International Society for Anaesthetic Pharmacology

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The Dose-Dependent Effect of S(+)-Ketamine on Cardiac Output in Healthy Volunteers and Complex Regional Pain Syndrome Type 1 Chronic Pain Patients

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BACKGROUND: Ketamine is used as an analgesic for treatment of acute and chronic pain. While ketamine has a stimulatory effect on the cardiovascular system, little is known about the concentration–effect relationship. We examined the effect of S(+)-ketamine on cardiac output in healthy volunteers and chronic pain patients using a pharmacokinetic–pharmacodynamic modeling approach.
METHODS: In 10 chronic pain patients (diagnosed with complex regional pain syndrome type 1 [CRPS1] with a mean age 43.2 ± 13 years, disease duration 8.4 years, range 1.1 to 21.7 years) and 12 healthy volunteers (21.3 ± 1.6 years), 7 increasing IV doses of S(+)-ketamine were given over 5 minutes at 20-minute intervals starting with 1.5 mg with 1.5-mg increments. Cardiac output (CO) was calculated from the arterial pressure curve obtained from an arterial catheter in the radial artery. Ketamine and norketamine plasma concentrations were measured. A novel pharmacokinetic–pharmacodynamic model was constructed to quantify the direct stimulatory effect of ketamine on CO and the following adaptation/inhibition.
RESULTS: Significant differences in pharmacokinetic estimates were observed between study groups with 15% and 40% larger S(+)-ketamine S(+)-norketamine concentrations in healthy volunteers compared to CRPS1 patients. S(+)-ketamine had a dose-dependent stimulatory effect on CO in patients and volunteers. After infusion an inhibitory effect on CO was observed. Pharmacodynamic model parameters did not differ between CRPS1 patients and healthy volunteers. The concentration of S(+)-ketamine causing a 1 L/min increase in CO was 243 ± 54 ng/mL with an onset/offset half-life of 1.3 ± 0.21 minutes. The inhibitory component was slow (time constant of 67.2 ± 17.0 minutes).
CONCLUSIONS: S(+)-ketamine pharmacokinetics but not pharmacodynamics differed between study populations, related to differences in disease state (CRPS1 or not) or age. The dose-dependent effect of S(+)-ketamine on CO was well described by the biphasic dynamic model. The effect of S(+)-ketamine on CO was similar between study groups with respect to its stimulatory and inhibitory components, despite group differences in age and health. (Anesth Analg 2012;115:536–46)

Ketamine, originally developed as an anesthetic, is increasingly used as an analgesic for treatment of acute pain in the perioperative setting and chronic pain in patients with complex regional pain syndrome type 1 (CRPS1) and cancer pain with and without neuropathic pain.[1–3] Indeed, various studies indicate that ketamine, the racemic mixture or the S(+)-enantiomer, is analgesic and in some studies in chronic pain patients even has a prolonged effect, i.e., the effect exceeds the duration of IV treatment.[3] An important disadvantage of ketamine treatment is its side effect profile.[3] The most significant side effects include nausea/vomiting, hallucinations/high feeling, and stimulatory cardiovascular effects (causing increases in systemic and pulmonary blood pressure, heart rate, and cardiac output [CO]).[3–5] Ketamine's effect on the cardiovascular system remains poorly studied especially in patients.[4,5] In the current study we examined the effects of the S(+)-ketamine enantiomer on CO in chronic pain patients with CRPS1 and healthy volunteers and correlated concentration to effect. Our approach allows the comparison between healthy, young subjects and the target population (chronic pain patients), often older and possibly with underlying diseases that may affect the interaction between ketamine and the cardiovascular system. For example, there are indications that the sympathetic system is involved in CRPS1.[6,7] We performed a pharmacokinetic (PK)–pharmacodynamic (PD)

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Accepted for publication February 29, 2012.

Funding: This study is partly funded by the TREND (Trauma Related Neuronal Dysfunction) organization (Delft, The Netherlands), a non-profit consortium of academic hospitals, technical research groups, and companies focused on the study of Complex Regional Pain Syndrome type 1.

The authors declare no conflict of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0b013e3182549 6f6

modeling study, which allows the assessment of between-groups differential effects of ketamine occurring at the PK or PD level or at both levels. We hypothesized that ketamine has a differential effect on CO in healthy volunteers and chronic pain CRPS1 patients, possibly related to differences in health.

We developed a novel PD model that considers ketamine's stimulatory effect on CO and counterregulatory (or depressant) effects on CO.[8] The latter effect causes an undershoot in CO (i.e., a transitory response in which the CO values are below baseline) after the termination of ketamine infusion. Next, we considered both measurement noise and dynamic noise (process noise) that enters through the dynamics of the system. Usually, PK/PD models allow interindividual variability of the structural model parameters and assume that the residual error (i.e., measurement noise) is uncorrelated. However, correlations between residuals may occur and as a consequence may lead to less reliable estimates of the structural model parameters.[9] Our model describes and quantifies both dynamic and measurement noise. By doing this the residuals related to measurement noise become uncorrelated.[9] Parameter estimation of the structural and noise model parameters was done by incorporation of the Kalman filter in the estimation algorithm.[10,11] The purpose of the Kalman filter is to get optimal estimates of model parameters from noisy data (random and correlated noise). It does so by performing a weighted averaging of model predictions and actual measurements and adopting model output values with best (i.e., most accurate) estimated uncertainty.[12]

METHODS

Subjects

Twelve healthy volunteers (6 men and 6 women; age >18 years; body mass index <28 kg/m^2) and 10 patients diagnosed with CRPS1 (all women; age >18 years) were recruited to participate in the study after approval of the protocol was obtained from the local Human Ethics Committee (Commissie Medische Ethiek, Leiden, The Netherlands). Written and oral informed consent were obtained before inclusion in the study. The subjects were instructed not to eat or drink for at least 6 hours before the study. The diagnosis of CRPS1 was based on the criteria of the International Association for the Study of Pain, which includes the following: the presence of an initiating noxious event or cause for immobilization; continuing pain, allodynia, or hyperalgesia; presence at some time of edema, changes in skin perfusion or abnormal sudomotor activity in the region where pain is felt; and exclusion of other conditions that could account for the pain and dysfunction. We excluded patients who had pain scores of 5 or less, used strong opioid medication (tramadol was allowed), were ages 17 years or less, were pregnant or lactating, had an increased intracranial pressure, or had a serious medical or psychiatric disease. Medications that were allowed were paracetamol, nonsteroid anti-inflammatory drugs, selective serotonin reuptake inhibitors, amitryptiline, and pregabalin or gabapentin.

S(+)-Ketamine Infusion, Blood Sampling, and CO Measurement

A venous line for drug infusion and an arterial line for blood sampling were placed in a brachial vein and the radial artery, respectively. In CRPS1 patients these lines were inserted preferentially in the nonaffected arm. The S(+)-ketamine infusion scheme was as follows: min 0 to 5: 0.02 mg/kg (given in 5 minutes); min 20 to 25: 0.04 mg/kg; min 40 to 45: 0.06 mg/kg; min 60 to 65: 0.08 mg/kg; min 80 to 85: 0.1 mg/kg; min 100 to 105: 0.12 mg/kg; and min 120 to 125: 0.15 mg/kg. Arterial blood sampling was performed at times t = 0, 5, 20, 25, 40, 45, 60, 65, 80, 85, 100, 105, 120, 125, 127, 130, 135, 140, 150, 160, 175, 190, 210, 230, 260, and 300 minutes. The analyses of S(+)-ketamine and its main metabolite S(+)-norketamine has been described.[13] In brief, 2 to 3 mL plasma was separated within 15 minutes of blood collection and stored at –25°C until analysis. Analysis was by high-performance liquid chromatography. For both analytes, the lower limit of quantitation was 10 ng/mL, and the lower limit of detection was 3 ng/mL.

