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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Biofeedback Treatment for Asthma*

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Study objectives: We evaluated the effectiveness of heart rate variability (HRV) biofeedback as a complementary treatment for asthma.

Patients: Ninety-four adult outpatient paid volunteers with asthma.

Setting: The psychophysiology laboratory at The University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, and the private outpatient offices of participating asthma physicians.

Interventions: The interventions were as follows: (1) a full protocol (*ie*, HRV biofeedback and abdominal breathing through pursed lips and prolonged exhalation); (2) HRV biofeedback alone; (3) placebo EEG biofeedback; and (4) a waiting list control.

Design: Subjects were first prestabilized using controller medication and then were randomly assigned to experimental groups. Medication was titrated biweekly by blinded asthma specialists according to a protocol based on National Heart, Lung, and Blood Institute guidelines, according to symptoms, spirometry, and home peak flows.

Measurements: Subjects recorded daily asthma symptoms and twice-daily peak expiratory flows. Spirometry was performed before and after each weekly treatment session under the HRV and placebo biofeedback conditions, and at triweekly assessment sessions under the waiting list condition. Oscillation resistance was measured approximately triweekly.

Results: Compared with the two control groups, subjects in both of the two HRV biofeedback groups were prescribed less medication, with minimal differences between the two active treatments. Improvements averaged one full level of asthma severity. Measures from forced oscillation pneumography similarly showed improvement in pulmonary function. A placebo effect influenced an improvement in asthma symptoms, but not in pulmonary function. Groups did not differ in the occurrence of severe asthma flares.

Conclusions: The results suggest that HRV biofeedback may prove to be a useful adjunct to asthma treatment and may help to reduce dependence on steroid medications. Further evaluation of this method is warranted. (*CHEST* 2004; 126:352-361)

Key words: airway resistance; alternative and complementary medicine; disease severity; heart rate variability; oscillation mechanics; psychology; self-regulation

Abbreviations: HRV = heart rate variability; LOCF = last-observation-carried-forward; NHLBI = National Heart, Lung, and Blood Institute; Zrs = pulmonary measures derived from the forced oscillation method

An effective nonpharmacologic alternative or adjunctive treatment of asthma could provide a potentially useful contribution to asthma care.¹ Adherence to asthma regimens tends to be low,² and the resort to complementary treatments is common despite the lack of evidence for effectiveness.^{3,4} The

long-term use of oral steroids is expensive and can have undesirable side effects.⁵ Although the weight of empirical evidence strongly indicates that the positive effects of inhaled corticosteroids in asthma far outweigh any negative consequences, there is

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some evidence for adverse effects for these medications as well,^{6,7} and, regardless of the weight of evidence, many asthma patients remain wary of the potential side effects, which, in turn, leads to non-adherence.^{8–10}

Preliminary research has found that biofeedback training to increase heart rate variability (HRV) produces a decrease in respiratory resistance¹¹ and improves spirometry performance in asthma patients,¹² although the mechanism of action has not been proven. HRV tends to be reduced in patients with asthma¹³ and various diseases affecting the cardiovascular and/or CNS.¹⁴ HRV biofeedback has been found to increase peak flow and resting baroreflex gain and high-frequency HRV among healthy adults,¹⁵ but a relationship between autonomic and pulmonary changes has not been established. The purpose of the study was to determine whether this biofeedback method can serve as an effective non-pharmacologic alternative or complementary treatment method for asthma.

MATERIALS AND METHODS

The design for this study was modeled after that used in a study by Löfdahl et al,¹⁶ evaluating montelukast sodium effects on tapering inhaled steroids. The study was approved by the Institutional Review Board of The University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. Subjects were interviewed about the study and gave written consent at their first study visit.

Sixty-four female and 30 male paid volunteers (mean age, 37.3 years; SD, 10.2 years) were recruited via physician referrals and advertisements. The inclusion criteria were as follows: age 18 to 65 years; history of asthma symptoms; and, within the past year, a positive bronchodilator test result (postbronchodilator FEV₁ increase of $\geq 12\%$), a positive methacholine inhalation challenge test result, or a documented recent history (*ie*, within the past year) of clinical improvement and FEV₁ increase of $\geq 12\%$ following instigation of inhaled steroid therapy among individuals with a protracted history of asthma. The exclusion criteria were as follows: a disorder that would impede performing the biofeedback procedures (*eg*, abnormal cardiac rhythm); a negative methacholine challenge test result; an abnormal diffusing capacity (tested among all subjects > 55 years old or with > 20 pack-years of smoking); or a current practice of any relaxation, biofeedback, or breathing technique.

Before randomization, we stabilized subjects on the lowest possible dose of controller medication (based on the standard protocol shown in Table 1, derived from National Heart, Lung, and Blood Institute [NHLBI] recommendations¹⁷) that eliminated asthma symptoms. We titrated medications downward weekly until symptoms reappeared, lung function abnormalities recurred, or a maximum of 2 months of titration had passed. The lowest stable dose was treated as the subject's baseline dose.

