

*Bruno Riou, M.D., Ph.D., Editor*

## Case Scenario: Management of Postesophagectomy Respiratory Failure with Noninvasive Ventilation

Pierre Michelet, M.D., Ph.D.,\* Dorothée Blayac, M.D.,† Samir Jaber, M.D., Ph.D.‡

**M**AJOR abdominal and thoracic surgeries are frequently associated with postoperative acute respiratory failure (ARF) as a result of atelectasis or pneumonia.<sup>1</sup> In the follow-up to this type of surgery, increasing numbers of reports suggest that noninvasive ventilation (NIV) may help prevent ARF.<sup>2-4</sup> The Case Scenario presented here illustrates the potential benefit of applying NIV. In addition, it highlights the importance of applying a multifaceted postoperative strategy rather than a single therapeutic strategy. This Case Scenario aims to identify key points that can help medical practitioners to make the correct choice as to whether to use NIV or not following invasive surgery.

### Case Report

A 63-yr-old man underwent transthoracic esophagectomy for adenocarcinoma; he experienced progressive ARF starting 24 h after surgery. The patient was scheduled for esophagectomy after neoadjuvant radiochemotherapy. His pulmonary function test did not demonstrate any abnormalities, revealing a forced expiratory volume of 3 l per second and a forced vital capacity of 3.43 l, both of which are more than 95% of the predicted value associated with normal gas ex-

change (table 1). The patient was a former smoker (10 cigarettes a day for at least 15 yr) but had stopped 5 yr before surgery; a moderate alcohol intoxication was noted at the time of surgery. The patient presented a 5 kg weight loss without impairment of nutritional status (serum albumin level of 28 g/l). Neuraxial analgesia was not planned because the patient presented a medical history of coronary disease, having undergone endovascular stent graft placement 2 yr before the intervention described here. This stent graft required continuation of antiplatelet therapy (acetylsalicylic acid). The surgical procedure for esophagectomy lasted 290 min; it included a median laparotomy with creation of a neoesophagus using the stomach, followed by a right thoracotomy with right pulmonary exclusion, with the patient placed in the left decubitus position. This allowed subtotal esophagectomy and esophageal reconstruction through the thoracic route. The patient was put under protective ventilation<sup>5</sup> throughout the procedure. This included 5 cm H<sub>2</sub>O positive end-expiratory pressure. During the two-lung ventilation period, tidal volume was 9 ml/kg; this was reduced to 5 ml/kg during the one-lung period (78 min). According to these settings, inspiratory fraction of oxygen levels were maintained at 60% during the whole anesthetic period, and oxygen saturation did not drop below 96%. No difficulties were encountered during either the surgical procedure or the immediate postoperative period. Tracheal extubation was performed before transfer from the operating theater to the intensive care unit. Postoperative analgesia was provided by intravenous acetaminophen (1 g every 6 h) and patient-controlled analgesia associating morphine and ketamine, with a bolus dose of 0.015 mg/kg each every 7 min; the number of doses was not limited. This analgesic strategy was initially associated with a visual analog pain score, which was maintained at less than 40 mm over the first 18 h. Respiratory rehabilitation consisted in twice-daily chest physiotherapy (30 min), incentive spirometry, and early mobilization. Unfortunately, from the end of the first postoperative day, the patient became resistant to physiotherapy and showed progressive sputum retention and moderate hypoxemia. On the second postoperative day, the patient's respiratory status worsened; tachypnea (less than 30 breaths/min), superficial ventilation, and confusion were observed. Moreover, the patient complained of thoracic pain (visual analog pain score

\* Associate Professor, † Research Assistant, Réanimation des Urgences, Pôle Réanimation Urgence Service d'Aide Médicale Urgente Hyperbarie, Centre Hospitalo-Universitaire de Sainte Marguerite, Marseille, France, and Faculté de Médecine, Université de la Méditerranée, Marseille, France. ‡ Professor, Département d'Anesthésie Réanimation B, Centre Hospitalo-Universitaire de Saint Eloi, Montpellier, France, and Université de Montpellier, Montpellier, France.

