Preliminary Assessment of Inhaled Nitric Oxide for Acute Vaso-occlusive Crisis in Pediatric Patients With Sickle Cell Disease

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VASO-OCCCLUSION IS ONE OF THE hallmarks and major complications of sickle cell disease (SCD), resulting in acute debilitating episodic pain and contributing to infection, acute chest syndrome, splenic sequestration, stroke, acute and chronic multisystem organ damage, and shortened life expectancy. Acute painful vaso-occlusive crisis (VOC) is one of the earliest manifestations of SCD, with crises often beginning in infancy.1,2 Beyond early childhood, VOC accounts for 90% of hospitalizations in children with SCD. The pathophysiology of vaso-occlusion is complex and not fully understood. Polymerization of deoxygenated hemoglobin S (HbS) produces sickled cells that result in vaso-occlusion. In addition, abnormal interactions between poorly deformable HbS and vascular endothelium result in dysregulation of vascular tone3-5; activation of monocytes,6 adhesion molecules,7 and procoagulant factors8; and reperfusion injury.9 These vascular disturbances increase red blood cell transit time, prolonging deoxygenation, which promotes further sickling and vaso-occlusion.

Despite advances in understanding of SCD including identification of potential targets for therapy, to date there are no effective, approved mechanism-of-disease–based therapies for acute VOC, and symptom-directed therapies (ie, analgesia and fluids) with

**Context** Vaso-occlusion is central to the painful crises and acute and chronic organ damage in sickle cell disease. Abnormal nitric oxide–dependent regulation of vascular tone, adhesion, platelet activation, and inflammation contributes to the pathophysiology of vaso-occlusion. Nitric oxide may have promise as a mechanism-of-disease–based therapy for treatment of vaso-occlusion.

**Objective** To explore the efficacy and safety of inhaled nitric oxide (INO) for treatment of vaso-occlusive crisis in pediatric patients.

**Design** Prospective, double-blind, placebo-controlled, randomized clinical trial with enrollment between September 1999 and October 2001.

**Setting** Urban, tertiary care children’s hospital in the United States.

**Participants** Twenty patients aged 10 to 21 years with sickle cell disease and severe acute vaso-occlusive crisis.

**Intervention** Patients were randomly assigned to receive INO (80 ppm with 21% final concentration of inspired oxygen; n=10), or placebo (21% inspired oxygen; n=10) for 4 hours.

**Main Outcome Measures** Change in pain at 4 hours of inhalation compared with preinhalation pain, measured on a 10-cm visual analog scale (VAS); secondary outcome measures were pain over 6 hours, parenteral narcotic use over 24 hours, duration of hospitalization, blood pressure, oxygen saturation, and methemoglobin concentration.

**Results** Preinhalation VAS pain scores were similar in the INO and placebo groups (P=.80). The decrease in VAS pain scores at 4 hours was 2.0 cm in the INO group and 1.2 cm in the placebo group (P=.37). Repeated-measures analysis of variance for hourly pain scores showed a 1-cm/h greater reduction in the INO group than the placebo group (P=.02). Morphine use over 6 hours was significantly less in the INO group (mean cumulative use, 0.29 vs 0.44 mg/kg; P=.03) but was not different over 4 hours (0.26 vs 0.32 mg/kg; P=.21) or 24 hours (0.63 vs 0.91 mg/kg; P=.15). Duration of hospitalization was 78 and 100 hours in the INO and placebo groups, respectively (P=.19). No INO toxicity was observed.

**Conclusions** Results of this exploratory study suggest that INO may be beneficial for acute vaso-occlusive crisis. These preliminary results warrant further investigation.

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only limited effectiveness remain the
mainstay of treatment. Development of
specific, effective disease-targeted treat-
ment of VOC is one of the most impor-
tant goals and greatest challenges in the
management of this disease.

