

# Characteristics of wheeze during histamine-induced airways obstruction in children with asthma

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## Abstract

**Background** – An automated system has been developed for the detection of sound patterns suggestive of airways obstruction in long term recordings. The first step, presented here, was tracheal sound recording during histamine-induced airways obstruction.

**Methods** – The tracheal sounds of 29 children aged 8–19 years with asthma were recorded during airways obstruction caused by histamine inhalation using a system for continuous respiratory telemetry and computer analysis. Sound patterns were analysed, classified, and related to airways obstruction measured by lung function tests based on the forced expiratory volume in one second (FEV<sub>1</sub>).

**Results** – Five sound patterns were identified, one dominant sensitive and four specific to a fall in FEV<sub>1</sub> of >20%. The presence of at least one of three specific sound patterns during unforced respiration predicted a fall in FEV<sub>1</sub> of >20% in 87.5% of the subjects. The inspiratory and expiratory sound patterns were almost equally informative of airways obstruction.

**Conclusions** – Wheezes can be differentiated with more precision than is currently accepted. Tracheal sound patterns are sensitive and specific predictors of histamine-induced airways obstruction. These patterns are neither invariably nor proportionally related to the results of lung function testing. However, they can be used for detection of airways obstruction on the basis of their presence or absence. (*Thorax* 1995;50:143–148)

Keywords: wheeze, asthma, children, digital analysis.

Ever since Forgacs<sup>1</sup> took the initiative to describe lung sounds objectively, their digital processing and spectral analysis has attracted many investigators. However, computerised lung sound analysis has not been clinically useful. Beck *et al*<sup>2</sup> recommended lung sound analysis as an alternative method for lung function testing in young children. Stoneman *et al*<sup>3</sup> explored the diagnostic potential of spectral analysis in predicting lung disease. We have been working on the development of an automated system for the analysis of continuously recorded tracheal sounds in children with asthma. When aiming

at computerised analysis of sound patterns indicative of airways obstruction, detailed knowledge of sound characteristics in relation to lung function is essential. Because the detection of target sound patterns is vulnerable to interference from background noise, a first step would be the specification of wheezes with strict criteria.

This study was undertaken to achieve a detailed analysis and classification of inspiratory and expiratory sound patterns associated with airways obstruction, indicated by a fall in the forced expiratory volume in one second (FEV<sub>1</sub>). The purpose of the study demanded external validity – that is, that sound patterns recorded in the laboratory should represent patterns associated with acute asthmatic attacks in the daily environment. This criterion was a major guideline in the study.

## Methods

### SUBJECTS

A sample of 29 children (19 boys, 10 girls) of mean (SD) age 12.2 (3) (range 8–19) years took part in a histamine challenge test. Twenty five of the children were resident in the asthma centre and the others came for observation.

The severity of their asthma was classified by the scoring system of the Dutch Society of Paediatricians, Lung Diseases section (see also the international consensus<sup>4</sup> on classification in five steps). There were 25 children with a diagnosis of severe asthma, all of whom were taking inhaled corticosteroids and bronchodilator drugs. One child was classified as having moderate asthma and was treated with cromoglycate and bronchodilators on demand, and three children with mild asthma were treated with bronchodilators on demand.

Sound recording was considered by the staff as part of the general consent signed by parents on first admission to the centre. The baseline lung function of one boy did not permit further testing (FEV<sub>1</sub> <55% predicted<sup>5</sup>), leaving 28 subjects for analysis.

### HISTAMINE CHALLENGE TEST

Tracheal sounds were recorded during a routine clinical test performed according to a structured protocol<sup>6</sup> to assess the degree of airway responsiveness. Histamine phosphate was prepared in a range of eight doubling concentrations from 0.25 to 32 mg/ml. The solutions were administered through a De Vil-

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biss 646 nebuliser with a gauged output of 0.13 mg/ml. The nebuliser was mounted within a valve box with an aerosol filter. Nebulisation time was 30 seconds during which the subjects were instructed to breath quietly through the mouthpiece while seated and wearing a noseclip. Before inhalation three measurements of FEV<sub>1</sub> were made with a pneumotachograph (Pneumoscreen II, Erich Jaeger, Germany) calibrated daily.

