Automated Responsiveness Test (ART) Predicts Loss of Consciousness and Adverse Physiologic Responses during Propofol Conscious Sedation

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Background: The authors evaluated a device designed to provide conscious sedation with propofol (propofol-air), or propofol combined with 50% nitrous oxide (N₂O; propofol-N₂O). An element of this device is the automated responsiveness test (ART), a method for confirming that patients remain conscious. The authors tested the hypotheses that the ART predicts loss of consciousness and that failure to respond to the ART precedes sedation-induced respiratory or hemodynamic toxicity.

Methods: The protocol consisted of sequential 15-min cycles in 20 volunteers. After a 15-min control period, propofol was infused to an initial target effect-site concentration of 0.0 μg/ml with N₂O or 1.5 μg/ml with air. Subsequently, the propofol target effect-site concentration was increased by a designated increment (0.25 and 0.5 μg/ml) and the process repeated. This sequence was continued until loss of consciousness, as defined by an Observer’s Assessment of Alertness/Sedation (OAA/S) score of 10/20 or less, or until an adverse physiologic event was detected.

Results: The OAA/S score at which only 50% of the volunteers were able to respond to the ART (P₅₀) during propofol-N₂O was 11.1 of 20 (95% confidence interval [CI]: 10.6–11.8); the analogous P₅₀ was 11.8 of 20 (95% CI: 11.4–12.3) with propofol–air. Failure to respond to the ART occurred at a plasma propofol concentration of 0.7 ± 0.6 μg/ml with propofol-N₂O and 1.6 ± 0.6 μg/ml with propofol-air, whereas loss of consciousness occurred at 1.2 ± 0.8 μg/ml and 1.9 ± 0.7 μg/ml, respectively. There were no false-normal ART responses. The ART can guide individual titration of propofol because failure to respond to responsiveness testing precedes loss of consciousness and is not susceptible to false-normal responses. The use of N₂O with propofol for conscious sedation decreases the predictive accuracy of the ART.

Conclusion: The ART can guide individual titration of propofol because failure to respond to responsiveness testing precedes loss of consciousness and is not susceptible to false-normal responses. The use of N₂O with propofol for conscious sedation decreases the predictive accuracy of the ART.

SEDATIVES and analgesics are commonly given to patients undergoing medical procedures. 1, 2 Conscious sedation 3 can be effective, practical, and safe in an ambulatory setting. 4 American Society of Anesthesiologists (ASA) guidelines specify that patients given conscious sedation by nonanesthesia personnel must remain arousable. 5 The American Academy of Pediatric Dentistry similarly specifies that “loss of consciousness should be unlikely . . . and [that] the drugs and techniques used should carry a margin of safety wide enough to render unintended loss of consciousness unlikely.” 6, 7 Nitrous oxide (N₂O) is a short-acting drug that alone rarely produces important respiratory or hemodynamic complications. 6 However, N₂O alone is often insufficient. The gas is therefore frequently combined with opioids or sedatives. Because propofol combines the advantages of excellent sedation, some analgesia, and antiemetic action, 7 it is a reasonable adjunct to N₂O administration for conscious sedation.

We evaluated a device designed to provide conscious sedation with propofol alone or propofol combined with 50% N₂O. The Vigilant Care System (Scott Laboratories, Inc., Lubbock, TX) includes three major elements: (1) all routine anesthetic monitors, including monitors for oscillometric blood pressure, electrocardiography, end-tidal partial pressure of carbon dioxide [Pco₂], and oxygen saturation; (2) a computer-controlled propofol infusion system; and (3) an automated responsiveness test (ART). In the responsiveness testing system, a computer-generated voice instructs subjects to press a button. Ability to press the button within 10 s is considered presumptive evidence of consciousness.

The primary hypothesis was that failure to activate the automated responsiveness system predicts loss of consciousness and adverse physiologic events during sedation with propofol and propofol combined with N₂O. Corroboratory hypotheses were that an unconscious subject would not reflexively respond during the 10-s request period (i.e., a false-normal response) and that conscious but deeply sedated subjects would be able to activate the system (i.e., lack of false-abnormal responses).

