

## Predictors of a better outcome of pneumatic dilatation in patients with primary achalasia

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### Abstract

**Objective** Pneumatic dilatation (PD) has been widely used in the treatment of primary achalasia. The aim of this study was to evaluate the effectiveness of PD and its predictive factors in Japanese patients with primary achalasia. **Methods** Fifty-five consecutive patients were treated using PD (Rigiflex balloon dilator). Diagnosis was established through radiographic and/or esophageal manometry. All patients underwent a pre-designed clinical evaluation prior to and 6 months after PD treatment. We defined success of PD as 6 months or more of clinical remission, with a total score (0–4)  $\leq 2$ , a decrease in the total score  $\geq 1$  and the score for each item  $\leq 1$ . Possible predictive factors to response were analyzed.

**Results** Successful PD was achieved in 41 of 55 (74.5%) patients. The median age (58.0 years) in the successful group was significantly older than in the failure group (37.5 years), but there were no differences in other factors between the groups. When the cut-off value was set at 40 years of age, the success rate of PD in the  $>40$ -year age group was 85.7%, while the  $<40$ -year age group achieved a rate of only 38.5%. Multivariate logistic regression analysis also demonstrated that older age was the only independent factor associated with the success of PD. There was no perforation related to PD.

**Conclusions** PD is a safe and effective treatment for achalasia, particularly in older patients who experience a better outcome than younger patients.

**Keywords** Achalasia · Pneumatic dilatation · Dysphagia

### Introduction

Achalasia, characterized by esophageal aperistalsis and incomplete relaxation of the lower esophageal sphincter (LES) with swallowing, is the most common primary esophageal motor disorder of the esophagus [1, 2]. Dysphagia, regurgitation, chest pain, and weight loss are among the most recognized clinical features of the disease [3, 4]. The aim of therapy in patients with achalasia is to reduce distal obstruction, which can be treated by botulinum toxin injection, pneumatic dilatation (PD) or surgical esophagomyotomy [3]. For many authors, PD is considered the first-line therapy in esophageal achalasia that can result in remission in 67–90% of patients [3]. Surgical myotomy should be offered to patients who do not respond to PD [5]. However, it is important to know PD outcomes and possible predictive response factors that can help select the group of patients most likely to benefit from early surgery. In Japan, however, there are few data regarding PD in patients with primary achalasia.

The aim of this study was to evaluate the effectiveness of PD and its predictive factors in Japanese patients with primary achalasia and to assess its safety and any adverse effects.

### Methods

This was a prospective study in which 55 patients were included consecutively. Patients had been previously

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diagnosed with primary esophageal achalasia between January 2002 and December 2007 in the Nippon Medical School Hospital. All patients were included in the PD protocol and were clinically assessed before PD, undergoing a barium esophagram, esophagogastroscope and esophageal manometry. Patients were excluded if they had previously received PD or surgical esophagomyotomy or had secondary achalasia. Patients were not treated with any drugs that could have altered the PD result.

#### Clinical evaluation

At the initial investigation and at each subsequent visit, the main symptoms (dysphagia and regurgitation) were evaluated and each was given a score between 0 and 2 (almost no symptoms = 0, occasional symptoms = 1 and daily symptoms = 2). Patients were considered to have reached clinical remission when the total scores (0–4) were  $\leq 2$ , a decrease in the total score was  $\geq 1$  and each item was  $\leq 1$ . Chest pain and body weight loss were also investigated. The success of PD was defined as 6 months or more of clinical remission.

#### Radiographic and endoscopic study

The maximum diameter of the esophageal body was measured before PD using a barium esophagram. The definition of achalasia by radiographic study is dilatation of the esophagus of more than 35 mm and/or liquid or food retention in the esophagus with the lower esophagus having the appearance of a “bird’s beak.” Achalasia was classified into three groups based on the maximum diameter of the esophageal body (<35 mm, 35–59 mm,  $\geq 60$  mm). Secondary achalasia was ruled out by an endoscopic examination of the cardia area.

