Long-term Results of Surgical Treatment for Gastroesophageal Reflux in Asthmatic Patients

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We report the long-term results of surgical repair of gastroesophageal reflux in 44 asthmatic patients who underwent surgery more than five years earlier (mean = 7.9 ± 1.5 years). The severe asthma was associated with clinically evident reflux, and repair was attempted by surgical technique Nissen transabdominal gastropexy, with the following results: total cure, 11 cases (25 percent); marked improvement, 17 (38 percent); moderate improvement, 11 (25 percent); no improvement, 15 (34 percent). Cure was attained in intrinsic asthma with a predominance of nocturnal crises, associated with nocturnal tracheitis and with significant reflux, objective signs of which had appeared before the beginning of the asthma. Other results concerned asthmas complicated secondarily by GER in which it was impossible to determine whether the reflux was only a complication, without effect on the respiratory illness, or exacerbating the asthma. The question of surgery in these patients should be considered with care, being reserved for cases of severe asthma, poorly controlled by antiasthmatic drugs, and complicated by a severe reflux that encompasses ulcerative esophagitis.

(Chest 1989; 96:40-45)

GER = gastroesophageal reflux

T he increased incidence of gastroesophageal reflux (GER) in asthmatic patients has been noted by several authors.1,4 This increase mainly concerns severe asthma, where the incidence of reflux has been evaluated at 30 to 60 percent of cases.

The main problem raised by this association is to determine whether the reflux aggravates the asthma or is only a complication, with no respiratory effects. Some authors6-9 have suggested clarifying the connection through study of the effect of medical antireflux treatment on asthma. Similarly, several publications investigated the influence of surgical treatment of reflux on the asthma process.1,7,9,10,11 These various data deal with short-term studies, however, and leave open the question of precisely when such surgery is indicated.

In 1980 we published results concerning 50 patients who had recently undergone surgery10 as follows: in 13 cases (26 percent), total disappearance of asthma; in 26 (52 percent), no improvement; in 8 (16 percent), moderate improvement and in 18 (36 percent), significant improvement. The analysis of these results showed that cure was related to intrinsic asthmas associated with major GER demonstrated by positive results of diagnostic tests (barium esophagram, esophageal fibroscopy, and manometry, pH determination).

These results were from patients who had had operations less than two years previously. The aim of this study is to determine whether cure or improvement of asthma lasts several years after surgical repair, and if it is possible to distinguish which GER asthma cases would benefit from surgery.

METHODS

Choice of Subjects

The study group was limited to those patients operated on more than five years earlier, i.e., between 1978 and 1982. Of a total of 62 cases, 44 were followed up regularly and examined during 1987. The 18 other cases could not be retained in this retrospective study; eight of them changed address, seven refused to undergo examinations, three died of illnesses not related to asthma (one lung cancer, one rectal carcinoma, and one accident). Of the 44 patients in this study, 18 were men and 26 were women (mean age 49.3 ± 1.6 years).

Asthmatic condition. 32 patients had severe chronic asthma with obstructive airways disease (FEV1/FVC, predicted = 0.84 ± 10.2 percent). 20 of these were dependent on corticosteroids. The 12 other subjects had episodic, incapacitating asthma, but no permanent obstructive airways disease. The mean duration of the disease was 12.1 ± 1 years. In 33 cases there was no allergic factor (intrinsic asthma). The 11 other subjects were extrinsic asthma, i.e., with an allergic component identified by cutaneous tests and the presence of specific IgE. Twenty-five of the cases suffered predominantly nocturnal crises, and in 27 there was marked nocturnal tracheitis.

Gastroesophageal reflux: All the patients recorded signs of reflux with postural pyrosis and retrosternal pain or burning. This clinical data alone indicated the existence of GER. In all cases the classic

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examinations were carried out—barium esophagogram, esophageal fibroscopy, and manometry, and pHmetry.

