LUNG MECHANICS DURING PROVOCATION OF ASTHMA

J. F. CADE, ANN J. WOOLCOCK, A. S. REBUCK AND M. C. F. PAIN

University of Melbourne Department of Medicine and Respiratory Unit, Royal Melbourne Hospital, and Department of Medicine, University of Sydney, Australia

(Received 29 September 1970)

SUMMARY

1. The mechanical properties of the lungs of five symptom-free asthmatic subjects and two normal subjects were measured before and during provocation with nebulized methacholine.

2. Before provocation abnormalities of some aspects of the mechanical function of the lungs were found in four of the asthmatic subjects.

3. Pulmonary resistance increased within one breath of the methacholine inhalation and was the measurement of lung function which changed most in response to methacholine in both asthmatic and normal subjects. However, asthmatic subjects had a much greater response than normal subjects.

4. The results of the study suggest that both the large and the small airways respond to provocation with methacholine. The larger airways appear to respond faster than the smaller airways and the response of the smaller airways appears to be more prolonged.

Abnormalities of the mechanical function of the lungs during acute and chronic spontaneous asthma are well recognized and the improvement which occurs during recovery from attacks has also been documented (Engström, 1964; Woolcock & Read, 1966; McFadden & Lyons, 1969). In addition, the mechanical function of the lungs frequently remains abnormal even in the completely symptom-free asthmatic subject (Gold, Kaufman & Nadel, 1967; McFadden & Lyons, 1968; Woolcock, Vincent & Macklem, 1969).

Acute provocation in asymptomatic patients with asthma provides a convenient model for examining some of the functional abnormalities which occur during an asthmatic episode. In the present study measurements of plethysmographic lung volumes, airways resistance, static elastic properties and dynamic compliance as a function of frequency, together with standard spirometric lung volume and gas-mixing measurements were made in young asthmatic subjects in the symptom-free state to document any residual abnormalities of function. Changes

Correspondence: Dr A. J. Woolcock, Department of Medicine, University of Sydney, Sydney, N.S.W. 2006, Australia.
in all of these indices, except static elastic properties, were then studied after the inhalation of methacholine, an agent particularly suitable for asthma provocation (Parker, Bilbo & Read, 1965; Itkin, 1967; Cade & Pain, 1971).

METHODS

Five asthmatic and two normal subjects were studied and their clinical details are summarized in Table 1. All were symptom-free at the time of the investigation. Subject C.M. had not had an attack since the age of 6 years but all the others had been symptomatic in the recent past with documented reversible airways obstruction. Two subjects were receiving corticosteroid therapy, three disodium cromoglycate, four inhaled bronchodilators and one no therapy at all.

All measurements were made with the subject seated in a body plethysmograph (Mead, 1960). A Godart Pulmotest spirometer was connected to the mouthpiece of the plethysmograph via a three-way tap which allowed the subject to breathe either from the room or from the spirometer. The spirometer was used to measure vital capacity (VC), forced expiratory volume in 1 s (FEV₁) and, with a Godart helium analyser, functional residual capacity by the closed-circuit helium method [FRC(He)]. The final helium reading was taken when the helium concentration had been stable for 2 min. Readings were taken at 10 s intervals during the initial 3 min and at 30 s intervals thereafter to permit two-compartment analysis, as described by Read (1958). The volume of the 'poorly ventilated space' (Vpvs), expressed as a percentage of the FRC(He), was used as an index of impaired gas mixing or maldistribution of ventilation. A value of more than 30% was considered abnormal.

The thoracic gas volume (VTG) was then measured by the method of Dubois, Botelho, Bedell, Marshall & Comroe (1956) by using the circuit described by Bernstein & Shepard (1966). Mouth pressure was recorded with a Sanborn 268B transducer and was displayed against an amplified volume signal on a storage oscilloscope (Tektronix 254). A calibrated graticule on the face of the oscilloscope was used to read the slope of the resulting line. Several measurements of VTG were made and related to the resting end-expiratory value to obtain plethysmographic functional residual capacity [FRC(P)]. Plethysmographic values for total

