Sympathetic Nervous System

Evaluation and Importance for Clinical General Anesthesia

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For more than 100 yr, scientists have studied the sympathetic nervous system and its cardiovascular control mechanisms. Muscle sympathetic activity is the most important direct and rapidly responding variable for evaluation of sympathetic neural outflow. Because of its significance in response to environmental challenges and its role in cardiovascular control, great attention has been paid to the sympathetic nervous system in both health and disease and, more recently, also during general anesthesia. In fact, general anesthesia can also be considered as an investigational tool to assess mechanisms of cardiovascular regulation. This review evaluates different methods for determination of sympathetic nervous system activity and describes its role in human neurohumoral circulatory control. Furthermore, the effects of general anesthesia on sympathetic nervous system activity and their relevance for clinical anesthesia are discussed.

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phy has been increasingly used to investigate human sympathetic nerve traffic under physiologic and pathophysiologic conditions.11

Tungsten electrodes (diameter: 200 μm) with a tip diameter of a few microns are used for recordings of sympathetic neural outflow. A peripheral nerve is localized by transcutaneous electrical stimulation (30–50 V, 100–200 mA, 2 ms) evoking motor or sensory effects. Afterward, a recording electrode is inserted intraneurally, and a reference electrode is placed subcutaneously a couple of centimeters apart. A suitable electrode position for intraneural recordings is found by minor adjustments of the electrode tip. The correct needle position is confirmed by a low threshold of intraneurial electrical stimulation (0.2–1.0 V, 100–200 mA, 2 ms) evoking muscle contractions or paresthesias as well as by recording of muscle (stretching of muscle tissue)– or cutaneous (light stroking or scratching of the skin)–derived afferent activity. Peak-to-peak amplitudes of multiunit raw signals usually range from 10 to 20 μV, with a signal-to-noise ratio of 3–5 to 1. The detected signal is amplified (gain × 50,000) and filtered (700- to 2,000-Hz band-pass filter). To obtain a mean voltage neurogram, a resistance-capacitance integrating circuit with a time constant of 0.1 s is used.15 The multiunit nerve recording is composed of several single nerve fiber discharges, which are grouped. These groups can be counted as bursts in the mean voltage neurogram.

The mean amplitude or the area under the curve of single bursts in the integrated signal is dependent on the number of recorded single unit discharges (neural recruitment) and also on the location of the needle relative to the nerve bundles. Therefore, slight movement may alter the needle tip location within the nerve so that area under the curve calculations should be analyzed cautiously. Finally, for the same reason, it is difficult to use these data on the same subject for comparisons between different days or experimental sessions.10,13

In peripheral nerves, efferent sympathetic activity to skin (skin sympathetic activity [SSA]) and to muscle vasculature (muscle sympathetic activity [MSA]) can be distinguished. In the supine position, the same resting MSA can be determined at different nerve recording sites (e.g., peroneal and median nerve), which is very reproducible in a given subject over more than 10 yr. Nevertheless, MSA tends to increase with age so that higher MSA at rest is observed in healthy patients older than 60 yr.14,15 This observation contrasts with a large intra-individual variability of less than 10 to more than 90 bursts/100 heartbeats between different healthy subjects.16 Because of this great intra-individual variability, there is no defined pathologic level of MSA.

Forearm venous norepinephrine plasma concentration significantly correlates with peroneal MSA. This relation is probably due to the large contribution of cardiac output to muscle blood flow (anywhere from 25% to 40%).17 Surprisingly, total-body norepinephrine spill-over, as well as renal and cardiac norepinephrine spill-over, correlates well with MSA despite the proposed differential control of sympathetic organ innervation at rest.18–20

Muscle sympathetic activity does not correlate with arterial pressure between different subjects as indicated by hypertensive patients with low MSA, hypotensive subjects with high MSA, and vice versa. Moreover, an insulin-induced increase in MSA is not associated with a change in arterial pressure.21 These observations suggest that other variables exert major influences on the individual level of arterial blood pressure and MSA.16,22,25

A relaxed subject at a comfortable ambient temperature has virtually no detectable SSA.24–26 By exposing a subject to warm (43°) or cold (15°) environments, a selective activation of either the sudomotor or the vasoconstrictor neural system is usually obtained, with suppression of spontaneous activity in the other system.25,27

In a comfortably warm subject, a deep spontaneous inspiration is followed by a strong increase of SSA, which consists of both sudomotor and vasoconstrictor activity.28,29 Similarly, a sudden arousal stimulus elicits a burst of SSA whereas, in contrast, MSA is not affected by such stimuli.12,30

With these findings, the traditional view of a whole-body activation of sympathetic outflow in response to stimuli is no longer tenable, though striking correlations between kidney, muscle, and cardiac sympathetic activity were observed at rest. Instead, it is suggested that the SNS has the capacity to selectively activate different subdivisions. This makes it difficult to generalize data derived from one subdivision to other effector organs or conditions without direct experimental evidence.

Therefore, microneurography is the only technique available to directly assess sympathetic neural activity in humans. Its advantage is the ability to detect rapid changes in nerve traffic. Accordingly, it is suitable to study not only static but also dynamic situations, e.g., determination of the offset and the gain in situations of sympathetic activation induced by certain challenges. In contrast, this technique is limited by its invasiveness, by motion artifacts, and by the fact that it is site specific so that it may reflect only regional effects.

**Assessment of Baroreflex Sensitivity.** Although MSA at rest does not correlate to the individual “normal” resting blood pressure, alterations in arterial blood pressure are associated with increases or decreases in MSA. The relation between spontaneous or induced (e.g., pharmacologically, neck chamber technique) arterial pressure changes to MSA can be used to describe baroreflex sensitivity (BRS).31–35

Different methods have been used to quantify the arterial baroreflex influence on MSA. The relation between spontaneous variations of blood pressure and nerve traffic in terms of threshold (i.e., whether a sym-
pathetic burst is generated) and BRS (i.e., the slope of the relation between the strength of a burst and the diastolic pressure in the corresponding heartbeat) has already been the subject of early studies. Obviously, there is a good correlation between diastolic pressures and the occurrence of sympathetic bursts so that low diastolic pressures usually and high diastolic pressures rarely are associated with a burst. These kinds of threshold variability diagrams are conveniently characterized by the blood pressure value at which 50% of the heartbeats were associated with a burst and the slope of the regression line, which gives a measure of the variability range of the blood pressure threshold. On the other hand, the number of activated sympathetic fibers (as indicated by the area of a burst) does not correlate with blood pressure.

