Hemoglobin Desaturation After Propofol/Remifentanil-Induced Apnea: A Study of the Recovery of Spontaneous Ventilation in Healthy Volunteers

Tiscia Bernadette Stefanutto, MB, ChB, John Feiner, MD, Jens Krombach, MD, Ronald Brown, BS, and James E. Caldwell, MB, ChB

BACKGROUND: In an earlier study investigating the “can’t ventilate/can’t intubate” clinical scenario, induction of anesthesia with thiopental 5 mg/kg and succinylcholine 1.0 mg/kg was associated with a significant risk of hemoglobin desaturation. It appeared that succinylcholine-induced apnea was responsible for the prolonged apnea. Our hypothesis was that using propofol and remifentanil for tracheal intubation might avoid prolonged apnea and subsequent desaturation attributable to muscle relaxation.

METHODS: Twenty-four healthy volunteers ages 18 to 45 years participated. After oxygen administration to end-tidal oxygen >90%, volunteers received 2 mg/kg propofol and remifentanil either 2 mcg/kg (group 1; n = 12) or 1.5 mcg/kg (group 2; n = 12). Oxygen saturation (SpO2) was measured at a finger, an ear lobe, and the forehead. If SpO2 decreased below 80%, volunteers received chin lift and, if persistent, assisted ventilation.

RESULTS: Desaturation (SpO2 < 80%) occurred in 5 volunteers: 4 in the higher remifentanil dose (2 mcg/kg) group and 1 in the lower dose (1.5 mcg/kg) group. Chin lift and assisted ventilation was necessary in 3 volunteers. The lowest SpO2 was 82.4 ± 10.5 (mean ± SD) in the higher-dose group vs. 92.4 ± 8.6 with the lower dose of remifentanil (P = 0.019). Apnea time was shorter (P = 0.0093) with the lower dose (4.7 ± 1.5) than with the higher dose of remifentanil (6.1 ± 1.0). Conditions for intubation were excellent or acceptable in 11 volunteers (92%; 95% confidence interval [CI], 65%–99%) in the higher-dose group, and in 8 (67%; 95% CI, 39%–86%) with the lower dose.

CONCLUSIONS: Administered with propofol 2 mg/kg, the remifentanil dose necessary to produce acceptable intubating conditions, 2 mcg/kg, produces apnea that carries a significant risk of desaturation, whereas a remifentanil dose of 1.5 mcg/kg does not reliably produce acceptable intubating conditions and does not eliminate the risk of desaturation. (Anesth Analg 2012;114:980–6)

In 2001 Heier et al. investigated hemoglobin desaturation after administration of thiopental 5 mg/kg and succinylcholine 1 mg/kg in volunteers to simulate the situation in which the lungs could not be ventilated, nor the trachea intubated—“can’t intubate, can’t ventilate.”1 They found that significant oxygen desaturation occurred before spontaneous breathing recommenced. Volunteers described being aware but unable to breathe. On the basis of the description of awareness under muscle paralysis by Heier et al., we also assumed that the action of succinylcholine had persisted after recovery from thiopental-induced hypnosis, which could have delayed the occurrence of spontaneous breathing.

In this study, we again investigate a similar “can’t intubate, can’t ventilate” scenario as studied by Heier et al. We sought to define an anesthesia induction regimen that would allow recovery of ventilation before desaturation occurred. The options we had were to repeat the Heier et al. study with a smaller dose of succinylcholine, or eliminate the use of succinylcholine altogether. We rejected the first option because small doses of succinylcholine (e.g., 0.5 mg/kg) may not provide uniformly good conditions for tracheal intubation.2,3 Instead, we studied an anesthetic technique using a combination of remifentanil and propofol without a muscle relaxant to facilitate tracheal intubation.4 Our hypothesis was that the proper doses of remifentanil and propofol in combination would allow adequate tracheal intubating conditions, while not producing apnea long enough to cause significant oxygen desaturation.