#### Esophageal manometry

Esophageal manometry was performed with a 21-channel manometric assembly (Dentsleeve, Wayville, Australia). Ten side holes, which were spaced at 1-cm intervals starting at 3 cm above the distal end of the assembly, monitored pressure from the proximal stomach, LES and distal esophagus. An additional seven side holes, spaced at 2-cm intervals, monitored pressure from the distal to the proximal esophagus; four side holes located at 3, 6, 10, 13 cm above the most proximal of the 2-cm interval side holes monitored pressure from the proximal esophagus to the pharynx.

Each lumen was perfused with degassed distilled water at 0.15 mL/min using a low compliance manometric infusion pump (Dentsleeve). Data were digitized with a computer and the digitized signals were displayed, stored,

and analyzed using Trace! Software (Dr G.S. Hebbard, Royal Melbourne Hospital, Melbourne, Australia).

Subjects were studied in the sitting position after fasting overnight. The manometric assembly was passed via an anaesthetized nostril and positioned so that the most proximal of the 1-cm interval side holes was 2 cm above the LES. The subjects were then allowed to adapt to the assembly for 10 min. Baseline recordings of LES pressure were made for 5 min, after which primary peristalsis was assessed.

Primary peristalsis and the lowest residual LES pressure were assessed in response to 10 swallows of a 5-mL water bolus. Each swallow was separated by a 30-s interval. For the analysis of patterns of LES pressure, the profile of pressure was used across the full extent of the ten 1-cm spaced, side-hole array that straddled the esophagogastric junction. Incomplete relaxation of the LES was defined as the mean of the 10 lowest residual LES pressures within 5-s of swallowing more than 4 mmHg compared to the gastric baseline [6]. Diagnosis of achalasia by esophageal manometry is made when esophageal aperistalsis and incomplete relaxation of LES is present in a patient.

#### Pneumatic dilatation

Four physicians (YT, KI, NK, HS), using a Rigidflex balloon dilator (Microvasive, Milford, MA, USA), performed all procedures on patients who had fasted overnight. First, a guide wire was placed endoscopically into the stomach and the dilator was positioned across the gastroesophageal junction over the guide wire under fluoroscopic control. The balloon was then inflated three times over the course of 180 s at 60-s intervals. During the first dilatation, the balloon was gradually inflated up to 3–4 psi in 20–30 s, followed by a second dilatation reaching 4–5 psi and a third dilatation of 5–7 psi. The pressure of the balloon was determined by the pain-threshold of individual patients. This method of carrying out PD has a long history of use in our hospital, with no serious side-effects (e.g. perforation). The first treatment of dilatation was always performed with a 30-mm diameter balloon. Dilatations were performed under sedation with intravenous injections of pentazocine (7.5–15 mg) and hydroxyzine (12.5–25 mg).

#### Protocol of iterative pneumatic dilatations

A second treatment using a 35-mm diameter balloon was performed a week after initial treatment if clinical remission had not been achieved. The dilatations were considered to have failed and the patients were proposed for a surgical esophagomyotomy if clinical remission had not been achieved following the second treatment. For patients in clinical remission, scheduled visits were planned at

2 months and then every 6 months after the last PD. The main symptoms were evaluated at each visit. Endoscopy examination was consistently carried out 12 months following the last PD; December 2008 served as the end-point for final clinical evaluation.

In case of a relapse after a 6-month period of clinical remission, a subsequent treatment of PD was performed with the same protocol. Subsequent treatment commenced from the last dilator size at which clinical remission was achieved. However, in case of a relapse within 6 months after clinical remission, the dilatations were considered to have failed and patients were proposed for a surgical esophagomyotomy.

### Statistical analysis

Frequencies, percentages and medians (interquartile range) were used in the descriptive statistics of the clinical variables. The effect of factors that predict the success response to PD in patients was first assessed using a univariate analysis with the Mann–Whitney *U* test for continuous variables and the Chi-square test for categorical variables. Possible predictive response factors to PD were determined by multivariate analysis based on a logistic regression model: age, gender, total symptom score, dilatation of esophagus, weight loss, basal LES pressure, lowest residual LES pressures after a swallow, and the number of months of having symptoms prior to the first dilatation. A *p* value <0.05 was considered statistically significant.

