

S(+)-Ketamine Increases Muscle Sympathetic Activity and Maintains the Neural Response to Hypotensive Challenges in Humans

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Background: **S(+)-Ketamine is reported to exert twofold greater analgesic and hypnotic effects but a shorter recovery time in comparison with racemic ketamine, indicating possible differential effects of stereoisomers. However, cardiovascular regulation during S(+)-ketamine anesthesia has not been studied. Muscle sympathetic activity (MSA) may be an indicator of the underlying alterations of sympathetic outflow. Whether S(+)-ketamine decreases MSA in a similar manner as the racemate is not known. Thus, the authors tested the hypothesis that S(+)-ketamine changes MSA and the muscle sympathetic response to a hypotensive challenge.**

Methods: **Muscle sympathetic activity was recorded by microneurography in the peroneal nerve of six healthy participants before and during anesthesia with S(+)-ketamine (670 μg/kg intravenously followed by 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Catecholamine and ketamine plasma concentrations, heart rate, and arterial blood pressure were also determined. MSA responses to a hypotensive challenge were assessed by injection of sodium nitroprusside (2–10 μg/kg) before and during S(+)-ketamine anesthesia. In the final step, increased arterial pressure observed during anesthesia with S(+)-ketamine was adjusted to preanesthetic values by sodium nitroprusside infusion (1–6 $\mu g \cdot kg^{-1} \cdot min^{-1}$).**

Results: **Anesthesia with S(+)-ketamine (ketamine plasma concentration 713 ± 295 μg/l) significantly increased MSA burst frequency (mean ± SD; 18 ± 6 to 35 ± 11 bursts/min) and burst incidence (32 ± 10 to 48 ± 15 bursts/100 heartbeats) and was associated with a doubling of norepinephrine plasma concentration (from 159 ± 52 to 373 ± 136 pg/ml) parallel to the increase in MSA. Heart rate and arterial blood pressure also significantly increased. When increased arterial pressure during S(+)-ketamine was decreased to awake values with sodium nitroprusside, MSA increased further (to 53 ± 24 bursts/min and 60 ± 20 bursts/100 heartbeats, respectively). The MSA increase in response to the hypotensive challenge was fully maintained during anesthesia with S(+)-ketamine.**

Conclusions: **S(+)-Ketamine increases efferent sympathetic outflow to muscle. Despite increased MSA and arterial pressure during S(+)-ketamine anesthesia, the increase in MSA in response to arterial hypotension is maintained.**

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RECEPTOR-MEDIATED effects are often dependent on the stereoconformation of the receptor ligand. In the case of ketamine, the *S*(+)-isomer has recently been approved for clinical use in Europe. Although significant pharmacokinetic differences between the isomers were not observed, *S*(+)-ketamine exhibits twofold greater analgesic and hypnotic potencies as compared with the racemic mixture.[1–3] Moreover, recovery from anesthesia was shorter when the *S*(+)-isomer was used in virtually every study published to date.[1,2,4–6] Similarly, the increase in catecholamine plasma concentrations and the cardiovascular response pattern observed in response to *S*(+)-ketamine appears not to differ from that reported after administration of the racemic mixture.[1,2,7] Nevertheless, animal experiments suggest that the *S*(+)-isomer inhibits both neuronal and extraneuronal uptake of catecholamines, whereas the *R*(−)-isomer does not alter extraneural uptake.[8,9]

Effects of *S*(+)-ketamine on cardiovascular regulation and efferent sympathetic nerve activity have not been reported in humans. Furthermore, it is not known whether *S*(+)-ketamine decreases muscle sympathetic activity (MSA) in a similar manner as reported for racemic ketamine.[10] Thus, we recorded MSA in humans to test the hypothesis that anesthesia with *S*(+)-ketamine increases MSA and does not alter the physiologic increase in MSA in response to a hypotensive challenge.

