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Ventilatory responses after major surgery and high dependency care

D. Nieuwenhuijs

Editor’s key points

- Disturbances in respiratory control occur frequently after surgery, and could contribute to complications.
- Ventilatory responses to hypoxia and hypercapnia that simulated airway obstruction were studied in patients after major abdominal surgery.
- Ventilatory responses to simulated airway obstruction were small, and did not improve at 6 weeks follow-up, indicating persisting defects in respiratory control.

Background. Disturbed breathing during sleep, with episodic upper airway obstruction, is frequent after major surgery. Ventilatory responses to hypercapnia and hypoxia during episodes of airway obstruction are difficult to investigate because the usual measure, that of ventilation, has been attenuated by the obstruction. We simulated the blood gas stimulus associated with obstruction to allow investigation of the responses.

Methods. To assess ventilatory responses, we studied 19 patients, mean age 59 (19–79), first at discharge from high dependency care after major abdominal surgery and then at surgical review, ≈6 weeks later. Exhaled gas was analysed and inspired gas adjusted to simulate changes that would occur during airway obstruction. Changes in ventilation were measured over the following 45–70 s. Studies were done from air breathing if possible, and also from an increased inspired oxygen concentration.

Results. During simulated obstruction, hypercapnia developed similarly in all the test conditions. Arterial oxygen saturation decreased significantly more rapidly when the test was started from air breathing. The mean ventilatory response was 5.8 litre min⁻² starting from air breathing and 4.5 litre min⁻² with oxygen breathing. The values 6 weeks later were 5.9 and 4.3 litre min⁻², respectively (P=0.05, analysis of variance). There was no statistical difference between the responses starting from air and those on oxygen.

Conclusions. After major surgery, ventilatory responses to hypercapnia and hypoxaemia associated with airway obstruction are small and do not improve after 6 weeks. With air breathing, arterial oxygen desaturation during simulated rebreathing is substantial.

Keywords: general surgery; pulmonary ventilation; respiratory insufficiency

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After major surgery, repeated cycles of upper airway obstruction and hypoxaemia are frequent during sleep.¹⁻³ These episodes end when the upper airway regains patency. An increase in airway dilator muscle activity is brought about by a combination of factors. These factors probably include arousal, hypoxaemia, hypercapnia, and sensory feedback from increasing inspiratory muscle effort.⁴ In patients after surgery, these stimuli seem to be impaired by opioid analgesia,⁻⁵ sleep deprivation,⁶ other centrally active medications,⁷⁻⁸ and the stress of major surgery.⁹ The exact effect of these factors is unknown. Most studies of such influences have involved healthy subjects, or patients with conditions such as obstructive sleep apnoea (OSA). Patients after surgery have been rarely studied, probably because of the substantial practical difficulties involved.

Some of these influences can persist for several days. Even when patients are considered ready to leave the high dependency unit (HDU) after recovery from major surgery, they can still have impaired ventilatory responses. If responses to hypoxaemia and hypercapnia remain impaired in these vulnerable patients, continued episodes of airway obstruction could cause more severe hypoxaemia,¹⁰ generate more severe cardiovascular and inflammatory responses,¹¹⁻¹² and lead to cardiovascular complications.

Adequate assessment of ventilatory responses is difficult in patients who have undergone major surgery. They are unable to carry out prolonged tests, which are needed for steady-state measurements, so full assessment with standard methods is impractical. Standard testing methods consider responses to hypercapnia and hypoxia separately, and
interpretation of the results of such tests can be complicated by factors such as an acute decline in the response to hypoxia, and the effects of previous hypoxia. In contrast, the actual stimulus presented during the progress of an obstructive episode in the surgical patient is one where hypoxemia and hypercapnia increase at the same time, although with different rates because of the very different body handling of the two gases.

