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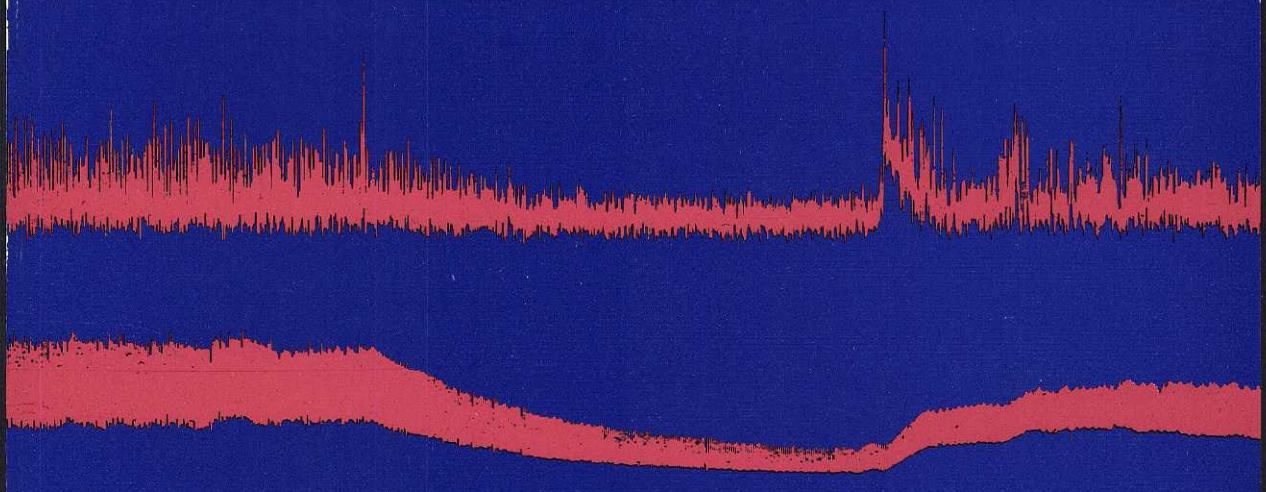
Cardiovascular control mechanisms during anaesthesia and surgery

with special reference to
muscle nerve sympathetic activity

Johan Sellgren



Göteborg 1993

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AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen
vid Göteborgs Universitet
kommer att offentligen försvaras
i föreläsningssal F3, Sahlgrenska Sjukhuset
fredagen den 12 mars 1993, kl 09.00

av

Johan Sellgren
leg. läkare

Avhandlingen baseras på följande delarbeten:

I **Anesthetic modulation of the cardiovascular response to microlaryngoscopy. A comparison of propofol and methohexital with special reference to leg blood flow, catecholamines and recovery.**
Sellgren J, Ejnell H, Pontén J, Sonander HG.
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Johan Sellgren, Department of Anaesthesia and Intensive Care, Sahlgren's Hospital, University of Göteborg, S-413 45 Göteborg, Sweden.

Thesis defended March 12th, 1993.

Abstract.

Knowledge of effects of anaesthetics on cardiovascular control is based mainly on studies during undisturbed anaesthesia. However, in the clinical situation the cardiovascular characteristics of different anaesthetics are related to the balance between the dose of the anaesthetic and the intensity of surgical stimulation. Therefore, a general **aim** of the present studies was to investigate the effects of anaesthetics on cardiovascular control mechanisms both during undisturbed anaesthesia and during surgery. Since the trend in general anaesthesia is to use anaesthetics with short duration, the studies were focused on propofol in particular but also on methohexitone and isoflurane. Microlaryngoscopy was used as a surgical stress model since microlaryngoscopy evokes an intense and relatively stable afferent stimulation associated with a reproducible pressor response.

Methods: A main method in the human studies was microneurography of sympathetic vasoconstrictor nerve traffic to skeletal muscle blood vessels. It was thereby possible to differentiate between neurogenic effects and direct effects on the blood vessels from circulating factors including the anaesthetics themselves. Cardiac output (impedance cardiography) and regional blood flows (leg plethysmography, skin laser Doppler flowmetry, photoelectric pulse plethysmography) were recorded. Arterial catecholamine concentrations were measured. In addition, an experimental open loop baroreflex model (isolated carotid sinuses) was studied in the cat.

