Racemic Ketamine Decreases Muscle Sympathetic Activity but Maintains the Neural Response to Hypotensive Challenges in Humans

Peter Kienbaum, M.D.,* Thorsten Heuter, † Martin C. Michel, M.D., ‡ Jürgen Peters, M.D.§

Background: Cardiovascular stimulation and increased catecholamine plasma concentrations during ketamine anesthesia have been attributed to increased central sympathetic activity as well as catecholamine reuptake inhibition in various experimental models. However, direct recordings of efferent sympathetic nerve activity have not been performed in humans. The authors tested the hypothesis that racemic ketamine increases efferent muscle sympathetic activity (MSA) and maintains the muscle sympathetic response to hypotensive challenges.

Methods: Muscle sympathetic activity was recorded by microneurography in the peroneal nerve of six healthy subjects before and during anesthesia with racemic ketamine (2 mg/kg intravenously plus 30 μg·kg⁻¹·min⁻¹). Catecholamine plasma concentrations, heart rate, and blood pressure were also determined. Muscle sympathetic neural responses to a hypotensive challenge were assessed by injection of sodium nitroprusside (2–10 μg/kg) before and during ketamine anesthesia. In the final step, increased arterial pressure observed during ketamine anesthesia was adjusted to preanesthetic baseline by sodium nitroprusside infusion (1–6 μg·kg⁻¹·min⁻¹).

Results: Ketamine significantly decreased MSA burst frequency (mean ± SD, 18 ± 9 bursts/min to 9 ± 8 bursts/min) and burst incidence (26 ± 11 bursts/100 heart beats to 9 ± 6 bursts/100 heart beats). However, when increased mean arterial pressure (85 ± 8 mmHg to 121 ± 20 mmHg) was normalized to the awake baseline by sodium nitroprusside, MSA recovered (25 ± 18 bursts/min; 23 ± 14 bursts/100 heart beats). During ketamine anesthesia, both epinephrine (15 ± 10 pg/ml to 256 ± 193 pg/ml) and norepinephrine (250 ± 105 pg/ml to 570 ± 270 pg/ml) plasma concentrations significantly increased, as did heart rate (67 ± 13 beats/min to 113 ± 15 beats/min). Hypotensive challenges similarly increased MSA both in the awake state and during ketamine anesthesia.

Conclusions: During increased arterial blood pressure associated with ketamine, sympathetic discharge to muscle blood vessels decreases at the same time that plasma concentrations of norepinephrine increase. When this increase in arterial blood pressure is reversed, MSA during ketamine is not changed from preketamine baseline recordings. Finally, hypotensive challenges still evoke an unchanged sympathetic reflex response. Thus, our results do not support the assumption that ketamine anesthesia increases sympathetic nerve activity in a generalized fashion. (Key words: Hemodynamics; hypotension; sodium nitroprusside.)

KETAMINE has been administered to patients for anesthesia as well as analgesia and sedation for > 30 yr. It is the only injectable anesthetic that induces increases in arterial pressure and heart rate.¹,² This cardiovascular stimulation is associated with increased catecholamine plasma concentrations.³ Because even small amounts of ketamine, when injected into the cerebral circulation in goats, induced a similar increase in arterial pressure and cardiac output (by increased heart rate) as a larger dose administered intravenously, it was assumed to evoke central sympathetic activation, although sympathetic activity had not been assessed directly.⁴ However, the observed cardiovascular stimulation may also be caused by vagal withdrawal, which has been reported during ketamine anesthesia.⁵ Pharmacologic investigations in isolated tissues suggested that ketamine inhibits neural and extraneuronal norepinephrine uptake.⁶–⁹ Accordingly, norepinephrine could accumulate in the synaptic cleft and increase arterial pressure irrespective of central sympathetic drive.

In awake and anesthetized humans, efferent sympathetic nerve activity is usually recorded in peripheral nerves to muscle (muscle sympathetic activity [MSA])
and closely related to arterial blood pressure control.\textsuperscript{10–14} Thus, recordings of MSA are suitable to directly assess sympathetic nervous system activity to muscle during ketamine anesthesia.

