Elective Surgery for Giant Bullous Emphysema*
A 5-Year Clinical and Functional Follow-up

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Background: So far, very few studies in the literature have reported data on the long-term follow-up of patients who have undergone surgery for giant bullous emphysema (GBE), and much still needs to be known on the late fate of these patients.

Aims: To evaluate patients who have undergone elective surgery due to GBE, early and late mortality following surgery, the early and late reappearance of bullae, and the early and late modifications of clinical and functional data.

Subjects and methods: Forty-one consecutive patients (36 men; mean [± SD] age, 48.4 ± 14.8 years) who underwent elective surgery for GBE were enrolled in a prospective study, and were studied both before and after undergoing bullectomy for a 5-year-follow-up period. Analyses were performed on the whole population and on two subgroups of patients who were divided on the basis of the absence of underlying diffuse emphysema (group A; n = 23) or the presence of underlying diffuse emphysema (group B; n = 18).

Results: The early mortality rate was 7.3% (within the first year), and the late mortality rate was 4.9% (overall mortality rate at 5 years, 12.2%; mortality rate in group B, 27.8%). Bullae did not reappear and residual bullae did not become enlarged in any patients at the site of the bullectomy. During the follow-up, the dyspnea score was reduced significantly soon after bullectomy and up to the fourth year of follow-up; intrathoracic gas volume also was reduced significantly (average, 0.7 L). The same was true for the FEV₁ percent predicted and the FEV₁/vital capacity ratio, which kept increasing until the second year; then, from the third year of follow-up these values were reduced, yet remained above the prebullectomy values until the fifth year of follow-up. When considered separately, the patients in group B appeared to be the most impaired, clinically and functionally (eg, FEV₁ showed a similar significant increase up to the second year in both groups after surgery, while a different mean annual decrease was appreciable from the second to the fifth year of follow-up: group A, 25 mL/year; group B, 83 mL/year. Furthermore, patients in group B were the only ones who contributed to the mortality rate, on the whole showing a behavior similar to that of patients who had undergone lung volume reduction surgery.

Conclusions: In patients with GBE who were enrolled in the study prospectively and were investigated yearly during a 5-year-follow-up period, elective surgery appears to have been fairly safe, and allowed clinical and functional improvement for at least 5 years. Better results may be expected in patients without underlying diffuse emphysema.

Key words: COPD; pulmonary function test; thoracic surgery

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; FRC = functional residual capacity; GBE = giant bullous emphysema; KCO = capacity of the lung for carbon monoxide; LVRS = lung volume reduction surgery; mBMRC = modified British Medical Research Council; PFT = pulmonary function test; TGV = intrathoracic gas volume; VC = vital capacity

In patients with giant bullous emphysema (GBE),1–5 (ie, those having large bullae occupying at least one third of a hemithorax), bullectomy is the treatment of choice. Indeed, patients have reported early improvement of dyspnea,1,6,7 hypoxemia and hypercapnia usually improve, and there is a rise in FEV₁, FEV₁/FVC ratio, and diffusing capacity of the

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lung for carbon monoxide (DLCO). In this respect, the preoperative size of bullae is the most important factor in determining the extent to which pulmonary function improves after surgery; in particular, determination of the preoperative bulla volume allows the prediction of the expected increase of postoperative FEV\textsubscript{1}. However, the duration of such an improvement in lung function is not well-known, since the long-term clinical and functional follow-up has been reported by few authors\textsuperscript{1,6–9,11} and data are difficult to interpret due to (1) the inhomogeneity of patient characteristics in different series, (2) the small number of patients included in studies, and (3) the variable length of the follow-up period. Also, data about long-term morbidity and mortality are not well-known. Most recently, a study by Schipper et al\textsuperscript{12} reported its 5-year follow-up experience in patients from the database of those undergoing surgery for emphysema.

Knowing the late effects of the removal of a giant bulla would surely give new insight into the clinical course of such patients; in addition, it could help to assess the late evolution of patients who have undergone lung volume reduction surgery (LVRS) for severe generalized emphysema, given the striking similarities between the two kinds of interventions.\textsuperscript{13}

Therefore, we followed prospectively, according to a predefined protocol, all of the consecutive patients who underwent elective surgery for GBE, with the aim of evaluating early and late mortality following surgery, detecting the early and late reappearance of bulla, and assessing the early and late modifications of clinical findings, dyspnea score, and pulmonary function data. The secondary purpose of this study was to investigate the above parameters in patients without and with associated diffuse emphysema, with the hypothesis that they may represent two different clinical entities.

