9 *The Edinburgh Ward 9 Study* or Ventilatory responses after major abdominal surgery and intensive care

IN THE FIRST few nights after major surgery, most patients have frequent episodes of airway obstruction and hypoxaemia.[156] These events cause cardiovascular responses which may contribute to the cardiovascular complications that occur at this time. The factors that cause these respiratory disturbances are not clear, but opioid analgesia, sleep deprivation, other centrally active medications, and the stress of major surgery may all play a part.[3,85,101,120] We have recently shown that hypoxaemia can be reduced by oxygen therapy, but nasal continuous airway pressure, which might reduce episodic airway obstruction, does not improve either oxygenation or the quality of sleep in patients after major surgery.[66] Indeed we felt that such patients, even when judged 'fit to leave' the high dependency or intensive care unit, appeared not well recovered from the impact of surgery and the postoperative period, with breathing still depressed by postoperative analgesics. If respiratory responses are impaired, then an obstructive episode might persist longer, causing more profound and prolonged hypoxaemia.[152]

In this study, we set out to assess how well patients after major abdominal surgery and intensive care were able to respond to episodes of airway obstruction, by simulating the changes in chemosensory input that they would experience during an episode of obstruction. To assess the response to obstruction, we devised a method to simulate the changes that would occur in the lung gases. We used a computer-controlled gas forcing system to increase CO_2 and reduce O_2 in the way these changes occur during obstruction. If the patient is in fact breathing clearly, then the changes in ventilation ($\dot{V}_e$) caused by this stimulus can be used as an index of the response the patient generates, although in a real obstructive episode increased breathing force would lead to increased muscle effort but not necessarily increased breathing. We also studied how the inflammatory response (indicated by the C-Reactive Protein (CRP) concentration), opioid medication, and opioid metabolites might be related to these responses.

METHODS

We studied respiratory responses to a combined hypoxic/hypercapnic stimulus in patients after abdominal surgery and 2 to 3 days intensive care (IC) in the high dependency unit (HDU) of the hospital (Ward 9 at the Royal Infirmary in Edinburgh; study period March - September 2000). Permission was obtained from the local ethics committee to recruit these patients before surgery and all subjects gave consent. Since the patients had to be moved to the respiratory laboratory, we were only allowed to do this when the patient was judged ready to leave the high dependency unit and return to the general surgical ward.

There were no restrictions in the use of drugs for induction and maintenance of general anesthesia. After surgery all patients were extubated. Initially, postoperative analgesia was

either epidural infusion of bupivacaine and morphine, or patient controlled intravenous analgesia (PCA) with morphine, according to the preferences of the attending anaesthetist. At the morning of discharge from the ICU all epidurals were removed and the patients set on PCA with morphine. All patients were asked to return for a review session 6 to 8 weeks after their discharge from the hospital.

Apparatus and Measurements
Patients were studied sitting in bed after discharge from the HDU in a semi-recumbent position, and in a comparable bed at their review visit. They breathed through a face mask (Vital Signs, Totowa, NJ) connected to a low resistance one way valve (Hans Rudolf model 2700). The exhaled gas from the valve passed through a heated pneumotachograph (Fleisch no. 2) 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 analyzed for O_2 and CO_2 concentrations by a mass spectrometer (VG Spectralab M, Winsford, UK) calibrated regularly with four standard gas mixtures. Breath by breath values for tidal volume (V_T), respiratory frequency (RR), instantaneous minute volume ($RR \times V_T$) and inspired and end-tidal partial pressures of O_2 and CO_2 were digitized (Dell 425 s/L computer, Dublin, Ireland) 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 O_2, CO_2 and N_2. These gases were delivered from mass flow controllers (Bronkhorst Hi-Tech, Veenendaal, The Netherlands) supplied with gas from precision regulators (RS components), and controlled by a computer (Elonex PT-5120/l) with a D to A converter (Amplicon PC24). This computer was supplied with data from the data acquisition computer. Custom written software calculated a rolling mean of the end-tidal O_2 and CO_2 from the last n breaths, where n could be adjusted between 1 and 10, and adjusted the mass flow controllers so that the inspired concentrations of the O_2 and CO_2 were the same as this mean end-tidal value. This caused a gradual decrease in inspired O_2 and concomitant increase in inspired CO_2. The value of n was adjusted so that a fall in S_PO_2 of 6% and an increase in end-tidal PCO_2 ($P_{ET}CO_2$) of 1 kPa occurred over 1-min. Sighing or swallowing cause sudden changes in the end-tidal concentrations, so breaths which differed from the target value by more than 5% were ignored. A pulse oximeter using an ear probe (Ohmeda 3700 set to an averaging time of 2 s, Ohmeda, Helsinki, Finland) and ECG (HP 78351A) were recorded throughout the study. We observed the patients carefully as well as monitored the EEG (A2000, Aspect Medical Systems, Newton, MA) for any evidence of sleep.