The sensitivity of the arterial baroreceptor reflex can also be calculated during arterial blood pressure changes during application of positive or negative pressure to the area of the neck over the carotid sinus receptors using the neck chamber technique. The correlation between heart rate (HR) and sympathetic neuronal response to arterial pressure changes was taken as a measure for reflex sensitivity.

Apart from these nonpharmacologic testing procedures, baroreflex influences on the SNS have been quantified by relating HR and/or sympathetic nerve activity to mild temporary alterations in arterial pressure induced by (sequential) intravenous administrated pharmacologic vasoconstrictors (phenylephrine) or vasodilators (sodium nitroprusside [SNP]) (Oxford technique) (fig. 1). Accordingly, distances between two R waves in the electrocardiogram can be plotted as a function of preceding systolic pressures during pressure perturbations. The slope of the (linear part) of this regression analysis can be plotted as a function of preceding diastolic pressure, giving an index of arterial sympathetic baroreflex responsiveness or sensitivity that is free of parasympathetic modulation (fig. 2).

Muscle sympathetic BRS during rest differs from BRS during evoked hypotension. The relation between mean MSA burst incidence and diastolic arterial pressure was compared before and after a pressure decrease caused...
by SNP (2–3 μg/kg intravenous) yielding an average baroreflex gain. Average baroreflex gain assessed by this conventional method was compared with baroreflex gain assessed during spontaneous arterial pressure fluctuations. Resting MSA was 28 bursts/100 heartbeats at a diastolic pressure of 71 mmHg. Baroreflex gain during spontaneous arterial pressure fluctuations was 4.0%/mmHg and was significantly greater than the average gain assessed during evoked hypotension (2.1%/mmHg). Baroreflex gain during spontaneous arterial pressure fluctuations differs from that assessed during SNP-evoked hypotension, possibly because of intrinsic effects of SNP on the baroreflex.59

**Method of Assessment of Sympathetic Activity by Heart Rate Oscillations.** Sympathetic traffic to the heart may be addressed by analysis of the power spectrum of HR oscillations. Changes of HR in time depend on physiologic control systems, including sympathetic and parasympathetic influences. When distances between R waves, derived from an electrocardiographic recording, are transformed into instantaneous HR and a fast Fourier transformation is applied to these data, a power spectrum with very low (around 0.03 Hz)–, low (around 0.05–0.15 Hz)–, and high (around 0.3–0.4 Hz)–frequency oscillations (frequency bands) can be obtained.40 Whereas most researchers agree that the area under the high-frequency oscillations relates to parasympathetic modulation, some authors have speculated that the area under the low-frequency oscillation or the “low-frequency to high-frequency power ratio” represents cardiac sympathetic drive.40–48 If this were true, HR spectral variability would be an easy and noninvasive way to assess cardiac sympathetic innervation. However, several clinical studies question the validity of HR spectral variability data.49–52

Despite sensory blockade from dermatomes C6 to T6 by thoracic epidural anesthesia (0.75% bupivacaine), the low-frequency band and the low-frequency to high-frequency power ratio did not change during supine rest and head-up tilt in humans. Accordingly, there was an incomplete blockade of cardiac sympathetic nerve traffic by epidural anesthesia, there was a lack of cardiac sympathetic activity at rest and during sympathetic challenge by tilt, or the low-frequency band and low-frequency to high-frequency ratio may not be an adequate measure of cardiac sympathetic function.53 In healthy volunteers during supine rest, HR variability did not correlate with HR, arterial pressure, norepinephrine plasma concentration, or peroneal MSA.54 When arterial pressure was decreased by SNP, changes in the low-frequency band of the power spectrum correlated with peroneal MSA but, interestingly, not during an increase in arterial pressure induced by phenylephrine.54 This observation was explained by a model of HR control in which low-frequency fluctuations of HR result from changing levels of both the sympathetic and parasympathetic inputs to the sinoatrial node. Furthermore, the low-frequency spectral power did not correlate with cardiac norepinephrine spillover in healthy volunteers or in patients with increased MSA activity because of cardiac failure.55 It was concluded that the low-frequency spectral power, in addition to cardiac sympathetic nerve traffic, depends on other factors, including multiple neural reflexes, cardiac adrenergic receptor sensitivity, postsynaptic signal transduction, and biochemical coupling, and is not related to cardiac norepinephrine spillover, the latter being a more direct measure of sympathetic nerve traffic.55 Furthermore, during general anesthesia, HR variability may be altered by positive-pressure ventilation, changing carbon dioxide tension, and respiratory frequency.

Together, determination of HR variability may be suitable to assess parasympathetic influences on HR, but it does not reflect cardiac sympathetic innervation.

**Methods of Assessment of Norepinephrine Plasma Concentration and Norepinephrine Kinetics.** From the time of von Euler’s56 demonstration that norepinephrine is the sympathetic postganglionic neurotransmitter, the potential value of measuring norepinephrine plasma concentrations as an index of nerve activity has been recognized. Plasma norepinephrine is derived largely from transmitter release by sympathetic nerve terminals with only approximately 2% released from the adrenal medulla (fig. 3).57–58 Lacking an acceptable compartment model to determine whole-body norepinephrine kinetics, investigators used norepinephrine plasma concentration as a crude overall index of SNS activity.61–64 However, norepinephrine plasma concentrations depend on the rate of immediate norepinephrine reuptake as well as norepinephrine clearance from the circulation, the latter depending on cardiac output, organ blood flow, and regional norepinephrine clearance capabilities.65–68 During anesthesia, cardiac output is often depressed and organ blood flow is altered, which may be particularly important when trying to relate norepinephrine plasma concentration to sympathetic outflow.

For norepinephrine analysis, either a single isotope radioimmunoassay or electrochemical detection after high-pressure liquid chromatography is used.61,69–72 The main advantage of the radioimmunoassay is its sensitivity of approximately 100 ps in 50-μl samples, permitting catecholamine determination in very small sample volumes. Concentrations of less than 100 ps can be detected by high-pressure liquid chromatography only with larger sample volumes. In contrast, high-pressure liquid chromatography is less time-consuming and has the advantage that occasional problems with interferences or poor sensitivity appear immediately on the chromatograms and may be identified or even corrected before final analysis.72
Usually, there are large intraindividual differences in norepinephrine plasma concentrations between arterial and different venous sampling sites. Norepinephrine plasma concentrations in supine young subjects under resting conditions are around 1–2 nM in forearm venous plasma. Arterial concentrations are as much as 25% lower than mixed venous concentrations because of norepinephrine clearance by the lungs during pulmonary transit.

