PNEUMONECTOMY IN RATS DELAYS GASTRIC EMPTYING RATE: EFFECT OF MEDIASTINAL SHIFT

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ABSTRACT

Objective: To elucidate possible alterations in the gastric emptying rate after pneumonectomy, we designed an experimental study in rats and looked for the mechanical and neural factors.

Methods: Following the intubations, a left thoracotomy was performed and the left lung was removed (pneumonectomy; n=48) or not removed (sham-operated; n=8). Control rats had no throacotomy (n=14). Gastric functions (gastric emptying rates of solid and liquid meals) were evaluated 1 week after the surgical procedure. In some rats with pneumonectomy, to test the involvement of thoracic vagal afferents in the gastric functions, capsaicin was applied perivagally, while in some rats hemithorax was filled with bone wax to prevent pneumonectomy-induced mediastinal shift.

Results: Gastric emptying rates of solid and liquid meals in the sham-operated and control groups were not different from each other. In the pneumonectomy group, gastric emptying rates of solid and liquid meals were significantly delayed compared to sham group (respectively; $p<0.001$ and $p<0.05$). Afferent denervation by capsaicin did not change gastric emptying rates compared with vehicle-treated animals. Intrathoracic application of bone wax abolished the delay in gastric emptying rates of both solid and liquid meals induced by pneumonectomy ($p<0.01$).

Conclusion: The present results suggest that pneumonectomy in rats delays gastric emptying rate and denervation of the capsaicin-dependent vagal afferent fibers has no effect, while filling the cavity of the removed lung with bone wax abolishes the pneumonectomy-induced delay in both liquid and solid emptying rates.

Key Words: Gastric emptying, Pneumonectomy, Capsaicin

INTRODUCTION

Lung transplantation has become an established therapeutic option for the treatment of end-stage pulmonary disease (1). Pneumonia and aspiration are the major causes of primary

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respiratory failure that can lead to adult respiratory distress syndrome and perioperative mortality following transplantation (2). Since oesophageal dysmotility and delayed gastric emptying have been reported after recipient pneumonectomy for thoracic organ transplantation, it was speculated that these may predispose to chronic aspiration and pulmonary sepsis (3). Similarly, a high prevalence of severe symptomatic gastroparesis (4, 5) and gastroesophageal reflux (6) were observed among lung and heart-lung transplantation patients. To the contrary, Au et al (7) have suggested that gastric emptying abnormalities are not associated with the development of respiratory morbidity or mortality.

It was hypothesized that injury of the vagus nerves during the operation may be the cause of oesophageal dysmotility and delayed gastric emptying in lung recipients (7). It was also stated that the modified surgical technique of Vouhé and Dartevelle (8) may decrease the risk of vagal injury. However, no prospective study involving a large patient population and no animal study is present to precisely define the gastric motility abnormality seen after pneumonectomy.

Vagotomy below the level of the recurrent laryngeal nerves abolishes the responses to the stimulation of pulmonary stretch, irritant and J-receptors (9). J receptors are vagal C–fiber afferents in the alveolar walls in juxtaposition to pulmonary capillaries and they are stimulated when the pulmonary capillaries are engorged with blood or when pulmonary oedema occurs (10). It was speculated that capsaicin could desensitize tracheal C-fibers, possibly containing substance P, that were involved in certain respiratory pathophysiologies (11). In spontaneously breathing rats, it was shown that pre-treatment of both cervical vagi with capsaicin blocks the conduction of C-fibers and thereby abolishes the anandamide-induced pulmonary chemoreflex responses (12).

Given the lack of any animal studies investigating pneumonectomy-induced gastric motility changes, the present study was designed to elucidate the mechanical and neural basis of possible alterations in the gastric emptying rate due to pneumonectomy.

MATERIALS AND METHODS

Animals

Sprague-Dawley rats of both sexes (250-300 g) were fed a standard pellet lab chow, and food was withdrawn overnight before emptying experiments, but access to water was allowed ad libitum. This study was approved by the Marmara University, School of Medicine, Animal Care and Use Committee.

Surgery

Each animal was anesthetized by intraperitoneal administration of 100 mg/kg ketamine and 0.75 mg/kg chlorpromazine mixture. An incision was made to expose the trachea and the animal was intubated without any tracheotomy incision. The lungs were ventilated through a cannula by a rodent ventilator (Ugo Basile) at a tidal volume of 10 ml/kg. A left thoracotomy was performed in the fourth intercostal space. The left hilum was dissected and ligated. The left lung was removed following the en bloc ligation of the hilum. Sham animals were operated in the same manner but the left lung was not removed. Gastric functions were evaluated 1 week or 2 weeks after the surgical procedure.

