Heart rate variability as a measure of autonomic function during weight change in humans

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HIRSCH, JULES, RUDOLPH L. LEIBEL, RONALD MACKINTOSH, AND ANDRES AGUIRRE. Heart rate variability as a measure of autonomic function during weight change in humans. Am. J. Physiol. 261 (Regulatory Integrative Comp. Physiol. 30): R1418–R1423, 1991.—Changes in autonomic function were studied during experimentally induced weight changes in seven subjects. A spectral analysis of heart rate variability (HRV) was used to evaluate autonomic activity during weight change. With a 10% increase in body weight above the usual or starting weight, there was a decline in parasympathetic power accompanied by a rise in mean heart rate. Heart rate declined during weight reduction, but the power of HRV did not change significantly. Because heart rate power at the frequency of respiratory rate can be affected by respiratory rate, three additional subjects were tested at a constant respiratory rate. Weight increases in this group also led to a decline in the power of HRV at a frequency attributable to the parasympathetic nervous system. Such a parasympathetic effect of weight increase may be one mechanism for the arrhythmias and other cardiac alterations that accompany obesity.

parasympathetic activity; sinus arrhythmia; obesity; energy metabolism

BODY WEIGHT AND THE LEVEL of stored calories in humans and animals remain constant over long periods of time, suggesting that integrative control mechanisms couple energy expenditure and food intake. A regulatory system that maintains constant energy storage is likely to involve complex interactions among humoral, neural, metabolic, and psychological factors, and it has been suggested that the autonomic nervous system may be central in the coordination of this system (5). Many experimental observations support this point of view. For example, with a diminution of caloric intake there can be a prompt and major decline in sympathetic activity, although an increase in sympathoadrenal activity has also been documented (12, 18). Also, animals overfeeding on palatable “cafeteria-type” diets increase sympathetic activity, acting in a direction that may mitigate further weight gain (18). Furthermore, exogenously administered sympathetic agonists can be shown to increase caloric expenditure (3). The parasympathetic branch of the autonomic nervous system has not been regularly studied in similar experimental situations, and there is no known mechanism whereby parasympathetic activity can directly influence energy metabolism; nevertheless, parasympathetic blockade by pharmacological means has been shown to influence thermogenesis induced by food intake (6, 11), and a relationship has been found between parasympathetic activity and total energy storage in humans (13). However, the exact role of the autonomic system in modulating energy storage in humans remains difficult to evaluate, and particularly difficult to evaluate is the effect of parasympathetic activity, because there are no easily accessible substances that correlate with the intensity of parasympathetic traffic.

Cardiac function is extremely sensitive to autonomic influences and is therefore an attractive candidate with which to evaluate autonomic status. Furthermore, catecholamine turnover within cardiac tissue has been shown to correlate strongly with autonomic effects that affect energy metabolism elsewhere in the body (10). Heart rate may not be a useful indicator of autonomic function, because it is determined by an unknown mix of sympathetic and parasympathetic inputs. However, the second-to-second variations in heart rate, termed heart rate variability (HRV), have sympathetic and parasympathetic elements that can be analyzed. Sinus arrhythmia or the component of HRV coupled with respiration is primarily vagal or parasympathetic in origin, and other lower-frequency inputs into heart rate, partly sympathetic origin, summate with sinus arrhythmia to produce total HRV. Sayers (15) has pointed out that a spectral analysis of HRV will reveal frequencies much lower than the respiratory frequency (~0.25 Hz), which introduce baroreceptor, thermogenic, and possibly other elements into the variability of heart rate. Akselrod et al. (2) showed that a spectral analysis of HRV in an “awake, adult dog” contains three major peaks: low frequency at ~0.04 Hz, midrange at ~0.12 Hz, and high frequency at 0.4 Hz. The sympathetic, parasympathetic, and the renin-angiotensin systems were believed by these investigators to make specific, pharmacologically isolable contributions to each of these peaks.

