Early Emphysema*
Ten Years’ Evolution
Maurits Demedts, M.D., F.C.C.P.; and Jef Aumann, M.D.

In this study, functional evolution over ten years was evaluated in 13 patients with early emphysema. The diagnosis was made on the basis of a decrease in single-breath Dco (35 ± 14 percent predicted, mean ± 1 SD), a loss of elastic recoil (Cl, st = 0.76 ± 0.25 L/cm H2O), and only minor airway obstruction (FEV1 = 87 ± 13 percent predicted, Sgaw = 0.09 ± 0.04 cm H2O·1·s·1), and compatible chest radiographs. During the ten years, there was a decrease in FEV1 of 0.89 ± 0.40 L (p < 0.001), with a range of 0.20 to 1.55 L (which could not clearly be related to smoking habits or to initial lung function), a decrease in elastic recoil (p < 0.05, with a decrease of Ptp/TLC by 6 ± 7 cm H2O; p = 0.05), an increase in TLC of 0.46 ± 0.50 L (p = 0.05), and in RV/TLC of 9 ± 3 percent (p < 0.001). The resistance of the upstream segment (ratio Ptp/Vmax) increased slightly but generally remained within normal limits. In conclusion, patients with early emphysema resemble those with classic COPD, with a mean yearly decline in FEV1 similar to that in COPD.

In a review article, Thurlbeck4 emphasized that pulmonary function tests are the most sensitive noninvasive indicators for emphysema. Among these tests the diffusing capacity for CO has in some hands shown the best correlation with the degree of morphologic emphysema.3,4 Elastic recoil properties of excised lung have presented better correlations with emphysema than pressure-volume lung characteristics measured in vitro; yet even in the latter condition relationships between some elastic recoil indices and the severity of emphysema have been remarkably good.1-9 Greaves and Colebatch10 emphasized that elastic recoil changes correlate even better than other lung function tests with emphysema.

Subclinical or early emphysema with, at most, minimal airway obstruction has been described by several authors.2,4,11 In our functional study,11 the upstream resistance (ratio of elastic recoil pressure and maximal expiratory flow at a given volume) was normal, which implied that no functionally measurable intrinsic small-airway pathology was present and that abnormalities in so-called sensitive tests (ie, maximal expiratory flow at low volumes, closing volume and capacity, ratio of dynamic to static compliance) were due to emphysema and not to small-airway disease. This finding agrees with pathologic data that show no association between small-airway inflammation and centrilobular emphysema12-14 and that even patients with severe emphysema may be free, or almost free, of central and peripheral airway lesions.5,10

In this study we evaluated pulmonary functional evolution over 10 years in patients with early emphysema and minimal airway obstruction. Our main question was whether the natural history, and especially the decline in expiratory volume per second (FEV1), is comparable to that in chronic obstructive lung disease (ie, a decline in FEV1 of 40 to 110 ml per year15-21 or to that of a healthy aging population (ie, a decline in FEV1 of 20 to 30 ml per year).22,23

Patients and Methods

Patients

Functional early emphysema was diagnosed on the basis of a decrease in single-breath diffusing capacity and in elastic lung recoil with hyperinflation and only minor airway obstruction, and with compatible chest x-ray film changes.11 In 1975, this diagnosis was made in 16 patients, and in 1985 a re-evaluation was undertaken. Lung function data could be obtained for only 13 after 10 years. Of nine patients whose initial data for 1975 had been published,12 two had refused further examination but were apparently still alive, and one had died of a lung tumor. Of the remaining six who were available for re-evaluation after 10 years, two died shortly thereafter, one of respiratory insufficiency and one of non-Hodgkin lymphoma. Seven new patients with subclinical emphysema diagnosed in 1975 were added to the study, and all of them are still alive.

The general characteristics of the patients are summarized in Table 1. All were men and smokers or ex-smokers, and several had been exposed to occupational hazards. There was often a history of exertional dyspnea and of expectoration and cough for many years. Their chest radiographs showed various signs of emphysema (eg, decreased and/or irregular markings, enlarged retrosternal space, hyperinflation, and flattened diaphragm).24

Lung Function Tests

In both 1975 and 1985, the lung function tests were performed with the same apparatuses and techniques, in accordance with the recommendations of the European Community for Coal and Steel.25 Vital capacity (VC) and FEV1 were obtained with a spirometer, maximal expiratory flow-volume curves (MEFV) with a pneumotachograph at the mouth, residual volume (RV) and total lung capacity (TL) with the helium dilution technique, and the diffusing capacity for CO (Dco) with the single-breath technique. Airway resistance

*From the Division of Lung Diseases, University Hospital of Pellenberg, Catholic University of Leuven, Belgium. Manuscript received September 21; revision accepted January 25.

