PRELIMINARY REPORTS

Nitric Oxide Metabolite Levels in Acute Vaso-occlusive Sickle-cell Crisis

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ABSTRACT

Objectives: 1) To measure nitric oxide (*NO*) metabolite levels in patients presenting to the ED in acute vaso-occlusive sickle-cell crisis (SCC), and 2) to determine whether a relationship exists between *NO* metabolite levels and pain.

Methods: A prospective, observational study of patients with documented sickle-cell anemia (SCA), aged ≥18 years, presenting in typical, acute SCC was conducted in an urban, university teaching hospital. Excluded were those with atypical pain or acute, coexistent disease (as evidenced by fever, tachycardia, tachypnea, or hypotension). Pain scores were measured by a 10-cm visual analog scale (VAS). Blood *NO* metabolite levels for SCC patients and control subjects (healthy volunteers, $n = 9$; SCA control subjects not in SCC, $n = 10$) were determined using an *NO*-specific chemiluminescence technique that measured plasma nitrite and nitrate, the stable end-products of *NO*. The acute SCC patients were divided into 3 groups, with the range for the SCC-normal ($n = 5$) group defined as within 2 SD of the healthy volunteer control patients. The SCC-low patients ($n = 21$) had *NO* metabolite levels below this range and the SCC-high ($n = 21$) patients had levels above this range.

Results: The SCA and healthy volunteer control groups had similar *NO* metabolite levels (25.3 vs 22.6 μmol; $p = 0.10$). The 3 acute SCC groups had the following mean *NO* levels: 1) SCC-normal = 21.3 ± 1.6 μmol; 2) SCC-low = 7.2 ± 1.1 μmol; and 3) SCC-high = 43.7 ± 3.5 μmol. The SCC-high *NO*-level group had significantly lower VAS pain scores when compared with the SCC-low and SCC-normal *NO*-level groups (6.52 ± 1.85 cm vs 8.76 ± 0.83 cm, and 8.62 ± 1.29 cm, $p = 0.02$).

Conclusion: *NO* metabolite levels vary in SCC patients. Elevated levels are associated with lower pain scores, while lower levels are associated with higher pain scores, indicating that *NO* metabolites may potentially represent a marker for compensatory mechanisms in SCC tissue ischemia. Further work is needed to delineate the usefulness of *NO* metabolites in assessing the severity of SCC.

Key words: nitric oxide; *NO*; sickle-cell anemia, vaso-occlusive crisis; sickle-cell painful crisis; emergency department.

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Sickle-cell anemia (SCA) is a disease that affects approximately 1 in 625 black people.[1] The great majority of ED visits in SCA are for acute, painful vaso-occlusive sickle-cell crisis (SCC). SCC is characterized by tissue ischemia secondary to local microvascular occlusion and hypoxia that results from sickled red blood cells (RBCs).[2]

One physiologic response to tissue ischemia is vasodilation. Nitric oxide (*NO*), formerly known as endothelium-derived relaxing factor (EDRF),[3,4] is a significant cardiovascular modulator that is synthesized from the ter-

minal guanine group of L-arginine by *NO* synthase.[4] Physiologic, endothelial-produced *NO* in mammals causes a baseline vasodilator state, thereby maintaining normal blood flow[5] (Fig. 1). Normal blood flow is also maintained by the potent antiplatelet aggregation effects of *NO*. In pathologic states such as ischemia–reperfusion, *NO* has been shown to play a significant role in protection against injury[1–3] through increased vasodilation and inhibition of platelet aggregation in various animal models. As a vascular effector, *NO* enhances blood flow to ischemic tissue[6,7] and modulates vascular permeability.[8]

Altered plasma levels of *NO* have been demonstrated in a number of human conditions, such as inflammatory bowel disease,[9] left ventricular failure,[10] and sepsis.[5,11] Rees et al.[11] determined that mean plasma concentrations of the metabolites of *NO* were elevated in admitted SCC patients when compared with healthy, non-SCA volunteers. The authors, however, did not examine the relationship between *NO* metabolite level and pain level. We hypothesized that *NO* metabolite levels are altered at the time of ED presentation for SCC and that there is a relationship between *NO* metabolites and SCC pain.

METHODS

Study Design: We conducted a prospective, observational study of consecutive SCA patients presenting to the ED with a chief complaint of typical, acute SCC 1) to determine *NO* metabolite levels in patients presenting to the ED in acute vaso-occlusive SCC, and 2) to determine whether a relationship exists between *NO* metabolite levels and pain. This study was approved by the Institutional Review Board of Thomas Jefferson University.

