

How mild is mild asthma?

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Nineteen asthmatic volunteers underwent methacholine-induced asthma to the point when tightness in the chest was just sensed (threshold symptom). Changes in the following indices of lung function were measured—static lung volumes, forced expiratory volume in one second, and airways conductance. The increase in airways resistance necessary for threshold detection was at least double that previously reported in experiments using external resistive loads. Despite the mildness of the symptom, increases in lung volumes to the levels previously described during acute and severe asthma were occasionally found. It is emphasised that there may be little leeway in respiratory reserve between the development of minor and severe symptoms in some asthmatic patients.

The abnormalities in lung function found during both interval asthma (Herschfus *et al.*, 1953; Gold *et al.*, 1967; Cooper *et al.*, 1974) and during acute asthmatic attacks (Woolcock and Read, 1966; Cade *et al.*, 1971; McFadden *et al.*, 1973; Mansell *et al.*, 1974) have previously been reported. Studies examining lung function at the time when symptoms first appear have, however, been limited to experiments using external hindrances to breathing (Bennett *et al.*, 1962; Campbell *et al.*, 1963; Wiley and Zechman, 1966; Newsom Davis, 1967). The aim of the present study was to examine in more detail the changes in lung function in asthmatics, at the point when tightness in the chest was just sensed. This was achieved by measuring various indices of lung function in a number of asthmatic subjects before and after bronchoprovocation to the point when tightness in the chest (threshold symptoms) were just sensed.

Material and methods

Nineteen subjects, each asthmatic since childhood, undertook bronchoprovocation tests on between one and seven occasions each. All gave informed consent. The subject, initially asymptomatic, was seated in a variable pressure plethysmograph and indices of lung function were measured. Bronchoprovocation was then undertaken to the point when tightness in the chest was just perceived and the measurements were repeated. If the subject felt more than 'just barely tight' the threshold was considered to have been passed and the experiment was not included for analysis.

The technique for bronchoprovocation was as follows: Aerosols of methacholine hydrochloride in isotonic saline were generated by Vaponephrin (Bennett) nebulisers driven with an oxygen flow of 5 litres/minute. Methacholine was administered from solutions in the following sequence: 0.5, 1.25, 2.5, 5.0, 10.0, and 25.0 mg/ml. The subject took single vital capacity inhalations of the aerosol through a 1 inch diameter tube in the wall of the plethysmograph at three-minute intervals until tightness in the chest was just sensed (threshold point). Despite the standard method of administration the subject was instructed that aerosols were randomised and that either isotonic saline or active drug may be presented.

The equipment used was as follows: Thoracic gas volume (FRC) and airways conductance (Gaw) were measured in a 900 litre variable pressure plethysmograph (laboratory constructed). A Fleisch No. 4 pneumotachygraph was used to record mouth flow and its signal integrated to show expired volumes. Pneumotachygraph and box pressure changes were recorded with Hewlett Packard P270 pressure transducers. Airways pressure measured while the patient was panting against occlusion was measured with a Hewlett Packard 1280B pressure transducer. Signals were amplified and then recorded on a six-channel SE Laboratories 2005 Ultraviolet Recorder and a Tektronix 531N Split Beam Oscilloscope. Lung volumes were corrected to litres BTPS. Pneumotachygraph derived volumes were assumed to be at BTPS.

The routine used for measurements was the

following: the subject breathed through the pneumotachygraph for six to eight breaths and then performed expiratory reserve volume (ERV) and vital capacity (VC) manoeuvres. This was repeated twice after 30-second intervals. The respiratory rate and tidal volumes were taken as the averages of the five breaths preceding the ERV manoeuvres. After one minute three to five measurements of Gaw and thoracic gas volume, as close as possible to functional residual capacity (FRC), were made according to the method of DuBois *et al.* (1956). Duplicate forced vital capacity (FVC) manoeuvres were then immediately performed. The greatest of the expired volumes, and means of the Gaw measurements and measurements of FRC were used to calculate the indices of airways calibre and static lung volumes (RV and TLC). Bronchoprovocation was begun two minutes after the final baseline FVC manoeuvre.

