Original article

Non-invasive ventilation for treatment of postoperative respiratory failure after oesophagectomy

P. Michelet[1], X. B. D'Journo[2], F. Seinaye[1], J. M. Forel[1], L. Papazian[1] and P. Thomas[2]

[1]Service de Réanimation, Pôle Réanimation - Urgence - Service d'Aide Médicale Urgente - Hyperbarie, and [2]Service de Chirurgie Thoracique, Pôle Thorax, Hôpital Sainte-Marguerite, Marseilles, France

Correspondence to: Dr P. Michelet, Service de Réanimation, Pôle Réanimation - Urgence - Service d'Aide Médicale Urgente - Hyperbarie, Hôpital Sainte-Marguerite, 270 Boulevard Saint Marguerite, 13009 Marseilles, France (e-mail: pierre.michelet@ap-hm.fr)

Background: **The aim of this case–control study was to compare the efficacy of non-invasive positive pressure ventilation (NPPV) with that of conventional treatment in patients who develop postoperative acute respiratory failure (ARF) after oesophagectomy.**

Methods: **Thirty-six consecutive patients with ARF treated by NPPV were matched for diagnosis, age within 5 years, sex, preoperative radiochemotherapy and Charlson co-morbidity index with 36 patients who received conventional treatment (control group).**

Results: **NPPV was associated with a lower reintubation rate (nine *versus* 23 patients; $P = 0{\cdot}008$), lower frequency of acute respiratory distress syndrome (eight *versus* 19 patients; $P = 0{\cdot}015$), and a reduction in intensive care stay (mean(s.d.) 14(13) *versus* 22(18) days; $P = 0{\cdot}034$). Anastomotic leakage was less common in patients receiving NPPV (two *versus* ten; $P = 0{\cdot}027$). These patients also showed a greater improvement in gas exchange in the first 3 days after onset of ARF ($P = 0{\cdot}013$).**

Conclusion: **The use of NPPV for the treatment of postoperative ARF may decrease the incidence of endotracheal intubation and related complications, without increasing the risk of anastomotic leakage after oesophagectomy.**

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Introduction

Carcinoma of the oesophagus continues to carry a high perioperative mortality rate ranging from 3 to 10 per cent[1,2]. Postoperative complications such as acute respiratory failure (ARF) and anastomotic leakage are common, and have been associated with postoperative death[3]. The most important factors predisposing to anastomotic leakage are ischaemia of the gastric conduit[4] and impairment in oxygen delivery[5]. Maintenance of adequate oxygenation in the postoperative period is of major importance, especially when pulmonary complications such as ARF occur[6]. Although invasive endotracheal mechanical ventilation (ETMV) has remained the cornerstone of ventilatory strategy for many years, several studies have shown that mortality associated with pulmonary disease is largely related to complications of postoperative reintubation and mechanical ventilation[1,6]. Therefore, a major objective in the treatment of ARF is to avoid ETMV while preserving oxygenation.

Non-invasive positive pressure ventilation (NPPV) is safe and as efficient as ETMV in improving gas exchange in patients with various patterns of ARF[7,8]. It has been reported to reduce the need for ETMV and the risk of death after solid organ transplantation[9] and thoracic surgery[10]. Recent results also support the safe use of NPPV in patients with ARF after upper abdominal surgery[11]. In the setting of oesophagectomy, the balance between the potential benefits of NPPV and its disadvantages, especially with respect to gastric tube reconstruction, is still unclear[12,13].

The aim of this case–control study was to evaluate the use of NPPV in patients with ARF after oesophagectomy. Outcomes were compared with those of similar patients with ARF treated by conventional means.

Methods

The institutional review board and ethics committee of the hospital approved the study, which was performed in accordance with the 1964 Declaration of Helsinki. Informed consent was obtained from all patients before operation. The study was controlled by the Assistance Publique des Hôpitaux de Marseille.

Between September 2003 and December 2006, all patients admitted to the intensive care unit (ICU) after transthoracic oesophagectomy, and who presented with ARF and pulmonary infiltrates, were included prospectively in the study. ARF was due to either postoperative infectious pneumonia or aspiration pneumonia. For each patient treated with NPPV, a matched control subject was chosen from a group of patients who had undergone oesophagectomy with postoperative pneumonia, who received conventional treatment in this ICU between 1999 and 2003. All patients had undergone intensive physiotherapy. Study patients and control subjects were matched for diagnosis of postoperative ARF, age (within 5 years), sex, preoperative radiochemotherapy and Charlson comorbidity index[14].

