Ketamine's second life : Treatment of acute and chronic pain

Sigtermans, M.J.

Chapter 4

S(+)-ketamine pharmacokinetics and effect on cardiac output in healthy volunteers versus CRPS type 1 chronic pain patients

Erik Olofsen, Marnix Sigtermans, Ingeborg Noppers, Marieke Niesters, René Mooren, Martin Bauer, Albert Dahan & Elise Sarton

submitted

4.1 Introduction

Ketamine, originally developed as anesthetic, is increasingly applied as analgesic for treatment of acute pain in the perioperative setting and chronic pain in patients with Complex Regional Pain Syndrome type 1 (CRPS-1) and cancer pain without and with 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 intravenous treatment.[3] An important disadvantage of ketamine treatment is its side-effect profile.[3] Most important 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).[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 cardiac output in chronic pain patients with CRPS-1 and healthy volunteers. 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 CRPS-1.[6,7] We performed a pharmacokinetic (PK)-pharmacodynamic (PD) modeling study, which allows the assessment of between-group differential effects of ketamine occurring at the PK or PD level or at both levels. In order to get an adequate analysis of the data, we developed a novel pharmacodynamic model that takes into account ketamine's stimulatory effects and counter-regulatory (or depressant) effects on cardiac output.[8]

4.2 Materials and methods

Subjects

Twelve healthy volunteers (6 men/6 women; age $>$ 18 years; body mass index $<$ 28 kg/m^2) and ten patients diagnosed with Complex regional Pain Syndrome type 1 (CRPS-1; 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, LUMC, 2300 RC Leiden, The Netherlands). Written and oral informed consent was obtained prior to the inclusion in the study. The subjects were instructed not to eat or drink for at least 6 h before the study. The diagnosis of CRPS-1 was based on the criteria of the International Association for the Study of Pain which includes: 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 and/or abnormal sudomotor activity in the region where pain is felt; exclusion of other conditions that could account for the pain and dysfunction. We excluded patients that had pain scores of 5 or less, used strong opioid medication (tramadol was allowed), were aged 17 years or less, were pregnant or lactating, had an increased intracranial pressure or had a serious medical or psychiatric disease. Medica-

tion that was allowed was paracetamol, non-steroid anti-inflammatory drugs, selective serotonin re-uptake inhibitors, amitryptiline, and pregabalin or gabapentin.

S(+)-ketamine infusion, blood sampling and cardiac output 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 CRPS-1 patients these lines were inserted preferentially in the non-affected arm. The S(+)-ketamine infusion scheme was as follows: min 0-5: 1.5 mg (given in 5 min), min 20-25: 3.0 mg, min 40-45: 4.5 mg, min 60-65: 6.0 mg, min 80-85: 7.5 mg, min 100-105: 9.0 mg, min 120-125: 10.5 mg. 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 min. The analyses of S(+)-ketamine and its main metabolite S(+)-norketamine has been described before.[9] In brief, 2 to 3 ml plasma was separated within 15-min of blood collection and stored at -25℃ until analysis. Analysis was by high performance liquid chromatography. The lower limit of quantitation was 10 ng/ml, the lower limit of detection was 3 ng/ml, for both analytes.
Cardiac output (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).[9,10] CO values were collected at 5-min intervals for further analysis.

Data analysis

Pharmacokinetic-pharmacodynamic (PK-PD) analysis

A tree compartmental model was fitted to the ketamine concentration data.[11] Since S(+)-norketamine concentrations remained low in this study we refrained from adding norketamine compartments to the model. In the PK analysis all doses used were per 70 kg. The pharmacodynamic model is an empirical model that describes the changes in cardiac output from changes in ketamine concentration due to a direct ketamine effect at the effect site and a feedback or counter regulatory effect.
The plasma ketamine concentration (Cp) has a direct effect on CO delayed by factor $t_{1/2}$(blood-effect-site equilibration half-life) with gain (or sensitivity) $1/C_{ONE}$, where C_{ONE} is the ketamine effect-site concentration (C_E) causing a 1 L/min increase in CO (figure 4.1):