METHODS

This study was approved by our local IRB (University of California, San Francisco, Committee on Human Research,
Office of Research Administration, San Francisco, CA), and 24 healthy volunteers gave written informed consent to participate. As a part of the consent process, volunteers were specifically informed of the risks of hypoxia, such as brain damage and cardiac arrest. In addition, they were counseled as to the possibility of being aware. Specific exclusion criteria were age younger than 18 years or older than 45 years; body mass index >30; Mallampati airway grade 2 to 4; known allergy to propofol, egg, or opioids; family history of anesthesia-related complications; or alcohol or drug abuse. The volunteers were informed specifically about the nature of the study drugs.

For the study, volunteers wore loose-fitting clothing and lay in the supine position on a gurney. Monitors were placed to measure noninvasive arterial blood pressure (every minute for 12 minutes, then every 5 minutes for a further 18 minutes), continuous electrocardiography, capnography, and pulse oximetry (AS5 monitor, General Electric, Fairfield, CT). Hemoglobin saturation (Spo2) was measured (Nellcor Model N-200; Mallinckrodt Inc., St. Louis, MO) continuously at an index finger (standard mode, averaging signals collected in 6-second epochs) and an earlobe (clinical research mode, for beat-to-beat monitoring) and at the forehead (Nellcor Model N-595; Mallinckrodt Inc., St. Louis, MO, fast sat mode). The laboratory temperature was maintained at 28°C to decrease potential peripheral vasoconstriction and thus abolish the potential for lag time of peripheral oximetry readings.5,6 A 20-gauge IV catheter was inserted for administration of fluid and drugs.

The volunteers breathed 100% oxygen, fresh gas flow 6 L/min, through a tight-fitting facemask for a minimum of 3 minutes and until end-expired oxygen concentration was >90%, and the time was recorded.7 Seven volunteers had end-tidal oxygen concentrations <90% after 3 minutes of oxygen administration and were, thus, given additional time for administration of oxygen. The mean preoxygenation time was 3.2 ± 0.5 minutes (range = 3.0 to 4.3).

While still awake, volunteers were asked to relax and stop breathing while the anesthesiologist applied positive airway pressure to ensure that investigators could ventilate each volunteer’s lungs.

Anesthesia was induced with remifentanil (2 µg/kg for the first 12 volunteers and 1.5 µg/kg for the remainder), followed immediately by 2 mg/kg propofol, both given as IV boluses over 5 to 10 seconds. One minute after the end of the propofol injection, patients were given 1 small positive pressure breath via the facemask. We then attempted tracheal intubation using a Macintosh #3 laryngoscope blade and a cuffed endotracheal tube (6.5 for females, 7.0 for males). After passage through the vocal cords, the endotracheal tube was withdrawn. Conditions for tracheal intubation were graded according to Good Research Practice guidelines.8 This was performed by the same anesthesiologist (T.B.S.) in all cases.

After this, the volunteer’s airway was left unsupported, the facemask was reapplied, and chin lift or assisted ventilation commenced only if the SaO2 decreased to 80%. This level of hypoxia was chosen on the basis of the Spo2 tolerated by volunteers in studies of pulse oximeter accuracy, and hypoxic ventilatory responsiveness,6 anticipating the potential for further decreases in Spo2 due to circulatory delay.9 The facemask was removed 10 minutes after the propofol bolus was administered, provided that Spo2 was >95%. Spo2 was measured continuously until values were stable and >95% for >10 minutes while the volunteer was breathing room air. The need for additional airway support (chin lift or assisted ventilation) was recorded.

Throughout the period from loss of consciousness until the volunteer had fully recovered, the investigators talked gently to the volunteer, reassuring him or her. Every 15 seconds the volunteer was asked to open the eyes and to squeeze the observer’s hand. The volunteer’s abdomen was observed continuously for respiratory movements. Two anesthesiologists judged duration of apnea, which was defined as the time until resumption of spontaneous ventilation, as determined by diaphragm movement. Separate times were recorded for eye opening or hand squeeze on command. Injection of propofol was considered time 0.

