However, several years ago, Haifer and Plit measured the temperature changes during two minutes' nebulization of histamine from a Wright nebulizer and found it to be exactly the same as in the present report.

They went on to investigate whether this temperature drop may have any clinical effect and compared the response to inhaled histamine (PC_{aw}) between nebulizers operating at different but constant temperatures. The nebulizers were designed to prevent any temperature drop during nebulization. Two groups of asthmatic patients were studied: one group inhaled the aerosol at constant 30°C, whereas the other inhaled the aerosol at constant 23°C. In both groups the results were compared to those obtained during the usual test performed at room temperature (23°C) without keeping the temperature constant. The results (PC_{aw} in mg/ml) are presented in the table.

Thus, keeping the temperature constant increased PC_{aw} (reduced airway reactivity) compared with the standard method. The higher the temperature was kept, the greater PC_{aw} (reactivity was further reduced).

Deducing from Cockcroft's study (Figure 2 and Discussion), one would assume that, compared to the usual method, keeping the temperature constant would prevent the observed reduction in nebulizer output and hence PC_{aw} should be smaller. The results of Haifer and Plit's study (which showed an opposite effect) contradicted this assumption. Moreover, the fact that the effect was enhanced at higher (constant) temperatures indicate a significant role for temperature in the results. Indeed, we have recently demonstrated the importance of temperature in modifying airway response even in normal subjects.

In view of Haifer and Plit's results, the report of Cockcroft et al is important not only in terms of standardization and methodology but also in clinical terms.

Table

<table>
<thead>
<tr>
<th></th>
<th>Usual, Room Temp</th>
<th>Constant 23°C</th>
<th>Constant 30°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0.39</td>
<td>-</td>
<td>3.29</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.75</td>
<td>2.35</td>
<td>-</td>
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</tbody>
</table>

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To the Editor:

We would like to thank Dr. Amirav for bringing the data of Haifer and Plit to our attention. We apologize for having missed their abstract.

The results of constant temperature PC_{aw} are interesting and have important clinical relevance. We carefully avoided any clinical predictions based on the results in our paper. Since the reduced output at cooler temperatures represents chiefly a reduction in evaporation, we would have expected warm vs cool nebulization to have produced little difference. Since there may be a tendency for reduced solute output (not certain from our calculations), we might have expected a small change in the opposite direction to that described in the abstract by Haifer and Plit.

The surprise in the data of Haifer and Plit is not the direction but the magnitude of the change; warm nebulization (30°C) produced almost a ten-fold reduction in response to histamine compared to room temperature (23° to 16°C). The mechanism of this difference remains unclear to us. The authors' speculation that two minutes of tidal breathing of an aerosol between 23° and 16°C might enhance airway responsiveness to histamine based on additive or synergistic effect of cold air seems unlikely, since this represents a very small thermal burden on the airways. It is more likely that the reduced responsiveness with the warm nebulization represents an alteration in the physical characteristics of the aerosol. Alterations in solute output or particle size could possibly explain these changes. The Wright nebulizer generally produces a small particle size (1.0 to 1.5 microns mass median diameter). Previous reports of Wright nebulizers produced from a new manufacturer showed that with similar mass output run at room air temperature, a four-fold reduced response was observed. Further investigations (Hargrave, personal communication) suggested the most likely explanation for this reduced output was an unacceptably low mass median diameter particle size of the order of <0.8 microns. This represents a rather small deviation from the usual Wright nebulizer particle size, and although we are not certain what happens to particle size with temperature, a small reduction in mass median diameter induced by the warmer solution could explain the results documented in the abstract.

D. W Cockcroft, M.D., F.R.C.P(C), and T. S. Hurst, M. Vet. Sc., Division of Respiratory Medicine, University Hospital Saskatoon, Saskatchewan, Canada

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Methemoglobinemia After Lidocaine Administration

To the Editor:

In an otherwise complete summary of adverse effects associated with the use of lidocaine topical anesthesia for flexible bronchoscopy, Dr. Kirkpatrick failed to mention an unusual but potentially dangerous complication that can be most confusing if unrecognized. After topical administration to the nasal mucosa, lidocaine occasionally causes severe methemoglobinemia in patients who have the heterozygous form of NADH-Methaemoglobin reductase deficiency. Benzocaine (an ingredient in cetracaine topical anesthetic) can rarely cause methemoglobinemia when applied to the mucous membranes of normal individuals.

The sudden and otherwise unexplained development of severe respiratory distress and cyanosis during or after bronchoscopy should raise the possibility of methemoglobinemia. The diagnosis is confirmed by the characteristic brown color of the blood and by two laboratory findings: 1) arterial oxygen tension may be normal, but oximetry shows a low arterial oxygen saturation, and 2) the quantity of methemoglobin in the blood (measured directly by spectropho-
tometric analysis) is elevated. Severe methemoglobinemia is rapidly reversed by intravenous administration of the reducing agent methylene blue (1-2 mg/kg in a 1 percent solution administered over 5 min). Because of the urgency of treating severe methemoglobinemia, particularly in patients who have underlying lung disease, bronchoscopists are well advised to maintain a stock of methylene blue in the bronchoscopy suite.