On both study occasions the patients first inhaled a normoxic gas mixture ($F_i = 0{\cdot}21$) for at least 2 minutes until ventilation was stable. Next, one to three combined ramp-like hypoxic/hypercapnic stimuli (see above, duration 1–2 min) were administered. Subsequently the inspired oxygen fraction was increased ($F_i = 0{\cdot}3$) and another one to three O_2/CO_2 stimuli (duration 1–2 min) applied. Each run was separated by at least two minutes of steady-state ventilation. If the baseline S_PO_2 was less than 95%, the inspired oxygen was increased ($F_i > 0{\cdot}3$) at the beginning of the study to increase the S_PO_2 to a value > 95%, and 3 to 6 stimuli were applied.

After the respiratory study was completed, venous blood was sampled and stored for assays of morphine (MOR), morphine-3-glucuronide (M3G), morphine 6 glucuronide (M6G) by HPLC,[121] and for C-reactive protein (CRP) measurement using the FPIA method on an Abbott FLX appara-

Table 1. Patient characteristics, types of surgery and baseline parameters in the initially recruited group of 40 patients

Age (years)	66 (53, 68)	Heart rate (beats/min)	78	(67, 87)
Female/male ratio	16/24	–CRP (mg/dl)	17·6	(9·4, 24·0)
Type's of surgery:		–Morphine (nM)	34	(12, 86)
–Abdominal aorta reconstruction	10	–M6G (nM)	29	(19, 54)
–Bowel surgery	11	–M3G (nM)	526	(250, 767)
–Liver surgery	6	S_PO_2 (%)	93	(92, 95)
–Whipple procedure	5	Ventilation (L/min)	9·6	(8·0, 11·1)
–Gastrectomy	4	*RR* (breaths/min)	15	(13, 19)
–Other abdominal procedures	3	V_T (ml)	613	(532, 762)
Length of stay in HDU (days)	2 (2, 3)	$P_{ET}CO_2$ (kPa)	5·3	(4·4, 6·3)
BIS	97 (95, 98)	$P_{ET}O_2$ (kPa)	13·3	(11·7, 15·7)

Values are median (25, 75 % quartiles); CRP, C-reactive protein; HDU, high dependency unit.

tus. Morphine and its metabolites were measured after leaving the high dependency unit only, CRP values were measured on both test occasions.

Data Analysis

Baseline parameters were averaged over one minute at the start of the measurements but prior to any change in inspired gas concentrations. The ventilatory response to the combined hypoxic/hypercapnic stimulus was analyzed using a non-parametric approach. Initially, we performed a linear regression of $\dot{V}_e$ on $P_{ET}CO_2$ on the linear part of the $\dot{V}_e$-CO_2 response (as judged by the eye). Next, the resultant slope (G) was divided by the measured drop in S_PO_2. A delay in S_PO_2 was taken into account because of the instrumentation and physiological delays.[182] This yielded the value S. However, due to the fact that we applied ramps in inspired gas concentration (end-tidal gas values and S_PO_2 were outcome parameters), especially in runs in which the inspired oxygen fraction was increased, no decrease in S_PO_2 occurred or the decrease was 4 % or less. In these cases we decided not to divide G by the drop in S_PO_2 and perform the statistical analysis on G rather than S.

Comparisons were made by non-parametric analysis (Kruskal-Wallis and Wilcoxon tests). Linear regression analysis was used to examine the relationships between variables (Sigmaplot 2001 for Windows, SPSS Inc.). P-values $< 0{\cdot}05$ were considered significant. All values are expressed as median (25, 75 % quartiles).

RESULTS

A flow chart of the data acquisition and analysis is given in figure 1. Initially a total of 40 patients were recruited and tested (table 1). Only 26 patients returned for a second session (table 2). The ventilatory responses in seven of these 26 were so irregular or unreliable that an analysis of the data was not possible. In eight other subjects additional inspired oxygen was given prior to the application of the respiratory stimuli. Although all subjects completed the studies without major side effects, some of them did feel uncomfortable during the studies. We consider this the main reason for the

