Potential for lung sound monitoring during bronchial provocation testing

Abraham B Bohadana, René Peslin, Hubert Uffholtz, Gabrielle Pauli

Abstract

**Background** - The use of lung sound monitoring during bronchial provocation testing has not been clearly demonstrated. The appearance of wheeze and changes in inspiratory breath sound intensity have been analysed and related to changes in spirometric parameters and to airways hyperresponsiveness.

**Methods** - Lung sounds were recorded in 38 patients undergoing a routine carbachol airway challenge (CAC) test. Spirometric testing was performed before and after the inhalation of each of five cumulative doses of 320 µg carbachol; a fall in forced expiratory volume in one second (FEV₁) by 20% or more was considered as significant. Lung sound analysis was carried out using a computerised system.

**Results** - The CAC test was positive (CAC+) in 21 patients and negative (CAC-) in 17. At the final stage of the challenge, wheeze was identified in 10 positive patients (48%) and in one negative patient (6%); in non-wheezers the inspiratory breath sound intensity decreased significantly from baseline in 11 CAC+ patients (mean (SD) change -35 (24%)) but not in 16 CAC- patients (mean (SD) change 5 (24%)). In all non-wheezers a linear relationship was found between breath sound intensity and the squared inspiratory airflow ($r^2=0.53-0.92$) which became looser after the inhalation of carbachol.

**Conclusion** - When undertaking bronchial provocation testing the accurate identification of wheeze may prove useful in avoiding or shortening the test because of the presumed relationship between wheeze and airways hyperresponsiveness. Changes in breath sound intensity may also be useful, but further studies are required to define the threshold for significant changes in this index.

(Thorax 1995;50:955-961)

Keywords: wheeze, breath sound intensity, lung sounds, carbachol airway challenge, airways responsiveness.

Non-specific bronchial responsiveness is a term used to describe the tendency of the airways to constrict upon exposure to non-allergic stimuli such as chemical mediators or physical stimuli. In the laboratory, bronchial responsiveness can be measured using inhalation provocation tests with either histamine or a cholinergic analogue such as carbachol. The bronchial response is usually assessed in terms of the provocative dose of the bronchoconstrictor agent leading to a 20% fall in the forced expiratory volume in one second (FEV₁). Obviously, the use of this technique is limited to subjects capable of performing technically acceptable forced expiratory manoeuvres.

It is a common clinical experience that lung sounds are generally abnormal in acute asthma. In mild disease expiratory wheezes may be heard over central airways. As the asthma becomes more severe, biphasic wheezes of varying pitch may be present all over the chest and, on occasion, they may be heard without the aid of a stethoscope. If asthma is severe wheezes may disappear and the chest may become silent, presumably because airflow is so markedly decreased that no energy is available for sound generation. These observations form the rationale for the many studies carried out over the past decade to examine the relationship between lung sounds and indices of airways obstruction in asthma or bronchial provocation testing. The main interest has been focused on wheezing sounds and on spectrum-describing parameters of breath sounds. Despite some promising results, no consistent quantitative data have been presented for individual patients, so no one acoustic index can be considered to reflect accurately the severity of airways obstruction.

Although disappointing, the reported loose relationship between acoustic and spirometric parameters could merely indicate that lung sounds supply information about the functional status of the airways whose nature is different from that supplied by spirometry. If this reasoning is correct, lung sound monitoring during inhalation provocation tests may provide information about airways responsiveness not available from spirometry. To test this hypothesis we used a computerised system to monitor lung sounds in selected patients undergoing routine inhalation provocation testing. Our attention was focused on two acoustic phenomena: the appearance of wheeze, which is the most specific clinical sign of airways obstruction, and changes in inspiratory breath (vesicular) sound intensity, an index likely to be noticeably decreased in pharmacologically induced airways obstruction.