Methods

With approval of the University of California–San Francisco Committee on Human Research, we evaluated 20 healthy volunteers of either sex. Age was restricted to 18–40 yr. Volunteers fasted at least 4 h before the study. They were positioned comfortably on an operating room table and flexed into a chaise-lounge position.
Table 1. Yellow and Red Alerts and Intervention Limits

<table>
<thead>
<tr>
<th></th>
<th>Yellow Alert Limits</th>
<th>Red Alert Limits</th>
<th>Intervention</th>
</tr>
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<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>&lt; 90 and &lt; 85% baseline</td>
<td>&lt; 85 and &lt; 70% baseline</td>
<td>&lt; 80 and &lt; 60% baseline</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>&lt; 55 and &lt; 85% baseline</td>
<td>&lt; 50 and &lt; 70% baseline</td>
<td>&lt; 45 and &lt; 60% baseline</td>
</tr>
<tr>
<td>PETCO₂ (mmHg)</td>
<td>&gt; 55</td>
<td>&gt; 60</td>
<td>&gt; 65</td>
</tr>
<tr>
<td>Respiration (breaths/min)</td>
<td>&lt; 3</td>
<td>&lt; 2</td>
<td>Apnea &gt; 40 s</td>
</tr>
<tr>
<td>PsO₂ (%)</td>
<td>&lt; 93</td>
<td>&lt; 90</td>
<td>&lt; 80</td>
</tr>
</tbody>
</table>

Autonomic responses defining yellow and red alerts, and intervention limits.

BP = blood pressure; PETCO₂ = end-tidal carbon dioxide; PsO₂ = oxygen saturation determined by pulse oximetry.

Targeted Drug Delivery

The drug delivery system consisted of a Harvard 2 (Harvard Clinical Technology, South Natick, MA) electronic syringe pump and a customized software driver (Scott Laboratories, Inc.). We used a three-compartment model and published pharmacokinetic data. Our predicted plasma and effect-site concentrations were compared with a validated standard, StanPUMP (copyright S. Shafer 1986-1995; revision May 11, 1996; steven.shafer@stanford.edu; Palo Alto, CA). The predicted StanPUMP and the plasma and effect-site concentrations of our software driver were virtually identical. The system targeted effect-site concentrations rather than plasma concentrations. The target-controlled infusion system was monitored in real-time by graphical and numerical presentation of the predicted plasma and effect-site propofol concentrations on the screen of the Vigilant Care System monitor.

Protocol

The Vigilant Care System monitors were applied to the participating volunteers, as were other study monitors. The ART apparatus was strapped loosely to the dominant hand of the volunteer. A 20-gauge venous catheter was inserted into the contralateral arm above the wrist. An 18-gauge catheter for blood sampling was inserted at the antecubital fossa on the dominant arm. Lactated Ringer’s solution (200 ml) was infused as a bolus; subsequently, fluid was infused at a rate of 100 ml/h. Forced-air warming was used to maintain tympanic membrane temperature between 37.0 and 37.5°C.

The volunteers were introduced to the ART system for 10–15 min before each sedation trial. The audible volume of the ART was adjusted to a level that they were able to hear easily. We confirmed that the volunteers responded promptly to the ART during this prestudy period.

Volunteers were initially studied during administration of propofol (Diprivan 1%, Zeneca Inc., Wilmington, DE) and 50% N₂O in oxygen (propofol-N₂O). This combination was delivered via the rebreathing circuit of a standard anesthesia machine (Modulus CD Anesthesia System; Ohmeda, Inc., Salt Lake City, UT) through a standard anesthesia mask. After a recovery period of at least 1 h, the volunteers were reevaluated using propofol and air-oxygen (propofol-air). Oxygen was administered at a concentration of 30% via a sealed anesthesia mask during the propofol-only trial and throughout both recovery periods. The propofol-N₂O always preceded the propofol-air trial because we wanted to avoid great accumulation of propofol in the plasma from the previous administration before starting N₂O administration.

