Reflex Heart Rate Control in Asthma*
Evidence of Parasympathetic Overactivity

J. M. Kallenbach, M. B., M. R. C. P., F. C. C. P.; T. Webster;
R. Doudeswell, M. B.; S. G. Reinach, D. Sc.;

The bronchial hyperreactivity characteristic of asthma may
be related to enhanced parasympathetic nervous activity.
We postulated that an abnormality in the autonomic control
of airway caliber might be reflected by a parallel change in
the reflex control of heart rate. We examined the heart-rate
variations induced by deep breathing (respiratory sinus
arrhythmia), the Valsalva maneuver, and standing up from
the recumbent position in asthmatic subjects and non-
asthmatic control subjects. The asthmatic patients had
evidence of enhanced parasympathetic neural drive to the
sinus node, as manifested by a significantly greater
magnitude of respiratory sinus arrhythmia, than the con-
trols (p <0.0005). We were unable to induce a similar change
in normal subjects by resistance breathing. A statistical
analysis suggested the presence of a relationship between
the magnitude of respiratory sinus arrhythmia and the
degree of bronchial hyperreactivity in a group of asthmatic
patients. Our results support the hypothesis that enhanced
parasympathetic activity is an important factor in the patho-
genesis of bronchial asthma.

Hyperreactivity of the airways to numerous phys-
ical, chemical, and pharmacologic stimuli is
characteristic of bronchial asthma. A considerable
number of pathogenetic mechanisms could account for
this phenomenon, including various types of "im-
balance" in the autonomic regulation of airway caliber;
each of which could predispose to airway narrowing. 1,2
Manifestations of both α-adrenergic hypersensitivity
and β-adrenergic hyposensitivity have been reported
to occur in asthma, 3,4 and previously led us to study the
metabolic responses to α- and β-adrenergic stimulation
in patients with the disease. We were unable to
detect any differences in these responses between
groups of asthmatic and nonasthmatic subjects. 5,6

That parasympathetic overactivity may be a patho-
genetic component of bronchial hyperreactivity was
suggested in 1917 by Eppinger and Hess 7 who
described an association between asthma and a state of
"vagotonia." The hypersensitivity of asthmatic patients
to cholinergic agonists and various vagally-mediated
stimuli is well known. In addition, increased eccrine
sweat-gland and pupillary constrictor responses have
been noted in allergic individuals and nonallergic
asthmatic patients. 8,9 We wished to investigate fur-
ther the possibility that an enhancement of para-
sympathetic activity may be an important factor in mediat-
ing bronchial hyperreactivity. As the rate of discharge
of the sinoatrial node is modulated by the vagus nerve,
the possibility exists that an abnormality in the para-
sympathetic control of airway caliber may be reflected
by a parallel change in the control of heart rate. The

Subjects and Methods

Study 1

Comparison of the Autonomic Nervous Control of Heart Rate in 15
Asthmatic Subjects and 18 Nonasthmatic Controls: The asthmatic
patients were all nonsmokers with a history of bronchial asthma as
defined by the American Thoracic Society. 10 The diagnosis was con-
Firmed in each patient by the finding of at least one of the following:
(a) a forced expiratory volume in 1 second of less than 65 percent
of the predicted value, with at least 30 percent reversibility following
inhalation of a bronchodilator aerosol, and (b) a fall in the peak
expiratory flow rate (PEFR) of at least 20 percent from the resting
value, provoked by exercise.

All were taking bronchodilator medications. Some, in addition,
were using disodium cromoglycate and/or beclomethasone dipropio-
nate by inhalation. Only one had ever required systemic cortico-
steroids, this being for a short period some months prior to the study.
All bronchodilator drugs were discontinued for at least a week prior
to the study. The subjects were all in a stable condition.

The control subjects were all nonsmokers with no history or
clinical features of bronchial asthma as defined by the American
Thoracic Society. 11 Three had a history of allergic rhinitis and 15 were
normal individuals. Each subject had normal pulmonary function,
and none had a significant fall in PEFR on exercise.

All subjects were studied in the early morning following an
overnight fast. Care was taken to achieve familiarity with the various
maneuvers by numerous practice runs. Each test was performed
twice and the mean of the two results calculated. Following each
maneuver, the heart rate was allowed to return to the resting level
before proceeding. We studied the variations in heart rate induced
by deep breathing (respiratory sinus arrhythmia), the Valsalva
maneuver, and standing up from the recumbent position.