CO was measured from the arterial pressure curve (obtained from the arterial line) using the FloTrac sensor and Vigileo monitor (Edwards Life Sciences, Irvine, CA) with third-generation software (last software upgrade on October 8, 2009).[13,14] CO values were averaged over 1-minute intervals for further analysis.

Data Analysis

PK–PD analysis. A 3-compartmental model was fitted to the ketamine concentration data.[15] Because S(+)-norketamine concentrations remained low, in this study we refrained from adding norketamine compartments to the model. The PD model is an empirical model that describes the changes in CO from changes in ketamine concentration due to a direct ketamine effect at the effect site and a feedback or counterregulatory effect. To eliminate a possible hysteresis between plasma concentration and effect, we postulated an effect compartment that equilibrates with the plasma compartment with a half-life $t½$ (i.e., the blood-effect-site equilibration half-life).

The PD Model Development Was Performed in Three Stages

Model 1. Initially, a linear PD model was postulated with the plasma ketamine concentration (Cp) having a direct effect on CO delayed by factor $t½$ (blood-effect-site equilibration half-life) with gain (or sensitivity) C_{ONE}, which is the ketamine effect-site concentration (C_E) causing a 1 L/min increase in CO (with units [ng/mL]/[L/min]) (PD model):

$$Y_N = BLN + Y_E + \varepsilon, \quad (1)$$

where Y_N is the predicted CO, BLN the baseline (i.e., predrug) CO, ε the measurement noise, and Y_E the drug-induced effect on CO and with

$$Y_E = C_E/C_{ONE}. \quad (2)$$

Model 2. To consider the undershoot in CO observed after termination of the ketamine infusion, we added a controller to the PD model (PD model + controller):

$$Y_N = BLN + (Y_E - Y_C), \quad (3)$$

where Y_C is the output from the controller, with

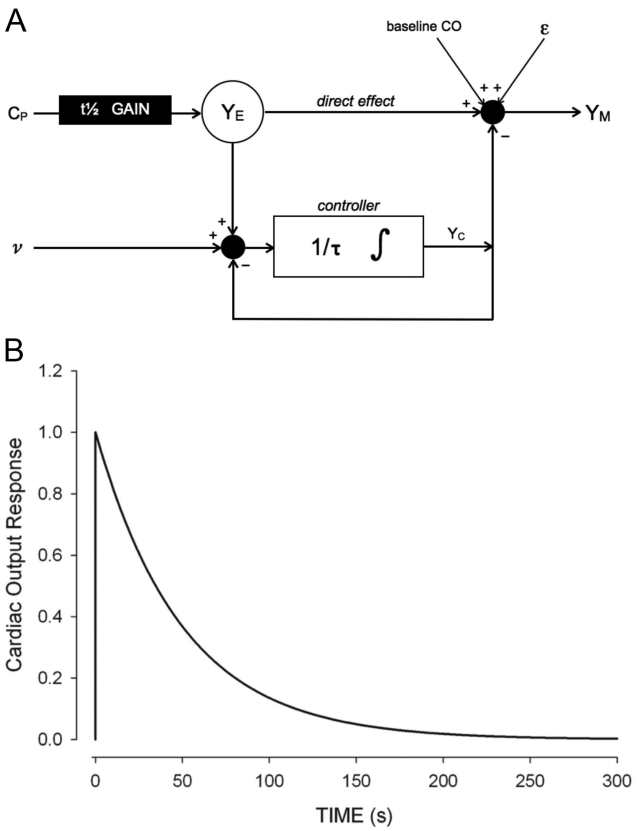

Figure 1. A, Schematic representation of the cardiac output (CO) response model. Cp is the plasma concentration of S(+)-ketamine that affects CO directly with a delay (t½) and a gain causing a change in CO (depicted by Y_E). The CO is further affected by a control system with inputs Y_E and process noise ν and that counterregulates CO with time constant τ. The measured CO (Y_M) is the sum of Y_E (direct drug effect), baseline CO, measurement noise (ε), and the output from the controller (Y_C). B, Example of the effect of the controller on a change in CO. Because of a change in S(+)-ketamine concentration, CO increases to 1 (=Y_E), which is subsequently slowly counterregulated by the controller (=Y_C) to baseline, with time constant τ of 60 seconds.

$$\tau \cdot dY_C/dt = Y_E - Y_C. \quad (4)$$

The control variable Y_C counteracts input component Y_E with time constant τ so that Y_N returns, with a delay, to baseline (Fig. 1, A and B).

Model 3. Finally, since (in some subjects) the residuals of the data fits suggested the presence of a process noise component (ν), this was modeled in the control system as follows (PD model + controller + noise component; Fig. 1A)[9–12]:

$$dY_C = (Y_E - Y_C)/\tau \cdot dt + \sigma_\nu \cdot dw, \quad (5)$$

where $\sigma\nu$ is the SD of the process noise component (with units $L \cdot min^{-1} \cdot min^{-0.5}$) and dw a stochastic (Wiener) process (Tornøe et al.,[11] where w has the units of $min^{0.5}$). The model can be viewed as a combination of a direct (with only a small delay t½) and an indirect response model, in which the indirect response is of the third form of the responses postulated by Dayneka et al.[16] with $k_{in} = k_{out} = 1/\tau$, and which counteracts the direct effect.

Statistical analysis. Data analysis was performed with the statistical package NONMEM VII (ICON Development Solutions, Hanover, MD).[17] NONMEM VII's Markov Chain Monte Carlo Bayesian analysis method was used for parameter estimation. This method yields probability distributions of the model parameters from which means, standard errors, and 95% confidence intervals (CI) can be obtained. Uninformative priors were used for the interindividual variability terms.[17] The burn-in samples were tested for convergence (all parameters and objective function over 20 iterations, each with 50 iterations apart; $P < 0.05$); 1000 iterations were used to obtain parameter distributions.

The PK/PD Analysis Was Performed in Two Stages

PK Analysis. From the first stage, empirical Bayesian estimates of the PK parameters were obtained. Sex and disease state (healthy versus CRPS1) were considered covariates. Concentrations were assumed to have constant relative intraindividual error.

PK–PD Analysis. In the second stage the PK parameters were fixed to those obtained from the first stage (i.e., empirical Bayesian estimates). To optimize parameter estimation, including the standard deviations of the process (σ_ν) and measurement noise (σ_ε) components, we implemented a Kalman filter (Appendix).[9–12] Sex and disease state (healthy versus CRPS1) were considered covariates. Model parameters were assumed to be log-normally distributed across the population. The effect parameter was assumed to have an additive intraindividual error.

Volunteer and patient data were combined in the analyses. Covariate search was performed using forward selection on the basis of the Akaike Information Criterion[18] and NONMEM's FOCI method, with disease state examined first and gender next.

Auto- and Cross-Correlation Functions. To get an indication of the goodness of fit, we calculated the auto- and cross-correlation functions and statistically tested for the 3 PD models according to Ljung.[10] The autocorrelation function of the residuals $R_\varepsilon(\Delta t)$ is a measure of the correlation between 2 residuals shifted by Δt in time. When the autocorrelation function is zero (except when $\Delta t = 0$; a residual has a correlation of 1 with itself), the residuals are called *white* or uncorrelated. The cross-correlation function $R_{\varepsilon,u}(\Delta t)$ measures the correlation between the residuals and the input (u; the input of the controller which is the PD model output), shifted by Δt in time, and is zero if the model explains the data completely (because the residuals should be completely random).

RESULTS

Patients and Volunteers

The mean patient age was 43.2 ± 13.0 (mean ± SD) years, and mean body mass index was 23.6 ± 3.9. The duration of CRPS1 (since diagnosis) was 8.4 ± 6.1 years (range 1.1 to 20.7 years). Volunteer age averaged to 21.3 ± 1.6 years; mean body mass index to 20.9 ± 1.6. All subjects completed the protocol without major side effects. The most frequent side effects were drug high and nausea occurring in both populations but rated of lesser intensity in the volunteer population.