Accordingly, we recorded MSA in humans to test the hypothesis that racemic ketamine increases MSA. Furthermore, we determined whether ketamine alters the normal increase in MSA in response to a hypotensive challenge.

**Material and Methods**

**Subjects**

The protocol of the study was approved by the ethics committee of the University GH Essen and is consistent with the declarations of Helsinki. All subjects were enrolled on a voluntary basis and gave written informed consent. Six male subjects who were not premedicated (three preoperative patients and three healthy volunteers) participated in the study. Subjects were young (mean $\pm$ SD, 30 $\pm$ 6 yr; range, 24–38 yr), of normal weight (body mass index, 22.6 $\pm$ 2.3 kg/m$^2$; range, 19.3–26.3 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 subjects was taking any prescription or nonprescription drugs.

No coffee, tea, or tobacco was allowed for 12 h before measurements. After an overnight fast, subjects 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 (2 ml $\cdot$ kg$^{-1}$ $\cdot$ 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$\text{_{5}}$), noninvasive blood pressure measurement, and pulse oximetry (Sirecust; Siemens, Erlangen, Germany).

**Measurements**

**MSA.** Multiunit postganglionic efferent MSA was recorded by microneurography in the peroneal nerve at the fibular head and identified as previously described.\textsuperscript{12–14} The nerve signal was amplified ($\times$ 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) and MSA burst incidence (bursts/100 heart beats), the latter also accounting for the maximum number of bursts possible. 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.\textsuperscript{14,15} Total MSA 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 noninvasively by the volume-clamp method using a plethysmographic cuff placed around the middle phalanx of the third finger (Finapres 2,300; 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.\textsuperscript{16,17} According to our experiences, the absolute level of blood pressure assessed by this method may depend on the selection of the appropriate cuff size and positioning of the cuff. 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 to those determined by oscillometry in the upper arm of the same extremity (Sirecust; Siemens, Erlangen, Germany) were obtained. Intermittent determination of blood pressure by oscillometry during the study showed results similar to those obtained with Finapres. Periods with Finapres calibrating signals were excluded from further analysis.

**MSA Response to a Hypotensive Challenge.** To evaluate the relationship between MSA and arterial blood pressure during a hypotensive challenge, 2–10 $\mu$g/kg sodium nitroprusside (SNP) was injected intravenously both in the awake subject (baseline) and during 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 decline were considered for analysis. The relationship between averages in sympathetic activity (burst frequency and burst incidence) and diastolic arterial pressure was compared before and after administration of SNP (ratios of MSA to arterial pressure show the closest relationships when
MSA is correlated to diastolic arterial pressure rather than to systolic or mean arterial pressure.10–12

Catecholamine Plasma Concentrations. Norepinephrine and epinephrine plasma concentrations were measured by high-performance liquid chromatography with electrochemical detection (lower detection limit, 10 pg/ml; coefficient of variation, 6.2% for norepinephrine and 6.8% for epinephrine). Briefly, venous blood drawn from an antecubital vein was sampled at specified time intervals in chilled EDTA tubes, cooled to 4°C in ice water, and immediately centrifuged. Plasma was stored at −80°C until analysis, as described previously.18,19

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.

Data Recording and Management
Analog variables (MSA, electrocardiogram, arterial pressure, respiration) were recorded on paper with a thermoarray recorder (TA-11; Gould Instrument Systems Inc., Valley View, OH; chart speed, 2.5 mm/s) and also stored on digital tape (RD-125T DAT Data Recorder; TEAC, Wiesbaden-Erbenheim, Germany). Signals were simultaneously fed into a personal computer after analog/digital conversion with a sampling frequency of 200 Hz (DT2,821; Data Translation GmbH, Bietigheim-Bissingen, Germany). All analyses were performed with computer support (offline) 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. Antecubital venous blood was sampled immediately after the resting period. Anesthesia was then induced by an intravenous bolus dose of racemic ketamine (Ketanest; Parke-Davis, Freiburg, Germany; 2 mg/kg, given more than 30 s) followed by a continuous infusion of 30 µg · kg⁻¹ · min⁻¹. MSA was averaged during the first 15 min of ketamine anesthesia in 5-min intervals.

A decrease in arterial pressure was induced (in duplicate) after the resting period before induction of anesthesia and again after 15 min of ketamine anesthesia.