**Methods**

**Patients**

We evaluated 38 patients undergoing routine carbachol airway challenge (CAC) tests at the pulmonary function laboratory of the Centre Hospitalier Universitaire de Nancy-Brabois, France. They were referred for inhalation provocation testing as part of an investigation of...
Table 1  Mean (SD) anthropometric characteristics, smoking habits, and baseline pulmonary function data of patients (n = 38) undergoing routine carbachol airway challenge (CAC) test

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>12:26</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.5 (11.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.5 (7.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.3 (13.6)</td>
</tr>
</tbody>
</table>

Smoking habits:
- Non-smokers: 27
- Ex-smokers: 7 (11.5 pack years)

Baseline pulmonary function tests*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.83 (0.9)</td>
</tr>
<tr>
<td>FVC</td>
<td>0.59 (1.0)</td>
</tr>
<tr>
<td>Vmax&lt;sub&gt;50&lt;/sub&gt;</td>
<td>0.59 (0.9)</td>
</tr>
</tbody>
</table>


dyspnoea (n = 3), cough (n = 7), urticaria (n = 7), bronchial asthma (n = 8), or chronic rhinitis associated or not with nasal polyposis (n = 13). They were asked to stop theophylline and anticholinergics for 48 hours and β<sub>2</sub> agonists for 12 hours before the study. No patients were receiving regular treatment with inhaled steroids or disodium cromoglycate. Their anthropometric characteristics, smoking habits, and pretreatment lung function parameters are shown in table 1.

PULMONARY FUNCTION TESTS

Spirometric tests were performed using an electronic spirometer (Auto Spiro AS 500 Minato Medical Science Co Ltd, Osaka, Japan). Forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>), and maximal expiratory flows at various lung volumes (Vmax<sub>x</sub>) were obtained by asking the subject to expire forcefully after a maximal inspiratory manoeuvre. At baseline at least three reproducible (within 5% for FVC and FEV<sub>1</sub>) forced vital capacity manoeuvres were performed. The largest FVC, Vmax<sub>x</sub> and FEV<sub>1</sub> values were retained for analysis. Results were expressed as standardised residuals (SR) (SR = observed value/predicted value/residual standard deviation) as recommended by the ad hoc committee of the European Respiratory Society. A standardised residual of zero indicates that the observed value is equal to the reference value—that is, at the 50th percentile; standardised residuals of -1.0 to 1.0 indicate that the results are at the 5th percentile and at the 97.5th percentile, respectively.

AIRWAYS RESPONSIVENESS

Carbachol airway challenge (CAC) test was performed according to a protocol used routinely in the pulmonary function laboratory of the Centre Hospitalier Universitaire of Nancy-Brabois. Five cumulative doses of 320 μg carbachol were administered in succession using an FDC 88 dosimeter (Mediprom 75014, Paris, France) delivering fixed doses of 80 μg carbachol per breath. A nose clip was worn and the aerosol inhaled through the mouth by slow inspiratory capacity manoeuvres each separated by a five second breath hold. One minute after the inhalation of carbachol, lung sound recording (see below) and spirometric tests were performed in that order. The sequence—carbachol inhalation, sound recording and spirometry—lasted 2–3 minutes and was repeated until the fifth dose of carbachol (cumulative dose 1600 μg) was inhaled or when FEV<sub>1</sub> fell by 20% or more from the baseline value (PD<sub>20</sub>). In patients in whom the test was positive the challenge was terminated by the inhalation of two puffs (200 μg) of salbutamol.

Patients whose FEV<sub>1</sub> fell by 20% or more were labelled CAC+. Those whose FEV<sub>1</sub> fell by less than 20% were labelled CAC-. The PD<sub>20</sub> in μg carbachol was calculated for each patient by plotting the percentage fall in FEV<sub>1</sub> against the dose of carbachol on a log scale and by interpolating the last two points.

SOUND AND AIRFLOW RECORDINGS

Lung sounds were recorded before and after each aerosol using a system described previously. Sound was picked up by an electronic stethoscope (Andries-Tek, Austin, Texas, USA) placed at the right posterior lung base, 5 cm below the angle of the scapula. Patients were instructed to perform inspirations from functional residual capacity (FRC) as fast and deep as necessary to produce a clearly audible breath sound and to expire passively, as uniformly as possible; however, the respiratory frequency was chosen freely by all subjects. Slight pressure was exerted on the head of the stethoscope in order to leave a mark over the chest which allowed successive recordings to be performed at exactly the same site. The audio signal was heard by auscultation and stored simultaneously on magnetic tape using a three channel tape recorder (Nagra IV-SJ, Kudelski, Switzerland) at a recording speed of 9.525 cm/s. Before recording the audio signal went through two stages of amplification using both the amplifier of the stethoscope and the amplifier incorporated into the tape recorder. The gains of both amplifiers were determined empirically before the study and remained fixed throughout the experiments: the gain of the stethoscope amplifier was at the maximal position whereas the gain of the recorder amplifier was at position -01.