The development of postoperative ARF was ascertained by the following criteria: severe respiratory distress with dyspnoea, respiratory rate more than 30 breaths per min, active contraction of accessory muscles, radiographic evidence of new and persistent lung infiltrates, temperature greater than 38·5°C, macroscopically purulent secretions, and an arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio of less than 200 mmHg while breathing oxygen through a Venturi mask. As all patients were extubated a few hours after surgery and ARF developed while breathing spontaneously, the underlying infection was ascertained in only a minority of patients because of the high risk of diagnostic procedures.

Patients were excluded from the study if they met any one of the following criteria: ARF related to an early surgical complication (such as anastomotic leakage or acute bleeding diathesis) or the occurrence of postoperative atelectasis involving two pulmonary lobes or more and requiring endoscopic treatment; the need for cardiopulmonary resuscitation or immediate intubation for life-threatening hypoxaemia (defined as oxygen saturation below 80 per cent despite maximum oxygen supply); coma or seizures; and cardiogenic or septic shock. Intolerance and refusal of NPPV were also considered as exclusion criteria.

Because of the difficulty in ascertaining the diagnosis of anastomotic leakage in patients who were breathing spontaneously, each patient who developed ARF underwent thoracic tomography and a contrast swallow. If there was clear evidence of anastomotic leakage after these examinations, the patient was reintubated and further endoscopic confirmation obtained. If the clinical status was such that immediate reintubation was required, fibroscopic assessment of anastomotic status was carried out first. Any patient with ARF secondary to anastomotic dehiscence or leakage was excluded from the analysis. This applied to both groups as the same diagnostic protocol was used for the whole study period.

A single surgical team operated on all patients using the same technique. All patients were admitted to the ICU immediately after surgery, and were extubated within 3 h. Analgesia was achieved with a thoracic epidural infusion at an initial flow of 6 ml/h, increased in increments of 2 ml/h every 10 min to a rate of 10 ml/h (20 mg/h ropivacaine and 5 μg/h sufentanil), plus intravenous paracetamol 1 g every 6 h. All patients had the same invasive devices (bladder catheter, central venous catheter, right chest and abdominal drains).

Rehabilitation was standardized with bronchial toilet beginning in the immediate postoperative period, to include intensive chest physiotherapy (30 min twice a day), incentive spirometry, early ambulation, and oxygen supply through a mask to ensure an arterial oxygen saturation of more than 90 per cent.

NPPV was delivered through a total facial mask (Inspir'aid®; Dräger, Lubeck, Germany) with the patient in a semirecumbent position and a ventilator designed for the ICU (Evita 4® or Evita XL®; Dräger). The pressure support was initially set at 8 cmH_2O over positive end-expiratory pressure (PEEP) and increased progressively to obtain an expired tidal volume of 68 ml per kg predicted bodyweight and a respiratory rate below 25 breaths per min. PEEP was initially set at 4 cmH_2O and increased by 2 cmH_2O up to a maximum level of 8 cmH_2O to achieve an arterial oxygen saturation of more than 90 per cent. The maximum inspiratory airway pressure was maintained below 25 cmH_2O to prevent oesophagogastric distension. All patients received nasogastric suction throughout NPPV. Air leaks were reduced by carefully fitting the mask, focusing on leaks around the nasogastric tube. Inspired gases were heated and humidified by a conventional humidifier (MR 730®; Fisher Paykel, Panmure, New Zealand). During the first 24 h, NPPV was maintained for periods of 45–60 min separated by intervals of 30–60 min. During the discontinuation periods, patients received oxygen through a mask. After the first 24 h, if oxygenation and clinical status improved, they were left to breathe with oxygen supplementation for increasingly longer times between NPPV sessions. Patients were weaned off NPPV once they could maintain a PaO_2/FiO_2 ratio above 200 mmHg without ventilatory support for more than 24 h.