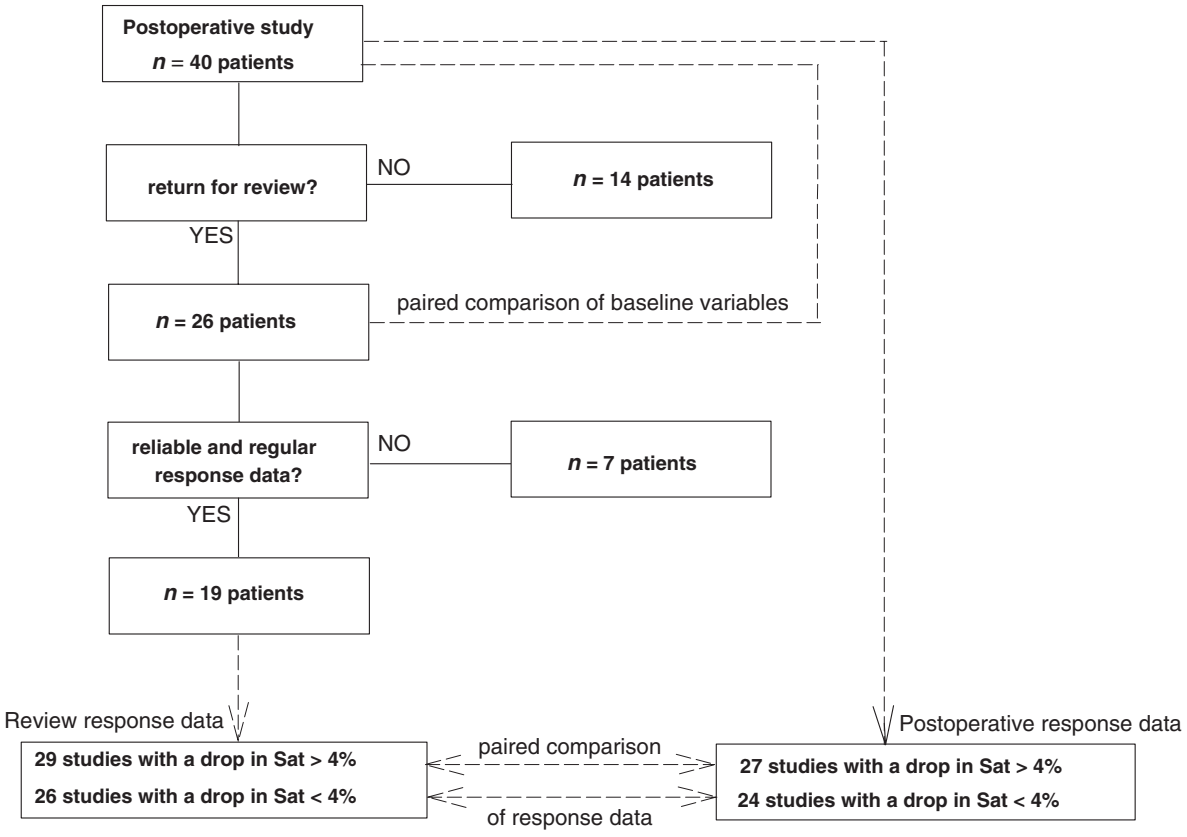

Figure 1. Flow chart of the data acquisition and data analysis of baseline variables and response data sets with and without drop in saturations.

rather disappointing return rate (26/40) and large number of curves that could not be analyzed (all curves in 7/26 patients). At the end of the study, response data from 19 patients were included in the analysis (48%).

In the initial studies, we noticed in none of the 40 subjects any subjective or EEG-related signs of sleep. Baseline parameters and blood concentrations of CRP, morphine and its metabolites are given in table 1. Note the large range of values (coefficients of variation were 78% (CRP), 149% (MOR), 70% (M3G) and 71% (M3G)). The variation in hospital $P_{ET}CO_2$ values but in none of the other variables could be partly explained by the plasma morphine concentration ($r^2 = 0{\cdot}34$, $P < 0{\cdot}05$). CRP, M6G and M3G values did not correlate significantly with any of the measured baseline variables.

After surgery and intensive care, patients showed evident signs of respiratory depression relative to the values obtained 6 to 8 weeks after hospital discharge (table 2), with greater $P_{ET}CO_2$ values, lower S_PO_2's, lower tidal volumes and lower $\dot{V}_e$ levels (18 patients had greater $\dot{V}_e$ levels on review). Although respiratory rate did not differ between the two test occasions, analysis of the pattern of breathing revealed that the duration of inspiration was 1·3 (1·1, 1·5) s in postoperative patients, while on return for review this value was significantly longer (1·6 (1·5, 1·9) s, $P < 0{\cdot}001$). The duration of expiration was similar in postoperative and review studies (postoperative 2·7 (1·9, 3·0) s *versus*