Material and Methods

Participants

The protocol of the study was approved by the Ethics Committee of the Medical School at the University of Essen, Essen, Germany (Ethik-Kommission der Medizinischen Fäkultat Essen) and is consistent with the revised Declaration of Helsinki. Six unpremedicated healthy volunteers (1 female, 5 male) participated in this study on a voluntary basis and gave written informed consent. Participants were young (26 ± 2 yr, mean ± SD; range, 23–29 yr), of normal body weight (body mass index, 22.8 ± 2.1 kg m^{-2}; range, 20.3–25.7 kg m^{-2}), normotensive, free of cardiovascular disease as assessed by medical history and physical examination, and were classified as American Society of Anesthesiologists physical status I. None of the participants was taking any prescription or nonprescription drugs.

No coffee, tea, or tobacco was allowed for 12 h before measurements. After an overnight fast, participants were

studied in the supine resting position at 8:00 AM. An 18-gauge venous cannula was placed in an antecubital vein for fluid replacement (Ringer's lactate, 2 ml · kg^{-1} · h^{-1}) and blood sampling. Patients were monitored with a continuous five-lead electrocardiogram recording with on-line ST-segment analysis (leads II and V_5) and noninvasive blood pressure measurement (Sirecust; Siemens, Erlangen, Germany).

Measurements

Muscle Sympathetic Activity. Multiunit postganglionic efferent sympathetic activity to muscle (MSA) was recorded by microneurography in the peroneal nerve at the fibular head and identified as previously described.[11,12] The nerve signal was amplified (×50,000), filtered (bandpass, 500–2,000 Hz), and fed through a discriminator for further noise reduction and audio monitoring. A mean voltage (integrated) signal was obtained by passing the original signal through a resistance-capacitance circuit (time constant, 0.1 s). During the study, neural activity and arterial pressure were monitored on a storage oscilloscope.

Bursts of MSA were counted and expressed as MSA burst frequency (bursts/min). Because a maximum of one MSA burst can be associated with each cardiac cycle, the maximum possible number of bursts increases with increases in heart rate and vice versa. Thus, MSA bursts were counted and also expressed as MSA burst incidence (bursts/100 heartbeats). Furthermore, the area under the curve of each MSA burst was assessed in arbitrary units as an estimate for the number of activated sympathetic fibers, indicating the strength of single bursts.[13] MSA total activity was calculated as the sum of MSA areas during a 5-min observation period and expressed in arbitrary units per minute.

Cardiovascular Variables. Arterial blood pressure was measured by the volume-clamp method using a plethysmography cuff placed around the middle phalanx of the third finger (Finapres 2300; Ohmeda, Madison, WI). When compared with intraarterial measurements, this method has been shown to provide reliable beat-by-beat measurements of blood pressure changes during a variety of test conditions.[14] Recognizing that the blood pressure measured in the upper arm may slightly differ from that assessed in a finger (Finapres), we adjusted the position of the finger cuff until measurements comparable with those determined by oscillometry in the upper arm of the same extremity were obtained.

Muscle Sympathetic Activity Response to a Hypotensive Challenge. To evaluate the relation between MSA and arterial blood pressure during a hypotensive challenge, sodium nitroprusside (SNP) was injected (2–10 μg/kg intravenously) both in the awake state (baseline) and during *S*(+)-ketamine anesthesia. SNP dosage was targeted to achieve a decrease in mean arterial pressure by approximately 20 mmHg. Thirty-second intervals of steady-state conditions immediately before administration of SNP and after reaching the nadir of the pressure decrease were considered for analysis. The relation between average MSA burst frequency and diastolic arterial pressure was compared before and during administration of SNP (ratios of MSA to arterial pressure reveal the closest relation when MSA is correlated to diastolic arterial pressure rather than to systolic or mean arterial pressure).[15]

Catecholamine Plasma Concentration. Norepinephrine and epinephrine plasma concentrations were determined using Beckmann System Gold HPLC device (Beckmann, München-Unterschleissheim, Germany) and Chromsystems 41,000 electrochemical detector (Chromsystems, München-Martinsried, Germany). A catecholamine detection kit was purchased from Chromsystems (catalog No. 5000), which included a probe preparation system, high-performance liquid chromatography column, and all necessary chemicals and buffers (lower detection limit, 10 pg/ml for both epinephrine and norepinephrine; coefficient of variation, 6.2% for norepinephrine, 6.8% for epinephrine).