## Results

Fifty-five patients were treated for esophageal primary achalasia in our hospital between 2002 and 2007. Forty-five of 55 patients were diagnosed using esophageal manometry, but the remaining 10 patients were diagnosed using an esophagogram because esophageal dilatation and the bend of the lower esophagus made it difficult to place the manometric catheter into the stomach. The clinical characteristics and demographic data of patients are summarized (Table 1).

### Outcome of PD

After the first treatment of PD, remission was achieved in 44 of 55 (80.0%) patients. Forty-two of 44 (95.5%) patients required 1 dilatation and 2 (4.5%) patients needed 2 dilatations to achieve remission. Three patients experienced recurrence within 6 months after the first treatment; as a result, PD was successfully achieved in 41 of 55 (74.5%) patients. PD failed to achieve clinical remission in 14 of 55 (25.5%) patients, who were then offered surgery.

**Table 1** Clinical characteristics and demographic data of patients with achalasia

Age (years)	54.0 (40.5–66.0)
Gender (male/female)	25/30
Weight loss (kg)	3.0 (0–8.0)
Duration of symptoms (months)	36.0 (18.0–87.0)
Dysphagia	55/55 (100%)
Regurgitation	45/55 (81.8%)
Chest pain	9/55 (16.4%)
Median (interquartile range)	

### Predictive PD response factors

The median age in the successful group was 58.0 years (47.8–66.0), which is significantly older than that of the failure group 37.5 years (27.0–58.0). Otherwise, there were no differences in other factors between the groups (Table 2). The success rate of PD in the >40 year age group (*n* = 42) was 85.7% (36/42) when the cut-off value was set at 40 years of age, but it was only 38.5% (5/13) in the <40 year age group (*n* = 13) (Fig. 1). Those under 30 had no clinical remission after PD. Multivariate logistic regression analysis also demonstrated that older age was the only independent factor (Odds ratio = 1.070, 95% confidence interval 1.009–1.133, *p* < 0.0227) associated with the success of PD.

### Follow up

The follow-up period after the first PD in the 41 patients with successful PD ranged between 12 and 74 months (28.0 months (19.8–41.5)). Three (7.3%) of these patients experienced a clinical recurrence after PD at 8, 18, and 24 months, respectively. The patient, who experienced recurrence at 8 months after PD, refused further PD treatment and instead received a surgical esophagomyotomy. The remaining 2 patients again received PD treatment and achieved clinical remission.

### Complications

There was no perforation related to PD. During follow-up, 3 of 41 patients who had successful PD had reflux esophagitis of grade B of the Los Angeles classification.

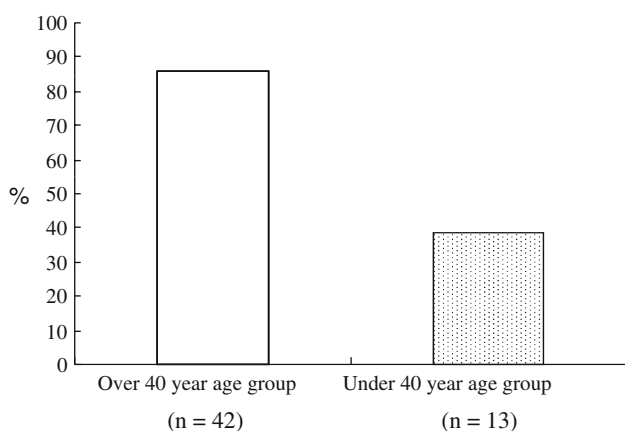
## Discussion

The main symptoms of achalasia are dysphasia, regurgitation and chest pain; all are symptoms usually used to parameters of the effectiveness of PD. Most of our patients had dysphagia and regurgitation but only approximately 9