To study the effect of weight change on autonomic nervous system in humans, a device as used by Akselrod et al. (2) was built, and HRV was studied in a group of subjects who were being studied during experimentally induced changes in body weight and energy storage.

METHODS

Subjects. Seven adults were studied during weight variations induced by dietary means while hospitalized in
the Clinical Research Center at the Rockefeller University Hospital. These subjects were enrolled in a separate study of the effects of weight change on energy metabolism. Studies of HRV were performed whenever possible as the measurement tools became available. Therefore all subjects were not measured during all dietary periods. Subjects varied in body weight from 66.0 to 141.7 kg at the start of studies. Body mass indexes at that time varied from 23.4 to 49.9, spanning the range from non-obese to morbidly obese (Table 1). No subjects were hypertensive or diabetic. Thyroid status and glucose homocostasis were normal by clinical and laboratory evaluation.

For most of the study, subjects were fed a fluid formula made in the Rockefeller University Diet Kitchen as a sole source of calories. The formula contained 40% of calories as corn oil, 45% carbohydrate as a mixture of cerelose and polycose, and the remaining 15% as milk protein; caloric density was 1.25 kcal/g of formula. Vitamin and mineral supplements, as well as 5 g iodized sodium chloride, were given daily. Water and noncaloric beverages without caffeine were available ad libitum. During periods of weight plateau (for 4–6 wk) subjects were fed the precise amount of formula required to maintain body weight. Figure 1 is a scheme of the weight changes. The initial plateau (S1) was at usual weight whether obese or normal. Other plateaus were at 10% above usual (S2), return in weight to S1 level (S3), ~10% below S1 (S4), and ~25% below S1 (S5). If S1 is represented by 100%, then the precise weights of the seven subjects studied, as percent of S1, were as follows: S2 = 109.5±1.2 (SD), S3 = 99.0±0.8, S4 = 88.3±1.0, and S5 = 73.5±5.3. Weight loss was achieved by feeding 800 kcal/day of the same formula used during maintenance periods. Weight loss periods were named as follows: LM, loss from S2 to initial weight; L10, loss to 10% below initial weight; and L20, loss to 20% below initial weight. Weight gain was achieved by feeding a wide assortment of solid foods to promote relatively rapid weight gain. The weight gain period (GM) separates S1 and S2.

As shown in Table 2, not all subjects were studied in all dietary periods. A total of 46 studies of HRV were done in the 9 dietary periods shown in Table 2 and Figure 1. Too few subjects had data in all dietary periods to permit a thorough statistical analysis of the effects of all dietary periods on HRV; but major dietary effects on HRV, e.g., weight loss or weight gain vs. usual weight, could be statistically evaluated by combining data as described under RESULTS.

Procedure. After at least 4 wk of the same diet and within 1 wk of the end of each plateau of weight constancy, or at the end of periods of weight gain or weight loss, a study of HRV was made. Subjects were studied in the postabsorptive state, between 8:00 and 10:00 A.M., in their own hospital rooms, which were air-conditioned to a temperature close to 22°C. Subjects who were smokers were requested not to smoke on the morning of their test day. While lying in bed, lightly clad, standard electrocardiogram (ECG) leads were placed on the lateral aspects of the thorax at approximately the sixth intercostal space, as well as on the right ankle. The ECG was continuously monitored on an oscilloscope screen. When minute-to-minute heart rate was close to constant and the patient was completely at ease, breathing normally and regularly, a 256-s sample of the ECG was taken and designated as the supine record. Thereafter, subjects were asked to stand at the bedside for 15 min, and at the end of exactly 15 min an additional 256-s sample was taken for the standing record. This was performed to elicit increased sympathetic activity for an evaluation of the effect of diet on this aspect of HRV.