The majority of patients were examined before 1980, when esophageal scintiscanning and prolonged pH testing were not yet widely used in France. The nine patients who had undergone these two tests in 1981 and 1982 had at least one of the two positive results (scintiscan positive in six cases; prolonged pH values abnormal in seven cases). Because of their restricted number, it is not possible to take these examinations into account in the statistical analysis of results. In 18 cases, surgical intervention was preceded by a three-month medical therapeutic trial, which involved taking daily metoclopramide, cimetidine, and sodium alginate. The result of the test was evaluated by a method of clinical scoring (see below).

Reflux Surgery and Postoperative Follow-up

Surgical repair was carried out between 1978 and 1982 by fundoplication (Nissen transabdominal gastropexy). This process involves the positioning of a double valve to form a cuff around the abdominal esophagus, one valve posterior and one anterior, stitched to each other along the right border of the esophagus. The bulk of the assembly normally prevents it from riding up to the hiatus and ensures a long life for the antireflux apparatus.

Results were evaluated by individual check-ups throughout 1987, on average 7.9 ± 1.6 years after surgical intervention. For the digestive system, results were judged by the persistence or disappearance of clinical reflux (all the patients presented before).

Respiratory system results were evaluated by a scoring system as follows:

- Clinical scores, based on the frequency of crises and the possible importance of intercritical dyspnea: 0 = no improvement; 1 = moderate reduction of symptoms (<50%); 2 = significant reductions of crises (>50%); 3 = total disappearance of respiratory symptoms.

- Treatment scores: related to the average consumption of bronchodilator and corticosteroids drugs: 0 = unchanged consumption; 1 = less than 50% reduction; 2 = greater than 50% reduction in consumption; 3 = complete cessation of treatment.

The combined respiratory results defined four patients groups:

- Group 1—0 score = failure of surgical treatment; group 2—1 and 2 scores = slight improvement; group 3—3 to 5 scores = marked improvement; group 4—6 scores = cure of asthma.

Failure of surgical treatment, improvement, and cure of asthma defined the dependent variable. The possible prognostic factors were the sex, age, duration and severity of asthma, predominance of night attacks, nocturnal tracheitis, etiology of asthma, clinical signs and diagnostic criteria of GER, results of medical antireflux treatment.

Statistical Analysis

Given the ordinal qualitative nature of the dependent variable and the small study group, we chose Kendall's tau to evaluate the significance of the correlation of the dependent variable and the different prognostic factors.

RESULTS

Overall Results

Gastroenterologic results: In 42 cases out of 44 patients, digestive signs were completely and permanently abolished following surgical repair of reflux. In the two remaining cases, the signs reappeared during the month following surgery.

Pulmonary results (Table 1): Group 1 (failures) consisted of 15 cases (34 percent), including two surgical failures. In all cases asthma and drug consumption were in no way modified after surgery; 12 patients from this group had chronic obstructive airways disease that persisted after surgery.

Group 2 (moderate improvement) contained 11 patients (25 percent); eight of 11 patients had chronic obstructive airways disease (FEV1/predicted = 66.6 ± 7 percent), which persisted with no improvement after surgery.

Group 3 (marked improvement) consisted of seven cases (16 percent); six had chronic obstructive airways disease (FEV1/predicted = 65.2 ± 4 percent). Despite clinical improvement, in all cases this disorder persisted but with a noticeable improvement (FEV1/predicted postoperative = 72.7 ± 3 percent).

Group 4 (cure of asthma) contained 11 cases (25 percent). It is interesting that seven of 11 patients presented before surgery with chronic obstructive airways disease which totally disappeared. Four of these patients were corticosteroid dependent and able to stop treatment completely.

Analysis of Results

Our aim was to see whether, by analyzing the clinical data from each group, we could obtain a profile particular to the type of asthma likely to benefit from surgical repair of reflux. Tables 2 and 3 summarize the main data from each of the groups.

Data on asthma: there was no difference between the four types of results regarding the duration and severity of the asthma. There exists, however, a negative correlation between the age of the patient at the time of surgery and the percentage of cure of asthma (p<0.05); the younger the patient, the better the result. This correlation is not linked to the duration of the disease, which is in turn not related to the age of the patients.