Airflow at the mouth was measured simultaneously using a 47304 Hewlett Packard flow measuring system equipped with a no. 3 Fleisch pneumotachograph and stored in the FM track (no. 3) of the tape recorder. This system is linear for flows up to 10 l/s, a threshold far beyond the expected values during deep inspiratory manoeuvres.

DATA ANALYSIS

The recorded sounds were played back in the sequence in which they were recorded, listened to cycle by cycle through earphones, and displayed simultaneously with the corresponding
flow signal on an oscilloscope (BBC Goerz Metrawatt) for quality control. Material free from voice, movement, or ambient noise artefact was selected for analysis. The amplified audio signal was bandpass filtered between 50 and 2000 Hz, whereas the flow signal was low pass filtered at 20 Hz (Multometrics Model AF 220 Active Filter). Data acquisition, analysis, and display were performed using a customised computer program developed for the purpose of this study. Because wheezes are musical sounds whereas breath (vesicular) sounds are not, their analysis was carried out separately as follows:

**Step I: screening for wheeze**

All sound recordings were first screened for wheeze. In our experience and that of others, this adventitious musical sound tends to be limited to a maximum frequency of 2000 Hz or lower. Thus, to cover its frequency range and allow a good spectral band width the audio signal was digitised (12 bit AD converter) at a sampling rate of 4096 Hz and fed into a microcomputer (Kenitec 486-DX 33). A sound segment of 18 seconds duration (73 728 data points) was saved in the computer memory, from which the first three respiratory cycles were drawn and stored in the computer's hard disk for analysis. Thus, the duration of the sound segment selected for analysis varied according to the respiratory rate. The corresponding flow signal was digitised at 4096 Hz and stored together with the audio signal, thus allowing the determination of the inspiratory and expiratory portions of the respiratory cycle.

The audio signal was submitted to time expanded wave form analysis and its frequency content was assessed by Fourier analysis. For the best audio signal was divided into short segments or data blocks with 50% overlapping between successive blocks. The data blocks were visualised on the computer screen along with the corresponding frequency spectrum. An example is shown in fig 1. Two options were available: blocks of 256 points (0.0625 s) which offered the best time resolution and a frequency resolution of 16 Hz (1/0.0625), and blocks of 512 points (0.125 s) which offered the best frequency resolution (8 Hz). Before Fourier analysis a Hanning window was applied to the data blocks to avoid aliasing. A wheeze was considered to be present when regular, sinusoidal-like oscillations were observed in the time expanded wave form analysis which corresponded to discrete narrow peak (or peaks) of power in the spectral analysis. Moreover, the following peak characteristics were required: (1) the peak had to be distinctly separate from its surrounding sound spectrum; (2) the peak amplitude had to be at least three times larger than the base it arose from; and (3) the width at half amplitude of the peak should not exceed three times the resolution of the measuring system (either 24 or 48 Hz for our system).

**Step II: evaluation of inspiratory breath sound intensity**

Sound recordings of non-wheezers were re-examined for changes in inspiratory breath sound intensity. Wheezers were excluded from this analysis for two reasons: (1) since we were looking for signs of bronchoconstriction, and since wheeze is the most specific sign of this condition, evaluation of breath sound intensity in wheezers would be redundant for this purpose; (2) although wheezes are easy to detect by computer analysis, they can hardly be extracted from the background breath sounds on which they are superimposed.