The basic protocol consisted of sequential 15-min cycles. After a 15-min-long control period without drugs, another 15-min cycle was tested with N₂O alone, and then propofol was infused to an initial target effect-site concentration. The propofol infusion was maintained throughout each 15-min cycle until an outcome was reached and then, after a 1 h recovery period, the propofol-air trial started. Pharmacokinetic modeling indicated that steady state effect-site concentrations would be obtained within 4 min. Consequently, we considered the period from 9 to 15 elapsed min within each cycle to be at steady state. Subsequently, the propofol target effect-site concentration was increased, by a designated increment and the process was repeated.

Based on previous studies, we started at a target effect-site concentration of 1.5 μg/ml during the propofol-air trial, and then incremented the target concentration by 0.5 μg/ml. In contrast, the initial target propofol concentration during N₂O administration was zero, and the concentration was increased by increments of 0.25 μg/ml.

The sequence of 15-min cycles at progressively greater propofol concentrations was continued until loss of consciousness was detected by an OAA/S score (see Measurements) of 10/20 or less (i.e., no response to the verbal command), “red-alert” limits were reached (table 1), or a loss of response to the ART was observed. In either of the first two cases, propofol or the combination of propofol and N₂O was discontinued, and the recovery portion of the study began. When the trigger was a loss of response to the ART, sedative drugs were discontinued only after the investigator confirmed that the volunteer was unconscious as determined by an OAA/S score of 10/20 or less.

The anesthesiologist took actions necessary to restore acceptable physiologic values only when the volunteers exceeded specific intervention limits (table 1). In keeping with good clinical practices, intervention was graded...
and based on need. Thus, inadequate ventilation or low oxygen saturation, for example, prompted repositioning of the head. If this proved to be insufficient, mild airway support was instituted, followed by moderate airway support or controlled ventilation.

**Measurements**

The ART consisted of a button incorporated into a handpiece that was linked to a computer-generated voice that instructed subjects *via* an earpiece to press the button. This request was repeated up to 5 times over a 10-s interval. With each repetition, the voice became louder and more insistent. Furthermore, the instructions were accompanied by progressively more vigorous vibration of the handpiece. The voice and the vibration both stopped immediately when the button was pressed. Failure to activate the ART button within 10 s after the request was considered a nonresponse and was displayed by the Vigilant Care System as a “yellow alert.”

Demographic and morphometric characteristics of the volunteers were recorded. All routine physiologic values from the Vigilant Care System were digitally recorded. These included heart rate (HR), noninvasive arterial blood pressure (systolic arterial pressure, diastolic arterial pressure, mean arterial pressure [MAP]), end-tidal P$_{\text{ETCO}}$_2, P$_{\text{ETCO}}$_2, and N$_2$O, respiratory rate (RR), and oxygen saturation (P$_{\text{SO}}$_2). Routine anesthetic data from each system were recorded as 1-min averages. The P$_{\text{ETCO}}$_2, oxygen, and N$_2$O were sampled from a sealed anesthesia mask by two different sample lines, one of which was directed to the Vigilant Care System monitor and the other to a Rascal II (Ohmeda, Inc., Salt Lake City, UT). However, noninvasive arterial blood pressure was measured and recorded at 2-min intervals during sedation, as was ART; however, both were switched to 3-min cycles during recovery. Volunteers were monitored closely for potential episodes of excitement or uncooperative behavior.

As in previous studies, level of sedation was assessed using the OAA/S score (table 2). The OAA/S test consists of four components; as described by Chernik et al., we summed the component scores. The OAA/S score sum is at least as reliable and valid as the visual analog scale and the digit–symbol substitution test. Sedation was always evaluated by the same investigator, who was not blind to the presence of N$_2$O or to the target effect-site propofol concentration. The scoring system was applied after the ART result was obtained after the 9 and 15 min of each concentration cycle to minimize the effect of verbal or tactile stimulation on the ART. The scoring system was also applied whenever results of the ART indicated loss of consciousness or when the physiologic values reached a red-alert limit. Scores exceeding 10/20 were considered to be evidence of consciousness.