Population and Setting: The study was conducted at an urban university ED with an accredited, 3-year emergency medicine (EM) residency program. The Thomas Jefferson University Hospital ED has an annual census of 52,000 patient visits and is staffed 24 hours a day by board certified emergency physicians (EPs). All patients are evaluated either primarily by the attending EP or by EM housestaff under the supervision of the attending EP. All patients evaluated primarily by EM housestaff are done so under the direct supervision of the attending EP. SCA patients who, in the opinion of the attending EP, are stable for release are sent home without the need for consultation with other housestaff or medical staff. SCA patients thought to require admission are evaluated by an internal medicine resident. The ED receives approximately 2,000 visits per year of acute presentations of various types of SCCs, by a sickle-cell population of about 160 patients.

All patients aged ≥18 years with a chief complaint of typical SCC pain were eligible for the study. "Typical" crisis pain was defined by the patient as pain consistent in duration, severity, quality, and distribution with prior episodes of SCC. All patients had sickle-cell SS disease as documented by hemoglobin electrophoresis on cellulose acetate, citrate agar, and isoelectric focusing in the Thomas Jefferson University's Sickle-Cell Center prior to enrollment in the study. Exclusion criteria included age <18 years, non-"typical" pain, refusal to enroll in the study, prior entry into the study, or evidence of acute, coexisting illness. Acute, coexisting illness was defined as an infectious illness, by history, of <7 days' duration, along with any of the following abnormal vital signs on presentation: fever >38.3°C (>101°F), tachycardia >120 beats/min, tachypnea >30 breaths/min, and/or systolic blood pressure <100 mm Hg. The exclusion criteria were independent and exclusive (i.e., the presence of any 1 of the criteria was cause for exclusion from the study).

Control groups were identified for validation of normal *NO* metabolite ranges. Healthy adult ED staff volunteers (normal control subjects) and patients with SCA who were in their usual steady state (SCA control subjects) served as these control groups. Blood samples from the SCA control subjects were obtained during their routine follow-up visits to our Sickle Cell Center.

Experimental Protocol: After initial clinical evaluation and before provision of analgesia, the patient's pain level was measured and a sample of blood was obtained for subsequent analysis.

Measurements: Demographic, historical, and physical examination data were obtained from the ED record. Pain was evaluated by use of a 10-cm visual analog scale (VAS) ranging from "no pain" to "the worst pain I've ever had." All physicians treating SCC patients were instructed how to use the VAS prior to the initiation of the study and were reminded immediately before each patient entry.

Blood was drawn into heparinized tubes after the history and physical examinations had been performed and prior to the administration of analgesics. Blood samples were immediately placed on ice, transported to the Emergency Medicine Research Laboratory, and centrifuged at 10,000 rpm at 4°C for 10 minutes. The plasma was then separated and stored at −20°C.

Nitric oxide is a soluble gas with a half-life of 3–15 seconds, making in-vivo measurement of *NO* levels extremely difficult and impractical. The plasma was analyzed for concentrations of nitrites and nitrates, the stable end-products of *NO*. The use of nitrite and nitrate measurements to quantify *NO* levels in animals[9] and humans[16,17] has been well-documented.

Nitrite and nitrate levels were measured using the previously reported vanadium III reduction method.[20,21] Briefly, 50 μL of plasma was injected into a water-jack-

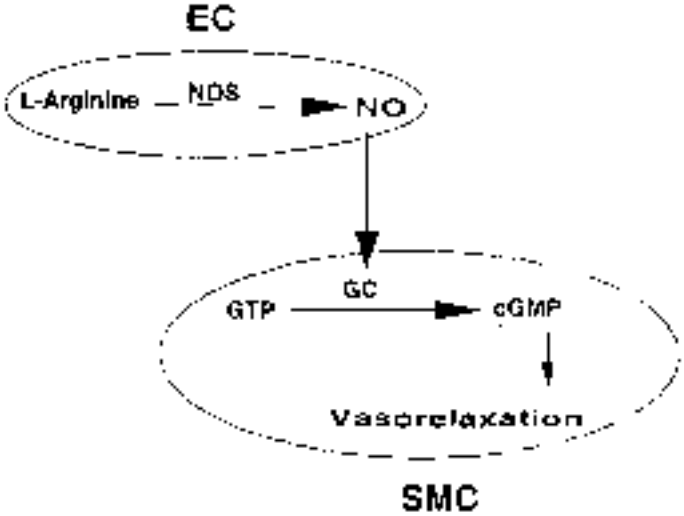

FIGURE 1. The relationship of nitric oxide (*NO*), the endothelial cell (EC) layer, and the vascular smooth muscle in the vasculature. NOS = nitric oxide synthase, GTP = guanylate triphosphate, GC = guanylate cyclase, cGMP = cyclic guanosine monophosphate, and SMC = smooth muscle cell.

