7 Response surface modeling of remifentanil–propofol interaction on cardiorespiratory control and bispectral index

THE COMBINED administration of opioids and anesthetics for induction and maintenance of anesthesia is common practice. The anesthetic is given to lose consciousness, prevent awareness and reduce movement responses, the opioid is given to suppress somatic, stress and adrenergic responses to surgical stimulation. An important advantage of combining an opioid and an anesthetic is the synergistic increase in these desired effects, with consequently the need for less drugs to attain the goal of adequate anesthesia relative to the amount of drug needed when only a single agent (*i.e.*, an anesthetic) is given.[110] Since this is not only true for patients that are intubated and ventilated but also for patients that maintain their own breathing, for example during 'monitored anesthesia care', it is of interest to address the issue of the effect of drug combinations on respiration. While it is known that anesthesia induces many 'side effects' it is acknowledged that respiratory depression is potentially life-threatening.[123] We therefore studied the effect of the opioid remifentanil and intravenous anesthetic propofol on the cardiorespiratory control. This combination of drugs is frequently used in patients under monitored anesthesia care for minor (without additional regional anesthesia) and major (with additional regional anesthesia) surgery. Knowledge on the quantitative and qualitative (additive *versus* synergistic) nature of their interaction is clinically important and may lead to specific dosing regimens aimed at the titration of sedation/analgesia *versus* respiratory effect.

To study the remifentanil-propofol interaction, we made use of the technique of response surface modeling.[82,89,129,191] This technique allows the observation of the concentration-effect relation among infinite combinations of remifentanil and propofol over the whole surface area in three dimensional space. In *Chapter 6* we made successful use of this technique to quantify the interactive effects of sevoflurane and alfentanil on cardiorespiratory control.

METHODS

Subjects

Twenty-two healthy male volunteers (aged 19–25 yr) participated in the protocol after approval was obtained from the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, 2300 RC leiden, The Netherlands). Oral and written consent was obtained from all volunteers.

Table 1. Results of the bootstrap based model selection

	MODEL																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	non-linear*	interaction**
Resting $\dot{V}_I$	0	0	0	1	1	68	**531**	81	74	46	3	145	12	5	33	929	998
$\dot{V}_{55}$	0	28	32	1	22	0	**431**	37	0	268	0	128	1	0	47	1000	912
Resting $P_{ET}CO_2$	53	29	56	11	41	130	**357**	150	35	68	10	31	13	7	9	717	810
S	22	81	16	24	16	3	**357**	18	4	261	1	106	2	3	86	974	841
Heart rate	156	**240**	133	121	20	69	210	7	8	0	6	10	0	1	0	769	311
MAP	**664**	3	13	6	11	140	81	9	18	2	3	23	4	11	1	193	292

Analysis was performed on 1000 data sets based on the original 22 studies created by the bootstrap method;
The values are the number of times that specific model was chosen using Akaike's Information-theoretic Criterion (*AIC*);
Bold numbers are the most frequent chosen ones. The corresponding model was used in the analysis of the original data set.
$*$ and $**$ Total number of times that a non-linear (models 2–5 + 7–10 + 12–15) or a non-additive interaction model (models 6–15) was chosen;
$\dot{V}_{55}$ is ventilation at a fixed $P_{ET}CO_2$ of 55 mmHg; S is the slope of the hypercapnic ventilatory response.
MAP is mean arterial pressure.

Apparatus
After arrival at the laboratory, an intravenous catheter was inserted in the left antecubital vein (for drug infusion) and an arterial line was placed in the right radial artery (for blood sampling). Subsequently, electrodes for EEG monitoring (BisSensor, Aspect Medical Systems, Newton, MA) were placed on the head as specified by the manufacturer and the subjects rested for 20 to 30 min. Next a face mask was applied over the mouth and nose and data collection started.

See METHODS section *Apparatus* of *Chapter 2* for a description of the procedure and apparatus. The EEG was recorded using an Aspect A-2000 EEG monitor (software version 3·3). The monitor computed the bispectral index (BIS) over 2-s epochs. We averaged the BIS values over 1 min-intervals.

Study Design
Resting ventilation and $P_{ET}CO_2$ (*i.e.*, without any inspired CO_2), blood pressure, heart rate, BIS and the ventilatory response to hypercapnia were measured before and during infusion of remifentanil, propofol and the combined infusion of these agents. Initially control (*i.e.* without the administration of any agent) values were obtained. Next the infusion of remifentanil was started and cardiorespiratory and BIS parameter values were obtained at steady state blood target concentrations. After this set of studies, the infusion was terminated and the subject rested for 1 hour. Next the infusion of propofol was started and cardiorespiratory and BIS parameter values were obtained at steady state blood target concentrations. Subsequently parameter values were obtained during the combined administration of remifentanil and propofol. In some subjects two to three studies were performed at different propofol-remifentanil combinations. The subjects were randomly assigned to a fixed scheme of target concentrations of remifentanil and propofol. The scheme was designed to ensure that, over the applied dose ranges, evenly spread data points were obtained.

The Ventilatory Response to Hypercapnia
The ventilatory response to CO_2 was obtained by using the 'dynamic end-tidal forcing' technique.[38–40] After assessment of resting variables, 3 to 8 elevations in $P_{ET}CO_2$ were applied to obtain data points for the steady-state ventilatory response. The elevations varied from 3 to 19 mmHg. The elevated $P_{ET}CO_2$ readings lasted at least 8 min. When on-line analysis revealed that a ventilatory steady-state had not been reached, the duration of hypercapnia was extended. The order of elevations was arbitrarily chosen. All hypercapnic studies were performed at a background of moderate hyperoxia ($P_{ET}O_2$ 120 mmHg).

The elevated $P_{ET}CO_2$ and the corresponding $\dot{V}_i$ breath-to-breath data were averaged over 10-breaths. Data points were obtained at the end of the $P_{ET}CO_2$ elevation. This procedure yielded 3 to 8 steady-state data points. We expressed ventilation as a linear function of $P_{ET}CO_2$: $\dot{V}_i = S\ (P_{ET}CO_2 - B_k)$, where S is the ventilatory CO_2 sensitivity and B_k the extrapolated $P_{ET}CO_2$ at zero $\dot{V}_i$. Parameters S and B_k were determined by linear regression of $\dot{V}_i$ on $P_{ET}CO_2$.