Results: Sympathetic activity to skeletal muscle (MSA) was depressed by propofol, methohexitone and isoflurane, whereas nitrous oxide was associated with an increase in MSA. The depression of MSA during undisturbed propofol infusion was to a large extent restored during microlaryngoscopy in spite of a more than three times increased propofol infusion rate. Vasodilation during propofol anaesthesia was caused by an inhibition of central sympathetic outflow and probably also by a direct vascular effect. In a comparative study during microlaryngoscopy, propofol was a better alternative than equianaesthetic doses of methohexitone, which in a low infusion dose was insufficient to control the microlaryngoscopy-induced pressor response and in a high infusion dose was associated with prolonged recovery. A large difference in leg blood flow was noted between the low and high-dose methohexitone groups whereas no difference was observed between the low and high-dose propofol groups. In the cat, the baroreflex sensitivity was better maintained during anaesthesia with propofol than with methohexitone or isoflurane. In humans, both cardiac and muscle sympathetic baroreflex sensitivities were depressed by propofol. The further depression of the cardiac baroreflex that was observed during surgery may have been due to a central vagal inhibition similar to that found in animals during defence area stimulation. The muscle nerve sympathetic baroreflex sensitivity was determined by a balance between an augmented central sympathetic outflow due to surgical stress and inhibition due to the anaesthetic.

Conclusions: Sympathetic activity to skeletal muscle is profoundly influenced by the choice of anaesthetic agent. A suppression of activity is more common than an increase. A decrease in MSA is counteracted by surgical stress. During propofol, methohexitone and isoflurane anaesthesia, the muscle nerve sympathetic baroreflex is qualitatively operative but the baroreflex sensitivity is depressed to a variable extent depending on the anaesthetic agent and depth of anaesthesia.

Key words: Anesthetics intravenous, propofol, methohexital; anaesthetics volatile, isoflurane, nitrous oxide; surgery, larynx; sympathetic nervous system; arterial baroreceptors; sympathetic microneurography; plethysmography, leg blood flow; skin, blood flow; cats; humans.

ISBN 91-628-0823-0, pp 1-58 , Göteborg 1993

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ISBN 91-628-0823-0, pp 1- 58, Göteborg 1993

To

Marie-Louise,
Anna, Erik and Fredrik

Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

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Contents

Abbreviations

A	Adrenaline
ANOVA	Analysis of variance
AP	Arterial blood pressure
ASA	American Society of Anesthesiologists
CO	Cardiac output
CO_2	Carbon dioxide
CUSUM	Cumulative sum
CVP	Central venous pressure
DAP	Diastolic arterial blood pressure
ECG	Electrocardiography
F_iO_2	Fraction of inspired oxygen
HFPPV	High frequency positive pressure ventilation
HPLC	High performance liquid chromatography
HR	Heart rate
IR	Infra-red
LBF	Leg blood flow
LVR	Leg vascular resistance
MAC	Minimum alveolar concentration
MAP	Mean arterial blood pressure
MSA	Muscle nerve sympathetic activity
MSAA	Muscle nerve sympathetic activity burst area
NA	Noradrenaline
O_2	Oxygen
OR	Operating room
P_aCO_2	Partial tension in arterial blood of carbon dioxide
P_aO_2	Partial tension in arterial blood of oxygen
PEEP	Positive end expiratory pressure
PLSD	(Fisher's) protected least significant difference
Rpm	Rounds per minute
RR	Recovery room
SAP	Systolic arterial blood pressure
SEM	Standard error of the mean
SNP	Sodium nitroprusside
SSA	Skin nerve sympathetic activity
SV	Stroke volume
SVR	Systemic vascular resistance

1. Introduction

Physiological background

Cardiovascular homeostasis includes maintenance of an adequate blood pressure and optimal local tissue blood flows according to present metabolic demands. The cardiovascular control mechanisms are complex and involve many components[1,2]. The heart and the vascular smooth muscles serve as effector organs in the dynamic short-term circulatory regulation, which is the subject of this thesis. The autonomic nervous system plays an important role in this regulation through cardiovascular reflexes mediated by neurohormonal pathways (fig. 1). Myogenic mechanisms[3,4], local metabolites[5,6], release of vasoactive substances such as histamine, bradykinin and prostaglandins[7], and local nervous reflexes[8] also contribute to the control of vascular tone and regional blood flow.