After 9 min of propofol administration at each target effect-site concentration, a venous blood sample for propofol concentration was obtained. Six minutes later, an additional sample was obtained to confirm steady state plasma concentrations. Samples were also obtained when loss of response to the ART and loss of consciousness were recognized and when the recovery score (see Measurements, last paragraph) first equaled or exceeded 12. All blood samples were obtained without tactile stimulation of the volunteers, and always after recording the results of the ART and OAA/S test.

Blood samples (5 ml) were stored in sodium fluoride tubes. These tubes were kept at 4°C for up to 10 weeks (propofol blood concentrations decrease less than 0.2%/week at 4°C). The samples were subsequently analyzed using a high-performance liquid chromatography assay modified from the method of Plummer. Nausea was evaluated by the subjects using a 4-point scale (none, mild, moderate, and severe). The volunteers were queried before drug administration and after 30 and 60 min of recovery. We also recorded the number of episodes of vomiting during drug administration and during the recovery period.

Fitness for discharge was evaluated at 3-min intervals using a modification of the Aldrete and Kroulik scoring system. The time elapsed between discontinuation of drug administration and a recovery score of 12 (85%) was considered to be the recovery duration.

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**Table 2. Observer’s Assessment of Alertness/Sedation Scale**

<table>
<thead>
<tr>
<th>Subscore</th>
<th>Responsiveness</th>
<th>Speech</th>
<th>Facial Expression</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
<td>Mild slowing or thickening</td>
<td>Mild relaxation</td>
<td>Glazed or mild ptosis</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is spoken loudly and repeatedly or both</td>
<td>Slurring or prominent slowing</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>2</td>
<td>Responds only after mild prodding or shaking</td>
<td>Few recognized words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Does not respond to mild prodding or shaking</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The final score is the sum of the responsiveness, speech, facial expression, and eyes component scores. Therefore, a “wide-awake” score = 20/20 and a “deeply sedated” score = 9/20 (1 [responsiveness] + 2 [speech] + 3 [faces] + 3 [eyes]).

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Data Analysis

The seven sets of autonomic responses and three sets of blood pressures and ART results obtained during each 6-min steady state propofol infusion (9–15 min of each concentration cycle) were averaged for each volunteer. These values were then averaged among the participating volunteers.

Plasma propofol concentrations, hemodynamic and respiratory responses were averaged among the volunteers who reached loss of response to the ART and loss of consciousness with and without N₂O. Recovery duration after each trial and the propofol concentration at recovery were similarly averaged among the volunteers who reached loss of consciousness. The sedation level, according to OAA/S score, and the hemodynamic and respiratory responses with and without N₂O of the volunteers who reached a red alert were presented individually.

Logistic regressions were used to model the probability of loss of response to the ART as a function of the OAA/S score separately for the two sedation trials, with the generalized estimating equations approach used to account for possible dependence among multiple measurements from the same person. The effect of the OAA/S score was modeled as a linear term unless higher order terms (quadratic or cubic) produced better fit at $P < 0.05$. The probability of loss of response to the ART at an OAA/S score of 10/20 or less was estimated separately using exact binomial calculations with one point for each subject.

Plasma propofol concentrations at 9 and 15 min of each concentration increment were compared with paired $t$ tests to evaluate the validity of our steady state assumption. All data were presented as the mean and standard deviation. $P < 0.05$ were considered to be statistically significant.

Results

The volunteers were aged 27 ± 6 yr, weighed 66 ± 10 kg, and were 169 ± 8 cm. Seven of 20 were men. The sedation period was 114 ± 46 min during the propofol-N₂O sedation, but only 58 ± 22 min during the propofol-air sedation. Plasma propofol concentrations at the beginning and end of each steady state period (9 and 15 elapsed min) differed by only 0.0 ± 0.2 $\mu$g/ml ($P = 0.85$).

Progressive increases in the propofol plasma concentration during propofol-N₂O and propofol-air trials induced changes in the cardiorespiratory physiology and are shown in figure 1. The OAA/S score at which only 50% of the volunteers were able to respond to the ART ($P_{50}$) occurred at 11.1/20 (95% CI: 10.6–11.8) during propofol-N₂O and of 11.8/20 (95% CI: 11.4–12.3) during propofol-air.

