Predictors for Treating Obstructive Sleep Apnea With an Open Nasal Cannula System (Transnasal Insufflation)

Georg Nilius, Thomas Wessendorf, Joachim Maurer, Riccardo Stoohs, Susheel P. Patil, Norman Schubert and Hartmut Schneider

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Obstructive sleep apnea (OSA) is a common disorder that is associated with increased morbidity and mortality. Although continuous positive airway pressure (CPAP) is the only treatment shown to reduce both cardiovascular and neurobehavioral morbidities, approximately 25% to 50% of patients with OSA will either refuse or not tolerate the use of CPAP therapy, primarily because of the mask and head gear required for maintaining positive pressure during sleep. Thus, improvements in nasal interfaces and overall comfort might improve adherence to therapy.

Background: Obstructive sleep apnea (OSA) is a disorder that is associated with increased morbidity and mortality. Although continuous positive airway pressure (CPAP) is the only treatment shown to reduce both cardiovascular and neurobehavioral morbidities, approximately 25% to 50% of patients with OSA will either refuse or not tolerate the use of CPAP treatment. In a small group of patients, it was recently shown that an open nasal cannula (transnasal insufflation [TNI]) can treat OSA. The aim of this larger study was to find predictors for treatment responses with TNI.

Methods: Standard sleep studies with and without TNI were performed in 56 patients with a wide spectrum of disease severity. A therapeutic response was defined as a reduction of the respiratory disturbance index (RDI) below 10 events/h associated with a 50% reduction of the event rate from baseline and was used to identify subgroups of patients particularly responsive or resistant to TNI treatment.

Results: For the entire group (N = 56), TNI decreased the RDI from 22.6 ± 15.6 to 17.2 ± 13.2 events/h (P < .01). A therapeutic reduction in the RDI was observed in 27% of patients. Treatment responses were similar in patients with a low and a high RDI, but were greater in patients who predominantly had obstructive hypopneas or respiratory effort-related arousals and in patients who predominantly had rapid eye movement (REM) events. The presence of a high percentage of obstructive and central apneas appears to preclude efficacious treatment responses.

Conclusion: TNI can be used to treat a subgroup of patients across a spectrum from mild-to-severe sleep apnea, particularly if their sleep-disordered breathing events predominantly consist of obstructive hypopneas or REM-related events but not obstructive and central apneas.

Abbreviations: CPAP = continuous positive airway pressure; NREM = nonrapid eye movement; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; REM = rapid eye movement; RERA = respiratory effort-related arousal; TNI = transnasal insufflation; TST = total sleep time.

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Recently, it has been demonstrated that the trans-nasal insufflation (TNI) of warm and humidified air at a flow rate of 20 L/min through an open nasal cannula system led to a therapeutic reduction of the sleep-disordered event rate in approximately one-third of the patients studied.9 Because of the small number of patients studied, it was not possible to determine polysomnographic predictors for treatment responses.

In the current study, we examined the polysomnographic responses to TNI in a larger clinical sample of patients. The primary goal of this study was to identify polysomnographic characteristics on a baseline sleep study that may be used to predict TNI treatment responses. Because the major mechanism of action of TNI appears to be through a small reduction of pressure should be sufficient to alleviate hypopneas.4,10 We therefore hypothesized that TNI would have a positive therapeutic effect in patients with sleep-disordered breathing and that TNI would be more effective in treating patients who predominantly have hypopneas rather than apneas.

Materials and Methods

The study was conducted under the supervision of the ethics committees of the Universität Witten-Herdecke and according to “Good Clinical Practices” and the Declaration of Helsinki.11 In addition, the study was reviewed and approved by the institutional review board of each participating center, including the reading center at the Johns Hopkins Sleep Disorders Center, which scored all sleep studies and performed the data analysis. Study procedures, risks, and benefits were reviewed, and written informed consent was obtained for each participant prior to enrollment in the study.