Volunteers were observed for an hour after recovery from anesthesia, and then discharged into the care of a responsible adult or one of the investigators. Volunteers were counseled that they should not drive or operate hazardous equipment for 24 hours. All volunteers were fully awake and alert at discharge. A follow-up telephone interview was conducted the next day to identify any concerns.

The initial sample size of 12 in group 1 was based on our prior study in volunteers using succinylcholine.1 Enrollment of an additional 12 volunteers would result in 80% power to detect a clinically important difference in nadir Spo2 if the lower-dose group experienced minimal oxygen desaturation, and a lower incidence of oxygen desaturation. Had the drug regimen proven successful in providing acceptable intubating conditions without oxygen desaturation, we did not plan to power this study to prove safety, which would have required 100 volunteers with no oxygen desaturation to provide an upper 95% confidence interval (CI) for failure of 3%.

For demographic data, differences between remifentanil 2.0 mcg/kg and 1.5 mcg/kg groups were analyzed using Student t test for continuous variables or Fisher exact test for categorical variables. Times and nadir Spo2 values were compared using the Mann–Whitney U test. The relationship between apnea duration and lowest Spo2 was analyzed by simple linear regression. Changes in cardiovascular variables from baseline were analyzed by paired t tests. Data are presented as mean ± SD unless otherwise indicated. P < 0.05 was considered statistically significant. Data were analyzed with JMP 5.1 (SAS Institute, Cary, NC).

RESULTS

Demographics

Six female and 18 male volunteers enrolled in the study. Demographic information is shown in Table 1. There were no significant differences between the remifentanil 2.0 mcg/kg and 1.5 mcg/kg groups, except for height, which was related to the nonsignificant differences in gender between the 2 groups.

Oxygen Saturation (Spo2)

Spo2 decreased to 80% or below in 5 volunteers (Table 2). Of these, 1 volunteer started spontaneous breathing as Spo2
reached 80%, 3 required chin lift only, and 1 required positive pressure ventilation for 28 seconds until spontaneous respiration resumed. The airway was easily maintained in all volunteers.

The first 12 volunteers (group 1) received 2.0 mcg/kg of remifentanil. Four of them experienced oxyhemoglobin desaturation below 80%. Thus, for the subsequent 12 volunteers (group 2) we decreased the dose of remifentanil to 1.5 mcg/kg. In the second group, Spo$_2$ decreased below 80% in only 1 volunteer. He responded to chin lift by starting spontaneous ventilation within 5 seconds.

The nadir Spo$_2$ values (mean ± SD) during apnea are shown in Figure 1, and were lower in the group receiving remifentanil 2 μg/kg for all 3 sites: fingertip (85.4 ± 11.0 vs. 93.8 ± 7.0, $P = 0.032$), ear lobe (87.7 ± 12.1 vs. 96.6 ± 5.5, $P = 0.027$), and forehead (beat to beat, 83.6 ± 9.3 vs. 93.7 ± 8.7, $P = 0.0084$).

**Recovery of Respiration and Responsiveness**

Times to return of spontaneous ventilation and times to eye opening and hand squeezing to command were significantly longer in the group with the larger dose of remifentanil (Table 2, Fig. 2). Eye opening coincided with the commencement of spontaneous respiration in 4 volunteers. In 3 volunteers all 3 modalities (time to spontaneous ventilation, eye opening, and hand squeezing) recovered simultaneously. The time to recovery of all modalities was 6.0 ± 1.8 minutes, while apnea time was 5.4 ± 1.4 minutes. This correlates with clinical experience of return to respiration preceding consciousness. There was a weak correlation ($r^2 = 0.20, P = 0.028$) of duration