**Table 2** Univariate analysis of factors associated with the success of pneumatic dilatation

Factor	Pneumatic dilatation		Univariate <i>P</i> value
	Success	Failure	
Clinical presentation			
Age	58.0 (47.8–66.0)	37.5 (27.0–58.0)	0.0141
Gender (male/female)	20/21	5/9	0.3966
Total symptom score	3 (3–4)	3 (3–4)	0.4989
Body weight loss (kg)	5.0 (0–8.0)	2.5 (0–8.0)	0.3846
Duration of symptoms (months)	36.0 (24.0–81.0)	36.0 (15.0–96.0)	0.7241
Esophageal dilatation (<35 mm/35–59 mm/≥60 mm)	13/20/8	6/7/1	0.5080
Manometric findings			
Basal LES pressure (mmHg)	20.0 (15.2–27.6)	25.3 (18.7–38.6)	0.1348
Lowest residual LES pressure (mmHg)	14.6 (10.4–17.5)	15.6 (13.7–24.1)	0.2543
Esophageal body pressure	4.0 (–3.1–5.5)	5.0 (3.8–5.9)	0.222

Median (interquartile range)  
LES lower esophageal sphincter

**Fig. 1** The difference in the success rate of pneumatic dilatation between age groups below and above 40 years

(16.4%) had chest pain. Considering these results, we excluded chest pain as a parameter of the effectiveness of PD.

The cumulative effectiveness of PD for achalasia was 74.5% in our study, although a previous study reported effectiveness around 80%—a little lower than a previous study [3]. The number of PDs used in 53 of 55 patients was one only; therefore, most of the balloons used in the PDs were 30 mm. The cumulative effectiveness of 30 mm balloons was 74% in previous studies [3], a result similar to that of our study when the diameter of the balloon is taken into account.

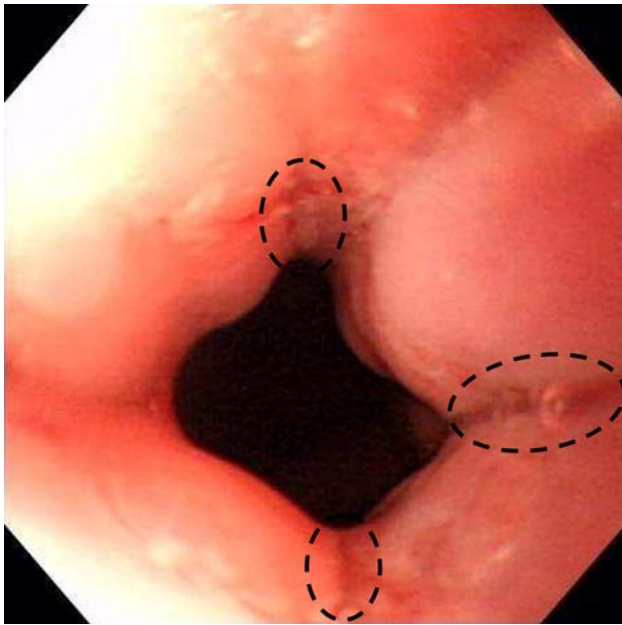
With regard to the number of PDs, it is thought that dilatations should continue until clinical remission is achieved. The American Society for Gastrointestinal Endoscopy recommends a second dilatation session if a single attempt (size of the balloon dilatator unspecified) does not produce satisfactory relief. Surgery is usually the next course of action if the second dilatation fails [7]. The results of previous PD procedures we have carried out lead

us to conclude that most patients who responded effectively to PD were able to achieve a clinical remission with only one treatment. For these reasons, if patients did not achieve clinical remission after the second treatment we regarded them as having failed PD treatment. Repeated PDs cause adhesions to the outside of the LES and adhesions make operating difficult. Because the effectiveness of surgery is good enough [3], we believe that repeated PDs should not be performed. The reduced number of PDs may also have had an affect on our cumulative effectiveness of PD, which is a little lower than that of previous studies.

