Sympathetic Muscle Nerve Activity, Peripheral Blood Flows, and Baroreceptor Reflexes in Humans during Propofol Anesthesia and Surgery

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Background: With percutaneous recordings of muscle nerve sympathetic activity (MSA), it is possible to study interactions between the autonomic nervous system and anesthetics. This study describes the effects of propofol infusion both before and during microlaryngoscopy.

Methods: Nine patients participated. MSA was recorded, muscle and skin blood flows were measured. Sodium nitroprusside–induced decreases in blood pressure were used to quantitate baroreceptor reflex sensitivity.

Results: During steady state propofol anesthesia (0.1 mg·kg⁻¹·min⁻¹), "total MSA" (MSA burst area per minute) was 37% (P < 0.05) of awake control value; leg blood flow recorded by strain-gauge plethysmography was 227% (difference not significant); and skin blood flow recorded by laser Doppler flowmetry and finger pulse plethysmography was 300% (P < 0.05) and 376% (P < 0.05) of respective awake control values. During microlaryngoscopy, when mean arterial blood pressure was controlled as close as possible to mean arterial blood pressure in the awake state by individually adjusted propofol infusion rates (average 0.33 mg·kg⁻¹·min⁻¹), MSA was restored to 93% of the activity before anesthesia, and leg blood flow increased further. Both cardiac and muscle sympathetic baroreflex sensitivities were depressed by propofol. During surgery the cardiac baroreflex sensitivity decreased further, whereas the muscle sympathetic baroreflex sensitivity was unchanged.

Conclusions: Propofol is a potent inhibitor of sympathetic neuronal activity and decreases the sensitivity of the baroreflex. When used to control the pressor response during surgery, the vasodilating effect of propofol overrides the neural vasoconstriction induced by surgery, and a further inhibition of the cardiac baroreflex is observed. (Key words: Anesthetics, Intravenous: propofol. Measurement techniques, plethysmography: leg blood flow. Measurement techniques: sympathetic microneurography. Reflexes: baroreceptors; pressoreceptors. Skin: blood supply. Surgery; microlaryngoscopy. Sympathetic nervous system.)

IN several studies, propofol has been shown to have potent hemodynamic effects, dominated by hypotension. Several underlying mechanisms, such as myocardial depression¹ and decrease in afterload¹,² or preload,³,⁴ have been suggested. The observed reduction of peripheral vascular resistance may be due both to a direct vascular effect⁵ of propofol as well as to a reduction of muscle sympathetic nerve activity (MSA).⁶,⁷

Baroreceptor reflexes are important for modulating changes of blood pressure, and an altered baroreflex efficacy may contribute to the circulatory effects of anesthetics. In the clinical setting, baroreflex function is often tested by measuring the compensatory response to injection of a vasoactive drug such as phenylephrine⁸,⁹ or sodium nitroprusside (Snp).¹⁰ The effect is usually ascribed to arterial baroreceptor mechanisms, although some contribution from low pressure receptors cannot be excluded. Previous studies of propofol effects on baroreflex sensitivity have been based mainly on recordings of heart rate and blood pressure. A recent investigation has also used MSA for studying baroreflex sensitivity during induction of anesthesia with propofol or etomidate.¹¹ The results concerning propofol have varied: no¹²,¹¹ slight,¹²,¹³ or marked¹⁴ depression of baroreflex sensitivity has been reported.

Because earlier studies on MSA during propofol anesthesia have investigated the effects only during induction of anesthesia,¹⁶,¹⁷ our first aim in this study was to evaluate the propofol effects on MSA during steady-state...
anesthesia (propofol 0.1 mg·kg⁻¹·min⁻¹) before and during surgery. To reduce difficulties interpreting hemodynamic changes at varying degrees of surgical stress we chose patients scheduled for microlaryngoscopy, a procedure that generates a relatively constant and reproducible pressor response. During microlaryngoscopy propofol infusion rates were individually adjusted so that mean arterial blood pressure (MAP) was kept at the awake control level. Thereby, arterial baroreceptors were exposed to similar tension both in the awake state and during surgery, and it would be possible to study the combination of higher doses of propofol and surgical stimulation on the baroreflex. Thus, the second aim was to investigate whether our experimental finding in the cut that propofol anesthesia causes relatively weak depression of the sympathetic limb of the baroreflex is valid also in the clinical setting. Our third aim was to investigate to what extent the large increases in leg blood flow (LBF) previously observed during microlaryngoscopy were related to propofol anesthesia as such. Because these data indicated a systemic vasoconstriction but a vasodilatation in skeletal muscle, simultaneous measurement of MSA and peripheral blood flows could elucidate the relative importance of neurogenic versus direct vascular effects of propofol.

