

# Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate

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HIRSCH, JUDITH ANN, AND BEVERLY BISHOP. *Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate.* Am. J. Physiol. 241 (*Heart Circ. Physiol.* 10): H620-H629, 1981.—The relationship of respiratory sinus arrhythmia amplitude (RSA) to tidal volume and breathing frequency was quantified during voluntarily controlled tidal volume and breathing frequency and spontaneous quiet breathing. Seventeen seated subjects breathed via mouthpiece and noseclip, maintaining constant tidal volumes at each of several breathing frequencies. Inspiratory breath hold was zero frequency. Log RSA was plotted vs. log frequency for each tidal volume. The large stable RSA for frequencies less than 6 cycles/min was called low-frequency intercept (LFI,  $20 \pm 5$  beats/min). Low-frequency intercept was inversely proportional to a subject's age only to 35 yr. At higher breathing frequencies above a characteristic corner frequency ( $f_C$ ,  $7.2 \pm 1.5$  cycles/min) RSA decreased with constant slope (roll-off;  $21 \pm 3.4$  dB/decade). The RSA-volume relationship was linear permitting normalization of RSA-frequency curves for tidal volume to yield one curve. Spontaneous breathing data points fell on this curve. Voluntarily coupling of heart rate to breathing frequency in integer ratios reduced breath-by-breath variability of RSA without changing mean RSA. In conclusion, low-frequency intercept, corner frequency, and roll-off characterize an individual's RSA-frequency relationship during both voluntarily controlled and spontaneous breathing.

tidal volume and heart rate; breathing frequency and heart rate; lung volume and heart rate; breath hold and heart rate

AT REST the heart rate increases on inspiration and decreases on expiration. This variation in beat-to-beat interval, which occurs during a respiratory cycle, has been of interest to cardiopulmonary physiologists since the middle of the last century (25). Although this phenomenon is called the respiratory sinus arrhythmia (RSA), rhythmic breathing movements are not required for its appearance. For example, a modulation of heart rate similar in time course may be seen at the onset of an inspiratory breath hold (5, 6, 30) and just before the termination of a prolonged breath hold (30).

Other investigators have studied the separate effects of breathing frequency, tidal volume, and static lung volume on the RSA amplitude (1, 24, 26, 28, 32) and wave form (5, 33) or phase angle (1, 20, 21, 24, 33). It has been demonstrated that when breathing frequency is increased, the amplitude of the heart rate oscillation decreases (1, 6, 21, 24, 28, 33), and when tidal volume (6, 8,

26, 28, 32) or static lung volume (11, 30) is increased, the amplitude of the heart rate modulation increases. In most of these studies the values for the amplitude of the RSA were obtained during spontaneous breathing with no voluntary control of tidal volume and breathing frequency (28, 29, 32) or with control of only one of these variables (6, 8, 26). A few studies have been designed to measure RSA during different breathing frequencies with controlled chest circumference (1), peak flow (6), or tidal volume (20, 21, 33); however, these studies were not designed explicitly to assess the relationship of the amplitude of the RSA to multiple tidal volumes over a wide range of controlled breathing frequencies. Thus the purpose of the present study was to define and characterize the relationship between the amplitude of the RSA and the breathing pattern when both tidal volume and breathing frequency were voluntarily controlled in healthy adults and to compare the amplitude of RSA to that obtained during spontaneous quiet breathing.

## METHODS

### Subjects

Ten men and seven women (22–78 yr) with no history of cardiopulmonary disease participated in this study (Table 1). All subjects engaged in regular physical activity and had resting heart rates of 59–78 beats/min. Twelve subjects had never smoked, and only 1 (*subj 5*) was currently a smoker (1½–2 pks/day). These individuals had participated in extensive respiratory studies for several years and were accustomed to all of the experimental conditions. Subjects were never informed either before or after an experiment about the specific purpose of the experiment. Since ventilatory and circulatory variables are known to exhibit diurnal variations (4, 15), each subject's experiments were performed at the same time of day, 2–4 h after the last meal or caffeinated beverage.

### Experimental Arrangement

The subjects were seated and breathed on a mouthpiece with noseclip from a bag-in-box system (Fig. 1). All signals were simultaneously recorded on a Grass polygraph (model 7D). Raw electrocardiogram activity (ECG) was recorded and played through a Grass tachograph (model 7P4), which converted the *R-R* interval to

heart rate. ECG could also be monitored with a Grass audioamplifier (model AM8). Oxygen and carbon dioxide were monitored at the mouth with a Vacumetrics mass spectrometer (model RMS-3). Inspired airflow was measured with a heated mesh-screen pneumotachometer (Hans Rudolph, model 3700) and was integrated (Grass, model 7P10) to obtain tidal volume. Changes in lung volume also were recorded with a wedge spirometer (Custom Engineering and Development, model 170). The

RSA was determined from the difference between the maximum heart rate after the onset of inspiratory flow and the immediately following minimum heart rate. A sample record is shown in Fig. 2.

#### Experimental Protocols

**Series I. A. SINUSOIDAL TIDAL VOLUME AT DIFFERENT BREATHING FREQUENCIES.** Each subject monitored his

TABLE 1. Subject characteristics

Subj No.	Sex	Age, yr	Ht, cm	Wt, kg	Resting HR, beats/min	VC, liters	Pk-Yr, pk·day <sup>-1</sup> /yr
1	M	30	183	91	72 ± 2.6	5.5	0
2	F	29	175	66	59 ± 1.1	4.5	0
3	F	27	185	67	64 ± 0.3	3.9	0
4	F	25	163	53	62 ± 0.7	3.5	0
5	M	32	188	72	76 ± 2.2	5.9	11
6	F	22	165	58	76 ± 1.2	3.2	1
7	F	24	157	50	74 ± 0.9	3.2	4.5
8	M	25	180	75	60 ± 0.4	5.7	0
9	F	72	161	57	78 ± 1.4	3.0	4
10	M	78	180	89	60 ± 1.5	5.3	42
11	M	45	188	82	81 ± 1.7	6.0	0
12	M	44	168	73	70 ± 1.1	4.8	0
13	M	47	173	66	65 ± 1.3	4.5	0
14	M	29	183	75	67 ± 4.1	5.0	0
15	M	36	178	79	62 ± 2.5	5.5	0
16	F	58	163	56	86 ± 1.0	2.8	0
17	M	37	177	81	80 ± 1.8	3.7	0

Resting heart rate determined over multiple 2-min periods of quiet breathing during steady state;  $\pm$  SD reflects variation in mean HR between different days. VC, vital capacity; Pk-Yr denotes subject smoking history (no. of packs/day  $\times$  no. of yr.).