Remifentanil and Propofol Administration, Blood Sampling and Assays.
Propofol and remifentanil were administered using target controlled infusion (TCI) systems. For propofol we used a Psion palm-top computer (London, England) programmed with a three compartment propofol pharmacokinetic (PK) data set to control a Becton Dickinson infusion pump (St. Etienne, France).[70,79] For remifentanil we used a custom build infusion pump which

Table 2. Population Pharmacodynamic Estimates

	$\dot{V}_I$ L/min	$\dot{V}_{55}$ L/min	$P_{ET}CO_2$ mmHg	S L min^{-1} mmHg^{-1}	MAP mmHg	HR min^{-1}	BIS
Baseline value	9·4 ± 0·3	31·4 ± 1·5	41·2 ± 0·1	1·87 ± 0·01	93·0 ± 1·6	64·1 ± 1·8	96·4 ± 0·4
95% c.i.	8·8 – 10·0	28·4 – 34·4	41·0 – 41·4	1·84 – 1·89	89·8 – 96·2	60·4 – 67·7	95·6 – 97·2
λ remifentanil (%)	27·7 ± 3·5	57·7 ± 3·5	15·4 ± 1·2	20·0 ± 5·4	3·7 ± 1·1	10·6 ± 2·7	–
95% c.i.	20·7 – 34·7	51·0 – 65·0	13·0 – 17·8	9·2 – 30·8	1·5 – 5·9	5·2 – 16·0	
λ propofol (%)	12·6 ± 3·3	44·3 ± 3·9	4·2 ± 0·9	51·0 ± 4·5	9·9 ± 1·8	11·9 ± 3·1	18·9 ± 1·4
95% c.i.	6·0 – 19·2	37·0 – 52·0	2·4 – 6·0	42·0 – 60·0	6·3 – 13·5	5·7 – 18·1	16·1 – 21·7
I_{max}	1·9 ± 0·2	1·2 ± 0·1	1·3 ± 0·2	1·3 ± 0·1	1	1	—
95% c.i.	1·5 – 2·3	1·04 - 1·38	0·9 – 1·7	1·1 – 1·5			
Q_{max}	0·5	0·5	0·5	0·5	0·5	0·5	—
γ	0·5 ± 0·1	0·4 ± 0·05	0·7 ± 0·1	0·4 ± 0·1	1	0·3 ± 0·1	1
95% c.i.	0·3 – 0·7	0·27 – 0·47	0·5 – 0·9	0·2 – 0·6		0·1 – 0·5	
$C_{50,R}$ (ng/ml)	3·3	0·7	5·4	8·6	13·5	142·0	—
$C_{50,P}$ (μg/ml)	15·8	1·4	34·4	1·0	5·1	98·1	2·7

Values are population estimate ± SE and 95% confidence interval (c.i.) as derived from the NONMEM analysis;
λ is the % decrease at 1 ng/ml remifentanil or 1 μg/ml propofol;
$C_{50,R}$'s and $C_{50,P}$'s are extrapolated values;
$\dot{V}_I$ is resting ventilation; $\dot{V}_{55}$ is ventilation at a fixed $P_{ET}CO_2$ of 55 mmHg;
S is the slope of the hypercapnic ventilatory respons; MAP is mean arterial pressure;
I_{max} and Q_{max} are interaction parameters (see text): I_{max} values > 1 indicate synergy, = 1 additivity.

was programmed with a remifentanil pharmacokinetic data set (Remifusor, University of Glasgow, Glasgow).[128] These systems allow a specified target plasma concentration of remifentanil and propofol to be rapidly achieved and maintained. Hypercapnic studies were performed ~10 min after blood remifentanil and propofol concentrations had reached their target levels. Since this equals >5-10 times the remifentanil and propofol blood–effect-site equilibration half-lifes, we assumed that brain and blood remifentanil and propofol concentrations were in equilibrium.

Before and after changes in target drug concentrations, arterial blood samples for determination of remifentanil and propofol concentrations were collected. Blood for propofol determination was collected in syringes containing potassium oxalate. Propofol concentrations were determined by reverse-phase high performance liquid chromatography .[132] Samples for the determination of blood remifentanil concentrations were collected into tubes containing sodium heparin and immediately transferred to tubes containing 50% citric acid (to inactivate esterases) before freezing at –20°C. The assay method is based on tandem mass spectrometry detection.[10]

Response Surface Modeling

Analysis was performed on the following parameters: resting inspired minute ventilation ($\dot{V}_I$) and $P_{ET}CO_2$ (*i.e.*, without any inspired CO_2), slope of the hypercapnic ventilatory response (S), ventilation at a fixed $P_{ET}CO_2$ of 55 mmHg ($\dot{V}_{55}$, calculated from S and B_K), mean arterial pressure (MAP), heart rate (HR) and BIS. The basis of the pharmacodynamic (PD) model is similar to the model described in *Chapter 6* The single-drug concentration (C) – effect (E) relationship is given by

$$E(C) = E_0 \cdot \left\{1 - \left(\frac{C}{C_{50}}\right)^{\gamma} \cdot \frac{1}{2}\right\} \tag{1}$$

where E_0 is the baseline drug effect, C_{50} the value of C which gives 50% depression, and γ a nonlinearity parameter; notice that the model is linear when $\gamma = 1$. A straightforward extension for two concomitantly administered drugs (C_r = remifentanil concentration, C_p = propofol concentration) is obtained by respecting Loewe additivity:[13]

$$E(C_r, C_p) = E_0 \cdot \left\{1 - \left[\frac{C_r}{C_{50,r}} + \frac{C_p}{C_{50,p}}\right]^{\gamma} \cdot \frac{1}{2}\right\} \tag{2}$$

Note that isoboles in the C_r – C_p plane are straight lines, irrespective of the value of γ. Deviations from additivity can be modeled as:

$$E(C_r, C_p) = E_0 \cdot \left\{1 - \left[\frac{C_r}{C_{50,r}} + \frac{C_p}{C_{50,p}}\right]^{\gamma(Q)} \cdot \frac{1}{2} \cdot I(Q)\right\} \tag{3}$$

with $I(Q)$ a smooth function (spline) with a parameter denoting maximum interaction $I_{\max}$ at $I(Q_{\max})$ and $Q = U_r/(U_r + U_p)$, $U_r = C_r/C_{50,r}$, $U_p = C_p/C_{50,p}$. To limit the number of parameters $\gamma(Q)$ was either a constant or a linear function going from γ_r at $Q = 1$ to γ_p at $Q = 0$. Since the concentration ranges used in the study for most parameters lie below the C_{50}'s, these parameters will be poorly estimated leading to wide asymmetric confidence intervals. A remedy would be to use C_{10}'s or C_{25}'s but one doesn't know the optimal parameters beforehand. In fact, it is better to use parameters that are centered according to the study design:

$$E(C_r, C_p) = E_0 \cdot \left\{1 - \left[\frac{C_r}{C_{h,r}} \cdot \lambda_r^{1/\gamma(Q)} + \frac{C_p}{C_{h,p}} \cdot \lambda_p^{1/\gamma(Q)}\right]^{\gamma(Q)} \cdot I(Q)\right\} \tag{4}$$

where $C_{h,r}$ and $C_{h,p}$ the values of C_r and C_p midway in the measured concentrations range, and Q redefined to be $Q = U_r/(U_r + U_p)$, $U_r = C_r/C_{h,r}$, $U_p = C_p/C_{h,p}$; λ_r and λ_p denote the degree of depression from E_0 when $C_r = C_{h,r}$ and $C_p = 0$ and vice versa, respectively. For parameter PCO_2, which increases from E_0, the model used was the same as eq. (4), except the minus sign was replaced by a plus sign.