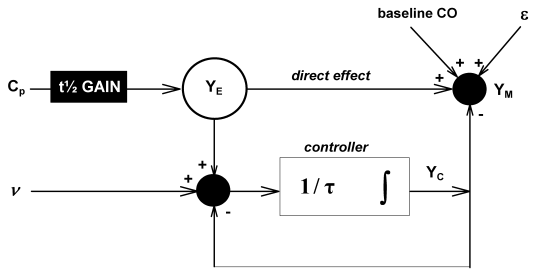
$$Y_N = BLN + Y_E + \epsilon \tag{4.1}$$

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

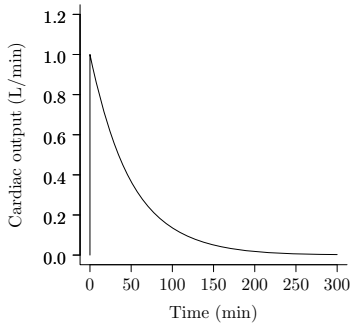
$$Y_E = \frac{C_E}{C_{ONE}} \tag{4.2}$$

Adding the controller:

$$Y_N = BLN + \frac{Y_E - Y_C}{\tau} \tag{4.3}$$



(a)



(b)

Figure 4.1: Schematic representation of the cardiac output response model and example of the effect of the controller on a change in cardiac output

a. Cp is the plasma concentration of S(+)-ketamine that affects cardiac output directly with a delay ($t_{1/2}$) 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 counter-regulates 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. Due to a change in S(+)-ketamine concentration CO increases to 1 (= Y_E), which is subsequently slowly counter-regulated by the controller (= Y_C) to baseline, with time constant τ of 60 s.

where Y_C is the output from the controller, with

$$\tau \cdot \frac{dY_C}{dt} = Y_E - Y_C \tag{4.4}$$

The control variable Y_C counteracts input component Y_E with time constant so that Y_N returns, with a delay, to baseline (figure 4.2).
The residuals of the data fits suggest the presence of a process noise component (ν). This component (ν) was modeled in the control system as follows:

$$\frac{dY_C}{dt} = \frac{Y_E - Y_C}{\tau} + \nu \tag{4.5}$$

Statistical analysis

Data analysis was performed with the statistical package NONMEM VII (ICON Development Solutions, Ellicott City, MD).[12] 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

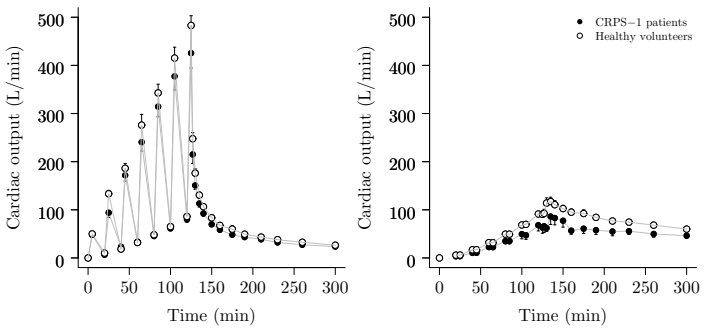


Figure 4.2: Mean values of S(+)-ketamine and S(+)-norketamine

Mean values (± SEM) of S(+)-ketamine (a) and S(+)-norketamine (b) in CRPS-1 patients (closed symbols) and healthy volunteers (open symbols).

and 95% confidence intervals (CI) can be obtained. Uninformative priors were used for the inter-individual variability terms. 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* CRPS-1) were considered covariates. Concentrations were assumed to have constant relative intra-individual error.

PK-PD analysis.