Materials and Methods

Nine patients (ASA physical status 1 or 2) not receiving vasoactive or cardiac medication, aged 26–59 yr (mean 44 yr), scheduled for elective microlaryngoscopy, participated in the study. The study was approved by the local Ethics Committee, and the patients gave their informed consent to participate.

Arterial blood pressure was measured (Kontron Minimon 7132, Everett, MA) via a radial arterial catheter and the electrocardiogram was monitored via surface electrodes. Respiratory movements were monitored by means of a strain gauge applied with a rubber band around the chest. Skin blood flow was recorded continuously with a laser-Doppler flow meter (Periflux 2B, Perimed AB, Stockholm, Sweden) on the plantar side of the right big toe. Electric calibrations for zero blood flow and for maximal signal (100%) were made before start of monitoring. During anesthesia, the laser Doppler signal exceeded the maximal signal in some of the patients and then the gain was adjusted. The analog output of this equipment gives no absolute values but measures relative changes of the flux of blood cells to a depth of about 1 mm. Skin blood flow was also assessed by measuring finger pulse amplitudes with a photo-electric pulse plethysmograph (modified van Gough type ILP/7A) on the volar side of the distal phalanx of the right middle finger. The pulse plethysmograph measures changes in skin blood volume and the changes of pulse amplitudes recorded in this way have been shown previously to be related to changes of skin vasoconstrictor nerve activity.

LBF was recorded intermittently by a venous occlusion plethysmograph with a calf mercury strain gauge (Elektro-Medizin AB, Gothenburg, Sweden) without occlusion of foot blood flow. The results were expressed as ml·100 ml tissue⁻¹·min⁻¹ or percent change compared to the control period. Leg vascular resistance was approximated from the ratio of MAP and LBF. Room temperature was stable and unchanged during each experiment.

Nerve Recordings

The nerve recording microelectrode (lacquer-insulated tungsten with a tip diameter of a few micrometers) was inserted manually through intact skin into a muscle fascicle of the peroneal nerve at the fibular head. A similar reference electrode but with a larger, uninsulated tip was inserted subcutaneously 2–3 cm away. A muscle nerve fascicle was localized with the aid of weak electric stimuli delivered through the recording electrode. Small adjustments of the electrode were made until a site with spontaneously occurring sympathetic activity was found. Details of the technique and evidence for the sympathetic nature of the activity have been published previously.

The nerve signal was amplified with a gain of 50,000, and the signal-to-noise ratio was improved by a 700–2,000-Hz bandpass filter and an amplitude discriminator. An RC (resistance capacitance)–integrating network with a time constant of 0.1 s was used to obtain a mean voltage display of the multunit nerve activity. Analog signals of original and mean voltage neurograms, along with other variables, were stored on VHS tape (Racal V-Store, Racal Recorders, Southampton, UK). During the experiments, neural activity was monitored on a storage oscilloscope (Tektronix 549, Tektronix, Beaverton, OR) and a loudspeaker.

# Sellgren J: Unpublished observations.

Anesthesiology, V 80, No 3, Mar 1994
Experimental Procedure

The patients received oral flunitrazepam (1 mg) 1 h before arrival at the operating room. A catheter was inserted into the left radial artery after local anesthesia. A forearm intravenous catheter was inserted for fluid (Ringer’s–acetate) and drug administration. Anesthesia was induced with a bolus injection of propofol 2 mg·kg⁻¹, and muscle relaxation was achieved with atracurium 0.8 mg·kg⁻¹. In some patients administration of additional propofol was needed (on average 0.41 ± 0.22 mg·kg⁻¹). Immediately after induction, infusions of propofol 0.1 mg·kg⁻¹·min⁻¹ and atracurium 0.5 mg·kg⁻¹·h⁻¹ were started. After 5–6 min of controlled ventilation with 100% oxygen through a mask, orotracheal intubation was performed. The patient's lungs were then mechanically ventilated with oxygen in air at an inspired oxygen fraction of 0.30 and an end-tidal carbon dioxide tension (Ultima, Datex, Helsinki, Finland) of 5 kPa (35–40 mmHg).

