Assessment of Neural Inspiratory Time in Ventilator-supported Patients

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Neural inspiratory time (TI) is a measurement of fundamental importance in studies of patient-ventilator interaction. The measurement is usually based on recordings of flow, esophageal pressure (Pes), and transdiaphragmatic pressure (Pdi), but the concordance of such estimates of neural TI has not been systematically evaluated. To address this issue, we studied nine ventilator-supported patients in whom we employed esophageal electrode recordings of the diaphragmatic electromyogram (EMG) as the reference measurement of neural TI. Comparison of the indirect estimates of neural TI duration, based on flow, Pes, and Pdi against the reference measurement, revealed a mean difference (bias) ranging from −54 to 612 ms during spontaneous breathing and from −52 to 714 ms during mechanical ventilation; the respective precisions (standard deviations of the differences) ranged from 79 to 175 ms and from 74 to 221 ms. Because an indirect estimate of neural TI duration could be identical to that of the reference measurement and yet be displaced in time, this lag or lead was quantified as the phase angle of neural TI onset. Flow-based estimates of the onset of neural TI displayed a systematic lag, which may be explained at least in part by concurrent intrinsic positive end-expiratory pressure. In conclusion, the indirect estimates of the onset and duration of neural TI in ventilator-dependent patients displayed poor agreement with the diaphragmatic EMG measurement of neural TI.

A major, if not the primary, goal of mechanical ventilation is to decrease a patient’s work of breathing. Achievement of this goal is dependent on satisfactory patient-ventilator interaction—that is, the machine needs to cycle in unison with the rhythmic contraction of a patient’s respiratory muscles. In a sense, perfect synchronization can be viewed as entrainment of a patient’s respiratory muscle activity with the cycling of the ventilator (1). To investigate the mechanisms that control the tightness of such entrainment, it is necessary to precisely measure the onset and offset of respiratory muscle activity. Most studies of patient-ventilator interaction have been based on indirect measurements, where the onset and offset of respiratory muscle activity have been estimated from recordings of airflow combined with airway, esophageal, or transdiaphragmatic pressures (2–6). The concordance between such indirect estimates and more direct measurements of neural activity has not been evaluated systematically. Contrast with healthy volunteers, surrogate measurements may be less accurate in ventilator-supported patients because abnormalities in pulmonary mechanics may confound indirect estimates of timing.

Based on the above considerations, we undertook a study to assess the accuracy of indirect estimates of the onset and duration of neural inspiratory time versus a reference measurement of the latter. Selection of the reference standard for such a comparison is not straightforward. Recording the phrenic neurogram would be attractive, but this is neither feasible nor ethical in critically ill patients. Since interest in patient-ventilator interactions has been focused primarily on inspiratory events, we employed the measurement that would most likely reflect phrenic neurogram activity, viz., the crural diaphragmatic electromyogram (EMG), to serve as a reference measurement of the onset and duration of neural inspiratory time. We assessed the accuracy of indirect estimates of neural inspiratory timing against this reference measurement in ventilator-supported patients during both mechanical ventilation and spontaneous breathing.

METHODS

Nine men with chronic obstructive pulmonary disease (age, 70 ± 3 5E yr) who were intubated, receiving mechanical ventilation, and clinically stable were recruited (Table 1). Patients were ventilated in the assist-control mode using either a Servo 900C ventilator (Siemens, Schaumburg, IL) or Puritan-Bennett 7200a ventilator (Puritan-Bennett, Los Angeles, CA). The study was approved by the Human Studies Subcommittee, and informed consent was obtained from each patient.

Experimental Setup

Flow and proximal airway pressure (Paw) were measured between the endotracheal tube and the Y of the ventilator tubing with a heated pneumotachograph (Hans-Rudolf, Kansas City, MO) and differential pressure transducer (MP-45 mm Hg; Validyne, Northridge, CA), respectively. Esophageal (Pes) and gastric (Pga) pressures were measured using conventional balloon-tipped catheters connected to pressure transducers (MP-45 mm Hg; Validyne, Northridge, CA). The esophageal balloon was filled with 0.5 ml of air and positioned in the mid esophagus (7); the gastric balloon was filled with 1 ml of air and positioned 60–70 cm from the nares. Transdiaphragmatic pressure (Pdi) was obtained by electronic subtraction of Pes from Pga.