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Duration of asthma</th>
<th>Current therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td>L.C.</td>
<td>F</td>
<td>22</td>
<td>163</td>
<td>Episodic since infancy</td>
<td>+</td>
</tr>
<tr>
<td>H.K.</td>
<td>F</td>
<td>21</td>
<td>165</td>
<td>Episodic since infancy</td>
<td>-</td>
</tr>
<tr>
<td>W.L.</td>
<td>F</td>
<td>23</td>
<td>165</td>
<td>Episodic since infancy</td>
<td>-</td>
</tr>
<tr>
<td>G.H.</td>
<td>F</td>
<td>23</td>
<td>163</td>
<td>Episodic since infancy</td>
<td>+</td>
</tr>
<tr>
<td>C.M.</td>
<td>F</td>
<td>22</td>
<td>156</td>
<td>None for 16 years</td>
<td>-</td>
</tr>
<tr>
<td>E.T.</td>
<td>M</td>
<td>33</td>
<td>164</td>
<td>Never</td>
<td>-</td>
</tr>
<tr>
<td>P.D.</td>
<td>M</td>
<td>33</td>
<td>177</td>
<td>Never</td>
<td>-</td>
</tr>
</tbody>
</table>

* Disodium cromoglycate.
Lung mechanics in asthma 383

lung capacity [TLC(P)] and residual volume [RV(P)] were also obtained. These values were all recorded at body temperature whereas the FRC(He) values were obtained with part of the equilibrating gas volume at room temperature and part of it at body temperature. Since the appropriate temperature correction is arguable, no correction was made to this volume. Normal values used were those of Goldman & Becklake (1959).

Before entering the plethysmograph each subject had an oesophageal balloon placed with its tip between 40 and 42 cm from the external nares. The catheter was positioned and the balloon volume adjusted in the standard manner (Milic-Emili, Mead, Turner & Glauser, 1964). Transpulmonary pressure was recorded with a Sanborn 268B transducer and flow was recorded by using a heated Fleisch flow head and a Sanborn 270 transducer. Pulmonary resistance (Rt) was measured by displaying transpulmonary pressure and flow on the other two axes of the storage oscilloscope, the loop was closed by the method of Mead & Whittenberger (1953) and the slope of the resulting line read with the graticule.

Mouth pressure, transpulmonary pressure, flow, volume, flow-resistant pressure and amplified volume were recorded on a six-channel Sanborn polyviso.

Static elastic properties were measured by having the subject inspire from FRC to TLC and back to FRC several times while the airway opening was occluded periodically for 1–2 s. Static transpulmonary pressure was then plotted against volume. Dynamic compliance (D\text{dy}) at different frequencies was measured by using a technique similar to that used by Woolcock et al. (1969). If it was less than 80% of C\text{stat} at 60 breaths/min C\text{dy} was considered to be frequency dependent.

After the initial measurements of mechanical function, methacholine aerosol was given in the manner described by Cade & Pain (1971). During each inhalation approx. 0.5 mg of methacholine was delivered as the 2.5% solution from a Bennett ‘Vaponephrin’ nebulizer driven by compressed air. Repeated measurements of Rt, FRC(P), VC, FEV\textsubscript{1} and C\text{dy} were then made. In the asthmatic subjects, further measurements were made after the administration of isoprenaline aerosol.

Before the study all subjects signed a written statement which indicated that they understood the nature of the procedure and were willing to participate in the study.

RESULTS

The initial physiological status of the normal and asthmatic subjects is listed in Table 2. One asthmatic subject (C.M.), symptom-free for 16 years, had completely normal mechanical function. In two subjects (H.K. and W.L.) the abnormalities detected were frequency dependence of compliance, an abnormally high plethysmographic FRC, an elevated RV/TLC ratio and impaired gas mixing. Subjects G.H. and L.C. had abnormalities of most indices of mechanical function. The mechanical function of the lungs of the control subjects was normal except for some frequency dependence of compliance in one (P.D.).

In general the subjects with the greatest degree of frequency dependence of compliance had the most overinflation as measured by plethysmography and the highest RV/TLC ratios. The abnormalities found did not correlate with FEV\textsubscript{1}, FEV\textsubscript{1}/VC ratio, FRC(He) or Rt which were close to normal in all subjects except L.C. and G.H.

The static compliance was normal in all subjects although the specific compliance (C\text{stat}/FRC) was marginally low in four (L.C., H.K., W.L. and G.H.). The static pressure-volume
curves when plotted as a function of predicted TLC, using TLC(P), were shifted up and to the left of the predicted curves for people of the same age group (Turner, Mead & Wohl, 1968) in all except C.M. and the two control subjects.