The recording microelectrode was inserted in the operating room before induction of anesthesia. After a recording site was obtained with good signal-to-noise ratio for sympathetic bursts, MSA and hemodynamic parameters were recorded during a ten min resting period, the last 3 min of which were used as the awake control period. Leg plethysmography was repeated three to seven times. Before induction of anesthesia recordings were also made during baroreflex tests evoked by bolus injections of SNP. The doses (1–7 µg·kg⁻¹) were adjusted individually to achieve a decrease in MAP of at least 20 mmHg and repeated three to five times. A new SNP dose was not given until MAP had returned to the pre-SNP level for at least 1 min. This usually resulted in approximately 5-min intervals between SNP injections. All measurements were repeated 15–40 min after the induction when propofol anesthesia was at pharmacologic steady state and during the first 25 min of microlaryngoscopy when the propofol infusion dose had been adjusted so that MAP was approximately at the awake control level. During the microlaryngoscopy the laryngoscope was fixed to a frame mounted on the operating table. Thereby, constant traction was applied to the supraglottic structures.

Data Analysis

The analog signals of the mean voltage neurogram, electrocardiogram, arterial blood pressure, laser Doppler blood flow, photoelectric pulse plethysmogram and time code were digitized (sampling frequency 200 Hz) and analyzed by computer. The program emulates the manual analysis by detecting each MSA burst in the mean voltage neurogram and then calculates its area. A sympathetic burst was identified on the basis of a monotonic increase and decrease with a local maximum occurring in the MSA signal within 1,000–1,800 ms from a preceding R-wave in the electrocardiogram. The parameters defining a burst could be changed manually and if the automatically detected bursts did not agree with the visually defined ones, parameters were changed and the automatic burst detection was restarted. The area of a burst was calculated from a relative baseline (mean value of background activity between bursts) set by the computer. Values of nerve activity, RR interval, systolic arterial pressure, MAP, and diastolic arterial pressure (DAP), laser Doppler blood flow and finger pulse amplitude were measured for each heart beat and stored. MSA is presented as bursts per 100 heart beats, bursts per minute, and mean MSA burst area per heart beat (MSAA). The MSA area per minute calculated from the product of mean MSAA and bursts per minute is used as an index of "total MSA."

Calculations of mean values for each parameter were based on 3 min of measurement in the awake control period, during propofol anesthesia and during microlaryngoscopy. However, in three patients the microlaryngoscopy measurement period was only 2 min and in one patient only 1 min. MSAA, LBF, leg vascular resistance, laser Doppler blood flow and finger pulse amplitude are presented as percent values of the awake control period (100%). Data were also quantified during the first 5 min of anesthesia, for analysis of induction effects of propofol.

Baroreflex Tests

The depressor test period used for analysis of baroreceptor reflex effects was delimited by the start of the SNP-induced decrease in MAP and the lowest MAP achieved within 60 s (fig. 1A). The data were analyzed by a modified baroreflex “slope method” similar to that described by Smyth et al. (fig. 1B). Because all heart beats are not associated with MSA bursts it is not possible to plot the individual MSA burst area against corresponding blood pressure value for every heart beat. Instead, during each period of measurement (awake control, anesthesia, microlaryngoscopy) all heart beats from all SNP-induced pressure decreases were pooled and sorted according to decreasing blood pressure. The blood pressure range was divided in ten equal intervals and the mean of all blood pressure val-
Autonomic effects of propofol