Device. A self-contained microprocessor was built for spectral analyses of HRV in real time at each patient's bedside. The device has been described by Tu (16). ECG and respiratory signals were monitored by means of a Healthdyne Infant Monitor (model 16000; Healthdyne, Marietta, GA). An R wave detector was built, which was a threshold comparator delivering a 5-V square-wave pulse at a specific height of the R wave. The triggering level of the R wave was set by the experimenter so that no heart beats were missed. Square-wave pulses were delivered to a 32 K TRS-80 color computer (Radio Shack, Tandy, Ft. Worth, TX). Data and calculations were plotted after every 256 s of recording on a strip plotter attached to the computer.

TABLE 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>F</td>
<td>164.0</td>
<td>79.6</td>
<td>29.6</td>
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<td>2</td>
<td>48</td>
<td>F</td>
<td>164.0</td>
<td>96.8</td>
<td>36.0</td>
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<tr>
<td>3</td>
<td>20</td>
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<td>168.0</td>
<td>66.0</td>
<td>23.4</td>
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<tr>
<td>4</td>
<td>33</td>
<td>F</td>
<td>169.0</td>
<td>137.8</td>
<td>48.2</td>
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<td>25</td>
<td>F</td>
<td>173.5</td>
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<tr>
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<td>34</td>
<td>M</td>
<td>188.0</td>
<td>94.0</td>
<td>26.6</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>F</td>
<td>165.5</td>
<td>136.7</td>
<td>49.9</td>
</tr>
</tbody>
</table>

BMI, body mass index = weight (kg)/[height (m)]²; M, male; F, female.

![FIG. 1. A schematic representation of weight changes in experimental subjects. See text for description of groups.](chart)

TABLE 2. Patient weights at time of study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>GM</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>96.8</td>
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<tr>
<td>3</td>
<td>66.0</td>
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<td>6</td>
<td>94.0</td>
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<tr>
<td>7</td>
<td>136.7</td>
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</tbody>
</table>

Values are in kg. See text for definitions of groups.
Analysis. During each 256-s sampling of heart rate, the computer developed a wave form of the smoothed beat-to-beat instantaneous heart rate (i.e., 1/R-R interval × 60). This is plotted as the first panel of the computer printout (see Fig. 2A). The ordinate is labeled as beats per minute (bpm) and the length of the wave form, as indicated, is 256 s. The wave form was sampled by the computer at a frequency of 4 Hz, providing a total of 4 × 256 (i.e., 1,024) samples of the curve of instantaneous heart rate over each 256-s interval. A fast Fourier transform is performed on these samples by the microcomputer, and the power density spectrum was then computed. The spectral display (Fig. 2B) consists of each element of the Fourier transform squared, plotted from 0 to 2 Hz. Mean heart rate is printed below, as well as the peak power or the power of the largest element of the Fourier series in arbitrary units. The ordinate maximum is fixed to equal the peak power. Figure 2C is the integral of the power spectrum or cumulative spectrum from 0 to 2 Hz; the numerical value of the total power (all elements summed) is also given. Low power is set to give the amount of power, i.e., variation in the wave form, attributable to frequencies occurring between 0.04 and 0.1 Hz (2.4–6 cycles/min). The next designation is the power occurring at the respiratory frequency ±0.06 Hz. An input into the computer permits prior designation of respiratory frequency, which is determined by clinical observation just before the recording is made. Finally, the ratio of low to respiratory power is calculated and printed. Figure 2D is a simultaneously derived power spectrum of the signal recorded from the respiratory sensor of the Healthdyne Infant Monitor. The large peak in the respiratory frequency was examined, and if it was found to be essentially the same as the observed respiratory frequency measured clinically, then the record was used. If there were motion artifacts or great variations in respiratory frequency, then the record was redone. This was required in about one out of every four recordings. A repeat record was made after the subjects had stood at the bedside for 15 min.