We randomized subjects to four treatment groups, balancing for age, sex, and end-of-stabilization asthma severity (*ie*, mild intermittent, mild persistent, moderate, and severe), based on medication level (Table 1), scored according to NHLBI criteria.¹⁷ The treatment groups were as follows: (1) the "full protocol" used in previous research on this method,¹⁸ including HRV biofeedback and training in pursed-lips abdominal breathing with pro-

longed exhalation (23 patients); (2) HRV biofeedback alone (22 patients); (3) a previously developed placebo biofeedback procedure^{19,20} involving bogus "subliminal suggestions designed to help asthma" (with no further details provided, and no actual suggestions given) and biofeedback training to alternately increase and decrease frontal EEG α -rhythms (24 patients); and (4) a waiting list control (25 patients). Subjects in the first three groups each received 10 biofeedback sessions, approximately weekly, and were each asked to practice at home for 20 min twice daily. HRV biofeedback subjects were lent a home trainer unit (KC-3; Biosvyaz; St. Petersburg, Russia). Placebo subjects were instructed to maintain a state of relaxed alertness during home practice, using mental strategies developed during biofeedback sessions, and were given a tape recording with classical music and supposed "subliminal suggestions" to improve their asthma, for use during home practice.

We collected data on asthma symptoms and twice-daily home peak flow readings (Mini-Wright peak flow meter; Clement-Clarke; Essex, UK) from a daily diary, pulmonary function test results from each biofeedback laboratory visit, and the results of monthly physical examinations by a study physician (one of five pulmonologists and one allergist who were blinded to experimental condition). Medication was titrated up or down approximately biweekly based on criteria similar to the 2002 NHLBI recommendations,¹⁷ as shown in Table 2, by the asthma specialists. (Note that the NHLBI recommends monthly reassessment, but we increased the speed of this process because of time constraints.) We assessed respiratory resistance at sessions 1, 4, 7, and 10 (or at approximately 3-week intervals in the waiting list condition), at approximately the same time of day for each subject, after 12 h of abstinence from albuterol. Spirometry was performed before each biofeedback laboratory session (triweekly for the waiting list group and weekly for the other three groups), using standard procedures²¹ with three forced maximal exhalations (Koko pneumotach-based spirometer; PDS Instrumentation; Louisville, KY), calibrated daily using a 3-L syringe (using the norms of Crapo et al²²), and periodically performed by the asthma physicians as part of monthly examinations. We analyzed the maximum value of the three trials for each measure. Subjects rested for approximately 15 min prior to each spirometry recording, during which daily diaries were reviewed and the subjects chatted with the researcher about their experience in the study. (Waiting list subjects were only given spirometry at testing sessions and at physician visits.)

HRV biofeedback was given using a physiograph (model I-330; J&J Engineering; Poulsbo, WA). ECG data were collected from the right arm and left leg, and were digitized at 512 Hz. EEG biofeedback was given using an appropriate device (Alphascan 400 U; Bioscan Corporation; Houston, TX). To assess baroreflex gain, beat-to-beat BP was recorded (Ohmeda Finapres model 223; Madison, WI), and digitized at a rate of 256 samples per second. The sensor was placed on the participant's left middle finger, and the hand was elevated on a table to approximately the level of the heart. α -Low-frequency baroreflex gain was calculated by cross-spectral analysis of the heart rate and BP, in which coherence between the two measures was > 0.8 (WinCPRS program; Absolute Aliens Oy; Turku, Finland).

Respiratory system impedance (Zrs) [between 2 and 32 Hz with 2-Hz increments] was measured using a pseudorandom noise forced oscillation system built for our laboratory.^{23–26} It was presented in 40 2-s bursts spaced equally throughout each trial (with tasks or individual rest periods after each task). To minimize the effects of possible partial glottal closure during exhalation, each burst was triggered by the beginning of an inhalation.

Table 1—Criteria for Rating Asthma Severity and Stepped Protocol for Asthma Medication*

| Severity Class† | Symptom Class‡ | Pulmonary Function | Medication Step | Medication Protocol§ |
|---------------------|---|---|-------------------|---|
| Mild intermittent | Symptoms (wheeze/cough/dyspnea) ≤ 2 times a week; Asymptomatic between exacerbations; Nighttime asthma symptoms ≤ 2 times/mo | FEV ₁ or PEF $\geq 80\%$ predicted and PEF variability $< 20\%$ | 1, 2 | No daily medications needed; Maximum 2 times/wk albuterol (4 puffs) except for exercise-induced asthma |
| Mild persistent | Symptoms > 2 times/wk but < 1 time/d; Exacerbations may affect activity; Nighttime asthma symptoms > 2 times/mo (3–4/mo) | FEV ₁ or PEF $\geq 80\%$ predicted; PEF variability 20–30% | 3, 4, 5 | Fluticasone, 44 μg 1p qd (44 μg); Fluticasone, 44 μg 1p BID (88 μg); Fluticasone, 44 μg 2p BID (176 μg) (up to 4 puffs of rescue albuterol/d can be added) |
| Moderate persistent | Daily symptoms; Daily use of inhaled short-acting β_2 -agonist; Exacerbations: ≥ 2 times/wk, may last days, affect activity; Nighttime asthma symptoms > 1 time/wk (≥ 5 times/mo) | FEV ₁ or PEF $> 60\%$ $\leq 80\%$ predicted; PEF variability $> 30\%$ | 6, 7, 8 | Fluticasone, 110 μg 1p bid (220 μg); Salmeterol or montelukast sodium; Fluticasone, 110 μg 2p bid (440 μg) (up to 4 puffs of rescue albuterol/d can be added) |
| Severe persistent | Continuous symptoms; Limited physical activity; Frequent exacerbations; Frequent nighttime asthma symptoms | FEV ₁ or PEF $\leq 60\%$ predicted; PEF variability $> 30\%$ | 9, 10, 11, 12, 13 | Fluticasone, 110 μg 3p bid (660 μg); Fluticasone, 110 μg 4p bid (880 μg); Salmeterol or montelukast sodium (continue the other of these drugs), up to 4 puffs of rescue albuterol/d; Fluticasone, 220 μg 4p bid (1760 μg); Prednisone burst (40 mg to taper) |

*PEF = peak expiratory flow during forced expiratory maneuver.