Subjects

Recruitment of participants for the study was conducted at four sleep disorder centers between November 2006 and August 2007. Participants were eligible if they met all of the following inclusion criteria: (1) a baseline sleep study that demonstrated a total non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stage respiratory disturbance index (RDI) of >5 events per hour, (2) presence of excessive daytime sleepiness by self-report, (3) clinical criteria for CPAP treatment according to the standard practice of care of each sleep laboratory, (4) patients had not previously used CPAP in the management of their disease, and (5) a CPAP titration study that demonstrated a nasal pressure less than the median prescribed pressure of each laboratory (range of CPAP pressure was from 8–11 cm H2O).

Patients were excluded from participating in the study, if they had significant comorbidities, including (1) a past surgery of the nose or pharyngeal structure in the last 12 months or other medical and mechanical treatment of OSA; (2) other sleep-associated disorders, such as restless leg syndrome, periodic leg movement disorder, central sleep apnea disorders, or Cheyne-Stokes breathing; (3) lung disorders (COPD) and heart failure; and (4) bleeding disorders or use of oral anticoagulation medication.

Study Materials

Polysomnography: Standard sleep studies were conducted using the study sites’ local recording platform (Alice [Respironics Deutschland GmbH & Co. KG; Herrsching, Germany], Bembrand [Medicare Deutschland GmbH; Wessling, Germany], Somnologica [Embla Systems GmbH; Munich, Germany], and Jaeger [VIAVSYX Healthcare GmbH; Höchberg, Germany]) according to standard clinical practice of each center and the guidelines of the German Sleep Medicine Society (Deutsche Gesellschaft für Schlafmedizin). All sleep studies consisted of the following signals: EEG (montage C3/A2 and C4/A4); right and left electrooculogram; chin, left and right leg electromyogram; a single, bipolar ECG; oxyhemoglobin saturation by pulse oximeter; nasal and oral airflow monitored by a nasal pressure transducer and an oronasal thermometer; chest and abdominal excursions by inductive plethysmography or strain gauges; snoring sounds with a neck microphone; and body position by a mercury gauge and video monitoring.

Recordings were stored in real time (European Data Format) and sent to a central reading center at the Johns Hopkins Sleep Disorders Center via an independent study monitoring agency (Marshall Assoc.; MaxMedical; Frankfurt, Germany). At the reading center, recordings were first deidentified and formatted to provide uniform scoring platforms for all studies. Sleep studies were scored by experienced registered polysomnographic technicians who were unaware of the purpose and hypotheses of the current study. Finally, all scored sleep studies were reviewed by a Diplomate of American Board of Internal Medicine, Sleep Medicine (S. P. P.), who was also masked to the treatment status. Polysomnographic indices were then entered into a custom-made database after quality assurance assessments confirmed reliability for scoring and reviewing sleep stages, respiratory events, and respiratory arousals, as previously published.9

Study Protocols

The study protocol consisted of three consecutive nights. Night 1 (baseline sleep study) was used for characterizing standard sleep and breathing indices off TNI. Night 2 (CPAP titration study) was used for the stepwise increase in nasal pressure and the observation of the airflow signal from the built-in pneumotachographs of the CPAP devices. The effective nasal pressure for CPAP was defined as the pressure at which inspiratory flow limitation was abolished and a normal non-flow limited airflow contour ensued during NREM and REM sleep. On the third night (TNI treatment night), participants were asked to initiate sleep on 10 L/min on TNI for reasons of comfort. After lights out, TNI was then increased in a ramp-like fashion (automatically) to 20 L/min over a period of 5 to 10 min.