Fig. 1. (A) Original recording. Muscle sympathetic neurogram and hemodynamic recordings from a typical depressor test in the awake state in one patient (arrow = intravenous injection of sodium nitroprusside [SNP] 2 μg·kg⁻¹). The depressor test period is delimited by the start of decrease in mean arterial blood pressure (MAP) and the lowest achieved MAP within 60 s (lines). Note the single, large bursts of muscle sympathetic nerve activity (MSA) caused by a sudden decrease in diastolic arterial pressure (DAP) after two spontaneous extrasystolic heart beats. (B) Baroreflex slope. x–y Plot of mean muscle sympathetic activity area per heart beat (MSAA) versus DAP and linear regression analysis of pooled data from four depressor tests before anesthesia in the same patient. MSAA is expressed as a percentage of the basal MSAA value during the awake control period. Dotted line = the MSAA set point, which corresponds to the pre-SNP reference blood pressure.

Values in each interval were plotted against corresponding values of MSAA and RR interval. DAP was used for plotting against MSAA²⁷ and MAP for plotting against RR intervals. In each patient the slopes based on pooled data from three to five SNP injections included on average 134 heart beats before anesthesia, 238 during anesthesia and 202 heart beats during microlaryngoscopy. The slope calculated by linear regression analysis represents baroreflex sensitivity (fig. 1B). Regression lines with a correlation coefficient below 0.5 were excluded. The baroreflex set point was defined as the RR interval or MSAA value that corresponded to a reference blood pressure (MAP or DAP, respectively) in the awake state before SNP was injected. In order to differentiate a pure neurogenic from a possible combined (neurogenic and hormonal) response separate analyses of baroslopes were also made during the first 20 s of the decrease in MAP. In two of the nine patients some depressor tests during anesthesia and surgery increased the baseline of the integrated neurogram (fig. 2). In both patients the baseline shift was directly related to increasing doses of SNP. Reintegration of the original neurograms using a shorter time constant (0.05 s; fig. 2) eliminated only part of the elevated baseline. This indicates that MSA was continuous and systolic baroreflex inhibition was incomplete. Because the continuous nerve activity was not included when calculating MSAA, sympathetic baroreflex sensitivity was underestimated in these subjects primarily during surgery when the effect was most marked.

Fig. 2. Original recording from a SNP-induced depressor test in one of the two patients with a shift in the neurogram baseline. Muscle sympathetic activity (MSA) is shown with the standard integrating time constant (τ, 0.1 s), with the shorter time constant (0.05 s), and without integration (discriminated MSA).
Results are presented as means ± standard error of the means. For statistical analysis, two-factor analysis of variance was used for overall statistical significance. For comparisons between periods paired Student’s t test was used with Bonferroni correction for multiple comparisons. Statistical analysis of the baroreflex slope method was made with one-factor analysis of variance and Tukey’s compromise post hoc test due to loss of regression lines in some patients. P values < 0.05 were considered to be significant.

Results

Four minutes after induction of anesthesia with propofol, MAP was 74% (P < 0.05) and heart rate was 110% (difference not significant [NS]) of the awake control values (fig. 3). After maintenance of anesthesia with continuous propofol infusion (0.1 mg·kg⁻¹·min⁻¹) for 15–20 min MAP was 87% (NS) and heart rate was 114% (P < 0.05) of the values in the awake control state (fig. 4). During microlyangoscopy MAP was kept as close as possible to MAP in the awake state by individual adjustment of the propofol infusion rates. This required an average propofol infusion dose of 0.35 mg·kg⁻¹·min⁻¹ (interindividual range 0.10–0.59 mg·kg⁻¹·min⁻¹) during the first 25 min of microlyangoscopy. Heart rate increased to 122% of the awake control state (P < 0.05).

Blood gas analysis in the awake control state showed pH 7.39 ± 0.01, arterial carbon dioxide tension 5.4 ± 0.2 kPa (40.5 ± 1.5 mmHg) and arterial oxygen tension 12.7 ± 0.4 kPa (95.3 ± 3.0 mmHg). During anesthesia and microlyangoscopy there were no changes in pH (7.40 ± 0.01 and 7.39 ± 0.01) or arterial carbon dioxide tension (5.14 ± 0.07 kPa [38.6 ± 0.5 mmHg] and 5.38 ± 0.14 kPa [40.4 ± 1.1 mmHg]), whereas arterial oxygen tension increased to 16.5 ± 1.3 kPa (123.8 ± 9.8 mmHg; P < 0.05) during anesthesia and to 16.4 ± 1.7 kPa (123.1 ± 12.8 mmHg; NS) during microlyangoscopy.