Ketamine Plasma Concentration. Ketamine was measured using high-performance liquid chromatography and photo-diode-array detector (models 2690 and 996; Waters, Eschborn, Germany). Briefly, plasma samples (500 μl) were mixed with 10 μl of internal standard (50 μg/ml etidocaine), and the substances of interest were extracted using a modified ethyl-ether extraction method as previously described.[16] The lower limit of detection (signal-to-noise ratio > 3) was 10 ng/ml, with a coefficient of variation of 3%.

Respiration. Respiration was continuously monitored with a piezoelectric transducer (Pneumotrace; UFI, Morro Bay, CA) placed around the lower chest at the level of maximum amplitude (usually at the level of intercostal spaces 8–12), and the number of inspirations per minute was recorded. Arterial oxygen saturation was assessed by pulse oximetry (Sirecust; Siemens, Erlangen, Germany).

Data Recording and Management

Analog variables (MSA, electrocardiogram, arterial pressure, respiration) were fed into a personal computer after analog–digital conversion with a sampling frequency of 200 Hz per channel (DT2821; Data Translation GmbH, Bietigheim-Bissingen, Germany). All analyses were performed by computer (off-line) using a dedicated program (Tomas Karlsson, Göteborg, Sweden).

Study Protocol

The last 5 min of a 15-min resting period were used for determination of baseline MSA in the awake state. Antecubital venous blood for measurement of catecholamine and ketamine plasma concentrations was sampled immediately after the resting period from an intravenous cath-

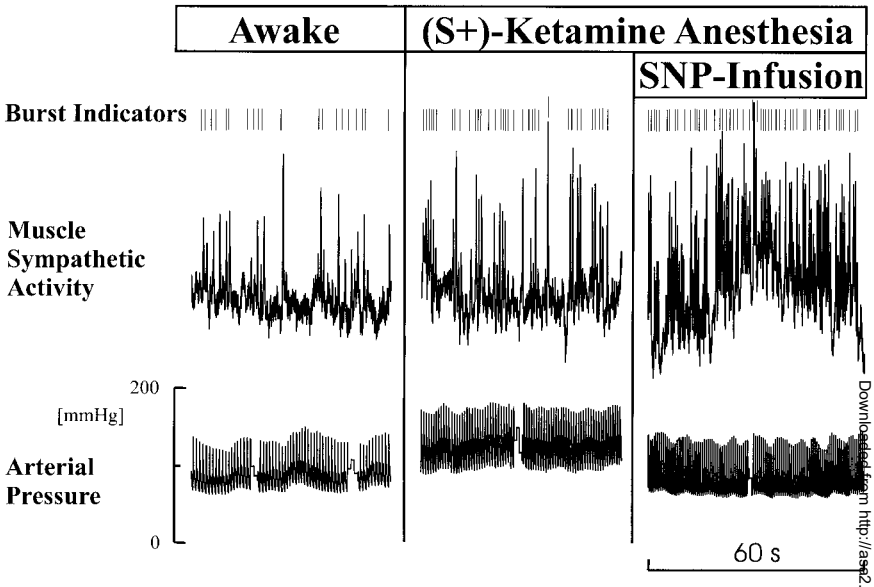

Fig. 1. Muscle sympathetic nerve activity and arterial pressure in the awake state (*left*), during anesthesia with *S*(+)-ketamine (*middle*), and during *S*(+)-ketamine anesthesia with arterial pressure adjusted to preanesthetic baseline by infusion of sodium nitroprusside (SNP; *right*). Original recording from a representative volunteer. Sympathetic bursts are indicated at the top of the muscle sympathetic activity recording. Ketamine anesthesia increased both muscle sympathetic activity and arterial pressure. Adjustment of arterial pressure by sodium nitroprusside during ketamine anesthesia to awake baseline further increased muscle sympathetic activity.