These norepinephrine plasma concentrations are thought to be devoid of important hormonal metabolic and hemodynamic effects. Norepinephrine plasma concentration typically has to be increased at least fivefold by infusion of norepinephrine to achieve a hemodynamic effect. However, neurally released norepinephrine contributing to norepinephrine plasma concentration may not be comparable to similar increases in norepinephrine plasma concentration by infusion of norepinephrine.

Although norepinephrine plasma concentrations can provide crude estimates of overall sympathetic activation, they do not indicate the dominant source of norepinephrine release in a given situation. Furthermore, increased norepinephrine plasma concentrations may result from decreased norepinephrine clearance rather than increased release.

**Plasma Norepinephrine Kinetics.**

Total-body Norepinephrine Spillover. As mentioned in the previous section, norepinephrine plasma concentration does not depend solely on neurotransmitter release but also on the uptake of neurally released norepinephrine by the sympathetic neuron itself and by extraneural structures. Norepinephrine plasma clearence and norepinephrine spillover rate into plasma (the fraction of endogenously released norepinephrine that appears in plasma) can be calculated by using steady state infusions of tracer amounts of tritium-labeled norepinephrine. In humans, total-body norepinephrine spillover is 10–20% of total norepinephrine release. The mean nervous system norepinephrine production rate in healthy humans at rest is approximately 20 nmol/min with a mean norepinephrine spillover into plasma of 2–4 nmol/min and a mean norepinephrine plasma clearance of 1.5–2.5 l/min. With an extraction rate of 0.9, the liver has an important role in norepinephrine clearance as indicated by increased norepinephrine plasma concentrations in liver disease.

Single-organ Norepinephrine Spillover. To locate the source for an increased total-body norepinephrine spillover or to evaluate sympathetic activity of particular organs, it is most useful to determine single-organ spillover as calculated from Fick’s principle as the product of the venoarterial plasma norepinephrine concentration difference across the organ corrected for the organ’s norepinephrine uptake and the plasma flow according to the following equation:

\[
\frac{\text{Organ norepinephrine spillover rate}}{\text{organ plasma flow}} = \left(\frac{\text{Norepinephrine}_{\text{venous}} - \text{Norepinephrine}_{\text{arterial}}}{\text{Norepinephrine}_{\text{arterial}}} \times \text{[H]Norepinephrine}_{\text{extraction}}\right)
\]

where norepinephrine_{venous} and norepinephrine_{arterial} represent the organ’s venous and arterial plasma concentration, respectively, and [H]norepinephrine_{extraction} represents the fractional extraction of titrated norepinephrine in passage through the organ. The contribution of major organ systems to total-body norepinephrine spillover is illustrated in figure 4. Possible important determinants besides the sympathetic nerve traffic are sympathetic nerve density, organ mass, blood flow, and norepinephrine uptake and metabolism. The fractional norepinephrine spillover of total norepinephrine released varies substantially between different organ systems (kidneys, 1:3; skeletal muscle, 1:12; heart, <1:20). This should be consid-
nerve spillover technique. There has been particular interest in cardiac norepinephrine spillover, which contributes only 2–3% (50–150 pmol/min) to total norepinephrine spillover under supine resting conditions in healthy, young volunteers. This value increases substantially with age (beyond age 40–60 yr by approximately 90%) and more than 3-fold in patients with cardiac failure (to 200–400 pmol/min) at rest. Furthermore, cardiac norepinephrine spillover increases more than 10-fold (to 1.3–1.6 nmol/min) during moderate dynamic exercise in young, healthy subjects. Therefore, the norepinephrine spillover technique is useful for determining whole-body and in particular single-organ norepinephrine release at rest and during sympathetic activation. The main disadvantages of this method are certain logistic requirements (e.g., isotopes) and its invasiveness, particularly for single-organ determinations. Furthermore, instantaneous changes in SNS activity cannot be assessed because a stimulus must last for a few minutes to allow detection of altered norepinephrine release and clearance.

Conclusion

Despite the widespread studying of norepinephrine plasma concentrations, determination of regional SNS activity by microneurography or norepinephrine kinetics is most appropriate to yield reliable data on sympathetic outflow values.

Role of the Sympathetic Nervous System in Human Neurohumoral Circulatory Regulation

Neurohumoral cardiovascular regulation, apart from brain and spinal cord, involves both afferent and efferent nerves as recognized since the original description of the depressor nerve. The presence of cardio depression nerves arising from the region of the aortic arch and great vessels was demonstrated in 1903. Both baroreceptors in the aortic arch and baroreceptors in the carotid sinus are “high-pressure” stretch receptors, which respond quickly to changes in wall tension to maintain an adequate blood pressure (fig. 5). Arterial baroafferent activity in the aortic arch and carotid sinuses reaches the nucleus tractus solitarius via

Fig. 4. Regional rates of norepinephrine spillover to plasma, expressed as a percentage of total spillover for lungs, kidneys, skeletal muscle, hepatomesenteric circulation, skin, heart, adrenals, and brain. Adapted from and used with permission from Esler et al.81

Fig. 5. Arterial baroreflex pathways that control vasomotor tone and heart rate. (1) Carotid sinus and aortic arch “high-pressure” stretch receptors. (2) Unmyelinated fibers running in glossopharyngeal and vagus nerve synapsing at nucleus tractus solitarii (NTS). (3) Parasympathetic preganglionic fibers running in vagus nerve emerging from nucleus ambiguus. (4) Intermediate neurons. (5) Inhibitory neuron from caudal ventrolateral medulla (CVLM) to rostral ventrolateral medulla (RVLM). (6) Afferent pathway for release of vasopressin. (7) Sympathetic cardiac and vasomotor fibers passing intermediolateral column of spinal cord and sympathetic chain ganglia. Adapted from and used with permission from Smit et al.88
the glossopharyngeal and vagal nerves, and changes nucleus tractus solitarius activity by N-methyl-D-aspartate- and non-N-methyl-D-aspartate receptor-mediated effects. Secondary neurons activate neurons of the caudal ventrolateral medulla, where baroreceptor and nonbaroreceptor input, e.g., from chemoreceptors or pulmonary afferents, are integrated. Neurons in the caudal ventrolateral medulla, in turn, inhibit or stimulate neurons in the rostral ventrolateral medulla, where sympathetic preganglionic neurons originate. Axons of these first sympathetic neurons pass through the lateral column of the spinal cord and reach sympathetic paravertebral ganglia, where a second postganglionic neuron is activated by acetylcholine release. Postganglionic sympathetic fibers reach their effector organs along with mixed peripheral nerves, sympathetic rami, or blood vessels.