To assess the response of the respiratory control system to the changes that evolve during airway obstruction, we devised a pragmatic method to simulate changes in respired gases to more closely resemble those occurring during an episode of obstruction. We used a computer-controlled feedback system to increase carbon dioxide and reduce oxygen in the same way that these values would change during obstruction, even though the patient was actually breathing clearly. In this way, we were able to use changes in ventilation during the test period to indicate the chemically mediated response of the respiratory controller to airway obstruction. We expected to find that responses at the time of discharge from the HDU would be impaired compared with those after full recovery. We also measured potential factors that could be related to this response, such as opioid medication and opioid metabolites. Another factor that could affect sleep and ventilation is the inflammatory response to surgery. Experimental inflammation causes substantial changes in sleep patterns. To assess the inflammatory response, we used C-reactive protein (CRP) concentration. Hall and colleagues noted that values for CRP were consistent over several days and thus a single CRP value can provide a reasonable ‘summary’ indicator of inflammatory response. We hoped to relate any reduced ventilatory responses to plasma opioid concentrations and CRP values.

**Methods**

We obtained permission from the local ethics committee to recruit patients who were about to have major abdominal surgery, and would receive postoperative care in the surgical HDU. Patients were interviewed before elective or planned urgent procedures and gave their written consent. The agents and methods used for anaesthesia were not standardized. Analgesia was with either epidural infusion of bupivacaine and opioid or patient-controlled i.v. opioid, according to the preference of the anaesthetist. Because patients had to be moved to the laboratory for these studies, the local ethics committee would not permit studies to be done until patients were about to leave the HDU and were ready to return to the general surgical ward. Patients were studied on the day of discharge from the HDU. The criteria for discharge from the unit were not specified exactly, and in addition to the condition of the patient, also depended on extrinsic factors such as staffing and ward activity. We invited patients to return to the laboratory for a repeat study when they attended the outpatient clinic for review, ~6–8 weeks after surgery.

**Measurements**

Patients were studied supported in a sitting position in bed after discharge from the ward, and in a comfortable chair at their review visit. Ear lobe pulse oximeter values (Ohmeda Biox 3700, set to rapid response) were recorded continuously. They breathed through a well-sealed face mask (Vital Signs, Totowa, NJ, USA) connected to a low resistance one-way valve (model 2700, Hans Rudolf, Shawnee, KS, USA). The exhaled gas from the valve passed through a heated pneumotachograph (Fleisch no. 2, P.K. Morgan, UK) and drying chambers to a dry gas meter (Parkinson Cowan CD4) modified to give a digital signal. This signal was used to calibrate the integrated expiratory flow signal and give an accurate breath by breath exhaled tidal volume. Gas was sampled at the mask and analysed for oxygen and carbon dioxide by a mass spectrometer (VG Spectralab M, Winsford, UK) calibrated regularly with five standard gas mixtures. Breath by breath values for tidal volume $V_T$, litre at body temperature and pressure, saturated with water vapour (BTPS), inspiratory time $T_i$, s, expiratory time $T_e$, s, respiratory frequency $f=60/(T_i+T_e)$, bpm, instantaneous minute volume $V_E=f \times V_T$, litre min$^{-1}$, and inspired and end-tidal partial pressures for oxygen and carbon dioxide were digitized (Dell 425 S/L computer) and stored on disc. The inspiratory side of the one-way breathing valve drew gases from a T piece with an open wide-bore reservoir and a closed mixing compartment fed with oxygen, nitrogen, and carbon dioxide. These gases were delivered from mass flow controllers (F202AC and F201AC, Bronkhorst Hi-Tech, Ruurlo, The Netherlands) supplied with gas at 2 bar from precision regulators (RS components), and controlled by a computer (Elonex PT-5120/l) with a D-A converter (Amplicon PC24). This computer received data from the data acquisition computer. Custom written software calculated a rolling mean of the end-tidal oxygen and carbon dioxide from the last 3 breaths, and then adjusted the mass flow controllers, so that the inspired concentrations of the oxygen and carbon dioxide were the same as this mean end-tidal value. This caused a gradual decrease in inspired oxygen and an increase in inspired carbon dioxide. The number of breaths was first set at 3 but could be adjusted, so that a decrease in $SpO_2$ of at least 3% (when the starting inspired gas was air), and an increase in $P_{eCO_2}$ of 1 kPa occurred over 1 min. Because sighing or swallowing cause sudden changes in the end-tidal concentrations, breaths which differed from the target value by more than 5% or the preceding value were ignored.

