Pleurodesis entails the instillation of an agent into the pleural cavity to achieve symphysis of the parietal and visceral pleura. This procedure is commonly used to treat recurrent pleural effusion or pneumothorax.

On occasion, air is present in the pleural space when pleurodesis is contemplated. Is pleurodesis less likely to be effective if there is air in the pleural space at the time the sclerosing agent is instilled? Pleurodesis is thought to result from inflammation of both pleural surfaces progressing to fibrosis. If air is present in the pleural space, the sclerosing agent might injure less of the pleura, thereby decreasing the effectiveness of the pleurodesis. In addition, the presence of air in the pleural space leads to separation of the visceral and parietal pleura, which would tend to make it more difficult to achieve a pleurodesis.

The objective of this study was to evaluate whether the presence of small amounts of air in the pleural space would decrease the effectiveness of talc pleurodesis in normal rabbits. We hypothesized that a small pneumothorax would decrease the effectiveness of the pleurodesis.

**Materials and Methods**

Talc, 400 mg/kg as a slurry, was injected intrapleurally in 60 New Zealand male white rabbits using methods similar to those we have described previously.1,2 This dose of talc was selected because previous studies have demonstrated that this relatively large dose is necessary to obtain an adequate pleurodesis in rabbits.2 Air (10 mL) was injected intrapleurally in 30 rabbits at the time of the talc injection. The rabbits were divided into six subgroups, each containing 10 animals, according to the day they were killed: 2, 14, or 28 days. The talc (Sigma Chemical Co; St.

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**Effect of Pneumothorax on Pleurodesis Induced With Talc in Rabbits**

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**Objective:** The purpose of this study was to determine if a small pneumothorax would influence the pleurodesis resulting from talc instillation.

**Methods:** Sixty rabbits received an intrapleural injection of 400 mg/kg talc slurry. One half also received 10 mL of air intrapleurally after the talc. Ten rabbits in each group were killed 2, 14, and 28 days after instillation.

**Results:** Two days after the injection, the mean volume of air in the animals that had received the air was 7.5±0.4 mL. There was no air present in any other rabbits. The volume of pleural fluid and the pleural fluid glucose, protein, cell count, and differential were similar in both groups on day 2, while the LDH level was significantly higher in the air group (p<0.05). The degree of gross adhesions and microscopic fibrosis was similar in both groups and increased with time.

**Conclusions:** A small pneumothorax does not decrease the efficacy of talc pleurodesis in our experimental model. These results suggest that the presence of a small amount of intrapleural air is not a contraindication to talc pleurodesis in humans. (CHEST 1998; 114:1143–1146)

**Key words:** pleural effusion; pleurodesis; pneumothorax; talc

**Abbreviations:** LDH=lactate dehydrogenase
Louis, MO) was sterilized at a temperature of 132°C for 2 h. This protocol was approved by the Animal Care Committee of the VAMC Long Beach, CA.

Rabbits were lightly anesthetized with ketamine hydrochloride (Fort Dodge Laboratories, Inc; Fort Dodge, Iowa), 35 mg/kg, plus xylazine hydrochloride (Miles Inc; Agriculture Division, Animal Health Products; Shawnee Mission, KS), 5 mg/kg, administered IM. The thorax was prepared by shaving the right chest wall and scrubbing the thorax with povidone-iodine and 70% alcohol. A 0.3-cm medial to lateral skin incision was made over the right anterior chest using a scalpel. A 16-gauge angiocatheter was then introduced into the pleural space. The catheter was connected to a transducer (DMS Monitoring System; Bentley Laboratories Inc; Irvine, CA) by means of a three-way stopcock. The transducer signal was displayed on an oscilloscope. A characteristic pleural pressure tracing (ie, negative deflections of the pleural pressure tracing during inspiration) was used to verify that the catheter was properly positioned in the pleural space. After placement of the catheter, any air within the pleural space was aspirated.4

The talc slurry was then injected through the catheter into the pleural space of both groups (air and control groups). The catheter was flushed with 0.3 to 0.5 mL of saline. In the air group, after the intrapleural instillation of talc slurry, 10 mL of air was also injected into the pleural space. After the catheter was removed, the wound was cleaned with povidone-iodine. The left hemithorax received no injection and served as a control. After the surgery, the rabbits were closely monitored for clinical evidence of pain (vocalization, tachypnea, and restlessness). All rabbits received 0.3 mL buprenorphine (Reckitt & Colman Products; Hull, England) immediately after recovery from surgery and as needed for distress thereafter.