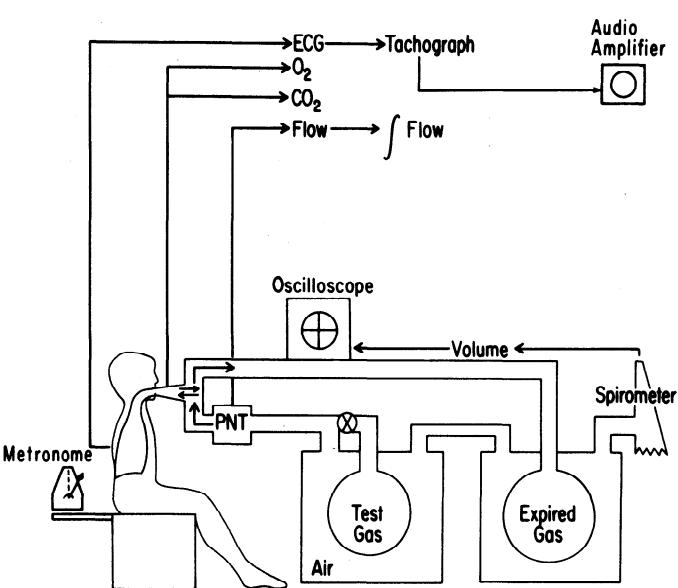


FIG. 1. Experimental set-up. Subject breathes via mouthpiece and nonrebreathing valve from a bag-in-box system as shown. Pneumotach (PNT) flow, spirometer volume, O<sub>2</sub> and CO<sub>2</sub> gas concentrations, ECG and tachograph output are continuously recorded on magnetic tape and polygraph paper.

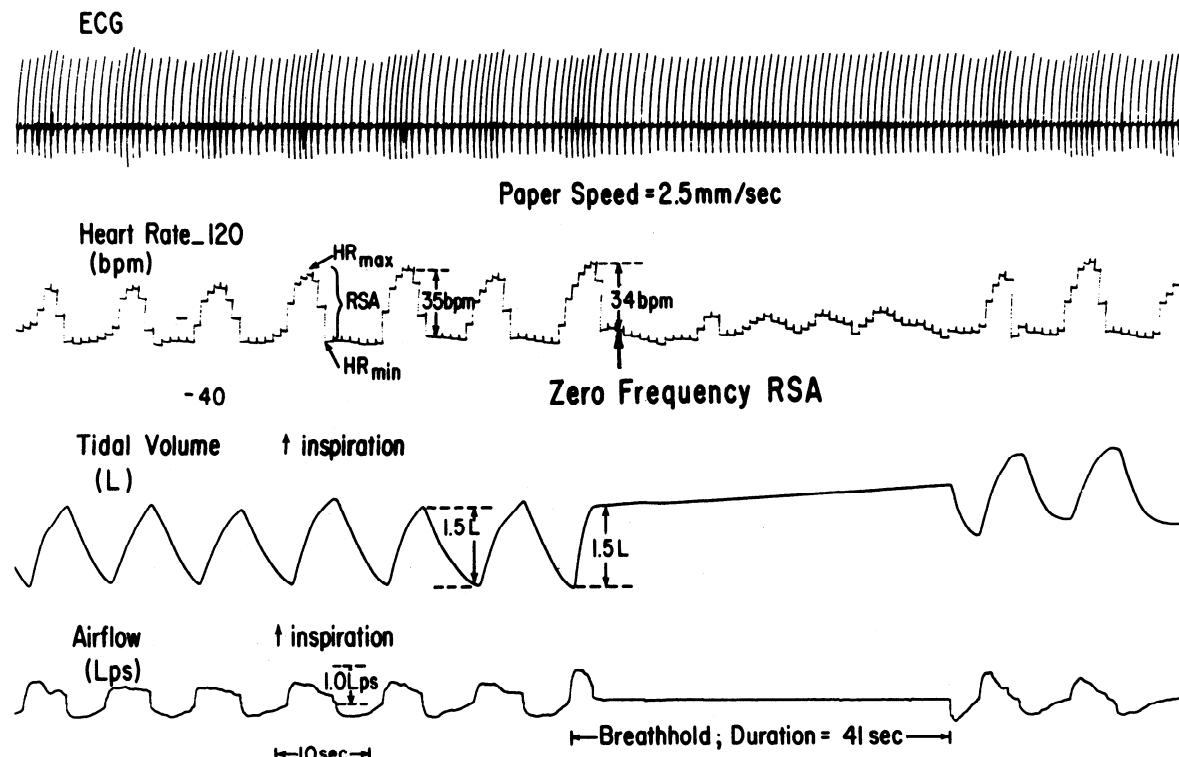


FIG. 2. Polygraph record showing oscillations in heart rate that occur during slow deep breathing and inspiratory breath hold. Traces

from top down are: ECG, heart rate obtained with an ECG tachograph, wedge spirometer volume, and pneumotach airflow.

own tidal volume, flow rate, and breathing frequency on an oscilloscope (Tektronics, model 564). A metronome (Seth Thomas, model 1104), which was set to 60 beats/min, assisted the subject in controlling breathing frequency. After a few minutes of practice all subjects were able to control both tidal volume (<10% of mean) and breathing frequency (5–12% of mean). Once an experiment had begun, the subject was instructed to keep his tidal volume sinusoidal and at a specified amplitude (1, 7, 27, 35) while breathing at several assigned breathing frequencies between 1 and 60 cycles/min. The subject breathed at each frequency for at least 1 min or 10 breaths. No fewer than three experiments were carried out at three different tidal volumes.

**B. WHOLE NUMBER RATIO.** In other experiments, the subject was instructed to maintain a constant tidal volume while coupling his breathing frequency to his mean heart rate by inspiring for six heartbeats and exhaling for six heartbeats (13). This procedure resulted in 12 heartbeats per breath, giving whole number ratio of 12:1. The subject repeated the maneuver for additional ratios of heartbeats per breath, ranging from 2:1 to 14:1. The whole number ratio maneuver resulted in breathing frequencies of about 5–40 cycles/min, a nonsinusoidal tidal volume associated with a controlled inspiratory airflow, and a passive expiration followed by an expiratory pause. The subject breathed at each whole number ratio for at least 1 min or 10 breaths. Each experiment was performed at two or more tidal volumes.

**Series II. A. ZERO BREATHING FREQUENCY.** At the end of the preceding experiments, the subject was instructed to perform a quick (i.e., square wave) inspiratory breath hold at an equivalent volume to the specified tidal volume. The zero-frequency RSA is defined as the first oscillation in heart rate during breath hold (Fig. 2). This maneuver was repeated several times, in each case, after end-tidal gases had returned to control values. The reported zero-frequency RSA is the mean of these repeated observations. The breath hold was maintained until breaking point to observe if any further heart rate modulations occurred.

**B. SPONTANEOUS QUIET BREATHING.** All of the preceding experimental conditions demanded that a subject exercise considerable volitional control over the respiratory act. It is not known whether this voluntary effort influences the relationships between the amplitude of the RSA, tidal volume, and breathing frequency. Therefore breath-by-breath data were collected during spontaneous quiet breathing, which in conscious man is characterized by variable breathing frequencies ( $SD/mean = 38\%$ ) and tidal volumes ( $SD/mean = 26\%$ ). The values of RSA amplitude measured during these periods of quiet breathing were normalized for tidal volume (as described in *Data analysis* below) and compared at each breathing frequency with those values obtained from the *Series IA*, *IB*, and *IIA* experiments using the paired *t* test and analysis of variance.

