in TRV and other echocardiographic estimates of pulmonary artery pressures than the placebo group, especially when stratified by degree of baseline elevation. Lower TRV in the treatment group correlated with increased plasma arginine bioavailability. Although pulmonary hypertension was common in this cohort, it was mild in most cases, with a mean TRV at presentation of 2.4 ± 0.7 m/s. The placebo group also showed improvement in TRV over the study period, which may bring into question the potential added benefit of this therapy. However, in the subset of patients with TRV of ⩾2.5 m/s, there was significant reduction in TRV over placebo, supporting a therapeutic impact of L-arginine, either directly on the pulmonary vasculature or secondary to systemic effects of the VOE (6).

The authors acknowledge the limitations of echocardiographic assessment of hemodynamics, as well as a limited patient severity and trial power to evaluate the impact of acute reduction of pulmonary pressure on length of stay or post-discharge outcomes. This mirrors the real-world challenges of balancing availability of invasive assessment of pulmonary hemodynamics with the potential procedural risks during VOE. As such, TRV has become the standard modality for assessing pulmonary hypertension in SCD. When measured in steady state in the outpatient setting, it is strongly associated with mortality risk and prevalence of pulmonary hypertension, either group 1 or group 2 disease (7). However, much less is known about the relevance of acute increases in TRV during hospitalization for VOE, especially in children, and if uncomplicated by ACS. Although elevated TRV in children has been associated with declines in exercise capacity at 22 months of follow-up and risk of death long term, the impact of acute increases during VOE remains unknown (8, 9). It is also important to recognize that the elevation of TRV can be related to both intrinsic increases in pulmonary vascular resistance as well as passive increases in pressure from diastolic heart failure and left ventricular fibrosis, which occur in patients with SCD (10, 11). In the current study, the improvement in multiple echocardiographic metrics of pulmonary artery pressure suggests oral arginine relieves vasoconstriction during acute VOE without worsening underlying diastolic dysfunction, if present (6).

L-Arginine is the substrate for *de novo* nitric oxide (NO) biosynthesis, catalyzed by a 5-electron oxidization of L-arginine by NO synthase enzymes to form NO and L-citrulline. Arginine can also be metabolized by arginase to form ornithine and urea, diverting substrate from NO formation. Erythrocyte hemolysis releases oxyhemoglobin and arginase-1 into plasma, with oxyhemoglobin inactivating NO and arginase-1 catabolizing arginine, dual processes that contribute to acute NO depletion and endothelial dysfunction. L-arginine concentrations are reduced and ornithine concentrations

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increased in patients with SCD, with more severe reduction in the arginine/ornithine concentration as the intensity of intravascular hemolysis increases and during acute VOE (12–14). In the current study, the arginine/ornithine concentrations were reduced and improved with L-arginine treatment (6).

L-Arginine has been shown to promote vasodilation and ameliorate pulmonary hypertension in adults (15, 16) and in infants with persistent pulmonary hypertension of the newborn (17). Nearly 20 years ago, preliminary studies showed oral L-arginine improved pulmonary hypertension in a small cohort with SCD, with corresponding increase in plasma concentrations (18). Arginine and NO bioavailability is reduced in patients with SCD, particularly during acute VOE and in patients with more severe baseline hemolytic anemia. Supplemental L-arginine likely works by increasing tissue perfusion and promoting pulmonary vasodilation in the setting of reduced NO signaling and uncoupling of endothelial NO synthase. Other efforts to restore NO signaling therapeutically have been frustrated by lack of efficacy in placebo-controlled trials or limited by medication side effects. Inhaled NO therapy for acute hospitalization in adults and children with VOE was well tolerated but not effective for reducing time to resolution of VOE, although effect on TRV was not evaluated (19). And despite improving pulmonary hypertension, chronic outpatient sildenafil therapy was associated with increased hospitalization for pain (20, 21). The current study revisits and potentially reenergizes efforts to enhance NO signaling with L-arginine supplementation but will clearly require testing in larger clinical trials with longer-term follow-up to assess impact on patient-centered outcomes. ■

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