Reprint requests: De Demedts, University Hospital, Weizgerdeel 1, Pellenberg, Belgium B-3041
Table 1—General and Lung Function Characteristics of Patients in 1975 and Changes in FEV₁ between 1975 and 1985

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Exposure†</th>
<th>Cigarettes (day)</th>
<th>Clinical history‡</th>
<th>Chest X-ray Film§</th>
<th>FEV₁ % pred (L)</th>
<th>TLC % pred (L)</th>
<th>Dco (ml/min/mm Hg)</th>
<th>CLo,vt (L/cmH₂O)</th>
<th>∆ FEV₁ 1975-85 (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>189</td>
<td>—</td>
<td>25 (+76)</td>
<td>&gt; 10</td>
<td>1,2</td>
<td>(2.0)</td>
<td>(8.4)</td>
<td>(22.4)</td>
<td>(0.76)</td>
<td>-0.20</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>178</td>
<td>1</td>
<td>20 (+70)</td>
<td>&gt; 2</td>
<td>1,2,3</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-0.35</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>166</td>
<td>—</td>
<td>20 (+78)</td>
<td>&gt; 2</td>
<td>1,2,3</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-0.41</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>173</td>
<td>—</td>
<td>50 (+75)</td>
<td>&gt; 5</td>
<td>1</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-0.70</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>171</td>
<td>—</td>
<td>20 (+60)</td>
<td>&gt; 20</td>
<td>1,2,3</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-0.82</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>167</td>
<td>27</td>
<td>25</td>
<td>&gt; 5</td>
<td>1,2</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-1.00</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>173</td>
<td>—</td>
<td>50 (+75)</td>
<td>&gt; 5</td>
<td>1</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-1.10</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>167</td>
<td>27</td>
<td>25</td>
<td>&gt; 5</td>
<td>1,2</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-1.22</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>178</td>
<td>1</td>
<td>20 (+70)</td>
<td>&gt; 2</td>
<td>1,2,3</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-1.25</td>
</tr>
<tr>
<td>10#</td>
<td>53</td>
<td>163</td>
<td>3</td>
<td>20</td>
<td>&gt; 10</td>
<td>1,2</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-1.25</td>
</tr>
<tr>
<td>11</td>
<td>46</td>
<td>162</td>
<td>22</td>
<td>30</td>
<td>&gt; 10</td>
<td>1,2,3</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-1.35</td>
</tr>
<tr>
<td>12#</td>
<td>63</td>
<td>178</td>
<td>—</td>
<td>10 (+75)</td>
<td>&gt; 30</td>
<td>1,2,3</td>
<td>(4.0)</td>
<td>(13.6)</td>
<td>(26.7)</td>
<td>(0.91)</td>
<td>-1.55</td>
</tr>
</tbody>
</table>

*Number reflects relative change in FEV₁.
†Mainly mine or metal industry.
‡Complaints of cough, mucus secretion, and/or dyspnea.
§Semiquantitative grading: 1 = decreased and/or irregular markings, 2 = flattened diaphragm with dome below dorsal bow of tenth rib, 3 = retrosternal space >2.5 cm.
∥Absolute values are in parentheses.
¶Year of smoking cessation in parentheses.
#Deceased.

(Raw) was determined during quiet breathing (ie, at ~ 20-30/min) in a constant volume body plethysmograph. Static transpulmonary pressure-volume curves (PtP−V) were obtained, during apnea, at several expiratory volumes (following two deep inspirations), using mouth volume and esophageal pressure (balloon length 10 cm, containing 0.5 ml of air and positioned about 45 cm from the nares). The tracings of several maneuvers were superimposed in order to construct a mean PtP−V curve. The static compliance (CL,st) was calculated as the slope of the mean curve between FRC and FRC + 0.5 L. For PtP-TLC, not the mean, but the highest value was selected. Upstream resistance (Rus) during forced expirations was calculated from Pp and maximal expiratory flows (MEF) at between 80 percent and 40 percent TLC. Arterial blood gases (PaO₂, PaCO₂) were measured by microelectrodes. On slow single-breath N₂ washout curves (following full inspiration of 100 percent O₂, the slope of the alveolar plateau was measured as the N₂ change over 1 L (ΔN₂).