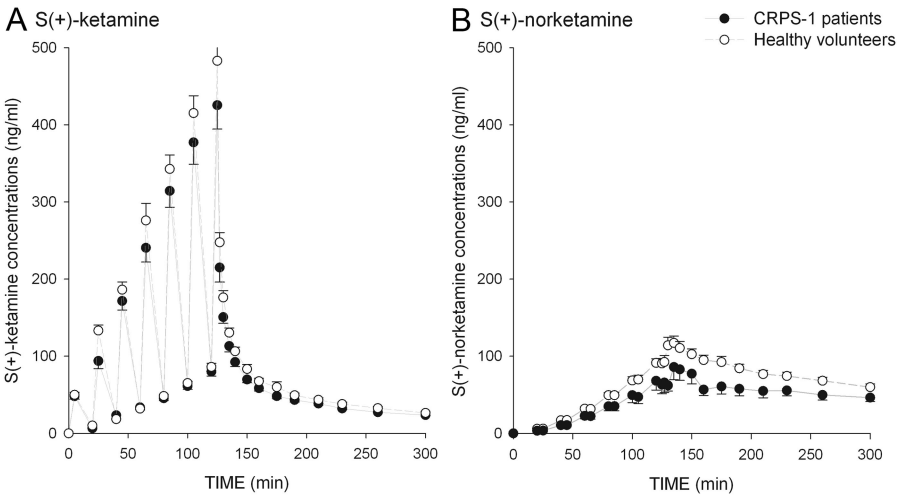

Figure 2. Mean values (±SEM) of S(+)-ketamine (A) and S(+)-norketamine (B) in complex regional pain syndrome type 1 (CRPS1) patients (closed symbols) and healthy volunteers (open symbols).

Pharmacokinetics

The mean plasma S(+)-ketamine and S(+)-norketamine concentrations are given in Figure 2, A and B. Peak S(+)-ketamine concentrations were lower in CRPS1 patients. During the washout phase, concentrations in patients remained below those measured in volunteers (peak S(+)-ketamine concentration = 425 ± 31 [mean ± SD] in CRPS1 patients versus 485 ± 20 ng/mL in volunteers; Figure 2A). Similarly, the S(+)-norketamine concentrations were lower in CRPS1 patients throughout the study: average values 45 ± 25 ng/mL in CRPS1 patients with a 85 ng/mL maximum at t = 135 minutes versus 64 ± 26 ng/mL in volunteers with a 117 ng/mL maximum at t = 135 minutes. The 3-compartment PK model adequately described the data. Best, median, and worst data fits are given in Figure 3. Inclusion in the model of covariates disease state and sex on V_3 and CL_2 (for disease state) and V_1 and CL_1 (for sex) improved the data fits significantly (Fig. 4). Parameter values are given in Table 1. Patients had a 30% larger volume of compartment 3 and a 50% greater clearance from compartment 2; males had a 30% larger volume of compartment 1 and a 10% larger clearance from this same compartment. Also, age was a significant covariate on V_3 (with V_3(age) = 1.37*AGE + 99.6, with the slope significantly different from 0) but not on CL_2 (CL_2(age) = 0.053*AGE + 3.0, slope not different from 0) (Fig. 4).

Pharmacodynamics

Mean CO values of the 2 populations are given in Figure 5. It shows the dose-dependent increase in CO with increasing doses of S(+)-ketamine and a undershoot in CO upon the termination of ketamine infusion below baseline values in both populations. In Figure 6, we give goodness-of-fit plots for the 3 models tested. While Model 1 resulted in correlated residuals in all subjects, Model 2 produced uncorrelated residuals in some subjects; the combination of Models 2 and 3 produced uncorrelated residuals in all subjects. Hence, the model incorporating the controller + Kalman filter (model 3) best described the data, with uncorrelated noise as determined from residual autocorrelation and cross-correlation functions. The improvement in model fits is exemplified in panels C, G, and K of Figure 6, showing residuals versus time. The residuals and a

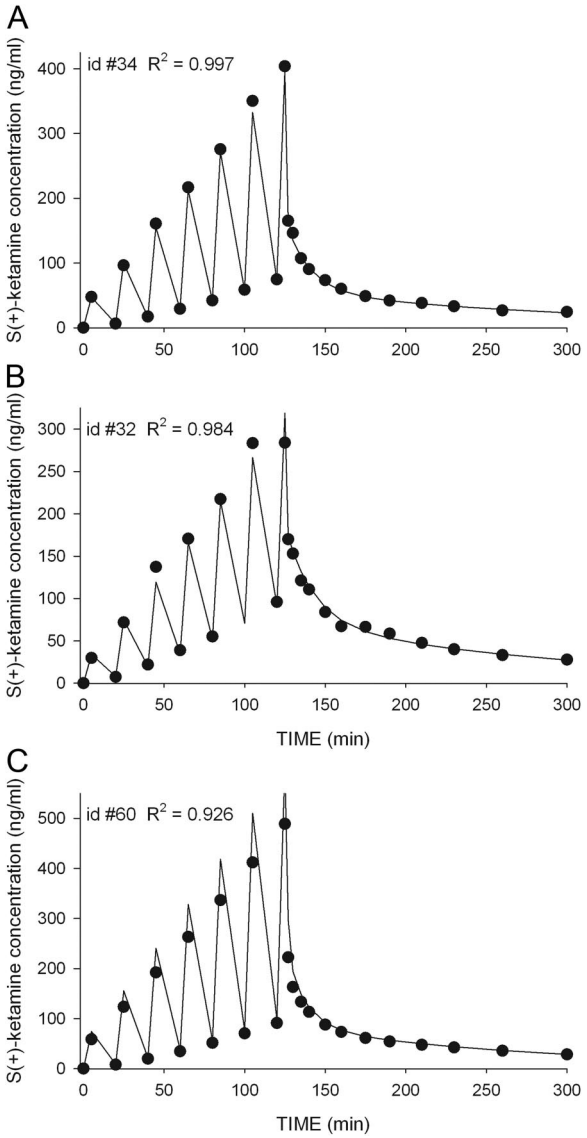

Figure 3. Best (A), median (B), and worst (C) pharmacokinetic data fits. The dots are the measured S(+)-ketamine concentrations, the continuous lines through the data, the data fits.