Predetermined criteria for endotracheal intubation were standardized regardless of the ventilation technique used, and included persistent arterial oxygen saturation below 85 per cent or PaO_2 below 60 mmHg despite maximum oxygen supply (17 l/min in the conventional group and

80 per cent of FiO_2 in the NPPV group), development of respiratory acidosis with pH < 7·20 (without a drop in bicarbonate), respiratory rate persistently more than 35 breaths per min, deterioration of mental status (Glasgow Coma Score below 10) without administration of neurotropic drugs, persistent haemodynamic instability (systolic blood pressure less than 80 mmHg) and intolerance of NPPV.

The main outcome was the rate of endotracheal intubation within the ICU stay after ARF onset. Secondary outcome variables were the occurrence of anastomotic leakage, septic shock[15] or acute respiratory distress syndrome (ARDS)[16], length of ICU and hospital stay, and postoperative death.

Pneumonia was defined as the occurrence of new and persistent lung infiltrates on chest radiography, with a temperature greater than 38·5°C, macroscopically proven purulent tracheal secretions and leucocytosis (more than 12×10^9/l or less than 4×10^9/l). The nature of the infection was deduced from the result of quantitative culture after protected bronchoalveolar lavage[17]. If clinical status (hypoxaemia) prevented distal airway sampling, the pneumonia was considered to be secondary to aspiration. Depending on the clinical severity, empirical administration of antibiotics was performed in the absence of other sites of infection. Patients with chronic obstructive airway disease were identified using standard criteria[18].

Statistical analysis

Continuous data are presented as mean(s.d.). Demographic and physiological characteristics were compared with Pearson's χ^2 or Fisher's exact test for categorical data, and Student's *t* test for continuous variables. Two-way repeated measures ANOVA (with the factors time and group) was performed for gas exchange and haemodynamic parameters. *Post hoc* pairwise multiple comparisons were made using Tukey's test. Kaplan–Meier curves were used to determine the probability of remaining free from endotracheal intubation during the ICU stay, and curves were compared using the log rank test.

Results

Over the period of study, 243 patients were admitted to the ICU after oesophagectomy. All were extubated within 3 h after surgery. During this period, seven patients who did not meet the study inclusion criteria required urgent reintubation: three with an early surgical complication (one massive bleeding and two early anastomotic leakage), two who had an acute cardiac ischaemic event and two who developed pulmonary emboli in the second week after surgery. Six other patients who developed ARF, but whose respiratory difficulties were related to anastomotic dehiscence, were also excluded from the analysis. Of 84 patients with postoperative ARF (34·6 per cent) who met the inclusion criteria, 36 treated with NPPV were correctly matched with 36 control patients. Among the 12 remaining patients, eight were treated with NPPV and four without. Five patients in the NPPV group and six in the control group had moderate chronic obstructive pulmonary disease. Comparison of other preoperative variables revealed no differences between cases and controls (*Table 1*). The two groups were also similar with regard to perioperative factors (*Table 2*). Infectious pneumonia was confirmed in 13 patients in the NPPV group and 12 in

Table 1 Matching criteria and preoperative characteristics

	NPPV ($n = 36$)	Control ($n = 36$)	P†
Sex ratio (M : F)	30 : 6	30 : 6	1·000‡
Age (years)*	62(8)	64(8)	0·292
Body mass index (kg/m^2)*	23(4)	23(3)	1·000
Smoking history	26	28	0·785‡
Diabetes mellitus	3	2	1·000§
Previous ischaemic heart disease	12	13	1·000‡
Charlson co-morbidity index			
2	16	16	1·000§
3	18	18	1·000§
4	2	2	1·000§
Tumour type			0·631‡
Squamous	20	23	
Adenocarcinoma	16	13	
pTNM stage			
I	5	4	1·000§
IIA	9	9	1·000§
IIB	3	2	1·000§
III	19	21	0·813§
Preoperative radiochemotherapy	16	16	1·000‡
ASA grade			
I	8	7	1·000‡
II	18	20	0·813‡
III	10	9	1·000‡
NYHA grade			
I	9	8	1·000‡
II	20	20	1·000‡
III	7	8	1·000‡
Pa_{O_2} (% of predicted)*	103(12)	101(12)	0·482
FVC (% of predicted)*	95(14)	92(16)	0·400
FEV_1 (% of predicted)*	92(14)	90(16)	0·574
FEV_1/FVC (% of predicted)*	96(14)	95(12)	0·746

*Values are mean(s.d.). NPPV, non-invasive positive pressure ventilation; pTNM, pathological tumour node metastasis; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association; Pa_{O_2}, arterial partial pressure of oxygen; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s. †Student's *t* test unless indicated otherwise; ‡Pearson's χ^2 test; §Fisher's exact test.