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Address correspondence to Dr. Michelet: Réanimation des Urgences, Pôle Réanimation Urgence Service d'Aide Médicale Urgente Hyperbarie, Centre Hospitalo-Universitaire de Sainte Marguerite, 270 Boulevard Sainte Marguerite, 13274 Marseille Cedex 9, France. pierre.michelet@ap-hm.fr. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

**Table 1.** Blood Gas Values for the Main Stages of Clinical Course

	pH	Pao <sub>2</sub> (mmHg)	Paco <sub>2</sub> (mmHg)	Sao <sub>2</sub> (%)	Oxygen Supply (l/min or %)	Respiratory Rate (breaths/min)
Preoperative	7.41	71	37	95	None	16
Postoperative	7.35	192	41	100	6 l/min	14
End of first postoperative day	7.39	107	38	98	6 l/min	18
Before paravertebral block second postoperative day	7.37	95	39	98	10 l/min	24
Before NIV use third postoperative day	7.40	72	37	96	11 l/min	31
4 h after NIV introduction third postoperative day	7.43	123	34	99	50%	28
24 h after NIV introduction (between NIV periods)	7.39	83	39	97	8 l/min	26
24 h after NIV introduction (end of NIV period)	7.41	111	38	98	40%	24
24 h after NIV optimization (between NIV periods) fifth postoperative day	7.39	121	38	99	8 l/min	19

NIV = noninvasive ventilation; Paco<sub>2</sub> = arterial partial pressure of carbon dioxide; Pao<sub>2</sub> = arterial partial pressure of oxygen; Sao<sub>2</sub> = arterial oxygen saturation.

higher than 60 mm) and required more pain relief (morphine consumption greater than 15 mg/8 h). Considering the preoperative alcohol intoxication noted, some of these symptoms might be attributed to delirium tremens. Nevertheless, the combination of hypoxemia and cumulative morphine doses explains our concern for these symptoms. Faced with the rapid degradation of the patient's health status and his increasing tachycardia, the potential benefit of neuraxial analgesia was suggested. Given the antiplatelet drug regime, the risk of infection, and a similar benefit in analgesic control, a paravertebral block was deemed preferable to epidural analgesia. Because a paravertebral block does not require epidural puncture, the risk of compressive hematoma is reduced. The paravertebral block infusion (2 mg/ml ropivacaine) started at an initial flow of 6 ml/h; flow was rapidly increased to 10 ml/h. This resulted in vertebral blockade from T6 to T10 and was associated with an improvement in patient compliance with care. A visual analog pain score lower than 40 mm with the paravertebral infusion allowed the patient-controlled analgesia to be stopped. Despite this change in analgesia, the patient's respiratory distress worsened on the third postoperative day with tachypnea greater than 30 breaths/min, active contraction of accessory muscles, temperature above 39°C, macroscopically purulent secretion associated with leukocytosis (white cell count of 16,000/mm<sup>3</sup>), and

hypoxemia requiring increased oxygen supply (table 1). These clinical signs were associated with the radiographic observation of right lower- and middle-lobe infiltrates, suggesting the development of pneumonia. In the immediate postoperative period, a surgical cause for these symptoms must be ruled out. Anastomotic leakage or pleural empyema were excluded because chest drainage discharge was normal and a methylene blue test through the nasogastric tube was negative. Therefore, the patient was treated with noninvasive positive pressure ventilation combined with a first-line antibiotherapy using an association of piperacillin/tazobactam and amikacin. Pressure support was initially set at 8 cm H<sub>2</sub>O over a positive end-expiratory pressure of 4 cm H<sub>2</sub>O for periods of 45 min separated by intervals of 60 min. Despite moderate delirium, the association of NIV, paravertebral block, and antibiotherapy led to progressively improved oxygenation, thus eliminating the immediate need for tracheal intubation and invasive mechanical ventilation. The thought process leading to the use of NIV in this case is summarized in table 2.

## Discussion

Important issues to consider in this case include the following.