Parameter Estimation and Model Selection
The above model has the following parameters to be estimated: E_0, λ_r, λ_p, $I_{\max}$, $Q_{\max}$, γ_r and γ_p. The following situations are of special interest:

- $I_{\max} = 1$, $Q_{\max} = 0.5$ denoting additivity,
- $I_{\max} \neq 1$, $Q_{\max} = 0.5$ denoting symmetric interaction,
- $I_{\max} \neq 1$, $Q_{\max} \neq 0.5$ denoting asymmetric interaction.

Notice that when $Q_{\max} = 0.5$ we could use Minto's parabolic function of Q instead of the spline $I(Q)$.[129] Furthermore, when two drugs are pharmacodynamically equivalent apart from a difference in potency, we would expect a symmetric interaction (since Q is based on normalized concentrations). For each of the above three cases, there are five situations that describe (non)linearity:

- $\gamma_r = \gamma_p = 1$ denoting linearity,
- $\gamma_r = \gamma_p \neq 1$ denoting nonlinearity described by one parameter,
- $\gamma_r \neq 1$ and $\gamma_p = 1$ denoting nonlinearity for drug R and linearity for P,
- $\gamma_r = 1$ and $\gamma_p \neq 1$ denoting linearity for drug R and nonlinearity for P,
- $\gamma_r \neq 1$ and $\gamma_p \neq 1$ denoting nonlinearity described by two parameters.

This results in a total of fifteen models to be investigated (see fig. 1). NONMEM was used to estimate the parameter values.[135] Since the models are non-nested, the likelihood ratio criterion is not applicable so Akaike's Information-theoretic Criterion was used instead:[135] $AIC = -2LL + 2P$, where $-2LL$ is the minimum value of the objective function calculated by NONMEM and P denotes the number of parameters. The model with the lowest AIC is considered 'best'. The population analysis was done under the assumption of lognormally distributed model parameters and constant relative (except for PCO_2 where it was assumed to be additive) normally distributed intra-individual error.

Model Stability Assessment using the Bootstrap
When, according to AIC criterion, a model is chosen for a certain effect parameter, that choice is not associated with a measure of confidence in that model. One would like to be more certain that the choice is not an artifact of particular individuals in the current data set, and that when a new data set would be obtained, the same model would be chosen. A way to generate surrogate data sets is given by the method of the bootstrap.[69] Basically, a bootstrap data set is formed by selecting, with replacement, the data from individuals until a set is obtained with the same total number of individuals. This data set is then subject to the same fitting procedure, and by repeating the process N times, N parameter estimates are obtained with N selections of one

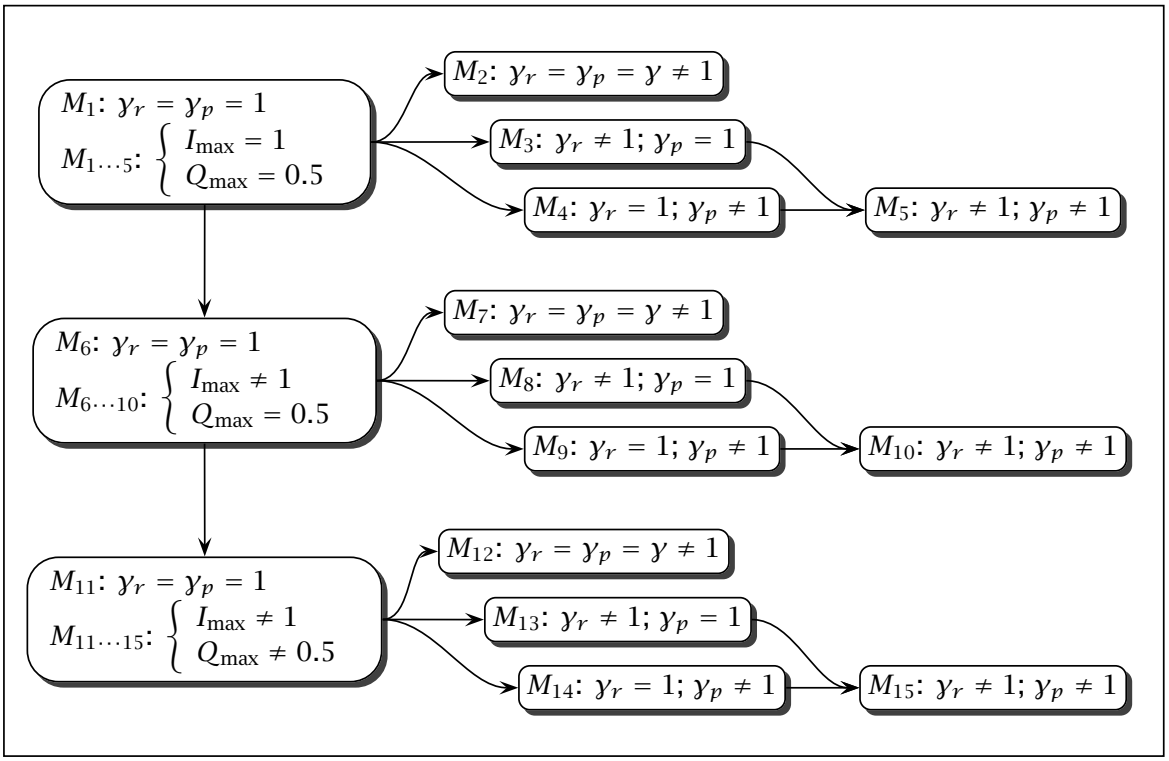

Figure 1. Schematic representation of the 15 different pharmacodynamic model (M) possibilities. Models 1 to 5: additive interaction between propofol and remifentanil; models 5 to 10: non-additive interactions at a value of $Q_{\max}$ equal to 0.5; models 11 to 15: non-additive interactions at a value of $Q_{\max}$ not equal to 0.5. Models 2, 7 and 12: linear relationships between propofol and remifentanil concentrations and effect; models 3, 8 and 14: a linear relationship between propofol concentration and effect, a non-linear relationship between remifentanil concentration and effect; models 4, 9 and 14: a non-linear relationship between propofol concentration and effect, a linear relationship between remifentanil concentration and effect. Models 5, 10 and 15: Non-linear relationships between propofol and remifentanil concentrations and effect.

of the fifteen models. From the parameter estimates confidence intervals and histograms can be constructed. The impact of constraining certain parameters to fixed values, and therefore identifiability, can then be studied visually. The number of times a model is selected is a measure of our confidence in the model.