Perivagal Application of Capsaicin; Intrathoracic Application of Bone Wax

To test the involvement of thoracic vagal afferents in the gastric functions after pneumonectomy, a 1 % solution of capsaicin (Sigma) or vehicle (10% Tween 80 in oil) was applied on the left hilum for 30 min. During surgery the rats were pretreated with atropine sulfate (2 mg/kg, ip) to decrease the acute effects of capsaicin on the respiratory and cardiovascular systems. The total dose of capsaicin applied in each rat did not exceed 1 mg. After application, the area was rinsed with sterile saline. Before the experiment, rats were tested for impaired chemosensitivity by an eye-wiping test. In capsaicin-treated rats, the corneal afferents were no longer sensitive to a solution of 1 % NH_4OH.

In another group of rats, mediastinal shift following pneumonectomy was prevented by filling the left hemithorax with bone wax (approximately 0.8 g/rat).

Measurement of Gastric Emptying of a Nutrient Solid Meal

The gastric emptying of a nutrient solid meal was measured with modifications of the method originally described by Robert et al. (13). Fasted rats had free access to water and preweight standard pellet lab chow for a 3-h period. Food and water were then removed, and gastric emptying of the ingested meal was assessed 5 h later. After decapitation, the abdominal cavity was opened, the pylorus and cardias were clamped, and the stomach was removed. The stomach was weighed and then opened, and the gastric contents were washed out with tap water. The gastric wall was dried and weighed. The amount (g) of food contained in the stomach was estimated as difference between the total weight of the stomach plus the content and the weight of the stomach after the content was removed. The solid food ingested by the animals was determined by the difference between the weight of the standard pellet lab chow before feeding and the weight of the pellet and spill at the end of the 3-h feeding period. The rate of gastric emptying during the 5-h experimental time was calculated according to the following equation: gastric emptying (% in 5-h) = 1- (gastric content / food intake) X 100

Measurement of Gastric Emptying of a Non-nutrient Liquid Meal

The methodology used to measure gastric emptying of a nutrient liquid meal was similar to that described previously (14,15) using a methylcellulose (MC) test meal. MC was dispersed in water with continuous stirring and phenol red (PR; 50 mg/100ml) was added. A volume of 1.5 ml of MC was given by gavage through a polyethylene tube. Gastric emptying was determined 30 min after administration of the meal. Gastric emptying was calculated according to the following formula: % gastric emptying = 1 – (amount of PR recovered from test stomach / average amount of PR recovered from standard stomachs) X 100

Statistics

Data are expressed as means ± SEM from 5-8 rats in each group. The statistical significance was determined using Student's unpaired t test. Differences were considered statistically significant if $p<0.05$.

RESULTS

Gastric Emptying of a Nutrient Solid Meal

Gastric emptying rates of solid meal in the sham-operated (71.2 ± 2.9 %) and control (75.7 ± 5.7 %) groups were not different from each other (Fig. 1). In the pneumonectomy group (44.8 ± 3.8 %) gastric emptying rate was significantly delayed compared to the sham group ($p<0.001$) and this effect was not observed in the 2 week-period following pneumonectomy (73.2 ± 6.2 %) (data not shown). In rats with capsaicin treatment (53.2 ± 6.6 %), gastric emptying rate was not significantly different from that of the vehicle (56.7 ± 4.9 %) (Fig.2). Intrathoracic application of bone wax (75.2 ± 8.9 %) abolished the delay in the gastric emptying rate of the solid meal induced by pneumonectomy ($p<0.01$).

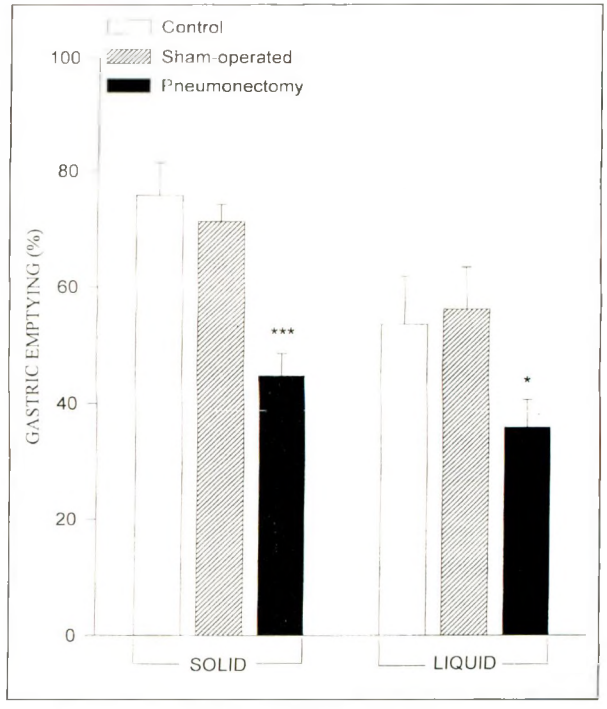

Fig. 1: Gastric emptying rates of solid and liquid meals in the control (n=7), sham-operated and pneumonectomy groups.
*p<0.05, ***p<0.001, compared to sham-operated groups.