We studied patients on two occasions, on the day of discharge from the HDU, and if possible when they returned to the hospital for review, 6–8 weeks later. Patients were not discharged from the HDU until they had completely recovered from epidural analgesia. On both measurement occasions, the patient was settled into the equipment and breathed 21% oxygen for at least 5 min until ventilation was stable. Three runs of hypercapnia and hypoxia were then administered, by the computer-controlled system,
each separated by 2 min breathing 21% oxygen (Fig. 1). The inspired oxygen was then increased to 30% and the same pattern of stimuli was repeated. If the baseline $\text{SpO}_2$ was $<92\%$, the inspired oxygen was increased to increase $\text{SpO}_2$ to this value, and the hypoxic/hypercapnic stimuli were done with that starting value of $F_{O_2}$. We observed the patients carefully for any evidence of sleep, because we wished, if possible, to assess the effects of sleep on the ventilatory responses.

Venous blood samples were obtained and assayed for morphine, morphine 3 glucuronide, and morphine 6 glucuronide (MOR, M-3-G, and M-6-G) by high-performance liquid chromatography\textsuperscript{16} (after discharge from the ward) and for CRP after leaving the HDU and at the time of review, using the FPIA method on an Abbott FLX apparatus.

Data analysis

Baseline breathing was measured over 1 min, and the average values were taken, before measurement of the responses to hypercapnia/hypoxia. To measure the mixed ventilatory response, we measured the rate of increase in ventilation over the time of application of the stimulus by fitting a linear regression to the relationship between instantaneous ventilation and time over the duration of application of the stimulus. Values for responses in each condition (ward discharge or review, normoxia or hyperoxia) were averaged. Similar calculations were made of the rate of change for inspired and end-tidal values of carbon dioxide and oxygen, and for the pulse oximeter saturation readings. We also calculated the ventilatory response to carbon dioxide, by pooling values of instantaneous ventilation and end-tidal carbon dioxide for all the runs in each condition (ward discharge or review, normoxia or hyperoxia) and plotting ventilation vs $F_E CO_2$. The linear part of the ventilation/$F_E CO_2$ plot was identified by applying the runs test for non-linearity (GraphPad Prism, version 3.01). Smaller data values were progressively eliminated until the runs test result was no longer significant, that is, the plot had become linear. The slope of the remaining data plot was calculated by linear regression and expressed as litre min\textsuperscript{-1} kPa\textsuperscript{-1}.

We had no prior measure of the variability of these measures in such patients, nor did we possess data that would reliably predict the responses of these patients after surgery. Others have reported considerable variability in ventilatory responses, partly related to gender.\textsuperscript{17} We intended to conduct a paired assessment so that the influence of interindividual variation could be minimized. In a review of the suppression of the ventilatory response to hypoxia, Pandit\textsuperscript{18} reported that the overall effects of low-dose anaesthetic agents, which could be considered a comparable effect, were to reduce the hypoxic response by 44%. We considered that our study should have sufficient power to detect such effects based on a coefficient of variation of the ventilatory response of about 30%. However, we were unable to predict our actual results, a priori.

Values are expressed as mean (sd), and the baseline values and the responses were compared with analysis of variance (ANOVA) followed by Tukey’s test, for variables that were not clearly non-Gaussian, and with the Kruskal–Wallis test followed by Dunn’s test for oxygen saturation values. Relationships between the responses and plasma opioid values, and the responses with the log CRP concentrations, were displayed graphically and any possible relationships were tested by linear regression. The relationship between ventilatory response over time and the decrease in pulse oximeter readings was explored by expressing the response as a fraction of the desaturation that occurred.

Results

We recruited 40 patients over a 6 month period of study. We were unable to test 11 patients for follow-up measurements. We could not obtain a complete set of respiratory measurements in another nine patients. Blood samples for CRP were lost in one patient and for morphine values in one patient. In one patient, the respiratory measurements made at discharge from the ward were later found to be inadequate for analysis, and in another, the measurements made at review were unsuitable for analysis. Consequently, we had 20 sets of data to analyse and only 19 were complete. The
average age was 61 yr (range, 19–79). However, most patients were more than 50 (quartiles 57, 69 yr). No patient was more than 120% of body weight expected for height and age, and six were female. The time from admission after surgery until discharge from the unit varied, but the median duration before discharge was 2 days after surgery (four patients on day 1, 10 on day 2, and the remainder on day 3 or later). The median dosage of morphine was 36 mg 24 h⁻¹ (quartiles 10, 65). Two patients required naloxone administration for low respiratory rate during their time in HDU. No patients were taking regular opioid analgesics when they returned for review. In nine patients at ward discharge, the pulse oximeter values while air breathing were too low to permit the testing process using 21% inspired oxygen, so studies could only be done with an increased inspired oxygen concentration. This remained true for five patients at review. In the figures, data are presented for 20 patients when possible.