The electromyogram (EMG) of the diaphragm was obtained using an esophageal probe (Ohmeda, Oxnard, CA). EMG signals were filtered below 10 Hz and above 1,000 Hz. EMG, flow, and pressure (Paw, Pes, Pga) readings were acquired at a sampling rate of 2,000 Hz, and recorded on a personal computer using digital acquisition systems (DataQ, Akron, OH).

Protocol

Patients remained in a semirecumbent posture throughout the study, and endotracheal suctioning was performed before each study. All patients were ventilated in the assist-control mode, and the settings for frequency, tidal volume, inspiratory flow, positive end-expiratory pressure (PEEP), and fractional inspired oxygen concentration were those selected by the primary physician. Each patient was breathing at a respiratory frequency higher than the set back-up rate on the ventilator. Flow, pressures (Paw, Pes, Pga), and EMG recordings were obtained over 15 min, and thereafter each patient breathed spontaneously through a T-piece circuit for at least 12 min (mean, 24 ± 6 min). The last minute of each recording was used for data analysis.
Processing and Reproducibility of the Reference Signal

Neural inspiratory time (TI) was measured from the diaphragmatic signal after signal processing. First, artifacts in the diaphragmatic EMG signal resulting from the electrocardiogram were removed using software that subtracted QRS templates from the original raw signal. Second, the onset of activity in the processed EMG signal was used to define the onset of neural TI. Third, the processed EMG signal was rectified and a moving average was obtained. Finally, the end of neural TI was defined as the onset of the rapid decline in activity on the moving average (Figure 1). In each patient, the first measurement of neural TI made by a single observer was taken as the reference standard. A second measurement of neural TI was then made from the same original tracings by the same observer, who was blinded to the positioning of cursors in the previous set of measurements. The differences in the onset, termination, and duration of neural TI between the first and the second set of measurements were calculated and expressed in milliseconds. Data were accepted for further analysis only if > 80% of the sets of measurements in a given patient were within ± 5% of each other (Figure 2); as a result, four patients were excluded from further analysis. This decision was taken to minimize the possibility of systematic error resulting from either artifacts or EMGs of poor quality. The EMG recordings obtained during mechanical ventilation and during spontaneous breathing were analyzed separately.

Indirect Estimates of Neural TI Versus the Reference Measurement

In the five patients who met the reproducibility criteria for neural TI, indirect estimates of neural TI were compared against the EMG-based measurement; breaths in which the reference measurements differed by more than 5% from each other were excluded (Figure 2). Six indirect estimates of neural TI were derived based on Pes, flow, and Pdi tracings by the observer who was blinded to the diaphragmatic EMG (reference) signal. The description of the start and end points for each of these estimates, and the rationale behind their choice, are described below.

Three estimates of neural TI were made from the Pes tracing. For each estimate, the onset of neural TI was taken as the point of rapid decline in Pes. Three different points were used to estimate the end of TI: the nadir in Pes, the point of zero flow between inspiration and expiration, and the peak in Pdi. The nadir in Pes was used because this point reflects the peak of global inspiratory muscle pressure (Pmus) during spontaneous breathing, and, thus, may correspond to the termination of neural TI (8). The point of zero flow between inspiration and expiration was used because this point has been used in investigations of work of breathing and patient effort (9, 10). The peak in Pdi was used because this point should correspond to the peak EMG activity of the diaphragm, which, in turn, has been used to define the end of neural TI (11).

Two estimates of neural TI were made from the Pdi tracing. For both estimates, the onset of neural TI was taken as the onset of the upward deflection in Pdi (12, 13); the end of neural TI was taken as either the return of Pdi to baseline (14) or as the point of zero flow between inspiration and expiration (15).