Inspection of Fig. 2C shows that it is possible to estimate the power of HRV for various frequencies from 0 to 2 Hz by noting the change in the ordinate between any specified frequencies. Initially, this was performed at various frequencies to estimate power at very low or other frequencies; however, it became evident that the findings to be described are demonstrable using power at low frequency (0.04–0.1 Hz) and respiratory frequency (respiratory rate ±0.06 Hz), powers that are calculated by the device. These two powers, labeled L and R, as well as heart rate and respiratory rate were used for analysis of the findings. L and R as given by the device are in units of power of HRV equal to the product of beats per minute squared and N²/2, where N equals 1,024 or the number of samples in 256 s [i.e., (bpm)² × N²/2] (4, 16). Data were therefore converted into (bpm)² by dividing L and R by (1,024)²/2, i.e., 2³. HRV power was further normalized for statistical analysis by logarithmic transformation.

RESULTS

Figure 2 shows typical results. These were obtained on a 21-yr-old, moderately obese female. In Fig. 2, left, data are shown that were obtained in the supine position. The respiratory frequency was noted clinically to be 0.2 Hz and corresponded well with the measure shown in Fig. 2D, left. The wave form of instantaneous heart rate in Fig. 2A has a frequency of ~10–12 cycles/min, i.e., there are ~5–6 crests and troughs per unit of time on the abscissa. (The time units of the abscissa are one-tenth of 256 s, i.e., close to 0.5 min.) These waves correspond to the respiratory rate of 0.2 Hz (12 cycles/min), and the spectral analysis (Fig. 2B) clearly shows a major peak at 0.2 Hz. The 0.2-Hz peak (±0.06 Hz) contains almost one-half of the total power and is about five times greater than the low power at 0.04–0.1 Hz. However, it is clear that there are additional frequencies even lower than 0.04 Hz that contribute to the total power. All peaks lower than 0.2 Hz are a mixture of parasympathetic and sympathetic activities of different types including baro-receptor and thermogenic inputs to HRV (8, 9). All data used for calculations were obtained from the record. L is

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**FIG. 2.** A typical analysis of heart rate variability in a 21-yr-old subject. BPM, beats/min; Int, total power value; Low Pow, low power; Lo/Resp, ratio of low to respiratory power.
low power shown as 791.296.004 in the supine position, and R is 0.2-Hz power shown as 3,516.672.02. By the calculation described above, these become 1.5093 and 6.7075 (bpm)$^2$. Heart rate is shown as 56.8164063, and the respiratory rate is 0.2 Hz, i.e., 12 cycles/min.

Figure 2, right (labeled standing), shows that a brief period (15 min) of standing, during which sympathetic activity is likely to have increased, had major effects. Thus heart rate increased from 57 to 96 bpm. It is also evident that Fig. 2A, right, showing instantaneous heart rate, has a predominant frequency much slower than that shown in the supine or resting position. The peaks and troughs number only 2–3 per 0.5 min, corresponding to a major peak in the spectral power plot of Fig. 2B at 0.08 Hz (4.8 cycles/min). This is likely to be baroreceptor input that occurs upon standing (8). It is also notable that the major frequencies in Fig. 2A at 0.08 Hz have an additional periodicity, waxing and waning at about three or four times over the 256 s of recording (a frequency of roughly 0.01–0.02 Hz). The power of these very low frequencies is seen as the short segment of the cumulative or integral curve in Fig. 2C to the left of the major rise that begins just beyond 0.05 Hz. The respiratory power at 0.2 Hz is barely visible in Fig. 2B. Similar changes in HRV and in the spectral distribution of power were found in many of the subjects across all dietary periods. There appeared to be no systematic change in standing power as a function of diet, but the data points were too few for statistical evaluation. The dietary effects will therefore be described in detail from data obtained with subjects in the supine position.