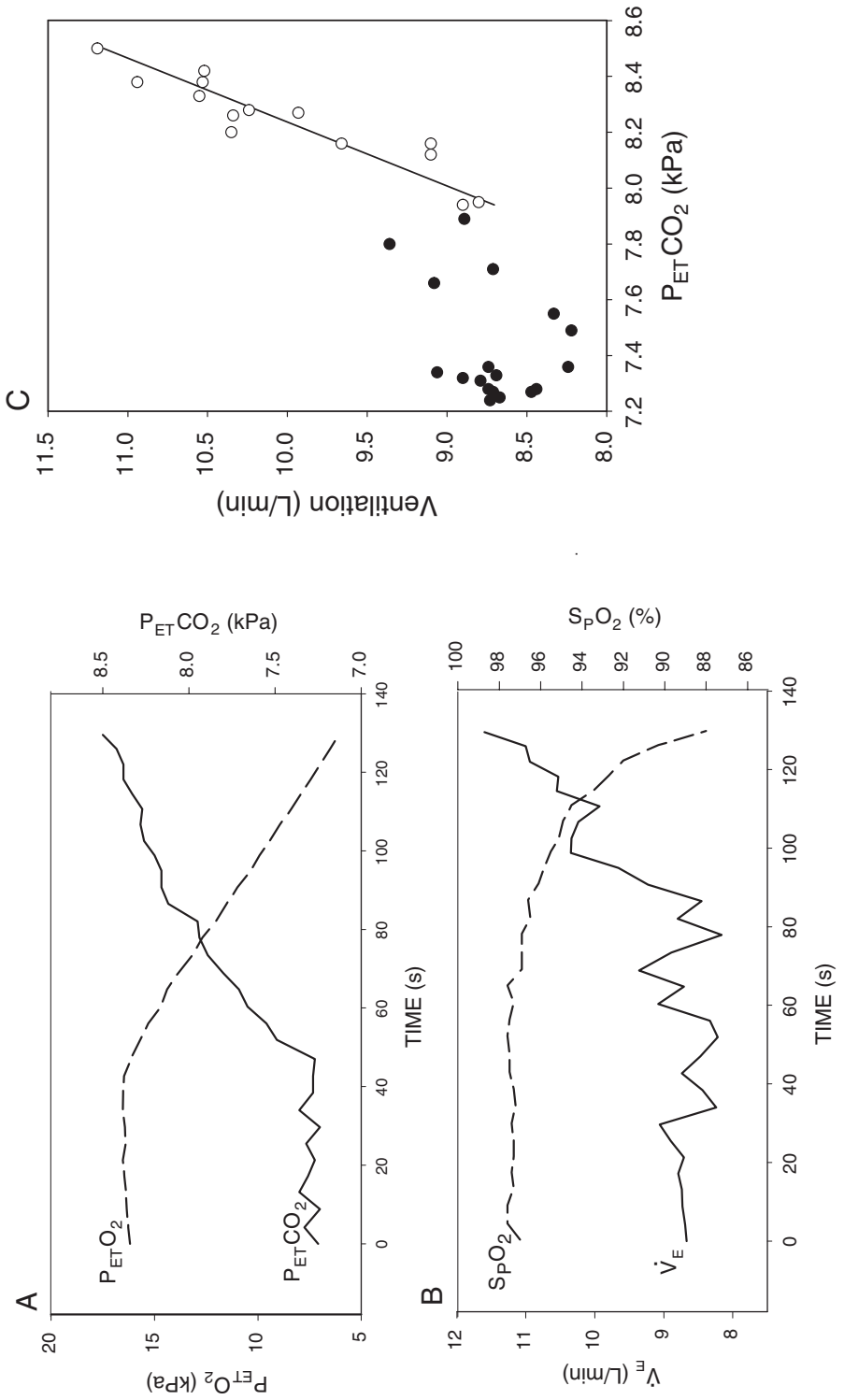

Figure 2. Example of the combined hypoxic/hypercapnic stimulus (A) and resultant changes in ventilation $\dot{V}_e$ and O_2-Hb saturation (S_PO_2) (B) of one subject. On the right (C), a plot of $P_{ET}CO_2$ *versus* $\dot{V}_e$ and the linear regression on the linear part of the curve. Open symbols denote date points used in the regression analysis. The slope of the response curve (*i.e.*, parameter G, which equals 4·4 L·min^{-1}·kPa^{-1}) was subsequently divided by the drop in S_PO_2 (see diagram B) of 11% (S = 0·4 L·min^{-1}·kPa^{-1}·%$^{-1}$).

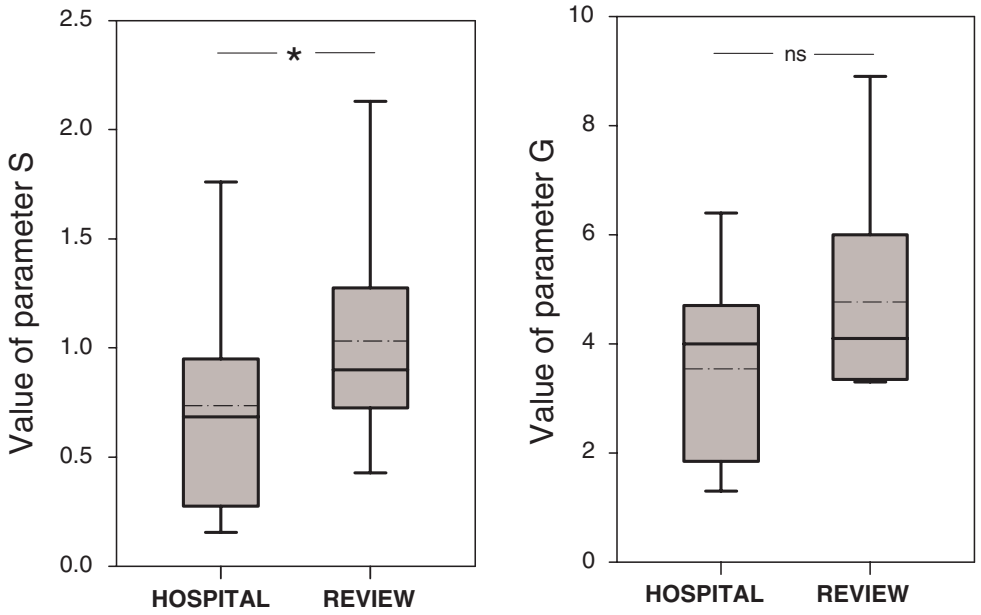

Figure 3. Box plots of the values of parameters S (left) and G (right). Values depicted are median (continuous lines), mean (dashed lines), 25 and 75% quartiles (top and bottom of boxes) and 10 and 90% quartiles (error bars) in data obtained postoperatively (hospital) and on review (6 to 8 weeks post hospital discharge) $*$ $P < 0{\cdot}02$; ns not significantly different (Kruskal-Wallis test).

review 2·4 (2·1, 2·8) s, ns).