The bootstrap procedure was implemented in a C++ program that generates bootstrap data sets, NONMEM control files with appropriately fixed parameters, runs NONMEM and reads back the estimated parameter values and the minimum value of the objective function. When NONMEM returned an error status regarding parameter boundary problems (despite carefully chosen initial conditions and boundaries) or rounding errors the model that was fitted was deemed to be not supported by the data. This, in principle, gives a bias towards the simpler models. Furthermore, to have a feasible procedure with respect to computer time, we opted not to investigate all possibilities for the statistical model. Initially, intra-individual variability was assumed to be present only on parameters E_0, λ_r, and λ_p. When the number of times the corresponding variance was estimated to be negligible exceeded $N/2$, this variability term was removed and the bootstrap redone. Confidence intervals were obtained in the traditional way

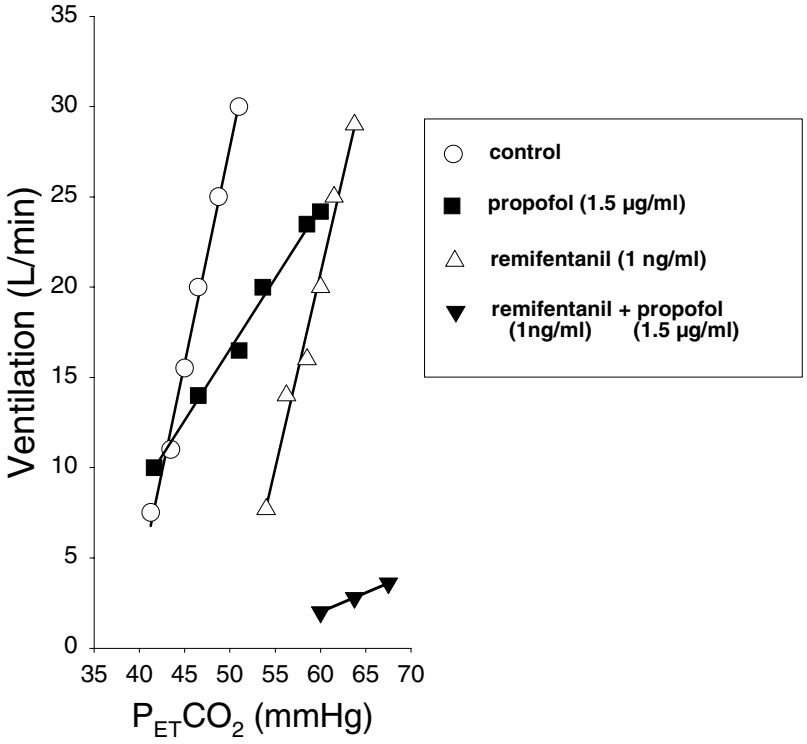

Figure 2. Four ventilatory carbon dioxide response curves of one subject. The control response had a slope of 2·4 L/min per mmHg. While propofol decreased the slope to 0·8 L/min per mmHg, remifentanil caused a parallel shift to higher PCO_2 values of about 12 mmHg (slope = 2·2 L/min per mmHg). The combined administration yielded both a reduction in slope of the response curve (slope = 0·2 L/min per mmHg) and a rightward shift of about 20 mmHg. These observations suggest synergy on the slope of hypercapnic response and ventilation at a fixed $P_{ET}CO_2$.

(i.e., estimate ± 1.96·SE) and the bootstrap BC_a (biascorrected and accelerated) method.[69]

RESULTS

All 22 subjects completed the protocol without major side effects. A total of 94 responses were obtained at different drug combinations. The range of the measured arterial remifentanil was 0-2 ng/ml. For propofol all measured concentrations were in the range of 0-2·0 μg/ml except one (2·6 μg/ml). Consequently $C_{h,r}$ and $C_{h,p}$ were set to 1 ng/ml and 1 μg/ml, respectively, in the pharmacodynamic model

A typical example of respiratory studies in one subject is given in figure 2. Its shows the control response (no drugs given) with a slope of 2·4 L min^{-1} mmHg^{-1}, the effects of 1·5 μg/ml propofol (a 66% reduction of the slope of the $\dot{V}_i$-CO_2 response to 0·8 L min^{-1} mmHg^{-1}) and 1 ng/ml remifentanil (a parallel shift of the response curve with a slope of 2·2 L· min^{-1}·mmHg^{-1}) alone, and the effect of that drug combination, which was greater than the sum of the effects of either drug alone (a > 90% depression of the

slope to 0·2 L min^{-1} mmHg^{-1}).

In table 1 the results of the bootstrap based model selection are given. For all respiratory parameters model 7 was best fitted to analyze the data (*i.e.*, non-linear relationship between drugs and effect, synergistic interaction, Q_{max} = 0·5, fig. 1). The population estimates ± SE and 95% confidence intervals, as derived from the NONMEM analysis, of the response surfaces are given in table 2 and for resting $\dot{V}_i$, resting $P_{ET}CO_2$, $\dot{V}_{55}$ and S in figures 3 and 4. At 1 ng/ml and 1 μg/ml, remifentanil and propofol caused ~28% and 13% depression of resting ventilation, respectively. Combining propofol and remifentanil at these same blood concentrations caused 58% depression (eqn. 4), indicating the synergistic nature of the interaction. Similar observations were made for resting $P_{ET}CO_2$, $\dot{V}_{55}$ and S, although the synergistic interaction strength was less (I_{max} resting $\dot{V}_i$ = 1·9 *versus* I_{max} resting $P_{ET}CO_2$, $\dot{V}_{55}$ and S = 1·2–1·3). At the combined infusion of 1 μg/ml propofol and 1 ng/ml remifentanil the depression of $\dot{V}_{55}$ was 82% (eqn. 4); the corresponding values for resting $P_{ET}CO_2$ and S were 23% and 69%, respectively.

To get an indication of the spread of data points over the surface and of the goodness of fit, we give bubble plots which show the distance of individual measured data points from the population surface (*i.e.*, residuals; figs. 3–5). These plots show evenly spread data over the tested dose ranges and the absence of overt misfits. The values of baseline MAP and HR indicate that the subjects were free of agitation or stress during the studies (table 2). The effects remifentanil and propofol on MAP and HR rate were not as remarkable as their effects on the respiratory parameters: depression at 1 ng/ml remifentanil and 1 μg/ml propofol ranged from 4 to 12% (table 2). The effect of the combination was expected from the concentration-response curve of the individual agents (*i.e.* additive interaction or I_{max} = 1, linear dose-effect relationship for MAP, non-linear relationship for HR, table 1).

The BIS was unable to unearth any sedative effect of remifentanil over the dose range studied by us (inert interaction, fig. 5). Furthermore, the effect of propofol on the BIS was independent of the remifentanil concentration. The propofol-BIS relationship was linear with 19% depression of the BIS at 1 μg/ml plasma level.

DISCUSSION

The main findings of our study are as follows: (1) Over the dose range tested, remifentanil (0–2 ng/ml) and propofol (0–2.6 μg/ml) caused a dose dependent depression of respiration, as observed by an increase in resting $P_{ET}CO_2$ and decreases in resting $\dot{V}_i$, slope of the $\dot{V}_i$-CO_2 response and ventilation at a fixed $P_{ET}CO_2$ of 55 mmHg; (2) While remifentanil shifts the $\dot{V}_i$-CO_2 response curve in a parallel fashion to higher $P_{ET}CO_2$ levels, propofol reduces the slope of the response rather than shifting its position (pivot point at resting $\dot{V}_i$); (3) When combined, the depressant effect of propofol and remifentanil on resting $\dot{V}_i$, resting $P_{ET}CO_2$, S and $\dot{V}_{55}$ is synergistic, with the greatest synergy observed for resting $\dot{V}_i$; (3) The depressant effect of remifentanil and propofol on blood pressure and heart rate is modest, when given separately; when combined their depres-