In the second stage the PK parameters were fixed to those obtained from the first stage. To optimize parameter estimation, including the standard deviations of the process (σ_ν) and measurement noise (σ_ϵ) components, we implemented a Kalman filter.[13,14] Sex and disease state (healthy vs. CRPS-1) were considered covariates. Model parameters were assumed to be log-normally distributed across the population. All effect parameters were assumed to have an additive intra-individual error.
Volunteer and patient data were combined in the analyses. Covariate search was performed using forward selection based the Akaike Information Criterion and NONMEM FOCEI method, with disease state examined first and next gender.[15]

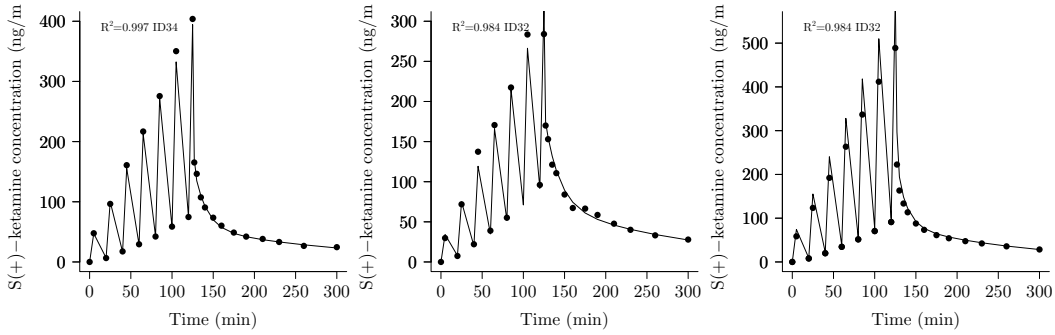


Figure 4.3: Best (a), median (b) and worst (c) pharmacokinetic data fits
The dots are the measured S(+)-ketamine concentrations, the continuous lines through the data, the data fits.

4.3 Results

Patients and volunteers

Mean patient age was 43.2 ± 13.0 (mean SD) years, mean body mass index 23.6 ± 3.9. The duration of CRPS-1 (since diagnosis) was 8.4 ± 6.1 years (range 1.1 – 20.7 years). Volunteer age averaged to 21.3 ± 1.6 years; mean body mass index 20.9 ± 1.6. All subjects completed the protocol without major side effects. Most frequent side effects were drug high and nausea occurring in both populations but rated of lesser intensity in the volunteer population.

Pharmacokinetics

The mean plasma S(+)-ketamine and S(+)-norketamine concentrations are given in figure 4.2. Peak S(+)-ketamine concentration were lower in CRPS-1 patients and also during the wash-out phase concentrations in patients remained below those measured in volunteers (peak S(+)-ketamine concentration = 425 ± 31 in CRPS-1 patients *versus* 485 ± 20 ng/ml in volunteers; figure 4.2a). Similarly, the S(+)-norketamine concentrations were lower in CRPS-1 patients throughout the study: average values 45 ± 325 ng/ml in CRPS-1 patients with a 85 ng/ml maximum at t = 135 min *versus* 64 ± 26 ng/ml in volunteers with a 117 ng/ml maximum at t = 135 min. The three-compartment pharmacokinetic model adequately described the data. Best, median and worst data fits are given in figure 4.3. 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. Parameter values are given in table 4.1. Patients had a 30% greater volume of compartment 3 and a 50% greater clearance from compartment 2; males had a 30% greater volume of compartment 1 and a 10% greater clearance from this same compartment.

	Estimate	SE	95% CI	ω^2	SE
$V_{1,Female},(l)$	6.64	0.77	5.01 - 7.94	-	
$V_{1,Male},(l)$	9.11	1.16	7.37 - 12.0	-	
$V_2,(l)$	21.3	2.55	16.6 - 26.3	0.29	0.12
$V_{3,Healthy},(l)$	124.0	15.4	91.8 - 151.2	0.20	0.09
$V_{3,CRPS\text{-}1},(l)$	164.7	21.2	130.8 - 208.7	0.20	0.09
$CL_{1,Female},(l/h)$	85.8	3.37	78.5 - 91.9	0.11	0.04
$CL_{1,Male},(l/h)$	77.9	6.26	65.8 - 90.8	0.11	0.04
$CL_{2,Healthy},(l/h)$	183.7	42.0	123.7 - 298.4	0.50	0.21
$CL_{2,CRPS\text{-}1},(l/h)$	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 versus CRPS-1 and Male versus Female denote significant different parameter values in the cohorts healthy volunteer versus CRPS-1 patients and males versus females. ω^2 is between-subject variability (in the log-domain).σ^2 is the residual error.

