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Pleurodesis: state of the art

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Pleurodesis: state of the art. F. Rodriguez-Panadero, V.B. Antony. ©ERS Journals 1997.

ABSTRACT: Pleurodesis aims to achieve a symphysis between parietal and visceral pleural surfaces, in order to prevent accumulation of fluid or air in the pleural space. Its major indications are malignant effusions and pneumothorax, and a re-expandable lung is essential for the success of the technique. Moreover, expectation of a reasonably long survival is important before attempting pleurodesis.

A successful lung re-expansion is unlikely if the pleural pressure falls more than 20 cmH₂O·L⁻¹ of fluid removed, because there is a central bronchial obstruction or the lung is trapped by tumour and/or fibrin. Pleural fluid pH (<7.20) is a good indicator of the presence of trapped lung; moreover, a successful pleurodesis is less likely when pH is low, and this parameter is also a good predictor for survival of the patients.

Among the many sclerosing agents that have been used for pleurodesis, talc has achieved the best results, with an average success rate of approximately 90%. The cellular and biochemical mechanisms involved in pleurodesis may be specific to the agent used, however, they may all follow a common final pathway leading to activation of the pleural coagulation cascade, the appearance of fibrin networks, and the proliferation of fibroblasts. The details of these mechanisms are still unclear and need to be further elaborated.

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The aim of pleurodesis is to achieve a symphysis between visceral and parietal pleural layers, in order to prevent accumulation of either air or fluid in the pleural space. Its main indications are malignant pleural effusions and pneumothorax. The choice of the right technique, sclerosing agent to be applied, criteria for selection of patients and evaluation of results are important and controversial issues. Furthermore, there is little information about the mechanisms that lead to pleural symphysis or the factors that influence the outcome of pleurodesis.

Pleurodesis in malignant effusions

Recurrent effusions of malignant origin are by far the most common indication for pleurodesis in clinical practice. This is because there is a lack of effective antitumoral treatment at later stages of the disease, and because palliative measures are necessary to improve symptoms related to the pleural effusion. Repeated thoracenteses are not usually suitable, since they may be troublesome to the patient and provoke important protein loss (about 40 g·L⁻¹ of pleural fluid that is withdrawn), with infection of the pleural space as an added risk.

There are several points that should be addressed before attempting pleurodesis in malignant pleural effusions.

Are the symptoms (especially dyspnoea) directly related to the effusion?

It is mandatory to have an affirmative response to this question. Thoracentesis should relieve the patient's symptoms of dyspnoea, and pleurodesis is not likely to help those whose symptoms persist in spite of therapeutic thoracentesis. In some cases, dyspnoea is due to lung parenchymal involvement, even if this is not clearly detectable through image techniques, rather than to the pleural effusion itself. Pleural malignant involvement frequently occurs as a tertiary seeding from the lung parenchyma, even in cases of tumours of extrathoracic origin (fig. 1) [1, 2].

Is the effusion recurrent?

This is commonly thought to be an important issue for consideration of pleurodesis. However, recurrence will occur sooner or later in most of the patients with a proven malignant effusion. Furthermore, successful pleurodesis is less likely if the pleural malignancy is advanced. Therefore, some clinicians advocate that pleurodesis be attempted sooner rather than later during the course of the disease [3, 4]. We currently agree with this position,

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Fig. 1. – Mechanisms of neoplastic pleural tumour involvement in lung cancer and extrathoracic tumours. a) In lung cancer, the pleura can be reached through tumoral embolization from the primary tumour, or through direct invasion of the mediastinal pleura. *: secondary spreading to the parietal pleura from the implants in the visceral pleura. b) Metastatic pleural spreading in extrathoracic tumours. (Drawn from [2]).

in order to avoid attempting pleural symphysis when the effusion is rapidly recurrent and the general condition of the patient has deteriorated.

Is the lung re-expandable?