The changes after methacholine and isoprenaline in the asthmatic subjects and after methacholine in the normal subjects are shown graphically in Figs. 1 and 2. The number of inhalations of methacholine and the time and magnitude of the maximal documented change in each measurement for all subjects are given in Table 3. Inhaled methacholine in very small doses

### Table 2. Initial values of lung mechanical function

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test</th>
<th>L.C.</th>
<th>H.K.</th>
<th>W.L.</th>
<th>G.H.</th>
<th>C.M.</th>
<th>E.T.</th>
<th>P.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC*</td>
<td></td>
<td>83</td>
<td>70</td>
<td>85</td>
<td>93</td>
<td>106</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>FEV₁*</td>
<td></td>
<td>56</td>
<td>89</td>
<td>101</td>
<td>77</td>
<td>109</td>
<td>104</td>
<td>101</td>
</tr>
<tr>
<td>FEV₁/VC†</td>
<td></td>
<td>48</td>
<td>95</td>
<td>89</td>
<td>62</td>
<td>77</td>
<td>91</td>
<td>76</td>
</tr>
<tr>
<td>FRC(He)*</td>
<td></td>
<td>107</td>
<td>103</td>
<td>112</td>
<td>133</td>
<td>92</td>
<td>108</td>
<td>99</td>
</tr>
<tr>
<td>FRC(P)*</td>
<td></td>
<td>153</td>
<td>150</td>
<td>152</td>
<td>166</td>
<td>98</td>
<td>110</td>
<td>111</td>
</tr>
<tr>
<td>ΔFRC†</td>
<td></td>
<td>42</td>
<td>45</td>
<td>35</td>
<td>24</td>
<td>7</td>
<td>10-5</td>
<td>12</td>
</tr>
<tr>
<td>TLC(He)*</td>
<td></td>
<td>108</td>
<td>87</td>
<td>97</td>
<td>111</td>
<td>106</td>
<td>95</td>
<td>108</td>
</tr>
<tr>
<td>TLC(P)*</td>
<td></td>
<td>131</td>
<td>114</td>
<td>123</td>
<td>135</td>
<td>109</td>
<td>104</td>
<td>118</td>
</tr>
<tr>
<td>RV/TLC(He)†</td>
<td></td>
<td>41</td>
<td>42</td>
<td>38</td>
<td>40</td>
<td>28</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>RV/TLC(P)†</td>
<td></td>
<td>47</td>
<td>50</td>
<td>46</td>
<td>46</td>
<td>27</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Vₚᵥₛ/FRC(He)†</td>
<td></td>
<td>31</td>
<td>30</td>
<td>49</td>
<td>51</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R₂ cmH₂O/LPS</td>
<td></td>
<td>5-0</td>
<td>1-5</td>
<td>1-2</td>
<td>1-6</td>
<td>1-5</td>
<td>0-9</td>
<td>1-8</td>
</tr>
<tr>
<td>R₁ × FRC(P)</td>
<td></td>
<td>21-5</td>
<td>6-5</td>
<td>5-3</td>
<td>7-4</td>
<td>3-7</td>
<td>3-4</td>
<td>7-7</td>
</tr>
<tr>
<td>C₁stat cmH₂O</td>
<td></td>
<td>0-167</td>
<td>0-200</td>
<td>0-185</td>
<td>0-190</td>
<td>0-167</td>
<td>0-200</td>
<td>0-240</td>
</tr>
<tr>
<td>C₁stat/FRC(P)</td>
<td></td>
<td>0-039</td>
<td>0-046</td>
<td>0-042</td>
<td>0-041</td>
<td>0-068</td>
<td>0-053</td>
<td>0-055</td>
</tr>
<tr>
<td>C₁dyn/C₁stat(f)‡</td>
<td></td>
<td>36 (30)</td>
<td>69 (60)</td>
<td>67 (60)</td>
<td>42 (60)</td>
<td>85 (60)</td>
<td>93 (60)</td>
<td>63 (45)</td>
</tr>
</tbody>
</table>

* Expressed as a percentage of predicted.
† Expressed as a percentage.
‡ Respiratory frequency at which measurement was made.

(one to five inhalations) produced an immediate increase in $R_L$ in all five asthmatic subjects, accompanied by symptoms similar to an attack of asthma of moderate (G.H. and L.C.) or mild (H.K., W.L. and C.M.) severity. There was a decrease in FEV₁ in all subjects, an increase in FRC(P) in four subjects and in one subject (G.H.) the TLC increased by more than 10%.