Table 4.1: pharmacokinetic model parameters

Pharmacodynamics

Mean cardiac output values of the two populations are given in figure 4.4. It shows the dose dependent increase in CO with increasing doses of S(+)-ketamine and a drop in CO in the wash-out period below baseline values in both populations. The model incorporating the controller and Kalman filter adequately described the data, with white noise as determined from residual auto-correlation and cross-correlation functions (data not shown). In contrast, a reduced model (eqns (1) and (2)), with just one direct component (equations 4.10 and 4.5) caused systematic misfits and colored noise. Two examples of data fits are given in figures 4.5 and 4.6. One subject (id 62) displayed high ketamine potency (a low value of C_{ONE} of 74 ng/ml, figure 4.5), the other exhibited low ketamine potency (a high value of C_{ONE} of 390 ng/ml, figure 4.6). The thick line through the measured data points (panel b) is the curve fit (equation 4.5), the thin line the deterministic component (*i.e.*, the fit without process noise modulation by the Kalman filter). The white residuals are included in the graphs (in panel a), together with the effect site S(+)-ketamine concentration (broken line in panel c). The population pharmacodynamic model parameter estimates are given in table 4.2. Covariates sex and health status did not give significant improvement of any of the model parameters. S(+)-ketamine increased cardiac output by 1 L/min for each increase in plasma concentration of 159 ng/ml (C_{ONE}) with a delay of just 3 min ($t_{1/2}$). The controller slowly counter-regulated the changes in CO with a time constant of 50 min.

Table 4.2: pharmacodynamic model parameters

	Estimate	SE	ω^2	SE
Baseline CO(l/min)	6.22	0.53	0.13	0.05
C_{ONE}*(ng/ml)*	243	54	0.53	0.22
$t_{1/2}$*(min)*	1.33	0.21	-	
τ*(min)*	67.1	17.0	-	
σ_ϵ	0.44	0.05	0.29	0.13
σ_ν	0.13	0.02	0.43	0.19

C_{ONE} is the S(+)-ketamine steady-state or effect-site concentration causing an increase in CO of 1 L/min; $t_{1/2}$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 between -subject variability (in the log-domain).

4.4 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 cardiac output as determined from the arterial pressure wave. We used a commercial device (FloTrac/Vigileo, Edwards Lifesciences, Irvine, CA) to measure cardiac output via the arterial catheter in the radial artery.[9,10] The device allows continuous cardiac output 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 based on pulmonary artery thermodilution, trend-effects are comparable in direction and magnitude.[9,10,16] 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 is obtained by other techniques. Furthermore, due to its relatively non-invasive nature PCM is applicable in human volunteers. We applied pulses in S(+)-ketamine to reduce the production of ketamine's active metabolites 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 50-60 ng/ml. Assuming that both metabolites are 2-3 times less potent than ketamine we assume no contribution from both compounds to the observed changes in CO in the current study. We therefore did not include a norketamine (or dehydronorketamine) component in our pharmacodynamic model. Furthermore, in a previous human study in which norketamine concentrations were elevated $>$ 150 ng/ml no contribution of the metabolite to S(+)-ketamine's effect on antinociceptive responses to heat pain could