The data were expressed in absolute values and also related to the reference values of Jouasset,26 Billiet et al,27 the European Community for Coal and Steel,28 Yernault et al,29 Bass,30 Ostrow and Cherniack,31 Black et al,31 and Buist and Ross.32

RESULTS

Table 1 shows the general characteristics of the 13 subjects, the radiologic and functional data on which the diagnosis of subclinical emphysema was made in 1975, and the changes in FEV₁ between 1975 and 1985. The chest films showed at least one of the following: decreased and/or irregular markings, flattened diaphragm, increased retrosternal space. Lung function was generally characterized by decreased diffusion capacity, increased compliance, and decreased elastic recoil pressure, especially at TLC, and an FEV₁ of at least 70 percent predicted. There was no good correlation between the changes in CL,st and in Dco. Between 1975 and 1985, the FEV₁ decreased by 0.2 to 1.55 L; this change was not clearly related to other functional data or smoking habits.

Table 2 shows the mean values and changes (±1 SD) in lung function and blood gases in 1975 and 1985. For the FEV₁, a decrease of 89 ± 40 ml per year was found, with a mean decline of 85 ml for the eight ex-smokers and 95 ml for the five current smokers. This decrease was accompanied by a significant decline in FEV₁/VC and PEF (p < .001). The decrease in...
MEF₅₀ and MEF₇₅ (expressed as a percentage of VC) was not significant, yet the maximal flows expressed as percentages of TLC were significantly decreased between 1975 and 1985 (ie, p<.001 at 80, 70, 60, and 50 percent TLC) (Fig 1, upper). Moreover, the volume axis of the MEFV curve was significantly shifted: ie, an increase of TLC of about 0.5 L (p<.05) and of RV of 0.9 L (p<.001), besides a decrease of about 0.5 L of VC (p<.001) (Fig 1, lower).

However, Raw and Sgaw were only slightly abnormal and did not change between 1975 and 1985.

The mean Dco was almost halved in 1975 and did not worsen thereafter, but the Dco/VA decreased further (p<.05 for absolute values). The PaO₂ decreased from 73 to 66 mm Hg between 1975 and 1985, which, however, was not significant. Also, ventilation inhomogeneity, as expressed by the single-breath N₂ slope, increased significantly (p<.05).

In 1975, the mean static V-Ptp curve was already shifted upward and to the left (Fig 2), with a high CL,st and low Ptp,TLC. This shift had clearly proceeded further by 1985 (p<.05 by analysis of variance on Ptp from 100 to 50 percent TLC, and p<.001 by t-test on Ptp,TLC), although CL,st at FRC did not change. One subject, however, showed a decrease in compliance and in TLC.

From the V-Ptp and Vmax-V values, we derived V max-Ptp curves (Fig 3). At a given volume (ie, 50 to 80 percent of TLC), the values were clearly shifted downward from 1975 to 1985 (ie, increase of resistance of the upstream segment) and to the left (ie, loss of recoil).

**DISCUSSION**

The diagnosis of early emphysema is based on the data of several studies showing that a reduction of both

**Figure 1. Mean (± SD) MEFV curves in 1975 and 1985. Upper panel: maximal flows at PEF, and 80, 70, 60, 50, 40 percent TLC (p<.001 for all ∆V). Lower panel: same maximal flow, taking into account the absolute TLC values.**
Early Emphysema (Demedts, Aumann)

Dco and of lung retractive forces indicates emphysema, even in the absence of clear-cut airway obstruction.\textsuperscript{1-5,10,23,32-36} It is, indeed, generally accepted that pulmonary function tests are much more sensitive in vivo indicators of emphysema than clinical signs and symptoms or radiographs.\textsuperscript{1,10,24,33} The Dco and especially the diffusion constant are well correlated with the severity of emphysema, and, although the correlations with tests of elastic recoil varied from one study to another, remarkably good correlations have been found in some.\textsuperscript{3,5,10} Generally, the tests of airflow obstruction show a high degree of association with the severity of emphysema;\textsuperscript{35} yet there have been several reports of moderate to severe emphysema with normal expiratory flow rates,\textsuperscript{2,4,10,18,34-36} and this condition has been termed "subclinical emphysema."\textsuperscript{9,18,36} It has also been emphasized that small-airway pathology and emphysema may not be causally related\textsuperscript{12,14} but that there is a high chance of association between both.\textsuperscript{10}