†Total asthma severity, determined after stabilization, was categorized according to the dimension (symptoms/pulmonary function/medication) with the highest severity level. Asthma severity categorization was used as a factor in randomizing subjects to groups.

‡Classes scored 1 to 4 for the four severity categories.

§The medication protocol was derived from recommended dosage levels for each level of asthma severity from the NHLBI categorization.^{1,12} In the event of severe asthma flares, prednisone was prescribed and gradually titrated downward over a period of 3 to 7 days, depending on the patient's condition. Afterward, the preflare medical regimen was resumed or altered, depending on the subject's clinical condition. Two patients were unable to tolerate fluticasone. One was instead given an equivalent dose of triamcinolone acetone, and the other was given budesonide inhalation powder, according to the NHLBI table of medication equivalence.¹⁴

||The choice of salmeterol or montelukast sodium was made by the physician for patients with moderate persistent asthma. In level 11 for patients with severe asthma, both drugs were given.

Also, a pair of large earphones was worn on the cheeks to firmly support the extrathoracic airways to minimize the potential confounding effects of airway wall flow shunting.²⁴ Data from bursts containing artifacts were eliminated through visual inspection, and edited data were averaged for each task. Three spectral features of respiratory resistance data (the real part of Zrs) and reactance data (the imaginary part of Zrs) were used to characterize the underlying respiratory mechanics, as follows: (1) resistance at 6 Hz (in cm H₂O/L/s); (2) frequency dependence of resistance (in cm H₂O/L/s) calculated as the difference between resistance at 6 Hz and at the frequency between 8 and 32 Hz yielding the minimum resistance; and (3) the resonant frequency (in Hz), defined as the lowest frequency at which the reactance crossed 0 from negative to positive.

To determine the relative plausibility of the placebo, we gave a three-item treatment credibility questionnaire to subjects in the three intervention groups at each of the four testing sessions,²⁷ comprising three 9-point Likert items anchored at "not at all" and "very (much)," as follows: (1) How much do you expect your asthma to improve as a result of participating in this program? (2) How effective do you think this method is, in general? (3) Would you be likely to recommend this technique to a friend or relative suffering from asthma?

RESULTS

Adherence, Dropouts, and Treatment Duration

The self-reported rate of adherence to biofeedback practice was $> 70\%$, and the rate of completion of daily home questionnaires was $> 80\%$ among those who completed the questionnaire. Eighteen subjects dropped out of the study (Table 3), approximately 20% in the three groups receiving a treatment, a rate similar to that of other asthma behavioral intervention studies from our laboratory.^{8,15,16} Because of occasional rescheduled sessions caused by patients' schedule conflicts, subjects in the waiting list group spent less time in the study than subjects in the other groups and had a lower dropout rate. The reasons given for dropping out of the study that were related to deterioration in the patient's condition occurred only in subjects of the two control groups.

Table 2—Criteria for Medication*

Criteria for changing medication
 Keep medication constant if any one criterion is present in the past 2 wk;
 Increase medication by one step if two or more criteria are present in the past 2 wk;
 Reduce medication by one step if no criteria are present in the past 2 wk
 1. FEV₁ < 80% of stabilization baseline at any time;
 2. PEF < 80% of personal best or PEF variability > 20% for ≥ 3;
 3. Nocturnal awakenings > 2 times due to asthma;
 4. Occurrence of one or more asthma flares within the past 2 wk, not resolved by 6 puffs of albuterol within 1 h;
 5. Average of 8 puffs of albuterol daily.

Criterion for resolution of asthma flare: achievement of green condition
 No cough, wheeze, shortness of breath, or chest tightness;
 Peak flow > 80% of personal best (defined as the highest level previously reported during the study);
 Can do usual activities

*Medication was titrated up or down by one level (as defined in Table 1), using criteria in this table. Medication adjustments were done at the time of the monthly physical examination and 2 weeks later, at which time symptom and pulmonary function data were faxed to the physician. See Table 1 for abbreviations not used in the text.

Baseline Asthma Severity

Subjects began the study with a mean poststabilization medication rating in the moderate persistent asthma range (Table 1). Baseline FEV₁ values were in the mild asthma range (mean [± SD], 77.2 ± 22.7% predicted). There were no significant differences between groups for either measure at the first session.

Statistical Model

We used mixed effects models for repeated measures (Proc Mixed, SAS; SAS Institute; Cary, NC). Based on exploratory analyses and the information criteria of Akaike,²⁵ we used an autoregressive model (order = 1) for prescribed medication, a compound symmetry model for Zrs and medication data, and a heterogeneous autoregressive model (order = 1) for treatment credibility. Autoregressive models assume that the correlations are stronger for measurements closer in time. Heterogeneous autoregressive models additionally allow the variance to change between repeated measures for each individual. The compound symmetry model assumes that closeness in time is unrelated to the correlation among observations.