In all subjects the changes produced by methacholine reached maximal values within a few minutes and then spontaneously began to subside, except in subject G.H. who was given isoprenaline before $R_L$ had begun to decrease spontaneously. When isoprenaline aerosol was given, a rapid return of all functional abnormalities towards pre-provocation values occurred in all subjects.

In the two normal subjects the response was slower and much smaller despite a considerably greater dose of methacholine. The most significant changes were in the values of $R_L$ and $C_{dyn}/C_{stat}$ at rapid respiratory rates.

In all subjects the measurement that changed most rapidly was $R_L$. In the asthmatic subjects
<table>
<thead>
<tr>
<th>Subject</th>
<th>No. of inhalations</th>
<th>$R_L$ cmH$_2$O/ LPS</th>
<th>% increase $R_L$</th>
<th>Time*</th>
<th>% increase FRC (P)</th>
<th>Time*</th>
<th>% decrease FEV$_1$</th>
<th>Time*</th>
<th>% decrease VC</th>
<th>Time*</th>
<th>FEV$_1$</th>
<th>RV*</th>
<th>$C_{dyn}$$^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.C.</td>
<td>3</td>
<td>29.0</td>
<td>480</td>
<td>2.0</td>
<td>51</td>
<td>6.0</td>
<td>69</td>
<td>8.0</td>
<td>72</td>
<td>8.0</td>
<td>51</td>
<td></td>
<td>20 (30)</td>
</tr>
<tr>
<td>H.K.</td>
<td>2</td>
<td>5.6</td>
<td>270</td>
<td>2.4</td>
<td>11</td>
<td>8.5</td>
<td>35</td>
<td>7.0</td>
<td>21</td>
<td>7.0</td>
<td>87</td>
<td>60</td>
<td>37 (60)</td>
</tr>
<tr>
<td>W.L.</td>
<td>5</td>
<td>22.0</td>
<td>1770</td>
<td>2.5</td>
<td>25</td>
<td>17.5</td>
<td>70</td>
<td>25.5</td>
<td>45</td>
<td>8.0</td>
<td>51</td>
<td>65</td>
<td>20 (60)</td>
</tr>
<tr>
<td>G.H.</td>
<td>1</td>
<td>27.0</td>
<td>1590</td>
<td>1.25</td>
<td>45</td>
<td>2.0</td>
<td>73</td>
<td>2.0</td>
<td>68</td>
<td>2.0</td>
<td>52</td>
<td>81</td>
<td>—</td>
</tr>
<tr>
<td>C.M.</td>
<td>3</td>
<td>9.0</td>
<td>500</td>
<td>2.0</td>
<td>12</td>
<td>6.0</td>
<td>18</td>
<td>6.0</td>
<td>8</td>
<td>2.0</td>
<td>69</td>
<td>31</td>
<td>18 (60)</td>
</tr>
<tr>
<td>E.T.</td>
<td>10</td>
<td>4.8</td>
<td>230</td>
<td>7.0</td>
<td>6</td>
<td>10.0</td>
<td>10</td>
<td>9.0</td>
<td>5</td>
<td>9.0</td>
<td>86</td>
<td>44</td>
<td>43 (60)</td>
</tr>
<tr>
<td>P.D.</td>
<td>10</td>
<td>5.3</td>
<td>139</td>
<td>4.0</td>
<td>8</td>
<td>4.5</td>
<td>13</td>
<td>7.5</td>
<td>6</td>
<td>7.5</td>
<td>70</td>
<td>37</td>
<td>47 (45)</td>
</tr>
</tbody>
</table>

* Time in minutes from end of last inhalation.

† Dynamic compliance (at the frequency in breaths/min in parentheses) as a per cent of $C_{stat}$. 

Lung mechanics in asthma 

385
FIG. 1. Changes in pulmonary resistance ($R_L$), forced expiratory volume in 1 s (FEV$_1$) and plethysmographic lung volumes ($V$) in response to inhalation of methacholine (M) followed by isoprenaline (I) in three of the asthmatic subjects. The values for functional residual capacity (FRC), total lung capacity (TLC) and FEV$_1$ are in litres and those for $R_L$ are in cm of H$_2$O l$^{-1}$ s$^{-1}$.
FIG. 2. Changes in the same parameters of lung function as those illustrated in Fig. 1 in two asthmatic subjects (upper part of figure) and in two normal subjects (lower part of figure). All values and abbreviations are the same as those in Fig. 1.
this rose to a maximum within 2.5 min and then fell rapidly in all subjects except H.K. in whom the response was smaller and was maintained for 6 min. In all subjects the changes in $R_L$ preceded the changes in FEV$_1$. The FRC(P) was not measured as frequently but it appeared to change at a rate between that of $R_L$ and of FEV$_1$.