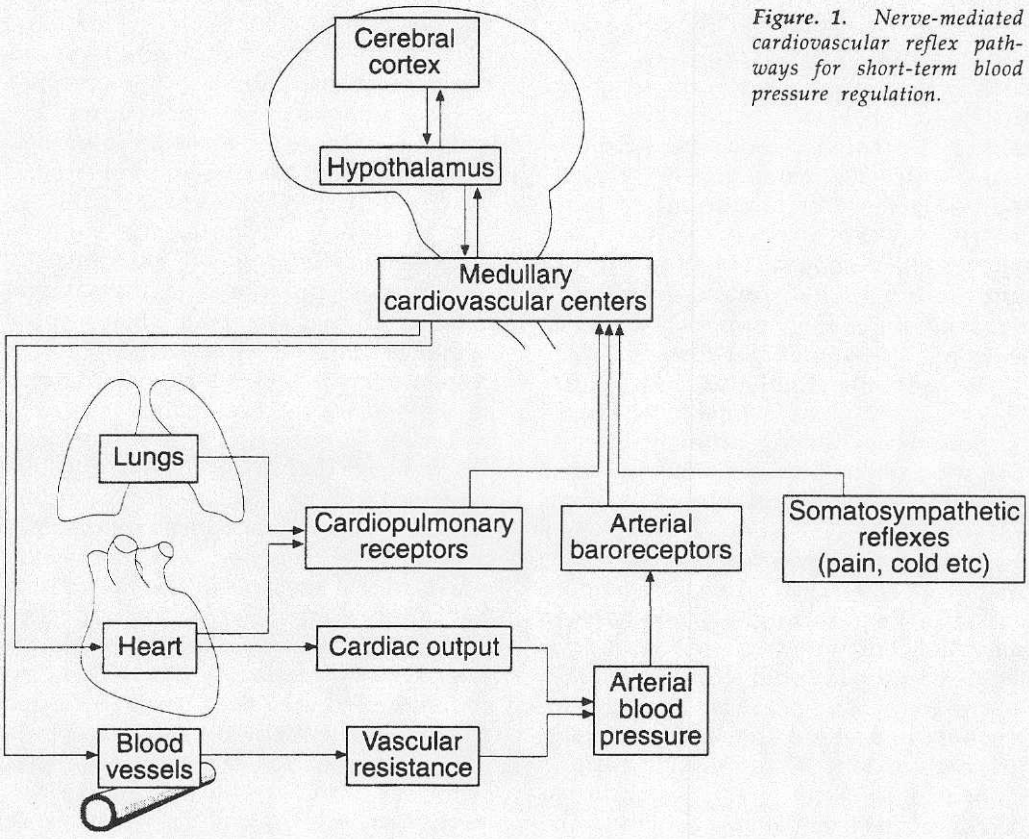


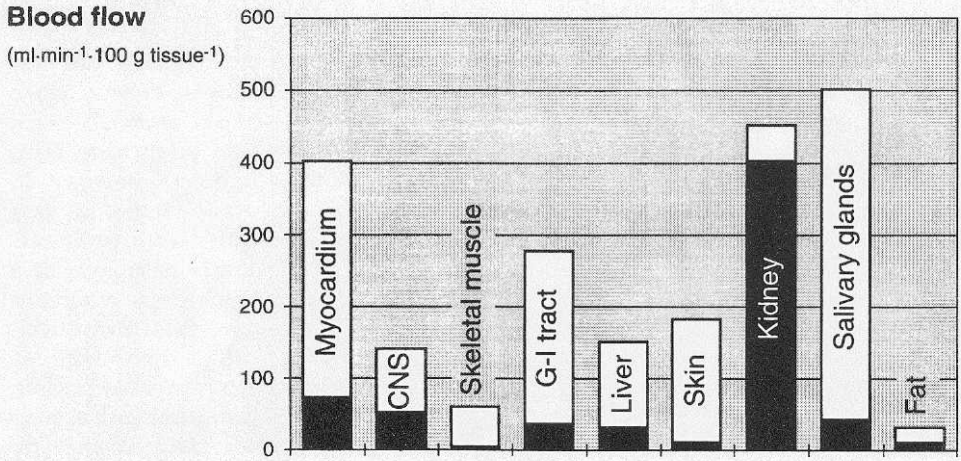
Figure. 1. Nerve-mediated cardiovascular reflex pathways for short-term blood pressure regulation.