Failure to respond to the ART occurred at a plasma propofol concentration of 0.7 ± 0.6 $\mu$g/ml (95% CI: 0.5–1.0) with propofol-N₂O and of 1.6 ± 0.6 $\mu$g/ml (95% CI: 1.3–1.9) with propofol-air, whereas loss of consciousness, as defined by an OAA/S score of 10/20 or less, occurred at 1.2 ± 0.8 $\mu$g/ml (95% CI: 0.8–1.6) and 1.9 ± 0.7 $\mu$g/ml (95% CI: 1.5–2.3). Speech, facial expression, and eye signs seen on the OAA/S score disappeared well before the volunteers became unresponsive. Loss of consciousness was therefore invariably defined by the responsiveness component of the OAA/S test. Hemodynamic and respiratory responses remained essentially normal at loss of response to the ART and loss of consciousness (table 3).

Low respiratory rates were the only cause of red alerts; most were associated with partial airway obstruction, as defined by paradoxical chest movement and the subjects’ capnographic evaluation. However, only a single intervention was necessary (simple head repositioning), and oxygen saturation never decreased to less than 91% (table 4). Only six episodes of loss of consciousness and two red-alert events occurred within the first 3 min of a 15-min concentration cycle. More than 70% of the red alerts occurred between the $P_{50}$ for the loss of response to the ART and loss of consciousness. Only one red alert occurred before the $P_{50}$ for the loss of response to the ART in each trial (fig. 2). No responses to the ART occurred in patients who were truly unconscious, as determined by the OAA/S score.

Forty-nine yellow alerts occurred during both sedation phases, and most (33) occurred in a single volunteer who had a slow baseline heart rate and a consistently low heart rate throughout the propofol-N₂O trial; the remaining yellow alerts occurred because of low respiratory rate (9), low blood pressure (4), low oxygen saturation, from 90 to 93% (2), and low heart rate (1).

Most volunteers reached a recovery score of 12 (85%) within 3 min, and all were rated as fit for discharge within 6 min. Plasma propofol concentrations at a recovery score of 12 averaged 0.5 ± 0.5 $\mu$g/ml after propofol-N₂O and 0.9 ± 0.5 $\mu$g/ml after propofol-air. Four red alerts and eight yellow alerts occurred during both recovery periods. All red alerts were respiratory in origin and associated with partial airway obstruction. Yellow alerts were associated with low blood pressure (4), low respiratory rate (3), and low heart rate (1).

One volunteer was mildly nauseated during the propofol-N₂O trial and one was severely nauseated and vomited. Two volunteers became excited during the propofol-N₂O trial. During sedation, most volunteers experienced altered sensation, perception, or mentation. These included paresthesia, numbness and tingling (which often occurred in the fingertips, toes, and perioral area), acoustic hypersensitivity, and a sense of floating or body acceleration “like being on a roller coaster.” None of the volunteers during the propofol-air trial became nauseated or excited. No nausea or vomiting occurred during the 1-h recovery period after either trial.

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Discussion

Loss of response to the ART consistently occurred before loss of consciousness. This difference was approximately 1 OAA/S unit and a 0.5-μg/ml plasma concentration of propofol during propofol–N₂O sedation; it was 2 OAA/S units and a 0.3-μg/ml plasma concentration of propofol with propofol–air sedation. Importantly, the majority of sedation red-alert events occurred within this range, indicating that the loss of response to the ART provides a reliable warning that unconsciousness will develop at only slightly greater propofol concentrations, and that greater concentrations are associated with a higher risk of adverse hemodynamic or respiratory complications.

The P₅₀ for loss of response to the ART occurred closer to loss of consciousness (as judged by the OAA/S score) during propofol–N₂O sedation than during propofol–air sedation. However, loss of response to responsiveness testing began at an OAA/S score of 20/20 (fully awake) when N₂O was included. This is consistent with previous reports that 50% N₂O in oxygen has a dissociative action at various levels within the central nervous system. This causes muscle relaxation and consequent difficulty initiating motor tasks; psychomotor performance²⁰ and some attention tasks²¹ are also adversely affected.