**Data analysis.** The values of the amplitude of RSA for each subject (Fig. 2) were plotted vs. the breathing frequency on a log-log scale (7, 27; as exemplified by the data of Fig. 3, A and B). A least-squares line was then fitted to the data points for low breathing frequencies

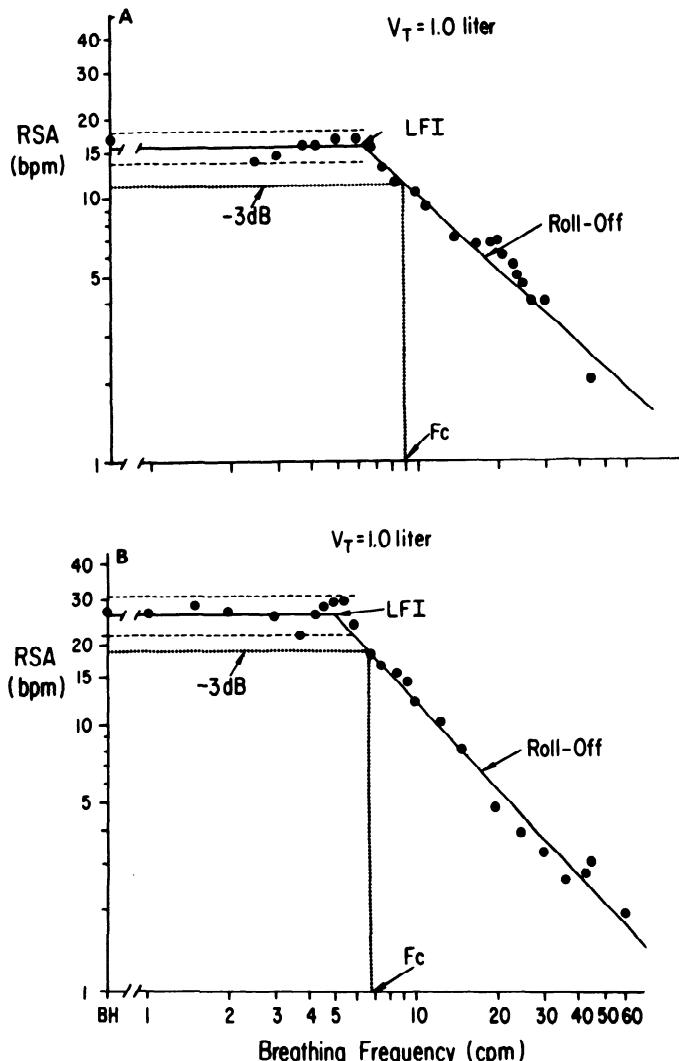


FIG. 3. Bode amplitude plot [log respiratory sinus arrhythmia (RSA) vs. log breathing frequency] for subject 5 (A) and subject 3 (B) breathing air at 1.0-liter tidal volume. Solid lines, least-squares regression lines. Dashed lines indicate  $\pm 2$  SD. LFI, low-frequency intercept. Dotted lines are  $-3$  dB level ( $0.707 \times LFI$ ).  $f_c$  is corner frequency.

below 6 cycles/min. The low-frequency intercept was the RSA amplitude at which that least-squares line intersected the ordinate. A second least-squares line was fitted to the data points for breathing frequencies above 6 cycles/min. The slope of this line in decibels per decade defined the system roll-off. The intersection of these two regression lines occurred at 6.4 cycles/min (subj 5) and 5.0 cycles/min (subj 3), ranging from 3 to 7 cycle/min. The value of RSA at that intersection point was multiplied by 0.707, giving a value for RSA which was 3 dB below the low-frequency intercept(7) and which fell on the roll-off curve. The breathing frequency at which that value of RSA occurred was defined as the corner frequency.

To test whether the system behaves linearly (7, 27), we normalized RSA for tidal volume over the entire breathing frequency range as follows. The RSA obtained during breath hold (i.e., zero-frequency RSA) was plotted vs. breath-hold volume above the end-expiratory lung volume during the quiet breathing immediately preced-

ing the breath hold. A regression line was calculated from these data and the  $y$ -intercept ( $Y_0$ ) was determined for each subject. The following empirically determined function was used to calculate the normalized RSA

$$RSA' = \frac{RSA - Y_0}{V} + Y_0 \quad (1)$$

where

$RSA'$  = normalized RSA in beats·min<sup>-1</sup>·liter<sup>-1</sup>

$RSA$  = RSA at each breathing frequency for every breath-hold volume or tidal volume

$Y_0$  = the  $y$ -intercept of the regression line for RSA vs. breath-hold volume (i.e., the theoretical RSA at the end-expiratory lung volume)

$V$  = the breath-hold volume or tidal volume at which the RSA was measured.

[See RESULTS: Effects of Breath-hold Volume on RSA Amplitude (Series IIA)]

## RESULTS

### Effects of Breathing Frequency on RSA (Series I)

In series IA experiments the amplitude of the RSA was measured during constant sinusoidal tidal volume. The results from one experiment in subject 5 are shown in Fig. 3A. The zero-frequency RSA value obtained during breath hold is the data point at 17 beats/min on the ordinate. The data points represent the mean RSA for at least 10 breaths. The extrapolated low-frequency RSA value shown by the low-frequency intercept of the solid line is  $15.5 \pm 1.0$  beats/min. The corner frequency is 8.9 cycles/min. At higher frequencies the amplitude of the RSA decreases significantly, and the slope of this roll-off is 19.4 dB/decade. Figure 3B shows an analogous curve for the data of one experiment for subject 3 who had a higher low-frequency intercept ( $26.6 \pm 2.2$  beats/min). Corner frequency is 6.7 cycle/min, and roll-off is 21.8 dB/decade. Table 2 shows the low-frequency intercepts (LFI), corner frequencies, and roll-offs for 14 subjects during three to six series IA experiments. Each subject had a stable large-amplitude RSA at all breathing frequencies between zero and the corner frequency. The mean RSA at each breathing frequency below the corner frequency varied from the low-frequency intercept by less than  $\pm 4$  beats/min, well within the 95% confidence limits of the least-squares regression line (dashed lines of Fig. 3). Corner frequency was relatively fixed in a given subject and varied from 4 to 10 cycles/min among the subjects. Above the corner frequency the amplitude of RSA decreased proportionately to the increase in breathing frequency. The slope of this decrease varied from 15.9 to 24.3 dB/decade among the subjects. Our results confirm the observations of other investigators (1, 6, 20, 21, 24, 28, 35) who have demonstrated that RSA is a frequency-dependent phenomenon.