Sleep Study Analysis

Polysomnographic indices were obtained from sleep studies that had at least 240 min of recording time or 180 min of sleep, and signal quality of airflow and respiratory effort belts allowed discerning the type and duration of sleep-disordered respiratory events. Out of a total of 65 enrolled patients, 56 patients met these criteria. Sleep stages and arousal were defined according to published criteria.12 Respiratory events were defined as follows: Obstructive apnea and presence of central sleep apnea was identified if the airflow was absent or nearly absent for at least 10 s. Hypopnea was identified when there was a >30% reduction in airflow that was associated with a decrease in oxyhemoglobin desaturation of more than 3%. In addition, respiratory effort-related arousals (RERAs) were identified as a series (more than three breaths) of flow-limited breaths that demonstrated either a discernible reduction in airflow from baseline of <30% or an increase in respiratory effort without concurrent increases in airflow that was terminated by an arousal. Central apnea was identified if the absence of airflow was associated without discernable excursions of either the
chest or abdomen. The RDI was defined as the number of apneas, hypopneas, and RERAs per hour for NREM, REM, and total sleep. The predominance of specific events was used to define three subgroups with mild upper airway obstruction: (1) Patients with increasing proportions of obstructive hypopneas were identified by the percent rate of hypopneas, which was computed by calculating the proportions of obstructive hypopneas to all respiratory events (apneas, hypopneas, and RERAs) for each patient during NREM sleep and creating subgroups of patients with increasing proportions of hypopneas (>50%, >66%, and >90% hypopneas, respectively). (2) Patients with a predominance of RERAs (upper airway resistance syndrome) were identified if the apnea and hypopnea rate was <10 events/h and if they had an RERAs to apnea + hypopnea ratio of >2:1. (3) Patients with REM-dependent sleep-disordered breathing had a NREM event rate of <10 events/h and a REM-to-NREM event ratio of >2:1, as described previously.3,4

Statistical Analysis

The primary outcome of treatment efficacy of TNI was defined as follows: for individuals with a baseline RDI >10 events/h, if the RDI fell more than 50% and below 10 events/h sleep, and for individuals whose baseline RDI was <10, if the RDI fell below five events/h and by more than 50% from baseline. Based on the findings of the previous study,9 a sample size calculation revealed that 40 subjects were needed with 80% power and type 1 error of 5% in order to detect a change in RDI of 20 events/h. A paired Student t test was used to compare the RDI between baseline and treatment conditions in all sleep stages.

In secondary analyses, we examined potential polysomnographic, demographic, and anthropometric factors that might predict a treatment response or nonresponse to TNI. These factors included the effects of age, sex, BMI, prescribed CPAP pressure, the proportion of hypopneic events, and central sleep apnea.

To determine whether the treatment responses observed differed from normal night-to-night variability of the RDI, we first determined the proportion of patients that were effectively treated for the entire group and for subgroups with increasing proportions of hypopneas (>50%, >66%, and >90% hypopneas, respectively). Since the treatment night was not randomized, the observed therapeutic effects of TNI may be attributed to the expected spontaneous night-to-night variability in sleep apnea severity. We therefore compared TNI response rates to the reported night-to-night variability in sleep apnea severity in the study of Stepnowsky et al.15 (13%), using the one-sample test of proportions. In the subset of patients who predominantly have REM-related obstructive sleep apnea, the Wilcoxon matched-pairs signed-rank test was used to compare differences between baseline and treatment condition, because of the nonnormal distribution of the data.

RESULTS

Subjects

Table 1 shows the anthropometric and polysomnographic characteristics of the baseline sleep study of all participants. The study population consisted mostly of men (79%). The majority of patients had obstructive hypopnea or obstructive apnea, suggesting a moderate-to-severe degree of upper airway obstruction, whereas only a minority had milder degrees of upper airway obstruction (upper airway resistance syndrome, n = 3; or predominant REM events, n = 11).

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Sleep apnea subgroups

Predominance of RERAs (UARS), No. of patients (%) 3 (5)
REM event predominance, No. of patients (%) 11 (20)
Predominance of hypopneas (>50%), No. of patients (%) 26 (46)
Predominance of apneas (>50%), No. of patients (%) 16 (29)

CPAP = continuous positive airway pressure; N1 = sleep stage 1; N2 = sleep stage 2; N3 = sleep stage 3; NREM = nonrapid eye movement; RDI = respiratory disturbance index; REM = rapid eye movement; RERA = respiratory effort-related arousal; SE = sleep efficiency; TST = total sleep time; UARS = upper airway resistance syndrome.