To minimize influences of arterial pressure on assessment of MSA during ketamine anesthesia, in a final step, SNP was continuously infused to decrease arterial pressure to the baseline value measured in the awake state. MSA was recorded for another 5 min during steady-state conditions with arterial pressure adjusted to preanesthetic baseline value.

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 mean values of variables (1) at baseline compared with observations during ketamine anesthesia alone and (2) when arterial blood pressure was adjusted to the baseline value in the awake state during ketamine anesthesia. A null hypothesis was rejected, and statistical significance was assumed with an α error (P) < 0.05.

Results
Ketamine anesthesia decreased sympathetic nerve activity compared with the awake state but increased catecholamine plasma concentrations, heart rate, and arterial pressure.

Figure 1 shows a representative original recording of MSA along with arterial pressure in the awake state and during ketamine anesthesia before and after adjustment of arterial pressure to awake baseline value by infusion of SNP.

Effects of Ketamine Administration
Muscle sympathetic activity burst incidence significantly decreased by 67%, from 26 ± 10 bursts/100 heart beats at baseline to 9 ± 6 bursts/100 heart beats, and MSA burst frequency decreased from 18 ± 9 bursts/min in the awake state to 9 ± 8 bursts/min during the 15-min observation period of ketamine anesthesia. Total MSA decreased from 445 ± 124 units/min in the awake state to 172 ± 128 units/min during ketamine anesthesia (fig. 2).

Mean arterial pressure increased from 85 ± 8 mmHg to 121 ± 20 mmHg after ketamine administration, whereas heart rate increased from 67 ± 13 beats/min to 113 ± 36 beats/min (fig. 3).

Both norepinephrine (250 ± 105 pg/ml to 570 ± 270 pg/ml) and epinephrine plasma concentration (15 ± 10 pg/ml to 256 ± 193 pg/ml) significantly increased after ketamine administration (fig. 3).
Effects of Adjustment of Arterial Pressure during Ketamine Anesthesia to Baseline

When increased arterial pressure during ketamine anesthesia was decreased to preanesthetic baseline value by infusion of SNP (3.5 ± 2.2 μg · kg⁻¹ · min⁻¹), MSA burst incidence significantly increased to 23 ± 14 bursts/100 heart beats, MSA burst frequency increased to 25 ± 18 bursts/min, and total MSA increased to 419 ± 271 units/min. These MSA values did not differ from awake baseline values (fig. 2).

During adjustment of arterial pressure to baseline value, norepinephrine plasma concentration further increased to 888 ± 327 pg/ml, whereas epinephrine plasma concentration was not significantly altered (269 ± 179 pg/ml; fig. 3).

MSA Response to a Hypotensive Challenge

A 21% decrease in mean arterial pressure was achieved by SNP injections both in the awake state and during ketamine anesthesia. Mean arterial pressure decreased from 91 ± 10 mmHg to 72 ± 12 mmHg in the awake state and from 112 ± 19 mmHg to 88 ± 16 mmHg during ketamine anesthesia. However, a significantly greater dose of SNP was necessary for this pressure decrease during ketamine anesthesia (5.0 ± 2.0 μg/kg) than in the awake state (2.3 ± 0.8 μg/kg; fig. 4).

In the awake state, the mean MSA response to the SNP-induced decrease in diastolic arterial pressure was −3.0 ± 2.7 bursts · min⁻¹ · mmHg⁻¹ (−3.0 ± 2.8 bursts/100 heart beats mmHg). This MSA response was not altered during ketamine anesthesia (−2.4 ± 2.1 bursts · min⁻¹ · mmHg⁻¹; −2.1 ± 1.7 bursts/100 heart beats mmHg; fig. 4).

Respiration

Breathing frequency (14 ± 2 breaths/min to 17 ± 4 breaths/min) and arterial oxygen saturation did not change (97 ± 1%) after administration of ketamine. There were no complications attributable to this study.

Discussion

The effects of racemic ketamine on the sympathetic and cardiovascular systems may involve at least two different mechanisms: (1) a centrally mediated increase in efferent sympathetic drive either to specific organs or in a generalized fashion; or (2) an inhibition of catecholamine uptake. In fact, both mechanisms may be expected to increase catecholamine plasma concentrations.