As can be seen from standard deviations of the low-frequency intercepts in Table 2, the values of RSA amplitude obtained breath-by-breath at low frequencies showed considerable within-subject variability. Weiss and Salzano (33) suggested that the variance of RSA was minimized and the amplitude of RSA was maximized

when breathing frequency was coupled to the heart rate in a whole number ratio. Our series IB experiments examined the effects of voluntary coupling of heart rate and breathing frequency on RSA amplitude and variance. The results are shown for 13 subjects in Table 3. We found no significant differences between the mean values of RSA amplitude of the series IA (Table 2) and series IB (Table 3) experiments. The coefficient of variation (SD/mean) for the low-frequency intercepts obtained

TABLE 2. Mean LFI,  $f_c$ , and roll-offs for the RSA amplitude-frequency relationship during constant sinusoidal tidal volumes (Series IA)

Subj No.	No. of Expts	LFI, beats·min <sup>-1</sup> ·liter <sup>-1</sup>	Coef of Variation, SD/mean	$f_c$ , cycles/min	Roll-Off, dB/decade
1	6	$19.9 \pm 5.2$	0.26	$7.5 \pm 0.2$	$21.8 \pm 1.9$
2	6	$22.3 \pm 3.4$	0.15	$4.3 \pm 0.3$	$19.9 \pm 0.6$
3	6	$24.4 \pm 3.5$	0.14	$6.2 \pm 0.3$	$19.1 \pm 2.4$
4	3	$24.0 \pm 5.0$	0.21	$6.0 \pm 0.5$	$19.0 \pm 2.3$
5	6	$15.0 \pm 2.7$	0.17	$9.0 \pm 0.4$	$19.6 \pm 1.6$
6	6	$28.3 \pm 3.3$	0.12	$7.2 \pm 0.5$	$24.3 \pm 4.8$
7	6	$27.4 \pm 6.1$	0.22	$8.0 \pm 0.9$	$22.5 \pm 1.4$
8	5	$25.3 \pm 5.4$	0.21	$6.3 \pm 0.4$	$23.1 \pm 3.5$
9	3	$17.1 \pm 2.8$	0.16	$9.4 \pm 0.4$	$18.6 \pm 0.9$
10	3	$14.9 \pm 1.9$	0.13	$7.3 \pm 0.3$	$15.9 \pm 0.8$
14	3	$19.6 \pm 3.1$	0.16	$6.7 \pm 0.7$	$23.5 \pm 2.6$
15	3	$19.7 \pm 3.0$	0.15	$5.5 \pm 0.3$	$19.2 \pm 0.8$
16	3	$17.0 \pm 2.5$	0.15	$9.2 \pm 0.2$	$18.7 \pm 2.5$
17	3	$15.0 \pm 3.2$	0.21	$8.8 \pm 0.4$	$23.9 \pm 2.1$
Mean		21.2		7.1	20.4
$\pm SD$		$\pm 4.4$		$\pm 1.5$	$\pm 2.4$
Coef of Variation		$17.2 \pm 4.2\%$			

Values for low-frequency intercept (LFI), corner frequency ( $f_c$ ), and roll-off are means  $\pm$  SD.  $n = 14$ .

TABLE 3. Mean LFI,  $f_c$ , and roll-offs for the RSA amplitude-frequency relationship during whole number ratio experiments at constant tidal volume (Series IB)

Subj No.	No. of Expts	LFI, beats·min <sup>-1</sup> ·liter <sup>-1</sup>	Coef of Variation, SD/mean	$f_c$ , cycles/min	Roll-Off, dB/decade
3	6	$28.3 \pm 2.3$	0.08	$6.6 \pm 0.4$	$21.6 \pm 2.8$
5	8	$18.7 \pm 2.0$	0.11	$7.7 \pm 0.5$	$17.8 \pm 3.7$
6	6	$27.5 \pm 1.6$	0.06	$7.8 \pm 0.4$	$23.7 \pm 3.9$
7	6	$27.1 \pm 3.0$	0.11	$8.1 \pm 0.6$	$21.7 \pm 1.1$
8	5	$26.0 \pm 3.5$	0.13	$6.2 \pm 0.3$	$23.4 \pm 0.6$
9	2	$17.6 \pm 1.7$	0.10	$8.7 \pm 0.6$	$16.4 \pm 2.8$
10	2	$15.4 \pm 1.8$	0.12	$6.7 \pm 0.2$	$16.9 \pm 1.9$
11	2	$15.3 \pm 1.5$	0.10	$8.4 \pm 0.8$	$23.9 \pm 1.3$
12	2	$12.9 \pm 2.1$	0.16	$5.9 \pm 0.4$	$18.4 \pm 2.5$
13	2	$14.9 \pm 2.3$	0.15	$7.2 \pm 0.7$	$20.0 \pm 1.7$
14	2	$19.5 \pm 1.6$	0.08	$5.9 \pm 0.2$	$20.7 \pm 1.9$
15	2	$22.7 \pm 1.9$	0.08	$6.7 \pm 1.4$	$21.3 \pm 1.2$
17	2	$15.4 \pm 1.1$	0.07	$8.2 \pm 0.3$	$23.3 \pm 1.1$
Mean		20.1		7.2	20.7
$\pm SD$		$\pm 5.6$		$\pm 1.0$	$\pm 2.6$
Coef of Variation		$10.7 \pm 3.0\%$			

Values for low-frequency intercept (LFI), corner frequency ( $f_c$ ), and roll-off are means  $\pm$  SD.  $n = 13$ .

during the whole number ratio experiments was significantly less ( $10.7 \pm 3.0\%$ ) than that for the low-frequency intercepts obtained during the sinusoidal tidal volume experiments ( $17.2 \pm 4.2\%$ ; Table 2). Hence our results show that the major effect of coupling heart rate and breathing frequency at a fixed tidal volume is to minimize the variability of RSA, with little effect on the mean value of RSA, corner frequency, or roll-off.

#### Effects of Tidal Volume on RSA Amplitude

The family of curves shown in Fig. 4 demonstrates the effect of tidal volume on the RSA amplitude-frequency relationship. The curve marked 1.0 liter is the same as that in Fig. 3A. When tidal volume is decreased from 1.0 to 0.5 liter, the low-frequency intercept decreases from 15.5 to 10.4 beats/min in this subject. When tidal volume is increased from 1.0 to 3.0 liters, low-frequency intercept increases from 15.5 to 30.3 beats/min. Thus the amplitude of RSA changes in concert with the tidal volume, confirming the suggestion of Luczak and Raschke (24) and the observations of Eckoldt and Schubert (8) that RSA is also tidal volume dependent. In contrast to the RSA amplitude, the corner frequencies and roll-offs of these curves remain constant regardless of the tidal volume. Thus the amplitude-frequency and amplitude-volume relationships appear to be independent.

