Fluctuations in End-Expiratory Lung Volume during Cheyne-Stokes Respiration

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We hypothesized that patients with Cheyne-Stokes respiration exhibit periodic increases in end-expiratory lung volume, mediated by changes in breath components, postinspiratory inspiratory muscle activity, or both. Calibrated inductive plethysmography revealed that 12 of 12 patients with Cheyne-Stokes respiration experienced increases in end-expiratory volume during hyperpnea: maximum 412 ± 112 (SE) ml (range 75–1,543 ml). Compared with quiet breathing, the breath with largest increase in end-expiratory volume had larger tidal volume (867 ± 107 vs. 567 ± 38 ml, p < 0.01) and shorter expiratory time (1.25 ± 0.11 vs. 1.66 ± 0.15 seconds, p < 0.05). During decrescendo, the breath with largest decrease in end-expiratory volume had smaller tidal volume (p < 0.01) and longer expiratory time (p < 0.01). Cross-correlation of time series revealed that end-expiratory volume was related to both breath components (p < 0.0001). Bipolar needle electrodes revealed that scalene muscle activity at end-expiration was 50.7 ± 14.0% higher at highest increase in lung volume than during preceding apnea (p < 0.05). Time series for scalene activity and end-expiratory volume were cross-correlated (p < 0.008). Increase in tonic scalene activity at end-expiration, however, was equivalent during crescendo and decrescendo phases: 50.6 ± 22.1 versus 42.0 ± 12.9% (p = 0.48). In conclusion, patients with Cheyne-Stokes respiration exhibit fluctuations in end-expiratory lung volume, primarily because of alterations in tidal volume and expiratory time rather than postinspiratory inspiratory muscle activity.

Keywords: breathing pattern; control of breathing; hyperinflation; scalene muscles; time-series analysis

Cheyne-Stokes respiration is a disturbed pattern of breathing, characterized by recurrent episodes of hyperpnea separated by apneas or hypopneas. The prevalence of Cheyne-Stokes respiration is higher than previously suspected, and recent studies reveal its occurrence in 30–40% of patients with congestive heart failure (1–3). The hyperpneic phases of Cheyne-Stokes respiration consist of crescendo–decrescendo changes in tidal volume, occurring on a periodic basis. Patients also display periodic alterations in several other functions, such as heart rate, blood pressure, cardiac output, cerebral perfusion, electroencephalographic activity, muscle tone, muscle reflexes, and pupil size (4–6). Oscillations in sympathetic neural output, which accompany the periodic changes in ventilation, may adversely affect cardiac performance and contribute to increased mortality (7, 8).

Among patients with congestive heart failure, Hanly and Zuberi-Khokhar (9) reported a mortality of 56% over 3.7 years in the subgroup who had nocturnal Cheyne-Stokes respiration compared with a mortality of 14% in the subgroup who did not have Cheyne-Stokes respiration. Subsequent investigations have confirmed the high mortality among patients who have congestive heart failure combined with Cheyne-Stokes respiration (3, 10).

Lung volume at the end of expiration is commonly shown as remaining constant during both the hyperpneic and apneic phases of Cheyne-Stokes respiration (7, 11–15). In preliminary observations, however, we have observed increases in end-expiratory lung volume during the crescendo of the hyperpneic episodes and decreases during the decrescendo and apnea. At least two mechanisms could contribute to periodic increases in end-expiratory volume. First, an increase in tidal volume combined with a decrease in the time available for lung emptying might prevent lung volume from returning to the normal relaxation volume of the respiratory system at the end of expiration (16). With this scenario, the increase in end-expiratory volume is achieved by purely passive, mechanical mechanisms. Second, active mechanisms may prevent the lung from reaching relaxation volume at the end of expiration. For example, the hyperinflation that occurs during acute bronchoconstriction in patients with asthma is largely mediated by increased tonic activity of the inspiratory muscles that persists into expiration (17, 18).

Based on these observations and reasoning, we hypothesized that patients exhibit increases in end-expiratory lung volume during the crescendo phase of Cheyne-Stokes respiration. We further hypothesized that these increases in lung volume are mediated by increases in tidal volume, decreases in expiratory duration, tonic activity of the inspiratory muscles that persists into expiration, or a combination of these factors. Some results of these studies have been reported in the form of abstracts (19, 20).