Table 2 Perioperative clinical characteristics

	NPPV ($n = 36$)	Control ($n = 36$)	P§
Perioperative blood loss (ml)*	592(213)	613(189)	0·660
Perioperative transfusion	13	14	0·990¶
Perioperative hypotensive events†	14	17	0·634¶
Duration of operation (min)*	320(84)	322(88)	0·922
Duration of single-lung ventilation (min)*	86(26)	82(16)	0·434
Duration of mechanical ventilation (h)*	10·5(5·1)	10·1(4·9)	0·735
Postoperative Pa_{O_2}/Fi_{O_2} ratio (mmHg)*‡	251(109)	274(143)	0·411

*Values are mean(s.d.). †Defined by a systolic arterial pressure lower than 80 mmHg for more than 5 min. ‡After admission to the intensive care unit under general anaesthesia. NPPV, non-invasive positive pressure ventilation; Pa_{O_2}, arterial partial pressure of oxygen; Fi_{O_2}, fraction of inspired oxygen. §Student's t test unless indicated otherwise; ¶Pearson's χ^2 test.

Table 3 Microbiological isolates in patients with postoperative pneumonia

Pathogen	NPPV ($n = 13$)	Control ($n = 12$)
Methicillin-resistant *Staphylococcus aureus*	1	1
Methicillin-sensitive *Staphylococcus aureus*	2	3
Escherichia coli	3	2
Haemophilus influenzae	2	1
Pseudomonas aeruginosa	2	3
Acinetobacter spp.	1	0
Morganella morganii	0	1
Seratia marcesens	1	0
Proteus mirabilis	0	1
Klebsiella pneumoniae	1	0

NPPV, non-invasive positive pressure ventilation.

the control group, with no difference in microbiological isolates (*Table 3*).

The mean(s.d.) interval between postoperative admission to the ICU and the onset of ARF was 5·1(1·9) days in the NPPV group and 4·9(2·5) days in the control group ($P = 0·704$). At the onset of ARF, the mean(s.d.) Simplified Acute Physiology Score II was similar in both groups (37·3(6·1) *versus* 36·9(5·3) respectively; $P = 0·767$), but the Pa_{O_2}/Fi_{O_2} ratio was lower in the NPPV group (137(13) *versus* 153(39) mmHg; $P = 0·024$).

The mean(s.d.) daily duration of NPPV was 9·5(4·6) h during the first 2 days, with an inspiratory support level of 13(2) cmH_2O and PEEP of 5(1) cmH_2O. The duration of NPPV was 6(2) days. The use of NPPV was associated with a reduction in reintubation rate and in development of ARDS (*Table 4*). The probability of avoiding reintubation was significantly higher in patients treated with NPPV than in those receiving conventional

Table 4 Comparison of outcome variables in cases and controls after the onset of acute respiratory failure

	NPPV ($n = 36$)	Control ($n = 36$)	P
Pneumonia			1·000†
Infectious	13	12	
Aspiration	23	24	
Postoperative SAPS II*	27(6)	28(7)	0·517‡
Reintubation	9	23	0·008†
ARDS	8	19	0·015†
Septic shock	7	16	0·043†
Anastomotic leakage	2	10	0·027§
ICU stay (days)*	14(13)	22(18)	0·034‡
Hospital stay (days)*	34(19)	40(21)	0·208‡
Postoperative death	4	7	0·512§

*Values are mean(s.d.). NPPV, non-invasive positive pressure ventilation; SAPS II, Simplified Acute Physiology Score II; ARDS, acute respiratory distress syndrome; ICU, intensive care unit. †Pearson's χ^2 test; ‡Student's t test; §Fisher's exact test.