**Materials and Methods**

Among all consecutive patients who underwent surgery for bullous emphysema between January 1985 and December 1999 at the Cardiac and Thoracic Department of the University of Pisa (Italy), the study included all of those who underwent elective surgery for the removal of giant bullae.

The study inclusion criteria were as follows: (1) the presence of giant bullae occupying over one third of a hemithorax; (2) signs of compression over the mediastinum (ie, mediastinal shift and/or herniation) or pulmonary parenchyma (ie, atelectasis lines or signs of vascular abnormalities known to be associated with bullae); (3) history of previous bullae complications (ie, pneumothorax, infection, and enlargement with time); and (4) the patient’s consent and the opportunity of performing follow-up (mostly based on geographic vicinity). The study exclusion criteria were as follows: (1) the presence of bullae occupying less than one third of a hemithorax; (2) current bullae complications (eg, pneumothorax and infections); (3) other medical conditions that contraindicated surgery and/or follow-up; and (4) refusal of consent for either the operation or inclusion in the study.

All patients included in the study underwent a prospective functional and radiologic evaluation for 5 years. An informed written consent was obtained from all patients, according to the requirements of the ethics committee of our institution.

**Clinical Functional Evaluation**

Patients were interviewed about their medical history, both recent and more distant, according to a predefined form; particular attention was paid to the presence of dyspnea, which was graded on the basis of a modified British Medical Research Council (mBMRC) score.\textsuperscript{14} The diagnosis of GBE was made by chest radiography and CT lung scan, which most of the time was performed after suspicion had been raised on the basis of history, clinical assessment, and pulmonary function test (PFT) results. With the hypothesis in mind that the presence of a bulla in patients with normal parenchyma perhaps represents a different clinical entity from that of a bulla in patients with generalized emphysema, the following two subsets of patients were identified on the basis of the above radiologic diagnostic techniques: those with bulla surrounded by normal or poorly damaged lung tissue (group A); and those with bulla surrounded by diffuse, generalized emphysema (group B).\textsuperscript{15,16}

Spirometry was performed by means of a pneumotachograph connected to a computer,\textsuperscript{17} and DLCO was measured by the single-breath technique and was compared with predicted values, using reference data from Cotes.\textsuperscript{18} Arterial blood samples were drawn while the patients were breathing room air. \(\text{PaO}_2\) values were corrected for age.

**Follow-up**

Patients were followed up for 5 years after undergoing surgery, with six control checkups scheduled within 3 to 6 months after surgery and, subsequently, at 1, 2, 3, 4, and 5 years after undergoing surgery. Each appointment was scheduled in advance, and one of the pneumologists in charge of the protocol guaranteed that the follow-up procedure was correctly performed. During such checkups, the same examinations that had been performed before surgery were repeated. During the 5-year follow-up period, patients were visited by one of the pneumologists involved in the study, who decided on the best medical treatment, which was standardized in each patient, and consisted of inhaled steroids, mucolytic agents, and antibiotic agents (when necessary). Patients were then instructed to contact the pneumologist in charge when they had any new or worsened respiratory symptoms.

**Statistical Analysis**

To compare unpaired and paired data, unpaired and paired \(t\) tests or Wilcoxon tests were used for quantitative variables, while the Fisher Exact Test and the McNemar test were used for qualitative variables. The time trend in quantitative variables was analyzed by analysis of variance with repeated measures, and multiple comparisons were performed by the Dunnet test, with the prebullectomy value used as the reference value. Comparison between groups A and B was performed by analysis of variance with repeated measures, and the simple main effects were analyzed in the presence of a significant interaction. A Pearson correlation was used to verify the association between quantitative variables. The relationship between the time trends of mean values of the mBMRC dyspnea score and that of mean values of functional parameters was analyzed by linear regression; an autoregressive error was considered if appropriate.
RESULTS

Of the 245 consecutive patients who were referred to our department for treatment of bullous emphysema, 193 (79%) met the criteria for surgery and underwent the intervention. Among them, 41 patients (21%) also met both inclusion and exclusion criteria for the present study, and were, therefore, set as the object of our study.