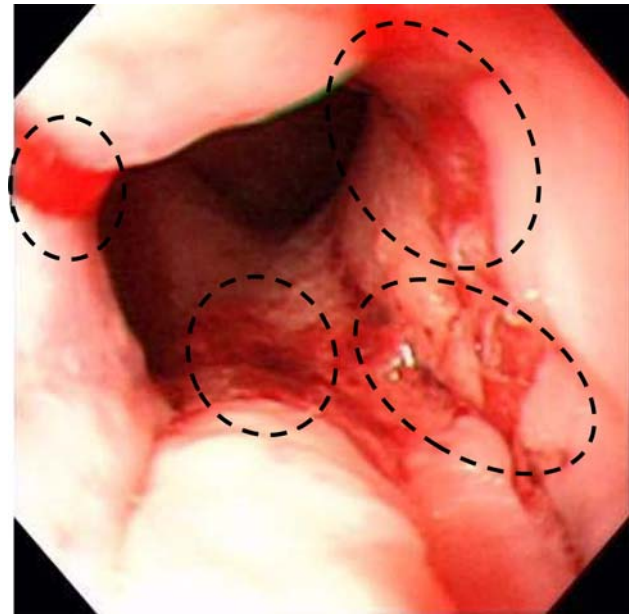
It has been previously reported that the inflation pressure of PD was 8–15 psi [8–10]; however, in our method, it was 3–7 psi. Although dilatations were performed under sedation, increasing the inflation pressure of the balloon was problematic for patients who complained of severe pain as pressure increased. The lower inflation pressure of the balloon may have also been a factor in the cumulative effectiveness of our PD results.

It is important to know the predictive response factors to PD in lasting clinical improvement. Multivariate analysis demonstrated that older age was the only independent factor associated with a better response to PD. In fact, patients who were referred for surgery after PD had failed had a median age of 37.5 years. Setting the cut-off value at 40 years of age resulted in a 87.8% cumulative effectiveness of PD in the >40-year age group but only 42.9% in the <40-year age group. Our result is consistent with other published data showing that older patients respond favorably to PD compared with younger patients [11–14], although it is not clear why older patients are more responsive to PD. Two or three small tears are usually at the position of the LES after PD, but no tear was present when PD was performed in a younger patient of 12 years. In other younger patients who had no response to PD, tears were smaller and shallower than in those of older patients, who experienced clinical remission after PD. The LES





**Fig. 2** An endoscopic picture after pneumatic dilatation (PD) of a young male patient of 26 years, who had no response to PD, reveals three very small, shallow tears



**Fig. 3** An endoscopic picture of clinical remission after PD in a 79-year-old female. Unlike the tears in the younger patient who had no response to PD, four larger, deeper tears are evident

muscle, therefore, in younger patients may be more flexible, one of the possible reasons why younger patients with achalasia did not respond favorably to PD. Figure 2 shows an endoscopic picture after PD, in a 26-year-old male patient who had no response to PD and Fig. 3 shows an endoscopic picture of a 79-year-old female patient who had a clinical remission after PD.

A previous study reported that women had a better outcome from a single dilatation [15] and that patients with a long history of dysphagia had greater success from PD compared with those with a short history [3]. In our study, however, gender and symptom duration, among others, were not factors in the response to PD.

Esophageal perforation is the most serious complication of PD. More recent studies indicate that the rate of esophageal perforations conducted with a Rigiflex balloon dilator is around 0.5–3.0% [15–17]. However, no patients in our study had an esophageal perforation during treatment from PD. Our results confirm that the method we used for PD characterized by a low number of PDs and low inflation pressure of the balloon was therapeutically safe. The most frequent complication is gastroesophageal reflux (GERD); the prevalence of GERD following PD varies widely between 2 and 38% [18, 19]. This may be due to differences in the diagnostic criteria of GERD used in these studies. In our study, 4 (9.8%) of 41 patients, with remission after PD, had reflux esophagitis with grade B of the Los Angeles classification, which responds well to proton pump inhibitors.

In conclusion, PD is an effective and safe treatment for achalasia and the major factor associated with a better outcome is older age. No patients younger than 30 years responded to PD, suggesting that in lieu of this therapy patients younger than 30 years should be offered a surgical esophagomyotomy.

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