A relative or absolute deficiency of ni-
tric oxide (NO) and/or defective NO-
dependent mechanisms in patients with
SCD may underlie many of the physi-
ologic disturbances that contribute to
vaso-occlusion.18 Nitric oxide is synthe-
sized endogenously in the conversion of
L-arginine to L-citrulline by NO syn-
thetic enzymes in a variety of cells and
tissues, including vascular endothel-
ium, activated macrophages, leuko-
cytes, monocytes, neutrophils, and plate-
lets.11 Of particular importance to SCD,
NO is a central regulator of vascular tone,
cellular endothelial adhesion, platelet ag-
ggregation, and thrombosis. Studies by
Lopez et al12 and Morris et al13 demon-
strate that levels of NO metabolites and
arginine are low during VOC and are in-
versely related to pain severity. Endo-
thelium-dependent vasodilation is mark-
edly impaired in steady state in response
to increased wall shear stress caused by
abnormal erythrocyte rheology and in-
creased cardiac output in patients with
SCD.14 Recent studies by Reiter et al de-
monstrate that NO is stoichiometrically
consumed by high concentrations of he-
molyzed erythrocyte-derived plasma cell-
free ferrous hemoglobin in patients with
SCD.14 They also demonstrate impaired
vasoregulatory forearm blood flow re-
sponse to NO donor infusions in these
patients. In sickle mice that express only
human Hbs, Nω-nitro-l-arginine methyl
ester (L-NAME) inhibition of NO syn-
thase induces vaso-occlusion.15 These ob-
servations suggest that NO has poten-
tial as an innovative mechanism-of-
disease–based therapy for treatment of
vaso-occlusion. Inhaled NO (INO) has
been shown to have important therapeu-
tic effects and to be safe in the acute
and long-term treatment of pulmonary
hypertension,16,17 acute respiratory fail-
ure,18,19 and reperfusion injury in car-
diac ischemia.20 Two reports of the use
of INO in a total of 3 patients with SCD
acute chest syndrome showed INO to be
associated with improved clinical sta-
tus.21,22 To date, there are no published
reports of INO for treatment of acute
VOC in human SCD.

The goal of this study was to ex-

plore the possibility that INO may be
an effective and safe mechanism-of-
disease–based treatment of VOC. We
hypothesized that INO, compared with
placebo, would result in greater im-
provement in pain, reduced parental
narcotic use, and decreased dura-
tion of hospitalization.

METHODS

Study Design

This pilot study was a prospective,
double-blind, randomized placebo-
controlled clinical trial to evaluate the
efficacy and safety of INO for the treat-
ment of VOC in pediatric patients with
SCD. The setting was an urban ter-
tiary care academic children’s hospital
that serves as an SCD center. The study
was approved by the hospital’s institu-
tional review board. An investiga-
tional new drug application was ob-

tained from the US Food and Drug

Administration Division of Cardio-
Renal Drug Products for use of INO in
this study.

Study Setting and Population

Pediatric patients aged 10 to 21 years
with sickle cell anemia (HbSS), hemog-
bolin SC (HbSC), or Hbs–β-thalasse-
mia (Hbs-βthal) who were experienc-
ing uncomplicated severe acute VOC
(score of ≥6 cm on a 10-cm visual ana-
log scale [VAS]) were enrolled from Sep-
tember 1999 to October 2001 by 1 in-
vestigator (D.L.W.). Exclusion criteria
included emergency department (ED)
treatment for VOC within the previous
24 hours; VOC concomitant with other
acute processes, including but not lim-
ited to acute chest syndrome and poten-
tial serious infection; transfusion or use
of investigational drugs other than hy-
droxyurea within the last 30 days; al-
lergy to morphine, smoking more than
½ pack per day; and pregnancy. The in-
vestigator was paged when patients ar-
in the ED for evaluation and treat-
mant of acute VOC. To maximize
enrollment, we used a dual notification
system whereby the investigator was
paged by the treating ED physicians/
nurses and by an automated paging sys-
tem. A software program initially de-
veloped at our hospital for notification
regarding critical laboratory values was
modified for this study to automatically
page the investigator when SCD pa-
tients followed at the hematology clinic
registered for an ED visit.23 Acute pain
crisis was defined as pain in the extremi-
ties, chest, abdomen, or back that could
not be explained by other complication
of SCD or by cause other than SCD. In-
terested patients/families meeting inclu-
sion and exclusion eligibility criteria pro-
vided written assent/consent and were
enrolled.