The new findings are as follows: (1) during the increased arterial blood pressure associated with ketamine, sympathetic discharge to muscle blood vessels decreases at the same time that plasma concentrations of norepinephrine increase; (2) when the increase in arterial blood pressure from ketamine is reversed, i.e., restored to awake baseline values, MSA during ketamine is not changed from preketamine awake baseline values; (3) the response of MSA to a hypotensive challenge seems well maintained during ketamine anesthesia even at higher arterial pressures.
Accordingly, these results do not support the concept that anesthesia with racemic ketamine increases sympathetic nerve activity in a generalized fashion, although it is possible that sympathetic nervous system activity elsewhere might increase. Furthermore, our data indicate that a hypotensive challenge during ketamine still evokes substantial muscle sympathetic neural responses.

These results emerged when studying healthy, spontaneously breathing, nonintubated subjects so as to not blur the response to ketamine itself. Clinically administered doses of ketamine do not cause significant respiratory depression except within the first minutes after a rapid bolus injection. In our subjects, arterial oxygen saturation as well as breathing frequency did not change during ketamine anesthesia. Although these variables do not fully reflect alveolar ventilation and arterial carbon dioxide tension, a clinically relevant decrease in minute ventilation will decrease arterial oxygen saturation when breathing room air. Because hypercarbia increases MSA, the observed decrease in MSA during ketamine cannot be attributed to unrecognized respiratory depression. Nevertheless, the effect of a slightly increased arterial carbon dioxide tension on MSA could have been blunted by ketamine, or MSA might be depressed even further without an increased arterial carbon dioxide tension.

Our recording period was limited to 90 min, including more than 15 min of ketamine anesthesia. Accordingly, we cannot extend our conclusions to effects of longer-lasting ketamine administration on the sympathetic nervous system.

**Effects of Ketamine on MSA**

Increased arterial pressure and heart rate associated with increased norepinephrine and epinephrine plasma concentrations were described shortly after racemic ketamine began to be used in clinical practice. Because even small amounts of ketamine, when injected into the cerebral circulation in goats, induced a similar increase in arterial pressure and cardiac output (by increased heart rate) as a larger dose given intravenously, central sympathetic activation was assumed to be responsible for cardiovascular stimulation during ketamine anesthesia, although sympathetic activity itself had not been determined directly. An alternative explanation for this cardiovascular stimulation may be withdrawal of vagal tone as reported during ketamine anesthesia in cats. Sympathetic nerve activity after administration of ketamine has not been previously recorded in humans. However, when efferent preganglionic cervical sympathetic activity was recorded in rabbits anesthetized with pentobarbital and cats anesthetized with nitrous oxide, sympathetic activity markedly decreased.
Contrast, recordings of renal sympathetic nerve activity in chloralose- or urethane-anesthetized rabbits showed controversial results when ketamine was injected in addition to these anesthetics: increased, decreased, and unchanged renal sympathetic nerve activity have been reported. Furthermore, renal sympathetic activity decreased during ketamine administration when prior baroreceptor deafferentiation had been performed by cutting the vagal, carotid sinus, and aortic depressor nerves. Thus, it is not known whether ketamine evokes an increased central sympathetic outflow, either in a generalized fashion or to specific organs.

In our study, during the blood pressure increase associated with ketamine, sympathetic discharge to muscle blood vessels decreased at the same time that plasma concentrations of norepinephrine increased. When the increase in blood pressure during ketamine was reversed, i.e., restored to awake baseline values, MSA during ketamine was not changed from preketamine baseline values. At that time, norepinephrine concentration in plasma was markedly increased compared with awake baseline value despite a similar MSA. These findings do not support the hypothesis that racemic ketamine evokes a generalized activation of the sympathetic nervous system. Because MSA correlates well with cardiac and renal norepinephrine spillover at rest and during baroreceptor stress, we speculate that sympathetic neural outflow to these organs might decrease as well.