**Baseline measurements**

The features of resting breathing at discharge and then at review are shown in Figure 2. The duration of inspiration in patients from the HDU was 1.2 (0.2) s, and on return for review, this was significantly greater, 1.5 (0.4) s (P<0.01). The duration of expiration was less at review than at ward discharge, but this difference was not significant. Resting ventilation at ward discharge was 9.1 (2.4) litre min⁻¹ and unchanged at review, 10.7 (3.6) litre min⁻¹. However, the end-tidal carbon dioxide values were greater in four of the patients, and the pulse oximeter values during air breathing were less and much more variable at ward discharge. The mean SpO₂ on discharge from the ward was 95 (1.5)% and this had increased to 97 (0.6)% at review (P<0.0001, Mann–Whitney U-test).

**Responses to the imposed rebreathing test**

Because oxygenation was poor in some patients breathing air, responses starting from air breathing are only available for some patients. Responses were obtained for all the patients during oxygen breathing. Details of the duration of the tests, and the changes in stimuli that occurred over this time, are summarized in Table 1. The duration of the

![Fig 2](image-url) Features of baseline breathing in the patients, at discharge from the ward and at subsequent review. (A) Pattern of breathing. Tᵢ, duration of inspiration; Tₑ, duration of expiration. (B) End-tidal CO₂ and pulse oximeter oxygen saturation values.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Duration of stimulus (s)</th>
<th>Rate of change</th>
<th>Change</th>
<th>Ventilatory response (litre min⁻¹)</th>
<th>Hypercapnic response (litre min⁻¹ kPa⁻¹)</th>
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<tr>
<td></td>
<td></td>
<td>̇Pᵩ₀₂ (kPa min⁻¹)</td>
<td>̇Pₑ₀₂ (kPa min⁻¹)</td>
<td>SpO₂ (%)</td>
<td>SpO₂ (%)</td>
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<tr>
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</tr>
<tr>
<td><strong>Normoxia</strong></td>
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stimulus applied differed between the groups (ANOVA, P<0.01). The test was stopped sooner when the ward patients started the test breathing air, resulting in the duration of this test being significantly less (mean 51 s) than the duration of the stimuli that could be applied when inspired oxygen was increased (mean 63 s), and when the patients returned for review (P<0.05, Tukey’s test) (Fig. 3). The durations of the tests done at ward discharge starting with hyperoxia, and the tests at review were similar and indistinguishable statistically. The mean decrease in oxygen saturation in each patient differed between the measurement conditions (Kruskal–Wallis test, P<0.001). The variances for these values were significantly different, so comparisons between the groups are not straightforward. Dunn’s multiple comparison test for the adjacent groups shown in the figure showed a significant difference between the responses observed during air breathing and during oxygen breathing, both at ward discharge and at review.

Figure 4 illustrates the responses to the rebreathing procedure. The rate of decrease in oxygen saturation differed (Kruskal–Wallis test, P<0.0001) depending on the starting $F_{\text{IO}_2}$. The carbon dioxide in exhaled gas progressively increased over the duration of the test by about 1 kPa as expected, and there was no difference in the rate of increase between the groups. Ventilation increased significantly in all the groups, and there was a small difference in the responses of the groups (Kruskal–Wallis test, P=0.026), but the 95% confidence intervals overlap considerably, and post hoc testing showed no differences. As expected, there was a significant relationship between the ventilatory response, expressed as change in ventilation with time, and the conventionally calculated ventilatory response to carbon dioxide (expressed as litre min$^{-1}$ kPa$^{-1}$) ($r^2=0.3844$). Linear regression did not show that greater reductions in $S_{\text{pO}_2}$ caused greater ventilatory responses.