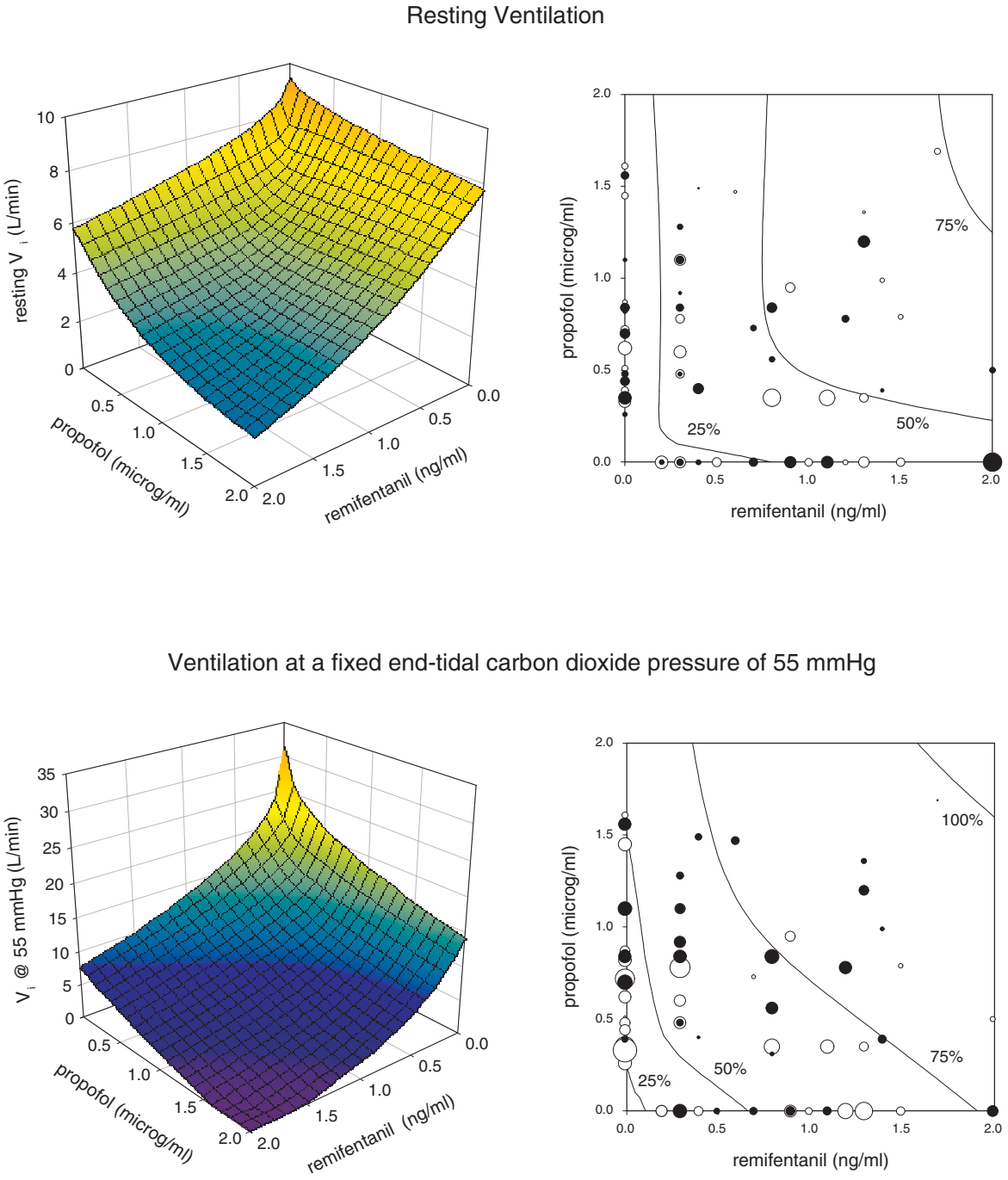

Figure 3. *TOP.* **Left: Response surface modeling of the interaction of remifentanil and propofol on resting $\dot{V}_i$. The population response surface shows that the propofol-remifentanil interaction is synergistic (I(Q) = 1·9 ± 0·2). Note further that the dose-response relationships between drugs and effect was not linear (for both drugs γ = 0·5 ± 0·1). Right: Individual data points and 25, 50 and 75% isoboles. Open circles denote data point above the surface, closed circles below the surface (control data points not shown). The area of the circles is proportional to the distance from that data point to the surface.** *BOTTOM.* **Left: Response surface modeling of the interaction of remifentanil and propofol on $\dot{V}_i$ at a fixed $P_{ET}CO_2$ of 55 mmHg. The population response surface shows that the propofol-remifentanil interaction is synergistic (I(Q) = 1·2 ± 0·1). The dose-response relationships was not linear (for both drugs γ = 0·4 ± 0·1). The model predicted apnea at several combinations of propofol and remifentanil,** *e.g.*, **1·6 ng/ml remifentanil and 2·0 μg/ml propofol or 2·0 ng/ml remifentanil and 1·6 μg/ml propofol. Right: Individual data points and 25, 50, 75 and 100% isoboles.**