It is important to demonstrate the ability to oppose the visceral and parietal pleura prior to attempting pleurodesis. The presence of a trapped lung should be suspected by the finding of very low pleural pressures as fluid is withdrawn during thoracentesis [5]. Thus, lung re-expansion is unlikely to be achieved easily if the pleural pressure falls more than $20 \text{ cmH}_2\text{O} \cdot \text{L}^{-1}$ of fluid removed. Extremely low pleural pressures after thoracentesis (even less than $-50 \text{ cmH}_2\text{O}$) can be due either to a lung trapped by fibrin or tumour, or to a central tumour occluding the main ipsilateral bronchus. However, under these circumstances, thoracentesis can be dangerous because of rapid changes in intrathoracic pressures. Instead, it is recommended that measurement of pleural fluid pH be used as a first approach to assess multiple factors in evaluating a patient prior to pleurodesis.

In a study performed on 180 patients with malignant pleural effusion, who were submitted to thoracoscopy and talc pleurodesis, we found that trapped lung was present in 36% of the patients with pleural fluid pH <7.20 , as opposed to 9% in those with higher pH levels ($p < 0.001$) [6]. However, a good pleural symphysis was obtained in as many as 11 of the 16 patients with trapped lung (69%). In another study, successful pleurodesis was obtained in 90% of the patients with pH >7.30 , in only 33% when pH was <7.20 , and in none of the patients with pH <7.15 , regardless of the presence or absence of a trapped lung [7]. Thus, pH levels had a surprisingly greater discrimi-

nant power to predict the outcome of pleurodesis than trapped lung itself, as observed during thoracoscopic exploration. These results suggest that, besides mechanical factors, there must be other biological implications in low pH patients that account for the outcome of pleurodesis. Based on these and other findings (see section on "Biological aspects of pleurodesis"), it is currently believed that certain characteristics of the neoplastic lesions in the pleura play a role, as important as the tumour burden, regarding the outcome of pleurodesis.

When complete lung re-expansion is not possible or pleurodesis fails, palliation of symptoms due to the pleural effusion can be obtained with other alternative options, such as pleuroperitoneal shunting or pleurectomy. PETROU *et al.* [8] inserted a pleuroperitoneal shunt in 63 patients with "trapped lung syndrome", and obtained relief of symptoms in more than 90% of patients. However, the shunt became blocked in 12% of the cases, and had, therefore, to be either removed or replaced several weeks after its insertion. Thoracotomy with pleurectomy can sometimes be a valid alternative, but it has significant morbidity and mortality, and needs to be applied to patients in good physical condition and with a reasonably long expected survival [9]. Video-assisted thoracoscopic pleurectomy has gained acceptance in recent years, and has achieved good results in selected patients, especially those with mesothelioma [10].

What is the life expectancy?

Obviously, aggressive techniques, such as pleurodesis, should not be attempted in patients whose expected survival is short. Certain clinical parameters (*e.g.* Karnofsky index) can be of help in making decisions. In our experience, pleural fluid glucose and pH determinations are very useful in selecting patients as candidates for pleurodesis. In 125 patients with metastatic pleural carcinoma, those who presented with a pH <7.20 and glucose $<60 \text{ mg} \cdot \text{dL}^{-1}$ had a very short life expectancy (1.9 months on average). A more conservative approach should, therefore, be considered in such patients [11]. The strong correlation found between glucose and pH values and survival is also found in the relationship between pH and tumour lesions [12]; thus, the lower the value of pH the bigger the tumour burden in the pleural space. Based on these results and those from SAHN and GOOD [13], pleurodesis is not recommended in patients with low pleural fluid glucose and pH levels. Other alternative measures, such as repeated thoracenteses or the measures mentioned above, may be used for palliation of symptoms.

Pleurodesis in benign conditions

Although malignant pleural effusions are the most common indication for pleurodesis, there are other instances in which this technique may be indicated. Among these, the most frequent benign condition requiring pleural symphysis is pneumothorax. Benign, recurrent pleural effusion can also be an indication for pleurodesis in some selected cases.