At the time of discharge from the ward, plasma CRP values were increased and almost all were in the normal range on return for review (P<0.0001, Mann–Whitney test) (Table 2). There was no discernible relationship between
the ventilatory responses to rebreathing measured at ward discharge and the CRP concentrations. Plasma morphine and morphine glucuronide values showed a large range of values. There was a weak correlation between plasma morphine concentration and the total dose of morphine given ($r^2=0.29$, $P<0.05$). There was no clear relationship between the ventilatory measurements or the response to rebreathing and the plasma morphine or morphine metabolite values, although the end-tidal carbon dioxide values during resting breathing could be partly explained by the plasma morphine concentration ($r^2=0.34$, $P<0.05$) (Fig. 5).

**Discussion**

The central finding of this study is that patients returning to a general surgical ward after major surgery have a poor response to stimulation of ventilation by hypoxia and hypercapnia, and particularly that this response is not importantly augmented by concomitant hypoxaemia. This may partly explain the prevalence of severe episodic hypoxaemia in such patients, and could contribute to complications. Morphine blood levels, despite showing a detectable effect on respiratory pattern and ventilation in some subjects, could not be related to the responses to hypercapnia and hypoxaemia. This apparent lack of influence of morphine is supported by the similar findings at review, 6 weeks after discharge from hospital. At that time, morphine would be unlikely to have persistent effects, although some long-term effects of hypoxia and surgery on central control systems might persist.

Disturbances of respiratory control, such as hypercapnia and apnoea, have been described frequently in reports of patients after surgery. The effects of agents such as opioids that are used for patients after surgery have been described, but generally in healthy volunteers: few studies have been done of respiratory responses to chemical stimuli in patients after surgery. Johnson and colleagues studied the ventilatory response to hypercapnia and hypoxia, in patients after hip surgery and found that intrathecal morphine did not depress chemoreflexes. Of interest, they found that about one-third had poor responses to hypoxia even before surgery. This would in part support our findings that after recovery, the responses to hypoxia were small.

Our test aimed to replicate the ventilatory stimulus of hypercapnia and hypoxaemia that would occur during an episode of airway obstruction, and then allow us to measure the ventilatory response that resulted. When the patients were breathing air, they were challenged with a substantial combination of both stimuli. In laboratory studies of volunteers subjected to similar stimuli, this hypercapnic stimulus would increase ventilation by more than 10 litre min$^{-1}$, and hypoxia would additionally augment this stimulation. In contrast, we found ventilatory responses to stimulation that were limited and similar. The effects of factors such as morphine and its metabolites, evidence of inflammation, reduced arterial oxygenation, or recovery from the surgical period all appeared to be small. These effects could have been limited because the ventilatory responses themselves were small, and thus the opportunity to detect changes would be limited. A further possible factor is the duration of the stimulus applied. If baseline ventilation is already augmented by additional drives to the respiratory system, such as pain, anxiety, or pulmonary afferent stimulation, then short-term application of hypoxia and hypercapnia may have less opportunity to augment ventilation.

In patients with OSA, repetitive hypoxic events, which we know are frequent in patients after major surgery, can change both the ventilatory response to hypoxia and also the baseline ventilation. These phenomena, known, respectively, as progressive augmentation and long-term facilitation are likely to alter responses in patients who are subject to intermittent arterial oxygen desaturation in the time after their surgery. Most studies of these phenomena have been done in sleep and with patients with OSA, and it is not clear how these effects alter airway control, or if the findings can be confidently extrapolated to post-surgical patients who sleep badly after surgery, have sparse rapid eye movement sleep, and do not respond to increased nasal airway pressure in the same way that OSA patients do.
Our study had weaknesses which warrant caution. We were confident that the imposed changes represented those present during episodes of obstruction, but the pattern of decrease in oxygen saturation and increase in carbon dioxide noted in postoperative patients is far from uniform. This is hardly surprising: obstruction is frequently incomplete, so the dynamics and magnitude of the changes in blood gases are likely to vary. The rate of oxygen desaturation depends on factors such as lung volume and cardiac output and the rate of change of carbon dioxide will also be affected by metabolism and cardiac output. Nevertheless, changes in oxygen saturation during rebreathing onset were similar to those we have recorded in a previous study. In addition, the measured end-tidal values provide a direct measure of the stimulation imposed on the patient.