The autonomic cardiovascular control centres are located in the medulla oblongata. Both the cardioinhibitory centres generating parasympathetic activity and the vasomotor centres responsible for sympathetic activity are affected by descending supramedullary differentiated activity. Efferent autonomic neural activity leaving the medulla is continuously modulated by afferent impulses from different sensory receptors. Arterial baroreceptors located in the carotid sinuses and aortic arch and cardiopulmonary baroreceptors in the caval vein, right atrium, right ventricle and lungs are mechanoreceptors responding to changes in blood pressure and ventilatory manoeuvres. A sudden hypotension decreases the afferent inhibitory effect of the baroreceptors on the vasomotor centre and causes an increase in efferent sympathetic nervous activity, which increases vascular resistance and restores blood pressure. The vasoconstrictor impulses are conducted in pre- and postganglionic sympathetic nerves to smooth muscles in the blood vessel walls. The nerve action-potential-induced release of noradrenaline (NA) in the synaptic cleft induces an α-receptor-mediated vascular muscle contraction. The released NA is removed mainly by re-uptake or local metabolic breakdown but some spillover to the systemic circulation also occurs. The strength of the sympathetic neural outflow varies among different organs. The sympathetic response also includes a release of catecholamines, mainly adrenaline (A), from the adrenal medulla to the systemic circulation. In small concentrations, adrenaline induces vasodilation through β_2-receptor activation but with high concentrations the α-receptor-induced vasoconstriction dominates. The cardiac baroreflex response to a sudden hypotension is due to some extent to increased cardiac sympathetic activity but mainly to decreased parasympathetic activity[9]. The parasympathetic impulses are conducted by cholinergic fibres in the vagal nerves to the sinus and atrioventricular nodes for heart-rate modulation.

Arterial chemoreceptors are located in the carotid and aortic bodies and respond to changes in P_aCO_2 and P_aO_2. Hypoxia or hypercapnoea will, in addition to the respiratory reflex response (increased minute ventilation), also have circulatory effects including increases in heart rate and sympathetic vasoconstrictor activity to skeletal muscle[10,11]. These increases are more prominent during hypercapnoea than during hypoxia. Simultaneous hypercapnoea and hypoxia has a synergistic effect on sympathetic activity.

Somatic afferent stimuli, like pain and cold, also evoke cardiovascular responses mediated by the autonomic nervous system[12]. Both medullary and supramedullary pathways are involved in these somatosympathetic reflexes. The efferent responses include increased heart rate and increased sympathetic nervous activity. However, in contrast to the baroreflex response, the somatosympathetically induced vasoconstriction is more prominent in the visceral and renal vascular beds than in the skeletal muscle vasculature[13]. This response seems to be functionally related to the defence reaction, which is evoked by rage or fear and prepares the organism for fight or flight. Experimentally, this reaction can be evoked by electrical stimulation of the hypothalamic defence area[13-18]. The increased heart rate, blood pressure and skeletal muscle blood flow are appropriate for instant physical activity. Normally, the increase of arterial blood pressure is modulated by a decrease of heart rate. However, during the somatosympathetic reflex response and defence reaction, the cardiac baroreflex is inhibited to improve cardiac performance[13-15].

The hypothalamic and medullary cardiovascular control centres are influenced continuously by several afferent stimuli. The efferent autonomic activity is therefore an integration of different reflex responses, which together with local factors regulate the blood flow distribution. There are large differences in regional blood flows (fig. 2)[5]. Although the total blood flows to the kidneys and skeletal muscles are similar at rest, each with about 20 % of cardiac output, their respective regional blood flows are quite different. The kidneys have a constant low vascular resistance and a high blood flow (300-400 $ml \cdot min^{-1} \cdot 100\ g^{-1}$) in order to support the renal clearance function while the skeletal muscles, which represent 45 % of total body mass, at rest have a low blood flow (2-5 $ml \cdot min^{-1} \cdot 100\ g^{-1}$) due to relative vasoconstriction. However, the renal blood flow is already close to its maximal flow, whereas the blood flow to skeletal muscle can increase more than 20-fold during physical exercise. Cholinergic vasodilatory nerve fibres, known to exist in cats, have not been found in humans and vasodilation in human skeletal muscle is therefore achieved by local metabolic factors and by inhibition of sympathetic vasoconstrictor activity. Skeletal muscle vessels are also more responsive to sympathetic vasoconstrictor impulses than renal vessels, although the sympathetically mediated increase in vascular resistance is most prominent in cutaneous vessels[2]. Due to the large skeletal muscle mass, even small changes in vascular resistance governed by efferent sympathetic activity are of importance for modulating the systemic vascular resistance and arterial blood pressure. Sympathetic control of the splanchnic circulation contributes to this response but in this vascular bed also has a major vasoconstrictor effect on the capacitance vessels[2]. Central blood volume is thereby restored and the preload and cardiac output are increased.