The test started with inhalation of a saline buffer aerosol. FEV<sub>1</sub> was measured within 30 seconds of each inhaled dose. When the FEV<sub>1</sub> fell the measurement was repeated after 90 and 180 seconds. A significant fall in FEV<sub>1</sub> (>20%) was used for calculation of the histamine threshold coefficient (PC<sub>20</sub>). A bronchodilator drug (two puffs of a  $\beta$  agonist) was administered for relief of airways obstruction. Ten minutes later the test ended with a final FEV<sub>1</sub> measurement.

#### RECORDING EQUIPMENT

The continuous respiratory telemetry system (EMCO Electronics, Assendelft, The Netherlands) was specially developed for the continuous recording of tracheal sounds in the subject's daily environment. The hardware comprised an electret microphone in a polyester cover (range 20–25 000 Hz within 3 db), a small transmitter, and a receiver which recorded up to 10 hours of sound on videotape. The microphone was placed over the suprasternal notch with a double-sided adhesive anti-allergic ring (ARBO T08). The transmitter and rechargeable battery were carried on a waistbelt. Tracheal sounds (not lung sounds) were selected for recording after pilot testing. During parallel recording of lung and tracheal sounds the tracheal sounds were found to be more informative of minor changes of airways obstruction. In addition, the tracheal microphone was easier to position and remove and the signal was less vulnerable to sound artefacts from clothes than were lung sounds recorded on the chest wall.

#### RECORDING PROCEDURE

Sound recording took place during quiet breathing without a mouthpiece or noseclip in order to achieve a good correlation between the sounds during the histamine challenge test and the daily environment (the external validity of the study). Western *et al*<sup>7</sup> showed that the breathing pattern during spirometric breathing changes qualitatively, which would affect the tracheal sounds recorded.<sup>8</sup>

#### ANALYSIS AND CLASSIFICATION OF SOUND PATTERNS

Tracheal sounds emerging during airways obstruction were traditionally categorised into the following classes: wheezes or high-pitched and low-pitched rhonchi, stridor, crackles, and crepitations.<sup>9 10</sup>

A total of 549 sound segments, each of 20 seconds duration, was analysed. The differentiation between monophonic, polyphonic,

and multiple monophonic wheezes as described by Forgacs<sup>1</sup> was irrelevant for pattern recognition. The initial categorisation resulted in five distinct sound patterns. The classification process included the following steps: (1) defining criteria for classification; (2) the qualitative description of the sound patterns; and (3) a recognition task. This was followed by a quantitative analysis of sound patterns and statistics (see later under "Analysis").

#### Criteria for classification and qualitative description of sounds

Two main sound categories associated with airways obstruction were identified: raised breath sound (pattern 1) and wheezes (patterns 2–5).

*Pattern 1: Raised breath sound.* The pitch of the breath sound was clearly raised. In general, the tracheal sound was raised in pitch, hoarse, thrill or whistling-like, sometimes associated with a prolonged expiration after bronchodilator administration. A raised pitch was common during various degrees of airways obstruction. It was usually audible near the mouth.

*Pattern 2: Thrill sound or stridor.* A high-intensity non-musical sound. A loud thrill or scraping sound, commonly occurring during forced inspiration from mild to moderate degrees of airways obstruction or during unforced respiration in severe airways obstruction. It was audible near the subject.

*Pattern 3: Background buzzing with or without concomitant sounds.* The pattern was not restricted to inspiration or expiration, but was also audible in between. This pattern was present in at least two consecutive respiratory cycles. It comprised an irregular, buzzing or musical background sound. The concomitant sounds varied from buzzing with musical irregularities to soft-toned peeps. The sound context sometimes resembled "moist" rhonchi, a term no longer used. This pattern could be detected with the stethoscope.

*Pattern 4: Series of high-pitched rhonchi.* Obvious high-pitched peeps present for at least two consecutive inspirations or expirations. The peeps varied from short thrill peeps to loud extended and sometimes mournful toned peeps. They were clearly detectable with the stethoscope, but also audible near the mouth and chest.