be demonstrated.[11]
The pharmacokinetics of S(+)-ketamine differed between CRPS-1 patients and healthy volunteers (Table 4.1): volume of compartment 3 was 30% greater and the clearance from volume 2 was 50% greater in patients. These differences are reflected by the fact that peak plasma S(+)-ketamine concentrations and concentrations during wash-out were lower in CRPS-1 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 CRPS-1 patients. The observed differences between study groups are difficult to explain but may be related to differences in age, body fat content, distribution of the cardiac output and/or to the underlying disease. The observed sex differences are comparable to an earlier finding in healthy volunteers.[11] Our CRPS-1 population was exclusively female (which is in agreement with the gender distribution of this disease). The population PK analysis indicated that the CRPS-1 PK (female) data fell 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 CRPS-1 male patients. The data do indicate that blind extrapolation of S(+)-ketamine PK data to chronic pain patients (in order to design ketamine infusion schemes) is not justified.
Ketamine has a biphasic action on the cardiovascular system: a direct cardio-depressive 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 re-uptake at peripheral nerves and non-neuronal tissues such as the myocardium, and norepinephrine release from sympathetic ganglia).[4,8,17,18] Cardiodepression precedes stimulation after high dose ketamine administration or occurs after repeated administrations when presynaptic catecholamine stores become depleted.[17] Cardiovascular stimulation already occurs after low dose-ketamine infusion and is characterized by tachycardia, systemic and pulmonary hypertension, increases in cardiac output and myocardial oxygen consumption.[4,8] Our data shows dose-dependent increases in CO but also displays an inhibitory component, which was most prominent in the ketamine wash-out phase with CO values below baseline (figure 4.4 and 4.5). Whether the inhibition is 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 model consisting of two components, one direct (stimulatory) component and a second additive component that counter-regulates the direct effects of ketamine on CO (the controller, figures 4.1a 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 S(+)-ketamine that causes an increase in CO of 1 l/min (159 ± 31 ng/ml; C_{ONE} recalculated as a sensitivity = 0.63 L/min increase in CO per 100 ng/ml S(+)-ketamine). Note that these values are related to acute changes in CO and that due the effect of the controller the CO slowly (with a time constant of 50 min) 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 h) at the background

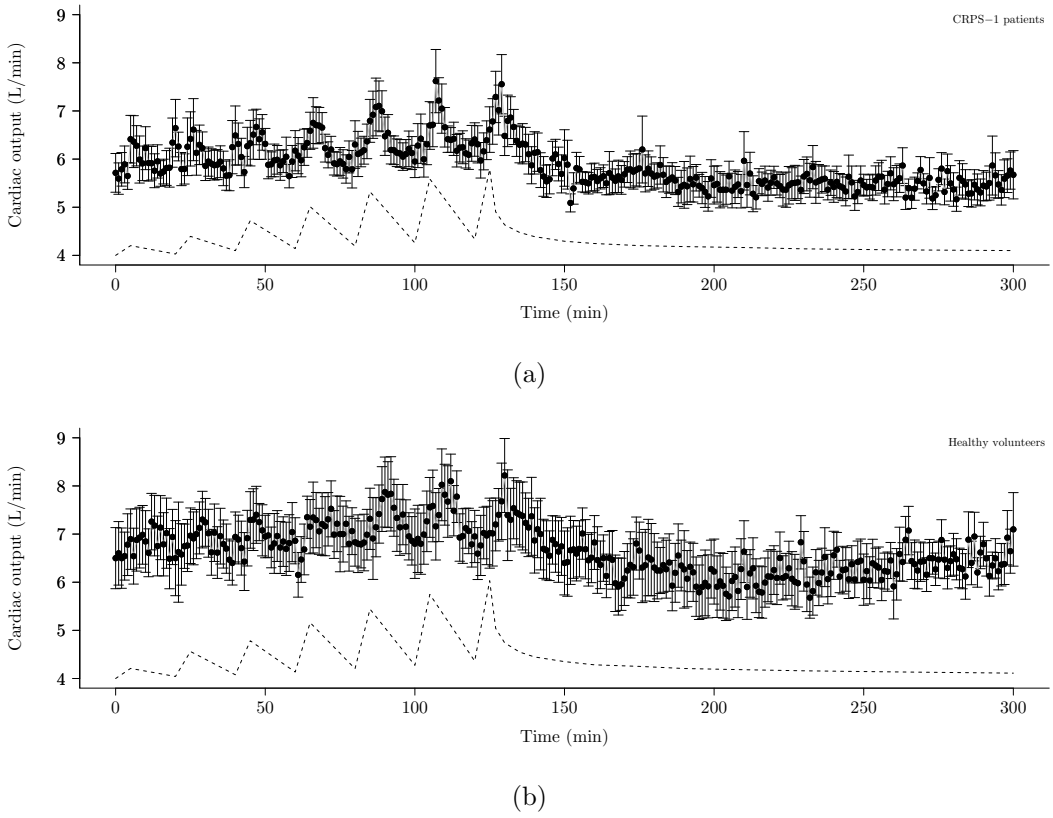
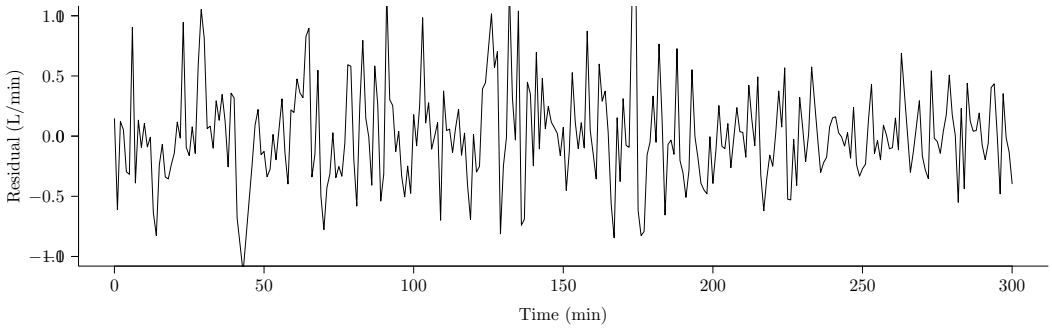