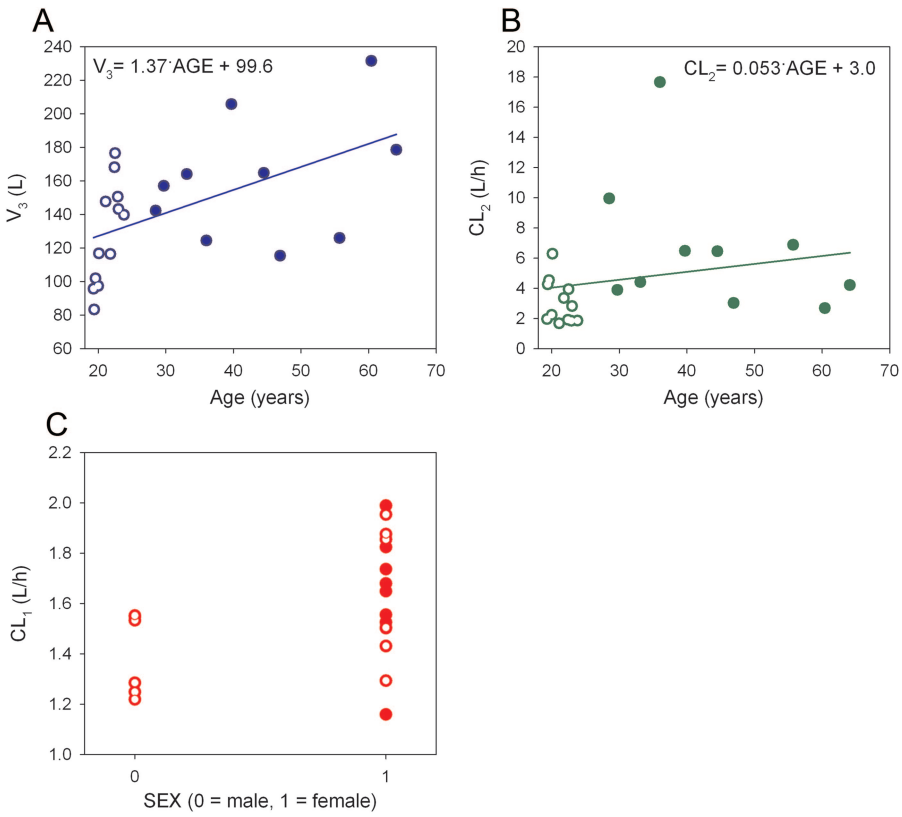

Figure 4. The effect of age on pharmacokinetic parameters V_3 (A) and CL_2 (B) and the effect of gender (C) for volunteers (open symbols) and patients (closed symbols). V_3 is the volume of the third compartment of ketamine; CL_2 is ketamine intercompartmental clearance 2.

Table 1. Pharmacokinetic Model Parameters

	Estimate	Standard error of estimate	95% CI	ω^2	SE of ω^2
$V_{1Female}$ (L)	6.64	0.77	5.01–7.94	—	
V_{1Male} (L)	9.11	1.16	7.37–12.0	—	
V_2 (L)	21.3	2.55	16.6–26.3	0.29	0.12
$V_{3Healthy}$ (L)	124.0	15.4	91.8–151.2	0.20	0.09
V_{3CRPS1} (L)	164.7	21.2	130.8–208.7	0.20	0.09
$CL_{1Female}$ (L/h)	85.8	3.37	78.5–91.9	0.11	0.04
CL_{1Male} (L/h)	77.9	6.26	65.8–90.8	0.11	0.04
$CL_{2Healthy}$ (L/h)	183.7	42.0	123.7–298.4	0.50	0.21
CL_{2CRPS1} (L/h)	387.1	102.5	209.5–572.1	0.50	0.21
CL_3 (L/h)	92.0	8.84	70.5–108.4	0.17	0.07
σ^2 (−)	0.015	0.001	0.013–0.017		

All values are scaled to 70 kg. V_1, V_2, and V_3 are the volumes of compartments 1, 2, and 3 with clearances CL_1, CL_2, and CL_3, respectively. Subscripts *Healthy* and *complex regional pain syndrome type 1* (*CRPS1*) and *Male* and *Female* denote significant different parameter values in the cohorts healthy volunteer versus CRPS1 patients and males versus females. The ω^2 is between-subjects variability (in the log-domain), and σ^2 is the residual error. CI = confidence interval.

smoothing function of the residuals of 1 subject is shown (orange data points, white lines), showing an improvement in model fits going from model 1 to models 2 and 3. In Figure 7 an example is given of the improvement in autocorrelation functions of the residuals. At $t = 0$ (no shift between residuals) the correlation is 1, while at values of $t > 0$ a clear correlation in residuals is observed for model 1, while no correlation is observed for model 3 (similar observations were made for the cross-correlation functions; data not shown). Two examples of data fits are given in Figures 8 and 9. One subject (id #62, a CRPS1 patient) displayed high ketamine potency (a low value of C_{ONE} of 74 (ng/mL)/(L/min); Figure 8); the other (id#61, a CRPS1 patient) exhibited low ketamine potency (a high value of C_{ONE} of 390 (ng/mL)/(L/min); Figure 9). The thick line through the measured data points (panel B) is the curve fit (model 3), the thin line the deterministic component (i.e., the fit of the structural model parameters). The uncorrelated residuals are included in the graphs (in panel A), together with the effect site S(+)-ketamine concentration (dashed line in panel C). The population PD model parameter estimates are given in Table 2. S(+)-ketamine increased CO by 1 L/min for each increase in plasma concentration of 243 ng/mL with a delay of just 1.3 minutes ($t½$). The controller slowly counterregulated the changes in CO with a time constant of 67 minutes. Covariates sex and health status did not give significant improvement of any of the model parameters, although there was a trend towards a greater ketamine sensitivity in healthy volunteers (C_{ONE} 315 [95% CI = 121 to 630] [ng/mL]/[L/min]

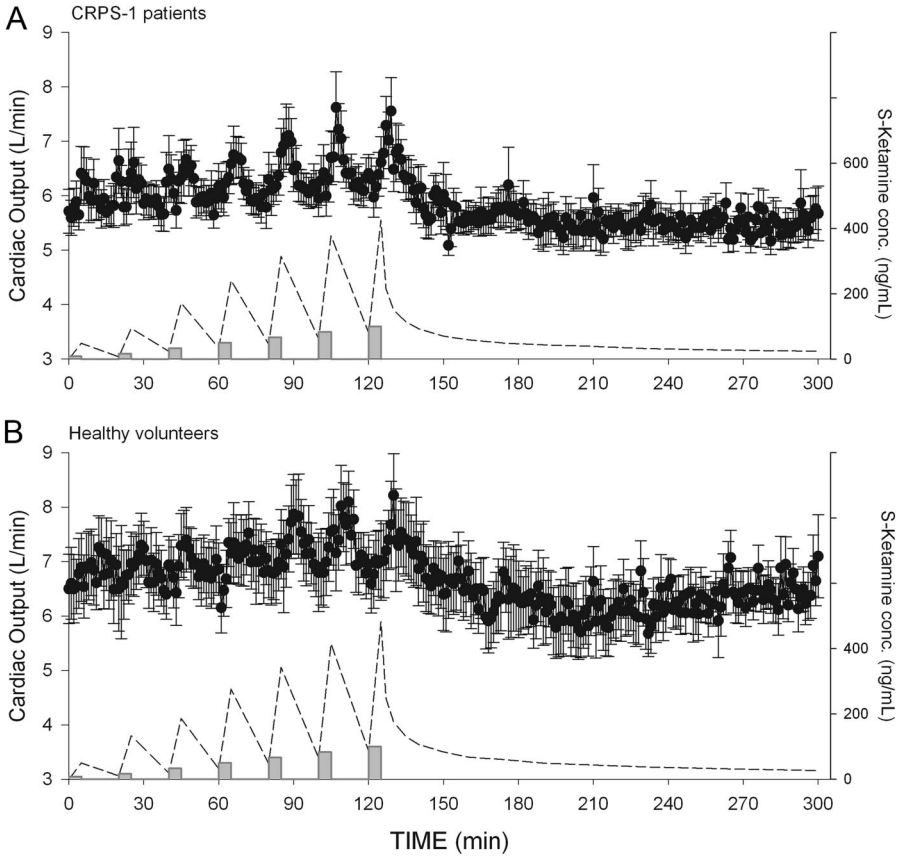

Figure 5. Mean cardiac output values in complex regional pain syndrome type 1 patients (A) and volunteers (B). Each dot is the between-subjects average of a 1-minute cardiac output average. The values are mean ± SEM. The dashed lines are the population plasma S(+)-ketamine concentrations. The gray bars represent S-ketamine infusion scheme.

versus 221 [125–413] [ng/mL]/ [L/min] in patients; $P > 0.05$).

Table 2 gives the parameter values of model 3. Parameter values of the deterministic parameters of models 1and 2 (data not shown) were essentially the same as those of model 3, with some minor changes in the interindividual variability (ω^2). Taking the large SEs of the ω^2, the significance of these changes is uncertain. In Figure 10, panel G of Figure 6 is plotted (PD model + controller), now with a smoothing curve for all subjects, showing that the deterministic or structural part of the model adequately describes the data. Overall, our analysis indicates that the PD parameters of the deterministic part of the model as described by model 2 are not affected by the incorporation of a noise component.