Predicted normal values for lung volumes and airways conductance were calculated from the tables of Goldman and Becklake (1959) and Pelzer and Thomson (1966) respectively. For any subject undergoing bronchoprovocation more than once, averages of the individual baseline and threshold lung function indices were used for calculations. The mean results for the group were derived from the 19 individual averages.

Results

MEAN CHANGES IN LUNG FUNCTION AT THRESHOLD
In order to obtain an overview of the changes in lung function needed to register a threshold symptom for the group, each individual's pre- and post-provocation results were combined, and the group means and standard deviations were obtained (Table 1).

Table 1 Comparison of lung function indices in the baseline state and threshold state

Lung function	Baseline values		Values after methacholine provocation		<i>t</i>	<i>P</i>
	Mean	SD	Mean	SD		
TLC	103.2	10.5	109.8	11.8	3.42	< 0.01
FRC	107.7	15.4	127.6	21.3	4.95	< 0.001
RV	141.4	33.5	181.3	41.2	4.53	< 0.001
FEV ₁	90.6	16.9	73.4	17.9	6.43	< 0.001
Gaw	75.1	19.3	39.6	15.2	11.48	< 0.001

TLC, FRC, RV, FEV₁, Gaw expressed as % of predicted values.
t = value for paired Student's *t* test.
P = level of significance of *t* value.

Statistically significant increases in all static lung volumes occurred in the change from the

asymptomatic to the threshold state. The increase in TLC although statistically significant was physiologically minor.

Similarly, statistically significant falls in airway calibre occurred. In particular, the mean change in Gaw required to produce a threshold symptom was of the order of 47%. Converted to its reciprocal, airways resistance (Raw), this is equivalent to an 89% increase in Raw.

DISTRIBUTIONS OF CHANGES IN LUNG VOLUME AND AIRWAY CALIBRE

Histograms for the distribution of baseline values and proportional changes of selected indices of lung function are illustrated in Figures 1 and 2.

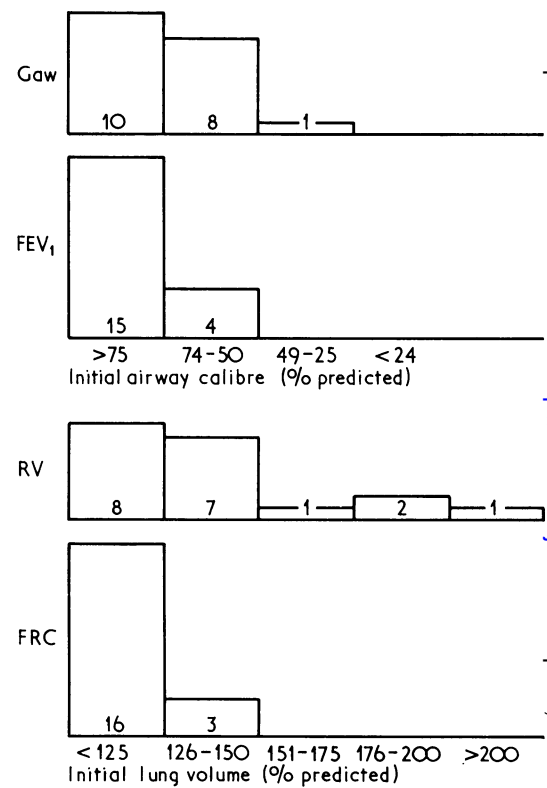


Fig. 1 Distributions for some indices of airway calibre and lung volumes in the baseline state.

None of the subjects had a forced expiratory volume—one second (FEV₁) of less than 50% predicted in the asymptomatic state. In every case a reduction in FEV₁ was documented at the time when symptoms developed. In four of the 14 subjects these falls were quite modest, being less than 10% of the baseline value.