METHODS

Subjects

Twelve men with congestive heart failure, left ventricular ejection fraction lower than 30%, and Cheyne-Stokes respiration participated in this study (Table 1). The study was approved by the Human Studies Subcommittee, and informed consent was obtained from each patient (see online supplement for further details).

Breathing Pattern

Ventilation was measured nonobtrusively with an inductive plethysmograph (21) (see online supplement for further details).

Protocol

All 12 patients breathed room air for 1 hour during resting wakefulness verified by electroencephalography. Six patients were studied during a second hour while receiving nitrogen through nasal cannulae at 2–4 L/minute, titrated to achieve an oxygen saturation of 87–91% during nonperiodic breathing. When steady state was reached, the patients breathed the hypoxic mixture for another hour with the intent of enhancing periodic breathing (see online supplement for further details).
Scalene Electromyography

Electromyographic (EMG) activity of the scalene muscles was recorded with a bipolar needle electrode over 1 hour of resting breathing in six patients (those not exposed to a hypoxic mixture). After subcutaneous anesthesia with 1–2 ml lidocaine 2%, the recording needle was inserted approximately 2 cm above the clavicle in the posterior triangle of the neck (22). The EMG signal was amplified, filtered, and played through a loudspeaker; the occurrence of the acoustic signal in synchrony with inspiration was used to identify the anterior scalene muscle (23) (see online supplement for further details).

Data Analysis

Changes in end-expiratory lung volume. The change in end-expiratory lung volume during each cycle was calculated by subtracting the value during the preceding apnea from end-expiratory volume for each breath during hyperpnea.

Spectral analysis. Power spectra of the data strings of tidal volume during both room air and hypoxia were obtained using a fast Fourier transform to detect significant oscillations and to quantify their magnitude (24–26).

Cross-correlation analysis. Cross-correlation analysis was employed to determine the time-dependent relationship between change in end-expiratory lung volume and both tidal volume and expiratory times (27).

Analysis of the scalene EMG. EMG activity was measured at the time of end-expiration indicated by the sum of the inductive plethysmography signal. The change in EMG activity during a hyperpnea was quantified by subtracting EMG activity at the end of a preceding apnea (EMGapnea) from EMG activity at end-expiratory lung volume (EMGhyperpnea) for each breath; this change in EMG activity was then normalized.

normalized EMG = \frac{EMG_{hyperpnea} - EMG_{apnea}}{EMG_{apnea}}

Crescendo and decrescendo analysis. To determine whether change in breath components contributed to the fluctuations in end-expiratory lung volume, three points in the Cheyne-Stokes cycles were analyzed: the breath exhibiting the largest increase in end-expiratory volume during the crescendo phase, the breath exhibiting the highest cumulative end-expiratory volume (peak of hyperpnea), and the breath exhibiting the largest decrease in end-expiratory volume during the decrescendo phase. When we refer to the peak of hyperpnea, we are referring to time of active breathing, during which time the maximal increase in end-expiratory lung volume was observed.

General statistical methods. Data were analyzed using one-way analysis of variance with repeated measures and Neuman-Keuls’ test for multiple comparisons when appropriate. Data are presented as mean ± SE. (Additional detail regarding the analysis is available in the online supplement.)

RESULTS

Changes in End-expiratory Lung Volume

During the hyperpneic phase of Cheyne-Stokes respiration, all 12 patients showed an increase in end-expiratory lung volume compared with that during the preceding apnea. The maximum increase in end-expiratory lung volume during the hyperpneic phase was 412 ± 112 ml; the increase varied from 75 to 1,543 ml among the 12 patients. The changes in lung volume and scalene muscle activity during three consecutive cycles in a representative patient are shown in Figure 1.