eter. Anesthesia was then induced by intravenous injection of *S*(+)-ketamine (Ketanest S; Parke-Davis, Freiburg, Germany) in a dose of 670 μg/kg administered over 30 s, followed by an infusion of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. MSA was averaged during 5 min when steady-state conditions were achieved during *S*(+)-ketamine anesthesia. Blood samples were withdrawn immediately at the end of this observation period. After initial recording during the resting period, a decrease in arterial pressure was induced (in duplicate) in the awake state before induction of anesthesia and again during ketamine steady-state anesthesia.

To minimize influences of arterial pressure on assessment of MSA during *S*(+)-ketamine anesthesia, in a final step, SNP was continuously infused to decrease arterial pressure to the baseline blood pressure measured in the awake state. MSA was then recorded for another 5 min during steady-state *S*(+)-ketamine anesthesia, and at the end of this period, venous blood was drawn for assessment of catecholamine and ketamine plasma concentrations.

Statistical Analysis

All data are expressed as mean ± SD unless otherwise indicated. Differences in mean values of variables over time were determined by a one-way repeated measures analysis of variance, followed by Newman-Keuls *post hoc* test. The following *a priori* null hypotheses were tested: There is no difference in means of variables at awake baseline compared with observations during *S*(+)-ketamine anesthesia alone, and when arterial blood pressure was adjusted during *S*(+)-ketamine anesthesia to awake baseline as well as to observations during *S*(+)-ketamine anesthesia. A null hypothesis was rejected and statistical significance assumed with an α-error (*P*) of less than 0.05.

Results

S(+)-Ketamine anesthesia increased efferent sympathetic outflow to muscle and norepinephrine plasma concentrations. Figure 1 shows a representative recording of MSA along with arterial pressure in the awake state and during anesthesia with *S*(+)-ketamine before and after adjustment of arterial pressure to the awake baseline value by infusion of SNP.

Effects of S(+)-Ketamine Administration

Anesthesia with *S*(+)-ketamine significantly increased MSA burst frequency (18 ± 6 to 35 ± 11 bursts/min) and MSA burst incidence (32 ± 10 to 48 ± 15 bursts/100 heartbeats; fig. 2). MSA total activity significantly increased by 170% from 494 ± 226 to 1,313 ± 576 units/min (fig. 2).

In parallel, norepinephrine plasma concentration significantly increased from 159 ± 52 at baseline to 373 ± 136 pg/ml (fig. 3). The response of epinephrine plasma concentration to *S*(+)-ketamine varied substantially between participants (range, −92–+332 pg/ml) and did not attain statistical significance (fig. 3).

Mean arterial pressure significantly increased from 87 ± 15 to 133 ± 19 mmHg after *S*(+)-ketamine administration, whereas heart rate increased from 56 ± 8 to 70 ± 12 beats/min (fig. 3).

Administration of *S*(+)-ketamine yielded ketamine plasma concentrations of 713 ± 295 μg/l and abolished corneal and glabellar reflexes. Furthermore, there were no responses in heart rate or movement to painful stimuli (pinching of the skin).

Effects of Adjustment of Arterial Pressure during S(+)-Ketamine Anesthesia to Awake Baseline

When increased arterial pressure during *S*(+)-ketamine anesthesia was decreased to preanesthetic baseline values