DISCUSSION

Ketamine's use in patients is limited by the occurrence of side effects.[1–4] Most studied are its psychomimetic and cognitive effects. However, an equally important side effect is stimulation of the cardiovascular system.[4,5] In the current study we examined the effects of increasing doses of S(+)-ketamine on CO as determined from the arterial pressure wave. We used a commercial device (FloTrac/Vigileo with third-generation software, Edwards Lifesciences, Irvine, CA) to measure CO via the arterial catheter in the radial artery.[13,14] The device allows continuous CO measurements using an algorithm that is based on the arterial waveform characteristics (pulse contour method, PCM) and patient demographic data. The algorithm is based upon the principle that pulse pressure is proportional to stroke volume. While there are differences in absolute CO values between the PCM and CO measurements on the basis of pulmonary artery thermodilution, trend-effects are comparable in direction and magnitude.[13,14,19] Hence, we believe that our continuous CO measurements are sufficiently valid to be used in our PK–PD study, which requires more data points (to track the rapid changes induced by the ketamine-pulses of our protocol) than are obtained by other techniques. Furthermore, because of its relatively noninvasive nature, PCM is applicable in volunteers.

We applied pulses in S(+)-ketamine to reduce the production of ketamine's active metabolite norketamine and dehydronorketamine. We measured the plasma S(+)-norketamine concentrations and observed values <120 ng/mL. We did not measure S(+)-dehydronorketamine but the literature indicates that dehydronorketamine concentrations are on average 50%–60% of those of norketamine.[5] Extrapolation of these findings to our study would give S(+)-dehydronorketamine peak concentrations of 50 to 60 ng/mL. Assuming that both metabolites are 2 to 3 times less potent (with respect to analgesia) than ketamine, we assume no contribution from both compounds to the observed changes in CO in the current study. Furthermore, in a recent study we observed that reduction of norketamine plasma concentrations by >50% using rifampicin as an inducer of norketamine metabolism had no effect on ketamine-induced changes in CO (A. Dahan, unpublished observations). This strengthens our argument that in the current study the low plasma concentrations of norketamine had little effect on our study outcome. We

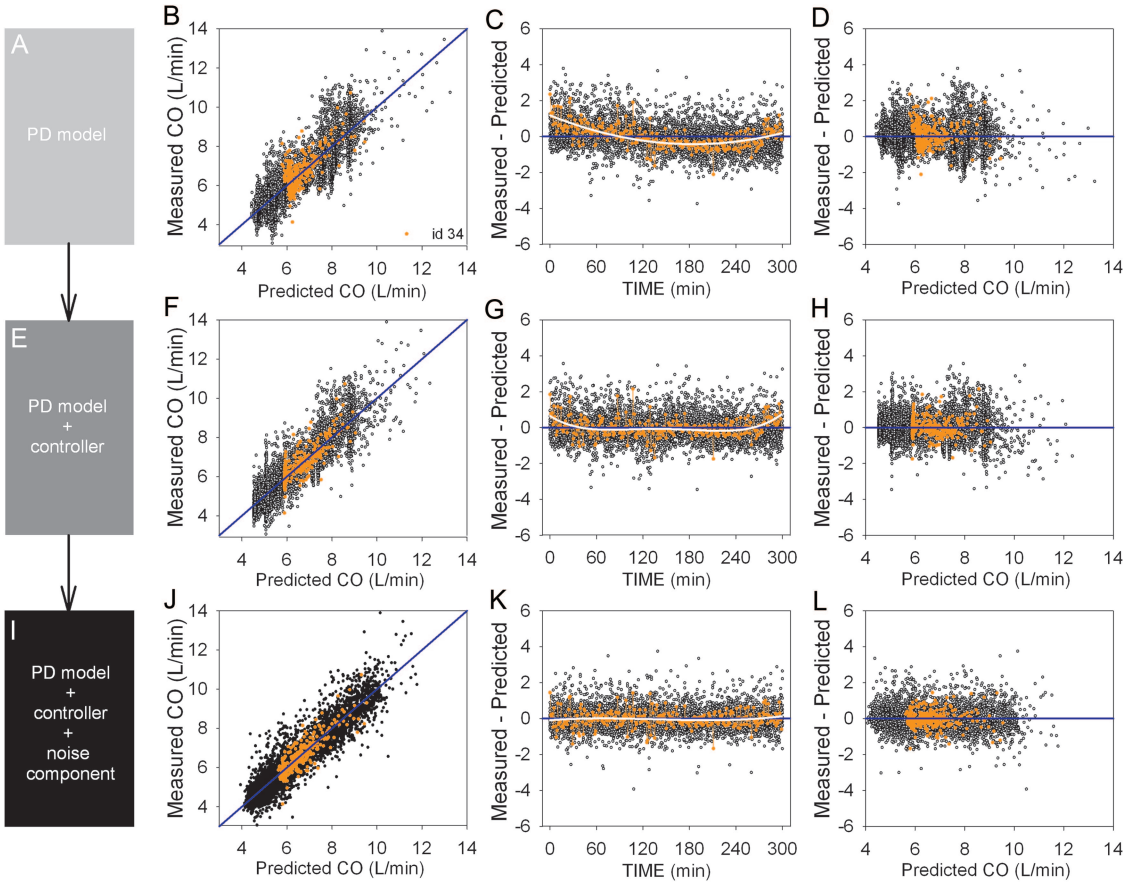

Figure 6. Model development and goodness of fit plots for (A–D) the initial pharmacodynamic (PD) model, (G–H) the PD model plus controller, and (I–L) the PD model + controller + Kalman filter. In orange are the individual data of subject id#67. To guide the eye, a smoothing curve (white line) was plotted through the data of subject id#67 for the residual versus time data (plots C, G, and K).

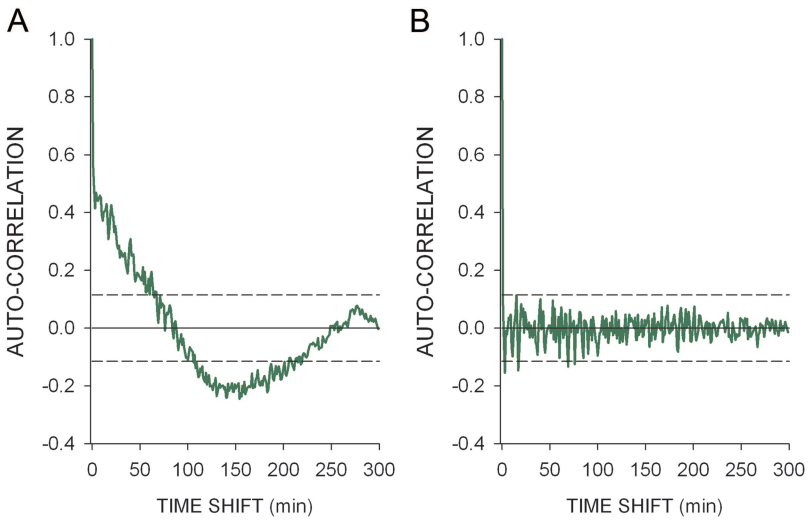

Figure 7. Autocorrelation function of the residuals of model 1 (A) showing correlated noise and uncorrelated noise observed with model 3 (B) of subject id#34. The horizontal lines are the zero line (continuous line) ± 95% confidence intervals.

therefore did not include a norketamine (or dehydronorketamine) component in our PD model.