As would be expected in a clinical study, our data were not complete. In addition to the discomfort and difficulty that patients have with complying with these complex measurements, clinical factors such as nausea, the presence of nasogastric and other drains, anxiety, depression, sleep deprivation, and physical limitation made the patients often unwilling or unable to co-operate. Our original intention was to analyse the data using a within-subject design. However, impaired oxygenation present in many of the subjects necessitated a more generic comparison between the groups.

Another confounding effect could be pulmonary dysfunction. Arterial oxygen values were reduced indicating impaired gas exchange. Factors such as reduced lung volumes, atelectasis or pneumonic changes, systemic inflammatory responses, and subclinical volume overload could contribute to this hypoxaemia. Indeed, the short duration of inspiration in many patients suggested an element of rapid breathing in the HDU patients, presumably related to reflex tachypnoea, which had resolved 6 weeks later at the time of review. Although the duration of expiration was not reduced in the post-surgery measurements, this may reflect the effects of opioids, which specifically prolong this phase of respiration. The resting breathing pattern may thus have reflected both stimulatory and depressant influences, which could over-ride the effects of chemo-sensation on respiratory changes. Our study results would probably have been affected by the degree of arousal of the subjects. Commonly, episodes of airway obstruction occur in patients who are left undisturbed. In contrast, our subjects were aroused, and this may have affected their resting ventilation, which was of a magnitude expected in alert, not drowsy, subjects. In these circumstances, the drive to breathe may not be increased by an increase in CO2 or a decrease in SpO2, until these factors ‘overtake’ the conscious drive. In this case, the responses to hypoxia and hypercapnia will be less prominent.

The duration of the applied changes could also be relevant. We were obliged to limit the imposed decrease in SpO2. Starting with air breathing, ward patients decreased their oxygen saturation to a mean of 89% (the minimum value was 85%) in 47 s. The mean decrease in oxygen saturation was 4.1%, and the greatest decrease was 7%. Thus, although these stimuli were substantial, they were not sustained for as long as the stimuli of the other tests, where oxygen was given, or lung function was better. Ideally, the duration of each test should have been the same. However, by using the rate of change (Table 1), we were able to correct for the small differences in duration of the tests. In addition, the rate of change of end-tidal gas composition and ventilation were linear. However, oxygen saturation values were significantly non-linear, showing a progressive increase in the rate of decrease.

During an episode of airway obstruction, chemical stimuli are not the only elements contributing to the drive to arousal and increased breathing. Muscular effects are relevant, and the level of consciousness or type of sleep are also important. These effects would not affect our measurements. Our patients were carefully observed throughout the test period and they remained alert and breathed clearly at all times.

Clearly, older patients having major surgery may have a number of co-morbid conditions. In this way, they may be similar to patients who have been discharged from the intensive care unit, who frequently have respiratory control disturbance. In such patients, airway obstruction, particularly combined with impaired oxygenation, can induce inflammation and endothelial dysfunction, and alter sympathetic activity, which could adversely interact with these risk factors to cause complications. Inflammatory responses to endotoxin include sleep disruption and changes in sleep patterns. However, our study suggests that responses to oxygen saturation levels do not have an important effect in augmenting ventilatory responses, and are unlikely to generate protective responses, either in the later postoperative period or in the recovery period, 6–8 weeks later.

In conclusion, we observed limited ventilatory responses to a combined hypoxic–hypercapnic stimulus in patients after major surgery. This remained limited 6 weeks later, after discharge from hospital. These data show that the respiratory control system is vulnerable to periooperative stressors such as stress, pain, inflammation, and surgery itself, while pulmonary dysfunction might play an additional role. The persistent small responses 6 weeks after surgery when inflammation, pain, and opioid use were absent suggests a slow recovery of ventilatory control for reasons that are currently not understood which could include plastic changes in the central nervous system that require prolonged periods to resolve or restore. Further studies for longer periods of time after surgery might resolve these possibilities.

Declaration of interest
None declared.

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