*Pattern 5: Solitary rhonchus.* A sudden rhonchus in inspiration, expiration, or between the two which was unrelated in pitch to the accompanying breath sound and not present in consecutive respiratory cycles. In general the pattern appeared as a high-pitched rhonchus, but occasionally (in some subjects) as a low-pitched rhonchus. The pattern was observed over a wide range of obstructive degrees, although it always suggested that a fall in FEV<sub>1</sub> of >20% was imminent.

#### Recognition task

A total of 120 sound segments, with and without wheezes, of 1–3 seconds duration were

copied onto a separate tape for a recognition task. This "recognition tape" contained 50 sound segments with raised breath sound and wheezes. They were randomly copied in between 50 sound segments associated with normal breathing. The sounds were recorded from 20 different subjects during the histamine challenge test. The sounds were distributed on the tape with five seconds pause between segments. The inspiratory and expiratory sounds were not separated.

The test started with the 10 naive raters listening to one of the sound patterns, separately recorded on one tape and repeated for one minute. Immediately afterwards they listened to the recognition tape and were instructed to report recognition of the target pattern by pressing a button. The maximum score per rater per sound pattern was 10 points. The raters scored all five sound patterns presented in random order over two days.

**FILTERING AND DIGITAL SOUND PROCESSING**

A total of 549 sound segments, each of 20 seconds duration, was digitised. The segments were prefiltered by a fourth order low pass Butterworth analog filter with a cut-off frequency of 1500 Hz. They were then digitised with 7500 samples/s by a 12-bit Keithley Model 580 analog-to-digital converter, and digitally filtered to 1300 Hz. The remaining signal was downsampled by a factor of two for data reduction. The 150 kbyte data were stored on the hard disc of a PC 80486 for analysis. The whole signal or its details could be viewed graphically on the PC screen while the sound was played back through a headphone. This allowed for parallel qualitative and quantitative sound analysis. The power spectrum – that is, the amount of signal power as a function of the frequency – was computed using the Welch algorithm<sup>11</sup> with a 512-sample Hamming window. The spectrum could then be inspected on the screen or plotted on paper, either on a power or log power (decibel) scale.

**ANALYSIS**

The statistical analysis of sound records included the following procedures:

*Table 1 Percentage of sound patterns correctly recognised (n = 10)*

	SP1	SP2	SP3	SP4	SP5
Percentage	49	92	82	88	86
SD	19	13	10	11	7

SP = sound pattern; SD = standard deviation.

*Table 2 Mean (SD) lung function during histamine challenge testing (n = 28)*

	FEV <sub>1</sub> (l)	FEV <sub>1</sub> (%)
Group I (n = 24)		
Baseline	2.19 (0.75)	92 (14)
After final histamine dose	1.47 (0.61)	61 (16)
10 min after medication	2.07 (0.78)	86 (16)
Group II (n = 4)		
Baseline	1.99 (0.91)	89 (14)
After final histamine dose	1.89 (0.81)	85 (18)
10 min after medication	—	—

Group I = subjects with a fall in FEV<sub>1</sub> of >20% after the final histamine dose; group II = subjects with a fall in FEV<sub>1</sub> of ≤20% after the final histamine dose.

1. Mean scores and standard deviations of the recognition task were calculated and expressed as percentages of sound patterns recognised.

2. Inspiratory and expiratory sound patterns were scored on their presence during four periods of histamine challenge testing: (1) baseline; (2) fall in FEV<sub>1</sub> of ≤20%; (3) fall in FEV<sub>1</sub> of >20%; and (4) 1–10 minutes after bronchodilator administration. The dependence between five sound patterns and a fall in FEV<sub>1</sub> of >20% was tested in a cross-tab analysis with Pearson's *c*<sup>2</sup> and the *j* association coefficient. This comprised the period between final histamine dose and bronchodilator administration.