The PKs of S(+)-ketamine differed between CRPS1 patients and healthy volunteers (Table 1): volume of compartment 3 was 30% larger, and the clearance from volume 2 was 50% larger in patients. These differences are reflected by the fact that peak plasma S(+)-ketamine concentrations and concentrations during washout were lower in CRPS1 patients. As a consequence, S(+)-norketamine concentrations were also lower by 40%–50% throughout the study, although we cannot exclude a reduction in ketamine metabolism in the liver of CRPS1 patients. The observed differences between study groups are difficult to explain, especially since the volunteer group was not matched by

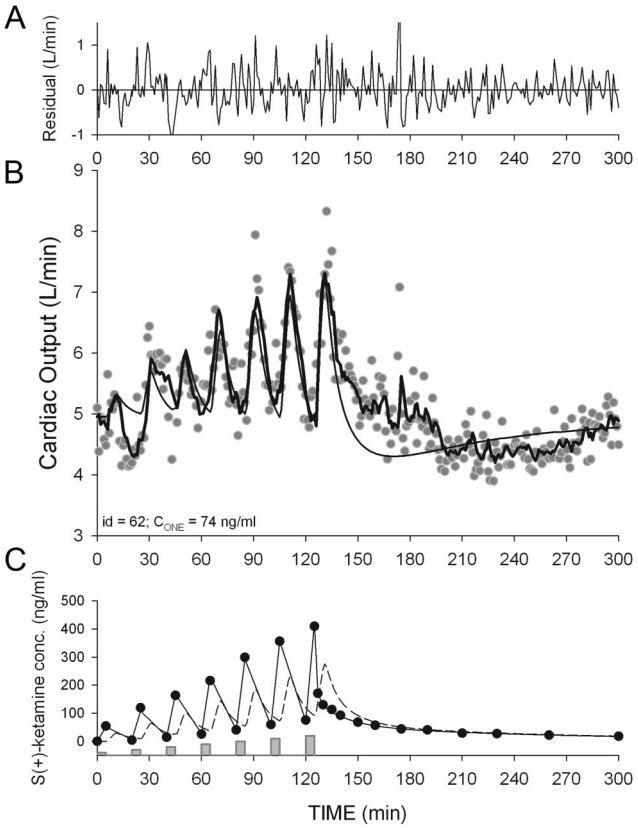

Figure 8. A–C, Example of a data fit of cardiac output of one subject (id#62) with a low value for C_{ONE} (74 ng/mL). The top panel (A) shows the residual between the measured data and the data fit. The gray dots are the 1-minute average cardiac output measurements (B). The thick line through the data is the data fit, and the thin line the deterministic component (i.e., fit without the Kalman filter). The bottom panel (C) depicts the measured plasma S-ketamine concentration (solid symbols), pharmacokinetic data fit (continuous line), and S-ketamine concentration at its effector site (dashed line). The gray bars represent S-ketamine infusion scheme.

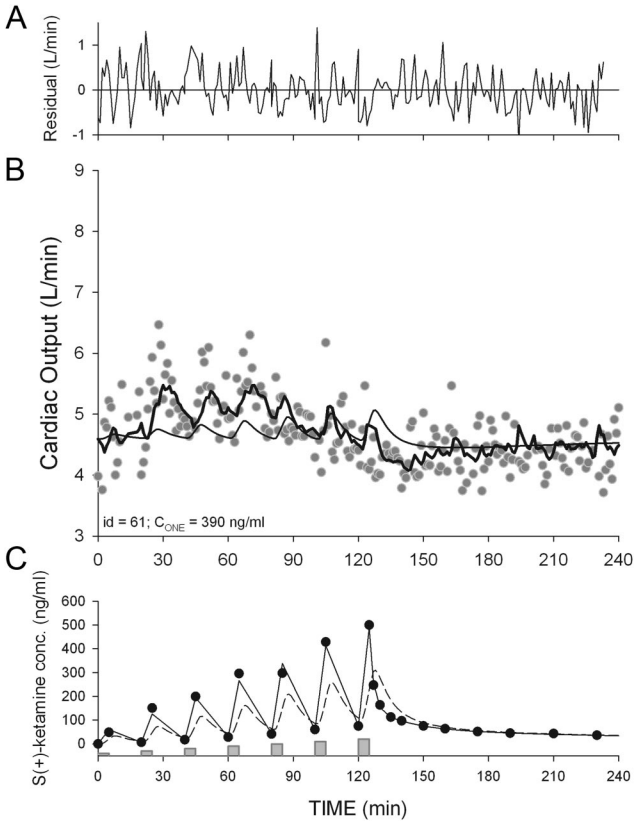

Figure 9. A–C, Example of a data fit of cardiac output of one subject (id#61) with a high value for C_{ONE} (390 ng/mL). The top panel (A) depicts the residual between the measured data and the data fit. The gray dots are the 1-minute average cardiac output measurements (B). The thick line through the data is the data fit, the thin line the deterministic component (i.e., fit without the Kalman filter). The bottom panel (C) shows the measured plasma S-ketamine concentration (solid symbols), pharmacokinetic data fit (continuous line), and S-ketamine concentration at its effector site (dashed line). The gray bars represent S-ketamine infusion scheme.

age to the CRPS1 patient group (a major limitation of our study design). Hence the observed differences may have been related to differences in age but also to differences in body fat content, distribution of the CO, or to the underlying disease. The observed sex differences are comparable to an earlier finding in healthy volunteers.[15] Our CRPS1 population was exclusively female (which is in agreement with the gender distribution of this disease). The population PK analysis indicated that the CRPS1 PK (female) data were well within the values observed in the overall female subgroup, distinct from values observed in healthy male volunteers. Our study does not provide information on the S(+)-ketamine PK of CRPS1 male patients. The data do indicate that blind extrapolation of S(+)-ketamine PK data to chronic pain patients (to design ketamine infusion schemes) is not justified. Note further that our PK model is valid only for the dose range tested and additionally over the CO range observed in the current study.

Ketamine has a biphasic action on the cardiovascular system: a direct cardiodepressive effect (i.e., a direct negative inotropic effect) and an indirect stimulatory effect (due to activation of the sympathetic system: ketamine causes the systemic release of catecholamines, inhibition of the vagal nerve, inhibition of norepinephrine reuptake at peripheral nerves and non-neuronal tissues such as the myocardium, and norepinephrine release from sympathetic

Table 2. Pharmacodynamic Model Parameters

	Estimate	Standard error of estimate	ω^2	SE of ω^2
Baseline CO (L/min)	6.22	0.53	0.13	0.05
C_{ONE} ([L/min] · [ng/mL]$^{-1}$)	243	54	0.53	0.22
t (min)	1.33	0.21	—	
τ (min)	67.1	17.0	—	
σ_ϵ (L/min)	0.44	0.05	0.29	0.13
σ_ν (L · min^{-1} · min$^{-0.5}$)	0.13	0.02	0.43	0.19

C_{ONE} is the S(+)-ketamine steady state or effect site concentration causing an increase in cardiac output (CO) of 1 L/min; t½; is the blood-effect-site equilibration half-life; τ is the time constant of the controller; σ_ϵ and σ_ν are the standard deviations of the measurement and process noise components, respectively; ω^2 is the between-subjects variability (in the log-domain).