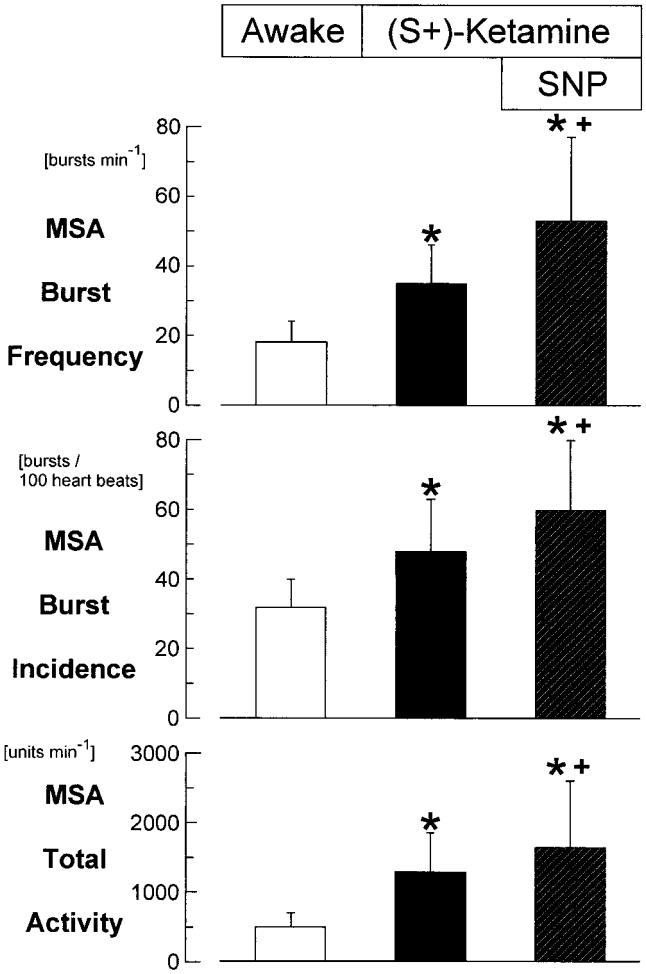

Fig. 2. Muscle sympathetic activity (MSA; burst frequency, burst incidence, and total activity) in the awake state, during anesthesia with *S*(+)-ketamine, and during *S*(+)-ketamine anesthesia with arterial pressure adjusted to awake baseline by infusion of sodium nitroprusside (SNP). Mean ± SD from six volunteers. MSA was doubled after induction of anesthesia with *S*(+)-ketamine both with respect to bursts per time and bursts per 100 heartbeats. Considering the strength of each individual burst by calculating the total activity MSA was almost tripled. When arterial pressure during *S*(+)-ketamine anesthesia was decreased to awake baseline by sodium nitroprusside, so as to inhibit baroreflex afferents, MSA markedly increased further, that is, beyond the increase observed during anesthesia with *S*(+)-ketamine alone. **P* < 0.05 *versus* baseline awake; +*P* < 0.05 *versus* *S*(+)-ketamine anesthesia.

by infusion of SNP (6.2 ± 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), MSA burst frequency (to 53 ± 24 bursts/min), burst incidence (to 60 ± 20 bursts/100 heartbeats), and total activity (to 1,616 units/min) increased further (fig. 2). Norepinephrine plasma concentration also increased further (to 571 ± 404 pg/ml), whereas epinephrine plasma concentration showed a similar relative increment that did not reach statistical significance because of greater variability (fig. 3). Ketamine plasma concentrations were unchanged until the end of the observation period (857 ± 362 μg/l).

Muscle Sympathetic Activity Response to a Hypotensive Challenge

A 24% decrease in diastolic arterial pressure was achieved by SNP injections both in the awake state and during anesthesia with *S*(+)-ketamine. Diastolic arterial pressure decreased from 74 ± 16 to 57 ± 15 mmHg in the awake state and from 93 ± 13 to 70 ± 10 mmHg during *S*(+)-ketamine anesthesia. A significantly greater dose of SNP was necessary for this pressure decrease during *S*(+)-ketamine anesthesia (6.3 ± 1.2 μg/kg; range, 5–10 μg/kg) than in the awake state (2.5 ± 0.1 μg/kg; range, 2–3 μg/kg).

In the awake state, the mean MSA response to the SNP-induced decrease in diastolic pressure was −2.0 ± 0.5 bursts · min^{-1} · $mmHg^{-1}$. This MSA response was not altered during *S*(+)-ketamine anesthesia (-1.8 ± 1.0 bursts · min^{-1} · $mmHg^{-1}$), as shown in figure 4.