John Hansen-Flaschen, M.D., F.C.C.P.,
Hospital of the University of Pennsylvania,
Philadelphia

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PCIRV—A Mode of Ventilation Associated with Problems

To the Editor:

Abraham and Yoshihara (Chest 1989; 96:1356-59) draw conclusions about the impact of pressure controlled-inverse ratio ventilation (PCIRV) on hemodynamics from only nine patients. The authors state that PCIRV is not associated with "any deterioration in hemodynamic or tissue oxygen metabolism parameters," although one patient demonstrated a significant decrease in blood pressure and cardiac index. Their conclusion stands in contrast to general experience.

The data analysis is questionable. Multiple t-tests are incorrect for analyzing this type of data. No attempt was made to account for the accumulating type II error by the use of a Bonferroni adjustment. Multivariate analysis of variance, with airway pressures included as covariates, would have been the right analysis and may have provided different results.

There were no definitive, prospective selection criteria used for patient enrollment. Furthermore, the authors did not report these important variables: intrinsic positive end expiratory pressure (PEEP), auto-PEEP,2 and mean airway pressure. Evaluation of PCIRV is difficult without these airway pressure measurements before and after initiation of PCIRV.

The precise rules for changing to and for controlling PCIRV are not stated. This information is important, not only for optimizing patient oxygenation and ventilation, but also for interpretation of the data. PCIRV is a complicated, difficult to use, and potentially hazardous form of ventilation in critically ill patients. Clinicians using PCIRV need to be aware of the risks associated with auto-PEEP. Auto-PEEP is no different from PEEP in its effects on many organ systems, including the cardiovascular system. Contrary to the conclusions in this article, hemodynamic changes are commonly associated with inverted ratio ventilation. We agree that further studies should determine any survival benefit of PCIRV and those patients who would potentially benefit from PCIRV.

Stephan H. Boehm, M.D.;
Lindell K. Weaver, M.D.;
Thomas D. East, Ph.D., and
Alan H. Morris, M.D., F.C.C.P.,
Pulmonary Divisions,
LDS Hospital and University of Utah,
Salt Lake City

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To the Editor:

Dr. Morris and colleagues state that "general experience" with pressure controlled inverse ratio ventilation (PC-IRV) has found that hemodynamic changes are commonly associated with this ventilatory modality. We are unaware of this "general experience." The paper that they cite to support their contention in fact showed that the hemodynamic changes associated with PC-IRV were similar to those found with PEEP. In the studies reported in that article, the addition of PEEP to intermittent positive pressure ventilation (IPPV) resulted in decreased cardiac output and oxygen delivery, as would be expected. Use of PC-IRV with an I:E ratio of 4:1 and maintenance of the same end expiratory volume as during the PEEP trial showed similar changes in hemodynamics as those found with PEEP. It therefore seems that the information generally available (ie, the previously published paper coupled with our own study) would indicate that few alterations in hemodynamic parameters beyond those that accompany PEEP occur with the initiation of PC-IRV.

"Auto-PEEP" was considered in our study and is referred to in the methods section of our paper as "end-expiratory pressure," which one of the reviewers felt to be a more accurate term. As noted in our methods section, end-expiratory pressure was kept at the same level as the PEEP used during volume-controlled ventilation. In this way, we were able to match the periods before and after institution of PC-IRV to prevent unsuspected auto-PEEP from producing any alteration in cardiorespiratory values. Mean arterial pressure increased slightly after the initiation of PC-IRV, from 28±9 cm H2O to 32±5 cm H2O. This degree of increase in mean arterial pressure with PC-IRV is similar to that found by other investigators.

The analysis of our data is not changed by using a Bonferroni adjustment. In particular, we still find that PC-IRV results in a significant increase in PaO2 without any alteration in the other cardiorespiratory values. Neither we nor our statistician can see any reason a priori to use multivariate analysis of variance to analyze our data.

We agree with Dr. Morris and his colleagues that PC-IRV is potentially hazardous in the critically ill patient. Indeed, as noted in our paper, one patient had hemodynamic deterioration when PC-IRV was used. However, eight of the nine patients showed either improvement or no change in hemodynamics when PC-IRV was initiated. Our experience, as well as that of other investigators, would indicate that PC-IRV correctly used—with attention to the risks associated with auto-PEEP—may be useful in patients with severe respiratory failure since this modality can produce improvement in PaO2 without significant alteration in hemodynamic parameters.

Edward Abraham M.D., F.C.C.P.,
Division of Pulmonary and Critical Care Medicine
University of California School of Medicine, Los Angeles

REFERENCE