1. *What Is the Pathophysiology of Respiratory Failure after Esophagectomy?*

**Table 2.** Thought Process in Favor of the Use of Noninvasive Ventilation during the Postoperative Period for the Case

Thought Stage	Clinical Application
Indication	Acute respiratory failure in the postoperative period
Expected benefit	Supporting muscle function and improvement of gas exchange Reducing atelectasis
Prerequisites	Avoiding mechanical ventilation and related complications Conscious patient with controlled analgesia Tolerant and cooperative patient Exclude surgical complications
Potential complications	Absence of hemodynamic instability Patient intolerance and agitation Gastric distension, aspiration Delayed reintubation

**Table 3.** Respiratory Complications after Esophagectomy

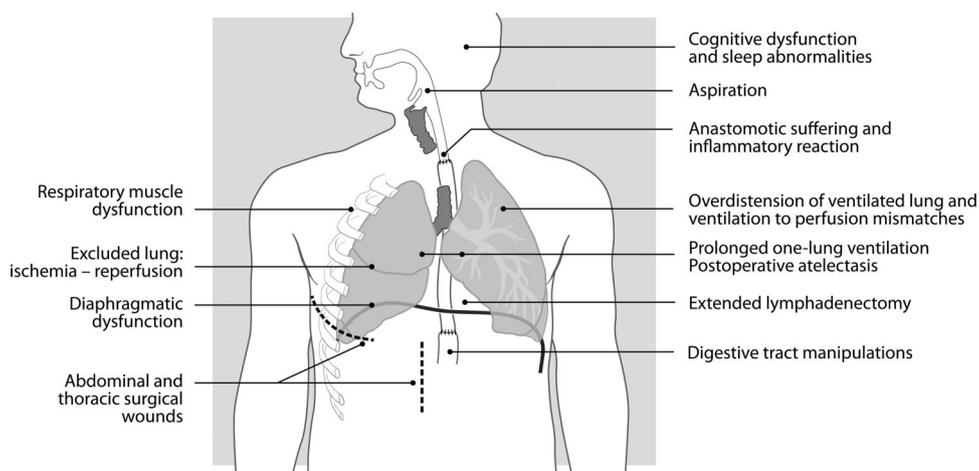
References	Patients (n)	PRC (%)	Pneumonia (%)	ALI/ARDS (%)	Hospital Death (%)
Karl <i>et al.</i> <sup>6</sup>	143	19	8	2	2.1
Doty <i>et al.</i> <sup>7</sup>	120	8	2.5	2.5	0.8
Chandrashekar <i>et al.</i> <sup>8</sup>	76	22	13	9.2	2.6
Fang <i>et al.</i> <sup>9</sup>	441	7	NA	NA	3.9
Atkins <i>et al.</i> <sup>1</sup>	379	16	15.8	NA	5.8
Ferguson <i>et al.</i> <sup>10</sup>	292	27	NA	NA	13.7
Avendano <i>et al.</i> <sup>11</sup>	81	36	32.8	9.8	11.5
Whooley <i>et al.</i> <sup>12</sup>	710	32	17	12	11
All studies	2,242	21.5%	16.7%	9.4%	7.7%

ALI/ARDS = acute lung injury/acute respiratory distress syndrome; NA = not available; PRC = postoperative respiratory complications.

Despite continuous progress in surgical, anesthetic, and intensive care techniques, carcinoma of the esophagus continues to carry a high perioperative mortality rate ranging from 3 to 14% (table 3).<sup>1,6-12</sup> Death generally results from the development of postoperative respiratory complications.<sup>11</sup> After esophagectomy, the development of respiratory complications may be explained by two pathologic mechanisms. The first is linked to surgical complications, notably with the occurrence of anastomotic leakage leading to mediastinitis, septic shock, and acute respiratory distress. The second is of medical origin, with multifactorial impairment of respiratory function.

Medical causes of respiratory complications can involve muscle dysfunction, alteration of pulmonary mechanics, and development of pulmonary atelectasis, leading to postoperative hypoxemia and inducing the further development of complications such as pneumonia or ARF.<sup>13</sup> Nevertheless, the frequency and significance of respiratory impairment in cases of thoracic or upper abdominal surgery, and particularly esophagectomy, require specific attention.<sup>14</sup> Along with the “classic” phenomena which are common after all major surgeries, esophagectomy is also characterized by the association of pre-, peri-, and postoperative pulmonary insult factors (fig. 1). The influence of several preoperative factors, including patient’s age, per-