We analyzed data in the following two ways: (1) last-observation-carried-forward (LOCF, intent-to-treat); and (2), for the primary outcome variable (medication level), completers (*ie*, those who completed the study), with noninformative dropout as-

Table 3—Subject Characteristics, Adherence, and Dropout*

| Condition | Time Spent in Study, † d | | Days Questionnaire, % | Home bfk Practice Days, % | Age, ‡ yr | Male Gender, % | Weight, ‡ kg | Height, ‡ cm | Dropouts, No. | Reported Reason for Dropout | | |
|---------------|--------------------------|--------------|-----------------------|---------------------------|-------------|----------------|--------------|--------------|---------------|-----------------------------|-------------|------------------------|
| | Completers | All Subjects | | | | | | | | Schedule Conflicts | Life Crises | Clinical Deterioration |
| Full protocol | 87 ± 5.5 | | 93.6 | 80.1 | 39.0 ± 11.9 | 26.3 | 79.5 ± 20.6 | 168.4 ± 12.8 | 6 | 5 | 1 | |
| HRV bfk | 95.1 ± 8.2 | | 82.3 | 74 | 37.9 ± 20.6 | 27.8 | 82.9 ± 34.6 | 168.6 ± 9.4 | 5 | 3 | 2 | |
| Placebo | 82 ± 4.2 | | 94.2 | 73 | 39.1 ± 14.0 | 40 | 78.8 ± 21.6 | 168.4 ± 10.2 | 5 | 3 | | 2 |
| Waiting list | 67.6 ± 3.0 | | 81.8 | | 38.6 ± 15.3 | 30.4 | 74.2 ± 21.3 | 165.3 ± 8.2 | 2 | 1 | | 1 |

*bfk = biofeedback.

†Values calculated for the treatment period only (not including the stabilization period). Values given as mean ± SE.

‡Values given as mean ± SD.

sumptions.²⁹ Zrs and measures of respiration rate and tidal volume yielded skewed data, so these analyses were performed on natural logarithm transformations.

Asthma Severity

Level of Prescribed Controller Medication: Medication levels at the four testing sessions changed differentially across groups (with the same p values for completers as in the LOCF analysis) [LOCF treatment \times session interaction: $F_{3,267} = 6.36$; $p < 0.0001$], and highly significant decreases in medication consumption occurred in the groups receiving HRV biofeedback (LOCF $t_{257} = 8.51$ and 6.61 , respectively; $p < 0.0001$ [for the full protocol and HRV biofeedback alone]). Decreases also were significant in the placebo biofeedback condition (LOCF $t_{257} = 2.48$; $p < 0.02$) but not in the waiting list condition (LOCF $t_{257} = 0.4$). They were significantly greater in the combined HRV biofeedback groups than in the placebo group, according to the treatment \times session interaction (LOCF $t_{3,201} = 5.03$; $p < 0.003$ [$p < 0.004$ in the analysis of completers]). There were no significant differences between the full protocol and HRV biofeedback alone. Medication levels in the HRV biofeedback groups tended to fall from the upper levels of moderate persistent asthma to the upper levels of mild persistent asthma by the last treatment session (Table 4), while medication levels remained in the moderate persistent asthma range in the two control groups. Although comparisons with the waiting list group may have been influenced by the duration of treatment, we noted (Table 4) that there was no tendency toward improvement over time in this group, although such a tendency was evident in the biofeedback groups, so it is unlikely that a longer passage of time would have produced greater changes.

Respiratory System Effects

Biofeedback produced significant decreases across sessions in airway resistance at 6 Hz (presession rest period: median at the first session, 2.2 cm H₂O/L/s;

median at the last session, 1.7 cm H₂O/L/s), frequency dependence of resistance (median at the first session, 0.9 cm H₂O/L/s; median at the last session, 0.5 cm H₂O/L/s), and resonant frequency of the airways (median at the first session, 18.2 Hz; median at the last session, 16.4 Hz), compared with the waiting list and placebo groups, in which no changes were observed (log values, for normalization, and probability statistics are in Fig 1 and Table 5). The significance of these patterns was tested using the treatment \times session interaction, adjusted for age, height, and weight, as shown in Table 5. However, when controlled for tidal volume and respiration rate to eliminate spurious findings (Zrs measures decrease as lung volumes increase during respiration³⁰), only the findings for resistance at 6 Hz remained significant. We found large and highly significant increases in tidal volume and decreases in respiratory frequency during biofeedback in the two groups receiving biofeedback (Fig 2) [treatment \times task: tidal volume, $F_{36,1057} = 7.51$ ($p < 0.0001$); respiratory frequency, $F_{36,1050} = 23.35$ ($p < 0.0001$)] (within-group comparisons for biofeedback vs rest periods were significant at $p < 0.0001$ for the HRV biofeedback groups but were not significant for the two control groups). Respiratory frequency dropped to approximately 0.1 Hz, as occurred in our previous research on this procedure.¹¹ The baseline presession respiration rate dropped significantly in the full protocol group from the first to last sessions (Fig 2), but not in the group receiving HRV biofeedback alone.

Biofeedback did not appear to have any immediate effects on Zrs. The groups did not differ significantly in within-session contrasts (*ie*, the treatments \times tasks interaction, contrasts between rest periods and biofeedback periods, and contrasts between beginning-of-session and end-of-session rest periods to test the within-session carry-over effect of training).