3. The correlations (as expressed by the product-moment correlation coefficient) between inspiratory and expiratory sound patterns and the intercorrelations among the patterns were calculated. The correlations were based on the presence of sound patterns in the same minute.

4. The predictive power of the sound patterns with regard to a fall in FEV<sub>1</sub> of >20% was tested with the *c*<sup>2</sup> and *j* coefficient. Diagnostic sensitivity and specificity percentages were also calculated. This comprised the period between the penultimate histamine dose and bronchodilator administration.

5. The spectra of the sound patterns were analysed and examined for their usefulness for future automated sound analysis.

**Results**

**RECOGNITION TASK**

Wheezes were easily distinguished from normal breath sounds, but quite a few errors in recognition were made with the high-pitched patterns 4, 5, and occasionally 3. The thrill sound or stridor (pattern 2) was most easily recognised, whereas the raised breath sound (pattern 1) was often not distinguished from normal breathing sounds (table 1).

**LUNG FUNCTION AND HISTAMINE THRESHOLD**

Four subjects did not achieve a fall in FEV<sub>1</sub> of >20% after histamine inhalation and did not receive medication. The lung function data are summarised in table 2. The histamine dose causing a fall in FEV<sub>1</sub> of >20% in the other 24 subjects varied from 1 to 32 mg/ml with a skewed distribution, mean (SD) 8 (10) mg/ml.

**DISTRIBUTION OF SOUND PATTERNS**

Wheezes generally commenced after the penultimate dose of histamine, increased after the final dose of histamine, and then diminished. The raised breath sound (pattern 1) was present over a wider range of airways obstruction. The wheezes often occurred only for a short period; in some subjects they were audible for one or two respiratory cycles only and faded before the administration of the bronchodilator. They were not a constant source of diagnostic information. Six subjects had four different sound patterns during the histamine challenge test and another three subjects had all five patterns.

Wheezes were absent in only two subjects with a fall in FEV<sub>1</sub> of >20%. They manifested only the raised breath sound (pattern 1) and one of them coughed increasingly towards the final histamine dose, which diminished after bronchodilator administration. Low-pitched rhonchi were only found in one girl.

#### Period 1: Sound patterns during baseline

The raised breath sound (pattern 1) was observed frequently. It was present in seven of the subjects (29%) who later achieved a fall in FEV<sub>1</sub> of >20%, but also in three of the subjects who did not. Wheezes were not observed.

#### Period 2: Fall in FEV<sub>1</sub> of ≤20%

A raised breath (pattern 1) was present during the inspiration of 14 subjects (58%) and in expiration of 18 subjects (75%) who achieved a fall in FEV<sub>1</sub> of >20% and in none of the subjects who did not. A thrill sound or stridor (pattern 2) was present during forced inspiration for FEV<sub>1</sub> assessment in eight of the subjects (33%) who achieved a fall in FEV<sub>1</sub> of >20% and in none of the subjects who did not. The other patterns were observed in a few subjects only. In this period wheezes were present in 12 subjects and they all achieved a fall in FEV<sub>1</sub> of >20%.

#### Period 3: Fall in FEV<sub>1</sub> of >20%

The five sound patterns were observed in all 24 subjects with a fall in FEV<sub>1</sub> of >20% and the wheezes (patterns 2–5) in 22 of them (table 3).

Table 3 Presence of inspiratory/expiratory sound patterns after histamine inhalation (n = 28)

	SP1	SP2	SP3	SP4	SP5
Group I (n = 24)					
No. of subjects	21/21	13/0	9/8	10/8	5/8
%	88/88	54/0	38/33	42/33	21/33
Group II (n = 4)					
No. of subjects	2/2	0/0	0/0	0/0	0/0
%	50/50	0/0	0/0	0/0	0/0

SP = sound pattern; Group I = subjects with a fall in FEV<sub>1</sub> of >20% after the final histamine dose; group II = subjects with a fall in FEV<sub>1</sub> of ≤20% after the final histamine dose.

Table 4 Correlations between inspiratory and expiratory sound patterns (n = 28)

	SP1	SP2	SP3	SP4	SP5
r	0.71	0.54	0.67	0.70	0.06
p	<0.001	<0.01	<0.001	<0.001	<0.01

SP = sound pattern; r = product-moment correlation coefficient.