formance status, comorbidity, neoadjuvant chemoradiotherapy, and poor respiratory function have commonly been found to associate with a worse respiratory outcome.<sup>10,11,15,16</sup> For example, the negative effect of chemoradiotherapy on preoperative pulmonary function and increased postoperative respiratory complications has been demonstrated by an impairment of the lungs’ carbon monoxide diffusion capacity.<sup>17</sup> On the basis of these factors, different preoperative scoring methods have been developed to predict the occurrence of respiratory complications.<sup>10,16</sup> For instance, Ferguson and Durkin have developed a scoring system using patient age, spirometry results, and performance status to help predict the likelihood of pulmonary and cardiovascular complications after esophagectomy (table 4).<sup>10,18</sup> However, these preoperative scores underestimate the influence of perioperative events that significantly impact postoperative respiratory outcome. Perioperative management, including the use of a mechanical ventilation strategy, duration of surgical procedure, surgeon’s experience, extended lymphadenectomy, and fluid management have all been shown to correlate with the postoperative respiratory status.<sup>5,19,20</sup> Several reports, including our own observations, demonstrate the influence of one-lung ventilation on the inflammatory process, on respiratory complications, and the importance of a protec-

**Fig. 1.** Postesophagectomy respiratory impairment factors.

**Table 4.** Ferguson and Durkin Scoring System<sup>10</sup>

Factor Evaluated	Segmentation	Score
Age > 50 yr	< 51 yr	A
	Between 51 and 60 yr	0
	Between 61 and 70 yr	1
	Between 71 and 80 yr	2
	> 80 yr	3
Forced expiratory volume in 1 s % of predicted	≥ 90%	B
	80–89.9%	0
	70–79.9%	1
	60–69.9%	2
	< 60%	3
Performance status*		C
	Fully active, able to carry on all predisease activities without restriction	0
	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature	1
	Mobile and capable of all self-care but unable to carry out any work activities	2
	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours	3
	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair	4
Predicted cardiopulmonary complications risk incidence based on the sum of three covariates	0–1	Total = A + B + C
	2–3	21%
	4–5	41%
	6–7	46%
	≥ 8	62%
		91%

\* Performance Status is based on the Eastern Cooperative Oncology Group Performance Status.<sup>18</sup>

tive respiratory strategy based on the decrease of tidal volume.<sup>5</sup> During the postoperative period, we suggest the involvement of a “stratified process” or a “multi-hit model” where different factors combine with each other and act synergistically to promote the development of ARF. In this way, the first steps are represented by pre- and perioperative respiratory impairment with reduced residual functional capacity, atelectasis, and related hypoxemia.<sup>21</sup> This status is aggravated during the first postoperative days if it is associated with persistent diaphragmatic dysfunction, progressive sputum retention, atelectasis, and respiratory muscle exhaustion. Insufficient analgesic management and respiratory rehabilitation could also be factors.<sup>8</sup> In parallel, and as regularly reported following both thoracic and abdominal surgery, a pulmonary inflammatory response can impair the lung parenchyma, rendering them more sensitive to further aggressions.<sup>5,22</sup> Unfortunately, after esophagectomy, the inflammatory response is not limited to the lung. Indeed, the physiologic insult resulting from esophagectomy is perhaps one of the most apparent because this surgery involves multiple surgical fields. The operative trauma is known to activate several immune cells, which results in the production of proinflammatory cytokines and promotes the development of a systemic inflammatory response.<sup>22</sup> Moreover, initiation of a systemic inflamma-

tory response has previously been correlated with the further development of postoperative complications and the onset of organ dysfunction.<sup>23,24</sup> All of these mechanisms occurring simultaneously probably negatively influence each other, thus resulting in a “vicious circle.”

Finally, the medical and surgical complications are closely linked in the case of esophagectomy. This specificity is explained by the influence of respiratory distress and inflammation on the anastomotic area. After ARF, the second most severe complication is the occurrence of anastomotic leakage. This is closely linked to ischemia of the gastric conduit<sup>25</sup> and impaired oxygen delivery,<sup>26</sup> both of which are observed when respiratory failure occurs in combination with systemic inflammation. It is therefore crucial to maintain adequate oxygenation throughout the postoperative period for both surgical and medical reasons, especially when ARF occurs.<sup>11</sup>

Although postoperative ARF is often characterized by the association of hypoxemia with hypercapnia, in our case, arterial blood gas analysis showed that ARF was characterized mainly by hypoxemia in the absence of hypercapnia. This is in accordance with previously published results.<sup>2</sup> However, this particularity requires confirmation through further study because of its impact on the management of ARF.