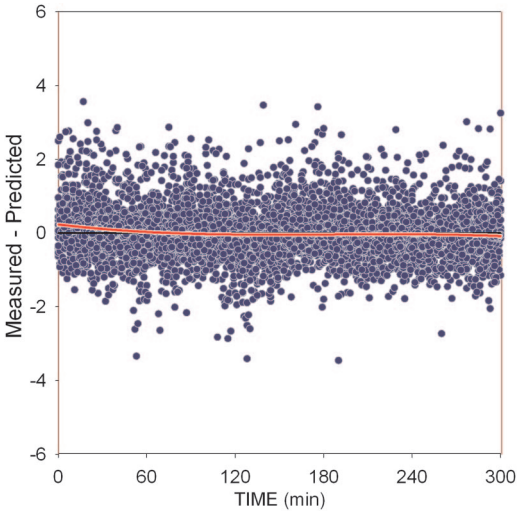

Figure 10. Goodness-of-fit plot of the pharmacodynamic model + controller. Shown is the residual cardiac output (measured – predicted) versus time of all subjects and a smoothing curve (white/red curve). This graph is similar to diagram G of Figure 6 but shows the deterministic part of the model.

ganglia).[4,8,20,21] Cardiodepression precedes stimulation after high-dose ketamine administration or occurs after repeated administrations when presynaptic catecholamine stores become depleted.[8] Cardiovascular stimulation already occurs after low-dose ketamine infusion and is characterized by tachycardia, systemic and pulmonary hypertension, increases in CO, and myocardial oxygen consumption.[4,8] Our data show dose-dependent increases in CO but also display an inhibitory component, which was most prominent in the ketamine washout phase, causing CO values below baseline (Fig. 5). Whether the inhibition was due to the depressant effect of ketamine or to an autoregulatory effect of the cardiovascular system remains unknown. We modeled the ketamine-induced changes in CO with a simple empirical (linear) model consisting of 2 components, one direct (stimulatory) linear component and a second additive component that counterregulates the direct effects of ketamine on CO (the controller, Fig. 1, A and B). This model adequately described the data and provided useful model parameter estimates. The potency of ketamine to induce changes in CO is defined by parameter C_{ONE}, which is the concentration of S(+)-ketamine that causes a unit increase in CO, equals 243 ± 54 (ng/mL)/(L/min); C_{ONE} recalculated as a sensitivity = 0.41 L/min increase in CO per 100 ng/mL S(+)-ketamine; an increase in CO of 1 L/min is about 50% of the average effect we observed (Fig. 5). Note that these values are related to acute changes in CO and that because of the effect of the controller, the CO slowly (with a time constant of 67.2 minutes) returns towards baseline values. It may well be that other infusion schemes will result in slower or faster adaptations towards baseline. In a clinical study in patients undergoing surgery under spinal or epidural anesthesia, S(+)-ketamine (bolus dose of 0.25 mg/kg followed by 0.06 mg/kg per hour) at the background of a low-dose propofol infusion (2 and 3 mg/kg per hour) caused a biphasic response with an initial increase in heart rate, systolic blood pressure, and rate-pressure-product, followed by a slow decline towards a new steady state just above baseline levels.[4] From the data provided, we estimated a time constant for adaptation of 30 to 40 minutes. These observations are in close agreement with ours and give strength to the model choice we made. We estimated a half-life for onset/offset of ketamine's effect on CO of 1 to 2 minutes. This is in close agreement with the time course for the increase in plasma epinephrine and norepinephrine and systolic blood pressure after an induction dose of ketamine in adult and pediatric patients.[20] This suggests that the stimulatory effect of S(+)-ketamine is secondary to the release of catecholamines, although we cannot exclude an (additional) direct effect of ketamine at the myocardium or cardiac neural tissue.

In contrast to the PK parameters, PD model parameters did not differ between CRPS1 patients and healthy young volunteers. This suggests that central sympathetic reactivity remained intact in our CRPS1 patients. Various studies indicate that the sympathetic system is affected in CRPS1 patients. For example, in acute CRPS1 patients, perfusion of the affected limb is often higher than that of the contralateral limb because of inhibition of cutaneous sympathetic vasoconstrictor neurons[6]; in chronic CRPS1 patients, peripheral vasoconstriction may occur despite lower norepinephrine levels at the affected side, again suggestive of a disequilibrium within the peripheral sympathetic system.[7] We observed that CO responses were comparable in CRPS1 patients with those in control subjects. We had to reject our hypothesis of an altered CO response to ketamine in our group of chronic pain patients. Our observations may be explained by S(+)-ketamine-induced generalized catecholamine reuptake inhibition or selective effects on specific efferent sympathetic pathways to the heart, both of which are compatible with altered central control of sympathetic motor activity to the limb affected by CRPS.

To obtain a more accurate estimation of the parameters of the deterministic part and noise components of the model, a Kalman filter was implemented.[9–12] In Figures 8 and 9 the deterministic components are plotted (thin lines through the data) together with the fit that incorporates the Kalman filter (thick line through the data). In contrast to a reduced model without Kalman filter, the autocorrelation and cross-correlation functions of the residuals now show absence of any significant correlations present (model 3, Fig. 7). This indicates a significant improvement in the data fits and consequently a more reliable estimation of variability and structural model parameters.[9–12] The magnitude of the noise normalized to the units of C_E is about 32 ng/mL or 5%–10% of the ketamine input during the infusion phase and up to 50%–100% during the washout phase (Fig. 2). These are realistic values and indicate that during the infusion phase the noise played little or no role in the measured CO values, whereas in the washout phase a large part of the signal is determined by the noise component. We previously used a similar modeling procedure when estimating the various components active in the ventilatory control system upon stimulation with carbon dioxide.[22] We similarly concluded that the residuals were without the presence of significant correlations when analyzing the data with a noise model with Kalman filter, and favored the more

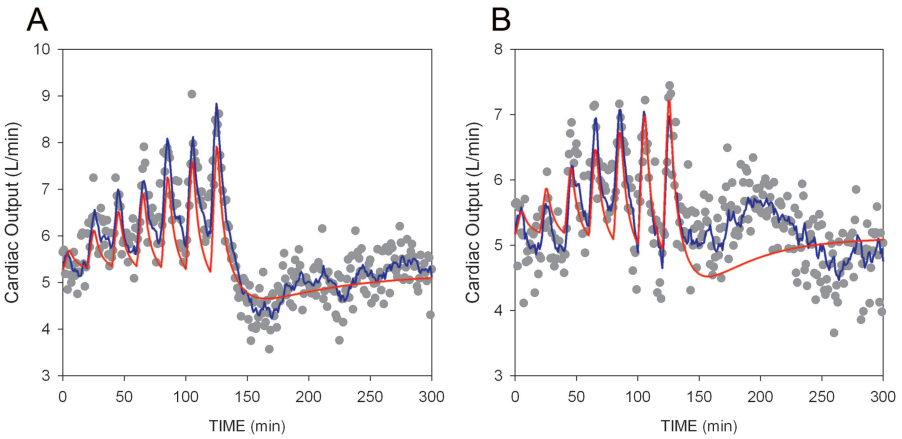

Figure 11. A and B: Two examples of simulated data fitted to the pharmacodynamic model. The gray dots are the simulated cardiac output data with added colored noise. The blue line is the data fit; the red line is the deterministic component that corresponds to the structural part of the model without noise component (equation 5 with $\nu = 0$). Note that the simulations are similar to the real data and data fits of Figures 8 and 9.

complex model to analyze the noisy respiratory data sets. Note that our model is valid over the dose range tested in the current study. Although it may be argued that model predictions are likely correct for different infusion regimens and doses, at much larger ketamine concentrations (e.g., >1000 ng/mL), the ketamine–CO relationship may not be linear and the counter-regulatory effects of ketamine may then possibly behave differently than those we modeled.

At first glance, the plot of the deterministic component in Figure 9B seems to indicate a model misspecification (from t = 130 to 200 minutes). We therefore performed simulations to obtain a model output with established parameter values, including the variances of the stochastic components of the system, and adding measurement noise (with different seeds for the random number generators). We next fit the model to the simulated data, with the knowledge that the model is correct. The simulations are shown in Figure 11. In panel A, the noisy, correlated model output is, by coincidence, close to the state of the noiseless system (the deterministic component is given by the red line in Fig. 11; this component is the output of equation 5 with noise parameter ν set to 0). In the right panel, the (correctly estimated) deterministic component diverges from the simulated noisy, correlated model output from t = 130 to 230 minutes. This behavior is close to the examples of real data fits presented in Figures 8 and 9. These simulations indicate that the structural part of our model is correct. We next tested whether a parallel noise model (with a noise component that runs parallel to the system with its own dynamics) rather than the current process noise model (with a noise component that runs through the system) allows correct estimation of the deterministic component (data not shown). Although the model adequately described the data with similar magnitudes of deterministic model parameters, the objective function indicated that this was inferior to the current analysis approach. Finally, (1) it is important to note the analysis sequence that we performed and depict in Figure 6 (we analyzed the 3 PD models sequentially). This approach allows assessment of significance of components, and consequently, inherent problems with one of the components will not be transformed into noise by the Kalman filter. (2) Plots of the residuals with respect to the deterministic parts of all models show large variability with respect to the systematic deviations, both in the on- and off-transients. For data fits using model 1 a criticism would be that because of the large and correlated misfits, the parameters would not be accurately estimated. At least in the present case, the analysis with model 3 proves that the estimates were quite good, something that would remain unknown without that analysis.

