Table 1. Precordial Statistics

<table>
<thead>
<tr>
<th>Monoject syringe size (ml)</th>
<th>Outer Diameter (mm)</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>9</td>
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<td>6</td>
<td>13</td>
<td>0.7</td>
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<tr>
<td>12</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>21</td>
<td>1.7</td>
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<tr>
<td>80</td>
<td>26</td>
<td>4</td>
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<tr>
<td>Commercial precordial stethoscopes</td>
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<tr>
<td>Martin-premie</td>
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<td>11</td>
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<tr>
<td>Martin-light</td>
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<tr>
<td>Martin-infant</td>
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<td>Wenger-child</td>
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<td>Wenger-adult</td>
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Subanesthetic Isoflurane and the Ventilatory Response to Hypoxia

To the Editor—Several years ago, I reported that 0.1 MAC isoflurane selectively impairs the ventilatory response to hypoxemia.1 Recently, Temp et al. observed that 0.1 MAC isoflurane reduces this response when sustained hypoxemia is induced with hypercapnia but not when hypoxemia is induced with normocapnia.2 They concluded that their "data indicate that 0.1 MAC levels of isoflurane do not affect the response to sustained normocapnic hypoxia."3 In considering possible reasons for the disparate conclusions of their study and ours, Temp et al. overlooked certain critical differences between the studies themselves.

Study Conditions. During testing, our subjects relaxed in a darkened and completely quiet room.1 The subjects of Temp et al. were "required to watch a documentary videotape" and may have been aware of the sounds of circuit motors. In addition, while exposed to 0.1 MAC isoflurane, Temp et al.'s subjects were touched or spoken to periodically to prevent presumed complicating effects of sedation or changes in level of consciousness.3 As Severinghaus has pointed out, all extraneous stimuli must be avoided when testing the response to hypoxemia because this particular response can be augmented falsely by even subtle stimuli—such as whispering by laboratory personnel.3 Further, Temp et al.'s rationale for imposing such stimuli appears misplaced because anesthetic-induced sedation does not in itself necessarily depress the hypoxicemic response3 and, even if it were to do so, it would be inappropriate to attempt to neutralize this component of its action when characterizing the effect overall.

Size of Control Response. When moderate normocapnic hypoxemia was induced in our subjects in the control condition over a period of 8–10 min, ventilation increased to 18.1 ± 1.0 L/min (mean

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When the same level of hypoxemia was induced in Temp et al.'s subjects abruptly, ventilation peaked at 26.2 ± 3.8 L/min and then settled to 15.9 ± 1.2 L/min over the subsequent 20 min. The control responses of our subjects were typical for the particular conditions to which they were exposed. But those of Temp et al.'s subjects appear unusually large. In the only studies closely comparable to that of Temp et al., i.e., with the identical level of hypoxemia induced over a similar time period, together with eucapnia and normal levels of resting ventilation, the peak hypoxic ventilatory response was 19.9 ± 5.0 L/min and the 20-min values 9.8 ± 0.2 and 9.9 ± 0.8 L/min. (Means ± SE.)

The apparently augmented control responses of Temp et al.'s subjects may have been due to extraneous stimuli (as suggested above) and/or to behavioral influences on breathing. Such biased responses could obscure an effect of isoflurane on the chemoreflex response per se. They also would explain why Temp et al. detected an effect of isoflurane when hypoxemia was induced with hypercapnia but not with normocapnia, because the more intense chemical stimulation of hypercapnic hypoxemia would reduce the relative impact of extraneous factors.

Statistical Inference. The conclusion of our study rejects the null hypothesis with an indicated type I error P < 0.05. The conclusion of Temp et al. accepts the null hypothesis, but without an estimate of power or the probability of a type II error. Temp et al. present 95% confidence limits for the effects of isoflurane on the control response in their subjects and infer that these limits "clearly exclude" our mean findings. Unfortunately, this inference may not be valid, because the mean control response of Temp et al.'s subjects was above the 95% confidence limits for the control responses of our volunteers. Further, the mean control values of hypoxic ventilatory responses in Temp et al.'s subjects, both the peak value and that at 20 min, are well beyond the 95% confidence limits tabulated for the corresponding values from the most comparable investigations.

Thus, these two studies differed in several important ways. One, performed in quiescent conditions, found that a typical response to hypoxemia was impaired by 0.1 MAC isoflurane consistently and inferred this effect of isoflurane with reasonable statistical probability. The other, performed with confounding extraneous stimuli, found that an unusually large response was affected variably and concluded the absence of an effect (as above) without statistical evidence. However, we do not believe that each of these differences, they should not be ignored.

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References

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In Reply—Knill suggests that knock has accepted a null hypothesis, a conclusion based upon a phrase in the text. Readers who went beyond the abstract found:

Thus, the major finding of the study is the inability to reproduce the large, dramatic reductions of the acute hypoxic ventilatory response previously reported with 0.1 MAC concentrations of inhalational agents. A small to moderate reduction, however, can not be excluded by the data.

In fact, we observed no significant effect of isoflurane on the acute hypoxic response, whether induced with normocapnia or with hypercapnia. The reduction of the sustained hypoxic response with hypercapnia, to which Knill alludes, was also substantially less than the 50–80% reductions previously reported for the acute response. We noted that the acute and sustained responses are mediated somewhat differently and that Knill et al. has studied only the acute response.

We went on to point out that "it seems probable that [Knill et al.]'s isoflurane confidence limits would overlap ours in the area of a 20–30% reduction" for the acute response. And the final sentence of the manuscript begins, "The difference between our results and

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