Respiration

Breathing frequency (13 ± 2 breaths/min in the awake state *vs.* 13 ± 3 breaths/min during *S*(+)-ketamine anesthesia) and arterial oxygen saturation did not change (98 ± 1% in the awake state *vs.* 99 ± 1% during *S*(+)-ketamine anesthesia) after administration of *S*(+)-ketamine while subjects were breathing room air. There were no complications attributable to this study.

Discussion

This study assessed sympathetic neural outflow to muscle in humans during general anesthesia with *S*(+)-ketamine. *S*(+)-Ketamine increased sympathetic outflow to muscle, increased norepinephrine plasma concentration, and was associated with increased arterial pressure. Furthermore, the MSA response to hypotensive challenges was fully maintained during anesthesia with *S*(+)-ketamine even at higher arterial pressures.

These results partly contrast to our earlier observations during anesthesia with racemic ketamine where sympathetic neural outflow to muscle decreased during increased arterial pressure,[10] thus demonstrating different effects of *S*(+)- and racemic ketamine on MSA. Accordingly, stereoselective differences of ketamine on sympathetic outflow in humans may be suggested.

Ketamine's main action is thought to be mediated by binding to the phencyclidine receptor in the NDA-channel, thus inhibiting glutamate activation of this channel in a noncompetitive manner.[17] Moreover, interactions with non-NDA glutamate receptors, opioid receptors ($\mu > \kappa > \delta$), γ-amino butyric acid receptor type A, nicotinuric and muscarinergic receptors, as well as with sodium, potassium, and calcium channels have been reported.[18] However, interactions with receptors other than *N*-methyl-D-aspartate receptors were only observed when ketamine's concentrations exceeded 10- to 100-fold the plasma con-

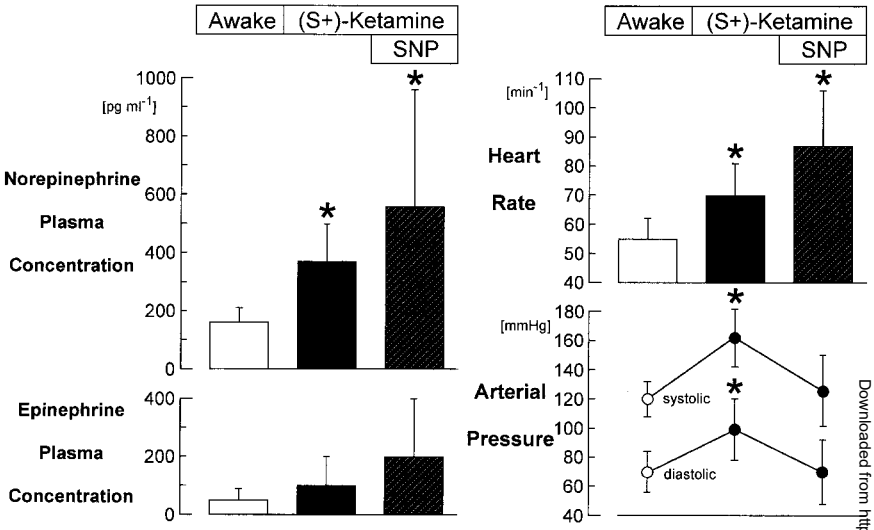

Fig. 3. Norepinephrine and epinephrine plasma concentrations as well as heart rate and arterial pressure in the awake state, during anesthesia with *S*(+)-ketamine and during *S*(+)-ketamine anesthesia with arterial pressure adjusted to awake baseline by infusion of sodium nitroprusside (SNP). Mean ± SD from six volunteers. Arterial pressure and heart rate significantly increased during *S*(+)-ketamine anesthesia, as did norepinephrine plasma concentrations. Note that at the end of the study, arterial pressure was decreased by sodium nitroprusside during *S*(+)-ketamine and did not differ from values in awake participants. Moreover, norepinephrine plasma concentration tended to increase further during infusion of sodium nitroprusside, in parallel to a significant increase in muscle sympathetic activity. In contrast, mean epinephrine plasma concentration did not significantly change during anesthesia with *S*(+)-ketamine. *$P < 0.05$ *versus* baseline awake.