All 41 patients (36 men; mean [± SD] age, 48.4 ± 14.8 years; age range, 15 to 77 years) underwent the removal of giant bullae (standard thoracotomy, 27 patients; video-assisted thoracoscopic surgery, 14 patients). The average operation time was 80 min; all patients were extubated in the operating room. The chest tube was removed on average on the fourth day (range, 2 to 9 days). Complications (ie, prolonged air leakage in all cases) occurred in three patients after surgery. The length of hospital stay was 5 days on average (range, 4 to 10 days). No patient required mechanical ventilation after undergoing surgery. No statistical differences were found between patients who underwent the two different surgical procedures (difference not significant) according to demographics, symptoms and signs, PFT results, and arterial blood gas parameters. When giant bullae were bilateral, the hemithorax that showed the largest bulla was operated on. Patients had been referred to our department because of the onset or worsening of dyspnea (7 patients; 17%), a history of recurrent bronchitis (16 patients; 39%), a history of a previous episode of pneumothorax (8 patients; 20%), and occasional discovery of bullae on chest radiography or CT lung scan (10 patients; 24%). On the basis of chest radiography and CT lung scans, 23 patients were assigned to group A, and the remaining 18 patients were assigned to group B. No patient needed to be rehospitalized within short periods after bullectomy, and no patient was lost to follow-up.

Mortality Rate

During hospitalization, there were no deceases, and all patients were able to perform the first clinical and functional assessment 3 to 6 months after undergoing surgery. Between the first and the second scheduled checkup (1 year after surgery), three patients (7.3%) died because of acute respiratory failure due to pulmonary infection; all three patients were in group B. Two patients (4.9%) died 2 years after undergoing surgery because of acute cardiovascular disease, and another patient died 3 years after undergoing surgery; all three patients belonged to group B. Therefore, the overall mortality rates 5 years after surgery were 12.2% (5 of 41 patients) and 27.8% (5 of 18 patients) in group B. No significant difference was observed between patients who had undergone standard thoracotomy and those who had undergone video-assisted thoracoscopic surgery for the overall mortality rate (14.5% vs 7.1%, respectively). At baseline, nonsurviving subjects significantly differed from those surviving as regards mean age (66.2 ± 7.1 vs 45.9 ± 13.9 years, respectively; p = 0.003), mean FVC (2.8 ± 1.2 vs 3.9 ± 0.9 L; p = 0.016), mean FEV₁ (1.2 ± 0.6 vs 2.4 ± 0.9 L [p = 0.005]; and 36.8 ± 15.9% vs 67.3 ± 22.1% predicted, respectively [p = 0.005]), FEV₁/VC ratio (36.3 ± 13.5% vs 55.5 ± 15.0%, respectively; p = 0.010), PaCO₂ (46.1 ± 7.4 vs 37.6 ± 5.1 mm Hg, respectively; p = 0.002), PaO₂ (61.3 ± 10.7 vs 87.4 ± 14.0 mm Hg, respectively; p = 0.000), and PaO₂ (76.2 ± 13.1% vs 97.6 ± 12.9%, respectively; p = 0.001). Thirty-six patients completed the follow-up by performing all the clinical and functional evaluations scheduled.

Reappearance of Bullae

Chest radiography and CT lung scan performed on patients during the follow-up period showed no new bullae at the site of bullectomy or any residual small bullae with significant enlargement; consequently, no patient required further bullectomy.

Clinical and Functional Data

By analyzing the data of the 41 predefined forms submitted to patients on study enrollment, we observed dyspnea in 36 of 41 patients (88%), with a mean dyspnea score of 2.2 ± 0.6. The overall mean dyspnea score of the 41 patients was 1.9 ± 0.9 (Table 1). Such a value showed a significant inverse correlation with FEV₁ (in liters; r = −0.31; p = 0.050), FEV₁ (percent predicted; r = −0.35; p = 0.027), and FEV₁/VC ratio (r = −0.31; p = 0.045) and a direct correlation with residual volume (r = 0.32; p = 0.038). No significant correlation was found between dyspnea and all other static volumes. The results of PFTs performed at baseline are shown in Table 1.

The mean dyspnea score for the 36 patients who completed the follow-up saw a prompt and significant reduction after surgery, going from 1.8 ± 0.9 to 1.4 ± 0.8 (p = 0.002), and a further progressive reduction over time. At the fifth year of follow-up, the score slightly increased, remaining, however, far below the value before surgery (Fig 1).

After surgery, the mean maximum increase in FEV₁ with respect to baseline was observed at the second year of follow-up (increase, 489 mL), with a mean annual increase of 244 ± 50 mL, while the highest annual decrease occurred between the second and the third follow-up years (Table 2). The
mean annual decrease calculated from the second to the fifth year of follow-up was 46 ± 25 mL.

Also the mean intrathoracic gas volume (TGV) and TGV percentage decreased significantly after bullectomy and remained constant throughout the entire follow-up period (p < 0.001) [Table 2]. During the follow-up period, significant inverse correlations were found between the dyspnea score trend and the main parameters are reported in Figure 2.