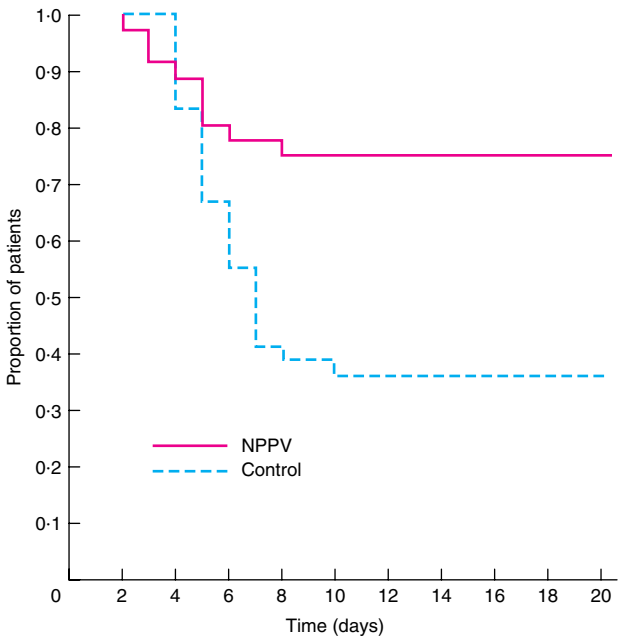

Fig. 1 Likelihood of avoiding endotracheal intubation in patients who received non-invasive positive pressure ventilation (NPPV) or conventional treatment (control group) during the postoperative course. $P = 0·003$ (log rank test)

care ($P = 0·003$) (*Fig. 1*). In the NPPV group reasons for reintubation were failure to improve gas exchange in four patients, absence of a sustained clinical improvement with progressive development of hypercapnic respiratory failure in two, septic shock in two and intolerance of the technique in one (agitation). No complications of NPPV such as

Table 5 Gas exchange and haemodynamic data

	NPPV ($n = 36$)			Control ($n = 30$)		
	Baseline	24 h	48 h	Baseline	24 h	48 h
Pa_{O_2}/Fi_{O_2} ratio (mmHg)	137(13)†	188(13)*	254(15)*‡	153(39)	151(57)	130(44)
Pa_{CO_2} (mmHg)	39·3(7·8)	42·1(5·8)	39·5(4·3)	39·4(3·2)	41·4(6·3)	40·5(6·0)
Arterial pH	7·39(0·08)	7·40(0·06)	7·42(0·05)	7·40(0·05)	7·38(0·07)	7·38(0·06)
MAP (mmHg)	80(14)	83(18)	87(20)	79(16)	80(16)	85(12)
Heart rate (beats per min)	106(14)	100(15)	100(15)	95(13)	102(15)	99(14)

Values are mean(s.d.). Data represent the worst values within the day for the first 3 days after the onset of postoperative acute respiratory failure. Complete data were available for only 30 patients in the control group. NPPV, non-invasive positive pressure ventilation; Pa_{O_2}, arterial partial pressure of oxygen; Fi_{O_2}, fraction of inspired oxygen; Pa_{CO_2}, arterial partial pressure of carbon dioxide; MAP, mean arterial pressure. *$P < 0{\cdot}001$ *versus* baseline; †$P = 0{\cdot}024$, ‡$P < 0{\cdot}001$ *versus* control group (Student's *t* test).

major gastric distension or skin necrosis were observed. Moderate air leaks occurred frequently but without the need to stop NPPV. In the control group, the need for reintubation was mainly related to the aggravation of hypoxaemia with progressive deterioration of mental status in ten patients and to development of septic shock in nine. A clear explanation was not available for the remaining four patients.

Patients in both groups mainly presented with hypoxaemic but not hypercapnic respiratory failure (*Table 5*). Apart from the Pa_{O_2}/Fi_{O_2} ratio, the baseline gas exchange and haemodynamic parameters were no different in NPPV and control groups. ANOVA showed that the Pa_{O_2}/Fi_{O_2} ratio varied significantly between the two groups ($P = 0{\cdot}013$), with a time effect ($P < 0{\cdot}001$) and an interaction between time and group ($P < 0{\cdot}001$). There was no change in the Pa_{O_2}/Fi_{O_2} ratio during the first 2 days after the onset of pneumonia in the conventional group. In contrast, the Pa_{O_2}/Fi_{O_2} ratio significantly increased after 1 and 2 days of NPPV. There was no difference between groups with regard to partial pressure of carbon dioxide and arterial pH. Haemodynamic parameters (including mean arterial pressure and heart rate) remained stable during the first 2 days.