Gastric Emptying of a Non-nutrient Liquid Meal

The gastric emptying rate of a liquid meal in the sham-operated group (56.4 ± 7.2 %) was not different from control group (53.7 ± 8.3 %) (Fig.1). In the pneumonectomy group (36.0 ± 4.8 %) gastric emptying rate was significantly

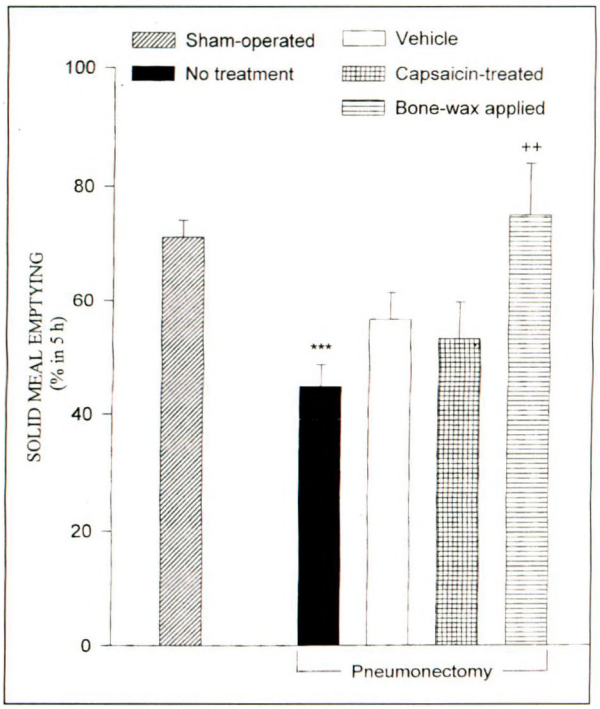

Fig.2: Gastric emptying rate of solid meal in sham-operated (n=8) and pneumonectomy (n=6) groups and pneumonectomy plus vehicle (n=6; 10% Tween 80 in oil), capsaicin-treated (n=5; 1%) and bone-wax applied (n=5) groups.
***p<0.001, compared to sham-operated group; ++p<0.01, compared to pneumonectomy group.

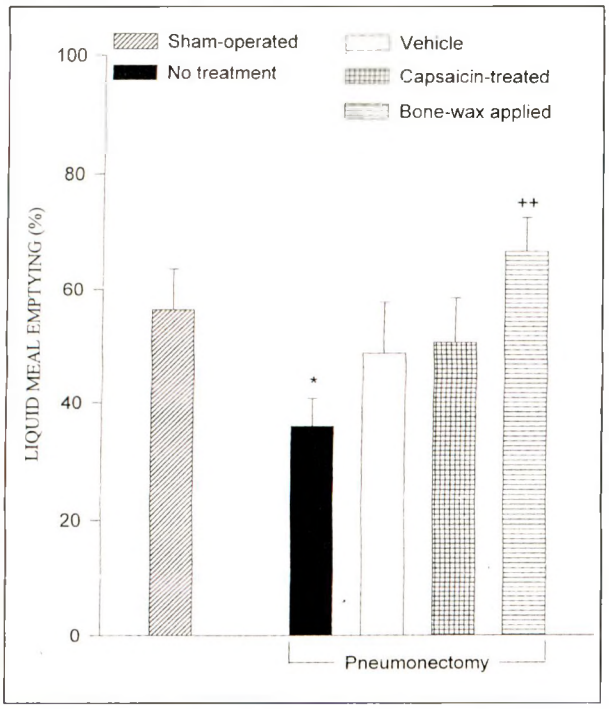

Fig.3: Gastric emptying rate of liquid meal in sham-operated (n=8) and pneumonectomy (n=8) groups and pneumonectomy plus vehicle (n=6; 10% Tween 80 in oil), capsaicin-treated (n=6; 1%) and bone-wax applied (n=6) groups.
*p<0.05, compared to sham-operated group; ++p<0.01, compared to pneumonectomy group.

delayed compared to the sham group (p<0.05). Afferent denervation by capsaicin (50.7 ± 7.9 %) did not change gastric emptying rate compared with vehicle-treated animals (51.0 ± 8.0 %) (Fig.3). Intrathoracic application of bone wax (66.8 ± 5.8 %) abolished the delay in the gastric emptying rate of the solid meal induced by pneumonectomy (p<0.01).