Spirometry

There were no interpretable changes in spirometry, either within or between sessions, in any of the treatment groups, and no significant differences between groups.

Table 4—Level of Prescribed Medication (13-Point Scale)*

| Session | Full Protocol | | | HRV Biofeedback Alone | | | EEG Biofeedback Placebo | | | Waiting List | | |
|---------|---------------|------|------|-----------------------|------|------|-------------------------|------|------|--------------|------|------|
| | No. | Mean | SD | No. | Mean | SD | No. | Mean | SD | No. | Mean | SD |
| 1 | 19 | 8.14 | 1.82 | 18 | 7.42 | 2.69 | 20 | 6.95 | 2.45 | 23 | 7.47 | 2.8 |
| 4 | 19 | 7.54 | 2.19 | 17 | 6.59 | 2.35 | 20 | 7.13 | 3.03 | 23 | 8 | 2.67 |
| 7 | 19 | 6.51 | 2.1 | 17 | 6.06 | 2.48 | 19 | 6.89 | 2.53 | 23 | 7.79 | 2.79 |
| 10 | 19 | 5.49 | 2.41 | 17 | 5.12 | 2.78 | 19 | 6.05 | 2.46 | 23 | 7.58 | 2.68 |

*Medication score was for the week prior to each of the four testing sessions. The medication score was increased by one level if a subject took an average of 8 or more doses of albuterol/d during any of these periods.

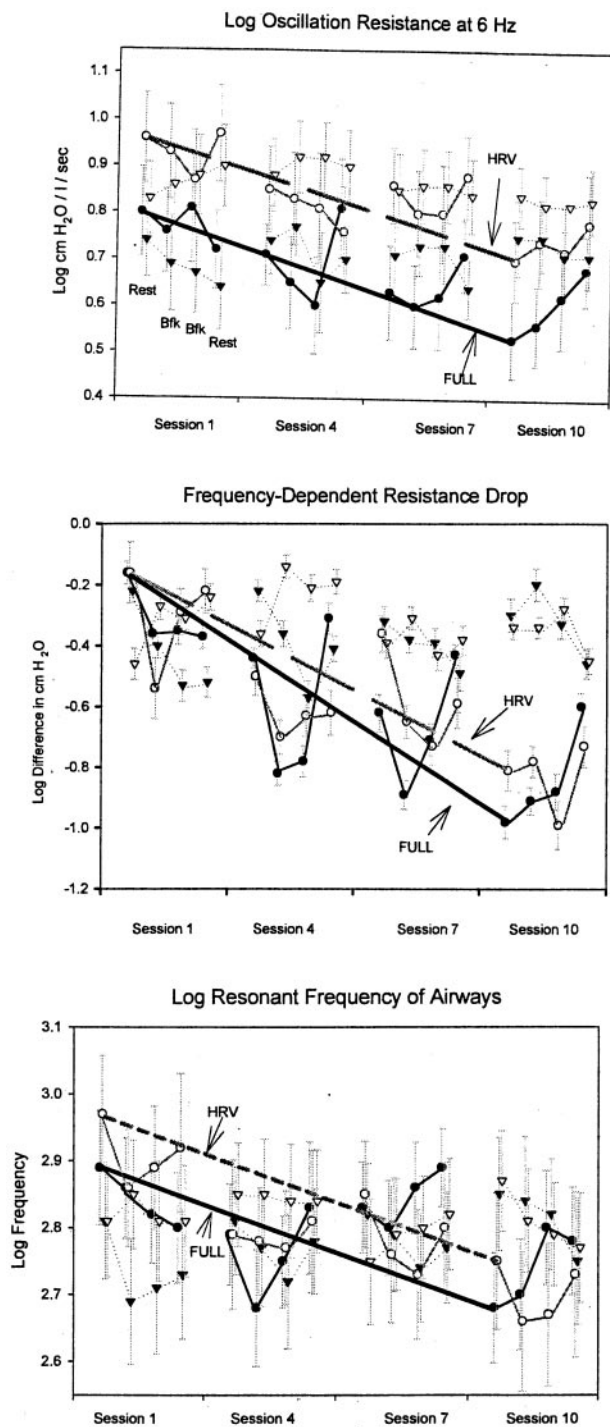


FIGURE 1. Top: log oscillation resistance at 6 Hz. Middle: frequency-dependent resistance drop. Bottom: log resonant frequency of airways.

Asthma Symptoms

Asthma symptoms were scored for the four levels of asthma severity (Table 1). The groups differed significantly (Fig 2) [groups \times sessions interaction, $F_{9,260} = 4.1$; $p < 0.0001$]. Symptoms decreased sig-

nificantly from the first to last sessions for the full protocol ($t_{260} = 3.05$; $p < 0.003$), for HRV biofeedback alone ($t_{260} = 2.39$; $p < 0.02$), and for the EEG biofeedback placebo ($t_{260} = 2.56$; $p < 0.02$). The change was not significant for the waiting list group ($t_{260} = 1.1$).

Treatment Credibility

We separately analyzed each of the three items on the credibility questionnaire. No significant between-groups differences emerged across groups on any of the questions ($p > 0.4$). Subjects gave high credibility ratings on all three questions (mean range, 6.5 to 7.5 [across groups on the 9-point scale]).