Basal Muscle Sympathetic Nerve Activity and Peripheral Blood Flows

Induction of anesthesia with propofol (2.0 ± 0.4 mg·kg⁻¹) reduced both the number of MSA bursts and their mean areas in all subjects (fig. 3). Four minutes after induction total MSA (MSA per minute) was 39% of the awake control value (P < 0.05).

MSA data from the three periods of measurements are summarized in table 1 and figure 4. During steady-state anesthesia total MSA (fig. 4) was reduced to 37 ± 7% (P < 0.05) of the awake control state (=100%). During microlyangoscopy total MSA increased to 90 ± 36% (NS compared to control).

Before induction of anesthesia, LBF was 1.73 ± 0.14 ml·100 ml tissue⁻¹·min⁻¹ (=100%). During anesthesia LBF increased to 227 ± 53% (NS) and during microlyangoscopy to 465 ± 89% (P < 0.05) of the awake control value (fig. 5). During anesthesia leg vascular resistance was reduced to 50 ± 8% (P < 0.05) and during microlyangoscopy to 30 ± 6% (P < 0.05) of the resistance in the awake control state (fig. 4).

During anesthesia laser Doppler skin blood flow and finger pulse amplitude increased to 300 ± 48% (P < 0.05) and 407 ± 74% (P < 0.05), respectively (fig. 5). During microlyangoscopy there were no further mean changes in these parameters of skin blood flow. However, individual changes in laser Doppler blood flow between steady-state anesthesia and microlyangoscopy correlated (r = 0.77; P < 0.05) with individual peroperative propofol infusion rates.

Baroreflex Tests

Bolus injections of SNP caused rapid decreases in arterial blood pressure (fig. 1). Before anesthesia the

Anesthesiology, V 80, No 3, Mar 1994
minimal MAP was reached within $31 \pm 3$ s after the start of the SNP-induced decrease in blood pressure. During anesthesia this period increased to $44 \pm 2$ s ($P < 0.05$) whereas it returned to the preanesthetic level, $34 \pm 2$ s during microlaryngoscopy. The maximal decrease in MAP (average for all patients) after SNP was $25 \pm 2$ mmHg before anesthesia, $30 \pm 3$ during anesthesia and $37 \pm 2$ mmHg during microlaryngoscopy.

This correlated with gradually increased average SNP bolus doses used before anesthesia ($2.8 \pm 0.2 \mu g \cdot kg^{-1}$), during anesthesia ($3.5 \pm 0.6 \mu g \cdot kg^{-1}$) and during microlaryngoscopy ($4.6 \pm 0.4 \mu g \cdot kg^{-1}$).

Average baroslopes calculated from individual slopes with correlation coefficients exceeding 0.5 ($n = 6–9$) are shown in figure 6. The RR interval versus MAP slope, which represents the cardiac baroreflex sensitivity, decreased during anesthesia and further during microlaryngoscopy. The results were similar both when calculated on data from the first 20 s and from the whole depressor test period (fig. 7). Note however, that cardiac baroslopes calculated on data from the whole depressor test period (pooled data from the awake control period, anesthesia and microlaryngoscopy) were significantly steeper than slopes based on the first 20 s of the depressor test period. The difference between 20 s slopes and whole period slopes was most prominent during anesthesia ($2.0 \pm 0.5$ vs. $4.2 \pm 0.4$ ms $\cdot$ mmHg $^{-1}$). The set point for RR interval at reference MAP in the awake state was similar before and during anesthesia ($889 \pm 53$ and $863 \pm 52$ ms, respectively) but was significantly decreased during microlaryngoscopy ($671 \pm 39$ ms).