HOMO:										
Rest. blood flow ($l \cdot min^{-1}$):	0,21	0,75	0,75	0,7	0,5	0,2	1,2	0,02	0,8	≈ 5
Max. blood flow ($l \cdot min^{-1}$):	1,2	2,1	18,0	5,5	3,0	3,8	1,4	0,25	3,0	≈ 38

Figure. 2. Regional blood flow at rest (black areas) and at maximal dilation (total areas) per 100 g tissue in different organs. Corresponding organ blood flows in a 70 kg man deduced on the basis of organ weights are shown below the figure. (Reprinted with permission from Mellander S and Johansson B, Pharmacol Rev 1968;20:117-197.)

Influence of anaesthesia and surgery

Anaesthetics interact with the cardiovascular regulation in several ways[19,20]. Interaction with the autonomic nervous system is common and can include both effects on supramedullary centres responsible for the tonic sympathetic outflow and effects on different cardiovascular reflexes. In addition, most anaesthetics have direct effects on heart rate, myocardial performance and vascular contractility. Since different anaesthetics affect the cardiovascular regulatory system at different sites and therefore have different circulatory characteristics, anaesthetic techniques may be individualized with regard to the type of operation and physical condition of the patient.

During anaesthesia, a general aim concerning circulation is to depress surgically induced somatosympathetic reflexes. These reflexes, inducing increases in blood pressure and heart rate, are similar to the fight-and-flight reaction[12] but inappropriate in the operating situation and may be dangerous in patients with coronary artery insufficiency or aneurysms in the aorta or the intracranial vessels. Although all anaesthetics, to varying extent, depress this somatic pressor response, the effect is not always related to the depth of anaesthesia. An effective reflex depression can also be achieved without general anaesthesia by, for example, regional blockade of the afferent somatosensoric nerve activity. Barbiturates have been shown to inhibit somatosympathetic reflexes at supramedullary level[21], whereas inhalation anaesthetics also have been shown to depress sympathetic ganglionic transmission[22]. The opiates act mainly through the opiate receptor endorphin system, which may explain their minor cortical and cardiovascular effects[23,24].

The effects of different anaesthetics on the baroreceptor reflexes vary. Whether it is desirable or not to depress these reflexes depends on the state of the patient and the surgical situation. For example, in a hypovolaemic patient, anaesthesia with a baroreflex-depressing agent such as thiopentone can induce severe hypotension. Similarly, hypotension can be caused by a high spinal or epidural anaesthesia which blocks efferent sympathetic vasoconstrictor reflex discharge. However, depression of the baroreflex can also be used as a tool to balance the somatosympathetic reflex induced by surgery. In several studies the baroreflex has been depressed by barbiturates[25-27], halothane[28-31], enflurane[32,33] and isoflurane[22,32,34,35], whereas nitrous oxide, and the previously used inhalation agents ether[36] and cyclopropane[37] have been associated with increased baroreflex responses. Opiates have been shown to have minor or no effects on the baroreflex response[26]

The trend in general anaesthesia is to use anaesthetics with short duration. It is thereby easier to obtain cardiovascular stability by adjustments of the dose when needed. The rapid recovery with these agents is also an advantage both for patient comfort and economically. In our studies, we have focused our interest on three short-acting anaesthetics: propofol, methohexitone and isoflurane. Propofol, which is a phenol solved in fat emulsion, was introduced in Sweden in 1987. Propofol is characterised by a very short duration, mainly due to redistribution but also to a high clearance rate, and is thereby associated with a rapid recovery[38-40]. Propofol has potent circulatory effects, with more pronounced hypotension during induction of anaesthesia than other intravenous induction agents[41-44]. No studies concerning the effects of propofol on the baroreceptor reflex were available when our studies started.

Methohexitone is the most short-acting barbiturate and therefore, in contrast to thiopentone, it has been used for both induction and maintenance of anaesthesia[45]. The main disadvantage compared with thiopentone has been excitatory effects such as movements, hiccups and laryngospasm. The circulatory effects of methohexitone are accompanied by depression of the baroreceptor reflex[25-27]. The inhalation agent isoflurane is, due to its comparatively lower blood gas solubility and low degree of biotransformation, associated with more rapid drug uptake and emergence from anaesthesia than halothane and enflurane[46-48]. Typical circulatory effects of isoflurane are a decrease in systemic vascular resistance and an increase in heart rate but also a depression of the baroreceptor reflex[22,32,34,35].