Occurrence of Asthma Exacerbations

Despite the decrease in inhaled steroid dosage in the biofeedback groups, there was no evidence for increased risk of a severe asthma flare. Throughout the study, two subjects each in the full protocol and the HRV biofeedback alone groups required emergency treatment with oral steroids, whereas four subjects in the placebo group and five patients in the waiting list required such an intervention. We also computed a life table analysis³¹ of medication levels during the week prior to each of the four testing sessions to examine distribution of increases in controller medication over baseline (Fig 3). We found no such increases in the full protocol group, three increases in the HRV biofeedback group over approximately 4 months, six increases in the placebo group, and seven increases in the waiting list group (log-rank test, 8.4088; degrees of freedom, 3; $p = 0.04$). Exacerbations began occurring in the control groups within < 20 days.

HRV and Baroreflex Gain

HRV increased in response to biofeedback during training sessions, as had been found previously among healthy subjects.¹⁴ Full-spectrum HRV (range, 0.005 to 0.4 Hz) as well as low-frequency HRV (range, 0.05 to 0.15 Hz) both differed significantly among treatment groups (treatment \times task interaction: full-spectrum HRV, $F_{36,612} = 1.95$ [$p < 0.001$]; low-frequency HRV, $F_{36,612} = 5.30$ [$p < 0.0001$]), increasing during biofeedback periods only for the groups receiving the full protocol (full-spectrum HRV, $t_{612} = 7.21$ [$p < 0.0001$]; low-frequency HRV, $t_{612} = 12.59$ [$p < 0.0001$]) and HRV biofeedback alone (full-spectrum HRV, $t_{612} = 5.61$ [$p < 0.0001$]; low-frequency HRV, $t_{612} = 11.67$ [$p < 0.0001$]). Baroreflex gain also increased significantly within sessions during biofeedback practice, only for the groups receiving the full protocol ($t_{589} = 2.95$;

Table 5—Forced Oscillation Pneumography: Mixed Models Analyses on Between-Session Effects*

| Long-term (Between-Session) Effects Measure/Group | Contrast | LOCF | | | Completers | | | Controlled for Tidal Volume and Respiration Rate | | |
|---|--------------------------|--------------------|--------|----------|--------------------|--------|----------|--|--------|----------|
| | | Statistic | Value† | p Value | Statistic | Value† | p Value | Statistic | Value† | p Value |
| Log Zrs 6-Hz Resistance | Treatment × session | F _{9,156} | 3.94 | < 0.0002 | F _{9,267} | 2.65 | < 0.006 | F _{9,264} | 2.75 | < 0.005 |
| Full protocol | Baseline session 1 vs 10 | t ₆₂₄ | -3.66 | < 0.0003 | t ₁₀₆₈ | -3.23 | < 0.002 | t ₁₀₅₆ | -3.41 | < 0.0007 |
| HRV bfk alone | Baseline session 1 vs 10 | t ₆₂₄ | -2.39 | < 0.02 | t ₁₀₆₈ | -3.2 | < 0.002 | t ₁₀₅₆ | -3.25 | < 0.002 |
| Placebo bfk | Baseline session 1 vs 10 | t ₆₂₄ | 0.73 | NS | t ₁₀₆₈ | -0.04 | NS | t ₁₀₅₆ | -0.04 | NS |
| Waiting list | Baseline session 1 vs 10 | t ₆₂₄ | -0.14 | NS | t ₁₀₆₈ | 0.09 | NS | t ₁₀₅₆ | 0.09 | NS |
| Log Zrs Freq Depend | Treatment × session | F _{9,156} | 3.33 | < 0.0009 | F _{9,267} | 2.73 | < 0.005 | F _{9,264} | 1.24 | NS |
| Full protocol | Baseline session 1 vs 10 | t ₆₀₈ | -3.66 | < 0.0003 | t ₁₀₆₆ | -3.73 | < 0.0002 | t ₁₀₅₄ | -0.19 | NS |
| HRV bfk alone | Baseline session 1 vs 10 | t ₆₀₈ | -1.83 | < 0.07 | t ₁₀₆₆ | -2.22 | < 0.03 | t ₁₀₅₄ | 0.01 | NS |
| Placebo bfk | Baseline session 1 vs 10 | t ₆₀₈ | 0.02 | NS | t ₁₀₆₆ | -0.35 | NS | t ₁₀₅₄ | -1.41 | NS |
| Waiting list | Baseline session 1 vs 10 | t ₆₀₈ | 0.4 | NS | t ₁₀₆₆ | 0.6 | NS | t ₁₀₅₄ | 0.67 | NS |
| Log Zrs resonant Freq | Treatment × session | F _{9,156} | 5.34 | < 0.0001 | F _{9,267} | 5 | < 0.0001 | F _{9,264} | 1.08 | NS |
| Full protocol | Baseline session 1 vs 10 | t ₆₂₄ | -2.36 | < 0.02 | t ₁₀₆₈ | -2.58 | < 0.01 | t ₁₀₅₆ | -1.17 | NS |
| HRV bfk alone | Baseline session 1 vs 10 | t ₆₂₄ | -2.01 | < 0.05 | t ₁₀₆₈ | -3.35 | < 0.001 | t ₁₀₅₆ | -0.05 | NS |
| Placebo bfk | Baseline session 1 vs 10 | t ₆₂₄ | 0.78 | NS | t ₁₀₆₈ | 0.14 | NS | t ₁₀₅₆ | -1.73 | NS |
| Waiting list | Baseline session 1 vs 10 | t ₆₂₄ | 1.21 | NS | t ₁₀₆₈ | 0.78 | NS | t ₁₀₅₆ | 1.64 | NS |

*NS = not significant; Freq = frequency. See Table 3 for abbreviations not used in text.