The MSAA versus DAP slope, which represents the muscle nerve sympathetic baroreflex sensitivity, de-

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**Table 1. Muscle Nerve Sympathetic Activity**

<table>
<thead>
<tr>
<th></th>
<th>Awake State ($n = 9$)</th>
<th>Anesthesia ($n = 8$)</th>
<th>Surgery ($n = 7$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bursts/100 heartbeats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>52 ± 6</td>
<td>29 ± 7*</td>
<td>34 ± 4*</td>
</tr>
<tr>
<td>Range</td>
<td>18–78</td>
<td>5–56</td>
<td>14–52</td>
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<tr>
<td>Bursts/min</td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SEM</td>
<td>34 ± 4</td>
<td>21 ± 5</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>Range</td>
<td>11–46</td>
<td>5–38</td>
<td>11–41</td>
</tr>
<tr>
<td>MSAA/heartbeat (%)</td>
<td></td>
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<tr>
<td>Mean ± SEM</td>
<td>100 ± 0</td>
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<td>83 ± 36</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>100 ± 0</td>
<td>37 ± 7*</td>
<td>90 ± 36</td>
</tr>
</tbody>
</table>

The reduced number of patients with MSAA recordings is due to altered recording site in one patient during intubation and loss of recording site in one patient during start of endoscopy.

* $P < 0.05$ versus awake state.
Fig. 5. Values (mean ± SEM, percentage of control, where control = 100%) of leg blood flow (LBF), laser Doppler skin blood flow, and finger pulse amplitude in the awake state (control) and before (15–20 min after induction of anesthesia) and during microlaryngoscopy (surgery). *Significant changes ($P < 0.05$).

Increased significantly during anesthesia but no further decrease was seen during microlaryngoscopy (fig. 7). In contrast to RR interval versus MAP slopes, the MSAA versus MAP slopes during the initial 20 s of decrease in MAP did not differ significantly from the slopes calculated from the whole depressor test period. The baroreflex set points for MSAA in the whole period slopes were 103 ± 9 (% of control) before anesthesia, 16 ± 19 during anesthesia and 98 ± 45 during microlaryngoscopy.

**Additional Findings on Sympathetic Nerve Activity**

In addition to the usual pulse-synchronous bursts, shown in figure 1, four of the nine patients displayed spontaneous, episodic neural discharges, occurring at a frequency of 1–3 discharges·min$^{-1}$ and having a duration of 2–3 s (fig. 8). Presumably, the activity was of sympathetic origin because the discharges were followed, after a delay of 3–4 s by transient increases of blood pressure lasting approximately 5 s. The frequency of the discharges was not altered during the SNP-induced decreases of blood pressure. In the quantitative analysis, these bursts, but not the corresponding transient increases in blood pressure, were excluded because their inclusion increased MAP with 0.2 mmHg only.

**Discussion**

The current results show that propofol anesthesia decreases MSA and increases peripheral blood flows in skeletal muscle and skin. During surgical stress MSA was restored toward the awake control level, although the propofol infusion dose was increased more than three times, illustrating the interaction between anesthetic depth and surgical stress on sympathetic activity.28 During propofol anesthesia before surgery (0.1 mg·kg$^{-1}$·min$^{-1}$) sensitivity decreased both in the cardiac (RR intervals) and the muscle sympathetic limb of the baroreceptor reflex whereas during microlaryngoscopy only the cardiac baroreflex sensitivity showed a further decrease.
Depressor test period including

the first 20 s

![Graph showing RR-int vs. MAP slope (top) and MSAA vs. DAP slope (bottom) for the first 20 s. C = control; A = anesthesia; S = surgery.]

the whole period

![Graph showing RR-int vs. MAP slope (top) and MSAA vs. DAP slope (bottom) for the whole period.]

Fig. 6. Average RR interval versus mean arterial blood pressure (MAP) slopes (top) and mean muscle sympathetic activity area per heart beat (MSAA) versus DAP slopes (bottom) calculated from individual baroslopes with correlation coefficient exceeding 0.5. The number of patients included in each slope is shown in figure 7 (below the bars). Slopes from depressor test periods including only the first 20 s (left) and tests including the whole period (right) are shown. C = control; A = anesthesia; S = surgery. MSAA is expressed as a percentage of the basal MSAA value during the awake control period.