#### Effects of Breath-Hold Volume on RSA Amplitude (Series IIA)

The previous experiments demonstrated that the RSA amplitude was related to the dynamic changes in lung volume. The series IIA or breath-hold experiments were designed to examine the effects of static or step changes in lung volume on RSA by measuring the amplitude of the first oscillation in heart rate during inspiratory breath holds at different lung volumes. The results are shown for two subjects (subj 5 and 7) in Fig. 5. Subject 5 is a tall large male with a large vital capacity and low RSA

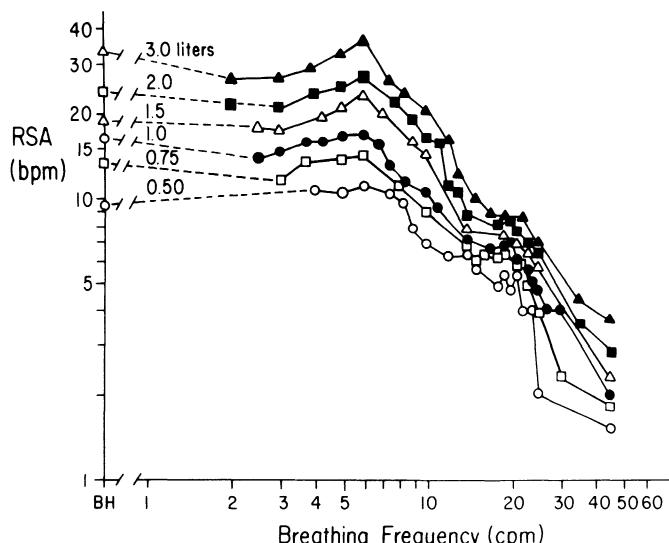


FIG. 4. Log respiratory sinus arrhythmia (RSA) vs. log breathing frequency for 6 different tidal volumes (0.5–3.0 liters). Subject 5 breathing air.

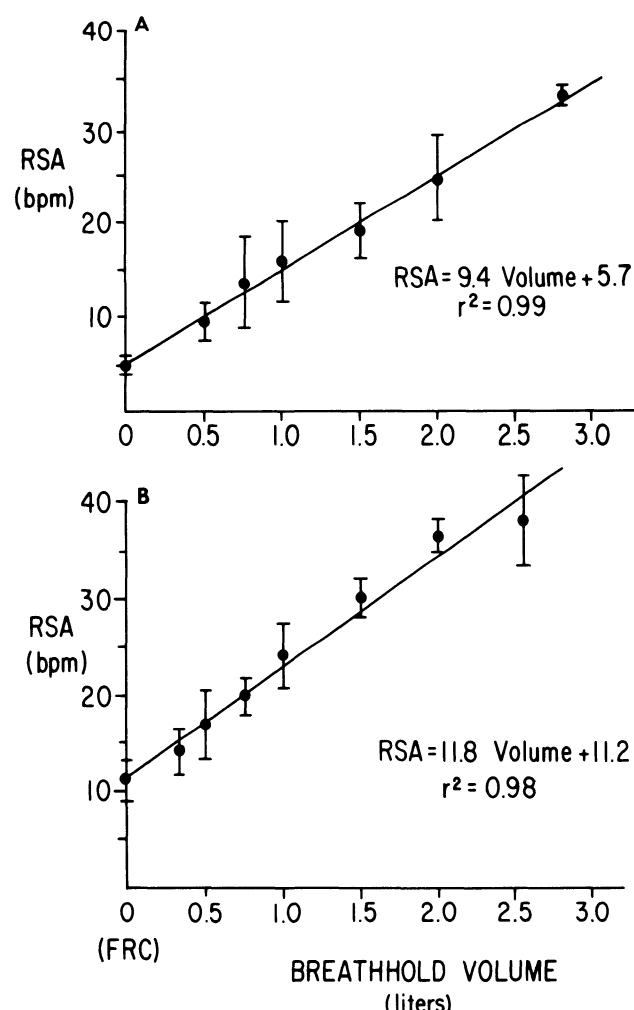


FIG. 5. Respiratory sinus arrhythmia (RSA) during inspiratory breath holds as a function of lung volume above functional residual capacity (FRC). A: subject 5. B: subject 7. Points and bars represent means  $\pm$  SD.

amplitude. Subject 7 is a short small female with a small vital capacity and a large RSA amplitude. In both subjects RSA amplitude is higher at the higher breath-hold volumes, and the amplitude-volume relationship may be well defined by a straight line ( $r^2$  values  $>0.9$ ). The slopes, intercepts, and  $r^2$  values of the RSA amplitude-volume relationship are listed for all the subjects in Table 4. These amplitude-volume relationships were linear in every subject, with  $r^2$  values ranging from 0.85 to 0.99. All slopes were positive, ranging from 6.4 to 13.8 beats·min $^{-1}$ ·liter $^{-1}$ . The  $y$ -intercepts, ranging from 5.7 to 12.9 beats/min, were similar in amplitude to the heart rate oscillation at the beginning of an expiratory breath hold at functional residual capacity.

#### RSA Amplitude Normalized for Tidal Volume

The relationship between RSA and breath-hold volume described above suggested that the system responds as if it were linear (7, 27). Thus to determine the range of frequencies over which the RSA amplitude-volume behavior is linear, RSA was normalized for tidal volume at each breathing frequency as described in METHODS (Eq. 1).

TABLE 4. Amplitude of RSA during inspiratory breath hold at different breath-hold volumes

Subj No.	Slope, beats·min <sup>-1</sup> ·liter <sup>-1</sup>	y-Intercept, beats/min	r <sup>2</sup>
1	12.0	11.9	0.94
2	12.5	12.9	0.95
3	13.8	12.4	0.98
4	13.5	10.1	0.98
5	9.4	5.7	0.99
6	10.7	12.1	0.85
7	11.8	11.3	0.98
8	11.9	11.9	0.98
9	10.1	7.5	0.98
10	6.4	8.9	0.97
14	7.6	8.5	0.99

n = 11. r<sup>2</sup>, coefficients of determination of regression lines. Subjects 11-13 and 15-17 had respiratory sinus arrhythmia amplitude measured during only 2 breath-hold volumes, so regression lines were not calculated. However, their breath-hold data for 1.0 liter is reported in Table 5 (next to last column).

Figure 6 shows the normalized RSA as a function of the breathing frequency for subject 5. All normalized points fell within two standard deviations of the 1.0-liter curve (Fig. 3A). Thus the system behaved as if it were linear over the entire frequency range. Data obtained on different days in the same individual also fall on the curve, showing the reproducibility of the phenomenon. The low-frequency intercept of this normalized curve (15.0 beats/min), the corner frequency (9.0 cycles/min), and the roll-off (19.6 dB/decade) are not significantly different from the values of the 1.0-liter curve of Fig. 3A. The normalized values for all experiments on all subjects are shown in Table 5. Thus during voluntarily controlled tidal volume and breathing frequency, the RSA amplitude-frequency relationship is completely characterized by these three parameters: low-frequency intercept, corner frequency, and roll-off.

#### RSA Amplitude During Spontaneous Quiet Breathing (Series IIB)

The values of RSA amplitude obtained during quiet breathing were normalized for tidal volume breath by breath and plotted vs. breathing frequency on a log-log scale. An example is shown in Fig. 7 for subject 3. These data were selected because the spontaneous breathing pattern of this subject was the most variable for all the subjects.

The solid curve shows the normalized results from all 12 experiments in which tidal volume and breathing frequency were voluntarily controlled as described above. This curve was not significantly different from the curve shown in Fig. 3B. The data points were obtained on two different days during quiet spontaneous breathing and fall within the 95% confidence limits (20.4-32.4 beats/min), represented as dashed lines around the solid curve. The low-frequency intercept of the solid line (26.4 ± 3.0 beats/min) is not different from either the low-frequency intercept obtained from the regression line of the quiet breathing points (23.2 ± 3.3 beats/min) or the breath-hold data (see series IIA, Table 5). The last column of Table 5 (series IIB) lists the quiet breathing low-frequency intercepts for all the subjects. Comparison of

corresponding parameters (i.e., series I, IIA, and IIB low-frequency intercepts; series I and IIB corner frequencies and roll-offs) shows no statistically significant differences. These results reveal that the RSA amplitude-frequency relationship is the same whether breathing is spontaneous or voluntarily controlled.