The rabbits were killed by the injection of 40 mg/kg pentobarbital solution (Abbott Laboratories; North Chicago, IL) into the marginal ear vein. Attempts were made to aspirate all air and fluid from both pleural spaces using a posterior transdiaphragmatic approach. The volume of air and pleural fluid was recorded. The level of glucose, protein, and lactate dehydrogenase (LDH) in the pleural fluid and the pleural fluid white cell count and differential were determined. The glucose level was measured using Chemstrip 1G and Accu-Chek (Boehringer Mannheim Corp; Indianapolis, IN). The protein was measured by Refractometer (American Optical; Buffalo, NY). The cell count was performed by Hemocytometer (Kodak Ektachem; Rochester, NY). The leukocyte differentials were determined by counting 100 cells on a Wright’s-stained smear. The LDH concentration was determined by using the Kodak method; the upper limit of normal for human serum is 630 IU/L.

The thorax was removed en bloc using methods previously described.1-3 Then 60 mL of 10% formalin was injected through the trachea to expand the lungs. After the injection, the trachea was ligated with silk and the entire thorax was submerged in 10% formalin solution for at least 48 h.

The macroscopic evaluation was performed by two of the investigators (CX, RWL), who were blinded to the treatment and the day of sacrifice of the rabbit. Each pleural cavity was carefully exposed using our previously described protocol.1-3

The degree of pleurodesis observed grossly was semiquantitated according to the following: 0=normal pleural space; 1=one to three small adhesions in the pleural space; 2=more than three scattered adhesions but lung easily separates from chest wall; 3=generalized scattered adhesions with areas where the lung can be separated from the chest wall only with difficulty; 4=complete obliteration of the pleural space by adhesions.

At the time that the pleura was evaluated grossly, samples of the parietal and visceral pleura and lung from each hemithorax were obtained from the lower lobes anteriorly and placed in neutral buffered 10% formalin. These tissue samples for histologic examination were processed routinely and stained with hematoxylin and eosin. The microscopic slides were evaluated blindly by one of the investigators (LRT) for the presence of inflammation and fibrosis. The degree of inflammation and fibrosis was graded, as previously described,1,3 from 0 to 4 for absent, equivocal, mild, moderate, and marked, respectively.

Statistical Analysis

All data were expressed as the mean±SE. The results in the two groups were compared using the unpaired t test if the data met criteria for normality and the Mann-Whitney rank sum test for data that failed the test for normality (Sigma Stat; Jandel Scientific; San Rafael, CA). Differences in the results were considered significant when p<0.05.

RESULTS

All 60 rabbits survived until their predetermined time for evaluation. Therefore, there were 10 rabbits for evaluation in each treatment group at the three different times.

In the group of animals that received 10 mL of air intrapleurally (air group) there was still substantial air remaining after 2 days. The mean amount of air aspirated at day 2 was 7.5±0.4 mL in the air group and was zero in the control group (p<0.0001, Mann-Whitney). There was no air present in any of the rabbits on day 14 or day 28.

The presence of the pneumothorax at the time that the talc was injected had little influence on the volume or characteristics of the pleural fluid present on day 2 (Table 1). There were no significant differences (p>0.05) in the amount of fluid aspirated, the pleural fluid protein level, the pleural fluid glucose level, or the mean white cell count or differential cell count in the two groups (paired t test). The LDH level was significantly higher in the air group (6,693±404 IU/mL) than in the control group (5,346±267 IU/mL) (p<0.05, paired t test). No rabbit had any pleural fluid present at either day 14 or day 28.

Table 1—Pleural Fluid Characteristics (Table 1—Pleural Fluid Characteristics (Mean±SE) 2 Days After Intrapleural Injection

<table>
<thead>
<tr>
<th>Pleural Fluid Fluid</th>
<th>Air Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume, mL</strong></td>
<td>6.8±0.8</td>
<td>7.5±1.5</td>
</tr>
<tr>
<td>Glucose, mg/100 mL</td>
<td>146±8</td>
<td>129±6</td>
</tr>
<tr>
<td>LDH, IU/L</td>
<td>6,693±404</td>
<td>5,346±267*</td>
</tr>
<tr>
<td>Protein, g/100 mL</td>
<td>4.7±0.1</td>
<td>4.4±0.1</td>
</tr>
<tr>
<td>WBC, cells/mm³</td>
<td>7,532±1,115</td>
<td>5,144±3,525</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>58±7</td>
<td>54±1</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>37±7</td>
<td>42±2</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>7.0±2.7</td>
<td>5.4±1.0</td>
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</tbody>
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*p=0.012 when control group was compared with the air group (paired t test).

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The presence of a small pneumothorax at the time of the talc injection did not significantly influence the pleurodesis induced by the talc slurry (Fig 1). The degree of pleurodesis increased with time in both groups (Fig 1). The mean gross adhesion score was slightly higher after 2 and 14 days in the air group, while it was slightly lower after 28 days. At 28 days, an effective pleurodesis (score of 3 or 4) was achieved in all but two rabbits, both of which were in the air group. In both groups of rabbits, the pleurodesis at 14 and 28 days was much greater ventrally (anteriorly), where the talc had collected, than it was dorsally.