Variation in Heart Rate Induced by Deep Breathing (Respiratory
Sinus Arrhythmia): With the subject semirecumbent and breathing
depth at a rate of 6 breaths per minute, 12,13 the ECG was recorded
for 60 seconds. The duration of each respiratory cycle was ten
seconds, with equal time for inspiration and expiration. The seconds
were counted aloud by a technologist who ensured that the breathing

*From the Departments of Medicine and Cardiology, University of
the Witwatersrand, and the Institute of Biostatistics, South African
Medical Research Council, Johannesburg, South Africa.
Manuscript received August 13; revision accepted October 29.
Reprint requests: Dr. Kallenbach, Department of Medicine, Univer-
sity of Witwatersrand Medical School, Johannesburg, South Africa
2193.
was continuous. Forced breaths and maximum respiratory maneuvers were avoided because of the possibility of provoking bronchospasm in the asthmatic subjects. From each ECG strip, we selected and measured the longest and shortest R-R interval and converted the results from milliseconds to beats per minute. The magnitude of respiratory sinus arrhythmia was expressed as the difference between the maximum and minimum heart rates in beats per minute. Mean heart rate during the deep breathing maneuver was estimated from the average of the maximum and minimum heart rates.

We compared the tidal volumes of eight asthmatic patients and eight control subjects breathing at a rate of 6 breaths per minute for two minutes in the semirecumbent position. In order to correct for height and weight differences, the average tidal volume of the 12 breaths from each subject was expressed as a percentage of both observed and predicted vital capacity.

Variation in Heart Rate Induced by the Valsalva Maneuver: While the ECG was being recorded, and with the subject semirecumbent, an inspiratory pressure of 40 mm Hg was maintained for ten seconds through a mouthpiece attached to a spiromyomanometer and then released. Care was taken to ensure that the pressure changes occurred abruptly at the onset and termination of the strain period. The difference between the shortest R-R interval during, and the longest R-R interval after the strain period was expressed in beats per minute.

Variation in Heart Rate Induced by Standing Up from the Recumbent Position: While the ECG was being recorded, the subject rose rapidly from the recumbent to the erect position. The difference between the shortest R-R interval at or around the 15th beat, and the longest R-R interval at or around the 30th beat after standing was expressed in beats per minute.

Comparison of data was done with the unpaired t test.

Study 2

The Effect of Resistance Breathing on the Magnitude of Respiratory Sinus Arrhythmia in Ten Normal Subjects: The subjects breathed through a resistance consisting of a perforated metal disc inserted into a pneumotachograph. This provided a linear resistance of 24 cm H₂O/L/sec. Measurement of the magnitude of respiratory sinus arrhythmia during both resistance and unloaded breathing was done as described above.

The results were compared by means of the paired Student's t-test.

Study 3

Statistical Analysis Investigating a Possible Correlation Between the Magnitude of Respiratory Sinus Arrhythmia and the Degree of Bronchial Hyperreactivity in 15 Asthmatic Subjects: We utilized the data from all 12 asthmatic patients in study 1 who had performed exercise tests. In addition, we included the data from three subjects with a history of atopy and bronchial asthma, as defined by the American Thoracic Society, who had been excluded from study 1 because each had only minor impairment of pulmonary function while off all bronchodilators. Measurement of the magnitude of respiratory sinus arrhythmia in these three subjects was done as described above.

The percentage of fall in PEFR on exercise was used as an index of bronchial hyperreactivity. The exercise consisted of eight minutes of treadmill running during which each subject achieved estimated maximum heart rate. The PEFR was measured at two-minute intervals during, and for 15 minutes after exercise, the lowest value obtained being used to calculate the percentage of fall from the baseline value.

The statistical analysis was done by means of a stepwise multiple regression procedure using the BMDP statistical package. The magnitude of respiratory sinus arrhythmia was entered as the dependent variable, and the percent fall in PEFR on exercise, age, baseline PEFR, and mean heart rate during the deep breathing maneuver as independent variables.

All studies of pulmonary function were performed with the Pulmolab 5300 and the Jaeger plethysmograph. Normal pulmonary function values used were those of Goldman and Becklake and Crapo et al.

None of the subjects studied was a trained athlete.