The use of NPPV was associated a lower rate of septic shock and anastomotic leakage, and a shorter ICU stay (*Table 4*). There was no difference between groups in overall hospital stay or hospital mortality. The rate of anastomotic leak was low (less than 5 per cent) among the 159 patients who did not develop ARF, and was no different between the two periods.

Discussion

This case–control study has demonstrated the safety and efficacy of NPPV in avoiding endotracheal intubation in patients who developed ARF after oesophagectomy. Patients in the NPPV group showed a better and sustained improvement in oxygenation, and a reduction in ICU length of stay. The use of NPPV was not associated with an increase in anastomotic leakage.

Despite advances in anaesthesia, surgical technique and postoperative management, pulmonary complications occur frequently after oesophageal resection. ARF is the most common clinically relevant pulmonary complication and may lead to death[1,6]. The severity of hypoxaemia and its potential impact on wound healing[5] have increased the recourse to invasive ETMV. Although this often allows control of hypoxaemia, invasive mechanical ventilation has been associated with increased morbidity and mortality in patients undergoing thoracic or abdominal surgery[10,19,20]. Therefore, a major objective in the management of postoperative ARF is to avoid endotracheal intubation while preserving oxygen delivery. Few studies have reported beneficial effects of NPPV after thoracic and abdominal surgery, although the efficacy of NPPV in treating postoperative respiratory distress has been demonstrated after lung resection[10]. A decrease in the incidence of endotracheal intubation and other severe complications has also been reported in patients with hypoxaemia after oesophagectomy by the use of continuous positive airway pressure (CPAP)[21]. Moreover, Jaber and colleagues[11] have recently demonstrated that NPPV may be an alternative to conventional ventilation in patients who develop ARF after abdominal surgery. However, uncertainty continues to surround the potential clinical benefits of CPAP or NPPV compared with conventional medical treatment in patients with acute hypoxaemic, non-hypercapnic respiratory insufficiency[22,23].

Data are lacking on the influence of NPPV on the potential risk of distension and disruption of bowel wall integrity leading to anastomotic leakage in the setting of oesophagectomy[12,13]. Allaying previous concerns[12,13], the present study has demonstrated the safety of NPPV in

this regard. The results are in agreement with previous clinical studies that demonstrated the safety of CPAP after major abdominal surgery[11,21,24]. The absence of gastric distension might be explained by the limitation of inspiratory pressure to below 25 cmH_2O, a level at which distension is unlikely[25]. Moreover, nasogastric drainage was employed throughout the postoperative period. These results seem to indicate that CPAP or NPPV in patients with postoperative hypoxaemia favours the protective effect of improvement of oxygenation over a hypothetical anastomotic leakage risk.

The best way of applying NPPV in the specific context of postoesophagectomy care remains unclear. In the present study, NPPV was used in patients who had already developed ARF, but it could be argued that it should be applied earlier, once hypoxaemia has occurred, to prevent the development of further complications[19].

Lack of precise information on the aetiology of postoperative ARF represents a limitation of the present study, which included patients with respiratory failure caused by nosocomial pneumonia of infectious or aspirative origin. In a high-risk hypoxaemic study population, it is difficult to perform systematic tracheal aspiration or bronchioalveolar lavage. Therefore, the accuracy of the clinical diagnosis, and the discrimination between aspiration and infectious pneumonia or simple colonization, remains a matter of debate. To improve the diagnostic specificity, a combination of new and persistent lung infiltrates on chest radiography with three clinical findings was used to ascertain the development of pneumonia. If it was not possible to sample the respiratory tract and no bacteria could be isolated from the blood culture or chest drain, the pneumonia was considered to be aspirative. Nevertheless empirical antibiotic therapy was always prescribed.

The case–control design is another limitation of the present study. This design was chosen because the authors had noted an apparent benefit of NPPV in clinical practice, supported by the publication of preliminary scientific results[11,21,24]. It seemed preferable to establish the value of the new strategy compared with the conventional procedure before embarking on a randomized study. A prospective randomized trial is now required to confirm these findings.

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