In conclusion, this is the first study to assess the stimulatory effect of multiple doses of S(+)-ketamine on CO in CRPS1 patients and healthy volunteers. We applied a PK–PD model to correlate S(+)-ketamine concentration to effect, where the PD model had one direct stimulatory component and one adaptive component. We observed differences in PK model parameters between study groups but none in PD parameters. Because it is assumed that ketamine causes cardiovascular stimulation through activation of the sympathetic system, our data suggest that the sympathetic system remains intact in CRPS1 patients.

APPENDIX: IMPLEMENTATION OF THE KALMAN FILTER

For the state of the controller and its variance we write (cf. Tornøe[11]):

$$dY_C/dt = g(Y_C, Y_E, \tau) = (Y_E - Y_C)/\tau \quad (6)$$

$dP/dt = AP + PA^T + \sigma_\nu \sigma_\nu^T$, with

$$A = \partial g(Y_C, Y_E, \tau)/\partial Y_C = -1/\tau \quad (7)$$

$$= \sigma_\nu^2 - 2P/\tau \quad (8)$$

The variance of the one-step-ahead prediction of CO (=RVR) is

$$RVR = P + \sigma_\varepsilon^2, \quad (9)$$

and the Kalman gain (K) is

$$K = -P/RVR, \quad (10)$$

where the minus sign comes from the fact that Y_C is subtracted from the model output in (3). If CO sampling time Δt is small with respect to the time constant τ of the control system, the differential equations for Y_C and P may be solved for discrete time steps i, in which Y_E is assumed to be constant, so that

$$Y_{C,i} = Y_{C,i} \cdot \exp(-\Delta t/\tau) + Y_{E,i} \cdot [1 - \exp(-\Delta t/\tau)] \quad (11)$$

$$P_i = P_{i-1} \cdot \exp(-2\Delta t/\tau) + \tau \cdot \tfrac{1}{2} \cdot \sigma_v^2 \cdot [1 - \exp(-2\Delta t/\tau)]. \quad (12)$$

The Kalman filter updates Y_C via $K \cdot (Y_M - Y_N)$, and P with a factor $-K^2 \cdot RVR$. In steady state this factor should equal the change in P_i in (12), assuming constant Δt. The steady state value (PS) of P_i can then be solved from a quadratic equation as implemented in the following NONMEM code:

```
FP1 = EXP(-2 *DTT/TAU)
FP2 = VRS*TAU/2*(1 - FP1)
DMB = VRM*(1 - FP1) - FP2
DMC = -VRM*FP2
PS = [-DMB + SQRT(DMB*DMB - 4*DMC)]/2
RVR = PS + VRM
KALG = -PS/RVR
```

where KALG is the Kalman gain, $VRS = \sigma_v^2$, and $VRM = \sigma_\varepsilon^2$. The approach outlined here has the advantages that NONMEM's data file does not need to have special Kalman filter update records, the control file remains simple, and the Kalman gain KALG is known throughout each individual's record (it does not need to be estimated recursively).

DISCLOSURES

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Name: Ingeborg Noppers, MD, PhD.
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Contribution: This author helped analyze the data and write the paper and revisions.
Name: Rene Mooren, MSc.
Contribution: This author helped measure Ketamine samples.
Name: Martin Bauer, MD.
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Name: Leon Aarts, MD, PhD.
Contribution: This author helped write the manuscript.
Name: Elise Sarton, MD, PhD.
Contribution: This author helped acquire the data and write the protocol and manuscript.
Name: Albert Dahan, MD, PhD.
Contribution: This author helped write the protocol, manuscript, and revisions, and helped with data analysis and data acquisition.
This manuscript was handled by: Steven L. Shafer, MD.

REFERENCES

1. Carsten M, Møller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth (in press) doi:10.1093/bja/aeq041
2. Bell R, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2003;CD003351
3. Sigtermans MJ, Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome type 1. Pain 2009;145:304–11
4. Timm C, Linstedt U, Weiss T, Zenz M, Maier C. Sympathomimetische Effekte auch bei niedriger Dosierungen von Esketamin. Anaesthesist 2008;57:338–46
5. Hijazi Y, Bodonian C, Bolon M, Salord F, Boulieu R. Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. Br J Anaesth 2003;90:155–60
6. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS 1): mechanisms and diagnostic value. Brain 2001;124:587–99
7. Niehof SP, Huygen FJPM, van der Weerd RWP, Westra M, Zijlstra FJ. Thermography imaging during static and controlled thermoregulation in complex regional pain syndrome type 1: diagnostic value and involvement of the central sympathetic system. Biomed Eng OnLine 2006;5:30
8. Perouansky MA, Hemmings HC. Intravenous anesthetic agents. In: Hemmings HC, Hopkins PM, eds. Foundations of Anesthesia: Basic Sciences for Clinical Practice. Amsterdam: Mosby Elsevier, 2006:295–310
9. Overgaard RV, Jonsson N, Tornøe CW, Madsen H. Non-linear mixed-effects models with stochastic equations: implementation of an estimation algorithm. J Pharmacokinet Pharmacodyn 2005;23:85–107
10. Ljung L. System Identification: Theory for the User. Englewood Cliffs, NJ: Prentice Hall, 1987
11. Tornøe CW, Overgaard RV, Agersø H, Nielsen HA, Madsen H, Jonsson EN. Stochastic differential equations in NONMEM: implementation, application, and comparison with ordinary differential equations. Pharm Res 2005;22:1247–58
12. Maybeck PS. Stochastic models, estimation and control. Volume 1. New York: Academic Press, 1979:1–16 (Available at: www.cs.unc.edu/~welch/media/pdf/maybeck_ch1.pdf)
13. de Waal EE, Kalkman CJ, Rex S, Buhre WF. Validation of a new arterial pulse contour-based cardiac output device. Crit Care Med 2007;35:1904–9
14. Manecke GR, Auger WR. Cardiac output determination from the arterial pressure wave: clinical testing of a novel algorithm that does not require calibration. J Cardothor Vasc Anesth 2007;21:3–7
15. Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, Olofsen E. S(+)-ketamine effect on experimental pain and cardiac output. Anesthesiology 2009;111:892–903
16. Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm 1993;21:457–78
17. Beal BL, Sheiner LB, Boeckman AJ, Bauer RJ. NONMEM User's Guide. Hanover, MD: Icon Development Solutions, 1989–2009
18. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974;19:716–2
19. Østergaard M, Nielsen J, Nygaard E. Pulse contour cardiac output: an evaluation of the FloTrac method. Eur J Anaesthesiol 2009;26:484–9
20. Takki S, Nikki P, Jäättelä A, Tammisto T. Ketamine and plasma catecholamines. Br J Anaesth 1972;44:1318–22
21. Miletich DJ, Ivankovic AD, Albrecht RF, Zahed B, Ilahi AA. The effect of ketamine on catecholamine metabolism in the isolated perfused rat heart. Anesthesiology 1973;39:271–7
22. Dahan A, Olievier ICW, Bekenbosch A, DeGoede J. Modelling the dynamic ventilatory response to carbon dioxide in healthy human subjects during normoxia. In: Swanson GD, Grodins FS, Hughson RL, eds. Respiratory Control: A Modeling Perspective. New York: Plenum Press, 1988:265–73