An increase in arterial pressure activates these “high-pressure” baroreceptors. In response, sympathetic neural outflow, e.g., to muscle vasculature, immediately decreases, resulting in decreased norepinephrine release as well as decreased regional vascular resistance and arterial pressure.

The occurrence of MSA bursts is determined mainly by fluctuations of arterial pressure and respiration. Pauses between successive bursts correspond to increasing systemic pressure inhibiting sympathetic nerve traffic.

The importance of these “high-pressure” baroreceptor afferents from the great vessels for blood pressure control was demonstrated by administration of local anesthesia to the vagal and glossopharyngeal nerves in humans. In this study, blockade of vagal and glossopharyngeal afferents induced a strong increase in MSA accompanied by temporal hypertension and tachycardia. Moreover, cardiac rhythmicity disappeared and MSA became similar to SSA.

On the other hand, “low-pressure” baroreceptors are located in the great veins as well as in the walls of the atria and the ventricles of the heart. Baroafferents reach the brain stem via the vagal nerve (fig. 5). These receptors are also linked to the release of atrial natriuretic peptide, controlling blood volume, which determines the static filling pressure of the system. Increased (right) cardiac filling activates “low-pressure” baroreceptors. In turn, similar to activation of “high-pressure” baroreceptor sympathetic outflow is decreased while parasympathetic tone is increased, which may result in changes in vasomotor tone, stroke volume, and HR.

Both “high-pressure” baroafferents and “low-pressure” baroreceptors play an important role in regulating MSA. Moderate levels of “lower body negative pressure” (up to −20 cm H₂O) decrease central blood volume and central venous pressure without affecting arterial pressure. Therefore, this technique was thought to be an appropriate method to examine the cardiopulmonary baroreflex. Under these conditions, MSA increased up to 250% of baseline during supine rest in healthy volunteers. However, the selectivity of low levels of lower body negative pressure in unloading cardiopulmonary baroreceptors has been questioned because computed tomographic scans have revealed small changes in aortic root diameter during mild lower body negative pressure, suggesting a possible involvement of aortic baroreceptors as well.

In healthy subjects, a slight pharmacologic decrease in diastolic pressure from 78 mmHg to 70 mmHg rapidly increased MSA to as much as 300% of baseline.

However, how does an increase in MSA change arterial blood pressure? MSA correlates well with muscle vascular resistance determined by occlusion plethysmography. A 50% increase in MSA (induced by lower body negative pressure) correlated linearly with significant decreases in both forearm and calf blood flow. Therefore, increased MSA may counteract arterial hypotension by increasing systemic vascular resistance, which in turn increases arterial blood pressure.

Analysis of spontaneous threshold for occurrence of MSA bursts and their strength (burst area) indicate that the baroreflex mechanisms that regulate occurrence and strength of MSA bursts are not identical. Therefore, different sites within the central nervous system may control the generation of MSA bursts and the strength of the single bursts. However, the physiologic meaning for this differential control of occurrence and strength of MSA bursts remains unclear so far.

During the past years, the modulation of arterial BRS and the control of MSA came to the scientific fore.

In patients with vasovagal syncope, resting MSA was increased, whereas baroreflex activation in response to lower body negative pressure is impaired. These data provide new recent insights into mechanisms of vasovagal syncope. The authors suggest that pharmacologic modulation of baroreceptor sensitivity may be a promising treatment strategy for neuromediated syncope.

Improved arterial BRS could be achieved by physical training in these patients, decreasing the incidence of syncope.

Moreover, exercise training also restored baroreflex control of MSA and HR in untreated hypertensive patients and normalized MSA and blood pressure in these patients. Therefore, physical training acts as a nonpharmacologic therapeutic alternative on sympathetic outflow and blood pressure control in patients with cardiovascular disease.

Often, there is an obvious respiratory periodicity in MSA with maximum activation during end-expiration and the first half of inspiration in spontaneously breathing subjects. However, maximum MSA also parallels the lowest blood pressure during the respiratory cycle. Because of these oscillations of arterial pressure with respiration, it is difficult to distinguish between primary central modulation and secondary baroreceptor reflex or lung receptor–induced changes in MSA.
A study in four patients after combined heart and lung transplantation–induced denervation of cardiopulmonary baroreceptors indicated that during normal tidal breathing, most of the respiratory influence on MSA observed is, at least in these patients, independent of baroreceptor-sensed fluctuations of intrathoracic or intracardiac pressures. Furthermore, stimulation of vagal afferents by lung inflation does not account for the observed changes. In turn, during hyperpneic states, vagally mediated feedback of lung inflation is the primary mechanism augmenting the within-breath variation of MSA in healthy humans.112 In a meta-analysis, major changes in the pattern of MSA were not observed comparing spontaneous breathing with mechanical ventilation. It was concluded that an inspiratory inhibition of MSA does not depend on increases in arterial pressure and baroreceptor output.108

Both hypoxia and hypercapnia activate MSA via peripheral and central chemoreceptors.113–115 Isocapnic hypoxia (10% O2, 90% N2) significantly increased MSA by 21% after 5 min, hyperoxic hypercapnia (7% CO2, 93% O2) by 53%, and a combination of both (10% O2, 7% CO2, 83% N2) by 108% in a synergistic fashion.29 After 4 min of severe hypoxia (8% O2), an increase in MSA by as much as 298% was reported, indicating that the maximum effect of sympathetic reflex activation induced by hypoxia is moderately delayed.116 Surprisingly, both noradrenaline spillover (+40) and noradrenaline clearance (+20) significantly increased during 20–30 min of hypoxia (10% O2), resulting in an only minor but significant increase in arterial norepinephrine of 20%.117 This observation is a good example that norepinephrine plasma concentration often does not mirror sympathetic activity.

In contrast to the effects on parasympathetic arm of baroreflex, baroreflex control of sympathetic outflow is not impaired with age. Collectively, changes in baroreflex function with age are associated with an impaired ability of the organism to buffer changes in blood pressure. This is evidenced by the reduced potentiation of the pressor response to bolus infusion of a pressor drug after compared with before systemic ganglionic blockade in older as compared with young adults.118

On the other hand, a recent study revealed insights on sex differences in sympathetic nervous activity. Women with hypertension had increased MSA compared with their normotensive counterparts, and MSA was significantly related to blood pressure but not to body mass index. MSA in men with hypertension was no different from that in normotensive subjects, but MSA was significantly related to body mass index. Diet resulted in similar weight loss in men and women but induced a decrease in MSA only in men.119

Table 1 summarizes the conditions that are known to cause an increase or decrease in resting MSA, subcategorized as perioperative and nonperioperative.120,121

<table>
<thead>
<tr>
<th>Increase of MSA</th>
<th>Decrease of MSA</th>
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<tbody>
<tr>
<td><strong>Perioperative</strong></td>
<td><strong>Nonperioperative</strong></td>
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<tr>
<td>Hypoxia</td>
<td>Aging</td>
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<tr>
<td>Hypercapnia</td>
<td>Obesity</td>
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<tr>
<td>Positive end-expiratory pressure</td>
<td>Obstructive sleep apnea syndrome</td>
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<td>Laryngoscopy</td>
<td>Intubation</td>
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MSA = muscle sympathetic activity.