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### Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Remifentanil 2.0 μg/kg</th>
<th>Remifentanil 1.5 μg/kg</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>7/5</td>
<td>11/1</td>
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<tr>
<td>Age (years)</td>
<td>29 ± 7 (22–41)</td>
<td>27 ± 3 (24–32)</td>
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<td>Weight (kg)</td>
<td>73.8 ± 19.6 (48.1–109.0)</td>
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<td>Height (inches)</td>
<td>68.9 ± 4.7 (61.5–75.0)</td>
<td>72.3 ± 3.0 (69.0–80.0)</td>
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<td>Body mass index (kg/m$^2$)</td>
<td>24.5 ± 3.9 (20.0–31.8)</td>
<td>23.1 ± 3.4 (17.8–29.9)</td>
<td>0.38</td>
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</table>

Data are mean ± SD (range) or $n$. M = male; F = female. Analysis by Fisher exact test or Student $t$ test.

### Table 2. Ventilatory and Other Variables

<table>
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<tr>
<th></th>
<th>Remifentanil 2.0 μg/kg</th>
<th>Remifentanil 1.5 μg/kg</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
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<tr>
<td>SpO$_2$ &lt;80%</td>
<td>4 (33%)</td>
<td>1 (8%)</td>
<td>0.32</td>
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<tr>
<td>SpO$_2$ &lt;90%</td>
<td>10 (83%)</td>
<td>4 (33%)</td>
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<td>Apnea duration (minutes)</td>
<td>6.1 ± 1.0 (4.4–7.5)</td>
<td>4.7 ± 1.5 (2.5–8.3)</td>
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<tr>
<td>Eye opening (minutes)</td>
<td>6.9 ± 1.6 (4.9–9.5)</td>
<td>5.0 ± 1.5 (2.4–8.4)</td>
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<tr>
<td>Squeeze hand (minutes)</td>
<td>7.0 ± 1.6 (5.0–10.0)</td>
<td>5.1 ± 1.5 (2.4–8.5)</td>
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<td>8</td>
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<tr>
<td>Unacceptable/failed</td>
<td>1—grade 3</td>
<td>4—1 not attempted because volunteer aroused</td>
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</table>

Values are mean ± SD (range) or $n$ (%). SpO$_2$ = lowest oxygen saturation during apnea measured by any pulse oximeter. Comparisons are by Fisher exact test or Mann–Whitney $U$ test.

**Figure 1.** Nadir oxygen saturation (Spo$_2$) during apnea for each of the pulse oximeters used. Data are mean ± SD. Group 1 (remifentanil 2.0 μg/kg) is shown with solid bars, and group 2 (remifentanil 1.5 μg/kg) is shown with open bars. Group 1 volunteers reached lower SpO$_2$ values during apnea for all oximeters: finger ($P = 0.032$), ear ($P = 0.027$), forehead ($P = 0.0084$), and for the lowest value reported by any oximeter ($P = 0.019$).
of apnea with the lowest oxyhemoglobin saturation reached (Fig. 3).

**Intubating Conditions**

Tracheal intubation conditions were excellent in 11 of 12 volunteers (92%; 95% CI, 65%–99%) in group 1 (Table 2). In group 2, intubation conditions were excellent or acceptable in 8 volunteers (67%; 95% CI, 39%–86%).

**Hemodynamics and Adverse Effects**

All volunteers experienced a significant decrease in both systolic and diastolic blood pressure with induction of anesthesia (Table 3). The recordings of volunteer #12 are shown in Figure 4. No volunteer required treatment for bradycardia or hypotension, even with 1 female volunteer having a baseline heart rate of 38 beats per minute (bpm). The apnea period was associated with significant increases in arterial blood pressure and heart rate in all 24 volunteers.