Figure 3 shows data obtained on HRV in the supine position in various dietary periods. HRV is given as the logarithm of L and R in (bpm)$^2$, derived as described above. Because too few data points were available for an analysis of the effects of each dietary manipulation, data were analyzed in pairwise comparisons addressed to specific dietary manipulations of interest. Thus data from five of the subjects studied at both S1 and S3 were used to examine whether a repeat study at usual weight, i.e., S1 vs. S3, showed any effect. As shown in the first column of Fig. 3, no significant effects were found in heart or respiratory rate or in HRV at L and R frequencies. Data on weight gain GM vs. usual weight are shown in the second comparison of Fig. 3. When both S1 and S3 usual weight data were available, the means of S1 and S3 were compared pairwise with GM. As can be seen, weight gain (GM) is accompanied by a significant increase in heart rate and a decline in R, HRV at respiratory frequency. Data on weight loss (L10, L20) and the maintenance of lower...
than-usual bodyweight, S4 S5, led to a decline in heart rate that was significant only during weight loss as shown in Fig. 3. Significant changes in HRV were not found in this small group of subjects, although in some individuals weight loss was accompanied by sharp increases in HRV at the respiratory frequency.

**DISCUSSION**

The findings document the utility of a noninvasive tool for the analysis of autonomic nervous system activity in humans. Although spectral analysis of IIRV has been utilized in the past to document a variety of physiological events (1, 14), this technique has not been used, to our knowledge, to examine autonomic variation induced by diet and weight change in humans. It is of interest that the only changes which could be statistically documented were in respiratory frequencies that are attributed to parasympathetic rather than to sympathetic activity. Studies of the autonomic nervous function by other methods during nutritional alteration have usually documented the importance of the sympathetic division (10). In the measures described in this report, R is likely to be a valid estimate of parasympathetic function; however, L is a mixture of parasympathetic and sympathetic activities. It is therefore no surprise that specific alterations in sympathetic activity would not be discerned. We have recently had the opportunity to study one individual undergoing weight changes as described in the current studies, utilizing spectral analysis of HRV as well as a pharmacological dissection of HRV by observing the effects of a muscarinic blockade by intravenous atropine and β-sympathetic blockade by a relatively cardioselective blocker, esmolol. It was encouraging to note the same decline in parasympathetic activity, i.e., a lessened rise in heart rate after muscarinic blockade, when weight increased. There were no significant changes in sympathetic function as measured by the effect of esmolol in heart rate across dietary periods.

The relevance of parasympathetic change to the regulation of energy metabolism is unknown. It is not known whether cardiovascular responses to weight change, mediated through parasympathetic effects, will occur in other organ systems as well. Nevertheless, a relationship between weight change and parasympathetic cardiac activity is of considerable interest in its own right, because alterations in vagal activity may constitute a specific risk factor for arrhythmias or other cardiac disorders (7). What fraction of the cardiac disability of obesity might occur via this mechanism should be an important matter for further study.

To address some of these points, we are now examining a larger number of subjects with a more sensitive and reliable device for measuring HRV (19), and we are combining the studies with pharmacological dissection of HRV as well as pupillometric analysis. We are also making repeat studies of HRV in the same individual under precisely specified dietary conditions, to evaluate the level of day-to-day variation. Variations are sufficiently small for the detection of dietary effects as already described. In one recently studied subject, HRV was measured four times over 27 days while on Sl. IIRV at the respiratory frequency averaged 0.5889[log(bpm)] with a coefficient of variation (cv) of 16.7%. Heart rate was 56.6 bpm (cv = 24%). Four measures over 6 days on diet GM showed a decline of HRV at the respiratory frequency to 0.257[log(bpm)] (cv = 15.7%). Heart rate rose to 70 bpm (cv = 3.3%). Such dietary induced changes are significant at levels of 0.008 for HRV and 0.001 for heart rate. Additional studies are in progress to determine the reproducibility of such findings in large numbers of outpatient obese and nonobese subjects. The finding of parasympathetic alterations in HRV, carried at the frequency of breathing, will also necessitate further studies of respiratory kinetics during weight change.

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**Fig. 4.** Effect of a 10% increase in body weight on HRV as studied in 3 subjects, with all measurements made at a constant respiratory rate of 0.24 Hz.