Pleurodesis in pneumothorax

When dealing with a spontaneous pneumothorax, there are several issues involved that have a significant influence

on the approach to treatment: 1) the relatively high incidence of spontaneous pneumothorax in young patients makes it mandatory to use techniques for pleurodesis that are both reliable and that would allow for a thoracotomy in the future, if necessary (*i.e.*, resection of lung cancer, lung transplantation, *etc.*). 2) the rupture of bullae or blebs requires specific intervention besides pleurodesis, in order to prevent recurrence; and 3) the largely normal pleural mesothelial surface in pneumothorax patients leads to significantly greater pleural responsiveness, making it necessary to use higher doses of analgesics. Moreover, a lower dosage of the sclerosing agent should be used to obtain an adequate response from the pleural mesothelium.

In addition to the above considerations, there are two particular circumstances that require a special approach, *i.e.* the pneumothorax occurring in patients with acquired immune deficiency syndrome (AIDS) and in those with cystic fibrosis.

The primary goal in the treatment of pneumothorax is to achieve complete lung re-expansion, which is usually accomplished with pleural drainage, and underwater seal in most cases. Evacuation of air from the pleural space can be achieved with a small-bore drainage coupled to a Heimlich-type valve in others [14–17]. However, the rate of recurrence of pneumothorax is unacceptably high when drainage alone is used, and it is, therefore, advisable to use any technique that is suitable to achieve a pleural symphysis. In a prospective randomized study, ALMIND *et al.* [18] compared the recurrence of pneumothorax using drainage alone and drainage plus tetracycline or talc, and found a rate of 36, 13 and 8%, respectively, after an average follow-up of 4.6 yrs. Furthermore, ALFAGEME *et al.* [19] had a 9% recurrence with tetracycline pleurodesis, as compared to 35% in patients with drainage alone.

In recent years, there has been a growing tendency to treat patients with pneumothorax using video-assisted thoracoscopic surgery (VATS), in order to achieve a resection of the bullae or blebs and achieve pleurodesis, either through local abrasion of the parietal pleura or localized apical pleurodesis [20–22]. However, this procedure is expensive, requires general anaesthesia and (usually) double-lumen tracheal intubation. Also, the rate of recurrence varies greatly, depending on identification and subsequent ablation of blebs, according to NAUNHEIM *et al.* [23].

The use of VATS or conventional thoracoscopy and pleurodesis, or thoracotomy, is dependent upon several variable factors [24–27], and there is no clear technique of choice so far. In young patients with recurrent pneumothorax, VATS would be recommendable, always combined with some technique aimed to induce pleural symphysis (usually mechanical pleural abrasion, or apical talc pleurodesis). Talc should not be used generously for achieving pleurodesis in pneumothorax in young patients, because the symphysis induced could make it impossible or exceedingly risky for the patient to undergo an open thoracotomy in the future [28]. On the other hand, conventional thoracoscopic talc pleurodesis can be used in elderly patients with spontaneous pneumothorax, which is frequently secondary to emphysematous lesions. These patients may not tolerate VATS because of the need for single-lung ventilation, and talc may be the sclerosing agent of choice [18, 27, 29, 30].

In pneumothorax, careful analgesia and titration of dosage of the sclerosing agent must be performed, as pointed out above, because the procedure may be much more painful than when treating malignant effusions. The talc dose for pneumothorax should not exceed 3–4 g (about 5–6 μ L of dry talcum powder).

Pneumothorax in patients with AIDS

Spontaneous pneumothorax occurs rather frequently in patients with AIDS and *Pneumocystis carinii* infection. According to METERSKY *et al.* [31] and WAIT and NOGARE [32] a history of cigarette smoking, aerosolized pentamidine treatment and the observation of pneumatoceles on chest films are associated with an increased risk, and chemical pleurodesis is, therefore, often indicated. KIMMEL *et al.* [33] have reported a technical modality of talc poudrage after bleb resection using VATS, so that even distribution of talc can be visually controlled. Conventional thoracoscopic talc poudrage can also be performed, and talc might even be instilled through the chest drainage without thoracoscopy (as we have done successfully in a few patients).