Polysomnographic Responses to TNI

Figure 1 shows mean and individual responses of the RDI to TNI compared with baseline for the entire night, and for NREM and REM sleep stages. On average, TNI led to a slight reduction of the RDI in NREM, REM, and the entire night, due to heterogeneous response rates between participants. Although TNI decreased RDI in the majority of patients, eight participants demonstrated a marked increase in the RDI (as defined by an increase of more

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Table 1—Anthropometric and Polysomnographic Indices at Baseline

**Figure 1.** Responses of RDI to TNI. ▲ = mean ± SD; x = example of a single responder (see Figure 2, case 1); # = example of a nonresponder (see Figure 2, case 2); NREM = nonrapid eye movement; RDI = respiratory disturbance index; REM = rapid eye movement; TNI = transnasal insufflation.
than 10 events/h compared with baseline) due to positional apneas and technical limitations. (See Limitations in “Discussion” section.)

Figure 2 shows the respiratory pattern at baseline and on TNI in one patient (see asterisk in Fig 1) who had a complete resolution of sleep-disordered breathing (Fig 2A) and in another patient (see x in Fig 1) in whom the RDI increased significantly with TNI (Fig 2B). In the patient shown in Figure 1A, TNI abolished inspiratory flow limitation and stabilized the breathing pattern. In contrast, in the patient shown in Figure 1B the RDI increased from 20 to 55 events/h because of a positional effect on sleep apnea severity. This patient spent considerably more time supine on the treatment night compared with baseline (43% vs 23% total sleep time [TST], respectively). When comparing the RDI for the supine position, the RDI decreased from 72 events/h with 54% apneas to 51 events/h with no apneas. Thus, albeit there was no clinical efficacious reduction in the RDI, TNI converted apneas to hypopneas.

For the entire group, we observed that TNI led to a conversion of apneas to hypopneas without increasing the rate of RERAs. Specifically, the percent rate of apneas to all events (apneas/hypopneas and RERAs) decreased from 46.3% ± 4.4% to 18.4% ± 4.1% (P < 0.05) during REM sleep and 34.4% ± 7.4% vs 27.4% ± 8.1% TST (not significant) during NREM sleep. The rate of RERAs during NREM and REM sleep combined was 5.8 ± 0.9 events/h at baseline and 3.9 ± 0.5 events/h at treatment night on TNI.

Predictors for Efficacious Responses to TNI

Anthropometric and Clinical Characteristics; Event Type and Rate: Anthropometric characteristics, including sex, age, BMI, prescribed CPAP pressure, and baseline polysomnograph indices, did not differ between those participants who met our definition for a response to those who had a suboptimal reduction in the RDI (see Table 2). Figure 3 shows how polysomnographic characteristics including sleep apnea severity (Fig 3A), event type (Fig 3B), and the degree of upper airway obstruction as defined by the proportion of hypopneas to all events in percent (Fig 3C) influence the response rate to TNI. First, we found that RDI did not predict response rates to TNI (Fig 3A). Second, in the eight individuals who had >10% central apneas at baseline (Fig 3B), none had a positive response rate to TNI. The response rate was greatest in patients who predominantly had obstructed compared with central events. Third, a greater hypopnea rate was associated with an increased response rate in a dose-dependent fashion (Fig 3C). Although patients who predominantly had apneas (>50% of all events) had a low response rate of 18.8% (three of 16 patients), the response rate increased from 33% (>50% hypopnea), 38% (>66% hypopnea), and to 50% (>90% hypopnea) with increasing degrees of hypopneas, respectively. The response rate to TNI was significantly greater in all patients with obstructive events (Fig 3B) and all groups independent of the proportion of hypopneas (Fig 3C) compared with the expected night-to-night variability in sleep apnea severity of 13%.

For the entire group, we observed that TNI led to a conversion of apneas to hypopneas without increasing the rate of RERAs. Specifically, the percent rate of apneas to all events (apneas/hypopneas and RERAs) decreased from 46.3% ± 4.4% to 18.4% ± 4.1% (P < 0.05) during REM sleep and 34.4% ± 7.4% vs 27.4% ± 8.1% TST (not significant) during NREM sleep. The rate of RERAs during NREM and REM sleep combined was 5.8 ± 0.9 events/h at baseline and 3.9 ± 0.5 events/h at treatment night on TNI.