Breath Components

Analysis of variance revealed significant differences in inspired tidal volume, expiratory time and mean expiratory flow between quiet (nonperiodic) breathing, the crescendo phase of Cheyne-Stokes respiration, the highest cumulative increase in end-expiratory volume, and the decrescendo phase (p < 0.007 in each instance). During the decrescendo phase, the mean largest increase in end-expiratory lung volume for one breath in the 12 patients was 214 ± 42 ml. Figure 2 shows the respiratory cycle for this breath and for quiet breathing. Compared with quiet breathing, the breath with the largest increase in end-expiratory lung volume had a larger inspired tidal volume (867 ± 107 ml vs. 567 ± 38 ml, p < 0.01), shorter expiratory time (1.25 ± 0.11 vs. 1.66 ± 0.15 seconds, p < 0.05), and higher mean expiratory flow (621 ± 114 vs. 399 ± 61 ml/second, p < 0.05).

During the decrescendo phase, the mean largest decrease in end-expiratory lung volume for one breath in the 12 patients was 134 ± 22 ml. Figure 3 shows the respiratory cycle for this breath and the breath with the highest cumulative increase in end-expiratory volume (peak of hyperpnea). Compared with the breath with the highest cumulative end-expiratory volume, the breath with the largest decrease in end-expiratory volume had a smaller inspired tidal volume (662 ± 75 vs. 910 ± 117 ml, p < 0.01), longer expiratory time (1.80 ± 0.24 vs. 1.35 ± 0.14 seconds, p < 0.01), and a tendency toward lower mean expiratory flow (680 ± 182 vs. 749 ± 165 ml/second, p = 0.059).

The change in end-expiratory lung volume was significantly cross-correlated with tidal volume (p < 0.0001 in each patient), being maximal at a lag of zero breaths. Change in end-expiratory lung volume was also significantly cross-correlated with expiratory time (p < 0.0001 in each patient), being maximal at a lag of zero breaths.

Scalene Activity and End-expiratory Lung Volume

In the six patients with recordings from the scalene muscle, electrical activity at end-expiration was 46 ± 16% higher over the entire time of hyperpnea (both its crescendo and decrescendo portions) than during the preceding apnea (p < 0.05) (Figure 1). For the breath with the highest end-expiratory lung volume
Figure 2. The respiratory cycles during quiet (nonperiodic) breathing and for the breath exhibiting the largest increase in end-expiratory lung volume during the crescendo phase in 12 patients. Compared with quiet breathing, the breath with the largest increase in end-expiratory volume had a larger inspired tidal volume (867 ± 1100 ml vs. 567 ± 38 ml, p < 0.01) and shorter expiratory time (1.25 ± 0.11 vs. 1.66 ± 0.15 seconds, p < 0.05). Lung volume at the end of expiration is higher for the crescendo breath than during quiet breathing. Bars represent ± SE.

Figure 3. The respiratory cycles for the breath at the highest cumulative increase in end-expiratory lung volume and the breath exhibiting the largest decrease in end-expiratory volume during the decrescendo phase in 12 patients. Compared with the breath with the highest cumulative increase in end-expiratory volume, the breath with the largest decrease in end-expiratory lung volume had a smaller inspired tidal volume (662 ± 75 vs. 910 ± 117 ml, p < 0.01) and longer expiratory time (1.80 ± 0.24 vs. 1.35 ± 0.14 seconds, p < 0.01). Lung volume at the end of expiration is lower for the decrescendo breath than at the highest cumulative increase in end-expiratory volume. Bars represent ± SE.

Figure 4. Cross-correlation of the change in end-expiratory lung volume and electrical activity of the scalene muscle in one patient during a 1-hour recording of Cheyne-Stokes respiration. The height of the bars represents the values of the cross-correlation coefficients, with those lying outside the isopleths (dashed horizontal lines) being statistically different from zero at p < 0.05. Cross-correlation was maximal at a lag of zero breaths, indicating that there was no lag between the fluctuations in the scalene and lung volume signals (the two signals were synchronously coupled).

Effect of Hypoxia

In the six subjects studied under both room air and hypoxic conditions, the power of significant oscillations in tidal volume was greater during hypoxia, 0.06 ± 0.01 L^2, than during air breathing, 0.04 ± 0.01 L^2 (p < 0.05), indicating an increase in the magnitude of the periodic change in tidal volume. The frequency of the significant oscillations in tidal volume was equivalent for air and hypoxia (0.09 ± 0.02 and 0.1 ± 0.01, respectively; p = 0.3), indicating that the duration of the Cheyne-Stokes cycles did not change.