## 2. How Is Postesophagectomy ARF Managed?

To deal with the complexity of ARF after esophagectomy, the patient must be treated by a multidisciplinary medical staff. The first step is to establish whether there is any involvement of surgical complications, such as anastomotic leakage, in particular with regard to the potential respiratory consequences.<sup>27</sup> This hypothesis requires that a surgeon be consulted; chest drainage discharge be examined for abnormalities; a methylene blue test through the nasogastric tube be carried out; computed tomography examinations of the chest be performed to identify mediastinitis or pleural empyema; and, if clinical status implies reintubation, a fibroscopic assessment of anastomotic status must be carried out. Once a surgical cause has been eliminated, the practitioners in charge of the patient need to promote respiratory rehabilitation with optimal analgesic control to ensure correct oxygenation. Our case illustrates this issue, highlighting the advantages of neuraxial postoperative analgesia, which not only limits the use of opioid analgesia, but can also improve respiratory function. For a number of years in cases where respiratory function worsens despite adequate analgesic control, as is the case here, invasive mechanical ventilation was the recommended ventilation strategy. Nevertheless, several studies have shown that respiratory morbidity was largely associated with the need for reintubation and mechanical ventilation, notably through the development of ventilator-associated pneumonia.<sup>11,28</sup> As a result of these studies, strategies changed, and practitioners chose to avoid endotracheal mechanical ventilation for the treatment of ARF, particularly when oxygenation could be preserved through the use of NIV.

## 3. Is There a Clear Indication for NIV, Taking into Account the Proximal Surgical Anastomosis and Current Recommendations for the Use of NIV when Faced with Pneumonia?

A recent review and guidelines have reported the potential interest of NIV in postoperative ARF.<sup>29</sup> However, only a few prospective randomized studies are available which have demonstrated that NIV reduces the need for invasive mechanical ventilation and the risk of death after solid organ transplantation<sup>30</sup> and thoracic surgery.<sup>4</sup> In addition, the clinical benefits of NIV compared with conventional medical treatment in patients with hypoxemic, nonhypercapnic ARF remain to be proven.<sup>31</sup> This is particularly the case in the setting of esophagectomy, where the balance between potential benefits of NIV and the hypothetical risk of anastomotic leakage must be carefully evaluated.<sup>32</sup> In the postoperative context, recent results support the safety of NIV in patients with ARF after upper abdominal surgery.<sup>2,33</sup> We have recently reported a case-control study demonstrating the safety of NIV for patients who developed ARF after esophagectomy and its efficacy in avoiding tracheal intubation.<sup>2</sup> Furthermore, the same study showed that the use of NIV was not associated with

increased anastomotic leakage.<sup>2</sup> These results corroborated those of previous clinical studies, demonstrating the safety of continuous positive airway pressure (CPAP) after major abdominal surgery.<sup>33,34</sup> Gastric distension is less problematic with NIV than with CPAP, this might be explained by the fact that inspiratory pressure is limited to less than 25 cm H<sub>2</sub>O in NIV. At this level, distension is unlikely to occur. In addition, nasogastric drainage is maintained throughout the postoperative period, and this may contribute to the prevention of tracheal acid aspiration.<sup>35</sup>

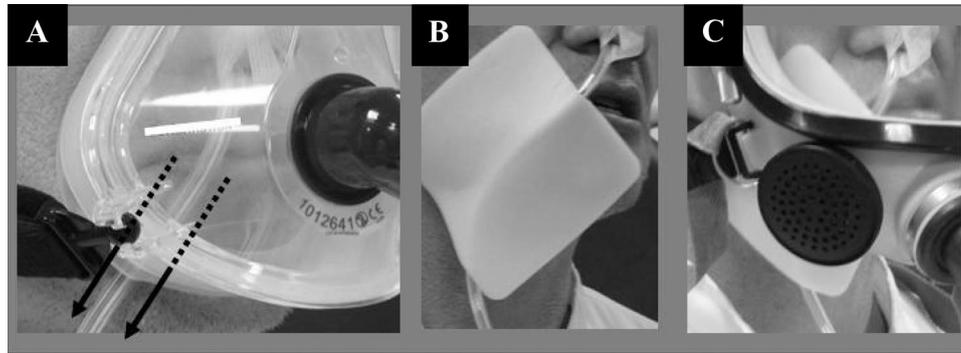
When considering the use of NIV during the postoperative period, the practitioner must determine when direct reintubation of the patient is preferable to starting NIV and when NIV should be stopped. When dealing with ARF, NIV should not be initiated in patients who are confused, in those unable to cooperate, or in patients presenting hemodynamic instability. Moreover, tracheal intubation should be performed immediately if the ARF worsens despite the correct use of NIV. This is particularly important because delayed reintubation may result in increased mortality.<sup>36</sup>