Table 5 Predictive power of sound patterns for a fall in FEV<sub>1</sub> of >20%. The calculations are based on scoring during the period from the penultimate histamine dose to bronchodilator administration (n = 24)

	%1	%2	c <sup>2</sup>	p	j
Sound pattern 1	91.7%	25%	1.8	<0.6	0.26
Sound pattern 2	62.5%	100%	6.22	<0.1	0.47
Sound pattern 3	42.0%	100%	4.04	<0.1	0.38
Sound pattern 4	45.8%	100%	3.02	<0.5	0.33
Sound pattern 5	70.8%	100%	7.21	<0.1	0.51

%1 = percentage of subjects with presence of sound pattern and a fall in FEV<sub>1</sub> of >20% (sensitivity percentage); %2 = percentage of subjects with both absence of sound pattern and absence of a fall in FEV<sub>1</sub> of >20% (specificity percentage); c<sup>2</sup> = Pearson χ<sup>2</sup>; p = significance level of c<sup>2</sup>; j = association coefficient phi.

#### Period 4: 1–10 minutes after bronchodilator administration

The raised breath sound (pattern 1) was still present in 10 (42%) of the subjects who had a fall in FEV<sub>1</sub> of >20% and in two of the subjects who had not. During forced inspiration at the beginning of the FEV<sub>1</sub> measurement two subjects presented the thrill sound or stridor (pattern 2). Towards the end of the histamine challenge testing (6–10 minutes after medication) solitary rhonchi (pattern 5) were present in three of the subjects who had a fall in FEV<sub>1</sub> of >20%.

#### Cross tab analysis

The statistical dependence between the sound patterns and a fall in FEV<sub>1</sub> of >20% was highest for the inspiratory thrill sound or stridor (pattern 2): c<sup>2</sup> = 4.04; p < 0.05; j = 0.38. A significant dependence was also found for the inspiratory raised breath sound (pattern 1): c<sup>2</sup> = 3.27; p < 0.05; j = 0.34 with almost equal result for expiration. The statistical dependence of the other sound patterns was not significant.

#### Correlations

The inspiratory and expiratory sound patterns were highly correlated, except with the solitary rhonchi (pattern 5; table 4). With the sound patterns during inspiration and expiration combined, the following intercorrelations were significant:

- pattern 2/3: r = 0.57 (p < 0.001);
- pattern 3/5: r = 0.47 (p < 0.01);
- pattern 4/5: r = 0.45 (p < 0.01).

#### Prediction of a fall in FEV<sub>1</sub> >20%

In the period between the penultimate histamine dose and bronchodilator administration sound patterns 2–5 were observed in 22 of the 24 subjects who achieved a fall in FEV<sub>1</sub> of >20%. The influence of the thrill sound or stridor (pattern 2) was derived mainly from forced inspiration during measurement of FEV<sub>1</sub>. At least one of patterns 3, 4, and 5 was present during unforced respiration in 21 of the subjects (87.5%) who achieved a fall in FEV<sub>1</sub> of >20%. The sound patterns most predictive of a fall in FEV<sub>1</sub> of >20% were: (1) thrill sound or stridor (pattern 2), dominantly in forced inspiration, present in 15 (63%) of subjects; (2) series of high-pitched rhonchi (pattern 4), present in 11 (45.8%) of subjects; (3) raised breath sound (pattern 1), perfect in sensitivity, being present in all 24 subjects who achieved a fall in FEV<sub>1</sub> of >20%, but also present in three subjects who did not (low specificity); and (4) solitary rhonchi (pattern 5), present in 17 (70.8%) of subjects.

These results are reflected in the statistics presented in table 5. The diagnostic significance of the sound patterns for a fall in FEV<sub>1</sub> can easily be interpreted from the sensitivity and specificity percentages.