†Minus sign in *t* tests represents direction of change from session 1 to 10, and from baseline to biofeedback tasks.

$p < 0.004$) and HRV biofeedback alone ($t_{559} = 4.56$; $p < 0.0001$), but the interaction was not significant. Cardiovascular measures did not change significantly across sessions, nor were between-session cardiovascular changes correlated with between-session effects in medication consumption, asthma symptoms, or forced oscillation pneumography.

DISCUSSION

HRV biofeedback appears to be promising as an adjunctive treatment for asthma, and it appears to maintain the condition of asthma patients with a reduced dose of inhaled steroids. A decrease of two to three medication steps occurred in the active-treatment groups. This change of approximately one level in asthma severity (from a mean in the upper level of moderate asthma to a mean in the upper level of mild persistent asthma, as defined in Table 1 and with results shown in Table 3) is clinically significant. No level changes occurred in the two control groups, and decreases in medication were greater in the HRV biofeedback groups than in the two control groups.

The results of biofeedback appear to reflect specific training effects rather than a placebo-like effect of treatment expectancy or response to increased therapeutic attention. The placebo condition had a very similar format to the real biofeedback conditions and was just as credible as an asthma treatment for subjects as HRV biofeedback, but it produced negligible effects on asthma severity. Consistent with the suggestive power of the placebo condition, the

improvement in asthma symptoms was as great as in the HRV biofeedback groups, despite the lack of change in measures of pulmonary function or physicians' medication prescriptions. HRV biofeedback also affected the physiologic parameters of asthma.

The mostly equivalent effects for the full protocol vs HRV biofeedback alone suggests that the biofeedback procedure, rather than abdominal or pursed-lips breathing, produced the therapeutic effects. However, the mechanism for the biofeedback effects was not proven. Although, as in previous studies of healthy people, the biofeedback procedure produced immediate changes in HRV and baroreflex gain, no longer term changes occurred in these measures that could explain the asthma improvements. One possible mechanism may be a long-term bronchodilation effect. The immediate bronchodilating effects of practicing the technique were not apparent, however, and may have been masked by changes in respiratory pattern. Nevertheless, some subjects informally reported that they had used the slow-breathing method to stop asthma exacerbations. Future research is necessary to verify whether such rescue effects of HRV biofeedback do occur, and to examine the effects of HRV biofeedback on inflammation and mucus secretion, particularly in view of evidence of neurogenic links to these processes.^{32,33}

However, if HRV biofeedback only produces bronchodilation, the use of the method as a substitute for antiinflammatory medication should be undertaken with caution. Although bronchodilator treatment may allow a reduction in conjoint antiin-