Depressor test period including

the first 20 s

![Graph showing RR-int vs. MAP slope (top) and MSAA vs. DAP slope (bottom) for the first 20 s. C = control; A = anesthesia; S = surgery.]

the whole period

![Graph showing RR-int vs. MAP slope (top) and MSAA vs. DAP slope (bottom) for the whole period.]

Fig. 7. Values (mean ± SEM) of slope values (i.e., regression coefficients) from the baroreflex tests, presented in the same order as in figure 6. Mean muscle sympathetic activity area per heart beat (MSAA) is expressed as percentage of basal MSAA during the awake control period. Nine patients were included in the study; during surgery the number was reduced to eight regarding RR intervals and seven regarding MSAA. Each bar is calculated from patients with correlation coefficients exceeding 0.5. *Significant changes (P < 0.05).
Skin sympathetic activity was not measured in the current study but the unchanged skin blood flow may either indicate that surgery elicited an increased neural vasoconstrictor drive to skin countereacting the direct vasodilatory effect of the increased propofol infusion or that skin blood vessels already were maximally dilated. Thus, considering our current and previous observations and data from other groups, propofol seems to have direct vascular effects both on capacitance and resistance vessels. If propofol, like in the current study, is used as the sole agent for modulating the pressor response to surgery, a large inter-individual dose range must be expected.

**Basal Muscle Sympathetic Nerve Activity and Peripheral Blood Flows**

We found a decrease of 61% in total MSA (MSAA per minute) 4 min after the bolus injection of propofol (2 μg·kg⁻¹), a finding that is similar to previous observations. When a pharmacologic steady state was established after 15–20 min of continuous propofol infusion (0.1 mg·kg⁻¹·min⁻¹), MSA stabilized at a level similar to that 4–5 min after the bolus induction of 2 mg·kg⁻¹. The decrease in MAP was, however more pronounced during the induction sequence and may be due to combined bolus effects of propofol and atracurium. This suggests that the hypotension usually associated with a bolus induction is more dependent on direct vascular effects from rapidly changing blood concentrations than on depression of sympathetic activity.

Propofol anesthesia in absence of surgery is associated with a decrease in cardiac output. Previously we showed that propofol anesthesia (0.1 and 0.2 mg·kg⁻¹·min⁻¹) combined with microlaryngoscopy caused no change in cardiac output when compared to that in the awake state. In the current study findings during propofol infusion (0.1 mg·kg⁻¹·min⁻¹) were those expected in the sense that MSA decreased and peripheral blood flows increased. This vasodilatation may be caused both by an inhibition of sympathetic outflow and a direct vascular effect of propofol. The pronounced increase in LBF from the awake control period to microlaryngoscopy, without net changes in MSA, supports the notion of a direct propofol-induced vasodilatation. Probably, the vasodilatation in the leg was confined to skeletal muscle because skin blood flow did not increase further when MAP was restored.

**Baroreflex Tests**

**Undisturbed Anesthesia.** Three previous human studies have addressed the question of propofol influence on cardiac baroreflex sensitivity. Our data agree with those of Ebert et al., who found a depressed sensitivity whereas in two other studies baroreflex sensitivity was unaffected. Even if the divergent observations in one study may be explained by simultaneous nitrous oxide administration, the anesthetic regime in the study by Samain was similar to ours. In both studies, however, propofol induced a decrease in heart rate, in contrast to our finding of an increased heart rate. Thus, the depressor tests in these studies started at a state with longer RR intervals than in our and Ebert et al.’s studies. Therefore, we suggest that a decrease in vagal tone induced by the depressor test should have had a greater impact on the RR intervals in their studies. Experimentally, it has been shown that changes in RR intervals are more closely related to neural activity in cardiac vagal nerves than activity in cardiac sympathetic nerves. Thus, the decreased cardiac baroreflex sensitivity in Ebert et al.’s and our study may be explained by a relatively low vagal tone before but also by only small decreases in vagal tone during the depressor tests.