cted, O_2-free purge vessel containing 5 mL of 0.1 mol vanadium III chloride (Aldrich, Milwaukee, WI) in 2 N HCl (Sigma, St. Louis, MO). Acidic vanadium III at 98°C quantitatively reduced both nitrite and nitrate to *NO*, which was then quantified by a chemiluminescence detector (Sievers 270B Nitric Oxide Analyzer, Boulder, CO) after reaction with ozone. Signals from the detector were collected and analyzed using a PC-based data recording and processing system (Duo 18, World Precision Instruments, Inc., Sarasota, FL). Standard curves were obtained using the area under the curve after each injection of 10 μL of 0, 12.5, 25, 50, 75, and 100 μmol sodium nitrate. The calculations to determine the *NO* metabolite content of the plasma were done by the slope of the regression analysis using the linear formula $y = a + bx$.

Data Analysis: For analysis, the patients were divided into 2 control groups (normal control and SCA control) and 3 *NO*-metabolite-level groups: SCC-low, SCC-normal, and SCC-high. The 3 groups were based on metabolite ranges after the manner of Rees et al.[11] The SCC-normal group was defined as within 2 SD of the mean *NO* metabolite of the normal control group. The SCC-low patients had *NO* metabolite levels below this range and the SCC-high patients had levels above this range. All data are expressed as mean ± SD.

Visual analog pain scores were tested for normality with the Kolmogorov-Smirnov test for normality and the Levene median test for equal variance prior to analysis. Continuous data were analyzed using analysis of variance. Post hoc testing was performed using the Bonferroni method. Categorical data were analyzed using chi-square testing with Yates' correction. Significance was set at $p = 0.05$, and 2-way analyses were used.

RESULTS

Of 55 consecutive patients who had SCC, 8 were excluded. Of those remaining, there were 27 men and 20 women. No coexistent illness was identified during the ED course. Additionally, the hospital records of the 23 admitted patients revealed no subsequent development of a secondary illness. Table 1 summarizes the measurements and characteristics of the control and study groups. Table 2 summarizes the final ED dispositions for the study groups.

Mean blood *NO* metabolite levels did not significantly differ for the normal control ($n = 9$) and the SCA control ($n = 10$) groups (22.6 vs 25.3 μmol; $p = 0.10$). There were 5 SCC-normal, 21 SCC-low, and 21 SCC-high patients. The 3 acute SCC groups had the following mean *NO* levels: 1) SCC-normal = 21.3 ± 1.6 μmol; 2) SCC-low = 7.2 ± 1.1 μmol; and 3) SCC-high = 43.7 ± 3.5

TABLE 1 Characteristics of the Control and Study Groups*

	Normal Control (n = 9)	SCA Control (n = 10)	SCC-normal (n = 5)	SCC-low (n = 21)	SCC-high (n = 21)	p value
NO (μmol)	22.6 ± 3.7	25.2 ± 2.6	21.3 ± 1.6	7.2 ± 1.1†	43.7 ± 3.5†	<0.001†
VAS§ score (cm)			8.62 ± 1.29	8.76 ± 0.83	6.52 ± 1.85‡	0.02‡
Age (years)	25.0 ± 5.1	27.1 ± 4.1	26.2 ± 4.4	25.5 ± 3.6	26.8 ± 4.1	0.44
Temperature (°F)			99.4 ± 0.6	98.3 ± 0.8	99.0 ± 0.6	0.11
Heart rate (beats/min)			102.5 ± 12.3	89.8 ± 14.6	95.5 ± 9.7	0.24
Systolic blood pressure (mm Hg)			119.0 ± 16.2	116.0 ± 18.6	122.0 ± 18.3	0.70
Diastolic blood pressure (mm Hg)			70.7 ± 15.7	61.4 ± 14.9	74.8 ± 16.0	0.35
Respiratory rate (breaths/min)			16.3 ± 2.9	18.0 ± 1.4	17.8 ± 2.3	0.43

*Normal control = healthy ED staff volunteers; SCA control = sickle-cell anemia (SCA) patients in a steady state, non-sickle cell crisis (SCC) period. *NO* = nitric oxide.