None of the volunteers experienced awareness during the period of apnea. On emergence from anesthesia, 1 volunteer complained of minor chest tightness similar to the feeling of a mild asthma attack. No volunteer appeared to have chest rigidity in response to the remifentanil. Eight volunteers experienced secondary decreases in SpO₂ after commencing spontaneous ventilation before achieving SpO₂ above 95%. These episodes were not associated with coughing. At 30 minutes after propofol...
administration, all volunteers maintained SpO₂ above 95% on room air. All volunteers stated that they would participate again because they felt that the study had not been an unpleasant experience (study data available as Supplemental Digital Content 1, http://links.lww.com/AA/A379).

DISCUSSION

As in the study by Heier et al. that used thiopental and succinylcholine, our volunteers failed to recover sufficiently rapidly after induction of anesthesia with propofol and remifentanil to avoid desaturation. In addition, we showed that decreasing the dose of remifentanil in an attempt to allow earlier resumption of spontaneous ventilation resulted in unacceptable intubating conditions.

In the previous study, it appeared that failure to resume ventilation was due to persistent paralysis from succinylcholine, as evidenced by recall of weakness in the volunteers who experienced oxygen desaturation. In the current study it was not paralysis, but persistent respiratory depression and apnea from propofol and remifentanil administration, that led to hemoglobin desaturation. Because we did not use a muscle relaxant, we had to use doses of propofol and remifentanil that would provide acceptable conditions for tracheal intubation.

We chose a dose of 2 mg/kg of propofol because this is at the lower end of the recommended clinical range for intubation without muscle relaxation. In addition, 2 mg/kg is a dose commonly used to facilitate tracheal intubation in combination with the potent opioids. We chose to use remifentanil to facilitate tracheal intubation because it has the shortest duration of action among the currently available opioids. Because we did not use a muscle relaxant, we needed the minimum dose of remifentanil to be adequate and produce good conditions for tracheal intubation. The available literature suggested that in combination with propofol 2 mg/kg, an appropriate dose of remifentanil was 2 mcg/kg.

Our results supported our choice of propofol 2 mg/kg and remifentanil 2 mcg/kg to facilitate tracheal intubation. We achieved acceptable intubating conditions in >90% of volunteers, but the resultant mean duration of apnea was 6.1 minutes. Moreover, this period of apnea led to significant desaturation in one third of the volunteers. As a consequence of this prolonged apnea in our first 12 volunteers, we decreased the dose of remifentanil to 1.5 mcg/kg for the subsequent 12. We chose this dose of remifentanil because an even lower dose, 1.0 mcg/kg, is inadequate to provide consistently good conditions for tracheal intubation. This reduction in remifentanil dose did in fact result in a statistically significant decrease in apnea duration to 4.7 minutes, but this reduction was not sufficient to prevent the occurrence of desaturation. Although Steven and Wheatley did find short durations of apnea with even higher doses of remifentanil, their model was significantly different from ours, and they were not able to test for oxygen desaturation. We conclude that propofol 2 mg/kg in combination with remifentanil cannot both produce consistently good conditions for tracheal intubation and allow sufficiently rapid recovery of spontaneous ventilation to prevent oxygen desaturation.

We might have considered using a small dose of succinylcholine in combination with propofol instead of relying on remifentanil to facilitate tracheal intubation. Decreasing the succinylcholine dose from 1.0 mg/kg, as used by Heier et al., to 0.5 or 0.6 mg/kg would produce a small decrease in duration of neuromuscular block, but only by 0.7 to 1.7 minutes. In addition, when used with only propofol, i.e., without opioid supplementation, succinylcholine 0.5 mg/kg does not produce consistently good conditions for tracheal intubation. We chose not to study a low-dose succinylcholine technique because one of our aims was to achieve good conditions for tracheal intubation. In studies in which low-dose succinylcholine provided good conditions for tracheal intubation, it was administered in combination with both propofol 2.0 to 2.5 mg/kg and a potent opioid, not propofol alone.