Results

Study 1

Age, sex distribution, pulmonary function variables, and the responses in peak flow rate to exercise of the asthmatic subjects and the control subjects are shown in Table 1. The forced expiratory volume in one second was significantly lower, and the airway resistance, functional residual capacity, and fall in PEFR on exercise was significantly greater in the asthmatic subjects than in the control subjects.

The magnitude of respiratory sinus arrhythmia and the heart-rate responses to the Valsalva maneuver and to standing are shown in Table 2. The magnitude of respiratory sinus arrhythmia was significantly greater in the asthmatic subjects than in the controls (p<0.0005). There was no significant difference between asthmatic and control subjects in the heart-rate responses to the other two maneuvers.

There was no statistically significant difference between the average tidal volume of eight asthmatic patients (49.6±14.1 percent observed vital capacity; 44.8±12 percent predicted vital capacity) and eight

<p>| Table 1—Age, Sex Distribution and Pulmonary Function Variables of Asthmatics and Controls* |
|--------------------|----------|----------------|----------------|---------------------------|</p>
<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>FEV₁ (% Predicted Value)</th>
<th>Airway resistance (cm H₂O/L/s)</th>
<th>Functional Residual Capacity (% Predicted Value)</th>
<th>% Fall in Peak Expiratory Flow Rate With Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthmatics</td>
<td>n = 15</td>
<td>21.9 ± 4.8</td>
<td>7M 8F</td>
<td>65.7 ± 16.6†</td>
<td>6.1 ± 3.9†</td>
</tr>
<tr>
<td>Control subjects</td>
<td>n = 18</td>
<td>22.2 ± 3.8</td>
<td>9M 9F</td>
<td>97.3 ± 16.0†</td>
<td>1.7 ± 0.5†</td>
</tr>
</tbody>
</table>

*Figures given are mean ± standard deviation. All pulmonary function studies in asthmatics performed off bronchodilator therapy. †p<0.0005. ‡p<0.05. §n = 12.
control subjects (60.9 ± 18.2 percent observed vital capacity; 60.3 ± 19.4 percent predicted vital capacity), breathing at a rate of 6 per minute in the semirecumbent position.

Study 2

The magnitude of respiratory sinus arrhythmia in ten normal subjects was 29.0 ± 6.4 beats per minute during resistance breathing as opposed to 32.4 ± 6.7 beats per minute during unloaded breathing. The difference was not statistically significant.

Study 3

There was a strong correlation between the magnitude of respiratory sinus arrhythmia and the degree of bronchial hyperreactivity as manifested by the percentage of fall in PEFR on exercise in 15 asthmatic subjects (r = 0.70, p < 0.005) (Fig 1). Age and mean heart rate were also significantly related to the magnitude of respiratory sinus arrhythmia (r = −0.57 and 0.55, respectively; p < 0.05). After adjustment for the effects of both age and mean heart rate, the partial correlation between the magnitude of respiratory sinus arrhythmia and the percentage of fall in PEFR on exercise generated an r value of 0.55 (p = 0.051).

No ectopic beat occurred during any ECG recorded in studies 1, 2, or 3.

Discussion

The reflex control of heart rate is dependent upon intact autonomic function. The maneuvers performed in study 1 have been extensively employed in the evaluation of patients with suspected autonomic neuropathy.13-15,18,24

Several physiologic mechanisms may contribute to respiratory heart rate variations, including reflexes involving pulmonary and atrial stretch receptors and baroreceptors. There may also be direct interaction between the respiratory and cardiovascular centers in the brainstem.25,26 Respiratory sinus arrhythmia is abolished by atropine25,27 and may be unaffected26 or increased by propranolol.27 It has been shown to be closely related to the activity of vagal fibers.26-28 Katona et al.28 showed that vagal efferent activity ceases in dogs during spontaneous, but not mechanical, inspiration regardless of arterial pressure. They concluded that brainstem connections were the primary origin of respiratory variations in heart rate. A recent clinical study,18 however, has suggested a close relationship between baroreceptor function and respiratory heart rate variations in diabetic patients.