When the visceral pleura was examined microscopically, the results were very similar in both groups on the three different observation days (Figs 2, 3). Pleural inflammation (Fig 2) tended to decrease with time in both groups, while pleural fibrosis (Fig 3) tended to increase with time in both groups. The microscopic changes in the underlying lung were minimal and also no different in the two groups (data not shown). In the left hemithorax (noninjected side) there were at most minimal changes in any of the rabbits.

**Discussion**

This study showed that in rabbits, the presence of a small pneumothorax did not affect effectiveness of pleurodesis after 2, 14, or 28 days. Moreover, the amount and characteristics of the pleural fluid were similar in rabbits with and without a pneumothorax, except for a significantly greater pleural fluid LDH level in rabbits with a pneumothorax.

The mechanism by which talc produces a pleurodesis remains unknown. The initial event in the production of a pleurodesis is an injury to the pleura. Forty-eight hours after the intrapleural injection of talc slurry, there is mesothelial denudement. In addition, as shown in this and previous studies, the injection of various agents that are effective in
producing a pleurodesis results in an acute exudative pleural effusion that persists for several days.\textsuperscript{6,7} However, injury to the pleura, as evidenced by the production of an acute exudative pleural effusion, is not sufficient to induce a pleurodesis. Many agents, when injected into the pleural space, produce an exudative effusion without producing a pleurodesis.\textsuperscript{7}

The response of the pleura to an injury is a complex, multifactorial process that can result in either the development of fibrosis with the obliteration of the pleural space, or restoration of the pleura to its normal state. A reasonable hypothesis is that the more severe the injury to the pleura, the more likely a successful pleurodesis is.

We hypothesized that pleurodesis would be adversely affected by the presence of air in the pleural space for two different reasons. First, we hypothesized that the injury to the pleura would be less if there were air in the pleural space. When air is present in the pleural space, the solution with the sclerosant will settle to the most inferior part of the pleural cavity. Accordingly, less of the surface area of the pleura will be in contact with the solution, and therefore the total injury to the pleura will be less. However, there is no evidence that the injury was less. The total volume of pleural fluid and the cell counts were similar in the two groups, and the level of pleural fluid LDH was actually higher in the air group. In addition, the degree of inflammation observed microscopically was not significantly less in the air group.

Second, when air is present in the pleural space, it might be more difficult to achieve pleurodesis because the visceral and parietal pleura are separated by the air. With this separation, it is difficult to form adhesions between the two pleural surfaces. If the air were absorbed very rapidly, this would not be a factor. Our rabbits with a mean weight of 2.5 kg received 10 mL of air. This would be equivalent to 240 mL of air in a 60-kg person. By 45 h after the injection, 25\% of the air had already been absorbed. If this rate of absorption continued, by 8 days all of the air should have been absorbed. Indeed, at 14 days none of the rabbits had any air in their pleural space. Since the fibrosis with pleurodesis occurs to a large extent after the first 7 days,\textsuperscript{8} the two pleural surfaces should have been in apposition by this time and therefore the fusion of the two pleural surfaces would not have been affected by the initial air.

What are the clinical implications from the present study? It is important to emphasize that the present study was done on animals with normal lungs. If air is present in the pleural space because the underlying lung is trapped by a thick visceral pleura, then pleurodesis is still contraindicated because the underlying lung can never expand so that a pleurodesis can occur.

The intrapleural injection of a sclerosing agent in this instance can only lead to a thicker visceral pleura.

It is also important to emphasize that the rabbits had only a relatively small amount of air in their pleural spaces. Since the spontaneous rate of air absorption in humans is approximately 1.25\% of the volume of the hemithorax every 24 h,\textsuperscript{8} one would expect complete absorption of a 10\% pneumothorax within 5 days. The results in the present study should not be extrapolated to a human with a moderate or large pneumothorax.

It should also be emphasized that the present study was done with talc, which persists in the pleural space.\textsuperscript{9} Comparable results might not have been achieved with a tetracycline derivative or bleomycin, which remain in the pleural space for only a short time. Last, it should be noted that the pleurodesis in both groups was greater in the inferior than in the superior part of the pleural cavity. One would prefer pleurodesis superiorly rather than inferiorly when treating pneumothorax.

From this study we conclude that the presence of a small amount of air (~4 mL/kg) does not significantly impair the production of a pleurodesis with talc slurry in normal rabbits. These results suggest that a small amount of air should not be considered to be a contraindication to pleurodesis. We caution that this extrapolation should only be made to humans with small pneumothoraces and lungs that are not trapped. It is unknown whether comparable results would be obtained with other sclerosing agents because talc is retained for longer periods in the pleural space.

References

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