A specially developed disposable spray canister is now available for talc pleurodesis [34], and can be used through a single-entry thoracoscopy or through a chest tube. However, its use is much more expensive than plain sterile talc preparations. A single canister is usually sufficient for pneumothorax, but not for treatment of recurrent malignant effusions, which may have a late relapse after an initial success. Unfortunately, the two drawbacks that we have found in this device are that the delivery catheter may accidentally detach from the nozzle as pressure is applied, and that the cold temperature generated by the suddenly decompressed talc provokes more discomfort than standard talc sprayed in the usual way.

Pneumothorax in patients with cystic fibrosis

These patients require special management, since they have a tendency to develop repeated and bilateral pneumothoraces, but can be candidates for lung transplantation as well. Therefore, they need a treatment that is both efficient and yet will allow for future thoracotomy. A chest drainage with underwater sealing and/or mild suction would be the choice for a few days, and subsequent VATS with bullectomy and apical pleurodesis should be performed afterwards if the air leak persists. Despite concerns about the use of talc in young patients, there are some authors who advocate applying localized apical talc pleurodesis through thoracoscopy in such patients, especially if a previous pleurodesis attempt has failed [35].

Pleurodesis in benign pleural effusions

Although the main indication for pleurodesis in effusions is diffuse pleural malignancy, there are a few circumstances in which pleural symphysis may be indicated in the absence of pleural neoplasm. According to SUDDUTH and SAHN [36], the following three criteria must be met: 1) the effusion must be symptomatic; 2) the presence of a trapped lung should be excluded; and

3) pleurodesis should be reserved for those cases where there is no other therapeutic alternative, or when this has already failed.

These three circumstances can be present in some cases of pleural effusions that are associated with cardiac failure, cirrhosis of the liver, nephrotic syndrome, chylothorax, or systemic lupus erythematosus. VARGAS *et al.* [37] have reported their experience using low dose (2 g) talc in such conditions, with a very good rate of success. It must be emphasized that the same precautions as mentioned above for pneumothorax should be applied in benign effusion regarding chemical pleurodesis, as the pleural surface is often well-preserved.

It should be acknowledged that this is a limited indication for pleurodesis, and that it should be performed after a complete thoracoscopic exploration of the pleural cavity. From our own experience, we would give some supplementary recommendations to those quoted by SUDDUTH and SAHN [36]. Firstly, talc pleurodesis in effusions of cardiac origin is usually successful, provided that standard medical treatment is not forgotten. Secondly, pleural effusions associated with cirrhosis of the liver are very difficult to manage, since there are usually communications between the abdominal and pleural cavity, which can sometimes be seen during thoracoscopy. Therefore, if ascites cannot be controlled, pleurodesis will most likely be unsuccessful. CANTO *et al.* [38] reported an 86% rate of successful pleurodesis when ascites was absent, as opposed to 40% when it was present, even if the pleurodesis procedure was performed immediately following evacuation of the ascites.

Thirdly, in our experience, pleural effusion associated with nephrotic syndrome has a markedly increased risk of re-expansion pulmonary oedema when applying suction through the chest tube following pleurodesis, due to the usually severe hypoproteinaemia, and to the increased leak of proteins into the pleural space after an irritant agent has been instilled. Finally, successful pleurodesis in chylothorax requires that chyle flux through the thoracic duct be reduced to a minimum, using a special diet or intravenous hyperalimentation.

Technical aspects of pleurodesis

In order to achieve a complete pleural symphysis, several conditions need to be met, and they can be classified into mechanical and biological aspects.

Mechanical aspects of pleurodesis

Obviously, the complete removal of air or liquid from the pleural space is needed to keep the visceral and parietal pleural layers in close contact, allowing for the establishment of a tight symphysis. These goals are obtained with application of suction through appropriate drainage, provided that a trapped lung is ruled out (as explained above). To prevent obstruction by clots, the chest tube should be large enough (we usually insert a 28 French). It is extremely important that careful progressive suction be applied following instillation of the sclerosant, in order to prevent re-expansion pulmonary oedema.