DISCUSSION

The results of the present study demonstrate that pneumonectomy in rats delays gastric emptying rate in the postoperative first week, while the gastric emptying rate returns to basal levels in the second week. This decreased gastric motility in the early period was observed when either liquid or solid meals were used for the determination of gastric emptying rate. Denervation of the capsaicin-dependent vagal afferent fibers had no effect on delayed gastric emptying, while filling the cavity of the removed lung with bone wax abolished the pneumonectomy-induced delay in both liquid and solid emptying rates. These results suggest that the symptomatic gastroparesis following pneumonectomy or lung transplantation may be dependent upon the mediastinal shift. On the contrary, it is not related with the injury of the vagal afferent fibers, which are said to be at risk during recipient pneumonectomy.

Lung and chest wall receptors in the lung parenchyma convert the stretching stimulus into nerve impulses and send information to the respiratory centre on the status of breathing through myelinated and unmyelinated vagal fibers. On the other hand, output from the central respiratory rhythm generator, which stabilizes the depth and rhythm of breathing, has control over swallowing and gastric emptying. It may be speculated that vagal injury during recipient pneumonectomy or diminished pulmonary stretch input due to reduced lung volume interrupts the central integration between the respiratory and gastric rhythms and results in gastroparesis. In the present study, local

capsaicin application on the vagi did not affect the pneumonectomy-induced delay in gastric emptying suggesting that unmyelinated afferent fibers are not involved in this mechanism. However, the involvement of the intact efferent limb or myelinated fibers in the reflex arc between the lung receptors and gastric smooth muscle cannot be excluded.

Visualisation of the hilar area during recipient pneumonectomy for lung or heart-lung transplantation may be difficult and the vagal nerve supply of the oesophagus and upper gastrointestinal tract may be damaged (16). Vagal injury may occur from direct trauma, from thermal injury or during oversewing of the posterior mediastinum for haemostasis before graft implantation (3). In these patients, postoperative oesophageal dysmotility and delayed gastric emptying (3, 17) were attributed to the damage of the vagus nerves during the operation owing to their proximity to the posterior of the hila. These sequel may predispose to chronic aspiration and subsequent respiratory failure and mortality (18). Au et al (7) have performed manometric and radioisotopic studies in patients who had undergone heart-lung transplantation and have found that oesophageal dysmotility and delayed gastric emptying are compatible with complete vagotomy. However, they have suggested that these upper gut abnormalities are not associated with gastroesophageal reflux and the development of pulmonary consequences. On the contrary, Roberts et al (19) have concluded that aspiration occurs in patients with impaired or delayed gastrointestinal tract transit and it can be a primary cause of respiratory failure which develops after lung resection. It was reported that severe symptomatic gastroparesis is a frequent complication that may promote microaspiration into the lung allograft (4, 5). Our results in rats show that lung resection leads to a transient delay in gastric emptying, which suggests that afferent nerve damage is not present. It seems that an adaptive filling of the mediastinal cavity with the overinflation of the remnant lung on the second week helps in the recovery of the gastric dysmotility. Similarly, mediastinal shift was prevented by bone wax application and thereby gastric emptying rate was not affected after lung resection. Although it is well known that pneumonectomy deviates the oesophagus toward the side of the resection (16) and alters the oesophageal functions, the relation between the mediastinal shift and gastroparesis was not suggested before.

It is well known that respiratory failure is the major cause of death after lung resection and thoracotomy. Chronic pulmonary inflammation secondary to recurrent aspiration may have a role in the derangement of pulmonary functions (3). The chance of gastroesophageal reflux with aspiration and the frequency of respiratory mortality were shown to be decreased with pre-emptive gastrointestinal tract management, including the use of nasogastric tubes, dietary management, and frequent abdominal examinations (17). Our results also indicate that delayed gastric emptying is a consequence of lung resection and apart from gastric drainage, an additional management following thoracotomy could be the early inflation of the remaining lung or the transplanted lung to facilitate the gastrointestinal transit as soon as possible.

In conclusion, the results of the present study when taken together with the clinical studies, suggest that delayed gastric emptying and gastroesophageal reflux are early complications of lung resection considered among the potential causes of allograft dysfunction after lung transplantation. The mechanism for the delay in gastric emptying appears to be dependent upon the insufficient inflation of the lungs. Therefore, the incidence of postoperative gastroparesis following lung resection and the risk of graft dysfunction after lung transplantation can be decreased by inhibiting the shift of the intrathoracic and subdiaphragmatic structures, while every effort should be made to prevent gastroesophageal reflux with aspiration.

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