#### Spectral signatures of sound patterns

Patterns 1 and 3 varied considerably in char-

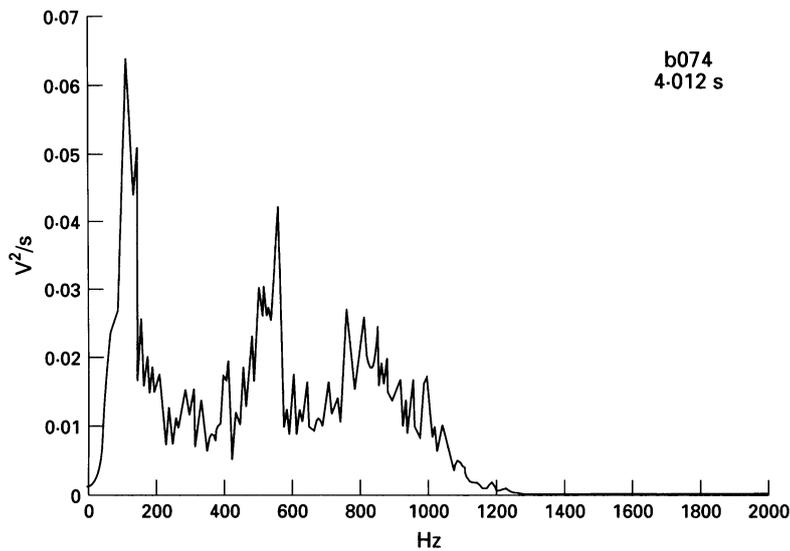


Figure 1 Frequency distribution of sound pattern 1 (raised breath sound). The heart tone at 91 Hz is clearly visible.

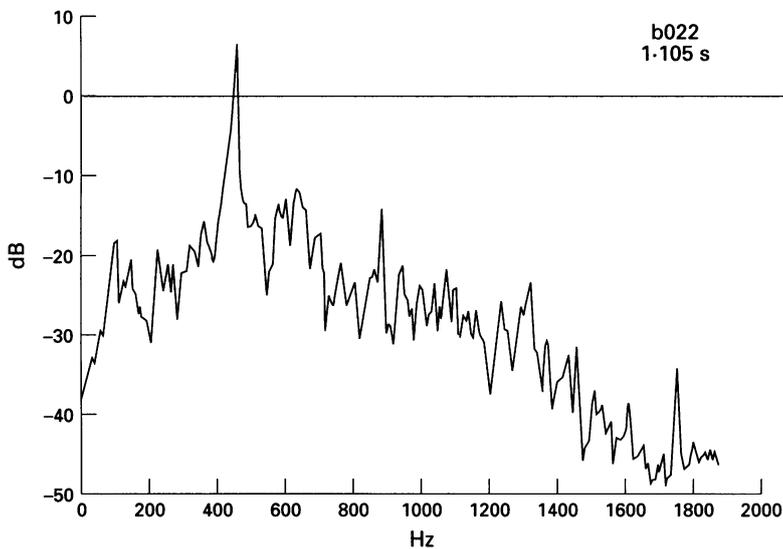


Figure 2 Frequency distribution of sound pattern 2 (thrill sound or stridor), strongly dominated by a tone at 440 Hz. Since the segment duration was more than one second, this means that this tone is highly persistent.