Effects of General Anesthesia on Sympathetic Nervous System Activity

General anesthesia is usually associated with changes in sympathetic activity that may be due to mechanical ventilation, specific anesthetic drugs, the direct circulatory effects they induce, and/or their effects on central or peripheral nervous system.

Role of Mechanical Ventilation

Mechanical ventilation, in particular positive end-expiratory pressure, often decreases cardiac filling, cardiac output, and arterial pressure by displacing blood from the thorax to the gut and liver.122 This raises the question of whether and to what extent these alterations are counterregulated by the SNS, both in the conscious state and during anesthesia.123

Reflex activation of the SNS is thought to be important for compensatory responses to mechanical ventilation. Sympathetic activation increased systemic vascular resistance124–127 and possibly also tone of capacitance vessels,128,129 and activated the renin-angiotensin system.130 Mechanical ventilation with increasing positive end-expiratory pressure (0–20 cm H2O) in conscious volunteers increased MSA by up to 82%. This response was paralleled by an increase in calf vascular resistance and in forearm venous norepinephrine plasma concentration (fig. 6).131

Table 1. Influences on MSA Level

<table>
<thead>
<tr>
<th>Increase of MSA</th>
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Several receptor populations can be considered to mediate such effects. Besides “high-pressure” baroreceptors in the carotid sinus region and aortic arch,132,133 “low-pressure” cardiopulmonary receptors are considered to be responsible for the cardiovascular reflex activation, but their respective roles have not been fully clarified.131 Because continuous positive airway pressure (10–12 cm H₂O) breathing in awake subjects decreases cardiac and intrathoracic blood volume by approximately 10% at unchanged arterial pressure,122 unloading of cardiopulmonary “low-pressure” baroreceptors may contribute to the observed increase in MSA during mechanical ventilation.

**Intravenous Anesthetics**

**Ketamine.** Ketamine is the only injectable anesthetic that increases arterial pressure and HR.134,135 This cardiovascular stimulation is associated with increased catecholamine plasma concentrations.136 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 HR) as a larger dose given intravenously, central sympathetic activation was proposed to be responsible for cardiovascular stimulation during ketamine anesthesia.137

In healthy volunteers, racemic ketamine increased arterial blood pressure and norepinephrine plasma concentrations, whereas MSA was markedly decreased (fig. 7A). However, when increased arterial pressure was normalized to awake baseline, MSA did not differ in comparison with values obtained in the awake state. At the same time, the MSA response to arterial hypotension was not altered by racemic ketamine.138 It can be concluded that during anesthesia with racemic ketamine, MSA was reduced because of baroreflex inhibition. Norepinephrine plasma concentrations may be increased because of inhibition of norepinephrine uptake by ketamine or increased sympathetic outflow to organs other than muscle.

In contrast, anesthesia with 3(+) -ketamine increased sympathetic outflow to muscle and increased norepinephrine plasma concentration, resulting in increased arterial pressure.139 The effects on resting MSA contrasts with earlier observations during anesthesia with racemic ketamine where sympathetic neural outflow to muscle

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Fig. 6. Effects of positive end-expiratory pressure (PEEP; 0–20 cm H₂O) on muscle sympathetic activity (MSA) in spontaneously breathing (SB), awake volunteers (mean ± SEM from eight healthy volunteers). Note the pressure-dependent (0–20 cm H₂O) increase in MSA resulting in a 100% increase of MSA with 20 cm H₂O PEEP. Recovery to baseline conditions was achieved within a few minutes after discontinuation of PEEP. Therefore, a further increase in intrathoracic pressure during mechanical ventilation with in addition PEEP is associated with increased efferent sympathetic activity to the vasculature of muscles. *P < 0.05, **P < 0.001. Derived from and used with permission from Selldén et al.131

Fig. 7. (A) Muscle sympathetic activity (MSA) burst incidence in the awake state, during ketamine anesthesia, and during ketamine anesthesia with arterial pressure adjusted to baseline by infusion of sodium nitroprusside infusion (SNP). Mean ± SD from six healthy subjects. MSA markedly and significantly decreased after induction of anesthesia with ketamine. When arterial pressure was decreased during ketamine anesthesia to awake baseline by SNP, as to inhibit baroreflex afferents, MSA normalized, indicating preserved muscle sympathetic activity during ketamine anesthesia. *P < 0.01 versus baseline awake. (B) Relations between diastolic arterial pressure and MSA burst incidence before and after injection of SNP in the awake state and during ketamine anesthesia. Mean ± SD from six healthy subjects. The muscle sympathetic response to hypotensive challenges as indicated by the slope of the regression line was maintained during ketamine anesthesia even at a higher arterial pressure level. Derived from and used with permission from Kienbaum et al.138
decreased during increased arterial pressure, thus demonstrating stereoselective effects on MSA.\textsuperscript{136,139} Similar to racemic ketamine, the MSA response to hypotensive challenges was fully maintained during anesthesia with \(\Delta S\)-ketamine even at higher arterial pressures (fig. 7B).

In contrast to racemic ketamine, barbiturates, propofol, and etomidate, \(\Delta S\)-ketamine, therefore, is the only intravenous anesthetic that increases MSA despite an increase in arterial pressure.

In summary, ketamine does not increase sympathetic outflow in a generalized fashion but shows differential effects of both ketamine isomers on the SNS. Interestingly, despite increased arterial pressure, the MSA responses to arterial hypotension were always maintained with both racemic and \(\Delta S\)-ketamine, which may contribute to cardiovascular stability during ketamine anesthesia.

**Opioids.** Opioid receptors are ubiquitously present in the heart, vasculature, and ganglia.\textsuperscript{140,141} \(\mu\)-Opioid receptor agonists are the subgroup of opioids most frequently used during general anesthesia and perioperative analgesia. Nevertheless, the acute effects of pharmacologic doses of \(\mu\)-opioid receptor agonists on the SNS are difficult to evaluate because baseline anesthesia, sedation, and respiratory depression by opioids alter SNS activity as well.