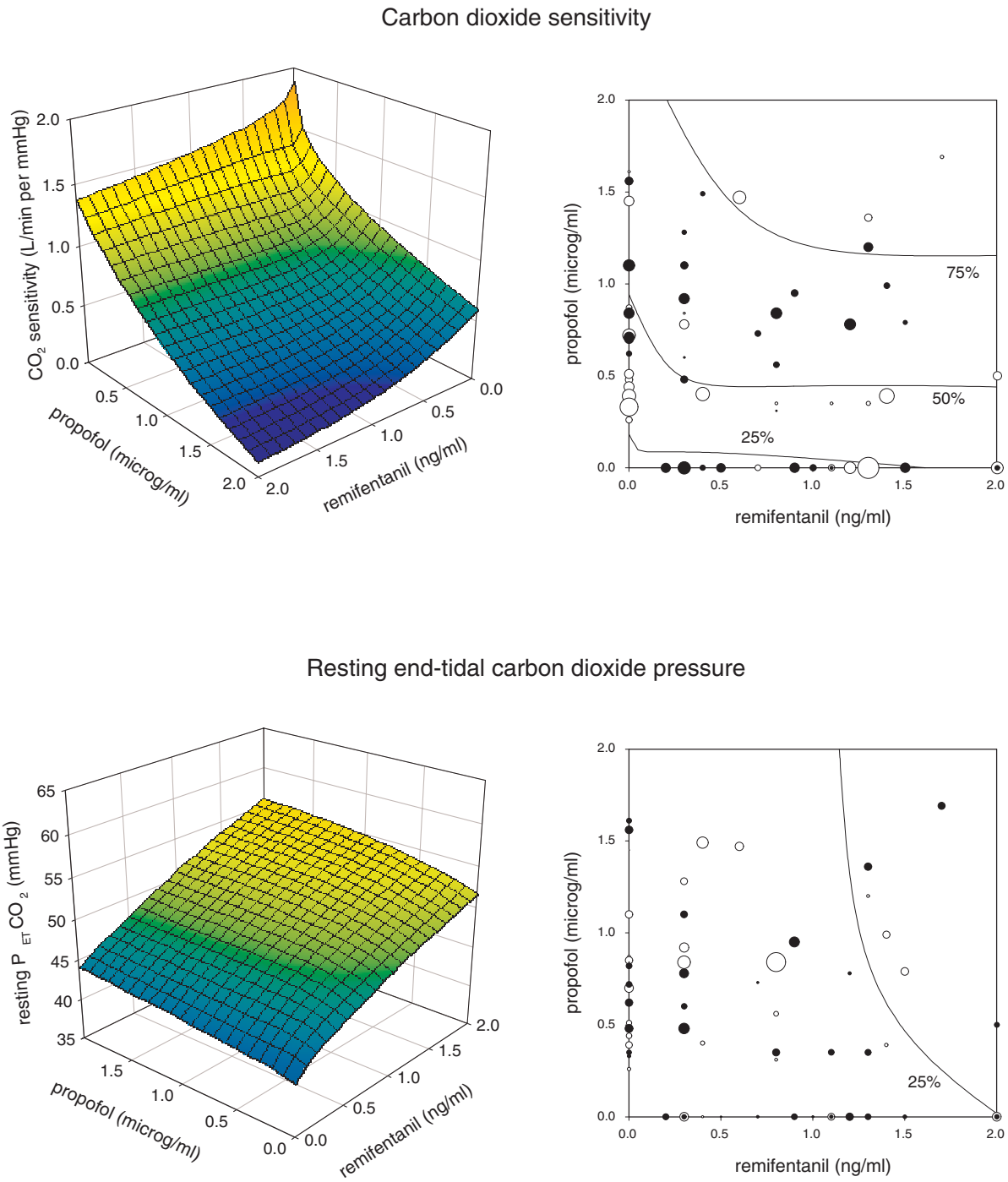

Figure 4. *TOP.* **Left: Response surface modeling of the interaction of remifentanil and propofol on the slope of the $\dot{V}_I$ response to CO_2 (CO_2 sensitivity). The population response surface shows that the propofol-remifentanil interaction is synergistic (I(Q) = 1·3 ± 0·1). The dose-response relationships was not linear (for both drugs γ = 0·4 ± 0·1). Note that the effect on slope was predominantly a propofol effect and to a lesser extend a remifentanil effect. Right: Individual data points and 25, 50 and 75% isoboles. Open circles denote data point above the surface, closed circles below the surface. The area of the circles is proportional to the distance from that data point to the surface area.** *BOTTOM.* **Left: Response surface modeling of the interaction of remifentanil and propofol on resting $P_{ET}CO_2$. The population response surface shows that the propofol-remifentanil interaction is synergistic (I(Q) = 1·3 ± 0·2). The dose-response relationships was not linear (for both drugs γ = 0·7 ± 0·1). Note that the x- and y-axes are different from the other response surface plots with the control point now facing the reader. Right: Individual data points and 25% isobole.**

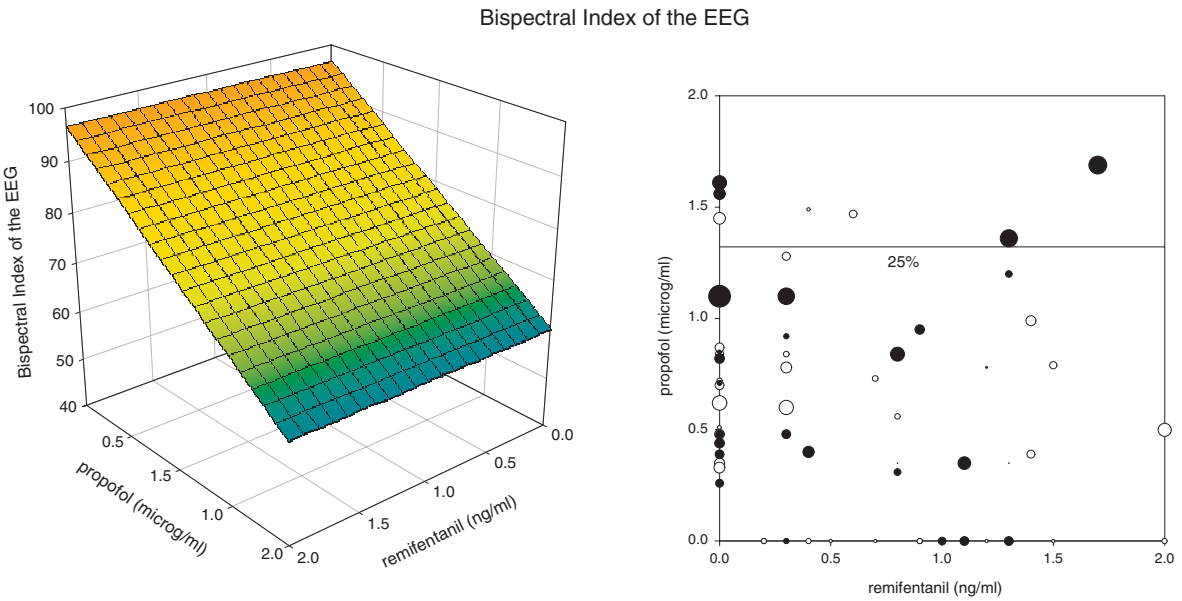

Figure 5. *LEFT:* **Response surface modeling of the interaction of remifentanil and propofol on the bispectral index of the EEG (BIS). The population response surface shows that the propofol-remifentanil interaction is inert since remifentanil had no effet on BIS irrespective of the propofol concentrations. Over this dose range, propofol causes a linear decrease in BIS with a 25% decrease occurring at 1·4 μg/ml.** *RIGHT:* **Individual data points and 25,% isobole. Open circles denote data point above the surface, closed circles denote data points below the surface. The area of the circles is proportional to the distance from that data point to the surface area.**

sant effect is additive; (4) The BIS is sensitive to propofol but not to remifentanil, even when these agents are combined.

Pharmacodynamic Modeling

The pharmacodynamic model. In common with the study described in *Chapter 6* the pharmacodynamic model used by us is based on the 'Richards model' which for one drug is written as:[157] $f(x) = \alpha \cdot [(1 + \delta \cdot x^{\gamma})^{1/\delta}]^{-1}$. By fixing $\delta = -1$ (*cf.* eqn. 1) a model is obtained which may be non-linear ($\gamma \neq 1$) or linear ($\gamma = 1$). The advantages of this approach have been discussed in *Chapter 6*. In short, in contrast to classical pharmacodynamic models, such as the inhibitory sigmoid E_{MAX} model, our model predicts apnea at and above certain drug concentrations; it predicts negative responses above certain drug concentrations;* and finally, linear respiratory dose-responses may occur over limited dose ranges.[48] Interaction was modeled as suggested by Minto *et al.*,[129] which is based on the following two ideas: (1) the combination of two drugs should be regarded as one new drug with its own properties, and (2) that these properties depend only on the concentration ratio Q. As before, interaction was defined by the function $I(Q)$, for which we chose a spline (for details see *Chapter 6*). Furthermore, the two drugs used in this study have dissimilar mechanisms of action so that we would not

*Negative responses may occur when testing the effect of opioids on the ventilatory response to hypoxia. See ref. 170 and *Chapter 6*.

expect their γ to be equal at equipotent concentrations. Therefore we also included the possibility of a linear $\gamma(Q)$. To our surprise $\gamma_r = \gamma_p = \gamma$ for all tested parameters.

