Linkage of hiccup with heartbeat

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Chen, B.-Y., K. Vasilakos, D. Boisteanu, L. Garma, J.-P. H. Derenne, and W. A. Whitelaw. Linkage of hiccup with heartbeat. J Appl Physiol 88: 2159–2165, 2000.—We explored a possible link between the cardiac cycle and the timing of recurrent hiccups in 10 patients with chronic, intractable hiccups. Recordings made during daytime naps in a sleep laboratory included sleep state; electrocardiogram; and respiration by means of a thermistor to detect airflow, bands around the rib cage and abdomen to assess expansion, and a bipolar surface electrode electromyogram over parasternal intercostal muscles. Hiccups could be detected on the abdominal bands and the parasternal electromyogram. The time of occurrence of each hiccup and each R wave in a continuous tracing of 100 or more hiccups were recorded and analyzed together with semiquantitative estimates of the phase of hiccup respiration. Whereas the hiccup rate ranged from approximately one-third to one-eighth of heart rate and was more variable than heart rate, hiccups showed a tendency, stronger in some subjects than others, to occur in mid systole. Variation in R-wave-R-wave (R-R) interval in association with hiccups was found in five patients. In three of these patients, hiccups were synchronized with respiration so that the cyclic change in R-R interval posthiccup could be explained as sinus arrhythmia, but, in two patients, the hiccups were not synchronized with respiration, so that hiccups are most likely responsible for the variation in heart rate. Also, the variation of R-R interval with hiccups suggests that there is some phase autonomic efferent activity associated with hiccups.

intractable hiccup; singulitis; entrainment; cardiac rhythm

ALTHOUGH NEARLY EVERYBODY has experienced hiccups and is familiar with tricks for ending a bout of them, the mechanism for their production remains open to speculation. Occurrence of hiccups in association with irritation of the esophagus, distension of the stomach, and a long list of thoracic and central nervous system disorders has led to the idea that they are a reflex response to afferent stimuli carried in the phrenic or vagus nerves. They tend to occur in bouts with a stable periodicity of their own, however, which is unlike the behavior of a simple reflex.

The idea that a hiccup consists of a complex, patterned motor act consisting of sudden, simultaneous, vigorous contraction of diaphragm and (inspiratory) external intercostal muscles, together with a slightly delayed contraction of (inspiratory) parasternal intercostal muscles and inhibition of (expiratory) internal intercostal muscles. The glottis closes at the time of the sudden inspiratory spasm, which is likely related to active adduction of the vocal cords. Newsom Davis also showed that increasing the blood concentration of carbon dioxide reduces the frequency of hiccups and can eliminate them, which is opposite to its effect on respiration. He proposed the existence in the brain stem of a specific neural circuit capable of generating hiccups. Although distinct from the respiratory rhythm generator, the hypothetical hiccup generator must have connections to it, because hiccup rhythms are usually linked to the respiratory rhythm, with a strong tendency to occur in inspiration (8). Recently, Arita and co-workers have shown that a single, patterned motor discharge identical to a hiccup can be provoked in an anesthetized cat by mechanical stimulation of the posterior wall of the pharynx at the level of the soft palate (9) or by electrical stimulation of a locus in the medullary reticular formation (1).

Research on hiccups is difficult because bouts usually happen at unpredictable times and last only briefly. Our laboratory has recently had the opportunity to study a group of patients with chronic, intractable hiccups who were referred to a special clinic established for this purpose. During polygraph recordings over several hours that included electrocardiograms and indicators of respiratory movement, we noted an unexpected synchrony between hiccups and the cardiac cycle in one patient and, therefore, conducted a systematic study to describe this relationship in detail and to determine whether such synchrony was common to all patients with hiccups. A preliminary report of this work has appeared previously (13).

METHODS

These patients were all men, aged 59–81 yr (mean 70 yr), and were healthy other than the hiccups. Of a consecutive series of 15 patients who passed thorough the laboratory, we report data from the 10 whose records permitted clear identification and timing of the hiccups. The patients had all been troubled by prolonged bouts of hiccups occurring on and off over 2–10yr and were either greatly inconvenienced or partly disabled by them. A comprehensive search for predisposing causes was carried out, including investigations by specialists in gastroenterology, respiratory medicine, and neurology.