## Subsequent Course

After 1 day of intensive NIV with periods of up to 2–3 h, the patient's clinical evolution was marked by a progressive deterioration of his condition. Although the capnia was maintained in a normal range, hypoxemia reappeared as soon as the NIV was suspended for a few hours (table 1). A follow-up chest x-ray highlighted this degradation, showing a spread of pneumonia to both lungs. Analysis of the potential causes of this adverse evolution revealed that there were air leaks from the nasobuccal interface, in particular around the exit of the nasogastric tube. These affected patient-ventilator synchrony. To reduce this problem a full facemask was used in place of the nasobuccal mask (fig. 2) and the pressure-support ventilation (Puritan Bennett 840; TYCO, Carlsbad, CA) settings were also modified in order to reduce air leaks. These changes included time-cycling instead of flow-cycling the inspiratory phase and reduction of the assisted inspiratory pressure. After these modifications, patient-ventilator synchrony was improved, and the patient was able to sleep with his new interface for a few hours during the night. Over the subsequent days, the patient was progressively weaned off NIV, and he was discharged from the intensive care unit after 7 days. During the second postoperative week, fibroscopic control of the anastomosis did not reveal any leakage.

## 4. Should NIV in This Setting Be Used Prophylactically Immediately after the Surgical Procedure or Only when ARF Is Diagnosed?

Another issue to contend with when considering the use of NIV in the postoperative period is the optimal time for implementation: faced with an established ARF (curative use) or by default immediately after the surgical procedure (prophylactic use). With regard to the clinical course of our patient, one could argue that preventive, rather than



**Fig. 2.** These photographs illustrate the improvement of noninvasive ventilation (NIV) efficacy by better patient-NIV interaction. (A) The use of the initial interface was associated with air leaks at the nasogastric tube exit (arrows) and a nose pain related to bending of the nasogastric tube. (B) A multilayered hydrocolloid was added ensuring a better air tightness. (C) Finally, the use of a new interface allowed the absence of nasogastric tube bending, leading to complete patient compliance with the technique.

curative, application of NIV might have avoided the development of respiratory distress. Although the definitive response remains unknown, some data are currently available for evaluation. One of the first well conducted studies of to the use of NIV during the postoperative period was carried out in the context of patient acute respiratory insufficiency after lung resection (curative use).<sup>4</sup> This study revealed a reduction in the need for endotracheal mechanical ventilation and in postoperative mortality.<sup>4</sup> Other papers have confirmed that curative NIV is of benefit in other thoracic or abdominal surgical procedures.<sup>2,30</sup> On the other hand, Squadrone *et al.*<sup>3</sup> have proposed the use of CPAP for the treatment of moderate hypoxemia at an earlier stage in the postoperative course after major abdominal surgery; this would constitute a preventive use. Consequently, although both strategies appear to give positive results, further studies are required to confirm the clinical benefits acquired through application of NIV earlier in the postoperative course.

##### 5. What Are the Optimal Settings for NIV in This Situation?

The first and, perhaps the most comfortable, mode of NIV is CPAP. Although CPAP does not correspond to true ventilation, this technique could be easily and rapidly started postoperatively. This would help prevent airway and alveolar collapse and would contribute to the maintenance of functional residual lung capacity, which would lead to an increase in oxygenation. The combination of positive inspiratory pressure support ventilation with CPAP could enhance the efficacy of NIV in improving the “pump” function with a decrease of work for the breathing apparatus. Nevertheless, to maintain patient comfort and interface acceptance, the initiation of NIV should be carried out with both moderate levels of inspiratory pressure support ventilation and positive end-expiratory pressure (which is called CPAP when used alone). In the present case, the initial inspiratory pressure support ventilation was set at 10 cm H<sub>2</sub>O. This value (potential felt as high by the patient during NIV initiation) probably contributed

to the patient’s discomfort and to the air leaks detected around the interface. The choice of interface is very important when applying NIV, and even more so when a gastric tube is present, as in the case described here. Consequently, and because there is no evidence to support the use of a particular interface in the surgical context, the physician in charge of the patient must try out several interfaces to find that which ensures minimal leaks.