DISCUSSION

It has previously been shown that in symptom-free asthmatic subjects some aspects of the mechanical function of the lungs remain abnormal. In particular, the distribution of ventilation remains uneven as indicated by abnormalities of gas mixing and frequency dependence of compliance (McFadden & Lyons, 1968; Woolcock et al., 1969), and overinflation may persist (Woolcock & Read, 1966; Gold et al., 1967). In the present study, despite the absence of symptoms, residual abnormalities of lung mechanical function were found in each asthmatic subject except the one who had been completely free from symptoms for 16 years. Uneven distribution of ventilation, as indicated by frequency dependence of compliance and impaired 'gas mixing', together with overinflation, as indicated by the high FRC(P) and plethysmographic RV/TLC ratios, were the most common abnormalities.

Pulmonary resistance and specific resistance ($R_s \times FRC(He)$) were abnormal in only one subject although, when $R_L$ was related to FRC(P), it was abnormal in two subjects. In the present study more residual abnormalities of mechanical lung function were detected when the plethysmographic rather than the helium dilution results for FRC were used.

A significant difference in the values of FRC determined by the two methods was found in four of the asthmatic subjects. This difference between FRC(P) and FRC(He), ($\Delta$FRC), is equivalent to the degree of 'gas trapping' described by Bedell, Marshall, Dubois & Comroe (1956). Meisner & Hugh-Jones (1968) measured TLC by these methods in both symptomatic and symptom-free asthmatic subjects and found the plethysmographic values to be considerably higher than these obtained by helium dilution. They suggested that helium dilution underestimates TLC in patients with moderately severe asthma, even when they are symptom-free.

In the present study the magnitude of $\Delta$FRC showed some relationship to RV/TLC ratio and to VC but the numbers were too small to permit statistical analysis. There was no correlation with other measurements, such as the volume of the 'poorly ventilated space'. If the difference is in fact due to underestimation of FRC by helium dilution, presumably there are non-ventilating yet aerated regions of the lung. Why such regions are present in some but not all asthmatics and why their size apparently bears no relationship to the degree of airways obstruction is unclear.

Methacholine caused a change in all measurements of mechanical function in the asthmatic subjects. There was considerable individual variation in reactivity, for in subject G.H. one inhalation caused a greater response than five inhalations in subject W.L. The subject whose lung function was within normal limits (C.M.) showed a response that was similar to that seen in the other asthmatics. Thus, in spite of 16 years without symptoms, the response of her lungs remained similar to that seen in the asthmatic rather than the non-asthmatic population (Cade & Pain, 1971).

The mechanical changes that occur during acute provocation can be more thoroughly analysed with the body plethysmograph and an oesophageal balloon than with simple spiro-
Lung mechanics in asthma

389

metry. With the value of $R_L$ for each breath displayed and stored on the oscilloscope it was possible to demonstrate in the asthmatic subjects that $R_L$ began to increase from the first breath after the inhalation of methacholine and that it then increased rapidly to a maximal value within 2.5 min. In normal subjects the response was much slower and of smaller magnitude. There was, however, a definite increase in $R_L$ in both normal subjects.

Because FRC can be measured rapidly in the plethysmograph, several measurements could be made during the course of the provocation. It was thus possible to document the magnitude and, to some extent, the time-relationships of the changes in FRC(P). Its rapid increase could in fact be seen to occur breath by breath on the volume tracing on the Sanborn polyviso. In all subjects FRC(P) reached a maximum value later than $R_L$ (Table 3) and then returned towards resting values at a slower rate than $R_L$. By using the data from all seven subjects, the maximal increase in FRC(P) was found to correlate well with the maximal value for $R_L$ ($r = 0.96$, $P<0.001$) and with the maximal decrease in VC ($r = 0.97$, $P<0.001$), but it correlated less well with the maximal decrease in FEV$_1$ ($r = 0.88$, $P<0.01$). In spite of the good correlation between maximal changes in FRC(P) and maximal values for $R_L$, in the resting state FRC(P) remained elevated in four of the asthmatic subjects although $R_L$ remained abnormal in only one. It would seem that in the resting state the lungs maintain a normal value for $R_L$ at the expense of residual overinflation.