An example of an O_2/CO_2 stimulus and resultant ventilatory response of one subject is given in figure 2. In 19 patients, a total of 27 responses with a fall in $S_PO_2 > 4\%$ and 24 with a fall $< 4\%$ were obtained after surgery and intensive care. On review the respective number of studies was 29 and 26. Values of the changes in S_PO_2 and $P_{ET}CO_2$ are given in table 3. On review, respiratory responses to an increase in CO_2 and decrease in S_PO_2 were about 25% greater than those obtained after surgery (S hospital = 0·69 (0·30, 0·85) $L{\cdot}min^{-1}{\cdot}kPa^{-1}{\cdot}\%^{-1}$ *versus* review = 0·90 (0·80, 1·20) $L{\cdot}min^{-1}{\cdot}kPa^{-1}{\cdot}\%^{-1}$, $P < 0{\cdot}02$; fig. 3), while no difference was observed for the responses to an increase in CO_2 with little to no change in S_PO_2 (G hospital = 4·0 (1·9, 4·7) L/min per kPa *versus* review = 4·1 (3·4, 5·0) L/min per kPa, $P = 0{\cdot}09$; fig. 3).

The distribution of values for C reactive protein in the ward and on return for review (table 2) show that the patients had a considerable inflammatory response at the time of discharge from the ward, which had returned to normal when they attended for review. We observed no correlation between CRP, morphine or its metabolites and degree of respiratory depression as determined from the ventilatory response to hypercapnia ± hypoxia (ventilatory depression expressed as the proportion of the responses obtained at follow up (G(hospital)/G(review) and S(hospital)/S(review)).

Table 2. Hospital *versus* review baseline variables in 26 patients

	Hospital data		Review data		*P*-value*
CRP (mg/dl)	18·6	(7·0, 21·0)	0·9	(0·0, 2·2)	< 0·001
Morphine (nM)	32	(19, 84)	—		
M6G (nM)	29	(21, 54)	—		
M3G (nM)	580	(300, 760)	—		
BIS	96	(95, 98)	97	(95, 98)	ns
$\dot{V}_e$ (L/min)	10·4	(8·0, 11·2)	10·6	(8·3, 12·6)	= 0·04
RR (breaths/min)	15	(13, 10)	16	(14, 18)	ns
V_T (ml)	629	(534, 817)	691	(611, 854)	< 0·05
$P_{ET}CO_2$ (kPa)	5·3	(4·0, 6·3)	4·7	(4·2, 5·1)	< 0·02
$P_{ET}O_2$ (kPa)	13·7	(11·9, 17·1)	14·1	(13·5, 14·7)	ns
S_PO_2 (%)	93	(92, 94)	97	(95, 98)	< 0·001
Heart rate (beats/min)	76	(66, 85)	74	(69, 88)	ns

Values are median (25, 75 % quartiles); ∗ Student-*t*-tests; ns = not-significantly different; See legend of table 1 for explanation of abbreviations.

Table 3. Median values of the changes in oxygen saturation (S_PO_2) and end-tidal CO_2 concentrations ($P_{ET}CO_2$) observed at the end of O_2 and CO_2 ramps in hospital and review studies. Data are grouped according to the fall in S_PO_2.

	n	ΔS_PO_2 (%)	$\Delta P_{ET}CO_2$ (kPa)
hospital $\Delta S_PO_2 > 4$ %	29	8·0 (6·1, 8·8)	0·8 (0·7, 1·0)
hospital $\Delta S_PO_2 < 4$ %	26	2·8 (1·4, 3·5)	1·0 (0·9, 1·1)
review $\Delta S_PO_2 > 4$ %	27	7·0 (5·0, 10·3)	1·1 (0·9, 1·3)
review $\Delta S_PO_2 < 4$ %	24	0·7 (0·5, 1·1)	1·0 (0·9, 1·1)

Values are median (25, 75 % quartiles). *n* is the number of runs.

DISCUSSION

In this study we compared respiratory variables and ventilatory pseudo-rebreathing responses in patients after abdominal surgery and intensive care and these same patients six to eight weeks after discharge from the hospital. The stimuli we used were intended to mimic changes in arterial oxygen saturation and CO_2 concentrations that occur once gas exchange has stopped due to upper airway obstruction. Due to the particular making of these stimuli (we used inspired control rather than end-tidal control of gas concentrations) a drop in saturation > 4% did not always occur, especially not when the study started with an increased inspired O_2 fraction. The oxygen reserve in the lungs and reduced oxygen metabolism are among the most likely causes for the absence in saturation fall in these patients during pseudo-rebreathing. Both kinds of stimuli do occur clinically in patients that develop upper airway obstruction for the same reasons as in our study. During upper airway obstruction, patients on oxygen de-

velop often high arterial CO_2 levels without any desaturations for many minutes, while patients that breathe air develop concomitant hypercapnia and hypoxemia.[152]

Because of our study design (see fig. 1) each patient served as its own control. Initially but not on review, all patients showed elevated C-reactive protein levels, a sign of inflammatory response (table 2).[85] We observed that relative to review, respiratory depression was modest in postoperative patients: $P_{ET}CO_2$ was 11% greater, the ventilatory response to a CO_2 stimulus and drop in oxygen > 4% was about 25% reduced. No difference was observed in the ventilatory response to a CO_2 stimulus when saturation did not fall > 4%, although an evident trend towards postoperative depression is visible in the data (fig. 3). While the low S_PO_2 value after surgery may be an indicator of reduced ventilatory drive, it must be remembered that oxygen saturation reflects the efficacy of gas exchange in the lungs and is not a measure of ventilation. The reduced values of S_PO_2 (~93%) may further be caused by atelactasis, a reduction in cardiac output, and/or increased oxygen metabolism.