Figure 4.4: Mean cardiac output values in CRPS-1 patients (a) and volunteers (b)
Each dot is the between-subject average of a 1-min cardiac output average. The values are mean ± SEM. The broken lines are the population plasma S(+)-ketamine concentrations.

of a low-dose propofol infusion (2 and 3 mg/kg per h) 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 30-40 min. These observations are in close agreement with ours and give strength to the model choice made by us. We estimated a half-life for onset/off set of ketamine's effect on CO of about 3 min. This is in close agreement with the time course for the increase in plasma epinephrine and norepinephrine and systolic blood pressure following an induction dose of ketamine in adult and pediatric patients. This then suggests that the stimulatory effect of S(+)-ketamine is secondary to the release of catecholamines rather than a direct effect of ketamine at the myocardium or cardiac neural tissue.

In contrast to the PK parameters, PD model parameters did not differ between CRPS-1 patients and healthy young volunteers. This suggests that central sympathetic reactivity remained intact in our CRPS-1 patients. There are indications, however, for a disturbance of the sympathetic system in CRPS-1 patients.[6,7] In acute CRPS-1 patients perfusion of the affected limb is often higher than that of the contralateral limb due to inhibition of cutaneous sympathetic vasoconstrictor neurons.[7] In chronic CRPS-1



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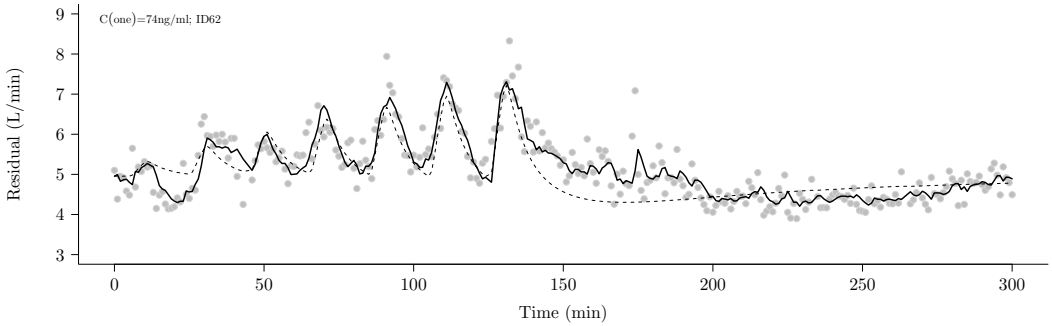

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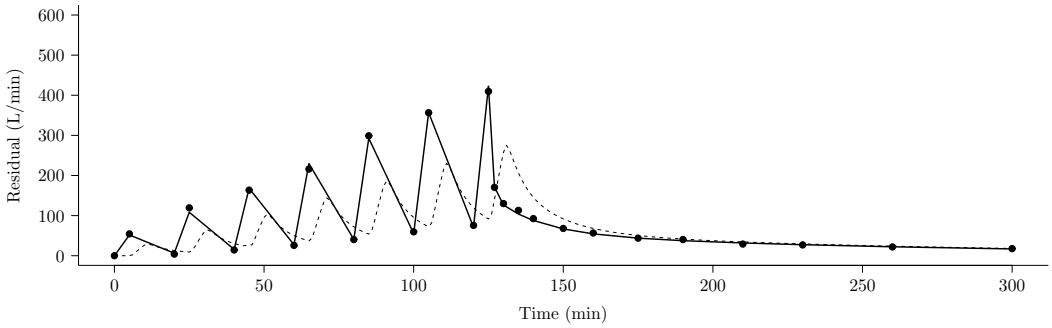