Knowledge of the effects of anaesthetics on cardiovascular control is based mainly on studies during undisturbed anaesthesia. However, in the clinical situation the cardiovascular characteristics of different anaesthetics are related to the balance between the dose and the intensity of surgical stress. A **general aim** in our studies was therefore to investigate the effects of several anaesthetics (propofol in particular but also methohexitone and isoflurane) on cardiovascular control mechanisms both during undisturbed anaesthesia and during surgery. Microlaryngoscopy was used as a surgical stress model since microlaryngoscopy evokes an intense and relatively stable somatic afferent stimulation associated with a reproducible pressor response. The **main method** in these studies was microneurography of sympathetic nervous activity to skeletal muscle vessels, a method enabling us to monitor the efferent vasoconstrictor activity. It was thereby possible to evaluate neurogenic effects of anaesthetics on the blood flow to skeletal muscle. The dynamic properties of the muscle sympathetic part of the baroreflex were also studied in relation to anaesthesia and surgery. Although the microneurographic technique of recording sympathetic activity was presented already in 1968, the present studies represent the first recordings of MSA during general anaesthesia[49].

2. Aims of the study

- To study the differentiation in systemic and peripheral (leg) blood flows during surgery and anaesthesia with either propofol or methohexitone.
- To evaluate the relative effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in an experimental open loop model.
- To describe the general characteristics of muscle nerve sympathetic activity during induction and maintenance of anaesthesia with different anaesthetics and the effects of different reflex stimuli and surgical stress.
- To study the effects on muscle nerve sympathetic activity of induction of anaesthesia with propofol and maintenance of anaesthesia with nitrous oxide and/or isoflurane.
- To study the effects on muscle nerve sympathetic activity and peripheral blood flows of undisturbed steady-state propofol anaesthesia and of surgical stress.
- To study the cardiac and muscle sympathetic baroreflex sensitivity during undisturbed steady-state propofol anaesthesia and during surgical stress.

3. Methodological considerations

Experimental carotid baroreflex open loop model

The baroreceptor reflexes are normally closed feed-back loops; that is, the baroreflex-induced change in blood pressure affects in itself the baroreceptor afferent activity. This regulatory feed-back system is essential for haemodynamic stability. However, when one is studying baroreflex responses the feed-back may be a disturbing factor. Therefore, a carotid baroreflex open loop model was studied in chloralose-anaesthetized cats (II). This model is well established in our laboratory[50-52]. Chloralose is a suitable basal anaesthetic in experimental cardiovascular studies since it preserves the baroreceptor reflexes[26,53]. If anything, the baroreflex sensitivity has been shown to be slightly increased by chloralose[54].

Both the carotid sinuses were partly isolated by ligation of the external and sometimes the internal carotid artery as well as all other arterial branches that could be ligated without endangering the integrity of the sinus nerve by the dissecting procedure. Catheters were inserted into the common carotid arteries bilaterally, allowing the carotid sinuses to be perfused with blood from the femoral arteries at any desired level of pulsatile pressure by means of a roller pump (fig. 3). In order to interrupt all closed baroreflex loops, the cardiopulmonary and aortic baroreceptors were denervated by bilateral sectioning of the vagal nerves. The remaining cardiac innervation was thus of sympathetic origin. This is of importance for interpretation of our data since vagal influence normally overrides sympathetic for the modulation of heart rate[9]. In order to allow adjustments of the carotid sinus perfusion pressure, when perfused by the pump, without changing the pump frequency (set at 175 rpm/min), an adjustable arteriovenous shunt was inserted between the carotid sinuses inflow tube and an external jugular vein. By means of a by-pass circuit parallel to the pump, the carotid sinuses could also be exposed to prevailing femoral arterial pressure. The carotid sinus perfusion pressure was recorded from a side branch of the tubing system. Systemic arterial pressure was recorded through a catheter inserted in a brachial artery. The systemic MAP was lower when the carotid sinuses were perfused by artificial pumping at