We have reported the fact that in our case, arterial blood gas analysis showed that ARF was characterized mainly by hypoxemia without hypercapnia, in accordance with previous results.<sup>2</sup> Consequently, the settings of NIV should be based on the preferential use of positive end-expiratory pressure rather than inspiratory pressure assist ventilation, as previously used by Squadrone *et al.*<sup>3</sup> Nevertheless, whether the use of positive end-expiratory pressure alone will prevent further muscle exhaustion remains to be answered.

##### 6. How Can the Analgesic Strategy Influence Patient Tolerance when Faced with Complications and Related Therapeutic Measures?

Patient compliance with treatment is mandatory for NIV to be effective. This can be notably enhanced by providing preoperative information, by ensuring interface acceptance, by adapting and progressively increasing pressure settings, and, not least, by skilled staff.<sup>31,33,37</sup> Within the context of postoperative respiratory rehabilitation, NIV use also needs a “positive atmosphere” to be optimal. Because of this, and particularly in the postesophagectomy situation, analgesic control appears of paramount importance. The case reported here clearly demonstrated that insufficient analgesic control could contribute to a loss of patient compliance and subsequent impairment of respiratory function. The use of neuraxial analgesia is associated with better relief of pain and fewer opioid-related side effects.<sup>8,38</sup> This results in a reduction in the need for postoperative ventilation.<sup>39</sup> Furthermore, Rigg *et al.*<sup>40</sup> have reported a positive influence of epidural analgesia on the outcome of major abdominal surgery. After esophagec-

tomy, specific effects of analgesic strategies should be highlighted. We have reported the benefit of epidural analgesia on the improvement of anastomotic perfusion.<sup>27,41</sup> This could partly explain the protective influence of this technique after esophagectomy. Unfortunately, epidural analgesia could not be used in the case described here because of the patient's antiplatelet therapy. Although we could retrospectively regret not having applied neuraxial analgesia for this patient in the immediate postoperative period, the balance between benefits and potential risks was considered to weigh against the placement of this technique by the physician in charge of the patient at that time. While the published literature remains insufficient, several studies have already highlighted the potential beneficial effects of a paravertebral block.<sup>42</sup> Taken together, all of these factors explain why we are so interested in the association of neuraxial analgesia with NIV. Indeed, this association probably results in a synergistic effect for both curative and preventive applications. Once pain is under control, patient compliance may be reinforced by the use of the best-adapted interface, that which provides the best match between the human and the "machine."<sup>31,37</sup>

### Knowledge Gap and Future Perspectives

Clinical studies are mandatory to confirm that NIV is relevant in the specific situation of esophagectomy. It is particularly important to determine the optimal time for introduction of the technique. Indeed, although data are still insufficient to conclude, a recent study supports the initiation of NIV before a thoracic procedure to optimize respiratory function at a very early stage.<sup>43</sup> Further research will also provide information concerning better (earlier) preservation of the respiratory function and control of the postoperative inflammatory reaction. In the case presented here, we have discussed how NIV and analgesic control can combine to contribute to patient comfort and well-being, but these techniques are currently employed more to correct an existing respiratory impairment. How the implementation of these two techniques could prevent the development of such abnormalities represents an interesting issue for the future.

An extensive analysis of the involvement of the abdominal muscles in postoperative respiratory dysfunction is also required.<sup>44</sup> This should be coupled to the development of analgesic techniques providing better abdominal recovery.<sup>45</sup> Similarly, it will also be necessary to study the specific influence of NIV on abdominal muscle dysfunction.

We have repeatedly mentioned the inflammatory response as one of the main factors influencing respiratory impairment. This aspect is probably highly significant, particularly when one considers the potential influence of postoperative respiratory complications and related immune abnormalities on cancer recurrence and long-term survival.<sup>17,46</sup> Therefore, for esophagectomy patients, one of the main knowledge gaps is how the immune response can be modulated without completely suppressing its capacity. How is the

inflammatory response affected by the use of NIV, of different analgesic strategies, and of combinations of the two?

Finally, we have mentioned numerous factors potentially involved in the initiation of respiratory complications. These factors can either protect against, or aggressively influence, respiratory complications. Further studies would provide the physician with new predictive scores to evaluate not only pre- but also peri- and postoperative factors.

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