When inducing pleurodesis in malignant pleural effusions, we initially leave the chest tube on underwater

seal alone for about 3 h following thoracoscopic talc pouddage; then slowly apply progressive suction, beginning with 2–5 cmH₂O, and doubling this rate every 3 h, until a final negative pressure of about 20 cmH₂O is reached in the system. This final suction is maintained until less than 100 mL of fluid·24 h⁻¹ is drained. Usually the chest tube can be removed after 2–3 days [39]. In our experience, the first 3 h of suction are the most critical period, during which complications can occur and patient discomfort may be high. When air leak is observed (which may occur even with no lung biopsy performed in some cases), it is crucial to reduce the rate of suction (even to zero if needed) until it ceases, and then maintain it for as long as necessary (usually less than 24 h). Once the air leakage has stopped, careful progressive suction can be applied again.

Biological aspects of pleurodesis

In order to achieve a complete symphysis, the pleural surface needs to be irritated, either mechanically with pleural abrasion or through the application of a sclerosing agent. Furthermore, and this is a recently developed concept, there is an increasing body of knowledge about the role of a functionally responsive mesothelium to the sclerosing stimulus.

Choice of the sclerosing agent

Since 1935, the year in which BETHUNE [40] reported the application of talc into the pleural space to provoke adhesions, more than 30 agents have been proposed as sclerosants to induce pleurodesis. One of the most detailed reviews of the literature in English about this topic was presented recently by WALKER-RENARD *et al.* [41]. They concluded that, once parenteral tetracycline production had been discontinued (doxycycline and minocycline are good tetracycline replacements), talc was the most effective and least expensive agent. From the review of these authors and others [11, 12, 42–44], we could summarize as follows.

Tetracycline hydrochloride. Tetracycline has a wide range of efficacy (45–77%). It requires heavy analgesia, but its main problem is that production of the parenteral form has been discontinued and the remaining stock is decreasing rapidly. Moreover, a relatively high rate of late recurrences has been reported.

Doxycycline. The average effectiveness of doxycycline is 72% but it often requires repeated doses, sometimes for more than 2 weeks, which is seen as a drawback.

Minocycline. Like doxycycline, minocycline has been proposed as a replacement for tetracycline. An overall success rate of 86% has been reported in some short series. It can provoke vestibular symptoms when the doses required for pleurodesis are used, and a high rate of haemothorax after application of those high doses has been reported in experimental studies [45].

Bleomycin. Although bleomycin appears to be more effective in clinical practice than in experimental animal studies [46], its main drawbacks are cost and systemic absorption, with risk of significant toxicity.

Corynebacterium parvum pleurodesis. Almost exclusively used in some European centres, the average effectiveness of this procedure has been reported to be 76%. However, in a randomized study with bleomycin it was effective in only 32% of cases [47].

Quinacrine. Frequently used in Scandinavia, quinacrine can provoke serious toxicity of the central nervous system, probably due to the high doses that are required [48].

Talc. Although talc has a reported effectiveness of 91%, in most series it has been used *via* thoracoscopy, which has a long learning curve and, therefore, requires extensive experience.

General anaesthesia or tracheal intubation is not necessary for thoracoscopic talc poudrage, though careful local anaesthesia with parenteral analgesia is mandatory. We have performed more than 300 procedures in the last 15 yrs, using the association of local anaesthesia (mepivacaine) and up to 100 mg of parenteral pethidine for analgesia/sedation, with a good overall tolerance and very few complications [39]. At the moment of writing this article, we have had 299 evaluable patients for results of talc poudrage, and have had an overall complete response (defined as absence of significant reaccumulation of the effusion during the whole follow-up, and determined by chest radiography) of 89%. However, when pleural pH was >7.30 we had a success rate of 95%, as compared to a 76% response in patients with pH <7.30 .

When thoracoscopy is not available, many groups are using a "talc slurry" (talcum powder suspended in variable amounts of saline), with an overall reported success of 91% which is comparable with that of talc insufflation [44, 49]. However, the studies on talc slurry are smaller than those involving talc poudrage, and we and others [50] believe that there will be some difference in favour of the dry form in the future. Talc is not water-soluble, and in the form of a suspension it may granulate to the dependent part of the pleural space shortly after its instillation. This phenomenon would prevent the sclerosing agent reaching as much mesothelial surface as possible, and, since there is increasing evidence that the role of the mesothelium as a "target" for pleurodesis is crucial (see below), the attempts at symphysis would be expected to fail more frequently.