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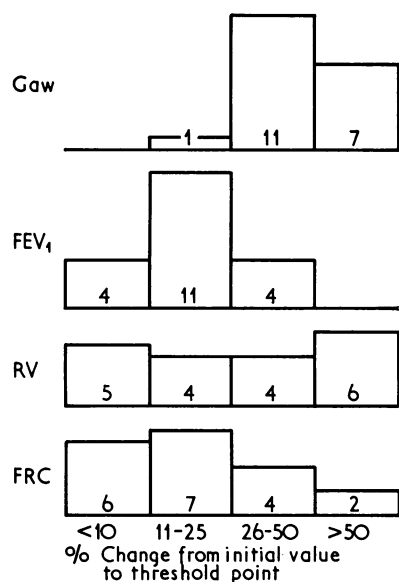


Fig. 2 Distributions for changes in indices of lung function in moving from asymptomatic to threshold state.

Similarly, reductions in Gaw were documented in every subject as symptoms developed. These were proportionately greater than the corresponding changes in FEV₁.

Broader distributions of change were seen in static lung volumes. An increase in FRC or RV was not invariably associated with the change from the asymptomatic to the threshold state. An increase in the static lung volumes was the general pattern seen. However, in some subjects, despite the modest symptoms, the increases amounted to more than 50% of the original static lung volume measured.

MAGNITUDE OF INDIVIDUAL CHANGES IN LUNG VOLUMES

Table 2 illustrates the comparison between an individual's FRC in the asymptomatic state and RV at threshold. If the latter was within 10% of baseline FRC the values were considered comparable; and similarly for asymptomatic TLC versus threshold FRC.

Of the 19 subjects, seven showed an RV at threshold comparable to or greater than FRC while asymptomatic. One subject increased her FRC, when threshold symptoms were just sensed, to almost that of her TLC in the asymptomatic state.

Table 2 Comparison of individuals' averaged lung volumes (litres BTPS) in the baseline and threshold states

Subject	Baseline FRC	Threshold RV	Baseline TLC	Threshold FRC
JA	4.38	3.76	8.01	4.56
LA	2.49	2.02	4.73	2.81
PA	3.83	2.60	7.10	5.27
MB	2.49	3.15 ¹	5.43	3.86
KG	2.64	2.62 ¹	5.10	3.36
AG	4.68	3.06	7.12	4.60
SH	3.70	4.08 ¹	6.42	4.71
ML	3.05	2.51	5.16	3.48
PL	4.23	2.90	7.78	4.90
NL	3.89	2.45	7.28	4.04
AMcC	4.63	4.55 ¹	6.79	4.75
DMcL	3.04	3.17 ¹	5.01	4.75 ¹
RM	3.70	1.54	7.44	3.87
MP	3.45	3.32 ¹	5.74	4.12
AR	5.20	3.98	7.75	5.80
AS	4.49	3.60	7.81	5.19
WT	3.69	2.10	6.58	4.38
DT	4.07	3.68 ¹	7.67	5.31
DW	3.45	1.77	5.68	3.38

¹ Signifies threshold RV approximately equal to or greater than baseline FRC (or threshold \geq baseline TLC).

Discussion

This study has concentrated on the abnormalities in lung function early in the evolution of asthma when symptoms of tightness in the chest were just barely sensed. In investigating such a potentially unstable situation certain compromises in methodology were accepted.

Indices of large airways calibre and lung volumes are reported. McFadden (1975) demonstrated that exertional dyspnoea may be due to dysfunction localised to the small airway in asthmatics. However, in a situation where large airways calibre is demonstrably compromised, small airways dysfunction cannot be easily quantified (Despas *et al.*, 1972). This aspect of pulmonary dysfunction has therefore been disregarded for the present.

Previous studies have demonstrated that lung function may transiently change after maximal respiratory manoeuvres (Nadel and Tierney, 1961; Lloyd, 1967). A compromise was accepted in the timing of the manoeuvres performed in obtaining the indices of lung function and in the timing of methacholine administration. In waiting one minute after VC manoeuvres and two minutes after FVC manoeuvres one would hope that the changes these manoeuvres may induce in susceptible subjects would have largely resolved. Similarly, it might be argued that lung function may not yet have stabilized three minutes after methacholine provocation. Cade *et al.* (1971), however,

demonstrated that this was the time for peak response to this agent, and the timing of our doses was based on this.