Compared with room air, hypoxia increased the cross-correlation between end-expiratory lung volume and tidal volume (r = 0.50 ± 0.05 vs. 0.35 ± 0.07, p < 0.05). The cross-correlation between end-expiratory lung volume and expiratory time was equivalent for air and hypoxia (r = −0.33 ± 0.05 and −0.42 ± 0.07, respectively; p = 0.3).

Figure 5. The average increase per breath in normalized electrical activity of the scalene muscle during the crescendo and decrescendo portions of hyperpnea as compared with the preceding apnea. The increases were equivalent during crescendo and decrescendo: 50.6 ± 22.1 vs. 42.0 ± 12.9% (p = 0.48).
The average increase in end-expiratory lung volume per breath over the entire time of hyperpnea (both its crescendo and decrescendo portions) was greater when subjects breathed a hypoxic mixture, 196 ± 41 ml, than during room air breathing, 138 ± 28 ml. The average contribution of the rib-cage compartment to the change in end-expiratory volume during hyperpnea was greater during hypoxia, 128 ± 29 ml, than during air breathing, 89 ± 21 ml (p < 0.03) (Figure 6). The average contribution of the abdominal compartment to the change in end-expiratory lung volume during hyperpnea was similar during hypoxia, 68 ± 23 ml, and air breathing, 49 ± 13 ml (p = 0.29). The average contribution of the rib-cage compartment to tidal volume over the entire phase of hyperpnea was similar during hypoxia, 328 ± 40 ml, and air breathing, 351 ± 65 ml (p = 0.73); likewise, the contribution of the abdominal compartment to tidal volume over the entire phase of hyperpnea was similar during hypoxia, 221 ± 24 ml, and air breathing, 235 ± 44 ml (p = 0.75).

**DISCUSSION**

Patients with Cheyne-Stokes respiration exhibited a cyclical change in end-expiratory lung volume of 412 ml (range 75–1,543 ml), occurring at the peak of the hyperpneic phase. The increase in end-expiratory volume was magnified when periodic breathing was enhanced by hypoxic exposure. The increase in end-expiratory volume was accompanied by greater demands on passive lung emptying—increases in inspired tidal volume and decreases in expiratory time—combined with increases in postinspiratory activity of the inspiratory muscles. (A more complete discussion is provided in the online supplement.)

**Fluctuations in End-expiratory Lung Volume**

What mechanisms can explain the cyclical increases in end-expiratory lung volume? The resting volume of the respiratory system is determined by an equilibrium between two static forces: outward recoil of the chest wall and inward recoil of the lungs (16, 28). When expiratory duration is decreased, or inspired tidal volume or the time-constant for lung emptying is increased, lung volume at end-expiration may no longer be determined by the equilibrium of static forces (29). The largest increase in end-expiratory lung volume for one breath during the crescendo phase of Cheyne-Stokes respiration was accompanied by a 53% increase in inspired tidal volume and a 25% decrease in expiratory time as compared with quiet (nonperiodic) breathing (Figure 2). That the changes in these two breath components are important determinants of the fluctuations in end-expiratory volume is further supported by the highly significant cross-correlations between change in end-expiratory lung volume and both inspired tidal volume and expiratory time (p < 0.0001 for each component in each patient).

In addition to passive influences, end-expiratory volume may be elevated because of dynamic mechanisms. In newborn infants, the relaxation volume of the respiratory system is close to residual volume because infants have highly compliant chest walls (30). Several groups of investigators have shown that infants actively maintain end-expiratory lung volume above their relaxation volume during spontaneous quiet breathing (31, 32). In part, the increase in lung volume results from a high respiratory rate combined with shortening of expiratory time (31, 33). In addition, infants exhibit airflow “braking” during expiration, mediated in part by modulation of laryngeal muscle activity (30). During quiet breathing, the size of the glottic aperture is actively determined by a net balance between activity of the laryngeal abductor muscles, such as the posterior cricoarytenoid, and the laryngeal adductors, such as the thyroarytenoid and arytenoideus muscles (34–36). Patients with Cheyne-Stokes respiration show cyclic activity in many functions other than ventilation, including alterations in muscle activity (4–6). Although direct recordings have not been reported, cyclic increases in thyroarytenoid activity or decreases in posterior cricoarytenoid activity could contribute to the increase in end-expiratory lung volume during the crescendo phase of Cheyne-Stokes respiration.