**Figure 2.** Respiratory pattern of a responder. (A) Case 1, marked with x in Fig 1. (B) Case 2, a nonresponder (marked with * in Fig 1). \( \text{SpO}_2 \) (%) = oxyhemoglobin saturation. See Figure 1 legend for expansion of other abbreviations.
Table 2—Comparison of Anthropometric and Clinical Data Between Responder and Nonresponder

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<th>Therapeutic Response</th>
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<td>Age, y</td>
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<td>BMI, kg/m²</td>
<td>28.4 ± 3.1</td>
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<td>Prescribed CPAP, cm H₂O</td>
<td>7.6 ± 1.9</td>
<td>7.1 ± 1.9</td>
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<td>TST, min</td>
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<td>SE, % TST</td>
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See Table 1 for expansion of abbreviations.

Subgroups With Mild Upper Airway Obstruction:
A predominance of RERAs (upper airway resistance syndrome) was observed in three individuals at baseline and in six on TNI. The total RDI decreased in two individuals below five events/h, and the third developed central apneas on TNI at a rate of 12 events/h, offsetting the reduction in RERAs in individuals with REM-sleep-disordered breathing. A predominance of REM-sleep-disordered breathing was observed in 10 individuals at baseline and five on TNI. As shown in Figure 4A, all but one individual with REM-sleep-disordered breathing at baseline reduced the REM RDI on TNI (mean decrease from 24.3 ± 2.0 to 11.6 ± 2.9 events/h). The nonresponder slept predominantly on his side during the baseline sleep study but mostly supine during TNI treatment night. For this group, 55% had an efficacious decrease in REM RDI as defined above (Fig 4B). Moreover, four of the 10 individuals decreased the total RDI below five events/h.

Discussion
In this study, we confirmed that TNI reduced the overall sleep-disordered breathing event rate below a clinically acceptable threshold in approximately one-quarter of patients who required CPAP therapy. Our findings indicate that: (1) Patients with a wide range of RDI had similar response rates, indicating that treatment responses to TNI are independent of the sleep apnea disease severity. (2) The response rate was markedly increased in patients who predominantly had hypopneas and patients with mild upper airway obstruction as indicated by a predominance of RERAs and REM-related events. (3) The presence of >10% central apneas predicted poor response. (4) Anthropometric characteristics and the level of prescribed CPAP pressure did not predict treatment responses. Thus, TNI treatment responses depend on the severity, but not the frequency, of upper airway obstruction.

Predictors of Response to TNI
As in our prior TNI pilot study,9 we found that TNI reduced apneas and hypopneas. The major reason for decreased RDI can be attributed primarily to the increase in pharyngeal pressure that is associated with an increase in the inspiratory airflow.10 At a rate of 20 L/min, TNI increases nasal pressure by approximately 2 cm H₂O and increases inspiratory airflow by approximately 100 mL/s.9 In general, the peak inspiratory airflow for hypopneas and for flow-limited breaths averages approximately 150 to 200 mL/s.10

![Figure 3](https://example.com/f3.png)

Figure 3. Predictors of efficacious responses to TNI. RERAS = respiratory effort-related arousals. See Figure 1 legend for expansion of abbreviations.
The additional flow from TNI, therefore, will increase the inspiratory airflow to 250 to 300 mL/second, a level previously associated with stabilization of breathing patterns. In the current study, we did not quantify airflow; thus, it was not possible to determine whether the individuals with hypopnea who did not respond had more severe upper airway obstruction as reflected by reduced levels of inspiratory airflow.

Additional, nonquantifiable factors that may have contributed to the therapeutic response include the following: First, small increases in pharyngeal pressure may have increased lung volume, which may improve both oxygen stores and upper airway patency. Second, as ventilation improves during sleep, enhanced sleep continuity (decreased arousal frequency) may further stabilize breathing and reduce the RDI. Finally, additional benefits may have accrued from insufflating air directly into the nose, producing concomitant reductions in dead space ventilation.