Clinical and Functional Data by Extension of Emphysema

Dyspnea was found in 20 of 23 patients (87.0%) in group A and in 16 of 18 patients (88.9%) in group B, with no statistical difference in mean dyspnea score between the two groups (Table 1). Patients in group B showed lower values of FEV\textsubscript{1}/VC ratio, FEV\textsubscript{1} (in liters), and FEV\textsubscript{1} percent predicted (difference not significant), higher values of functional residual capacity (FRC) [p = 0.018] and FRC percent predicted (difference not significant), similar values of TGV (difference not significant), and significantly lower values of PaO\textsubscript{2} (p = 0.011) and PaO\textsubscript{2}% (p = 0.043) [Table 1].

During the follow-up, the dyspnea score markedly improved in both groups without any significant difference between the groups. Static volumes were greater in group B than in group A during the whole period of follow-up. As for TGV, a significant decrease was observed in both groups (group B, p = 0.005; group A, p = 0.000), with a quicker reduction in group A. FEV\textsubscript{1}/VC ratio showed a significant rise in group A alone (p = 0.043), while FEV\textsubscript{1} and FEV\textsubscript{1} percent predicted increased significantly in both groups (group B, p = 0.014 and 0.006, respectively; group A, p = 0.001 and 0.000, respectively), with no significant differences between groups during the whole follow-up period.
The statistically significant increase of FEV₁ until the second year of follow-up was 255/11006 336 mL/yr (median, 205 mL/yr) in group A and 226/11006 240 mL/yr (median, 215 mL/yr) in group B (difference not significant), while the annual decreases from the second to the fifth year of follow-up were 25/11006 173 mL/yr (median, 27 mL/yr) and 83/11006 104 mL/yr (median, 50 mL/yr), respectively (difference not significant) [Fig 3].

**Discussion**

The first result of this study, with no patient lost through follow-up, concerns the absence of early postoperative mortality and the presence of acceptable overall early and late mortality rates. As a further result, no new bullae appeared on the site of the bullectomy and no residual small bullae became enlarged during the follow-up period. Such results demonstrate that elective surgery, independently of the type of surgical approach chosen, is safe in both the short term and the long term. Specifically, death occurs in our study only in patients in whom bullae are surrounded by diffuse emphysema (27.8%), who are the most seriously ill basally.

We are aware that the lack of early postoperative mortality in the patients in our series could in part be due to the design of the study, which excluded

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<th>Table 2—Functional Values Obtained Before Surgery and During the 5-Year Follow-up Period in 36 Patients Who Completed the Follow-up*</th>
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*Values are given as the mean ± SD.
†p < 0.001 (Dunnet test for paired data, with prebullectomy values used as a reference).
‡p < 0.05 (Dunnet test for paired data, with prebullectomy values used as a reference).
§p < 0.01 (Dunnet test for paired data, with prebullectomy values used as a reference).

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22032/) Correlation between dyspnea score and pulmonary functional indexes in 36 patients who completed the 5-year-follow-up.
patients who underwent surgery under emergency conditions (e.g., due to acute pneumothorax); however, the mortality rate due to respiratory failure within the first year after surgery was also acceptably low (7.3%). The overall early mortality rate in our series is in agreement with mortality rates, which range from 0 to 22.5%, in the low range that have been reported in the literature.\textsuperscript{1,2,11,12,19–23} and it is similar to the weighted mean mortality rate of 8.0% calculated by Snider\textsuperscript{13} in 262 patients with giant bullectomy and not giant bullae. The overall mortality rate was acceptably low (12.2%), even if it must be said that comparisons with data in the literature are not easy since many studies with retrospective designs report incomplete and conflicting data, do not have predefined intervals of time between checkups of patients, and often include patients with giant bullae and not GBE.\textsuperscript{6–9} Our data, on the contrary, were obtained in a prospective way in a consecutive series of patients who were followed up yearly with a clinical and functional evaluation during a 5-year follow-up. In view of this, the data are comparable with those reported recently by Schipper et al\textsuperscript{12} in a contemporary series.