In spontaneously breathing, awake humans, fentanyl induces a dose-dependent increase in norepinephrine plasma concentration by 70% and in epinephrine plasma concentration by 180%.\textsuperscript{142-144} In contrast, fentanyl administered to healthy volunteers and awake, premedicated patients did not alter MSA during a 5-min observation period.\textsuperscript{120,145} This first view contradiction may be resolved considering opioid-induced respiratory depression responsible for sympathetic activation in the first study. When hyperventilation is avoided in anesthetized dogs, high doses of fentanyl even decreased HR, arterial pressure, left ventricular dp/dt, and norepinephrine and epinephrine plasma concentrations due to decreased sympathetic outflow.\textsuperscript{146}

Second, as classically shown for meperidine and morphine, some opioids can exert both a probably direct and also unspecific histamine release–related vasodilatation with a consecutive decrease in arterial pressure.\textsuperscript{147-149} This decrease in arterial pressure may also induce the reflex activation of sympathetic neural outflow observed in some studies.\textsuperscript{25}

Moreover, effects of endogenous opioids have been studied by administration of opioid receptor antagonists. When \(\mu\)-opioid receptors were blocked by administration of the \(\mu\)-opioid receptor antagonist naloxone, hemodynamics, catecholamine plasma concentrations, MSA, and arterial baroreflexes were not changed at rest.\textsuperscript{150-156} In contrast, cardiopulmonary baroreflexes and the MSA response to exercise were augmented after administration of naloxone in humans.\textsuperscript{152-158}

Finally, chronic \(\mu\)-opioid receptor stimulation, as obtained in opioid-addicted patients, markedly decreases MSA, norepinephrine plasma concentration, and arterial baroreflexes, whereas arterial blood pressure and HR did not differ from those in healthy volunteers (fig. 8). Moreover, when opioid receptors were blocked by acute administration of naloxone for detoxification from opioids, MSA, norepinephrine plasma concentration, and BRS increased despite deep general anesthesia.\textsuperscript{159-161}

Therefore, chronic opioid receptor stimulation markedly depresses sympathetic outflow at rest and during cardiovascular challenges.

Moreover, chronic \(\mu\)-opioid receptor stimulation markedly decreased the MSA response to hypotension compared with healthy subjects despite similar arterial blood pressure and HR at rest. In contrast, the HR response to hypotension did not differ between addicted patients and healthy subjects. Opioid receptor blockade during
propofol anesthesia markedly increased the MSA response to hypotension even beyond awake values, whereas the HR response remained unchanged. Therefore, chronic μ-opioid receptor stimulation results in uncompensated depression of cardiovascular sympathetic neural regulation and exerts differential effects on efferent sympathetic nerve activity to muscle and on HR control in response to arterial hypotension.

In conclusion, acute administration of opioids alone has little effect on sympathetic outflow and cardiovascular variables in uncompromised volunteers. However, when opioids are given for an extended period, depression of SNS may be expected.

**Sedative Hypnotics**

**Barbiturates.** The central nervous system–depressive effect of barbiturates has been known for more than 40 yr. Tachycardia after induction is most likely due to inhibition of cardiac vagal outflow rather than sympathetic activation. Depressant effects on myocardial contractility and arterial pressure are probably attributable to both a direct negative inotropic effect and decreased efferent sympathetic drive. SSA is abolished within 1 min after induction of anesthesia with thiopental. Furthermore, MSA was suppressed after methohexital administration (fig. 9). When BRS was determined by sequential bolus injections of SNP and phenylephrine, baroreflex slopes relating MSA to induced changes in arterial pressure were almost abolished. Nevertheless, intense stimulation, e.g., by laryngoscopy or intubation, is still accompanied by an increased MSA, indicating that sympathetic reflex activation from stimulation of laryngeal and tracheal receptors is not fully suppressed by barbiturates in clinically used dosages.

In conclusion, barbiturates depress both SSA and MSA and decrease BRS substantially, indicating marked inhibition of sympathetic outflow and reflex activation.

**Benzodiazepines.** In resting patients, intravenous administration of benzodiazepines usually induces only minor cardiovascular changes. Nevertheless, diazepam, or flunitrazepam, when given to healthy volunteers, decreased catecholamine plasma concentrations and attenuated baroreflex responses. A study that observed the effects of benzodiazepines in patients with panic disorder demonstrated that anxiolytic therapy with alprazolam increases MSA and HR not only in patients with panic disorder but also in healthy controls.

In contrast, several studies suggested that diazepam reduces both arterial blood pressure and MSA. After diazepam administration, systolic and mean blood pressure and MSA decreased significantly. In conclusion, the hypotensive effect of diazepam in human is mainly due to the central mechanism. However, direct recordings of efferent sympathetic nerve activity in humans have not been reported. In contrast to direct negative inotropic effects of diazepam in isolated rat heart muscle, diazepam given to dogs anesthetized with chloralose did not change baseline renal sympathetic nerve activity. However, BRS, when determined as changes in renal sympathetic nerve activity in response to arterial pressure perturbations, was markedly decreased. Whereas midazolam in rabbits had no effect on mean arterial pressure or HR at baseline, HR response after bilateral carotid occlusion was significantly attenuated. In contrast, no effects on mean arterial pressure response were observed, suggesting differential effects on cardiac and baroreflex control. Moreover, when diazepam was combined with...
opioids (e.g., fentanyl, morphine), decreases in arterial pressure, cardiac output, systemic vascular resistance, and catecholamine concentrations in plasma were observed in dogs anesthetized with thiopental, in healthy volunteers, and in patients before coronary artery bypass graft surgery, which did not occur when fentanyl was given alone.143,173–175

In summary, benzodiazepines may decrease baseline SNS activity and the ability to respond to arterial pressure changes. Moreover, it has to be emphasized that a combination of benzodiazepines with opioids typically results in profound reduction of SNS activity associated with decreases in systemic vascular resistance and arterial pressure. These cardiovascular changes are even more pronounced when SNS activity is increased, e.g., during cardiac failure.

**Propofol.** Propofol induces hypotension, particularly when injected rapidly. Responsible mechanisms have been suggested to include myocardial depression,176–178 decreased vascular resistance,177,178 and diminished cardiac preload and output.179,180 The observed decrease of peripheral vascular resistance in patients with artificial hearts points to a direct vasodilatating effect of propofol or a decrease in sympathetic vasoconstrictor activity.109,181 In contrast, propofol increases myofilament Ca\(^{2+}\) sensitivity in pulmonary artery smooth muscles, and this effect involves the protein kinase C signaling pathway, which could in general serve as a target for anesthetic agents that alter vasomotor tone.182 If this observation was clinically relevant, vasoconstrictor tone would be increased at similar sympathetic outflow.