Each tape was replayed and the amplified audio signal was bandpass filtered between 50 and 700 Hz whereas the flow signal was low pass filtered at 20 Hz (Multometrics Model AF 220 Active Filter). Both signals were then digitised at a sampling rate of 1536 Hz into the microcomputer. This sampling rate was chosen because we had found in preliminary experiments that inspiratory breath sounds in non-wheezing subjects contained no detectable acoustic energy above 500 Hz. A sound segment of 18 seconds duration (27 648 data points) was momentarily saved in the computer memory, from which the first three respiratory cycles were drawn and stored in the computer's hard disk for analysis. Since breath sound occurring during a quiet, passive expiration is too weak and contains almost no sound energy, analysis was restricted to inspiration.
Breath sound intensity was calculated in terms of RMS sound amplitude on successive data blocks of 32 points (1/48 s); the flow signal was averaged over the same periods. Since the sound amplitude is highly flow-dependent, several ventilatory parameters were calculated from the flow signal: (a) inspiratory time (Ti) in seconds; (b) tidal volume (VT) in litres; (c) ratio of tidal volume over inspiratory time (VT/Ti); and (d) the slope and the correlation coefficient (r) of the relationship between the RMS sound amplitude and the corresponding squared inspiratory flow obtained by linear regression analysis; this relationship was examined because a linear correlation between these two variables has been reported in healthy humans. 

Airflow and breath sound intensity signals in a patient free from wheeze are shown in fig. 2. In a preliminary study the variability (dispersion of successive measurements) and the short term reproducibility (difference at a certain time interval) of sound amplitude parameters were determined in five healthy volunteers from the laboratory by repeating the measurements 10 minutes apart. For each acoustic index intrasubject variability was assessed calculating the standard deviation (SD) of the data obtained on three successive respiratory cycles and their mean coefficient of variation (CV% = [SD/x] x 100). Short term reproducibility was assessed by taking the unsigned difference (Am%) between the mean value of the first (m1) and second (m2) examinations expressed as a percentage of their average: $\Delta m% = 2 \times [m1 - m2] \times 100 \ [m1 + m2]$.

### Statistical Analysis

Standard statistical analysis was by means of the Mann-Whitney U test and Wilcoxon signed rank sum test as appropriate. For all analyses the SAS statistical pack was used.

### Results

Of 38 patients, 21 (55.3%) had a positive CAC test (CAC +) and 17 had a negative test (CAC −). Of the 21 CAC+ patients seven had asthma, eight had rhinitis and/or nasal polyposis, three were investigated for cough, two for dyspnoea, and one had urticaria.

At baseline wheeze was identified in five patients. In two wheeze was inspiratory only, in one expiratory, and in two biphasic. The FEV1 of the wheezers was not significantly different from that of the non-wheezers (mean (SD) 0.83 (0.98) standardised residuals versus 0.82 (0.97) respectively, p = 0.4). An example of inspiratory wheeze is shown in fig. 1. At the end of the challenge these sounds were identified in 11 subjects (inspiratory in four, expiratory in four, and biphasic in the remaining three). Finally, in the post-bronchodilator step of the challenge wheezes were still present in six patients (inspiratory in three and expiratory in three).

Wheeze is identified at PD20 in 10 of the 21 CAC+ patients (47.6%). In three the dose of carbachol at which the wheeze appeared (PDw) coincided with PD20 in two wheeze was identified respectively one and three steps before reaching PD20 so that PDw<PD20 in the remaining five wheeze was present already at baseline and persisted throughout the test even after the inhalation of salbutamol. Wheeze was also identified after all aerosols of carbachol in one of the 17 CAC− patients (5.9%). Thus, at the final step of the challenge wheezes were 48% sensitive and 94% specific to detect a drop in FEV1, by 20% or more.

In the 21 CAC+ patients the presence of wheeze correlated well with the severity of the spirometric response to carbachol: in wheezers (n = 10) the mean (SD) percentage fall in FEV1 was 7.4 (8.4).
at PD20 was 38 (14) (range 20–62) compared with 24 (3) (range 21–30) for non-wheezers (n = 11) (p<0.05). Conversely, for wheezers the mean PD20 value in µg carbachol was 279 (455) (range 221–1412) compared with 934 (427) (range 398–1513) for non-wheezers.

The normal variability and reproducibility of the various acoustic and ventilatory variables were within acceptable limits and are shown in table 2. The mean CV% ranged from 3%, seen for VT in session 2, to 11%, observed for breath sound intensity in session 2; for Δm% the lowest and highest values were, respectively, 7% for the correlation coefficient of the breath sound intensity/squared flow relationship and 31% for the slope of this relationship.