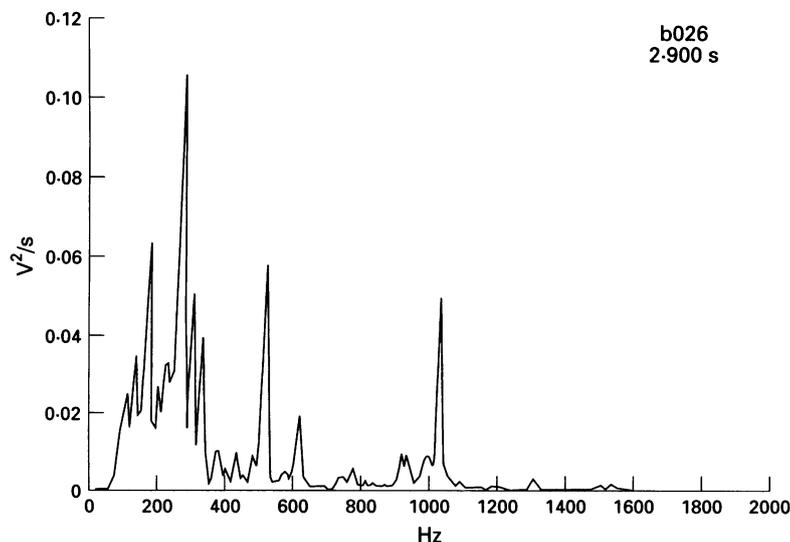


Figure 3 Frequency distribution of sound pattern 3 (buzzing background with or without concomitant sounds). Notice the harmonic relationship of some of the spectral lines.

acteristics and this diversity was reflected in the spectra. Pattern 2 was dominated by components between 200 and 500 Hz, while in the spectra of patterns 4 and 5 components in the band 500–1000 Hz prevailed. In figs 1–5 spectra are shown as examples from each of the five sound patterns (marked by identification code and time span). In each graph the horizontal axis is linear with frequency, running from zero to 1875 Hz. The figures show the power spectra of the signal segments in volts squared per second ( $V^2/s$ ), with the exception of fig 2 where a logarithmic (decibel) scale is used. The digital filter used in processing the signals had its cut-off frequency at 1300 Hz, while the horizontal scale extends to 1875 Hz. The digitisation noise power was about  $7.5 \times 10^{-5}$  units and was thus negligible in the examples shown.

**Discussion**

Wheezes and a raised breath sound during histamine-induced airways obstruction were divided into five separate sound patterns following defined criteria. The presence of one of the specific sound patterns during unforced breathing predicted a fall in FEV<sub>1</sub> of >20% in 21 of 24 subjects. The inspiratory and expiratory sound patterns were almost equally informative of airways obstruction. The patterns were neither constantly present during, nor linearly related to, a fall in lung function. Nevertheless, it was concluded that they could be used on an absent/present basis in the automated detection of sound patterns indicative of airways obstruction. In addition, it was shown that wheezes can be specified and used with more diagnostic precision than is currently accepted.

The inspiratory and expiratory sound patterns were initially analysed separately. Spence *et al*<sup>12</sup> averaged the respiratory cycle, whereas Anderson *et al*<sup>13</sup> restricted analysis to inspiration because it was expected that the unpredictable opening of bronchi during expiration would impair the reproducibility of analysis. In the present study both inspiration and expiration provided informative sound patterns, and no justification was found to restrict the analysis to any particular part of the respiratory cycle. Indeed, high correlations between inspiratory and expiratory sounds allowed averaging over the respiratory cycle in most subjects. Averaging may also be a practical necessity in the automated pattern detection.

The results of the recognition task were based on the subjective recognition of short sound segments. The patterns were presented as isolated, short peeps without much context facilitating detection. This affected the detection of pattern 5 because its isolated occurrence was a main characteristic and this was lost in the short sound segments presented to the raters, causing mislabelling between patterns 4 and 5 and 3 and 5.

During the histamine challenge test the respiratory system is affected by forced respiration, inhalation of histamine, mucus and saliva. There was hardly time for physiological