We found that the sensitivity of the cardiac baroreflex calculated from the first 20 s of the decrease in arterial blood pressure was lower than when calculated from the whole period of decreasing pressure (fig. 7). This phenomenon was most pronounced during undisturbed propofol anesthesia when the time necessary to buffer a decrease in blood pressure was significantly prolonged. The finding may indicate that the depressor test also induced a humoral response that influenced cardiac baroreflex sensitivity. The time for establishing a humoral (adrenal) response is unknown. However, in heart transplant patients with denervated hearts the
heart rate response to exercise is assumed to be due to humoral factors. Although, this response is delayed, the increase in heart rate begins within 1 min. To summarize, we suggest that effects of propofol on the cardiac baroreflex sensitivity depend on two factors, the first being preexisting vagal tone and the second whether the analysis includes a humoral response or not.

In contrast to Ebert et al., we chose not to mix both unloading (SNP) and loading (phenylephrine) of the baroreceptors. During propofol anesthesia a phenylephrine-induced increase in blood pressure will further depress an already weak MSA and very few heart beats will be associated with bursts of MSA. Instead, in order to increase the number of bursts and thereby accuracy in the calculations, SNP injections were repeated three to five times during each period of measurement. This technique and our use of burst area instead of burst amplitude may explain why the preanesthetic sympathetic baroreflex sensitivity is 1.7 to two times higher in this study compared to that by Ebert et al. Irrespective of these methodologic differences both studies show that propofol not only decreases the strength of muscle sympathetic activity but also the sensitivity in the muscle sympathetic limb of the baroreflex.

No doubt, this hampers cardiovascular control during propofol-induced hypotension. On the other hand, it should be stressed that the rapid clearance of the drug facilitates reestablishment of baroreflex sensitivity.

Surgery. During surgery, MAP and MSA were restored to the preanesthetic level, presumably because the individually increased dose of propofol was balanced by the surgery-induced sympathetic excitation. In contrast, sympathetic baroreflex sensitivity remained significantly depressed. In two patients this could in part be due to an underestimation of sensitivity during surgery (see methods) but this is unlikely to be the main explanation. A putative contributing factor may be direct effects of the very high propofol doses on the baroreceptor-harboring vessels. Propofol relaxes the rat aorta in vitro. If present in humans in vivo, this effect may cause a lower SNP-induced change of afferent baroreceptor nerve activity per millimeter mercury reduction in blood pressure during surgery than during undisturbed anesthesia. Such an effect would explain a reduced baroreflex sensitivity in the face of a restored central excitability. In contrast to muscle sympathetic baroreflex sensitivity, sensitivity in the cardiac baroreflex limb was further depressed during surgery. This may be due to an augmented differentiation between sympathetic and vagal reactivity, as previously observed during hypothalamic defense area stimulation described by Djojosugito et al. and by Gebber and Snyder. Hypothalamic stimulation did in those studies cause an inhibition of the cardiac baroreflex (representing mainly vagal effects) but did not affect sympathetic vasoconstrictor activity. Because the cardiovascular response to hypothalamic defense area stimulation is similar to that of stimulation of somatic afferent nerves, the response to defense area stimulation can be used to explain cardiovascular effects of surgical stress. This implies that noxious stimulation from surgery inhibits baroreflex mechanisms and adds to the reduced vagal response that was observed during undisturbed propofol anesthesia.

The aberrant sympathetic bursts observed during propofol infusion have not been described previously in human microneurographic studies. Because they were not preceded by a decrease in blood pressure an underlying baroreceptor reflex mechanism is unlikely. They may represent a spontaneous discharge triggered by propofol anesthesia in conjunction with factors related to the ventilatory technique.

In conclusion, this study demonstrates that MSA is reduced by a continuous infusion of propofol and that tonic sympathetic activity to a large extent is restored during microlaryngoscopy in spite of more than three times increase of the propofol infusion rate. The decrease in leg vascular resistance during propofol anesthesia is caused not only by a reduction in MSA but also by a direct vasoconstricting effect of propofol, which overrides the increase in neural activity during surgical stress. Both the cardiac and muscle sympathetic baroreflex sensitivities are depressed by propofol. During surgery baroreflex responses are differentiated with further decrease in cardiac baroreflex sensitivity whereas muscle sympathetic baroreflex sensitivity is unchanged.

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Anesthesiology, V 80, No 3, Mar 1994


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Anesthesiology, V 80, No 3, Mar 1994