El-Orbany et al. studied succinylcholine 0.6 mg/kg with several induction drugs, finding good intubating conditions, with apnea times of 3 to 4 minutes. We acknowledge that it still may be possible to find a dose of succinylcholine that
would provide adequate intubating conditions with recovery of spontaneous ventilation before oxygen desaturation in our model.

We simulated a “worst-case scenario” model for upper-airway obstruction with a failure to provide even apneic oxygenation. The results are likely to underestimate the actual incidence of desaturation that would occur in the general patient population in this same situation. Our volunteers were young, lean, and healthy. The preoxygenation that they received ensured optimal denitrogenation of the functional residual capacity. This is not always possible with sick or obtunded patients. Our volunteers had no comorbid conditions, such as extreme age or lung disease, that would contribute to more rapid desaturation.

This assumption of higher risk of desaturation in patients is supported by the results of Naguib et al. They found a 45% incidence of desaturation to <90% in patients who received only propofol 2 mg/kg and fentanyl 2 mcg/kg. This was a higher incidence of desaturation, yet occurred with an apnea duration of only 2.7 minutes, in comparison with 4.7 minutes in our group 2 in which the incidence of desaturation was 33%.

The timing of intubation is imperative to achieve optimum conditions with remifentanil and propofol. We performed tracheal intubation at 90 seconds to coincide with peak effect-site concentration of propofol and remifentanil. To have the peak effect of remifentanil and propofol coincide, we administered the drugs as bolus doses in rapid succession. At exactly 1 minute after the end of the propofol bolus, a test breath was delivered via facemask. This was a safety maneuver because we needed to ascertain that we could rapidly commence manual ventilation of the lungs should the volunteer develop significant desaturation.

Similarly, for reasons of volunteer safety, we attempted to minimize delay in detection of desaturation by using fast-mode analysis, which measures beat to beat rather than averaging saturation readings over 6-second epochs. In addition, we used forehead (supraorbital) monitoring, which is a more direct measure of central SaO2 and is not influenced by peripheral vasoconstriction. In this study, forehead oximetry (Fig. 2) consistently measured the lowest oxygen saturation achieved with a minimal lag time in comparison with the other 2 sensors, although delay of all oximeters was minimized by heating the study room.

Sneyd and O’Sullivan have called into question the whole concept of tracheal intubation without the use of muscle relaxants. They argued that there needs to be a good clinical reason why intubation should be attempted without a muscle relaxant. We do not disagree with that position, and in our study we attempted to define a very specific role for such a technique, namely, providing good conditions for tracheal intubation combined with recovery of spontaneous respiration before desaturation.

In conclusion, our results show that significant hemoglobin desaturation occurs in one third of healthy adult volunteers after the induction of anesthesia with propofol 2 mg/kg and remifentanil 2 µg/kg, albeit with good intubating conditions. Decreasing the remifentanil dose to 1.5 µg/kg decreased, but did not abolish, the risk of desaturation, and intubating conditions were no longer satisfactory. We conclude that after remifentanil and propofol in doses sufficient to produce good conditions for tracheal intubation, spontaneous ventilation does not return sufficiently rapidly to avoid hemoglobin desaturation if mask ventilation or tracheal intubation cannot be performed.

DISCLOSURES
Name: Tiscia Bernadette Stefanutto, MB, ChB.
CONTRIBUTION: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
ATTESTATION: Tiscia Bernadette Stefanutto has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

Name: John Feiner, MD.
CONTRIBUTION: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
ATTESTATION: John Feiner has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

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CONTRIBUTION: This author helped design the study, conduct the study, and write the manuscript.
ATTESTATION: Jens Krombach has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

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CONTRIBUTION: This author helped design the study, conduct the study, and write the manuscript.
ATTESTATION: Ronald Brown has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

Name: James E. Caldwell, MB, ChB.
CONTRIBUTION: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
ATTESTATION: James E. Caldwell has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

This manuscript was handled by: Sorin J. Brull, MD, FCAARC (Hon).

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