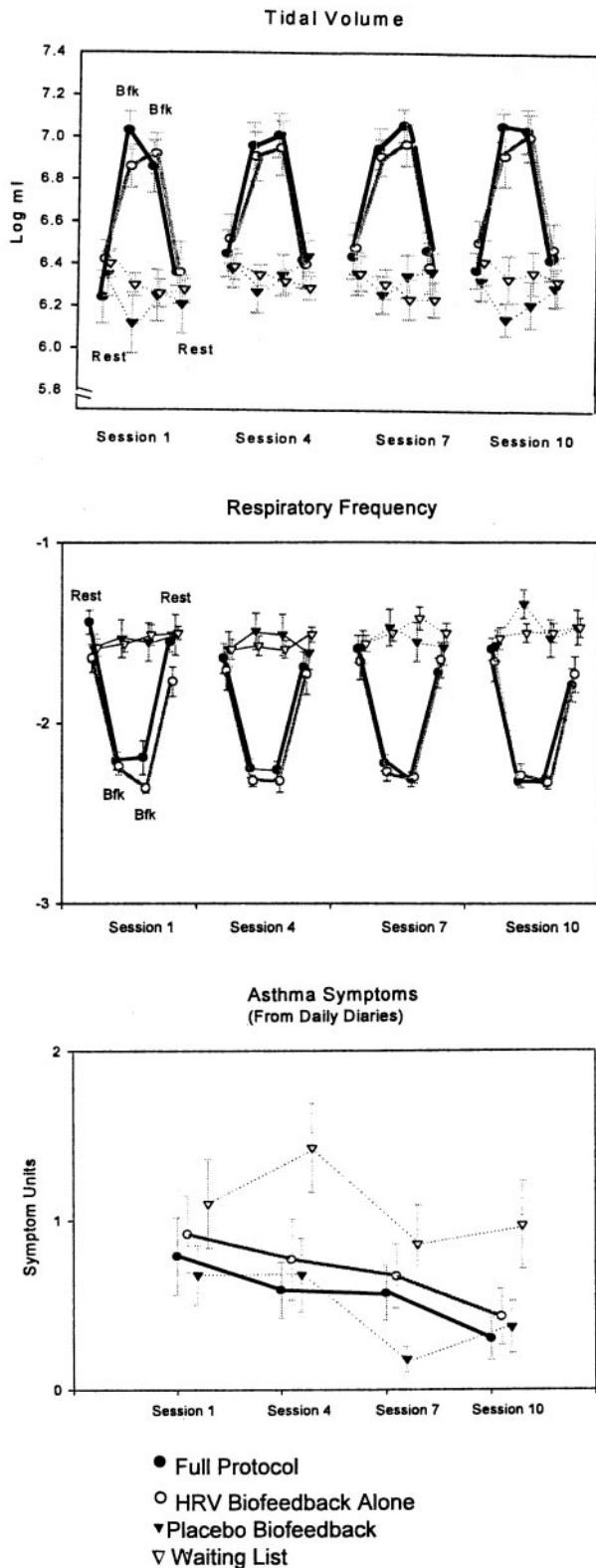


FIGURE 2. Top: tidal volume. Middle: respiratory frequency. Bottom: asthma symptoms (from daily diaries).

flammatory treatment, the total elimination of such treatment increases the risk of asthma exacerbation.³⁴ Our exacerbation data suggest that fewer exacerbations may have occurred in the group receiving HRV biofeedback, despite the decrease in inhaled steroid dosage. It is possible that biofeedback may have a steroid-sparing effect without some of the long-term side effects of salmeterol, possibly including ischemic heart disease.³⁵

The limitations of this study include its relatively short duration and its lack of follow-up to assess long-term effects. Also, the placebo condition may have required less task involvement than the HRV biofeedback conditions, and thus may have had a smaller placebo effect, although such differences were not found in our measures of treatment credibility. In addition, this highly controlled experimental protocol may have attracted patients with higher treatment motivation than would occur in the general population, and personality characteristics of the single biofeedback therapist in this study, who was not blinded, may have affected the efficacy of the intervention. Fourth, differences between the waiting list group and other groups in the duration of the protocol and the frequency of assessment sessions may have affected the size of the medication changes in the current study, although we believe it is unlikely that this played a role, because there was no perceptible cross-session trend in asthma severity in this group, while such trends did occur in the HRV biofeedback groups. Additionally, some asthma exacerbations may have been missed during periods other than the week prior to each testing session. Finally, because functional residual volume and resting lung volume were not measured during forced oscillation pneumography, it is possible that changes

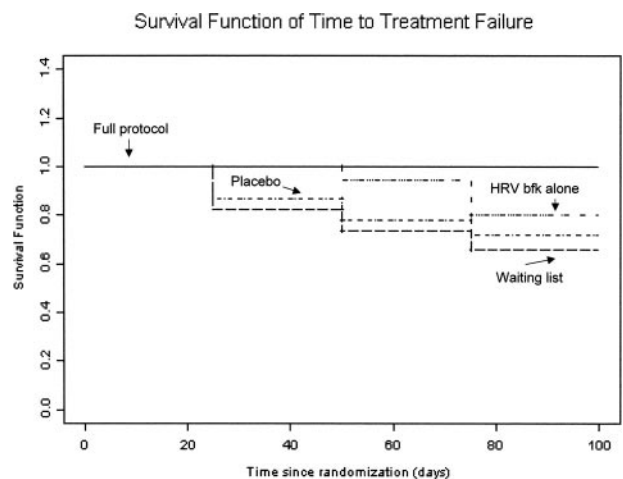


FIGURE 3. Survival function of time to treatment failure. See Table 3 for abbreviation not used in text.

in Zrs values could have been caused by increases in these values, particularly during voluntary respiratory maneuvers in biofeedback in which the behavioral effects many have overridden the more automatic physiologic control of breathing. We note, however, that the Zrs effects, particularly resistance at 6 Hz, persisted during rest periods, during which no special breathing maneuvers were performed, after factoring out the effects of residual changes in respiratory patterns while at rest. The effects of HRV biofeedback on respiratory resistance thus were independent of the effects of voluntary respiratory maneuvers. It is also unlikely that more general changes occurred in functional residual capacity or resting lung volume, because spirometry data show no changes in full vital capacity, suggesting the absence of air trapping, and subjects had been instructed to exhale as fully as was voluntarily possible.

The lack of spirometry findings probably reflects the use of spirometry as a principal criterion for adjusting medication (*ie*, improvements directly led to decreases in medication, which would prevent further improvement in spirometry values). It is notable that the study by Löfdahl et al,¹⁶ using this same experimental design for evaluating montelukast sodium, similarly found decreases in inhaled steroid dosage but no changes in spirometry values. Asthma symptoms, which also were a criterion for medication adjustment, decreased, although the results were not as strong as those for medication dosage or Zrs. Zrs measures were apparently sensitive to aspects of lung function that were not assessed by spirometry. The fact that, of the Zrs measures, only resistance at 6 Hz remained significant after adjustment for respiratory patterns, suggests an increase in airway caliber, rather than in other airway and chest wall tissue properties (*eg*, tissue compliance).²³ Airway caliber would be particularly relevant for asthma.

Further research is needed to verify whether, as suggested by our findings, this biofeedback method can have a safe but significant steroid-sparing effect in clinical practice. Caution is advised at this time in using this method for treating asthma, until the mechanisms of action are better understood and the long-term protective effect has been documented. The decrease in the use of steroid medications with this method did not appear to pose a risk of asthma exacerbation in the current study, but it is possible that such effects might become evident in a longer trial.

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