**Postinspiratory Inspiratory Activity**

Activity of the inspiratory muscles that is carried over into expiration can also cause an increase in end-expiratory volume. When patients with asthma inhale a bronchoconstrictor, such as histamine, end-expiratory lung volume increases by 20–25% of functional residual capacity (at baseline) (37). Martin and coworkers (17) found that progression of bronchoconstriction and hyperinflation is accompanied by maximum expiratory pleural pressure becoming increasingly positive. Pleural pressure, however, remained lower than that predicted for the relaxed chest wall. This observation indicates that outward recoil of the chest wall is increased during expiration, as produced by persistent activity of the inspiratory muscles throughout expiration. Employing EMG electrodes, Muller and coworkers (18) observed tonic activity of the intercostal muscles and diaphragm during acute bronchoconstriction. The increase in lung volume was correlated with the increases in tonic intercostal (r = 0.82) and diaphragmatic (r = 0.89) activity. Recordings of scapular EMG in the six patients with Cheyne-Stokes respiration revealed that electrical activity at end-expiration was 46 ± 16% higher throughout the hyperpneic phase than during the preceding apnea (Figure 1). On cross-correlation analysis, the maximal correlation between scapular muscle activity and end-expiratory lung volume (r = 0.32 ± 0.17) occurred at a lag of zero breaths, indicating that the relationship between these two variables was in phase and that maximal coupling between the two time series was synchronous (Figure 4).

If persistent activity of the inspiratory muscles during expiration were a major cause of the increase in lung volume, one
would expect the postinspiratory inspiratory activity to be greater during the crescendo than the decrescendo phase. On the contrary, the increase in normalized scalene activity (compared with the preceding apnea) was equivalent during the crescendo and decrescendo phase, 50.6 ± 22.1 vs. 42.0 ± 12.9% (p = 0.48) (Figure 5 and Figure E1). This observation appears to conflict with the strong relationship between hyperinflation and tonic inspiratory muscle activity observed by Muller and coworkers (18). The nature of the stimulus, however, is different in the two situations: bronchoconstriction produces a constant and persistent stimulus, whereas patients with Cheyne-Stokes respiration experience changing levels of respiratory motor output.

The equivalent increase in postinspiratory scalene activity during the decrescendo and crescendo phases raises the possibility that postinspiratory inspiratory activity is not an important cause of the increase in end-expiratory volume (Figure 1). Instead, it is possible that an increase in end-expiratory volume induces postinspiratory inspiratory activity. This possibility is supported by the cross-correlation analysis, which revealed that the maximal correlation between scalene activity and end-expiratory lung volume (r = 0.32 ± 0.17) occurred at a lag of zero breaths, indicating that postinspiratory inspiratory activity did not lead the changes in end-expiratory volume (Figure 5). In awake dogs, Easton and coworkers (38) observed significant postinspiratory inspiratory muscle activity in the crural diaphragm and external intercostals, but little or no such activity in the para-sternal intercostals and costal diaphragm. Because the costal diaphragm and the para-sternal intercostals have greatest inspiratory effects in dogs, Easton and coworkers (38) questioned the functional significance of postinspiratory inspiratory activity. Likewise, postinspiratory inspiratory muscle activity may have contributed little to the increase in end-expiratory lung volume during the crescendo phase, and the increased scalene activity may be reflecting heightened respiratory drive during hyperpnea.

Another finding raising doubts about the mechanical effect of postinspiratory inspiratory activity is the change in mean expiratory flow. If postinspiratory inspiratory muscle activity were an important mechanism for the increase in end-expiratory lung volume during the crescendo phase (by means of a braking action), one would expect a decrease in expiratory flow. Yet, for the breath experiencing the largest increase in end-expiratory lung volume, mean expiratory flow was 56% higher than during quiet breathing (621 vs. 399 ml/second, p < 0.05). The higher flow, however, does not necessarily mean that postinspiratory inspiratory activity was having no mechanical action. In the absence of postinspiratory inspiratory activity, the expiratory flow might have been even higher than the value recorded.