#### Effects of Age and Mean Heart Rate

The low-frequency intercepts show considerable variation among individuals and range from 12.9 to 27.8

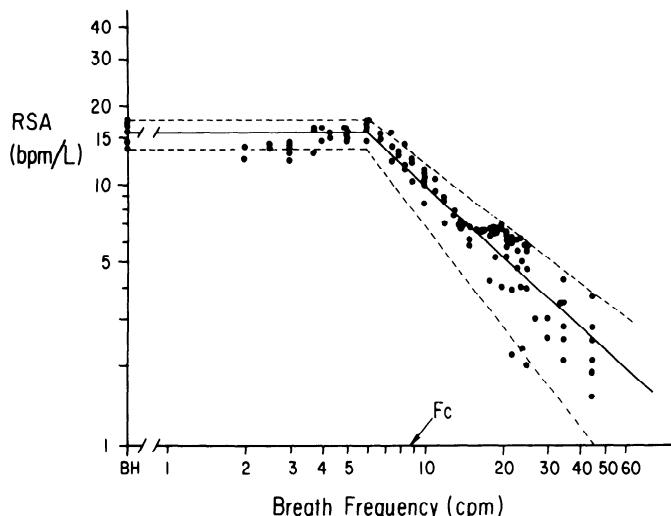


FIG. 6. Data of the 6 expts of Fig. 4, normalized for tidal volume. Log respiratory sinus arrhythmia (RSA) vs. log breathing frequency. Solid curve represents regression lines for the 1.0-liter expt. Dashed lines indicate ± SD.

TABLE 5. Normalized LFI, f<sub>c</sub>, and roll-off for all experiments

Subj No.	Age, yr	Sex	Series I			Breath-hold RSA, beats·min <sup>-1</sup> ·liter <sup>-1</sup>	Quiet Breathing RSA, beats·min <sup>-1</sup> ·liter <sup>-1</sup>
			LFI, beats·min <sup>-1</sup> ·liter <sup>-1</sup>	f <sub>c</sub> , cycles/min	Roll-off, dB/decade		
1	30	M	19.9±5.2	7.5±0.2	21.8±1.9	20.3±1.7	18.3±5.2
2	29	F	22.3±3.4	4.3±0.3	19.9±0.6	22.8±1.3	19.5±6.3
3	27	F	26.4±3.0	6.4±0.3	20.3±3.7	24.6±3.7	23.2±3.3
4	25	F	24.0±5.0	6.0±0.5	19.0±2.3	24.5±3.1	18.6±5.0
5	32	M	17.1±2.4	8.3±0.5	18.7±1.6	14.5±1.3	14.3±3.3
6	22	F	27.8±2.6	7.5±0.6	24.0±4.2	25.0±2.2	24.3±4.4
7	24	F	27.3±4.8	8.0±0.9	22.1±2.0	24.0±0.4	28.2±6.4
8	25	M	25.7±4.6	6.2±0.4	23.3±2.8	25.8±6.7	23.8±5.6
9	72	F	17.3±2.4	9.0±1.1	17.5±1.8	16.3±2.5	16.5±2.9
10	78	M	15.1±1.9	7.0±0.4	16.4±2.1	15.4±4.6	13.3±2.1
11	45	M	15.3±1.5	8.4±0.2	23.9±1.3	15.0±1.6	15.1±3.2
12	44	M	12.9±2.1	5.9±0.4	18.3±2.5	10.9±3.3	11.4±1.8
13	47	M	14.9±2.3	7.2±0.7	20.0±1.7	14.8±2.5	15.8±1.6
14	29	M	19.6±2.5	6.3±0.7	22.1±1.8	21.8±2.1	20.6±1.6
15	36	M	20.9±2.6	6.0±0.9	20.0±1.0	21.3±3.1	20.4±7.7
16	58	F	17.0±2.5	9.2±0.2	18.7±2.5	17.3±3.2	15.9±5.3
17	37	M	15.2±2.4	8.6±0.4	23.7±1.9	15.8±1.2	17.0±2.9
Mean ±SD			19.9 ± 4.9	7.2 ± 1.3	20.6 ± 2.4	19.4 ± 4.7	18.6 ± 4.4

Values for low-frequency intercept (LFI), corner frequency (f<sub>c</sub>), roll-off, and breath-hold and quiet-breathing respiratory sinus arrhythmia (RSA) are means ± SD. n = 17.

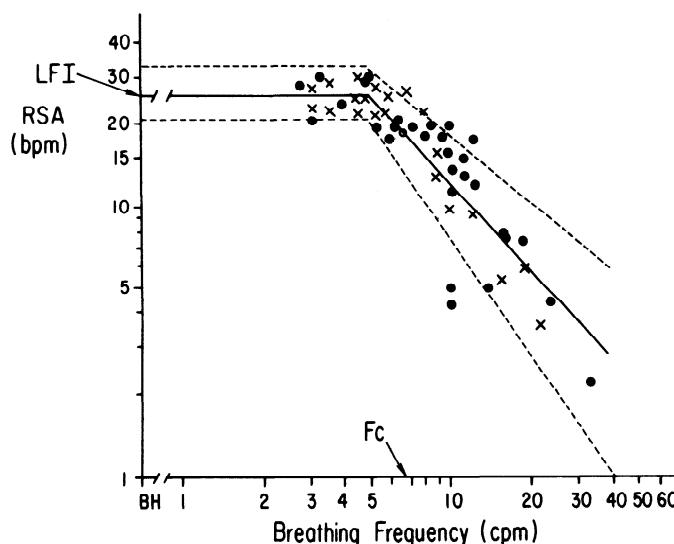


FIG. 7. Log respiratory sinus arrhythmia (RSA) normalized for tidal volume as a function of log breathing frequency during quiet spontaneous breathing for subject 3. Solid curve shows results from 12 expt in which tidal volume and breathing frequency were voluntarily controlled. Dashed lines indicate  $\pm 2$  SD. Dots and X's, data points obtained during quiet breathing from 2 experiments performed several months apart.

beats/min (Table 5). Other investigators have suggested that individual differences in RSA amplitude may be related to the subject's age (13, 29, 34), mean heart rate (22, 29), degree of exercise training (13), or lung size (5). In the present study the only significant correlation observed for RSA amplitude was an inverse linear relationship between RSA and age in subjects under 35 yr of age (Fig. 8;  $r^2 = 0.92$ ). This inverse linear relationship holds only over a limited age range, because healthy physically active subjects over 35 yr showed no further decrease in their low-frequency intercepts. In fact the 78-yr-old male and the 37-yr-old male have the same low-frequency intercept.