centrations observed in humans during anesthesia.[18,19] With regard to the sympatho-adrenergic system, ketamine inhibits neural and extraneuronal catecholamine uptake.[8,9,20]

Studies in animals and humans demonstrated that *S*(+)-ketamine exhibits a two- to fourfold greater analgesic and hypnotic potency compared with the *R*(−)-isomer,[21] although their pharmacokinetic properties do not differ.[3] Accordingly, a decrease of the ketamine dose by 50–70% has been recommended when the *S*(+)-isomer is used alone. Because adverse psychotropic effects have been attributed to the *R*(−)-isomer,[1,2,5] a decrease in side effects has been anticipated with the introduction of the *S*(+)-isomer.

Administration of *S*(+)-ketamine in our volunteers yielded plasma concentrations of approximately 800 μg/l, that is, concentrations in the range (250–1,000 μg/l) that have been shown to provide "surgical anesthesia" and that are approximately half of those observed in our previous study, where MSA was recorded during anesthesia with racemic ketamine.[1,2,10]

Consistent with previous studies, these *S*(+)-ketamine plasma concentrations were associated with increased norepinephrine plasma concentration as well as arterial pressure and heart rate.[1,2,4,7] Although *S*(+)-ketamine inhibits not only neural, but also extraneural, catecholamine uptake in comparison with the *R*(−)-isomer,[8,9] differences in heart rate, arterial blood pressure, and norepinephrine and epinephrine plasma concentrations were not observed in randomized, double-blinded comparisons between racemic and *S*(+)-ketamine anesthesia.[1,2,7]

It is unknown, however, whether sympathetic neural outflow is altered by *S*(+)-ketamine. Our results demonstrate an increase in efferent sympathetic neural outflow to muscle in response to *S*(+)-ketamine. This increase in sympathetic nerve traffic is even more pronounced when increased arterial blood pressure was decreased to preanesthetic awake baseline values. This increase in MSA during *S*(+)-ketamine anesthesia paralleled the increase in norepinephrine plasma concentration and is likely to have contributed to increased norepinephrine plasma concentrations.[22] Thus, increased sympathetic outflow to muscle is one mechanism likely to increase norepinephrine plasma concentration during anesthesia with *S*(+)-ketamine in humans. The observed increase in both MSA and arterial pressure during anesthesia with