Both estimates of neural TI were obtained during both mechanical ventilation and spontaneous breathing. The sixth, and final, estimate of neural TI was made from the flow tracing. This estimate was taken as the time between points of zero flow, as has been employed in studies of patient–ventilator in-

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### Table 1: Characteristics of Patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Age (yr)</th>
<th>ETT (ID)</th>
<th>Duration of ventilator support (d)</th>
<th>Intrinsic PEEP* (cm H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COPD</td>
<td>80</td>
<td>8</td>
<td>8</td>
<td>10.2 ± 1.6</td>
</tr>
<tr>
<td>2</td>
<td>COPD</td>
<td>80</td>
<td>8</td>
<td>25</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>3</td>
<td>COPD</td>
<td>74</td>
<td>8</td>
<td>5</td>
<td>8.1 ± 1.12</td>
</tr>
<tr>
<td>4</td>
<td>COPD/CHF</td>
<td>60</td>
<td>8</td>
<td>27</td>
<td>6.7 ± 1.6</td>
</tr>
<tr>
<td>5</td>
<td>COPD</td>
<td>74</td>
<td>8</td>
<td>6</td>
<td>6.9 ± 3.6</td>
</tr>
<tr>
<td>6</td>
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<td>8</td>
<td>22</td>
<td>12.5 ± 2.5</td>
</tr>
<tr>
<td>7</td>
<td>COPD</td>
<td>79</td>
<td>8</td>
<td>14</td>
<td>2.9 ± 1.6</td>
</tr>
<tr>
<td>8</td>
<td>COPD</td>
<td>60</td>
<td>8</td>
<td>14</td>
<td>1.8 ± 1.2</td>
</tr>
<tr>
<td>9</td>
<td>COPD</td>
<td>50</td>
<td>8</td>
<td>11</td>
<td></td>
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</table>

Definition of abbreviations: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ETT = endotracheal tube; ID = internal diameter in millimeters.

* Intrinsic positive end-expiratory pressure measured during spontaneous breathing (= SD).

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[Figure 1. Representative tracings of the raw crural diaphragmatic electromyogram (EMG<sub>diaph</sub>), the processed EMG<sub>diaph</sub>, achieved by removing EKG artifacts by computer, the moving average (MA) of the processed EMG<sub>diaph</sub>, esophageal pressure (Pes), and flow in a patient breathing spontaneously. The relationship between an indirect estimate of the onset of neural inspiratory time (TI) and its onset on the diaphragmatic EMG signal was assessed by calculation of the phase angle (θ), expressed in degrees. If the indirect estimate of the onset of neural TI coincided with its onset on the EMG signal, the phase angle was zero. If the indirect estimate of the onset of neural TI commenced before its onset on the EMG tracing, a negative phase angle resulted (−20° in this case for Pes). If the indirect estimate of the onset of neural TI commenced after its onset on the EMG tracing, a positive phase angle resulted (120° in this case for flow).]
interaction (16–18), and it was made during both mechanical ventilation and spontaneous breathing.

The differences between each indirect estimate of the duration of neural TI versus the reference standard were calculated in milliseconds, and expressed as bias (mean of the differences) and precision (the standard deviation of the differences) (19). The overall duration of neural TI obtained indirectly could be equivalent to the reference measurement, yet the times of onset and offset could differ considerably. Accordingly, the lag, or lead, in spatial timing of the indirect estimates of the onset of neural TI with respect to the reference standard was measured as the phase angle (i), and expressed in degrees (20) (Figure 1). Data on indirect estimates of the offset of neural TI are not presented as this can be deduced from the data on the onset and total duration of neural TI.

Five patients were selected on the basis of reproducible calculations of total neural TI on the diaphragmatic EMG signal; the two sets of neural TI calculations, however, could differ considerably in phase relationship. Accordingly, the magnitude of the phase angle between the first and second measurements of the onset of neural TI was calculated; this represents the degree of systematic error attributable to the methodology and observer. A remed with the knowledge of the magnitude of systematic error (attributable to the methodology and observer), we were able to better gauge the significance of phase angle errors of indirect neural TI measurements. The indirect measurements of neural TI were compared against the reference measurement and errors in both the onset and duration of neural TI were determined for both mechanical ventilation and spontaneous breathing.