On the other hand, when propofol was infused in the brachial artery, achieving local anesthetic plasma concentrations, vasodilatation did not occur.183 Accordingly, central mechanisms must be responsible for the observed vasodilatation during propofol anestheisia.184,185

Propofol decreased mean arterial pressure from 100 mmHg to 73 mmHg, which was accompanied by a 66 ± 7% decrease in MSA within 3 min and a threefold to sevenfold increase in leg blood flow.34,55,186,187 BRS, as determined by bolus injections of SNP, was almost abolished.35

Propofol in sedation dose significantly reduced sympathetic nerve activity by 65% and 92% at moderate and deep sedation. At the same time, forearm vascular resistance significantly decreased. These effects resulted in significant decreases in mean blood pressure at moderate and deep sedation, respectively. Propofol also reduces reflex increases in sympathetic nerve activity. Recapitulatory sedation doses of propofol, which did not compromise respiratory function, had substantial inhibitory effects on sympathetic nerve activity and reflex responses to hypotension, resulting in vasodilatation and significant decrease in mean blood pressure (fig. 10).188

These data clearly demonstrate that propofol markedly decreases SNS basal activity as well as the ability of the SNS to respond to hypotensive challenges.

**Etomidate.** Etomidate is probably the induction anesthetic with the fewest hemodynamic effects and has therefore been advocated in patients with cardiovascular disease or hypovolemia. The mechanism for the hemodynamic stability after etomidate administration has been elucidated by direct recordings of MSA, demonstrating that both sympathetic efferent activity and sympathetic reflex activation by hypotensive challenges are not impaired.186

**Sedative Hypnotics: Conclusion.** Except for etomidate, barbiturates, benzodiazepine, and propofol all decrease resting SNS activity and attenuate baroreflex responses to changes in arterial pressure189 (table 2). Nevertheless, it is difficult to compare sedative hypnotics in their effects on SNS activity and baroreflex function in a rigid manner, because dose–response relations are not available in humans and equi-potent sedative effects are difficult to establish.

**Nitrous Oxide**

Nitrous oxide is a centrally acting stimulant of sympathetic outflow. An increase in MSA by 60% paralleled by an increase in forearm vascular resistance of 30% has been observed during spontaneous breathing of subanest-
thetnic nitrous oxide concentrations.\textsuperscript{190} In patients breathing nitrous oxide, baroreflex-mediated tachycardia decreased by approximately 39\% during hypotension induced by SNP.

Moreover, cardiovagal reflex response is not affected by nitrous oxide, \textit{per se}, and spontaneous baroreflex responses closely reflect beat-to-beat dynamic modulation of the cardiac cycle by the parasympathetic nervous system during inhalation of 67\% nitrous oxide.\textsuperscript{191}

Unlike the results demonstrated in adults, a study on the use of nitrous oxide in children showed few cardiovascular effects of nitrous oxide. Furthermore, whereas in adults nitrous oxide is associated with an excitatory cardiovascular profile, in children this agent seems to be associated with a depressant cardiovascular profile.\textsuperscript{192}

However, in adults the MSA increase in response to arterial hypotension remained unchanged.\textsuperscript{165} Withdrawal of nitrous oxide during isoflurane anesthesia (0.6\% end-tidal) in healthy volunteers was associated with a substantial decrease in MSA (~40\%), a slight increase in HR, and unchanged mean arterial pressure, despite the depth of anesthesia being reduced (minimum alveolar concentration: 1.0–0.5; fig. 11).\textsuperscript{187}

Nitrous oxide, therefore, counteracts SNS depression of volatile anesthetics when both drugs are administered simultaneously. This mechanism may explain the classic clinical observation that similar anesthetic depths can be achieved with less cardiovascular depression by coadministration of nitrous oxide–volatile anesthetic compared with administration of a volatile anesthetic alone.\textsuperscript{193}

\textbf{Xenon}

In contrast to the well-known volatile anesthetics (chlorofluorocarbons), xenon does not cause circulatory depression.\textsuperscript{194–196} Even hints of circulatory activation have been observed in animal models and patients.\textsuperscript{197,198}

Recent studies showed that xenon did not reduce heart variability, indicating favorable cardiovascular stability in patients with cardiac disease during xenon anesthesia during inhalation of 67\% nitrous oxide.\textsuperscript{191}  

\textit{Volatile Anesthetics}

Cardiovascular effects of volatile anesthetics have been investigated extensively, including evaluation of SNS ac-

\begin{table}[h]
\centering
\caption{Development of MSA after Different Drug Applications}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\textbf{Dosage} & \textbf{Mean Arterial Pressure, mmHg} & \textbf{Heart Rate, beats/min} & \textbf{MSA, \% vs. Baseline} & \textbf{Study} \\
\hline
Ketamine & $2 \text{ mg/kg}$ + $30 \mu g \cdot kg^{-1} \cdot min^{-1}$ & $+37 \pm 19^* $ & $+38 \pm 26^* $ & $-58 \pm 26^* $ & Kienbaum et al.\textsuperscript{138} 2000 \\
Ketamine & After blood pressure normalization (SNP) & $+3 \pm 7 $ & $+40 \pm 28^* $ & $+6 \pm 9 $ & Kienbaum et al.\textsuperscript{138} 2000 \\
S(+)-Ketamine & $670 \mu g/kg + 15 \mu g \cdot kg^{-1} \cdot min^{-1}$ & $+39 \pm 21^* $ & $+14 \pm 9^* $ & $+119 \pm 43^* $ & Sellgren et al.\textsuperscript{145} 1992 \\
Fentanyl & $2 \mu g/kg $ & $-8 \pm 7^* $ & $-2 \pm 6 $ & $+2 \pm 8 $ & Penacente et al.\textsuperscript{120} 1995 \\
Fentanyl & $5 \mu g/kg $ & $+1 \pm 5 $ & $-2 \pm 8 $ & $+1 \pm 2 $ & Ebert et al.\textsuperscript{132} 1990 \\
Thiopental & $4 \mu g/kg $ & $+8 \pm 6^* $ & $+11 \pm 11^* $ & $-54 \pm 65^* $ & Sellgren et al.\textsuperscript{137} 1990 \\
Propofol & $2 \mu g/kg + 100 \mu g \cdot kg^{-1} \cdot min^{-1}$ & $-27 \pm 10^* $ & $+11 \pm 8^* $ & $-66 \pm 7^* $ & Sellgren et al.\textsuperscript{137} 1990 \\
Propofol & $3 \mu g/kg + 200 \mu g \cdot kg^{-1} \cdot min^{-1}$ & $-22 \pm 10^* $ & $-14 \pm 7^* $ & $-73 \pm 20^* $ & Ebert et al.\textsuperscript{136} 1992 \\
Etomidate & $0.3 \mu g/kg + 15 \mu g \cdot kg^{-1} \cdot min^{-1}$ & $+23 \pm 10^* $ & $-4 \pm 7 $ & $-13 \pm 12^* $ & Ebert et al.\textsuperscript{136} 1992 \\
\hline
\end{tabular}
\end{table}

Data are presented as value ± SD.