Predominantly nocturnal attacks and/or nocturnal tracheitis were a frequent feature in those cases improved or cured by surgery. The incidence of these symptoms before surgery in groups is significantly different. The predominance of nocturnal attacks existed in only 17 cases of 33 in groups 1, 2, and 3 and 10 of 11 in group 4 (p<0.05); the presence of a nocturnal tracheitis existed in 15 cases of 33 in groups.

Table 1—Long-term Effectiveness of Surgical Repair of Reflux in Asthmatic Patients*

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Failures</td>
<td>15 (34)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate improvement, 25-50%</td>
<td>11 (25)</td>
</tr>
<tr>
<td>3</td>
<td>Marked improvement, 75%†</td>
<td>7 (16)</td>
</tr>
<tr>
<td>4</td>
<td>Cure</td>
<td>11 (25)</td>
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*Results are taken from 44 subjects operated on more than 5 years previously.
†Improvement was judged by a method of clinical and therapeutic scoring.
Table 2—Clinical Profiles of Asthmas Classified According to Results of Gastroesophageal Reflux Surgery, No. (%)

<table>
<thead>
<tr>
<th>Group 1 Failure (n = 15)</th>
<th>Group 2 Moderate Improvement (n = 11)</th>
<th>Group 3 Marked Improvement (n = 7)</th>
<th>Group 4 Cure of Asthma (n = 11)</th>
<th>Kendall's Tau</th>
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<tr>
<td>Sex M</td>
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<td>F</td>
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<td>Age, yr ≤50.5 (median)</td>
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<tr>
<td>&gt;50.5</td>
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<td>Duration</td>
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<tr>
<td>Severity</td>
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<tr>
<td>- Episodic Asthma</td>
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<tr>
<td>- Chronic</td>
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<td>Predominance of night</td>
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<td>- Yes</td>
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<td>- No</td>
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<td>Nocturnal attacks</td>
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<td>- Yes</td>
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<tr>
<td>- No</td>
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<tr>
<td>Aetiology of asthma</td>
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<tr>
<td>- Intrinsic</td>
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<tr>
<td>- Extrinsic</td>
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1, 2, and 3 and 10 of 11 in group 4 (p<0.05). Etiologically, group 4 (cures) is set apart by the constant absence of the allergic element. It is nonetheless interesting that its presence cannot be taken as an argument against surgery, since it was also noted five times in groups 2 and 3. For the total study group of patients, the improvement after surgical cure (group 4) was more significant for intrinsic asthma than for extrinsic asthma (p<0.05). Moreover, all the patients who were cured had had intrinsic asthma (four). No extrinsic asthma was completely cured by surgery.

We observed that obstructive airways disease was present in the majority of cases from the four groups. Thus, its presence or absence is no indication of the

Table 3—Data on Gastroesophageal Reflux in Patients Classified According to the Results of GER Surgery, No. (%)

<table>
<thead>
<tr>
<th>Clinical signs of GER</th>
<th>Group 1 Failure (n = 15)</th>
<th>Group 2 Moderate Improvement (n = 11)</th>
<th>Group 3 Marked Improvement (n = 7)</th>
<th>Group 4 Cure of Asthma (n = 11)</th>
<th>Kendall's Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>- GER appeared before asthma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9 (100)</td>
<td></td>
</tr>
<tr>
<td>- GER appeared after asthma</td>
<td>15 (42.9)</td>
<td>11 (31.4)</td>
<td>7 (20)</td>
<td>2 (5.7)</td>
<td>(–0.62) p&lt;0.001</td>
</tr>
</tbody>
</table>

Diagnostic criteria of GER

- All positive | 5 (22.7) | 4 (18.2) | 4 (18.2) | 9 (40.9) | (–0.34) p<0.01 |
- Conflicting results | 10 (45.5) | 7 (31.8) | 3 (13.6) | 2 (9.1) |               |

Results of medical antireflux treatment (n = 19)

- Positive | 0 | 3 (30) | 2 (20) | 5 (50) | (0.52) p<0.01 |
- Negative | 3 (33.3) | 3 (33.3) | 3 (33.3) | 0 |               |

Postoperative development of clinical signs of GER

- Disappearance | 13 (31) | 11 (26.2) | 7 (16.7) | 11 (26.2) | (–0.2) p<0.05 |
- Persistence | 2 (100) | 0 | 0 | 0 |               |
possible results of surgery. In group 2, its persistence without significant change after surgery corresponds to moderate clinical improvement. Within the group of patients who improved clinically to a marked degree (group 3), FEV₁ also improved, but the persistence of obstructive airways disease clearly shows that the GER was simply another etiologic element of the asthma, and so not solely responsible for the chronic obstruction.