RESULTS

Error in the Reference Measurement

For the total duration of neural TI, the bias (mean difference) between the first and second measurement during spontaneous breathing ranged from 3 to 7 ms among the five patients, and the precision (SD of the difference) ranged from 9 to 23 ms. During mechanical ventilation, the bias ranged from –3 to 6 ms and the precision ranged from 10 to 16 ms. For the onset of neural TI, the bias between the two determinations of the phase angle ranged from –1 to 2° during spontaneous breathing, and from –2 to 2° during mechanical ventilation; the precision of the phase angles ranged from 7 to 11° during spontaneous breathing and from 4 to 19° during mechanical ventilation.

Indirect Estimates of Neural TI Duration

Esophageal pressure. During spontaneous breathing, the bias of the indirect estimate of neural TI duration versus the reference measurement (diaphragmatic EMG) ranged from –29 to 163 ms among the five patients when the offset of neural TI was based on the nadir of Pes (Figure 3, upper left panel), from 183 to 321 ms when the offset of neural TI was based on flow (Figure 3, upper right panel), and from –54 to 143 ms when the offset of neural TI was based on peak Pdi (Figure 4, upper left panel); for these criteria of neural TI offset, precisions ranged from 89 to 157 ms, from 87 to 152 ms, and from 87 to 173 ms, respectively. During mechanical ventilation, the bias of the indirect estimate of neural TI ranged from 32 to 164 ms when the offset of neural TI was based on the nadir of Pes (Figure 3, lower left panel), from 54 to 715 ms when the offset was based on flow (Figure 3, lower right panel), and from –44 to 128 ms when the offset was based on peak Pdi (Figure 4, lower left panel); the precisions ranged from 92 to 217 ms, from 118 to 221 ms, and from 93 to 212 ms, respectively.

Flow. During spontaneous breathing, the bias of the indirect estimate of neural TI duration versus the reference measurement ranged from –4 to 161 ms, and the precisions ranged from 79 to 140 ms (Figure 4, upper right panel). During mechanical ventilation, the bias of the indirect estimate of neural TI ranged from –52 to 264 ms, and the precisions ranged from 74 to 158 ms (Figure 4, lower right panel).
Parthasarathy, Jubran, and Tobin: Neural Ti in Ventilator-supported Patients 549

Transdiaphragmatic pressure. In one patient, the tracing of Pga was not available due to kinking of the catheter. During spontaneous breathing in the remaining four patients, the bias of the indirect estimate of neural Ti duration versus the reference measurement ranged from 340 to 612 ms when the offset of neural Ti was based on return to the baseline of Pdi (Figure 5, upper left panel), and from 169 to 276 ms when the offset of neural Ti was based on flow (Figure 5, upper right panel); for these criteria of neural Ti offset, the precisions ranged from 93 to 175 ms and from 102 to 133 ms, respectively. During mechanical ventilation, the bias of the indirect estimates of neural Ti duration was based on return to baseline Pdi (Figure 5, lower left panel), and from 270 to 580 ms when the offset of neural Ti was based on flow (Figure 5, lower right panel); the precisions ranged from 129 to 205 ms and 109 to 207 ms, respectively.

Indirect Estimates of Neural Ti Onset

Esophageal pressure. The phase angle between the indirect estimate of the onset of neural Ti and its onset on the reference signal (diaphragmatic EMG) ranged from -69 to 27° during spontaneous breathing, and from -85 to 10° during mechanical ventilation (Figure 6). The SD of the difference in the phase angle ranged from 29 to 67° during spontaneous breathing, and from 32 to 87° during mechanical ventilation.

Flow. The phase angle between the indirect estimate of the onset of neural Ti and its onset on the reference signal ranged from -2 to 130° during spontaneous breathing, and from 17 to 255° during mechanical ventilation. The SD of the difference in the phase angle ranged from 26 to 41° during spontaneous breathing, and from 39 to 116° during mechanical ventilation (Figure 6).

DISCUSSION

Surrogate estimates of the onset and duration of neural Ti based on flow, Pes, and Pdi displayed measurable errors in the magnitude of neural Ti and poor reproducibility. The discrepancies are of sufficient magnitude that conclusions concerning patient–ventilator interactions are susceptible to error.