In contrast the mean resting heart rates and vital capacities were not correlated with RSA amplitudes (low-frequency intercept). But resting heart rate was significantly correlated with corner frequency (Fig. 9;  $r^2 = 0.73$ ). The physiological significance of this relationship remains obscure; however, the quiet breathing frequency observed in each subject was always higher than the corner frequency and was also significantly correlated with mean resting heart rate.

## DISCUSSION

### Effects of Breathing Frequency on RSA

The results of the present study confirm that RSA amplitude depends on both the depth and frequency of breathing. At constant tidal volume RSA amplitude is relatively stable for low breathing frequencies. Below the corner frequency, some investigators have observed a peak in the RSA amplitude (1, 20, 21, 24, 33). Angelone and Coulter (1), Womack et al. (33), and Luczak and Raschke (24) also have reported a dip in RSA amplitude at about half the frequency as that of the peak. The difference from trough to peak was about 10 beats/min

in their studies. In the present study some subjects had a peak in RSA amplitude just below the corner frequency (see Figs. 3 and 7 for *subj 5* and 3) and a dip in RSA amplitude at roughly 3–4 cycles/min. These deviations were generally small (less than  $\pm 4$  beats/min) and fell within the 95% confidence limits of the regression line for the low-frequency data. The peak did not occur at every session but occurred most often and was most prominent in the female subjects. At breathing frequencies greater

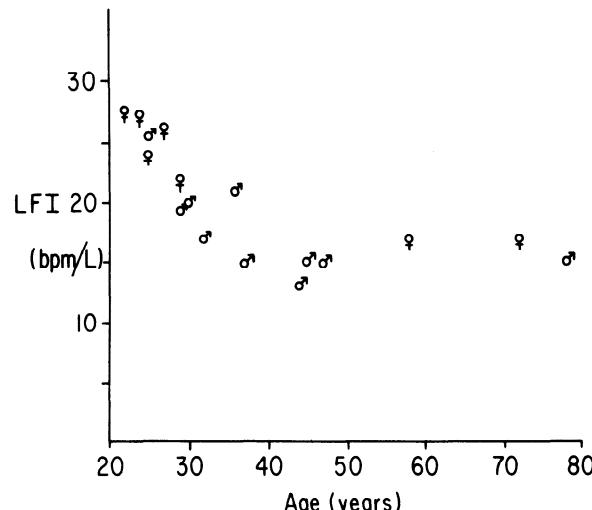


FIG. 8. Mean low-frequency intercepts (LFI) from normalized respiratory sinus arrhythmia (RSA) data as a function of age. Symbols ( $\circ$ ,  $\square$ ) indicate sex of subjects. ( $n = 17$ ).

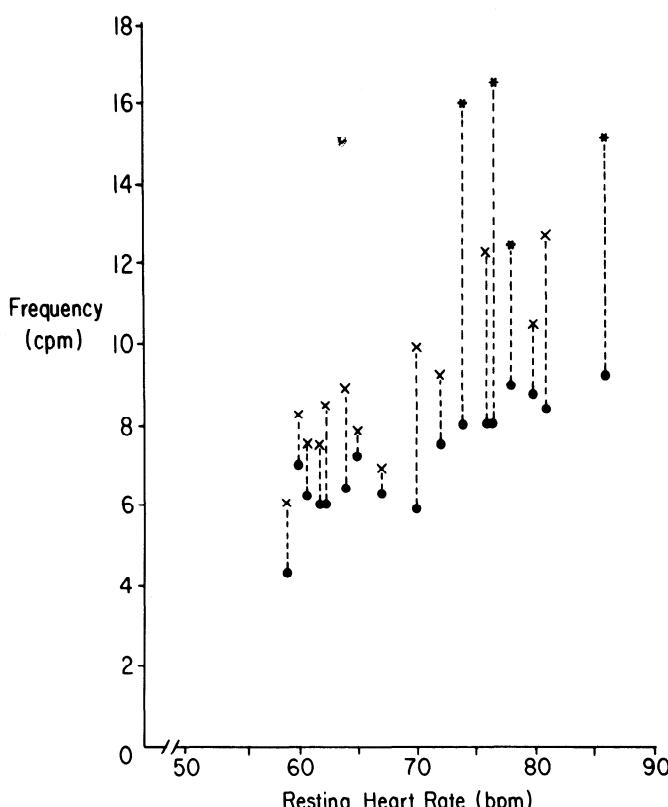


FIG. 9. Corner frequency (●) and quiet breathing frequency (×) as function of resting heart rate. (\*) indicates subjects whose vital capacities were 3.2 l or less ( $n = 17$ ).

than the corner frequency, RSA amplitude decreases with a slope greater than 20 dB/decade.

#### *Effects of Tidal Volume on RSA*

The use of an RSA amplitude-log frequency response plot by Angelone and Coulter (1) has proved valuable in describing the behavior of the relationship between heart rate modulation and breathing rate. However, since these authors monitored thoracic circumference with a single pneumograph, they could not analyze the influences of the tidal volume on the respiratory modulation of heart rate. Luczak and Raschke (24) plotted RSA magnitude and phase angle vs. log breathing frequency (Bode plot; 7, 27) to compare the behavior of a model of heart rate control with data obtained experimentally. At the higher breathing frequencies RSA was greater for the model than for the experimental data. These authors attributed this difference to the higher tidal volume of the model, which was maintained constant as compared with that of the subject, which decreased with increasing breathing frequency.

In the present study each RSA amplitude-frequency response curve was obtained experimentally at a constant tidal volume. Kelman and Wann (20) performed similar experiments, maintaining constant tidal volume at different breathing frequencies, and showed RSA-frequency response curves similar to those of Luczak and Raschke (24). Our study differs from that of Kelman and Wann in that we obtained the constant volume RSA-frequency plot at several different tidal volumes in each subject. Our results show that, when tidal volume is increased, the frequency response curve of the RSA at the new volume exhibits the same characteristic slopes and corner frequencies but that the RSA amplitude is increased at each breathing frequency.

#### *Effects of Breath-Hold Volume on RSA*

The initial oscillation of heart rate obtained on inspiratory breath hold (i.e., zero frequency or step function input) showed the same amplitude as that at the equivalent tidal volume during low breathing frequencies. Thus the RSA amplitude is not different whether the volume was attained by tidal volume or breath hold. These results suggest that rhythmic afferent activity stimulated by dynamic respiratory movements is not responsible for the genesis of the heart rate oscillation and does not solely dictate its amplitude.

During a sustained breath hold the heart rate oscillation continues, but its amplitude decreases over the first 10–20 s (6, 33). Subsequently, a 6–7 cycles/min heart rate oscillation appears, which continues and may even increase in frequency until the breath hold is terminated (30; see Fig. 2). These heart rate oscillations appear at about 30–50 s after the initiation of breath hold and coincide with or even precede the involuntary respiratory efforts (14 and J. A. Sterba, personal communication). At the release of the breath hold another increase and decrease in heart rate occurs.