The large number of patients that did not return for a review session and the relatively large number of data runs that could not be analyzed due to breathing instabilities may have under/overestimated the effect of surgery and analgesia on the response data. The median values of the O_2/CO_2 responses with and without fall in S_PO_2 in the 14 subjects that did not return for review were 0·61 (0·33, 1·1) $L \cdot min^{-1} \cdot kPa^{-1} \cdot \%^{-1}$ and 3·9 (2·4, 4·2) L/min per kPa, respectively. These values are not different from the 19 subjects that were included in the paired comparison. Hence we do not believe that the low return rate and sometimes poor data quality did influence our results significantly. Poor quality and increased variability of responses, relative to responses obtained in healthy volunteers, is inherent to the collection of clinical respiratory data. The large variability in the postoperative data may have been one of the reasons for not finding a significant effect on G between hospital and review (fig. 3). A *post-hoc* power analysis revealed that at this level of variability at least 30 patients were needed to get a significant 25% difference between studies.

Taken into account the complexity of the stimulus and resultant responses (see ref. 38 on the difficulties in the interpretation of CO_2 pseudo-rebreathing responses), we felt that it was necessary to develop a non-parametric method of describing the ventilatory response to the simultaneous hypoxic/hypercapnic stimulus. However, this non-parametric method will require some normalization by the level of the stimulus since the degree of hypercapnia and/or desaturation was not identical in all subjects and runs. In contrast to the gains of the peripheral and central chemoreflex loops as determined from single CO_2 steps (which represent the $\dot{V}_e$-CO_2 sensitivity of the peripheral and central chemoreceptors),[36,38] one has to be cautious in assigning physiological to G or S in our analysis. However, since the drop in S_PO_2 > 4% at the background of mild hypercapnia must have stimulated the carotid bodies,[45] we believe that S in contrast to G incorporates respiratory responsiveness mediated *via* the peripheral chemoreflex loop (part of which may be O_2-CO_2 interaction at the carotid bodies).[45]

We observed a difference in $P_{ET}CO_2$ of 0·6 kPa between the hospital and review visits. A similar value was observed in healthy volunteers who were without pain or inflamma-

tion and had similar estimated plasma levels of morphine.[43] We relate the increase in $P_{ET}CO_2$ in both studies to the respiratory depressant effect of morphine. Furthermore, in postoperative patients respiratory muscle function is often impaired due to a decrease in phrenic motoneuron output, which may be (vagal) reflex related to minimize irritation of the peritoneum after abdominal surgery.[213] This may be the cause of the reduced tidal volume we observed after surgery. The M6G levels were relatively low and most probably did not contribute to the respiratory effects of morphine. M6G concentrations > 300 nM are required for significant respiratory effect.* Our finding that S was depressed while G remained unaffected suggests that the peripheral chemoreflex loop was affected more than the central chemoreflex loop in our group of postoperative patients. This observation is in agreement with an earlier observation that the ventilatory response to a hypercapnic/hypoxic stimulus is affected at lower anesthetic and opioid concentrations that the response to a CO_2 stimulus when no fall in S_PO_2 is allowed.†

A Comparison with Volunteer Data

The depressant effect of morphine on respiration in healthy volunteers is well documented. For example, 0·1 mg/kg morphine bolus dose, followed by 30 μg/kg per h continuous infusion (median steady-state morphine plasma levels estimated to be > 100 nM),[174] caused sex-dependent respiratory depression with about 50% depression of the ventilatory response to CO_2 steps in female volunteers and no effect on the step response in male volunteers but a parallel shift of the response slope to greater $P_{ET}CO_2$ values.[43] In another study, 0·07 and 0·20 mg/kg iv morphine depressed the ventilatory response to a ramp increase in $P_{ET}CO_2$ by 40% and 50%, respectively.[24] Although care has to be taken in comparing patient data with volunteer data and plasma morphine concentrations were considerably higher in some of the volunteer studies (see above), our results suggest that depression in postoperative patients on morphine was significantly less than depression observed in volunteers on morphine.[24,43] This is not surprising taken into account the fact that respiration in perioperative patients is related to the balance between stimulation from pain, stress and activated chemoreflexes and depression resulting from sedation, the direct effect of analgesics and anaesthetics on respiratory neurones and the effect of surgery (see above). In our study depression of ventilatory responses occurred due to morphine (via its effect on μ-opioid receptors at central and peripheral sites),[6,44,171] while stimulation of the responses may have occurred due to pain,[21,23,172] stress, inflammation and discomfort. Interestingly, pain may both cause respiratory depression (patients that change their pattern of breathing to minimize diaphragmatic descent; the reduced inspiratory times may be the relection of such a mechanism (table 2)),[213] or stimulate breathing, often but not always *via* chemoreflex-independent mechanisms.[21,23,172]

*Unpublished observation.