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Polygraphic daytime nap studies (mean sleep latency tests) were performed in a clinical sleep laboratory to determine whether hiccups had caused somnolence by disrupting sleep. In addition to electroencephalogram, electrooculogram, and electromyogram of muscles under the chin, the recordings included an electrocardiogram and monitoring of respiration by means of thermistors near the mouth and nose to detect flow, together with bands around the chest and abdomen to assess expansion, and an electromyogram of parasternal muscles from a bipolar surface electrode on the upper anterior chest wall. The polysomnograms were recorded with ink pens on paper at a speed of 15 mm/s and were reduced to numerical data with a ruler and magnifier within the limits of resolution set by the thickness of the ink line. Typical tracings are shown in Fig. 1.

In all patients, hiccups could most easily be identified by large, quick deflections in the tracing from the abdominal band. In all subjects, extensive sections of the record of the parasternal electromyogram showed a deflection due to muscle activity during the hiccup. Consecutive series of 100–150 hiccups/subject were identified, and the time of each hiccup and the subsequent R wave in the continuous record were recorded. Respiration could not be timed exactly from the thermistor tracing or chest wall bands, but the approximate phase of the respiratory cycle in which each hiccup occurred (early or late inspiration, early or late expiration) was noted.

To test whether hiccups were independent of heartbeats, the time between each hiccup and the previous R waves was calculated and tabulated in a frequency histogram. If the individual hiccups were independent of the heartbeat, then they would be uniformly distributed throughout the R wave-to-R wave (R-R) interval. The null hypothesis that the hiccups were distributed uniformly throughout the R-R interval was tested by using the K prime goodness-of-fit test. The expected distribution is a slight modification of the uniform distribution, because the R-R intervals were not of equal length. The expected distribution was calculated by assuming a uniform distribution for each R-R interval and summing up the distribution over the range of R-R intervals (see APPENDIX).

To test whether the duration of R-R intervals was unaffected by individual hiccups, the durations of the R-R intervals just before each hiccup, containing the hiccup, first after the hiccup, and second after hiccup were compiled. The resulting matrix was then tested by using the Kruskal-Wallis rank sum test with the null hypothesis that no difference existed among the four groups. In cases in which a significant difference was found, post hoc analysis with the use of the Wilcoxon signed rank test for paired data was utilized to identify which groups had significant differences.

All statistical analyses were completed by using the S-Plus package (Mathsoft, Seattle, WA).

RESULTS

The subjects were awake during parts of the recordings and in light non-rapid-eye-movement sleep in other parts. State of alertness had no effect on the results reported here.

Stationarity and variance of R-R and H-H intervals. Figure 2, A and B, shows that R-R intervals and hiccup-hiccup (H-H) intervals, respectively, were reasonably stationary over the recording period for each subject. Table 1 shows that the standard deviation of R-R intervals averaged 0.10 s, whereas the standard deviation of H-H intervals averaged 0.67 s.

Timing of hiccups in the cardiac cycle. The distributions of hiccups in the cardiac cycle are shown in Fig. 3. As demonstrated by the Kolmogorov-Smirnov goodness-of-fit test, these distributions were different from the expected uniform distribution in nine subjects (all except subject 5, Table 1). By visual inspection, these nine subjects showed peaks in frequency of hiccups near the middle of the R-R interval, usually just before the midpoint (Fig. 3).

Histograms of the time between each hiccup and the subsequent R wave were also drawn. These histograms, however, give much the same information as the histograms shown in Fig. 3, because the R-R interval in all subjects except subject 10 was nearly fixed (see variance in R-R intervals in Table 1) so that the H-H intervals were almost exactly equal to the mean R-R interval minus the R-H intervals, and the histograms of H-R intervals were mirror images of the histograms of R-H intervals.