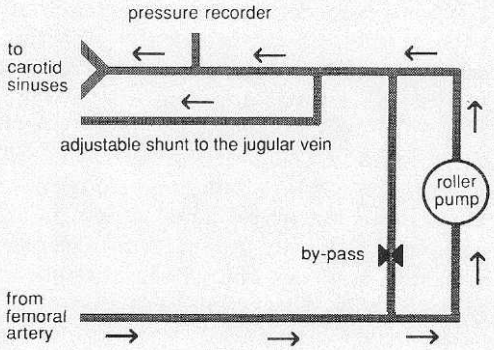


Figure. 3. The model for carotid sinus perfusion. The carotid sinuses were perfused with blood from the femoral arteries either at prevailing systemic arterial pressure (by-pass open, pump off, jugular vein shunt closed) or at any desired pump- and jugular-shunt-controlled pressure level (by-pass closed, pump on and jugular-shunt variably open).

a perfusion pressure equivalent to prevailing baseline MAP than when perfused by the cardiac-generated pressure (via the by-pass). This difference may to some extent depend on the pressure gradient (6 ±2 SEM mm Hg) in the femoral-carotid shunt tubes. However, the altered pulse pressure amplitude and pulse wave-form during pump-generated carotid perfusion as compared to when the pressure was generated by the heart is probably more important. Since these conditions were essentially constant during the experiment, it is likely that such factors did not influence the results.

Baseline data were obtained by exposing the carotid sinuses to the prevailing femoral arterial pressure through the by-pass. Baroreceptor function was assessed by investigating how induced changes in the artificially pump-controlled carotid sinus perfusion pressure influenced systemic mean arterial pressure (MAP) and heart rate (HR). Carotid sinus pressure was thereby varied in steps of 25 mm Hg over a pressure range of 50-200 mm Hg and for each level of sinus pressure corresponding data for AP and HR were recorded after steady-state had been attained (5-20 sec). In this way the open loop gain, i.e. the inverse change in systemic arterial pressure or heart rate per unit change in carotid sinus pressure, could be calculated for each step of 25 mm Hg carotid sinus pressure change throughout the investigated range. Data obtained during basal chloralose anaesthesia alone, before administration of each anaesthetic, were used as control values.

In order to study the dynamic range of the baroreceptor reflex response, systemic mean arterial pressure and heart rate at carotid sinus pressures of 50-150 mm Hg were analysed in detail. The influence of the different anaesthetic agents on the baroreceptor reflex was evaluated by assessing the effects on the following characteristics of baroreceptor reflex function:

1. The overall baroreflex capacity to regulate systemic mean arterial pressure and heart rate (when carotid sinus pressure was varied from 50 to 150 mm Hg).

2. The baroreflex set point evaluated by identifying the carotid sinus pressure interval associated with the maximal open loop gain in systemic mean arterial pressure and heart rate response.

3. The baroreflex sensitivity defined as the efficiency of the baroreceptor reflex to influence systemic mean arterial pressure and heart rate as derived from the carotid sinus pressure interval which was associated with the maximal open loop gain. Sensitivity was expressed as changes in systemic MAP or HR induced by 1 mm Hg change in carotid sinus pressure.

Microneurography

Direct microelectrode recordings of sympathetic discharges in human extremity nerves were first presented by Hagbarth and Vallbo in 1968[55]. This efferent autonomic activity is conducted in unmyelinated C-fibres located intrafascicularly in somatic nerves. Sympathetic nervous activity has been recorded in nerves conducting vasoconstrictor impulses to skeletal muscle (muscle nerve sympathetic activity; MSA)[56,57] and in nerves conducting both vasoconstrictor and sudomotor impulses to skin (skin nerve sympathetic activity; SSA)[58,59]. Most recordings have been made from the peroneal, tibial and median nerves.

Recording technique

The recording microelectrode is made of lacquer-insulated tungsten wire with a diameter of 200 μ, which has been electrolytically pointed to a diameter of a few μ. The present recordings have been made in the peroneal nerve at the fibular head. After locating the nerve with weak cutaneous electrical stimuli, the electrode was inserted manually through intact skin into the underlying nerve. A reference electrode was placed subcutaneously about 2 cm from the recording electrode, which was advanced during simultaneous weak electrical stimulation (1-3 V, 1 Hz). The nerve contains fascicles innervating skeletal muscle and skin which can be differentiated on the basis of the effects evoked by stimulation through the needle and the afferent responses induced by certain peripheral stimuli. After a muscle nerve fascicle had been located, the postganglionic sympathetic nerve fibres were found by small adjustments of the recording electrode within the fascicle (fig. 4).