Parameterization. Frequently, pharmacodynamic models incorporate C_{50}'s to describe and compare potencies. Since in our study the applied concentration ranges lie well below the C_{50}'s, these parameters are poorly estimated with wide and asymmetric confidence intervals. In order to overcome this problem we introduced the parameter λ which is the percentage depression at the concentration midway in the plasma concentration range (see eqn. 4).

Bootstrap Model Selection. The method of the bootstrap was applied here to assess the stability of the model selection based on *AIC*. Confidence in a model is then expressed as the number of times a model is chosen. Note that this confidence is not equivalent with the type I or type II error in traditional hypothesis testing. In the space of two nested models, however, the *AIC* is closely related to the type I error and the model selection percentage closely related to the power of the test.[178] When NONMEM produced an error message concerning boundary errors, the model that was tested was most probably overparameterized and would not be selected by *AIC* anyway.

Characteristics of Parameter Distributions. Parameter distributions can be estimated by constructing histograms of the estimated parameter values from the bootstrap runs. With the parameterization utilizing λ's, their distributions were neither wide nor skewed so that the confidence intervals (obtained from the NONMEN population estimates ± 1·96·SE, table 2) turned out to be equivalent with those obtained from the bootstrap parameter distributions. For example, for $\dot{V}_{55}$ the corresponding values are baseline value 29·0–34·0 L/min, λ_r 51·0–67·0%, λ_p 37·0–52·0%, $I_{\max}$ 1·08–1·39 and γ 0·22–0·50.

Parameter Values

The effects of 1 ng/ml remifentanil and 1 μg/ml propofol on resting $\dot{V}_i$ was considerably less than their effect on $\dot{V}_{55}$ (the ratio of λ's is 0·5 for remifentanil and 0·3 for propofol). This is not surprising taking into account the fact that while resting $\dot{V}_i$ is measured under closed-loop conditions and part of the respiratory depression is offset by the gradual increase in resting $P_{ET}CO_2$, $\dot{V}_{55}$ is measured under open-loop conditions and the pharmacokinetics and pharmacodynamic of CO_2 (and the effect the tested drugs have on CO_2 PK/PD) have been effectively removed. Recent studies indicate that C_{50} values obtained from studies using a fixed $P_{ET}CO_2$ input to the chemical control system and studies on the dynamic effect of drugs on resting ventilation, which do take into account the dynamics and kinetics of carbon dioxide, were of the same order of magnitude.[22] For example, the C_{50} of alfentanil for depression of ventilation at a raised fixed $P_{ET}CO_2$ is about 75 ng/ml,[†] while the C_{50} derived from resting ventilation (i.e., without any inspired CO_2) is 60 ng/ml.[22]

The extrapolated C_{50} values from this study correspond well with studies from the literature. For example, the remifentanil C_{50} of $\dot{V}_i$ at a raised and fixed $P_{ET}CO_2$ obtained from a single bolus of 0·5 μg/kg was of the same order of magnitude as our observa-

[†] see Chapter 6

tion (1·1 ng/ml *versus* 0·7 ng/ml in this study, table 2).[4] Note that in this latter study remifentanil concentrations were not measured but obtained from the literature. These C_{50} values are a factor of 10 smaller than those observed for changes in spectral edge frequency of the EEG,[128] and 4 to 5 times smaller than those observed for 50% probability of adequate anesthesia during abdominal surgery (in combination with 66% nitrous oxide).[65] These findings indicate the higher opioid sensitivity of CNS sites involved in ventilatory control compared to sites involved in behavioral state control and suppression of somatic and autonomic responses. Remifentanil is about 80–100 times more potent than alfentanil in depressing $\dot{V}_{55}$.‡ At present we are unaware of any previous respiratory PK/PD data for propofol.

Clinical Considerations

While response surface modeling provides a compact mathematical formulation for describing the interactions of two (or more) drugs, it can be difficult to translate this surface into a clinically useful interpretation. The isoboles (figs. 3–5) provide a horizontal 'cut' through the response surfaces, however, vertical cuts through the response surfaces may provide a more useful clinical graph. While remifentanil and propofol are often given at the same time to patients, they are not mixed together and infused at a constant ratio. General clinical use is for both drugs to be given at a constant rate (resulting in a steady state with constant plasma levels) and then one of the drugs adjusted up as needed for additional analgesia/sedation or down if less respiratory depression is important. The parameters of the response surface for resting $P_{ET}CO_2$ and ventilation can be used to predict how these important clinical variables will change with changing infusion rates. Since $P_{ET}CO_2$ is the more easily clinically monitored variable, figure 6 shows how $P_{ET}CO_2$ changes with the infusion rates. In the top panel, the increase in $P_{ET}CO_2$ with changes in propofol plasma concentration at constant remifentanil levels is shown, while the bottom panel shows the same for constant propofol concentration and remifentanil is adjusted. The non-linear shape of the response surface results in marked differences between these two figures. Figure 6 predicts that the $P_{ET}CO_2$ increases regularly with increasing remifentanil with some potentiation by the addition of propofol. However, the amount of propofol added does not change the amount of depression until higher levels of remifentanil are reached. These curves predict that while remifentanil causes hypercapnia, once beyond an initial additional rise in $P_{ET}CO_2$ when the propofol is started, there is little further respiratory depression as the propofol plasma level is increased. These graphs indicate that it might be safer to titrate the propofol dose with a constant remifentanil background if more or less sedation is needed, since there should be little change in the amount of respiratory depression, but if less respiratory depression is required, then the remifentanil would need to be reduced.

The above applies best to patients who maintain their breathing during anesthesia. In order to extrapolate our findings to postoperative patients, we plotted in figure 7 the