†See *Chapter 6*.

Clinical Considerations

Postoperative patients on opioid analgesics titrated to effect, seldom require intervention for apneic or periodic breathing. However, several studies showed frequent occurrence of upper airway obstruction and hypoxic episodes related and unrelated to upper airway obstruction in both awake and sleep states.[61,66,155,156,189] We did not measure sleep-related breathing in our patients. But there is no reason to doubt that these patients did not experience upper similar airway patency problems and hypoxic events like those patients reported in the literature. Whether the mild to moderate depression of the ventilatory control system as observed in our group of patients plays some causative role in the occurrence of upper airway obstruction remains unknown but is plausible.[152] A more important question is whether the ventilatory responses set at the restoration of blood gases in between episodes of upper airway obstruction remain sufficiently effective. The mild reduction in response data observed in our patients seems to suggest that this may indeed be the case. However, the ample data showing sometimes severe nocturnal hypoxemia after major abdominal surgery, which in some studies remains unaffected by oxygen or nasal continuous positive airway pressure therapy, suggests the contrary.[66,189] Evidently, further studies on the effect of surgery and pain relief and their interaction on (hypoxia and CO_2 stimulated) breathing are required to improve our insight in this important part of postoperative patient care.

APPENDIX: *A Modeling Approach to the Data Analysis*

While a simultaneous ramp increase in $P_{ET}CO_2$ and a decrease in S_PO_2 provides a stimulus that is similar to clinical conditions (*e.g.*, airway partial obstruction), it does present some practical and theoretical problems with analysis. The physiological response to hypercapnia (at a constant saturation) is a linear increase in ventilation arising from both peripheral and central chemoreceptors.[36] As saturation is decreased (at a constant $P_{ET}CO_2$) there is also a linear increase in ventilation arising from stimulation of the peripheral chemoreceptors.[45] The interaction between saturation and CO_2 has been expressed as the change in the slope of the hypercapnic response for a decrease in saturation. The dynamics of both these response (hypoxic and hypercapnic) have generally been modeled with differential equations and given an appropriate input all these gains can be determined (along with the associate time delays and time constants).[40] With some reasonable assumptions, it is possible to modify our previously used two compartment dynamic CO_2 model used for parameter estimation and to obtain estimates of physiological parameters from this clinical data.

The relative slow changes in both the $P_{ET}CO_2$ and S_PO_2 does not provide an input that is 'persistently exciting' and the central and peripheral time constants cannot be estimated with any confidence. However, from past experience we can assume the peripheral time constant to be ~10 s and the central time constant to be ~120 s.[40] However, we can assume that the change in the saturation only effects the peripheral input. This allows us to modify our parameter estimation program to assume that the central and peripheral inputs are known signals (S_C and S_P) and the steady state ventilation is determined by a central and peripheral gain on these two signals:

$$S_C = P_{ET}CO_2$$
$$S_P = (\alpha \cdot S_PO_2 + \beta) \cdot P_{ET}CO_2$$
$$\dot{V}_i = G_C \cdot (S_C - B_k) + G_P \cdot (S_P - B_k) + C \cdot t$$

The saturation data needs to be time shifted (and interpolated) to match the breath-by-breath CO_2 and ventilation data. B_k is the so called apneic threshold and a trend term, C, is also included. These