Relation between hiccups and the respiratory cycle. Although the thermistor tracings did not permit exact timing of respiration, in some subjects they gave consistent signals approximating sine waves, so that it was possible to ascertain roughly whether hiccups were distributed through the respiratory cycle or usually occurred in the same quarter of the cycle. Those that almost always occurred in the same quarter of the cycle were called synchronized with respiration. Of the seven subjects in whom phase could be determined in this way, four showed synchrony and three did not (Table 2).
Possible influence of hiccups on R-R interval. A possible effect of hiccups on heart rate was examined in all subjects except subject 10, whose electrocardiogram showed a very irregular rhythm because of multifocal atrial ectopic beats. For the remaining nine subjects, the R-R intervals around each hiccup were tabulated (see METHODS). Figure 4 shows scatterplots for three subjects. Statistical testing in subject 1 showed no correlation between R-R interval and time of hiccups. Subject 4, whose hiccups were synchronized with respiration, and subject 6, whose hiccups were not synchronized with respiration, showed slight lengthening of the R-R interval after a hiccup. This can be appreciated by noting that, in subject 4, the third cluster of points is slightly higher than the second cluster, and there is a similar increase in the mean height of points between the hiccup R-wave intervals of 1 and 2 s in subject 6. Kruskal-Wallis tests were positive in five subjects and negative in four (Table 2). Of the five subjects with a significant Kruskal-Wallis test (found to have significant variation in their R-R intervals), three had hiccups that nearly always fell in the same quarter of the respiratory cycle, and two subjects had hiccups that were distributed throughout the respiratory cycle (Table 2).

**DISCUSSION**

In all subjects but one, the data show a significant tendency for hiccups to occur in the same part of the cardiac cycle, near midsystole. We discuss here possible mechanisms for this synchrony and the implications
the findings may have concerning the process for generating hiccups.

Synchrony between hiccup and heartbeat could result from hiccup entraining heart rhythm, or from heartbeat entraining hiccup rhythm, or from a third process entraining both. The first and third possibilities are unlikely on physiological grounds. The cardiac rhythm is determined by its intrinsic pacemaker whose

Table 2. Results of tests of the effect of hiccup on heart rate

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Kruskal-Wallis Statistic</th>
<th>P Value</th>
<th>Pattern</th>
<th>P Value, R-R(−1) vs. R-R(0)</th>
<th>P Value, R-R(0) vs. R-R(1)</th>
<th>P Value, R-R(1) vs. R-R(2)</th>
<th>Synchronized with Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.79</td>
<td>NS</td>
<td>= = =</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>&lt;0.001</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>47.76</td>
<td>&lt;0.001</td>
<td>↓ ↑ ↓</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>&lt;0.001</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>1.84</td>
<td>NS</td>
<td>= = =</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>Uncertain</td>
</tr>
<tr>
<td>4</td>
<td>24.45</td>
<td>&lt;0.001</td>
<td>= = =</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>2.42</td>
<td>NS</td>
<td>= = =</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>34.50</td>
<td>&lt;0.001</td>
<td>= = =</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>2.82</td>
<td>NS</td>
<td>= = =</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Uncertain</td>
</tr>
<tr>
<td>8</td>
<td>37.70</td>
<td>&lt;0.001</td>
<td>= = =</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>44.67</td>
<td>&lt;0.001</td>
<td>= = =</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>Yes</td>
</tr>
</tbody>
</table>

In the 5 subjects for which significant results were found, sequential intervals were compared (i.e., R-R interval previous to hiccup vs. R-R interval encompassing hiccup, R-R(−1) vs. R-R(0), etc.) with the Wilcoxon signed rank tests for paired data to analyze which groups had significant differences. The pattern of variation of R-R interval is displayed with ↓ indicating an increase in R-R interval, ↑ indicating a decrease in R-R interval, and = indicating no significant change in R-R interval compared with the previous R-R interval. The P values for each comparison also appear, along with an indication as to whether hiccups were synchronized to respiration. Yes indicates that hiccups were synchronized to respiration, No indicates that hiccups were not synchronized to respiration, and Uncertain indicates that, due to poor thermistor recording, the degree of synchronization was uncertain.
rate can be influenced by extrinsic autonomic tone. Sympathetic or parasympathetic discharge commanded by a hiccup center could slightly advance or retard individual heartbeats but could not arrange the timing of each beat so systematically in the middle of the R-R interval as was seen in many of our subjects. To shift heartbeat timing to coincide with hiccups would require the variation in the R-R interval to be on the order of one-third to one-half of the R-R interval. The observed variation was much less than that (standard deviation of the R-R intervals averaged 0.10 s). The observation of some synchrony in the subject whose heart rhythm was very irregular because of multiple atrial ectopic beats is further evidence against this possibility.