Study Protocol

Patients meeting eligibility criteria re-
cieved standard ED treatment with mor-
phine (0.1 mg/kg to a maximum of 6
mg) and fluids (isotonic sodium chlo-
ride solution, 10 mL/kg over 30 min-
utes). Patients who continued to meet
eligibility criteria after completion of ED
evaluation and standard treatment were
randomized to receive INO (80 ppm
with 21% final concentration of in-
spired oxygen) or placebo (21% in-
spired oxygen). Patients were admit-
ted to the general clinical research cen-
ter, where NO or placebo inhalation
therapy, administered by face
mask, and morphine, delivered by pa-
tient-controlled administration (PCA)
pump (0.025 mg/kg per dose with a
7-minute lockout and a 0.3-mg/kg
4-hour cumulative dose lockout), were
initiated simultaneously within 90 min-
utes of the initial ED morphine dose.
Inhalation was continued for 4 hours.
Nitric oxide, 780 ppm in nitrogen
(manufactured for Pulmonox Medical
Corp [Tofield, Alberta] by Matheson
Gas [Joliet, Ill]) was mixed with oxy-
gen immediately prior to administra-
tion to deliver 80 ppm of NO using the
Pulmonox IIRT delivery system). Con-
centration of NO and nitrogen diox-
ide (NO2) delivered in the gas mixture
was continuously monitored by an
alarm-equipped electrochemical NO/
NITRIC OXIDE FOR ACUTE VASO-OCCLUSIVE CRISIS

No2 side-stream analyzer built into the delivery device.

Pain assessment, blood pressure determination, oxygen saturation (measured by pulse oximetry), and laboratory studies were performed immediately prior to inhalation, each hour during the 4 hours of inhalation, and for 2 hours after inhalation. The amount of parenteral narcotic used during the first 24 hours was recorded. For each hour of inhalation, the mask was removed for 5 minutes for patient needs immediately after pain assessment, vital signs, and laboratory studies were obtained. Morphine along with diphenhydramine for pruritus and ondansetron for nausea were the only medications allowed be-
cured by pulse oximetry), and labo-

dation (SpO2, minimum systolic blood pressure, minimum SpO2, maximum concentration of delivered No2, and maximum concentration of methemoglobin.

Outcome Measures
The primary outcome measure was the change in pain score at 4 hours of inhalation. The primary pain assessment tool was a 10-cm horizontal undemarcatedVAS labeled with “0” to correspond to no pain at one end and “10” to indicate worst pain at the other. The VAS test was administered by the same investigator (D.L.W.) throughout the study using standardized instructions. Secondary outcomes included amount of parenteral narcotic used 4, 6, and 24 hours after initiating inhalation and length of hospitalization. Narcotic use over 4 and 6 hours was calculated as milligrams per kilogram of morphine and over 24 hours as morphine equivalents using standard conversion formulas (1 mg dilaudid = 5 mg morphine; 1 mg fentanyl = 10 mg morphine) because after 6 hours, pa-
tients could change to alternative nar-
cotics. Safety assessments included minimum systolic blood pressure, minimum SpO2, maximum concentration of delivered No2, and maximum concentration of methemoglobin.

Data Analysis
With a sample size of 20 patients (10 per group), the study had 80% power to detect a mean difference of at least 2.0 cm in the change in VAS pain score between groups at 4 hours of inhalation compared with immediately prior to inhalation, using an unpaired 2-tailed t test with a .05 significance level assuming a common SD of 1.5 cm. The study was not powered to detect differences in secondary outcome measures. The study was monitored for safety throughout by an independent data and safety monitoring board. A formal interim analysis to evaluate study safety and potential early evidence of efficacy was planned and conducted after approximately 50% of patients completed the study. Sample size was adequate to allow an interim and a final analysis without compromising study power (Lan DeMets sequential monitoring procedure using an O’Brien Fleming spending function; EeSt-2000, Cytel Software Corp [Cambridge, Mass]).

Changes in pain score were compared using an unpaired 2-tailed t test. Baseline characteristics and secondary outcome measures were compared using unpaired t tests for continuous variables and the Fisher exact test for categorical variables. We explored the longitudinal effects of INO and nargocic use on pain and the effect of INO on narcotic use using a repeated-measures analysis of variance linear mixed-effects model. All statistical analyses were carried out using SPSS, version 9.0 (SPSS Inc, Chicago, Ill) and SPLUS 2000 (Insightful Corp, Seattle, Wash).

RESULTS
Patient Population
Seventy-nine patients were approached based on the eligibility criteria of SCD, age 10 to 21 years, and uncomplicated, severe acute pain crisis. Thirty-one of these patients were ineligible because of other criteria. An additional 23 declined to participate, leaving 25 patients who were randomized (FIGURE 1).