In the breath-hold experiments (*series IIA*) only the initial oscillation of heart rate was plotted against the volume above functional residual capacity. As breath-

hold volume increased, the amplitude of the RSA increased (Fig. 5, Table 4). The slopes of the amplitude-volume regression lines (Table 4) were about 0.5 of RSA measured at 1.0 liter. Our slopes were  $10.8 \pm 2.3$  beats/min, somewhat greater than the 7 beats/min slope calculated from data of Eckholdt and Schubert (8) who described a similar linear relationship between tidal volume and RSA amplitude. Our y-intercepts were  $10.3 \pm 2.4$  beats/min, or 49% of the RSA at low breathing frequencies for tidal volume of 1.0 liter, compared with the y-intercept of 5 beats/min or 42% of RSA at 1.0 liter for the data of Eckoldt and Schubert (8). These authors attributed about 40% of the RSA amplitude to respiration, because the y-intercept of 5 beats/min was 60% of the RSA at rest ( $\dot{V}T = 450$  ml). However, these authors gave no indication of the breathing frequency at which their measurements were taken; thus we cannot directly compare our data with theirs. The differences in the results of the two studies may be related to the careful control of breathing frequency in the present study.

#### *Normalizing RSA for Volume*

The linear RSA amplitude-volume relationship from the breath-hold data (i.e., zero-frequency RSA) remained constant for the entire range of breathing frequencies studied. Thus the RSA amplitude-volume and amplitude-frequency relationships were independent of each other. The linear relationship of RSA amplitude to breath hold or tidal volume (Figs. 5 and 6) would suggest that the behavior of the RSA could indeed be modeled as a "quasilinear" system (7, 27). Therefore the regression lines of Table 4 permitted us to normalize the RSA in each individual for tidal volume using both slope and y-intercept (Eq. 1). The normalized RSA plotted vs. breathing frequency yielded a single curve, which could be described by three parameters, the low-frequency intercept, corner frequency, and roll-off. These parameters uniquely characterize the system for a subject and provide a quantitative description of the relationships of the RSA amplitude to breathing frequency and tidal volume for each individual when the breathing pattern is voluntarily controlled.

#### *RSA During Spontaneous Breathing*

In this study data from spontaneous-breathing experiments (*series IIB* in Table 5, Fig. 7) are not significantly different from those of voluntarily controlled breathing experiments (*series I* in Table 5). The information carried by descending neural pathways involved in voluntary control of breathing appear to have only a small effect on the relationships of RSA amplitude to breathing frequency and tidal volume. Thus the mean RSA amplitude in an individual may be predicted for any given combination of depth and frequency of breathing during quiet respiration as well.

#### *Effects of "Coupling" Heart Rate and Breathing Frequency*

Hildebrandt (15) observed over periods of several days that the ratio of heart rate to breathing frequency in

humans, or "Puls-Atem Quotient," was an integer value (usually 4:1) under resting conditions more often than would occur solely by chance. The ratio of heart rate to breathing rate was most often an integer during night sleep, during times of relaxation, and during recovery from stress in healthy fit individuals (4).

This phenomenon of cardiorespiratory coupling in whole number ratios and its relationship to the sinus arrhythmia and breathing pattern were studied by Weiss and Salzano (31) in the spontaneously breathing anesthetized dog under conditions of chemostimulation and vagotomy in order to elucidate the mechanisms of the coupling. When heart rate and breathing frequency were coupled in the whole number ratios there were more heartbeats during inspiration, the RSA amplitude was higher, and the breath-by-breath variability in RSA was reduced. However, the authors also observed an increase in tidal volume under conditions of whole number ratio formation, which could have been responsible for the increased RSA amplitude.

In the present study, when heart rate and breathing frequency were voluntarily coupled in whole number ratios (13), the variability in RSA for a given tidal volume and breathing was reduced. The relationships of RSA amplitude to the depth and frequency of breathing were not altered, however, and we saw no evidence of maximization of RSA if tidal volume remained constant. In a few observations where tidal volume was not voluntarily controlled during voluntary coupling of heart rate and breathing frequency, the amplitude of RSA was increased, but so was the tidal volume.

#### *Influence of Age on RSA*

Schlomka (29) reported an exponential decrease in RSA amplitude with increasing age and heart rate but did not report breathing frequency or volume in these subjects. Subsequently, Hellman and Stacy (13) measured the RSA amplitude in humans at a voluntarily controlled whole number ratio of 12 heartbeats per breath and found an inverse linear relationship between the RSA amplitude and age (21–54 yr). In contrast, Wheeler and Watkins (32) found no further decrease in RSA after age 50 yr in normal subjects. Hellman and Stacy (13) included data of subjects who were obese, who did not engage in regular physical activity, and who had some degree of heart disease in their RSA-age relationship. The present study shows an inverse relationship of RSA amplitude and age that rapidly decreases from 20 to 35 yr and then shows no further decrease up to 78 yr. This discrepancy might be related to the selection of healthy active subjects in the present study.

#### *Neural Mechanisms*

The observed relationships of RSA amplitude to breathing pattern suggest a functional link between the brain stem neurons that control respiration and heart

rate (2, 14, 18). A number of investigators have demonstrated other components of heart rate modulation that are of longer periods and that are related to natural oscillations in blood pressure (10, 16, 25, 28) and muscle blood flow (10, 16). Thermoregulatory (16, 17) and hypothalamic inputs (19) have also been demonstrated to influence heart rate modulation. The following brief discussion concerns specifically the mechanisms proposed for the respiratory modulation of heart rate.

Three mechanisms are generally proposed to explain the modulation of heart rate associated with respiration: 1) a direct influence of medullary respiratory neurons on cardiomotor neurons (2, 14, 18, 19, 23); 2) an indirect influence on heart rate of blood pressure changes secondary to respiratory movements that is mediated via arterial baroreceptors (2, 6, 12) or atrial stretch receptors (22, 26); and 3) a reflex response to lung inflation mediated by thoracic stretch receptors (5), most likely from the lungs (2, 9, 11) and chest wall (5).

Although artificial variation of either lung volume or blood pressure may result in modulation of heart rate resembling RSA, when respiratory movements and blood pressure fluctuations are eliminated experimentally a modulation of heart rate persists (3, 18, 23) as long as there is central inspiratory activity. When the respiratory center is depressed by hyperventilation (3) or by deepening anesthesia (23) under the same conditions, heart modulation disappears. RSA persists after bilateral vagotomy (23), vagal cooling (22), paralysis (18, 22, 23), and sinoaortic denervation of arterial baro- and chemoreceptors (P. C. Szlyk and J. A. Krasney, personal communication). The preceding observations suggest that the genesis of RSA has an important central component. The RSA amplitude-volume relationship shown in the present study also suggests a contribution by receptors that respond to changes in lung volume or respiratory blood pressure fluctuations, but the experimental design does not distinguish between them.

In conclusion, we have described a method of assessing the amplitude of the respiratory modulation of heart rate that takes into consideration the influences of tidal volume, breathing frequency, mean heart rate, and voluntary control of breathing on this phenomenon. The relationships of RSA amplitude to the depth and frequency of breathing are similar whether breathing is spontaneous or voluntarily controlled. A single curve quantitates an individual's response and can be characterized by three parameters: low-frequency intercept, corner frequency, and roll-off.

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