Data on gastroesophageal reflux: study of the respective date of commencement of respiratory and digestive signs is of great interest (Table 3). Most of the asthmas cured by reflux surgery were those pertaining to patients whose digestive problems began before their respiratory signs (sometimes several years previously). This was true in nine cases of 11. In the three other groups, reflux was secondary in patients already subject to asthma (9/11 compared with 9/33) (p<0.0001). Consequently, the reflux was a possibly aggravating complication of the respiratory disorder, and cure of the reflux will not result in the disappearance of the asthma.

Similarly (Table 3), we observed that in group 4 the results of the four diagnostic reflux tests (barium esophagram, esophageal fiberoscopy, manometry, and determinations) confirmed the clinical data and were all positive in nine cases of 11 (81.8 percent), while in the other three groups this positive concordance of the four tests was noted in only 13 out of 33 cases (39.3 percent, p<0.01).

We must note that in all subjects with conflicting results in the diagnostic reflux tests there were always at least two positive tests confirming the clinical reflux.

Predictive value of medical antireflux treatment (Table 3): This treatment resulted in an improvement in the asthma ten times out of 19, i.e., in 52.6 percent of cases. For the total study group of patients there was a significant relation between efficiency of medical treatment and surgical treatment (p<0.01). Failure of the treatment was constant in cases where surgery also failed (group 1, three cases). Conversely, medical treatment had always been effective in the patients ultimately cured by surgery (group 4, five cases). The results of medical treatment were variable in patients who were eventually improved by surgery (groups 2 and 3), since the asthma was improved five times of 11 and not in remaining six cases. It was not possible for us to isolate the particular clinical features leading to identification of patients likely to respond or not to respond to treatment and thus explain these discordances.

**DISCUSSION**

Long-term results of GER surgery in asthmatic patients are very close to those noted earlier, which we reported in 1980. They thus confirm the possible interest in this surgery and make it possible to establish that there is not a simple, one-way relation between asthma and GER since, while surgical repair of reflux can abolish reflux and asthma at the same time, such surgery can also heal reflux without having any effect on asthma. This indicates that the reflux can be a complication of the asthma without necessarily aggravating it (group 1) or, on the contrary, it may have a seriously harmful effect on the disease (groups 3 and 4). The problem thus revolves around the possibility of predicting which is the case in each individual patient. Analytical study of our results can supply only a partial answer to the problem, not a solution.

Asthma can be secondary to reflux—indeed, caused by it—and therefore remediable by reflux surgery (group 4). But this is a rare situation, associated with intrinsic asthma, which is in general severe, and with marked GER. It appears that these cases of asthma do not present highly individual clinical features, except that they are mostly accompanied by serious nocturnal tracheitis and that the attacks are often nocturnal. However, these characteristics are not exclusive to such cases of asthma (Table 2). The most important clinical feature is that the reflux symptoms appear prior to the pulmonary disease: a knowledge of the order in which the symptoms occur is therefore essential to define the situation. However, in two cases of 11, it was not possible to apply this theory (Table 3). In these patients GER is always an apparent, major clinical feature, and the diagnostic reflux tests all correlated positively in the majority of cases. The etiology of reflux is for the most part indeterminate. In two of our patients the reflux was posttraumatic.