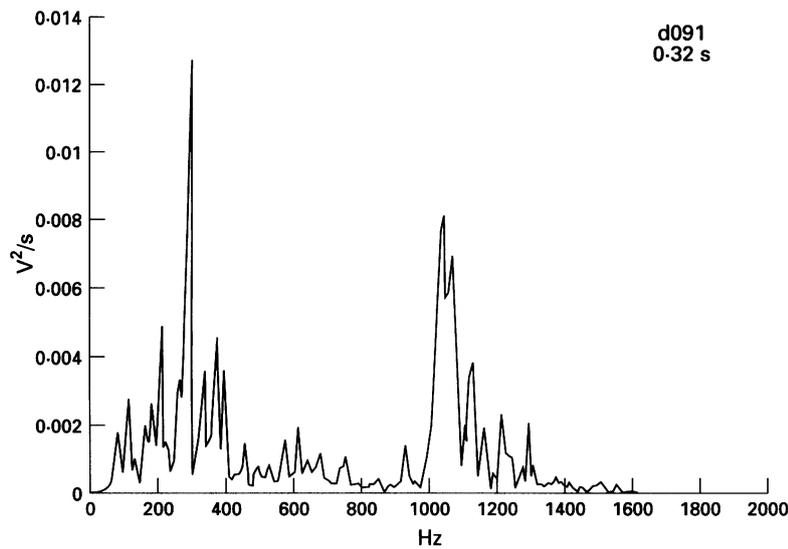


Figure 4 Frequency distribution of sound pattern 4 (series of high-pitched rhonchi). The high-pitched wheezing characteristic for pattern 4 is clearly discernible.

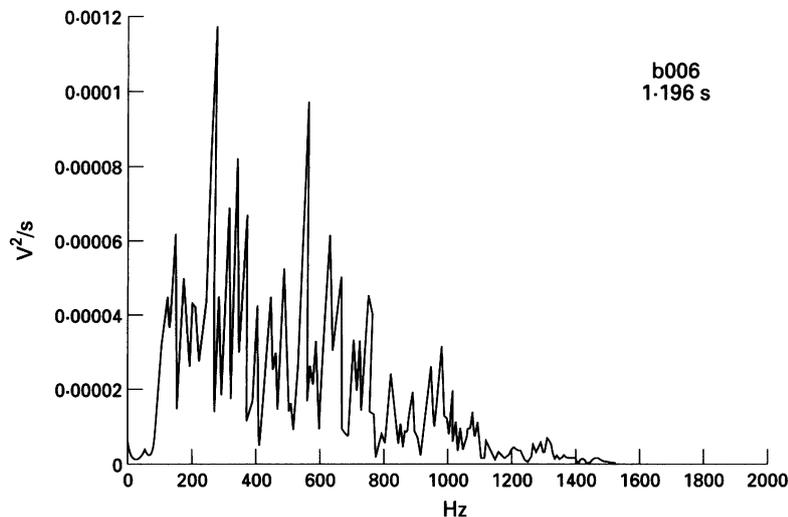


Figure 5 Frequency distribution typically found for sound pattern 5 (solitary rhonchus).

adjustment and a sound rhythm did not develop. The tracheal sound can also change dramatically after coughing or moving. Voluntary coughing before recording may aid the uniformity of the sound, as one cause of variance (extensive mucus) is held constant, but was not used in the present study. The subjects remained seated during sound recording and torso movements were discouraged.

The sound level varied appreciably between the subjects. This may have physiological causes, but also depends on the placement of the microphone. A related effect was that, in some cases, the heart beat was almost invisible on the spectrograph while in others it was a dominant feature. It was decided not to filter out the low frequency components of the spectra because the spectral region of interest may extend down to 150 Hz. The heart tones did not disturb other spectral components.

We did not express the features of the power spectra in statistics such as mean frequency, standard deviation, or percentiles because respiration sound signals are temporarily inhomogeneous. It is a general problem with the power spectrum that it masks the temporal

characteristics of the sound. This is clear in fig 5 where the signal was composed from three in-time, non-overlapping, short peeps which was completely lost. The problem can be avoided by computing the power spectrum over time frames of 25–100 ms, either equidistant in time or in synchrony with, for example, airflow level crossing.<sup>14–16</sup> The latter approach would not be useful for continuous sound recording, whereas the former has the disadvantage of poor time location of sound characteristics. A second objection to computed spectra in simple statistics is that they inadequately describe the frequency distribution such as the harmonics shown in fig 3. It is very likely that these patterns represent phenomena within the reach of physical explanation. Since a satisfactory physical model for the phenomena discussed is lacking,<sup>15</sup> model-based spectral analysis techniques are less useful. Moreover, for the intended clinical applications the analysis must be performed on-line, which precludes the latter processing (averaging) that is often needed for obtaining stable statistics. More relevant for the automated recognition of sound patterns would be real-time techniques in the wavelet signature, comprising both time and frequency information.

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