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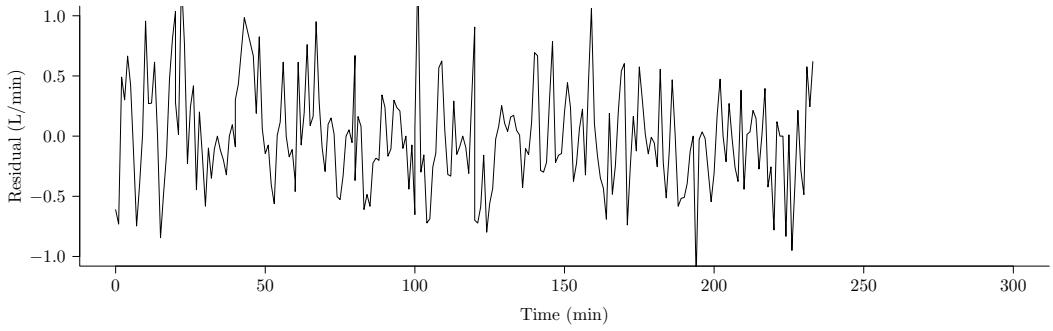
Figure 4.5: Example of a data fit of cardiac output of one subject (id 62) with a low value for C_{ONE} (74 ng/ml)

The top panel (a) shows the residual between the measured data and the data fit. The grey dots are the 1-min 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) depicts the measured plasma S(+)-ketamine concentration (filed symbols), PK data fit (continuous line) and S(+)-ketamine concentration at its effector site (broken line).



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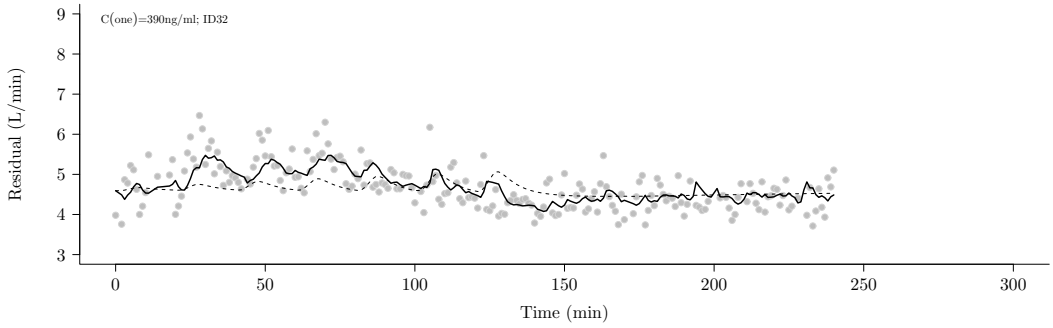

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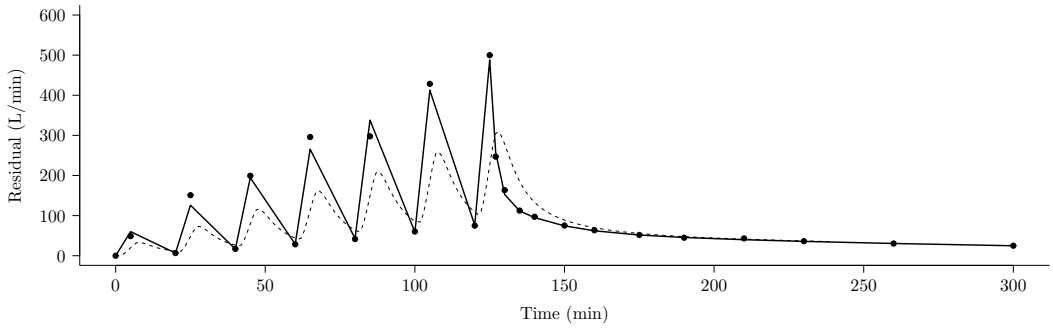