Some broad general observations can be made regarding the indirect estimates of the onset and total duration of neural Ti. (1) The discrepancies between the indirect and direct estimates constituted a substantial portion of neural Ti duration. For example, when neural Ti duration during mechanical ventilation was estimated as the time between the initial deflection in Pdi and its return to baseline, the bias and scatter (± 2 SD) of the estimates were, respectively, 57 and 87% of Ti measured on the diaphragmatic EMG. (2) Of the indirect estimates of neural Ti during mechanical ventilation, the bias errors were least when the onset of neural Ti was taken as the point of rapid decrease in Pes and the end of neural Ti was taken as either the peak in Pdi (Figure 4, lower left panel) or
the nadir in Pes (Figure 3, lower left panel). (3) During mechanical ventilation, the bias errors for the indirect estimates of neural TI duration based on flow were also small in size (136.9 ± 52.4 ms, n = 5). The flow-based estimates of neural TI onset, however, tended to lag significantly behind the reference measurement (Figure 6, lower panel), 132.7 ± 39.6°, compared with estimates based on the Pes and Pdi tracings, −21.8 ± 17.3° (p = 0.01), and 10.1 ± 22.4° (p = 0.01), respectively (Figure 6, lower panel). (4) The largest bias in the estimation of neural TI duration occurred during both spontaneous breathing and mechanical ventilation when the offset of TI was taken as the return of Pdi to baseline (Figure 5, left panels).

The indirect estimate of neural TI duration with the least bias error was the time between the rapid decline in Pes until the peak in Pdi (74.6 ± 25.4 ms) (Figure 4, lower left panel). The superior performance of this estimate of neural TI is in keeping with the findings of Fernandez and coworkers (8). These investigators noted a close correlation between an indirect estimate of neural TI duration, taken from measurement of Pmus, and a reference measurement, based on the diaphragmatic EMG (r = 0.78 to 0.93). Fernandez and coworkers (8) employed linear regression analysis, whereas bias and precision were used to evaluate the accuracy of the indirect estimates of neural TI duration in the present study. The assessment of precision revealed a large scatter of the indirect estimates of neural TI duration (626.3 ± 105.4 ms) (error bars, Figure 4, lower left panel) despite a small bias error (74.6 ± 25.4 ms).

Several factors likely contributed to the discrepancies between the indirect estimates of neural TI and the reference measurement. These include the presence of dynamic hyperinflation, expiratory muscle activity, activity of accessory muscles of inspiration, postinspiratory activity of inspiratory muscles, and rib cage distortion and diaphragmatic morphometry.

PEEP
Intrinsic positive end-expiratory pressure (PEEP,) could contribute to inaccuracies in the indirect estimation of neural TI onset (from pressure and flow tracings). A n increase in PEEP, results from an increase in end-expiratory elastic recoil and/or expiratory muscle activity (21). In the case of an elevated end-expiratory elastic recoil pressure, achievement of a change in pressure (esophageal and transdiaphragmatic) requires inspiratory muscle contraction to first overcome any disadvantage in length–tension relationship. Compared with the onset of electrical activity in an inspiratory muscle, the time taken for the development of a pressure deflection will cause a positive phase angle between the measurements of neural TI onset based on pressure and the diaphragmatic EMG. This phase angle is generally very small, because muscle reaction time is about 60 ms; the phase angle, however, could be magnified during dynamic hyperinflation as a result of the flattening and increase in the radius of curvature of the diaphragm. When flattened, the diaphragm can be ineffective in generating a positive or negative intrathoracic pressure (22). Such a lack of efficiency could account for the lack of a discernible change in Pdi, despite EMG electrical activity. The increase in Pdi that was observed after the EMG electrical activity was presumably due to the activation of rib cage muscles rather than diaphragmatic contraction. Following the onset of pressure generation, an additional time lag will arise before airflow is initiated if the negative intrathoracic pressure has to counterbalance the elastic recoil of the respiratory system (23). For flow-based estimations of TI onset, a clear delay (positive phase angle) was noted in all but one patient (No. 2) during spontaneous ventilation (Figure 6, upper panel). In the same patients, the flow-based estimate of TI onset was further delayed during mechanical ventilation (Figure 6, lower panel), presumably because of the inevitable time taken to trigger the ventilator (12, 13). The Pes- and Pdi-based estimates of neural TI onset were widely scattered on both sides of the reference measurement of neural TI onset during both spontaneous breathing and mechanical ventilation (as indicated by the width of the bars). The factors accounting for this scatter in pressure estimations are complex, and we attempt to explain them below.