After randomization but before initia-
tion of inhalation, 5 patients did not meet final eligibility criteria. All 20 patients who began inhalation completed the study. The investigators, patients, and parents of patients remained blinded

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throughout the study. Demographics and clinical characteristics of the 10 patients in each group were similar (TABLE 1). Other baseline characteristics and measurements such as number of VOCs requiring outpatient and inpatient treatment at a hospital within the previous year, number and location of painful sites and duration of current pain prior to morphine, initial white blood cell count, hematocrit, mean corpuscular hemoglobin concentration, reticulocyte count, and lactate dehydrogenase were similar in the 2 groups (Table 1). Patients in the placebo group were younger than those in the INO group ($P = .05$).

**Outcome Measures**

Mean VAS pain scores were similar between groups at the time of presentation to the ED prior to morphine and fluid administration, as well as immediately prior to inhalation ($P = .80$; Figure 2). The decrease in VAS pain score between groups at 4 hours compared with preinhalation, the primary end point, was greater in the INO group (2.0 cm vs 1.2 cm in the placebo group), but the difference was not statistically different ($P = .37$). At the 3-hour point, this difference approached statistical significance ($P = .05$). Six hours after the start of inhalation (ie, 2 hours after completion of inhalation), the mean VAS pain score in the placebo group was unchanged from that at 4 hours, but in the INO group the mean VAS pain score increased and was similar to the mean VAS pain score in the placebo group. Repeated-measures analysis of variance showed a decrease in the VAS pain score of 1.0 cm more each hour in the INO group than in the placebo group ($P = .02$).

The INO group used less parenteral morphine during the 6-hour period than did the placebo group (mean cumulative morphine use, 0.29 vs 0.44 mg/kg; $P = .03$; Figure 3). The difference in use of parenteral narcotics during the 4-hour inhalation period and over 24 hours was lower in the INO group but was not statistically significant (over 4 hours, 0.26 vs 0.32 mg/kg; $P = .21$; over 24 hours, 0.63 vs 0.91 mg/kg; $P = .15$). In addi-
tion, 3 patients in the placebo group but only 1 in the INO group reached the 4-hour lockout morphine dose prior to 4 hours. After the 6 hours during which parenteral morphine was the only analgesic allowed, 4 patients were given a different analgesic by the treating physician; 2 in the INO group and 1 in the placebo group were given PCA dilaudid, and 1 patient in the placebo group was given PCA fentanyl.

Repeated-measures analysis of variance showed that the INO group used 0.025 mg/kg per hour less morphine than the placebo group ($P = .01$). Furthermore, lower VAS pain scores were associated with lower cumulative morphine use ($P = .01$). Each 0.15-cm decrease in pain score was associated with 0.1 mg/kg less morphine used.

Although there was a trend toward shorter duration of hospitalization in patients in the INO group compared with the placebo group (median, 78 vs 100 hours), the difference was not statistically significant ($P = .19$). There were no episodes of hypotension, clinically significant decreases in SpO2, clinically significant increases in methemoglobin, or toxic concentrations of NO2 delivered (TABLE 2). The difference in serum NO2 concentration between the INO and placebo groups was expected, since NO2 is generated as a by-product when NO is mixed with O2. Nitrogen dioxide levels in the INO group remained at or below the 1- to 5-ppm legal permissible exposure limit established by the Occupational Safety and Health Administration (http://www.osha.gov).

**COMMENT**

Treatment of acute VOC remains a critical goal and challenge in the management of patients with SCD. To date, there are no disease-specific therapeutic agents approved for acute VOC. Our current understanding of SCD offers insights into potential mechanism-of-disease-based therapies. In particular, relative or absolute NO deficiency and/or abnormal NO metabolism contributes to the vaso-occlusion that causes painful crises and to the other acute and chronic sequelae of the disease. Levels of NO and arginine are low in patients with SCD during VOC and are inversely correlated with pain severity. Reiter et al postulate that scavenging of NO by the high concentration of plasma cell-free hemoglobin in patients with SCD results in a deficiency of bioavailable NO. In sickle mice that express only human HbS, L-NAME inhibition of NO synthase induces vaso-occlusion. Inhaled NO treatment in sickle mice exposed to hypoxia has been shown to improve survival.