(c)

Figure 4.6: Example of a data fit of cardiac output of one subjects (id 61) with a low value for C_{ONE} (390 ng/ml)

The top panel (a) shows the residual between the measured data and the data fit. The grey dots are the 1-min 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) depicts the measured plasma S(+)-ketamine concentration (filed symbols), PK data fit (continuous line) and S(+)-ketamine concentration at its effector site (broken line).

patients vasoconstriction may occur despite lower norepinephrine levels at the affected side, again suggestive of a disequilibrium within the sympathetic system.[7] Our data suggests that since central sympathetic responses remain intact in CRPS-1 patients that the earlier observations in affected versus contralateral limbs are of peripheral rather than central (*e.g.*, spinal) origin. This hypothesis does not agree with findings of intact neuronal tissue (*i.e.*, absence of overt nerve lesions) in the skin of CRPS-1 patients.[19] However, subtle functional changes in cutaneous sympathetic fibers cannot be excluded as causative factor. Evidently, this is an important issue that needs further study.

In order to obtain a more accurate estimation of the parameters of the deterministic and noise components of the model, a Kalman filter was implemented.[13,20] In figures 4.5 and 4.6 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 auto-correlation and cross-correlation functions of the residuals now indicated 'white' noise without any significant correlations present (data not shown). We previously used a similar modeling procedure when estimating the various components active in the ventilatory control system upon stimulation with carbon dioxide.[20] We similarly concluded that the residuals were 'white' without the presence of significant correlations when analyzing the data with a noise model with Kalman filter, and favored the more complex model to analyze the noisy respiratory data sets. One possible complication of using a Kalman filter may be that an accurate estimation of between-subject variability is more difficult as between-subjects noise components may be lost in the dynamics of the process noise. However, no such problems occurred in the current data set as we obtained realistic values for between subject variability (ω^2s in Table 4.2). This may be related to the relatively slow effect of ketamine on CO ($t_{1/2}$= 2-3 min), much slower than the noise observed in the data.

In conclusion, we assessed the stimulatory effect of S(+)-ketamine on cardiac output in CRPS-1 patients and healthy volunteers using a PK-PD modeling approach. The PD model had one direct stimulatory and one adaptive component. We observed differences in PK model parameters between study groups but none in PD parameters. Since it is assumed that ketamine causes cardiovascular stimulation through activation of the sympathetic system, our data suggests that the sympathetic system remains intact in CRPS-1 patients.

Appendix: Implementation of the Kalman filter

For the state of the controller and its variance we write (conform Tornøe *et. al.*[14]):

$$\frac{dY_C}{dt} = g\dot{(}Y_C, Y_{E,\tau}) = \frac{Y_E - Y_C}{\tau} \tag{4.6}$$

$$\frac{dP}{dt} = AP + PA^T\sigma\nu\sigma\nu^T, withA = \partial g(Y_C, Y_E, \tau)/\partial Y_C = -1/\tau \tag{4.7}$$

$$\sigma\nu^T - 2P/\tau \tag{4.8}$$

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

$$RVR = P + \sigma_\epsilon^2, \tag{4.9}$$

and the Kalman gain (K)

$$K = -P/RVR \tag{4.10}$$

where the minus sign comes from the fact that YC is subtracted from the model output in equation 4.3. 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

$$Y_{C,i} = Y_{C,i} \cdot exp(\Delta t/\tau) + Y_{E,i} \cdot (1 - exp(\Delta t/\tau)) \tag{4.11}$$

$$P_i = P_{i-1} \cdot exp(-2\Delta t/\tau) + 1/2 \cdot \sigma^2 \cdot (1 - exp(-2\Delta t/\tau)) \tag{4.12}$$

The Kalman filter updates Y_C *via* K (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 equation 4.12, 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 = σ_ν^2 and VRM = σ_ϵ^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 that the Kalman gain KALG is known throughout each individual's record (it does not need to be estimated recursively).

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