Imprecision in the estimation of neural TI onset may also result from the component of PEEP, due to increased expiratory muscle activity (21). Contraction and subsequent relaxation of the expiratory muscles of the abdomen (21) and rib cage (24) could cause an early deflection in the Pes signal just before the onset of diaphragmatic EMG activity. Such an occurrence would produce a negative phase angle between the two measurements; that is, the opposite effect to that produced by the elastic recoil component of PEEP.

Breath-to-breath variation in PEEP, and its components may have contributed to the variability in the estimates of neural TI onset; this may be one explanation for the witnessed deviation of the surrogate estimates on both sides of the reference measurement of neural TI onset (Figure 6). Variation in the relative contributions of expiratory muscle activity and elastic recoil to PEEP, which have opposing actions on the pressure tracings, would further magnify the lack in precision. Moreover, potential exists for the introduction of a systematic error on the part of the observer because pinpointing the initial deflection on a pressure tracing is inevitably more difficult than...
defining a change from zero on the flow tracing. These factors could explain why thePes- and Pdi-based estimates of Ti onset resulted in both positive and negative phase angles, whereas flow-based estimates of Ti onset were more consistent in direction (positive phase angle in most patients) (Figure 6).

We compared the relationship between the errors in estimates of neural Ti onset and duration with the two components of PEEPi, elastic recoil and expiratory muscle activity contribution, using linear and polynomial fit functions. A reasonably strong correlation (r = 0.59) was observed between the average values of the bias of the phase angle and PEEPi in each patient during spontaneous breathing, although statistical significance was not achieved since data were available in only five patients.

Rib Cage Movement
The muscles acting on the rib cage prevent its distortion by the diaphragm (25); to achieve this end, it is necessary that they become active before, or in unison with, the diaphragm. Contraction of the rib cage muscles before that of the diaphragm could account for deflections in Pes and Pdi before the onset of diaphragmatic EMG activity, registered as negative phase angles (Figure 6) (26). During maximal ventilatory maneuvers, healthy subjects display activity of the scalenes for as long as 200 ms before the onset of inspiratory flow (27). Conversely, excursions in Pes and Pdi could still be evident after the diaphragmatic EMG signal has become silent if postinspiratory inspiratory activity of the accessory muscles lasts longer than that of the diaphragm; this phenomenon may have contributed to the overestimations of neural Ti duration from the Pes and Pdi tracings (Figures 3 and 5).

Contraction of the expiratory muscles of the rib cage and abdomen causes a decrease in lower rib cage volume and lengthens the diaphragm, making it convex in relation to the rib cage compartment (24). The stretched diaphragm will cause muscle tension, in the form of an increase in Pdi during expiration (28). Subsequently, abrupt relaxation of the rib cage expiratory muscles before that of the abdominal muscles leads to expansive recoil of the distorted rib cage, which serves to further lengthen the diaphragm (29), and, thereby, further increase the tension and Pdi generated. The expansive recoil of the rib cage may also tend to flatten the diaphragm in the direction of the abdominal compartment. The inertia of the abdominal contents may oppose the flattening of the diaphragm, and thereby tend to counter the decline in Pga that accompanies the relaxation of the expiratory muscles in the supine patient. Accordingly, relaxation of the expiratory muscles produces a slower rate of decline in Pga than in Pes, which in turn leads to a positive deflection in the Pdi signal. Such an occurrence, in addition to the decline in Pes that accompanies relaxation of the expiratory muscles, could partly explain the deflections in Pes and Pdi tracings that preceded the onset of diaphragmatic EMG activity (Figure 6).

In conclusion, the observed errors in the indirect estimates of neural Ti onset and duration could cause problems in patient care. The operation of a mechanical ventilator is based on algorithms that employ estimates of neural Ti based on flow and airway pressure recordings. Errors of bias in the estimation of neural Ti could contribute to patient-ventilator dysynchrony, leading to wasted effort and patient discomfort.

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