We found in our patients with functional diagnosis of subclinical emphysema an overall evolution toward increased airflow obstruction during forced expiration, increased hyperinflation, and a loss of elastic recoil (Ptp), \textit{i.e.}, an evolution toward more classic COPD. The mean decrease in FEV\textsubscript{1} was 90 ml per year, which is very similar to the data in large series of patients with chronic obstructive pulmonary disease.\textsuperscript{17,19-21}

There are, however, in our limited group of patients, some points of possible interest. First, it is striking that these patients with already long histories (up to 30 yr) of chronic bronchitis and often clear dyspnea at the start of the study still had an almost normal FEV\textsubscript{1} in 1975. An explanation could be that FEV\textsubscript{1} only started to decrease after some years of symptoms or that patients had a high initial FEV\textsubscript{1}. The latter phenomenon was also found in patients with COPD by Fletcher et al\textsuperscript{13} and by Pern et al.\textsuperscript{21} Second, there was a large interindividual variation in the rate of decline in FEV\textsubscript{1} that could not be related to other variables such as age, initial FEV\textsubscript{1}, or smoking habits. Indeed, the mean evolution was not strikingly different between the group of eight patients who had stopped smoking cigarettes and the five who continued smoking. This finding contrasts with that for large patient populations where smoking cessation decelerates the fall in FEV\textsubscript{1}.\textsuperscript{15,16} This difference could be coincidental, or it could reflect differences in evolution of emphysema versus airway lesions after smoking cessation. Still, the subjective respiratory condition often improved in our patients who had stopped smoking, a

\textbf{FIGURE 2. Mean (± SD) V-Ptp curves in 1975 and 1985. Left: the Ptp at 100, 80, 70, 60, 50, 40 percent TLC (ΔPtp<.05 by analysis of variance). Right: same Ptp, taking into account the absolute TLC values.}

\textbf{FIGURE 3. Mean (± SD) V-Ptp curves (ie, Rus curves) in 1975 and 1985. The numbers 40 to 80 represent volumes in percentage of TLC. The shaded area indicates the normal zone.\textsuperscript{30,21}}
finding that agrees with the literature.17 Almost half the patients had also been exposed to occupational hazards known to be risk factors for the development of emphysema.17,36 a fact which may result in an increased decline in FEV1 in exposed smokers versus nonexposed smokers.12 Third, the decline in FEV1 was not always accompanied by parallel changes in other lung function tests. The DCO did not show further changes, which is in agreement with observations frequently made in patients with classic COPD. It appears, indeed, that, while airway obstruction progressively increases, the DCO may present a stepwise change. Also, the CLst measured at FRC did not change over the ten year period; yet this was at least partially explainable by the increase of FRC, since the elastic recoil pressures between 100 and 50 percent TLC significantly decreased and the slope of the V-Ptp curve became steeper (Fig 2). The decline in FEV1 was, as expected, accompanied by increasing ventilation unevenness as expressed by the single-breath N2 slope, and by a tendency for lowered PaO2. Finally, the decrease in FEV1 between 1975 and 1985 was not accompanied by an increase in Raw or decrease in Sgaw; ie, there was increasing airflow obstruction during forced expirations but not during quiet breathing. This suggests that the decrease in FEV1 is largely due to airway collapse by loss of recoil, and not to intrinsic airway narrowing. Bronchodilating agents had only a minimal effect on FEV1 in this group of patients, even in 1985. The fact that Rus (ie, the ratio of Ptp to Vmax) tended to increase, although it remained within normal limits, indicates, however, that there was also progressive intrinsic airway pathology. Petty et al.30 found that in excised lungs changes in elastic recoil are generally associated with, and secondary to, small-airway disease. Whether our patient group behaves differently (ie, that intrinsic small-airway disease appeared later than the emphysema) or whether it was only later functionally measurable remains open for discussion.

REFERENCES

10 Greaves IA, Colebatch HJH. Observations on the pathogenesis of chronic airflow obstruction in smokers: implications for the detection of "early" lung disease (editorial). Thorax 1986; 41: 81-87
12 Petty TL, Silvers GW, Stanford RE. Mild emphysema is associated with reduced elastic recoil and increased lung size but not with air flow limitation. Am Rev Respir Dis 1987; 135:867-71


Higgins M. Epidemiology of COPD. Chest 1984; 85 (suppl): 35-88


Petty TL, Silvers GW, Stanford RE. Small airway disease is associated with elastic recoil changes in excised human lungs. Am Rev Respir Dis 1984; 130:42-45