A nonresponse to verbal command followed by a response to mild physical stimulation has been used extensively to indicate loss of consciousness.²²–²⁴ This endpoint corresponds to an OAA/S sum of 10/20. Reliability of the OAA/S sum is at least as great as the OAA/S composite score during sedation.¹⁶

Previous reports indicate that loss of consciousness occurs at plasma propofol concentrations between 1.0 and 1.8 μg/ml.¹¹,¹²,¹⁴ Casati et al.²⁵ also report that unresponsiveness to mild prodding or shaking occurred...
Propofol–N₂O and propofol–air distinguish between the trials with and without nitrous oxide.

HR = heart rate; SAP = systolic arterial pressure; PETCO₂ = end-tidal carbon dioxide; PsO₂ = oxygen saturation determined by pulse oximetry.

at a target propofol concentration of 2 µg/ml. We similarly found that the loss of consciousness with propofol alone occurred at a plasma propofol concentration of 1.9 µg/ml. However, there was considerable variability in the associated propofol concentrations at loss of consciousness. These relatively large ranges suggest that plasma concentrations that are sufficiently low to avoid loss of consciousness in most of the population may provide inadequate sedation for many others.

The few red-alert and loss-of-consciousness events that occurred within the first 3 min of a concentration cycle may have been associated with an initial overshooting of the effect-site propofol concentration. Only 8 min of red alerts were observed during a total of 3,423 min of sedation (0.2%). All red alerts resulted from low respiratory rates. However, a better clinical criterion for "potentially serious" states would be those necessitating physician intervention. Only a single event qualified, requiring simple head repositioning, and even then oxygen saturation exceeded 90%.

Most of the red-alert events (five of eight) occurred during the propofol–N₂O trial. Nitrous oxide is a mild respiratory stimulant.²⁶ However, reduction of PETCO₂ from hyperventilation in the presence of N₂O can cause apnea, which, if untreated, can lead to hypoxemia.²⁷ Despite its weak anesthetic effect, N₂O has been shown to affect upper airway muscle function and produce obstructive phenomena.²⁸ Beydon et al.²⁹ also report that 50% N₂O in oxygen induces longer and deeper sleep with more frequent respiratory events of central and peripheral type than does 50% O₂. The combination of N₂O with propofol may thus produce a sleep physiology prone to apneic–hypopneic events. Because N₂O aggravates physiologic responses and reduced our ability to predict unconsciousness, we conclude that combining N₂O with propofol for conscious sedation will increase response variability and hamper accurate titration of drug concentrations based on individual responses.

Recovery was rapid with or without N₂O, averaging only 4 min. Nausea and vomiting were restricted to the propofol–N₂O trial, and the incidence was 10%, which is consistent with previous reports.³⁰ Excitement-increased sensory perception and perceptual illusion are well-known complications of N₂O,³⁰ ³¹ and were only observed during propofol–N₂O sedation. Some respiratory red alerts occurred (0.2%), but no serious hemodynamic complications occurred after administration of the drug was discontinued. Furthermore, all the red-alert events occurred within the first 4 min of recovery. We therefore conclude that serious respiratory or hemodynamic events are rare and occur early during recovery after propofol–air or propofol–N₂O sedation. However,
it is likely that variability in the responses and sedation-induced toxicity will be greater in actual patients than in our uniform volunteer population.

We never observed false-normal ART results. Therefore, there were no potentially dangerous episodes during which the ART result incorrectly indicated that the volunteer was conscious. The ART thus errors on the side of safety, as defined by maintaining consciousness.

We conclude that the ART, with a negative predictive value for loss of consciousness of 100%, can serve as a basis for individual titration of conscious sedation with propofol. Serious respiratory or hemodynamic events are rare before or concurrent with loss of response to the ART, especially during propofol-air sedation. The major outcome is this: it is safer to stop augmenting the ART, especially during propofol–air sedation. The use of \( N_2O \) with propofol for conscious sedation increases the risk of adverse physiologic responses and other adverse events, such as nausea and excitement, and decreases the predictive accuracy of the ART.

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