The goal of this preliminary study was to begin investigating the possible efficacy and safety of INO for the treatment of acute VOC. While the results of this small pediatric study with short treatment duration do not provide definitive evidence for the role and safety of INO, they do suggest possible efficacy compared with placebo in the relief of pain and narcotic use. The difference in change in VAS pain score between groups increased over the inhalation period, reaching a maximum at 3 hours. For all patients in the INO group, VAS was at its minimum at 3 hours of inhalation, while for patients in the placebo group, minimum VAS was evenly distributed between hours.
1, 2, and 4. Pain scores did not change in placebo patients in the 2-hour postinhalation period but increased in patients in the INO group to equal that of the placebo group, suggesting a waning effect of INO after inhalation that is consistent with the short half-life of INO. The observation that patients in the INO group used less narcotics than those in the placebo group also may suggest a clinically significant effect of INO. The hourly difference in narcotic use between groups may actually be underestimated, particularly at hour 4, given that more patients in the placebo group used the 4-hour maximum amount of narcotics, and this group of patients had a greater increase in their narcotic use during the fifth hour. There was a modest though not statistically significant trend toward shorter hospitalization in patients in the INO group. This result must be interpreted cautiously, given the short duration of INO therapy and the numerous biopsychosocial factors that influence discharge. There were no apparent safety or toxicity concerns in this small number of patients.

According to US Department of Health and Human Services guidelines on the management of SCD, self-reporting of pain is the most reliable indicator of the presence and intensity of pain.20 The VAS is an easy to use, reliable pain assessment tool in patients older than 5 years27 and has been extensively validated in patients with SCD.28 The magnitude of change in VAS pain scores observed in this study was similar to that observed by Hardwick et al29 in a comparison of effectiveness of morphine with and without ketorolac for treatment of VOC over a similar period. We are unaware of studies assessing the clinical significance of decreasing VAS in patients with acute VOC; therefore, we cannot determine whether the greater decrease in VAS in the INO group, which was at least 1.36 cm at each point, was clinically significant compared with decreases of 0.76 to 1.2 cm in the placebo group. Several studies in adult ED patients with acute pain or acute exacerbations of chronic pain suggest that a decrease of 1.3 cm or greater appears to be clinically significant, as determined by comparing VAS with other patient response scales.30,31

In considering the mechanisms by which NO is postulated to have therapeutic potential, it is most likely, given only a 4-hour duration of inhalation, that the major effect of NO in this study is on regulation of vascular tone. Belcher et al30 showed that abnormal endothelium-dependent vasodilation in response to increased wall shear stress due to abnormal erythrocyte rheology and increased cardiac output is markedly impaired, even in steady state in patients with SCD. Reiter et al34 observed impaired vasoregulatory forearm blood flow response to NO donor infusions in patients with SCD in steady state and demonstrated restoration of response in vivo with inhalation of NO and in vitro with conversion of plasma hemoglobin to nonferrous forms. Although NO is postulated to modulate expression of monocytes,6 adhesion molecules,7 and platelet activating factors,6 it is unlikely that these effects would be significant within 4 hours. One proposed but unsubstantiated mechanism of action for NO in SCD was that NO increases oxygen affinity for HbS, resulting in increased oxygen delivery to tissues.32 There is overwhelming evidence from several studies that NO, at the concentration used in this study, would be insufficient to generate enough S-nitrosyl-hemoglobin to produce a clinically significant increase in hemoglobin oxygen affinity; therefore, the partial pressure of oxygen required for 50% hemoglobin saturation (P50) was not measured in this study.33-35

Inhaled NO has been shown to be safe and have important therapeutic effects in acute and long-term treatment of pulmonary hypertension,16,17 acute respiratory failure,18,19 reperfusion injury in cardiac ischemia,20 and, possibly, in acute chest syndrome in SCD.21 Because the mechanism of action of NO in treatment of acute VOC likely differs from that of other pathophysiologic conditions for which it has been used, an NO dose at the high end of what is thought to be the safe range was chosen to maximize the likelihood of a therapeutic effect. Even at this high dose, there were no obvious adverse effects in this carefully monitored, albeit small, pediatric patient population.