The second major result of our study is that elective surgery for the treatment of GBE improves the clinical and functional conditions of treated patients and such an improvement persists in the long term. Indeed, most patients experienced early and late improvement of dyspnea. The degree of dyspnea, as evaluated by the mBMRC dyspnea score, decreased markedly soon after surgery and kept diminishing until the fourth year of follow-up when it increased again during the fifth year, yet remained under the level observed before surgery. This fact highlights the difference between patients who undergo LVRS, in whom the relief from dyspnea persists for only until 1 or 2 years after surgery, and a very small proportion of patients who undergo surgery (15.0% vs 61.1%, respectively, in our study) who still show an improvement after 5 years of follow-up.\textsuperscript{24} The degree of dyspnea was inversely correlated with DLCO (and Kco), increasing significantly until the fifth year of follow-up, and directly correlated with TGV (and TGV percent predicted) during the follow-up period, with and remaining unchanged during the entire follow-up. In this regard, the constant value of TGV (and TGV percent predicted) after the initial decrease supports the observation that no new bullae reappeared during the follow-up period and might perhaps be taken as a marker of a favorable outcome. Furthermore, dyspnea remained strictly connected to the bronchial obstruction, as shown by the consistent inverse correlation with FEV\textsubscript{1}, FEV\textsubscript{1} percent predicted, and FEV\textsubscript{1}/VC ratio, and, consequently, was related to the mechanical effects of bullectomy. Indeed, the removal of a bulla decompresses the functioning lung and the ipsilateral bronchi. On the other hand, FEV\textsubscript{1} and FEV\textsubscript{1} percent predicted improve until the second year of follow-up, when they increase, on the average, by 0.5 L with respect to baseline. After that, FEV\textsubscript{1} decreases by about 200 mL at the third year of follow-up and then remains quite steady until the end of the follow-up period. By considering the difference between the second and the fifth year of follow-up, we observed a mean annual decrease of 46 mL/yr that is slightly below the range (48 to 91 mL/yr) observed in patients with COPD.\textsuperscript{25} At the end of the fifth year of follow-up, FEV\textsubscript{1} was still definitely higher than the baseline value, in that reproducing the above-mentioned behavior of dyspnea.

Patients who presented with diffuse emphysema at study enrollment (group B) were on average more seriously ill than patients without diffuse emphysema (group A) and were the only contributor to mortality. Slight differences in static lung volume may be observed in patients from the two groups who completed the follow-up. Although the behavior of dyspnea severity was similar in the two groups, static lung volumes (i.e., total lung capacity, TGV, residual volume, FRC) were smaller in group A at each single step of follow-up and DLCO increased to a greater extent. No significant difference was found in arterial blood gas parameters. Therefore, on average it is conceivable that patients in both groups benefited from surgery, although to a different extent and in different numbers of individuals. As to airflow limitation, patients in group A had a mean annual decrease in FEV\textsubscript{1} of only 25 mL, while those in group B had a mean annual decrease of 83 mL (i.e., a progressive functional impairment that was similar to...
that of patients with severe COPD).\textsuperscript{26} In particular, in group A patients the increase in FEV\textsubscript{1} during the first 6 months after surgery was over threefold the decrease during the following 5 years. In the group B patients, such an increase was almost totally cancelled out in the following years, in which decreases occurred that were similar to those occurring in patients who underwent LVRS, which inevitably provokes the issue of when patients should undergo surgery.

In calculating the overall correlation between bullectomy and LVRS regarding the consequences of such surgery on clinics and pulmonary function, it can be shown that the baseline clinical and functional conditions of patients undergoing bullectomy for GBE, taken as a whole, or undergoing LVRS for diffuse emphysema are markedly different. In fact, patients who undergo LVRS have a higher mean age, higher mean dyspnea score, and lower Pa\textsubscript{O\textsubscript{2}}, DL\textsubscript{CO}, and FEV\textsubscript{1} values compared to those who undergo bullectomy.\textsuperscript{24,27–36} Moreover, those patients show remarkably different mortality rates, as shown by Gelb et al\textsuperscript{24} in 26 patients who were followed up for 5 years, by Naunheim et al\textsuperscript{27} in 330 patients after undergoing unilateral LVRS and in 343 patients after undergoing bilateral LVRS who were followed up for 3 years, and, most recently, by the National Emphysema Treatment Trial.\textsuperscript{26} Nevertheless, the early functional changes after surgery are qualitatively similar. In particular, in both the patients who underwent bullectomy and in those who underwent LVRS, dyspnea decreases and FEV\textsubscript{1} increases during the first 6 months after surgery.\textsuperscript{29–32} Such an improvement is greater and more consistent in the former group, where it persists for at least 5 years, while a progressive worsening of lung function is reported on the average already 1 year after the patient undergoes LVRS.\textsuperscript{24,31,33–36} However, in a 2003 study\textsuperscript{37} that was performed in a stringently selected group of patients, LVRS resulted in beneficial effects for dyspnea score and quality of life for at least 5 years after surgery.

In conclusion, results of the study show that giant bullectomy is a rather safe technique that improves the early and late clinical and functional conditions of patients; such an improvement is, however, almost totally reversed after 5 years in patients who present with underlying diffuse emphysema.

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