At PD20, the inspiratory breath sound intensity decreased noticeably from baseline in CAC+ non-wheezers but not in CAC− non-wheezers; the mean (SD) individual variation in breath sound intensity expressed as a percentage of the initial value for the two subgroups was −35 (24)% and 5 (24)%, respectively (p<0.001).

The absolute values of breath sound intensity and other acoustic and ventilatory variables observed at each step of the challenge are shown separately for the two subgroups of non-wheezers in table 3. The main differences between these two subgroups can be summarised as follows: (a) in CAC+ patients inspiratory time increased significantly after the inhalation of carbachol but did not return towards baseline after the inhalation of salbutamol; (b) in CAC+ patients both breath sound intensity and inspiratory flow (VT/TI) decreased significantly after the inhalation of carbachol and increased back towards baseline values after the inhalation of salbutamol; (c) in both subgroups a positive linear relationship was found between breath sound intensity and the corresponding squared inspiratory airflow with correlation coefficients (r) at baseline ranging from 0.53 to 0.92, and (d) in CAC+ patients both the slope and the coefficient of correlation of the breath sound intensity/squared flow curve decreased significantly at PD20.

**Discussion**

This study identified wheeze in 48% of those subjects with a positive carbachol challenge test and in the remainder the breath sound intensity fell markedly, whereas in those with a negative challenge test only one subject (6%) wheezed and in the remainder breath sound intensity was essentially unchanged. These results suggest a possible role for lung sound monitoring in the context of tests for bronchial hyperresponsiveness.

Wheeze is an adventitious musical sound usually associated with obstructive disorders of the airways. The results of this study confirm our previous observations21 and those of others24,29 that this sign is a poorly sensitive but highly specific detector of airways obstruction. This finding is in keeping with the mechanism of wheeze generation as proposed by Grothberg and Davis21 and by Gavrieli and coworkers28,29. According to these authors, wheeze would result from the coupled oscillation of the airway gas and the airway wall in partially collapsed central airways which occurs when airflow velocity increases above a critical threshold, and the pleural pressure reaches a critical value greater than that required for airways limitation. Since wheeze generation requires airways limitation at a local level, this sign can, but does not necessarily have to be, related to FEV1, an index expressing overall airways limitation. Conversely, overall airways obstruction may coexist with an absence of wheeze.

A clinically useful approach is to analyse the appearance of wheeze during airway inhalation tests in the light of its presumed relationship with airways hyperresponsiveness. Holgate and coworkers28,29 have stressed that, from a symptomatic point of view, airways hyperresponsiveness is related to bronchial irritability (which presents as attacks of wheezing, chest tightness, or shortness of breath upon exposure to various stimuli27), and that “bronchial hyperresponsiveness and irritability are intimately associated with paroxysms of bronchospasm that characterise asthma and comprise a major part of its clinical definition”.28 It therefore seems reasonable to consider that wheeze triggered by non-specific stimuli is in itself a manifestation of airways hyperresponsiveness, a concept that seems to be shared by others.4

The adoption of the above concepts in pulmonary function testing would have had several practical consequences for our patients. Firstly, smaller doses of carbachol would have been
administered to two patients who wheezed before reaching PD_{20}. Secondly, the result of the provocation test would have changed from negative into positive in one female patient who started wheezing after the first dose of carbachol (PD_{W} = 320 μg carbachol) but whose FEV\textsubscript{1}, fell only by 19% at the end of the challenge. Incidentally, this 41 year old non-smoker complained of wheezing, chest tightness, and dyspnoea upon exposure to cotton dust in the textile industry. Her symptoms started characteristically on Monday morning, got worse during the week, and improved considerably over weekends and holidays. Finally, at least four out of five patients who wheezed before the administration of carbachol could have been exempted from provocation testing. Although their baseline FEV\textsubscript{1} was acceptable they had strong clinical and laboratory evidence of asthma (n = 3) or allergic rhinitis (n = 1). In this clinical context, and considering that they were referred for diagnostic purposes only, the presence of wheeze before the challenge could have been reasonably interpreted as enough evidence of airways hyperresponsiveness.