The more plausible explanation is that heartbeat has an effect on the hiccup generator. The amount of variation found in the interhiccup interval shows that the range of possible adjustment of hiccup timing is sufficient to achieve synchrony. Neural mechanisms do exist by which heartbeat could influence hiccups. Cycles or bursts of discharge generated by heartbeat are found in myelinated afferents from cardiovascular receptors sensitive to blood pressure or atrial or ventricular distension. Baroreceptors show phasic systolic in-

creases in discharge frequency (5). Atrial mechanoreceptors show bursts of activity synchronous with the “a” wave of atrial contraction and the “v” wave of ventricular contraction (10). There are also ventricular mechanoreceptors that may fire in systole (3). Somatic mechanoreceptors in the chest wall (diaphragm or rib cage) may be stimulated when these structures are shaken by systole, as shown by the observation of phasic activity linked to the cardiac cycle in spindle afferents from intercostal muscles (2). Movement of the heart could excite receptors in the stomach or esophagus. It seems likely that beating of the heart sets off a hiccup through one or more of these peripheral sensory inputs.

Not every heartbeat triggers a hiccup, however. Instead, as illustrated in Fig. 5, hiccups tend to occur regularly with every fourth, fifth, or Nth heartbeat, which suggests that there is some other periodic influence modulating the hiccup rhythm. In addition, in many subjects, hiccups occur in all parts of the cardiac cycle, which implies that phasic input from cardiovascular...
lar receptors is not the only important mechanism for setting off a hiccup.

To explain the relation between hiccup and heartbeat, one may postulate that there is a brain stem circuit capable of generating a slowly oscillating signal with a frequency somewhat lower than the mean hiccup frequency. A hiccup is set off when this signal reaches a certain threshold of intensity. Periodic afferent activity produced by heartbeats could interact with the slowly oscillating signal. When the latter is close to threshold, the cardiac input would be sufficient to push the signal above threshold and set off an immediate hiccup. Such an integrate-and-fire model, though, is insufficient to explain all the observed variability in the hiccup data. The cardiac rhythm is not the only factor influencing the timing of hiccups.

Hiccups have been associated with bradycardia (6) and atrioventricular block (4, 12) in clinical case reports. The mean heart rates of the subjects in this study were below usual population means. In five subjects, we observed a phasic variation in heart rate in association with hiccups that might be explained by a fluctuation in parasympathetic or sympathetic influence of the heart due to a hiccup central pattern generator. Also, intrathoracic pressure changes transiently with each hiccup, which can lead to changes in systemic arterial pressure and stroke volume (7). These changes, in turn, may influence the sympathetic and parasympathetic tone and alter heart rate. In the three subjects whose hiccups were tightly synchronized with respiration, the possibility that the variations in the R-R interval are simply a respiratory sinus arrhythmia cannot be ruled out. Recently, more complex interactions between the respiratory and cardiac rhythms have been proposed (11), which may help explain the observed synchrony between hiccup and heartbeat. In the remaining two subjects, the hiccup-associated variation was probably due to the hiccups, which were distributed throughout the respiratory cycle.

APPENDIX

This appendix derives a modified uniform distribution function used in the Kolmogorov-Smirnov goodness-of-fit test. Consider a population of N hiccups (denoted H1, . . . , HN) in N R-R intervals of varying lengths. The null hypothesis is that the hiccups are distributed uniformly throughout the R-R intervals. The probability of a hiccup occurring at time t [PH( t)] within an R-R interval of length Ti is

\[ P_H(t) = \frac{1}{T_i}; \quad 0 \leq t \leq T_i \]

We further assume that each hiccup is an independent event, thus

\[ P_{H1}(t) = P_{H2}(t) = \ldots = P_{Hi}(t) = P_H(t) = \frac{1}{T}; \quad 0 \leq t \leq T \]

where subscript i is interval and T is the mean R-R interval length. If all the R-R intervals are of the same length T, the distribution function for the population is

\[ P_H(t) = \frac{1}{N} \sum_{i=1}^{N} \frac{1}{T_i} = \frac{1}{T} \]

For R-R intervals of different lengths T_i, a hiccup can only occur at time t if t ≤ T_i, i.e.

\[ P_{Hi}(t) = \frac{1}{T_i}; \quad 0 \leq t \leq T_i \]

\[ 0; \quad T_i < t \]

For the population of N hiccups, the distribution function PH(t) is again obtained by summation

\[ PH(t) = \frac{1}{N} \sum_{i=1}^{N} \frac{1}{T_i} = \frac{F_H(t)}{T} \]

where F_H(t) is the number of hiccups whose R-R intervals have T_i ≥ t.

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REFERENCES