‡see *Chapter 6*

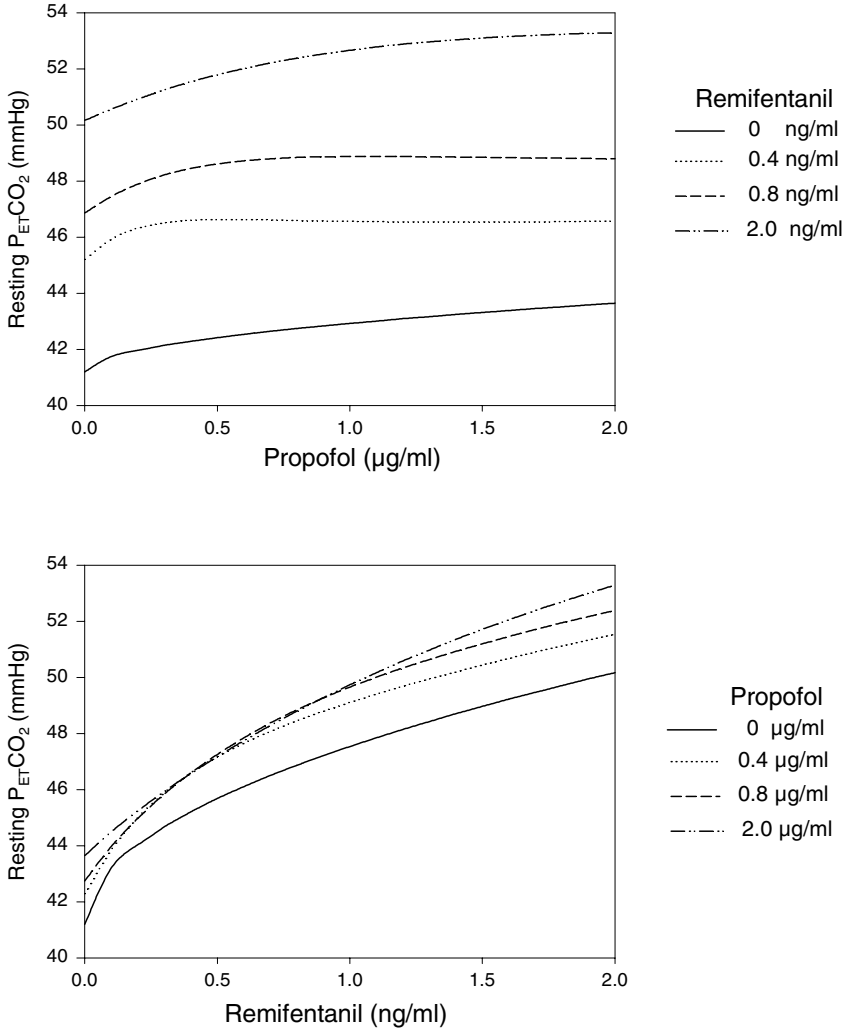

Figure 6. *TOP.* **The influence of the steady-state or effect-site propofol concentration on resting $P_{ET}CO_2$ at various constant remifentanil concentrations.** *BOTTOM.* **The influence of the steady-state or effect-site remifentanil concentration on resting $P_{ET}CO_2$ at various constant propofol concentrations. Changing remifentanil concentrations causes marked increases in resting end-tidal PCO_2, irrespective of the propofol concentration, while changes in propofol concentrations have less of an effect on resting $P_{ET}CO_2$, irrespective of the remifentanil concentrations.**

10–60% isoboles of increasing resting $P_{ET}CO_2$ with the isobole for 50% probability of regaining consciousness after general anesthesia for abdominal surgery (and the isobole for 50% probability of no somatic/autonomic response to surgical stimuli).[125] This plot shows (1) the synergistic interaction between propofol and remifentanil on the 50% probability to 'wake-up' after anesthesia (and thus shows in contrast to the bispectral index data (fig. 5) the sedative/hypnotic effect of remifentanil); (2) whether consciousness has been regained or not, ventilation improves best by reducing the remifentanil concentration (*i.e.*, the return of the wakefulness drive is of limited importance at least

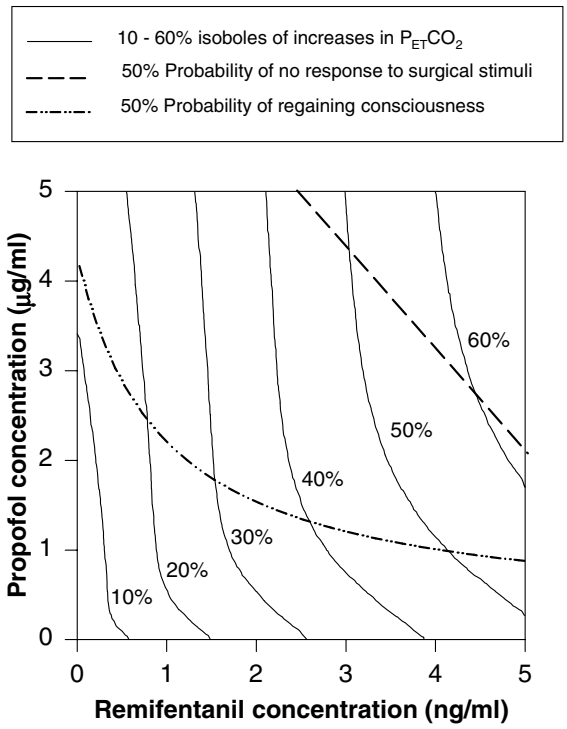

Figure 7. Comparison of isoboles of respiratory depression (10–60% isoboles for increases in $P_{ET}CO_2$, data from this study), consciousness and adequate anesthesia (50% probability lines for consciousness and adequate anesthesia in patients undergoing abdominal surgery, data from ref. 125).

when the subject is not stimulated or reminded to breathe); (3) without the addition of propofol, remifentanil concentrations up till 2 ng/ml cause only limited respiratory depression and may be applied for postoperative pain relief.

Because in our study ventilation and plasma drug levels were at steady state when data points were obtained we did not get information about the time-course of respiratory effects. Furthermore, especially for rapidly acting drugs, such as remifentanil and propofol, the degree of non-steady-state respiratory depression may be dependent on the rate of drug infusion. Further studies are needed to study the blood gas and $\dot{V}_i$ dynamics caused by different infusion schemes of opioids and anesthetics.

Pharmacological Considerations

In this study we tested two agents with distinct respiratory properties and mechanisms of action. The opioid remifentanil caused a parallel shift of the $\dot{V}_i$-CO_2 response towards higher PCO_2 values with little effect on the slope (fig. 2). On the other hand, the anesthetic/sedative propofol caused a reduction of the slope of the $\dot{V}_i$-CO_2 response curve (S) with little to no effect on the position of the curve at resting $P_{ET}CO_2$ values (fig. 2). We consider these effects typical respiratory effects of opioids and anesthetics/sedatives. The effect of the opioid is because of activation of μ-opioid receptors at sites involved

in ventilatory control (*e.g.*, the carotid bodies, the preBötzinger complex);[44] the effect of the anesthetic is most probably related to less specific mechanisms such as changes in the level of arousal/consciousness and consequently a reduction in input from sites in the CNS involved in behavioral-state control (*e.g.*, the cortex, brain stem reticular system) to the ventilatory control system in the brainstem. The observation that the slope of the $\dot{V}_i$-CO_2 response during sedation with propofol was reduced is in agreement with the finding that the slope of the morphine $\dot{V}_i$-CO_2 response is reduced by physiological sleep.[72] Previously, we observed large differences in the effect of i.v. morphine on the slope of the $\dot{V}_i$-CO_2 response in men and women.[43,171] with no effect of morphine on the slope in men but a large reduction in women. Taken into account the above, it would be appropriate to suggest that in our previous studies morphine produced greater sedation in women than in men and consequently greater effects on S in women. Indeed, in a recent study in which we assessed the effect of morphine's active metabolite, morphine-6-glucuronide (M6G), on the level of sedation using a numerical rating score, we found greater sedation in women than men while plasma M6G concentrations were equal (unpublished observation). Note however, that our suggestion do not exclude more fundamental sex differences in CNS responses to opioids such as sex differences in μ-opioid receptor density and affinity in regions involved in ventilatory control and pain response.[174]