†$p < 0.001$ vs control.

‡$p = 0.02$ vs SCC-normal and SCC-low *NO* group.

§VAS = visual analog scale.

μmol. The mean *NO* metabolite levels for the control groups (Table 1) are consistent with those for prior studies examining *NO* in healthy, normal humans.[13]

DISCUSSION

Acute, painful SCC, with its accompanying regional ischemia, represents the most common presentation of sickle-cell hemoglobin-SS patients to the ED.[22,23] The normal physiologic vascular response to ischemia is vasodilation,[24,25] which attempts to restore adequate O_2 to the ischemic area. *NO* is a vasodilator that is produced by the vascular endothelium, resulting in a baseline vasodilator state in mammals.[5] During ischemia, *NO* has been shown to play a major role in protection against injury through a variety of mechanisms. Most importantly, as a vascular effector, *NO* causes significant vasodilation, resulting in increased blood flow to the ischemic area, thereby increasing O_2 and nutrient supply. Other studies have shown that *NO* attenuates tissue ischemia via inhibition of neutrophil activation,[7] adhesion,[8] and accumulation[9] as well as platelet adhesion and aggregation,[11] thereby ensuring an adequate blood flow. It has been postulated that, in SCC, the occlusion of the microvasculature may lead to an increase in *NO* production in an attempt to avoid tissue infarction.[15]

Rees et al.[15] measured plasma nitrite and nitrate levels (the stable end-products of *NO*) in 34 patients admitted for acute SCC. They found that nitrite/nitrate levels were higher in SCC patients vs healthy control subjects, but that there was no difference between the SCC patients and the SCA "steady-state" control subjects. No attempt was made to relate clinical presentation or pain scores in their study group to *NO* metabolite level. Our study examines *NO* metabolites in acute SCC patients presenting to the ED and relates these levels to pain severity.

We found a variable distribution of *NO* metabolite levels in the SCC patients presenting to our ED. The SCC group who had high levels had significantly lower pain scores as measured by the VAS, whereas those who had "normal" or low levels had significantly higher pain scores. This suggests a relationship between *NO* metabolite levels and the patient's clinical presentation in SCC.

A possible explanation of this relationship is the vasodilatory property of *NO*. In the clinical setting, ischemia and tissue hypoxia generally manifest as pain.[26] An elevated plasma nitrite/nitrate level suggests an increase in whole-body, endogenous *NO* production, indicating a more vasodilated state.[27] The diminished pain score in the group who had the high *NO* metabolite levels may reflect a compensatory, more vasodilated state in response to vascular occlusion and tissue ischemia. The enhanced vasodilation should lead to improved blood flow and increased oxygenation at the tissue level, thereby decreasing painful ischemia. In the face of ischemia, increased *NO* with a resultant vasodilation is a well-described response to myocardial,[28] neurologic,[29] and gastrointestinal[30] ischemia. The SCC-low group may reflect a less vasodilated group, implying a higher degree of tissue ischemia and, therefore, a likelihood of experiencing a higher degree of pain. Although the SCC–normal group had "normal" *NO* metabolites, this level may not be sufficient to adequately compensate for their tissue ischemia during SCC given the lower O_2-carrying capacity of their sickled RBCs. Inadequate vasodilation may therefore result in a higher level of tissue ischemia and pain. This explanation must be tempered by the fact that *NO* has not been linked as a causal factor in ischemia and infarction, but it is often theorized based on associative relationships.

TABLE 2 Dispositions of the 47 Study Patients*

	Admit	Release
SCC-low *NO*	2 (60%)	2 (40%)
SCC-normal *NO*	14 (67%)	7 (33%)
SCC-high *NO*	6 (29%)	15 (71%)

*$p = 0.23$, χ^2 with Yates' correction. SCC = sickle-cell crisis; *NO* = nitric oxide.

Interestingly, there was a trend (though not statistically significant) toward higher ED release rates for the patients who had high *NO* levels, as well as a trend toward higher hospital admission rates for the patients who had lower *NO* metabolite levels (Table 2). This may suggest that a lower level may be an index of the severity of vaso-occlusion and subsequent tissue damage. This may further support our hypothesis regarding *NO* metabolite levels in relation to SCC pain.