REM Sleep Apnea: TNI was more effective in improving sleep-disordered breathing in REM sleep compared with NREM sleep, as indicated by a shift from apneas to hypopneas for REM events and by the response rate in individuals with predominant REM apneas in which all but one patient had a significant reduction in the REM event rate with TNI. REM sleep is associated with a loss in muscular tone and a decrease in ventilatory demand. It is possible that small increases in pharyngeal pressure are more effective in stabilizing upper airway musculature in the presence of a hypotonic musculature of the pharynx and chest wall during REM sleep as compared with a more tonic state in NREM sleep. Alternatively, TNI might have increased tidal inspiratory volumes and satisfied patient’s ventilatory demand during REM sleep. Regardless of the mechanism, our finding is comparable to that of a recently documented study in which a high response rate to TNI was observed in children if they had predominant REM events but flow limitation during NREM sleep.

Limitations

There are several limitations that merit consideration. First, nine initially enrolled patients were excluded from the analysis because the sleep studies did not meet our criteria for study participation as mentioned in the “Methods” section. We do not believe that the exclusion affected our results because insufficient sleep at baseline rather than at TNI nights was the primary reason for exclusion. Second, our primary intention was to emulate usual clinical care, which includes changes in body position and displacement of the nasal cannula (which occurred), and thus the effectiveness of therapy in certain individuals was underestimated. The major limitation of the study was the lack of quantification of airflow that might have helped to predict responses to TNI more accurately. We predict that patients with RERAs or hypopneas of at least 150 mL/s would be the most likely to respond for the reasons noted above.

Additional logistical concerns include the following: First, we did not determine the night-to-night variability of the RDI in our study population. Instead, we used reported night-to-night variability in RDI. The therapeutic response rate was twice as high as the 13% one would anticipate, making polysomnographic responses to TNI most likely attributable to the mechanisms of action as discussed above. Second, all patients were first titrated on CPAP according to clinical standards in each laboratory. Although a comparison on the efficacy of CPAP vs TNI would be potentially of interest, it would have required randomizing TNI and CPAP nights, which was beyond the scope of the current study.
study. Finally, we observed an increase in the RDI in eight individuals. Increases were related to (1) positional sleep apnea (n = 5), wherein subjects spent disproportionately more time supine with TNI compared with the baseline; (2) an inadvertent reduction the TNI flow rate below 17 L/min (n = 1), and (3) an increase in central apneas on the night with TNI (n = 2). These limitations have to be considered in future clinical trials.

Clinical Implication

TNI offers an alternative to the standard CPAP therapy in patients who predominantly have obstructive hypopnea. The efficacy of TNI can be easily assessed within a single night and can be predicted on the basis of the presence of at least 90% hypopnea and RERAs. It is of note that a predominance of hypopneas are seen in children, and RERAs are seen in patients with upper airway resistance syndrome and females with fibromyalgia, therefore, these populations may be ideal for this form of therapy. Finally, more precise measurements of inspiratory airflow may provide a quantitative way of predicting patients who will respond to TNI. Thus, further trials, on subgroups of patients with sleep-disordered breathing using TNI over a longer period of time are necessary to determine its clinical usefulness.

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Dr Wesselndorf: contributed to conception and design of the study, acquisition of data in the study center Essen, critical revision of the draft, and final approval.
Dr Maurer: contributed to conception and design of the study, acquisition of data in the study center Mannheim, critical revision of the draft, and final approval.
Dr Stoohs: contributed to conception and design of the study, acquisition of data in the study center Dortmund, critical revision of the draft, and final approval.
Dr Patil: contributed to conception and design of the study, analysis of the data in the central reading center, statistical analysis, draft of the article, critical revision of the draft, and final approval.
Dr Schubert: contributed to analysis of the data in the central reading center, statistical analysis, critical revision of the draft, and final approval.

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REFERENCES


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