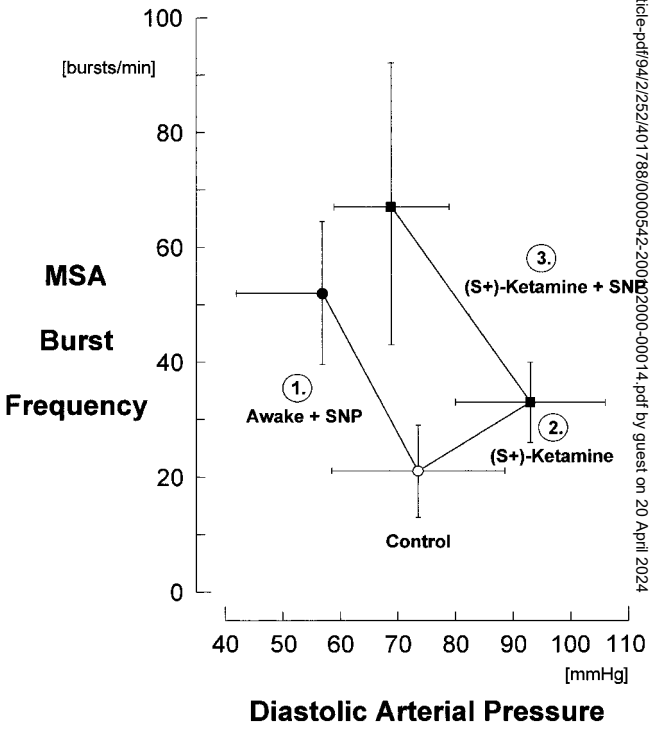

Fig. 4. Relations between diastolic arterial pressure and muscle sympathetic activity (MSA) burst frequency in response to a hypotensive challenge by sodium nitroprusside (SNP) in the awake state and during anesthesia with *S*(+)-ketamine. Similar increases in MSA in response to an evoked decrease in diastolic arterial pressure were obtained in the awake state (1) and during anesthesia with *S*(+)-ketamine (3). Mean ± SD from six participants. Thus, the muscle sympathetic response to a hypotensive challenge is maintained during anesthesia with *S*(+)-ketamine.

S(+)-ketamine is quite remarkable because in awake subjects, even a slight increase in arterial blood pressure abolishes efferent sympathetic activity to muscle almost immediately.[15]

Furthermore, in a previous study,[10] racemic ketamine evoked a decrease in MSA despite a similar increase in arterial pressure as during *S*(+)-ketamine anesthesia in this study. In contrast to racemic ketamine, barbiturates, propofol, and etomidate,[10,15,23–25] *S*(+)-ketamine, therefore, is the only intravenous anesthetic that increases MSA despite an increase in arterial pressure. Thus, our data may also suggest stereoselective effects of ketamine on sympathetic neural outflow to muscle. Despite the increase in arterial pressure, the muscle sympathetic response to hypotensive challenges was well-maintained during anesthesia with *S*(+)-ketamine, which is in concordance to our earlier findings with racemic ketamine.[10]

One could argue that sympathetic activation observed during *S*(+)-ketamine anesthesia may be the result of respiratory depression. However, clinically administered doses of ketamine do not cause significant respiratory depression except within the first minutes after a rapid bolus injection.[26,27] Moreover, arterial oxygen saturation was always more than 96% and remained unchanged during *S*(+)-ketamine anesthesia with room air breathing. Thus, relevant hypoxemia and hypercarbia can be excluded. In fact, even severe combined hypoxia and hypercapnia (inspiratory gas fractions, 10% oxygen, 7% carbon dioxide) does not increase MSA total activity beyond the values observed during *S*(+)-ketamine anesthesia in our study.[28] Accordingly, even undetected minor hypercarbia could not have evoked increases in MSA as profound as observed in our volunteers.

The increase in neural sympathetic outflow to muscle and maintenance of sympathetic baroreflexes during *S*(+)-ketamine anesthesia may be explained by at least two different mechanisms. First, NDA receptors have been identified in central nuclei known to be involved in the baroreflex loop, such as the nucleus tractus solitarius.[29–31] In animal experiments, intracerebral, intrathecal, and systemic administration of NDA-receptor antagonists decreased baroreceptor-dependent nucleus tractus solitarius neuronal activity and evoked a decrease in preganglionic sympathetic discharge.[32–35] Thus, sympathetic neural outflow may be disinhibited during *S*(+)-ketamine, but with maintained baroreflex sensitivity and increased arterial blood pressure. Moreover, because activation of adrenergic receptors in various cardiovascular nuclei, such as the locus ceruleus, alters sympathetic outflow central catecholamine uptake, inhibition evoked by *S*(+)-ketamine may have influenced the sympathetic neural response to ketamine as well.[7,8,20,29] However, this still does not explain why *S*(+)-ketamine and racemic ketamine, although both preserving the sympathetic neural response to muscle during arterial hypotension, affect MSA differently despite a similar increase in arterial pressure.

In summary, anesthesia with *S*(+)-ketamine increases MSA in humans despite an increase in arterial pressure and maintains the MSA increase in response to hypotensive challenges. Because racemic ketamine decreases MSA while increasing arterial pressure,[10] stereoselective differences of ketamine on cardiovascular regulation and neural sympathetic outflow to muscle may be involved.

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