Other agents that may have effects similar to INO have been and are currently under investigation. In a large pediatric/adult clinical trial, poloxamer 188, a nonionic surfactant with hemorheologic and antithrombotic properties, produced a small but significant decrease in duration of crisis and an increase in the number of patients who attained resolution of crisis.36 While not currently in use for treatment of acute VOC, hydroxyurea37,38 and arginine,39 which produce NO, may have the same NO-mediated benefits as INO.

In addition to the study limitations already discussed, we recognize that sample size was inadequate to allow subgroup analyses that may have revealed group-specific effects of INO. Genotype for hemoglobin and other factors that may modulate clinical expression of SCD, patient age, concurrent use of hydroxyurea, and duration, intensity, and sites of pain could all be factors that influence response to NO. The study also did not attempt to evaluate dose response. We cannot explain the disproportionately high enrollment of patients with SCD given their frequency in the available study population. Future studies extending the duration of NO inhalation, modifying the INO dose, examining patient subgroups, and evaluating NO donor compounds are warranted.

CONCLUSIONS

This study is the first completed clinical trial to evaluate INO for treatment of acute VOC in children with SCD. Based on our results and what is known about the likely role of NO deficiency/defective function in the pathophysiology of SCD, NO may offer promise as a therapeutic agent for VOC. These encouraging results are worthy of further investigation. We hope that this study provides a foundation for the more rigorous studies required to evalu-
ate efficacy, safety, and mechanism of action of INO. In addition, studies that evaluate physiologic effects of NO in SCD will be critical for further understanding the complex pathophysiology of this disease.

**Author Contributions:** Weiner had full access to all of the data in this study and takes full responsibility for the integrity of the data and the accuracy of the statistical analysis.

**Study concept and design:** Weiner, Hibberd, Betit, Brugnara.

**Acquisition of data:** Weiner, Betit, Brugnara.

**Analysis and interpretation of data:** Weiner, Hibberd, Botelho, Cooper, Brugnara.

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Median ethanol consumption was 0 g/d per kg for never and former drinkers, 0.25 g/d per kg for those consuming less than 0.5 g/d per kg, 0.70 g/d per kg for those consuming 0.5 to less than 1.0 g/d per kg, and 1.14 g/d per kg for those consuming 1.0 g/d per kg or more. The mean ODI level correlated positively with ethanol intake among total participants (P = .003 for trend) (Table). For all participants with an ODI of 5 per hour or greater, the ORs for SDB were 1.45 (95% confidence interval [CI], 1.02-2.04) for those with ethanol intake of 0.5 to less than 1.0 g/d per kg and 1.95 (95% CI, 1.15-3.31) for those with an intake of 1.0 g/d per kg or more. For participants with an ODI of 15 per hour or greater, the ORs for SDB for these same categories were 1.94 (95% CI, 1.06-3.54) and 3.08 (95% CI, 1.30-7.29), respectively. For participants with an ODI of 5 per hour or greater and the greatest ethanol consumption, the association with SDB was stronger in those with lower BMI than in those with higher BMI (OR, 2.31; 95% CI, 1.13-4.72 vs OR, 1.13; 95% CI, 0.52-2.44, respectively). There were similar associations between alcohol consumption and mean values of oxygen desaturation (data not presented). When we analyzed alcohol consumption on the night of study, we found similar results, with a somewhat lower association for participants with an ODI of 15 or greater among men with an ethanol intake of 1.0 g/d per kg or more (OR, 2.35; 95% CI, 0.96-5.75).

Comment. We found a significant positive association between usual alcohol consumption and the severity of SDB among middle-aged Japanese men, independent of age, BMI, and smoking. There was an association with SDB even among men with a moderate ethanol intake (0.5 to <1.0 g/d per kg). We believe that the smaller effect found with alcohol consumption measured on the night of the study may represent usually heavy drinkers modifying or underreporting their alcohol consumption at that particular time. The overall findings are concordant with the results of an experimental study demonstrating an increase in the mean apnea-hypopnea index from 7.1 to 9.7 per hour following ingestion of ethanol prior to sleep at a dose of 0.5 g/kg.4 Alcohol depresses hypoglossal muscle activity and waking ventilatory responses to asphyxia. The association between alcohol intake and SDB among men with higher BMI may have been masked by a strong effect of excess weight on SDB. The stronger association between alcohol intake and SDB among nonoverweight patients with SDB emphasizes the importance of alcohol abstinence in this group.

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