Pain and *NO* have been linked, but it is unclear whether *NO* in and of itself can cause or relieve pain.[31] The few studies available examining the role of *NO* and pain appear to support *NO* as either evoking[32] or attenuating[33] pain. Further research is needed to clarify the role of *NO* in pain.

The measurement of *NO* metabolites in patients in SCC may have potential as an objective method of assessing and managing their pain.

LIMITATIONS AND FUTURE QUESTIONS

Several limitations to our study deserve comment. First, our sample size is small. Although we were able to find a statistically significant association between groups based on *NO* metabolite levels, there was only a weak correlation between *NO* metabolite level and VAS pain score ($r = 0.41$, $p < 0.01$). Second, we measured *NO* metabolite level and pain score as a 1-time determination. No conclusion can be made regarding changes in *NO* metabolite levels during the course of the ED treatment or with changes in the patient's pain level. Third, the patients

were not standardized in terms of duration of pain prior to entry, location of pain, and prior analgesic therapy. These factors could certainly influence the actual *NO* metabolite measurement as well as the interpretation of the particular level.

Fourth, the subjective nature of pain has inherent difficulties regarding its evaluation. Although we used a commonly accepted standardized approach to documenting pain level, we did not validate our scale against other measures of pain intensity (e.g., analgesia requirements, duration of ED care, or need for hospitalization). Fifth, because of the difficulty and impracticality of measuring actual tissue ischemia, we were unable to quantify the actual amount of tissue ischemia or relative perfusion present in each patient. Sixth, we did not standardize tourniquet time or technique in this study, nor did we specifically attempt to exclude hemolysis during venipuncture. Although we did not control for these factors, our SCA-control patient population would have similar vascular access problems to those of our SCC patients. The SCA-control patients had *NO* metabolite levels quite similar to those of our normal control patients. Furthermore, we noted no gross hemolysis in the analyzed blood samples.

Seventh, we did not measure actual *NO* levels, but instead used the more commonly measured *NO* metabolite levels. Tracking actual *NO* levels might more accurately reflect the patient's current mediator status. The lag time in metabolite changes following *NO* level rises remains unknown. Finally, the diets of the patients enrolled were uncontrolled. Diets high in vegetables have been shown to alter nitrite and nitrate levels in healthy volunteers.[34]

Future studies should address the above limitations. In addition, studies might be done to answer the following questions: How does the *NO* level change during the course of ED analgesic therapy? Is *NO* related to the duration of pain prior to ED presentation? Is it related to the location of pain (i.e., extent of muscle mass involved)? How does it vary during the evolution of the crisis? Could manipulation of *NO* (e.g., pharmacologically) in SCC hasten recovery? Answers to these questions may determine whether *NO* levels can serve a useful role in assessing or treating patients who have acute SCC.

CONCLUSION

Elevated *NO* metabolite levels are associated with lower pain scores in SCA patients presenting to the ED with acute SCC. The patients who had lower levels generally had higher pain scores, suggesting less compensatory vasodilation. *NO* metabolites may potentially represent a marker for compensatory mechanisms in SCC tissue ischemia. Further study is needed to delineate the exact interaction between *NO* and SCC.

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Comparison of Staples vs Suturing for Securing Central Venous Catheters

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ABSTRACT

Objective: To determine whether skin staples can be used to secure central venous catheters as effectively as does suturing.

Methods: A prospective, randomized trial of techniques to secure a central venous catheter was performed in a medical school human anatomy laboratory using human cadavers. Central lines were secured to the upper left thorax using either standard suture material (000 silk) or skin staples (5.7 mm × 3.8 mm). Once secured, an upward force was applied to the hub of the catheter perpendicular to the skin. The amount of force needed to break the catheter hub free of the skin was measured in kg. A total of 10 measurements were made for each of 3 methods for securing the catheters (2 sutures, 2 staples, 4 staples). In addition, the site of catheter breakage was recorded.

Results: Those catheter hubs secured by 2 sutures required a mean force of 3.1 ± 0.5 kg to cause breakage, and the break always occurred at the suture. Those hubs secured by 2 staples gave way at 3.0 ± 0.3 kg ($p = NS$), while those secured with 4 staples gave way at 4.5 ± 1.4 kg ($p < 0.05$). Although 1 hub did break, in all other stapled cases, the break occurred at the staple.

Conclusions: Based on this cadaver model, use of staples appears to be as effective as suturing for securing central venous catheters. Further studies of safety and time for placement are needed.

Key words: sutures; staples, central venous catheters; needlestick injury; sharp injury; securing catheters.

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