A hypoxic gas mixture was used to enhance periodic breathing in six patients. Compared with breathing room air, hypoxia increased the power of significant oscillations in tidal volume (0.06 ± 0.01 vs. 0.04 ± 0.01 L2) and induced a greater increase in end-expiratory lung volume (Figure 6). The contribution of the rib-cage compartment to end-expiratory lung volume was greater during hypoxia than with room air. The greater rib-cage contribution with hypoxia is similar to the pattern in patients with hyperinflation secondary to bronchospasm, where the increase in lung volume is largely accommodated by the rib-cage compartment, specifically the portion apposed to the diaphragm (37).

Decrescendo Phase
During the decrescendo portion of the hyperpnea, patients exhibited a progressive decrease in end-expiratory lung volume. As in the case of the increase in lung volume during the crescendo phase, changes in inspired tidal volume and expiratory duration accompanied the decrease in lung volume during the decrescendo. The largest decrease in end-expiratory lung volume for one breath during the decrescendo phase was 134 ml. The fall in lung volume during apnea may have arisen in part from loss of normal respiratory muscle tone, which is known to fluctuate in patients with Cheyne-Stokes respiration (6). Administration of neuromuscular blocking agents and anesthesia cause a decrease in functional residual capacity, suggesting that some degree of inspiratory muscle tone contributes to the maintenance of end-expiratory lung volume during normal quiet breathing (39, 40).

Methodologic Considerations
We used respiratory-inductive plethysmography for measuring change in lung volume. The accuracy of inductive plethysmography for detecting change in tidal volume has been extensively investigated. When the device is carefully calibrated and artifact from motion or change in posture is diligently avoided, volumes within 5–10% of volumes measured by spirometry can be obtained (21, 24–26). The reliability of inductive plethysmography for detecting change in end-expiratory lung volume has been less extensively investigated. Lennox and coworkers (41) found that changes in functional residual capacity measured by inductive plethysmography were within 7% of changes measured by body plethysmography. Changes in functional residual capacity measured with the two techniques were closely correlated (r = 0.91) and did not differ from the line of identity. The oscillator unit of the inductive plethysmograph is temperature-sensitive, which can give rise to drift. Lennox and coworkers (41) found that drift of an inductive plethysmography signal was only 22% of the drift arising from changes in temperature within a body plethysmograph. Other investigators (42–44) have also reported that drift of inductive plethysmography is small over short periods. Artifactual changes in volume related to drift were further minimized by relating changes in end-expiratory lung volume to a reference point within that same cycle of Cheyne-Stokes respiration, namely the lung volume during the preceding apnea. Finally, the inductive plethysmograph was used in the direct current mode, which avoids the self-adjusting changes to lung volume that arise with use in the alternating current mode.

In summary, patients with Cheyne-Stokes respiration exhibited fluctuations in end-expiratory lung volume. During the crescendo phase, the increase in end-expiratory volume was accompanied by an increase in tidal volume and shortening of expiratory time. Conversely, these two breath components changed in the opposite direction when end-expiratory volume was progressively falling during the decrescendo. Time-series analysis revealed that the breath-by-breath change in end-expiratory volume was significantly cross-correlated with tidal volume, expiratory time, and postinspiratory inspiratory scalene muscle activity. Postinspiratory inspiratory muscle activity, however, was equivalent during the decrescendo and crescendo phase. In conclusion, end-expiratory lung volume increases during the crescendo phase of Cheyne-Stokes respiration, primarily because of alterations in the demands placed on passive lung emptying rather than a dynamic action of postinspiratory inspiratory muscle contraction.

Conflict of Interest Statement: T.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.J. was Deputy Editor of the AJRCCM at the time of manuscript submission and received a fixed stipend from the American Thoracic Society; she does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.J.T. was Editor of the AJRCCM at the time of manuscript submission and received a fixed stipend from the American Thoracic Society. He does not receive financial support for research from pharmaceutical, biotechnology, or medical device companies and he does not serve as a consultant to or on the advisory board of any company. He receives royalties from two books on critical care published by McGraw Hill, Inc.
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Acknowledgment: The authors thank Andre DeTroyer, M.D., for advice on technical aspects of recording the scalene electromyogram and its analysis; Eugene Bruce, Ph.D., for advice on time-series analysis; and Michael Pinsky, M.D., for advice on cardiopulmonary interactions.

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