Although the hypothesis that ketamine increases cerebral sympathetic outflow has not been tested directly, ketamine decreases norepinephrine uptake in isolated animal hearts. In fact, 90% of norepinephrine released in humans at rest does not reach the circulation but is subject to both neural and extraneural uptake and metabolism. Because ketamine plasma concentrations after a single 2-mg/kg intravenous injection in humans are in the range of the half maximum inhibitory concentration (IC50) for catecholamine uptake inhibition reported in isolated organs, decreased uptake or metabolism of norepinephrine may explain the twofold increase in norepinephrine plasma concentration observed in this and other studies.

Therefore, inhibition of catecholamine amine transporter systems by ketamine independent of sympathetic nerve activity is likely to explain the increase in norepinephrine plasma concentration. This conclusion is further supported by markedly increased norepinephrine plasma concentrations when arterial blood pressure was restored to awake baseline values during ketamine, and MSA levels did not differ compared to preketamine values.

In contrast, a different line of arguments applies for epinephrine. Although the same amine transport systems are responsible for neural and extraneural norepinephrine and epinephrine uptake, resulting in similar plasma clearances of 1–3 l/min at rest, inhibition of transporter systems by ketamine does not fully explain the greater increase in epinephrine plasma concentration.
tion in comparison to norepinephrine in this and previous studies.30

Finally, additional effects of ketamine on the adrenal medullary system may contribute to the marked increase in epinephrine plasma concentration. Of interest, differential effects on sympathetic outflow to the adrenal glands are not uncommon and have been suggested, e.g., during hypoglycemia.34 Irrespective of these considerations, the increase in norepinephrine plasma concentration after ketamine administration despite a decrease in MSA suggests inhibition of uptake or metabolism of catecholamines as an important mechanism for cardiovascular stimulation during ketamine anesthesia.

**MSA Response to a Hypotensive Challenge**

When increased arterial blood pressure during ketamine was adjusted to awake baseline value by SNP, complete recovery of MSA was observed. Accordingly, decreased MSA during ketamine anesthesia is likely related to baroreflex-mediated inhibition.35

Of interest, this result is similar to baroreflex-mediated inhibition of MSA observed after administration of cocaine, which, like ketamine, also inhibits norepinephrine uptake.36

During anesthesia, compensatory mechanisms to maintain circulatory homeostasis in response to a hypotensive challenge are of major importance. We demonstrated that, in contrast to other injectable anesthetics such as propofol or barbiturates,10,11,37 ketamine did not attenuate the response of MSA to a nitroprusside-induced decrease in arterial blood pressure. These findings indicate that the central baroreflex response is well preserved during ketamine anesthesia. This mechanism may also account for the reported “stability of arterial blood pressure” observed after injection of ketamine even during hemorrhagic shock.38,39 Nevertheless, direct vasodilatory and negative inotropic effects have been described under certain experimental conditions and in patients with cardiac failure.40–42 In fact, these effects of ketamine may be unmasked when the sympathetic nervous system is extensively activated at baseline.39

In summary, anesthesia with racemic ketamine evokes an increase in arterial blood pressure and plasma catecholamines but a baroreflex-induced inhibition of MSA. Therefore, our results do not support the assumption that ketamine induces a generalized increase in sympathetic outflow to the cardiovascular system. In contrast to results with other injectable anesthetics (such as propofol or barbiturates), muscle sympathetic neural responses to hypotensive challenges were well maintained during ketamine anesthesia.

**References**

1. Tweed WA, Minuck MS, Mymin D: Circulatory response to ketamine anesthesia. ANESTHESIOLOGY 1972; 37:613–9
6. Salt PJ, Barnes PK,Beswick EJ: Inhibition of neural and extraneur- 
al uptake of noradrenaline by ketamine in the isolated perfused rat heart. Br J Anaesth 1979; 51:835–8
9. Graf BM, Vicenzi MN, Martin E, Bosnjak ZJ, Stowe DF: Ketamine has stereospecific effects in the isolated perfused guinea pig heart. ANESTHESIOLOGY 1995; 82:1426–37
41. Pagel PS, Kampine JP, Schmeling WT, Wartlter DC: Ketamine depresses myocardial contractility as evaluated by the preload recruitable stroke work relationship in chronically instrumented dogs with autonomic nervous system blockade. ANESTHESIOLOGY 1992; 76:564–72