The results reported use averages for each individual's indices of lung function. The nature of the study, however, has precluded a more objective measure of a threshold, such as that used in studies transiently adding an external load to breathing, ie, threshold load is that detected on only 50% of the occasions presented. On the other hand, the subjective threshold reported by our subjects probably more closely represent symptoms during spontaneous asthma.

While we describe an 'internal load', we are aware that our measurements of lung function give only a limited indication of the mechanical changes seen during the attacks. The lack of data obtainable with more invasive procedures was offset by the advantages of having our subjects available for repeated studies.

Finally, we have considered absolute R_{aw} rather than the more common index, specific airway resistance (ie, R_{aw} /thoracic gas volume). Our reasons are these: FRC and R_{aw} were the indices measured at the lung volume present when symptoms developed. These measurements, furthermore, did not require forced or maximal respiratory manoeuvres. Since each independently provides information about the resistive and elastic components of the induced load, we considered that each should be compared in isolation.

Before extrapolating from the present experiments to a situation of spontaneous clinical asthma, it must be admitted that the induced attacks are merely models used to study the perception of this illness. However, we have demonstrated in 10 subjects that the abnormalities in lung function measured during such induced thresholds were comparable to those measured when the subjects presented spontaneously, with similar symptoms (unpublished data). We feel justified in accepting this model as an acceptable mimic of spontaneous asthma. Given these compromises a number of points have emerged, illustrating the fact that symptomatically mild asthma may be associated with unexpectedly gross physiological abnormalities in lung function.

In many of the 19 subjects studied, the changes in lung function required to induce a threshold symptom were modest. A reduction in airways calibre was documented in each subject. In some subjects this was as little as a 10% change from the initial FEV_1 . This is less than the 20% fall quoted by Haydu *et al.* (1974). On the other hand, their study was not designed to study lung function at the first onset of symptoms.

In a small but possibly important minority of our patients, however, large changes in lung volumes and airways calibre occurred despite the threshold symptom. These changes are emphasised by a comparison of absolute lung volumes at the threshold state compared to the asymptomatic state. In seven of the 19 subjects RV at threshold was approximately equal to or greater than the baseline FRC. In one subject the FRC at threshold had increased to approximately the asymptomatic TLC.

Woolcock and Read (1966), in studying 30 subjects requiring admission to hospital because of severe asthma, documented in about two-thirds of their subjects an increase in RV to the levels of post-treatment FRC. In almost a third of their patients, FRC was of the order of post-treatment TLC. The presence of subjects currently reported with similar degrees of hyperinflation (and concomitant reduction in airway calibre) despite only threshold symptoms emphasises the fact that some asthmatics may have very little leeway in respiratory reserve between the first onset of symptoms and incapacitating asthma.

It is of interest to compare the current alterations in airway calibre needed to induce a threshold symptom with prior studies on threshold detection of externally loaded breathing. Bennett *et al.* (1962) and Wiley and Zechman (1966) documented that subjects required an increase of approximately 25% in total respiratory resistance just to perceive an externally added resistive load. The mean reduction in G_{aw} needed for threshold detection of internal loading in the present study was approximately 47% (equivalent to an 89% increase in R_{aw}). While comparisons between internal and external loading experiments may be invalid, the present data suggest that threshold detection of internally loaded breathing seems less sensitive than that of loads transiently added to the mouth. This highlights the limitations of external loading experiments as biologically appropriate models for the quantitation of sensations associated with breathing (Wood, 1970).

In conclusion, the present study has documented a broad range of alterations in lung volumes and airways calibre among 19 subjects provoked to the point when chest tightness was just perceived. A minority of subjects demonstrated alterations in lung volumes of a degree previously described only in subjects with asthma severe enough to require admission to hospital. That a few subjects with minimal symptoms may have a dramatically diminished respiratory reserve emphasises the need for aggressive treatment of acute attacks of symptomatic asthma.

This work was undertaken with the informed consent of each subject reported; the study was approved by the Ethics Committee of the Royal Melbourne Hospital.

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