Complications related to talc are rare, provided that a sterile and asbestos-free form is used. Severe pain is less frequent than with tetracycline, in our experience, and mild fever (probably related to the inflammatory process) is commonly seen for 2–3 days after the procedure. A few major complications have been reported in the literature, but they may be related to excessive dosage and/or other independent factors [51].

Fibrin glue. This agent has been successfully used as a sealant for air leaks in pneumothorax [52], but its use in effusions is more controversial, due to cost and lack of evidence of experimental effectiveness [53]. Moreover, we have recently demonstrated that failure of pleurodesis in malignant effusions is associated with increased pleural fibrinolysis, which could lead to rapid destruction of the fibrin glue applied in malignancy [54].

Role of the mesothelium in pleurodesis

Until recently, it was assumed that severe damage to the mesothelial layer was necessary to achieve a pleural symphysis. This is true when mechanical pleural abrasion or pleurectomy is performed, but recently there is increasing evidence for a new concept (fig. 2) that the mesothelium itself is the primary initiator of the biological cascade leading to pleurodesis. We already know that production/release of mediators for inflammation and fibrosis by the mesothelial cells themselves are essential to achieve a good pleural symphysis, provided that mechanical conditions (see above) have been accomplished. This fact implies that the sclerosing agent must reach the maximum surface area of normal mesothelium for best results. Thus, when the mesothelial surface is covered by tumour or fibrin, and this circumstance is associated with low glucose and pH levels, the rate of failure is much higher. This is also the reason why much lower doses of sclerosing agent are required to induce pleurodesis in pneumothorax (in which the mesothelial surface is almost completely preserved) than in malignant effusions.

The cellular mechanisms involved in pleurodesis are not yet fully known, but it seems that, besides mesothelial cells, inflammatory cells recruited from the blood stream (namely neutrophils and mononuclear phagocytes) play an essential role [55, 56]. There is also some evidence that the superior effectiveness of talc as sclerosing agent may be related to phagocytosis of its particles following instillation into the pleural space [57, 58].

The recruitment and proliferation of fibroblasts in the pleural space is obviously essential for the process of pleurodesis, and we now have evidence that both tetracycline and talc stimulate mesothelial cells to produce/release fibroblast growth factor [59, 60].

One of the first phenomena taking place after the sclerosing agent has been instilled is an activation of the pleural coagulation cascade. AGRENIUS and co-workers [61, 62] demonstrated an increase in pleural coagulation and decrease of fibrinolytic activity after the instillation of a sclerosing agent. Since it is assumed that a fibrin mesh formation is a necessary step for fibroblast recruitment (through "haptotaxis" mechanism) and subsequent proliferation into the pleural space [63], we hypothesized that either an impaired fibrin formation or an increased endopleural fibrinolysis would lead to failure of

Fig. 2. — New concept about the role of pleural mesothelium in pleurodesis.

Fig. 3. — Mechanisms involved in the first steps of talc pleurodesis. PAI: plasminogen activator inhibitor.

pleurodesis in malignant effusions (fig. 3). According to this hypothesis, we have recently demonstrated that failure of talc pleurodesis is associated with an increased pleural fibrinolysis [54]. At the present time, we believe that the mesothelium itself regulates the pleural coagulation/fibrinolysis balance and the first steps of the pleural fibrosis process. Furthermore, there is a growing body of knowledge concerning the association of fibrinolytic activity with tumour aggressiveness in other organs. Thus, it seems likely that the strong fibrinolytic activity that was detected in our failed cases of pleurodesis comes, at least in part, from the neoplastic cells in the pleural space.

The cellular and biochemical mechanisms involved in pleurodesis may be specific to the agent used. However, they may all follow a common final pathway leading to activation of the pleural coagulation cascade, the appearance of fibrin networks and the proliferation of fibroblasts. The details of these mechanisms are still unclear and need to be further elaborated. Understanding the pathways involved in pleurodesis should eventually aid in a better understanding of management of patients with pleural disease.

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