\( ^* P < 0.01. \)

MSA = muscle sympathetic activity; SNP = sodium nitroprusside.
tivity and BRS. Halothane,200–206 enflurane,204,207,208 sevoflurane,209 and isoflurane218,204,210–213 decrease SNS activity and baroreflex activation in animals. Most components of the baroreflex loop (afferent and efferent nerves, central nervous system, peripheral ganglia, myocardium, smooth muscle) are suppressed by volatile anesthetics. In contrast, carotid baroreceptor afferent activity in rabbits increased with deeper halothane anesthesia irrespective of cardiac filling and output.205 This mechanism, in addition to direct effects on the heart and vessels, may further contribute to the decrease in arterial pressure observed during halothane anesthesia.

Desflurane and isoflurane induce vasodilatation and seem to have similar cardiodepressant effects.214,215 Some data, however, indicate that there are substantial differences between the actions of isoflurane and desflurane with respect to the SNS.216 Desflurane caused a similar blood pressure decrease to isoflurane but was associated with higher resting MSA at equianesthetic steady state concentrations.216–219 In addition, when the inspired concentration of desflurane was rapidly increased, a surge in sympathetic outflow was observed, associated with a 2- to 3-min-lasting increase in HR and blood pressure (fig. 12). That is why desflurane is not recommended as the sole agent for anesthetic induction of patients with coronary artery disease or any patient where increases in HR or blood pressure are undesirable. The increase in basal MSA at a high steady state concentration of desflurane did not seem to be due to baroreflex mechanism.220 In contrast, BRS was preserved with low concentrations (up to 1.0% end-tidal) of isoflurane but not with desflurane. This finding could possibly explain the isoflurane-induced tachycardia at low minimum alveolar concentrations. However, greater inspiratory concentrations were associated with similar depression of BRS with both volatile anesthetics.221,222 Investigators have tried to identify a central or peripheral site, e.g., airway irritation, involved in the aforementioned activation of the SNS. It was demonstrated that central sites contribute more than pulmonary sites to the hemodynamic activation associated with rapid increases in inspired desflurane concentrations and that lower airway sites dominate upper airway sites.221,222

With sevoflurane, there is no neurocirculatory excitation observed with rapid increases in inspiratory concentrations. At steady state, increasing sevoflurane concentrations were associated with lower MSA but similar mean arterial pressure and HR when compared with equianesthetic desflurane in humans.223

**Anesthetic Adjuvants**

**Ganglionic Blocking Drugs.** Historically, N,N-nicotinic receptor antagonists such as trimethaphan have been administered in experimental and clinical settings to achieve profound arterial hypotension by autonomic ganglionic blockade. Ganglionic blockade results in near-complete interruption of the efferent arc of the baroreflex (sympathetic and parasympathetic), as indicated by a variety of autonomic function tests. Intravenous administration of trimethaphan abolished resting MSA as well as the MSA and HR response to induced changes in arterial pressure. At the same time, norepinephrine plasma concentrations decreased.224

**α2-Receptor Agonists.** α2-Receptor agonists, e.g., clonidine, dexmedetomidine, or mivazerol, have been used to reduce dosages of opioids and volatile anesthetics. Moreover, a reduction in ST-segment changes in patients undergoing peripheral vascular surgery was demonstrated for clonidine, suggesting an improvement of
the ratio of myocardial oxygen supply and demand in patient with coronary artery diseases.225

In healthy volunteers, oral clonidine decreased resting MSA and norepinephrine plasma concentration by 50%.226 In contrast, the MSA response to changes in arterial blood pressure was unchanged. When clonidine was intravenously administered, arterial blood pressure decreased and MSA tended to increase in response to hypotension when clonidine plasma concentrations were low.227 Therefore, this decrease in arterial pressure may be due to direct vasodilating effects of clonidine. However, with higher dosages, MSA decreased in parallel to the decrease in arterial blood pressure, indicating a resetting of arterial baroreflexes at a lower pressure level.

Dexmedetomidine has been show to decrease MSA as well. The combination of dexmedetomidine and glycopyrrolate, a muscarinic receptor antagonist, mimics ganglionic blockade.228

Clinical Correlations and Conclusions

Most anesthetics interfere with sympathetic neural outflow and cardiovascular regulation. Accordingly, cardiac output and systemic vascular resistance are destabilized, causing arterial hypotension. These effects are even more pronounced in states of chronically elevated MSA, including normal aging, which places patients at risk of profound hypotension when anesthetized with, e.g., propofol, thiopental, or volatile anesthetics. At the same, anesthetized patients with severely decreased MSA and baroreflexes are prone to severe hypotension in the presence of hypovolemia or systemic administration of vasodilators with only modest increases in HR. Conversely, the α-adrenoceptor agonist phenylephrine increases arterial pressure, which in turn slows HR by increased vagal outflow. Similar to certain anesthetics, diseases that attack the SNS, e.g., multisystem atrophy (Shy-Drager syndrome) and pure autonomic failure (Bradbury-Eggleston syndrome), are associated with decreased sympathetic outflow and impaired cardiovascular control. Of interest, these patients present with supine hypertension and postural hypotension, potentially challenging blood pressure control in the perioperative period. Patients with baroreflex failure may serve as a clinical model of impaired sympathetic cardiovascular control presenting with extreme arterial pressure changes during cardiovascular challenges, e.g., mental stress, painful stimuli.229 Taken together, these patients demonstrate the importance of sympathetic cardiovascular control mechanisms in the awake state.

In patients with severe hypertension, physiologic cardiovascular control mechanisms can be manipulated. In these patients, carotid sinuses stimulators were implanted to further increase baroreceptor afferent activity, which in turn decreases sympathetic outflow and arterial pressure.230

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EFFECTS OF GENERAL ANESTHESIA ON THE SYMPATHETIC SYSTEM


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