The magnitude of respiratory sinus arrhythmia has been well evaluated clinically as a test for autonomic function and has an acceptable degree of intrasubject repeatability,17,24 even at an interval of three to eight months.17 Abnormally diminished respiratory variations in heart rate are generally accepted as providing proof of the presence of autonomic neuropathy. The finding, therefore, of an increased magnitude of respiratory sinus arrhythmia in asthmatic patients compared with nonasthmatic patients may be interpreted as evidence of enhanced autonomic nervous activity primarily involving the parasympathetic nervous system. Although vagal pathways are clearly important in the heart rate responses to both the Valsalva maneuver and assumption of the upright posture,14,29 there was an absence of correlation in our study—as in others—between the magnitude of the changes in heart rate induced by these maneuvers and the magnitude of respiratory sinus arrhythmia.15,16 It has been suggested that, although the vagus constitutes the efferent pathway for all these reflexes, the strength of the afferent input may vary considerably between them.15,16

The magnitude of respiratory sinus arrhythmia has been shown to be related to mean heart rate, rate of respiration, and age.15,17,30,31 None of these variables

![Image](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21466/ on 06/21/2017)
could have accounted for the observed difference in our study between the asthmatic and the control subjects. The effect of tidal volume on respiratory heart rate variations is small, a 50 percent increase in tidal volume resulting in only a 15 percent increase in sinus arrhythmia. Although the difference was not statistically significant the average tidal volume of the eight asthmatic subjects in whom it was studied tended to be smaller than that in the control subjects. It is most unlikely, therefore, that the increased magnitude of respiratory sinus arrhythmia found in the asthmatic subjects was related to differences in tidal volume.

Large intrathoracic pressure swings, such as occur with severely obstructed breathing, may cause fluctuations in cardiac performance, and therefore, in arterial blood pressure, provoking finely modulated compensatory heart rate changes mediated by the separate outputs of intrathoracic and extrathoracic baroreceptors. The asthmatic patients in our study all had relatively mild disease, in that each was able, without difficulty, to discontinue all bronchodilator drugs for at least a week, and only one had ever required systemic corticosteroids. All of them were in a stable condition at the time of the study. Nonetheless, we still wished to investigate the possibility that the increased respiratory variations in heart rate observed in the asthmatic subjects might be the result of a baroreceptor effect caused by fluctuations in cardiac output associated with obstructed breathing. For this reason, we attempted to simulate the mechanical abnormalities characteristic of asthma by the application of a resistive load to the airways of normal subjects, a maneuver which has also been shown to produce hyperinflation with a rise in the functional residual capacity. We found no change in the magnitude of respiratory sinus arrhythmia in normal subjects during resistance breathing. Although an extrathoracic resistance is not strictly analogous to diffuse intrathoracic airway obstruction, we suggest therefore that the increased respiratory heart-rate variations observed in the asthmatic patients are unlikely to be primarily related to an abnormality of pulmonary mechanics.

The only study attempting to establish age-related normal values for the magnitude of respiratory sinus arrhythmia, in which the protocol followed was comparable to ours, has recently been reported by Wieling et al. However, whereas their measurements were also made in the supine position and at a respiratory rate of 6 per minute, the heart-rate variations in their study were elicited by forced maximal breaths—which we specifically avoided. The effect of tidal volume on R-R interval variability is small, but the relative effect of forced as opposed to quiet breathing is uncertain. Also, inasmuch as the study of Wieling et al. was designed to establish normal values for comparison with those from patients with autonomic neuropathy, it is quite possible that their subjects were not carefully screened to exclude individuals with a history of current or remote asthma, which may be present in almost 10 percent of a random population group. Nonetheless, superimposition of our data on their regression curve still shows that the majority of our asthmatic subjects fall at or near the upper limit of their very wide normal range.

The finding of an increased magnitude of respiratory sinus arrhythmia in asthmatics is convincing evidence of enhanced parasympathetic output to the sinoatrial node. However, the basic premise underlying this study, and others, namely that autonomic events in the lungs are reflected by those at other sites, has not been verified. The existence of a relationship between the magnitude of respiratory sinus arrhythmia and the degree of bronchial hyperreactivity in a group of asthmatic patients may be evidence of a parallel enhancement in the level of the parasympathetic output to both sinoatrial node and airways.

The complexity of the pulmonary effects of the autonomic nervous system, and of autonomic interactions in the lungs and elsewhere, is considerable, and our knowledge in this field remains little more than elementary. Our results, therefore, do not permit exclusion of the possibility that the disease itself is, in some way, the cause of the increased magnitude of respiratory sinus arrhythmia noted in our asthmatic subjects, rather than being the result of a primary autonomic abnormality. Nevertheless, our study provides support for the hypothesis that enhancement of parasympathetic function is an important factor in the pathogenesis of bronchial asthma.

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