In the majority of cases (groups 1, 2, and 3), reflux appeared secondarily during the asthmatic disease. Several factors have been suggested to explain the frequency of the secondary reflexes. The most common explanation is overdistention of the lung and lowering of the diaphragm, which stretches the gastroesophageal junction and widens the angle of Hiss. In other cases several antiasthmatic drugs, such as theophylline, corticosteroids, and β-agonists, can decrease the pressure of the lower esophageal sphincter, allowing reflux to occur. Whatever the case, in this situation, it is obvious that treatment of reflux cannot hope to cure the respiratory disease. The crux of the problem, therefore, is to determine whether the reflux is a simple complication of the asthma and is not a causal factor of the latter, or whether it plays an exacerbating role. Clinical analysis cannot completely answer this question. At best, in our experience, one may suspect this exacerbating role in cases of longstanding asthmatics, with or without allergic components, or in asthmatics that become worse, especially at night, for no apparent reason, and also when antiasthmatic

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medicaments lose their efficacy. However, when signs of GER disappear after surgery, there seems to be no explanation of why the asthma is sometimes improved and sometimes unaffected. Study of pulmonary clinical data or gastroenterologic data sheds no light on the problem.

Several authors have stressed the significance of the predictive value of a medical treatment trial. We have seen that the trial result was always positive when surgery was effective and always negative when surgery failed. On the other hand, the medical trial may be negative when surgery improves the asthma without it being possible to differentiate patients who will respond well from those who will not. Thus, it is not possible to base the indications for surgery on medical drug trial results. Nevertheless, when this trial fails, reflux surgery should only rarely be proposed and in particular be reserved for cases where the reflux is badly tolerated and complicated by ulcerative esophagitis.

Regarding the extrinsic or intrinsic nature of asthma, only one clear fact may be drawn from our study: surgery of the reflux in a patient suffering from extrinsic asthma cannot cure the asthma. This is normal, since such a cure cannot act in any way on the allergic element. It may, however, improve the respiratory condition of the same patients. On the other hand, in intrinsic asthma, surgical cure can abolish the asthma. It is nonetheless more common for surgical intervention to result in partial improvement. Last, in both cases, failure is always possible.

The mechanism by which the reflux acts on the tracheobronchial tree is still not fully understood. Several authors have suggested that aspiration of gastric contents may take place. As this occurs when in a recumbent position, it would explain the nocturnal incidence of crises in asthmatic patients with reflux. Esophageal scintiscanning makes it possible to study this mechanism, rarely present in adults. A more likely cause would seem to be the esophagobronchial vagal reflex, demonstrated by Mansfield and colleagues; however, this reflex can only lead to bronchoconstriction in cases where a state of bronchial hyperreactivity exists. If the vagal reflex is the cause of reflux-induced bronchoconstriction, practice of the acid perfusion test perfected by Bernstein and Baker should prove highly interesting, since the occurrence of bronchoconstriction following perfusion bears witness to the noxious nature of acid reflux.

However, even when resting values of ventilatory function remained unchanged following acid instillation, the bronchial responsiveness to stimuli such as methacholine and cold air increased. Nevertheless, we do not yet know if the asthmatic patients likely to be improved by reflux surgery are those for which the acid perfusion test is positive. Further studies are necessary to clarify this problem, all the more critical since at present we have no objective criterion by which to classify indications for surgery.

Studying our surgical results and the relation between asthma and gastroesophageal reflux enables us to identify those asthmatics provoked by reflux and likely to be cured by surgery. Most frequently, GER develops secondarily, and it is not possible to distinguish those refluxes which exacerbate the asthma and are therefore possibly amenable to surgery. It is for this reason that recourse to such surgery should be made with great care.

**References**

8th Annual Cardiology Symposium and Rehabilitation Update

The Gulf South Heart Center of East Jefferson General Hospital will present this program September 18-20 at the Hotel Meridien, New Orleans. For information, contact Patti O'Rourke, RN, Symposium Coordinator, East Jefferson General Hospital, 4200 Houma Blvd, Metairie, Louisiana 70011 (504:454-4145).

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The Department of Radiology, Charlotte Memorial Hospital and Medical Center, will present this course in Dublin, Cong and New Market (Irish castles) September 2-10. For information, contact Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, Georgia 30077-1925 (404:641-9773).

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