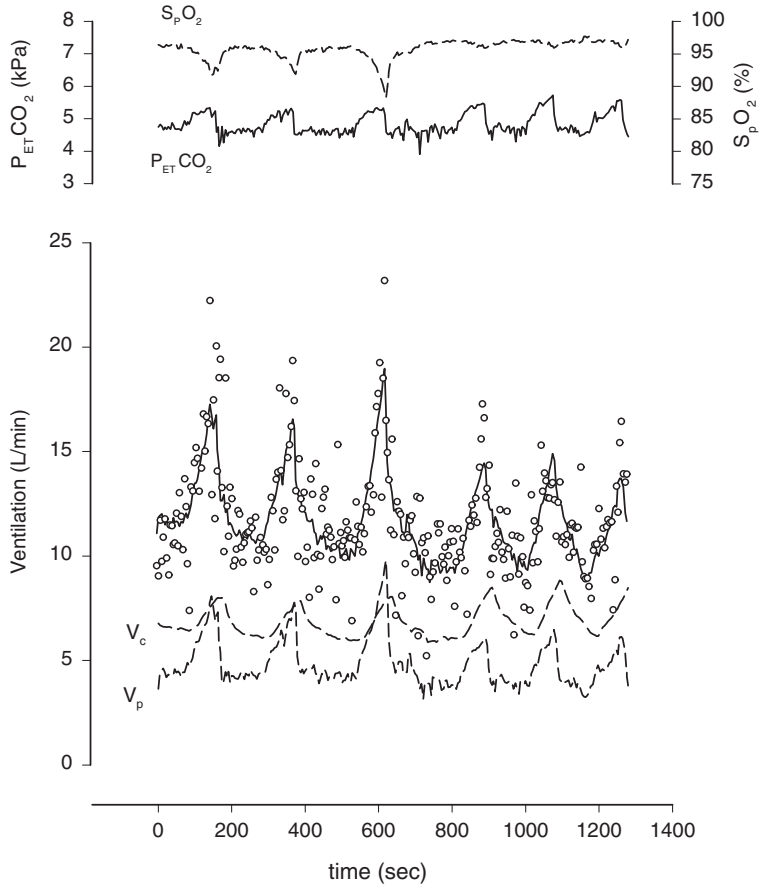

Figure 4. Example of a model fit in six sequential ramps in hypoxia/hypercapnia (initial three ramps) and hypercapnia. The data are from a patient returning for review. The upper panel shows the end-tidal CO_2 and saturation waveforms. The bottom panel shows the measured $\dot{V}_e$ (open circles) and the model fit (the solid line going through the circles). The bottom two curves show the estimated central ($\dot{V}_c$) and peripheral ($\dot{V}_p$) components. Note that the peripheral component responds much faster and is altered by the level of saturation.

equations represent the steady state form of the model and in the parameter estimation program first order dynamics, with the assumed time constants given above, are included on each of the signals. The factors α and β are scaling factors that are chosen such that the value of the estimated G_P is of similar magnitude to that estimated in step hypercapnic experiments. The values chosen result in the hypoxic factor equal to 1 for 98% saturation and equal to 2 at 80% saturation. Note that these values are arbitrary in that they function only as scale factors and do not effect the final parameters estimated from the data set. Thus for this model the total CO_2 gain (change in ventilation for a change in CO_2 at 100% saturation) is:

$$G_T = G_C + G_P \cdot (100 \cdot \alpha + \beta)$$

and the percentage increase in the total gain for a 10% decrease in saturation:

$$\%\Delta G_T = \frac{10 \cdot \alpha}{G_T} \cdot 100\%$$

Figure 4 illustrates the curve fit of this model utilizing the whole data set which included 6 ramps, the first three are combined O_2/CO_2 stimuli, the last three hypercapnic stimuli. The data set was obtained

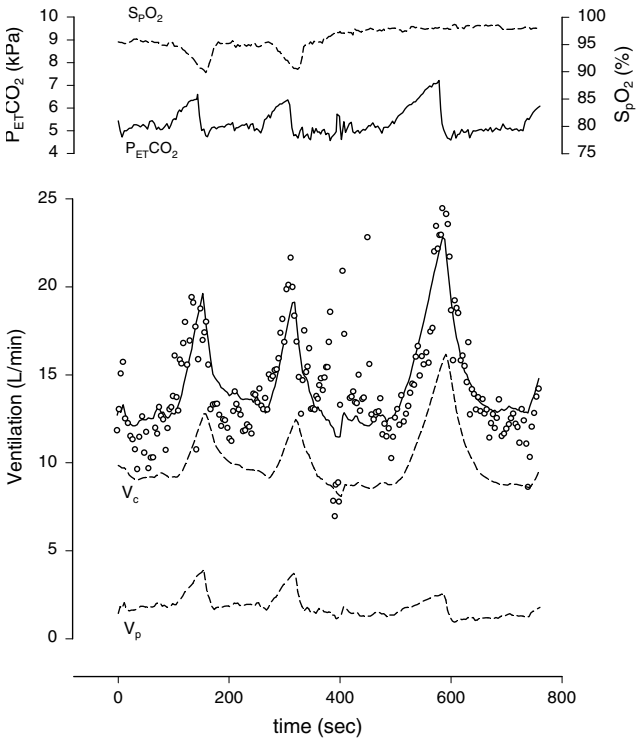

Figure 5. Example of a model fit in three sequential ramps in hypoxia/hypercapnia (first two ramps) and hypercapnia. The data are from a patient after surgery and intensive care. See Figure 4 for explanation of the symbols.

in a patient returning for review. Due to the absence of a hypoxic stimulus, the lasts three ramps elicit a much smaller peripheral signal. Note that the large increase in $\dot{V}_e$ for the third ramp is apparently due to the deeper desaturation and the resulting larger peripheral component is seen in the figure. The parameters estimated for this data set was a total CO_2 gain of $7{\cdot}05$ L min^{-1} kPa^{-1} and a change in total hypercapnic gain with a 10% decrease in saturation of 21%. These values are comparable to those found in normal subjects.

Figure 5 illustrates another fit, this time to three ramps, two combined hypoxic/hypercapnic ramps and one hypercapnic one. This data set was obtained in a patient upon discharge from the high dependency unit. Note that for the third ramp the increase in CO_2 was greater than for the first two CO_2 ramps and even though there was no of desaturation, the resulting ventilatory increase was larger. This indicates that there is only a small amount of hypoxic-hypercapnic interaction. In fact, when this data set was curve fitted, we found that the total CO_2 gain was $7{\cdot}15$ L min^{-1} kPa^{-1} but the change in total gain with a 10% decrease in saturation was only 6%.

This dynamic parameter estimation technique requires a data set with little ventilatory instability or noise. As can be seen by the ventilation instability between the second and third ramps in figure 5, there can be significant ventilatory alterations that cannot be modeled as resulting from changes in CO_2 or saturation. Unfortunately, due to the clinical nature of our data sets, these types of ventilation changes were frequent and prevented us from applying this model to most of the data.

Summary and Conclusions