The TLC increased by 14% within 2 min of the inhalation of the methacholine in one subject. The magnitude of the response in this subject led to her being given isuprel before any further measurements could be made. More than one measurement of TLC would be needed to validate this observation, but, if true, it suggests that it is possible to increase TLC acutely. Such an increase probably means that a rapid change in the pressure–volume characteristics of the lung itself has occurred.

The FEV$_1$ decreased in all subjects in response to methacholine and increased after isoprenaline, but it lagged behind the changes in $R_L$ and FRC(P). Although on many occasions $R_L$ fell immediately after the recording of an FEV$_1$, indicating that the full inflation involved may have prevented further increase in $R_L$ or hastened its fall during recovery, this phenomenon is not large enough nor does it last long enough (Nadel & Tierney, 1961) to account for the delay in recovery of the FEV$_1$. In addition, the maximal change in FEV$_1$ was poorly related in magnitude to maximal change in FRC(P) or to the maximal value of $R_L$.

Changes in VC related well, both in time and magnitude, to changes in FEV$_1$ and correlated better with FRC(P) and maximal values of $R_L$ than did the changes in FEV$_1$. The change in FEV$_1$/VC ratio, so often used as an index of airways obstruction, showed no relation to any other measurement of function and in one subject (L.C.) it actually increased at the time of maximal response to methacholine.

Although it is not possible to determine the exact site of the airways narrowing during a spontaneous or provoked attack of asthma, some indication can be obtained from the changes in mechanical function. McFadden & Lyons (1968) and Woolcock et al. (1969) showed that in patients with symptom-free asthma the distribution of ventilation remains uneven while other parameters of function are normal, indicating residual abnormality in the small airways. It is known that changes in $R_L$ predominately reflect changes in the large airways (Macklem & Mead, 1967) whereas FEV$_1$ is determined mainly by the elastic recoil of the lung and the resistance of the airways upstream from the equal pressure point (Macklem & Mead, 1967). Thus McFadden & Lyons (1969) postulated that during a spontaneous attack of asthma both up-
stream and downstream segments of the bronchial tree were involved, the upstream or smaller airways to a greater and more prolonged extent than the downstream or larger ones.

Bouhuys, Van De Woestijne, Kane & Wayenburg (1970) used cotton dust as a provoking agent in non-asthmatic cotton workers and found two different types of response. In one group of subjects, FEV₁ and flow rates decreased with little change in $R_L$ whereas in the other group changes occurred in $R_L$ alone (expressed as airways conductance divided by thoracic gas volume). They postulated that the smaller airways were primarily involved in the first group and the larger airways in the second group. It would appear in the present study that methacholine caused a response at both sites in the asthmatic subjects, but the response of the larger airways was faster and of shorter duration than the response of the smaller airways. Subject H.K., compared with the other subjects, had a relatively small change in $R_L$ and FRC with a larger response in FEV₁. In this subject the response of the smaller airways may have been more marked. Variations in the degree to which different parts of the bronchial tree respond may account for the disparity between FEV₁ and $R_L$.

In the normal subjects the small but definite increase in $R_L$ indicates that their larger airways also responded to methacholine. The response began immediately but was slower to reach its maximal value than in the asthmatic subjects. Whether or not the smaller airways of the normal subjects responded to methacholine is more difficult to assess. The change in FEV₁ and VC were small, but the large inflations necessary to record them may have overcome some airway narrowing and caused these values to be only slightly decreased. The value of dynamic compliance at 60 breaths/min was decreased markedly when $R_L$ was elevated, but even after $R_L$ had returned to pre-provocation values $C_{dyn}$ remained abnormal, suggesting that the small airways were affected as well as the larger ones (Woolcock et al., 1969).

The reason for the different rates of response of the larger and smaller airways is unclear. The immediate change in $R_L$ suggests either a reflex action or a direct effect on sensitized bronchial muscle while the methacholine may have reached the smaller airways at a later time either by diffusion through the mucosa or perhaps via the blood stream.

Why the smaller airways take longer to recover and in fact remain abnormal to some extent, is even more uncertain. However, residual damage to clearing mechanisms from repeated attacks of asthma could impair removal of excess secretions produced during the acute phase and this could cause abnormal function even if there was no muscle contraction present.

ACKNOWLEDGMENTS

We wish to acknowledge the expert technical assistance of Mrs I. Verrochio. This work was supported by the Asthma Foundation of New South Wales, the Royal Australasian College of Physicians and the National Health and Medical Research Council of Australia.

REFERENCES


Lung mechanics in asthma