In this study a significant decrease in inspiratory breath sound intensity at PD_{20} was noticed in CAC+ non-wheezer. The relationship between faint breath sounds and airway obstruction was first described by Laennec\textsuperscript{30} in patients with chronic airways obstruction, and confirmed subsequently by several authors.\textsuperscript{31-35} Based upon these studies and on our own experience we reasoned that, if the above relationship holds also in acute conditions, a fall in FEV\textsubscript{1} by 20% or more should be accompanied by a noticeable decrease in inspiratory breath sound intensity over the chest, regardless of the presence of wheeze; such an expectation has been somewhat confirmed in a small group of selected patients.\textsuperscript{10}

The relationship between inspiratory breath sound intensity and airway patency is complex, especially because the mechanism and site of sound production are not entirely known.\textsuperscript{36} Shykoff and colleagues\textsuperscript{20} observed recently that, in intact men, the inspiratory breath sound intensity was highly correlated with the square of the simultaneous flow at the mouth, and suggested that inspiratory breath sound could be generated by pressure fluctuations in the airway bifurcations. In this study we observed a similar significant linear correlation between breath sound intensity and squared flow in all patients tested. However, at PD_{20} not only the correlation coefficients became looser but the slope of this relationship decreased noticeably in CAC+ non-wheezer, a trend which was reverted by the inhalation of salbutamol (table 3, fig 3). This finding supports the view that, in these patients, either the site of sound generation or the sound transmission properties of the lung parenchyma are altered, or both. In fact, had the decrease in RMS observed after carbachol been merely a matter of lower inspiratory flows – as suggested by the observed decrease in Vt/Ti (table 3) – no significant changes would be expected to occur in the slope of the breath sound intensity/squared flow relationship.

The changes in breath sound intensity reported herein are at variance with two previous reports. In one, Tinkelman and colleagues\textsuperscript{17} claimed breath sound intensity to significantly increase at PD_{20} during methacholine challenge testing in children between two and six years old. However, in that study the two phases of the respiratory cycle were not examined separately, neither were wheezers separated from non-wheezer. Thus the hypothesis that the low energy breath sound was “contaminated” by the high energy wheezes cannot be ruled out. In the second study, aimed primarily at examining the changes in frequency spectra of breath sounds during histamine challenge testing, Malmberg and coworkers\textsuperscript{12} measured breath sound intensity simultaneously at the trachea and over the chest in 12 adult asthmatic subjects and six healthy controls. In both groups the average inspiratory breath sound intensity over the chest did not change significantly at end of challenge, despite a mean fall in FEV\textsubscript{1} of 27%. However, these authors recorded breath sounds at much lower inspiratory flows (target peak flow 1-25 l/s) than in our study.

Our observed changes in breath sound intensity could have been influenced by variations in the site of successive recordings, even if they were small.\textsuperscript{38} However, this factor cannot be
entirely responsible for the trend we observed because, had small variations in the site of recording occurred, the chance would be identical for this to produce either spuriously high or low breath sound intensity values in all subjects and not systematically low values as seen in CAC+ patients (table 3). Regarding the variability of our acoustic indices, no similar data are available for comparison. However, compared with indices of lung function, our figures are higher than those seen for FEV₁, but within the range of those of plethysmographic indices.

In conclusion, this study showed that wheeze identification before and after the inhalation of a cholinergic agent is clinically useful provided the concept is accepted that pharmacologically triggered wheeze is as legitimate a manifestation of airways hyperresponsiveness as is a fall in FEV₁. In practice this should prompt the discontinuation of the challenge test or, at least, the lowering of the next dose of the provocative drug. In turn, the presence of wheeze before the challenge can, in the appropriate context, be considered as enough evidence of airway hyperresponsiveness to exempt the patient from the test; if deemed necessary the latter could be carried out employing a low dose protocol as for asthmatics, regardless of the baseline FEV₁. Finally, by extension, the monitoring of inspiratory breath sound intensity seems to be potentially useful; however, as this index has a quantitative dimension further research is necessary to define the range of normal variation.

The authors thank Dr S Meghrebi for performing airway provocation challenge, Mr S Metropolitan for the computer program for data acquisition, and Mr P Wild for help with the statistical analysis.

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Thorax 1995 50: 955-961
doi: 10.1136/thx.50.9.955

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