The criteria for acceptable recordings of MSA, upon which our studies were focused, were as follows:

- weak electrical stimulation through the electrode elicited involuntary muscle contraction of appropriate muscles but not paraesthesiae,
- tapping or stretching muscles or tendons innervated by the impaled fascicle evoked afferent mechanoreceptor discharges but similar activity was not elicited by stroking the skin,
- spontaneous pulse-synchronous bursts of sympathetic impulses occurred intermittently and increased during expiratory apnoeas and during the hypotension induced by the Valsalva manoeuvre (phase II and III).

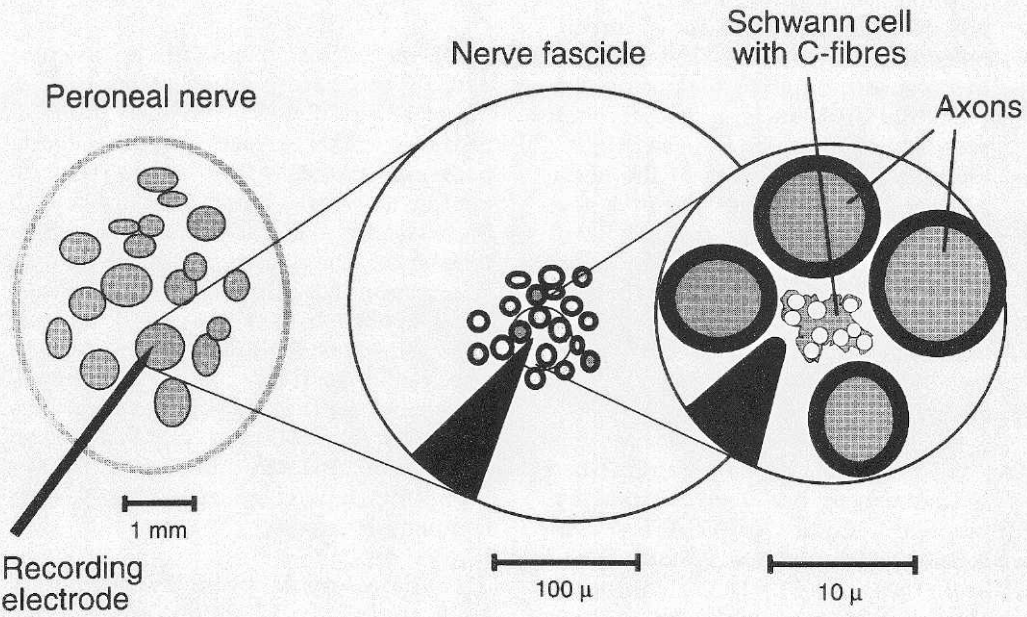


Figure. 4. A schematic view of the recording electrode inserted intrafascicularly in the peroneal nerve. The unmyelinated sympathetic C-fibres are depicted as light inclusions in the Schwann cell.

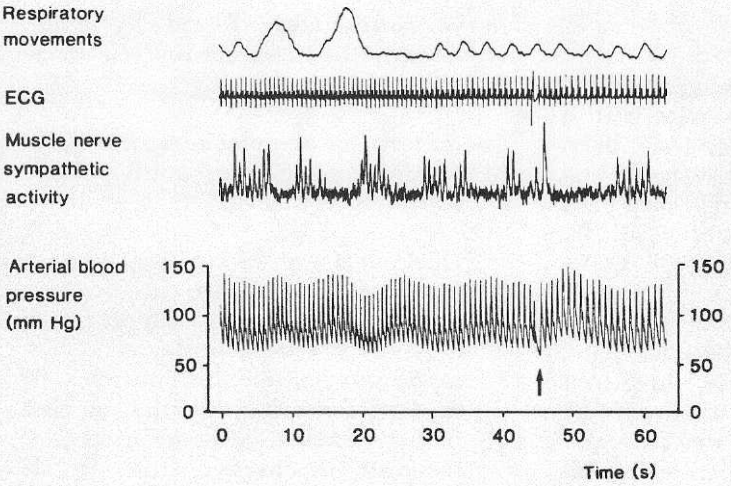


Figure. 5. Muscle nerve sympathetic activity (MSA) from a peroneal recording in the awake state. MSA bursts are related to decreases in the arterial blood pressure. Note the large MSA burst evoked by the prolonged diastole after an extrasystolic heart beat (at arrow).

Evidence that the recorded nerve activity is of sympathetic origin comprises the following observations [60]:

- injection of local anaesthetic around the nerve proximal but not distal to the recording site eliminates the activity,
- the conduction velocity of the impulses is approximately 1 m/s, which is appropriate for unmyelinated C-fibres,
- intravenous infusion of a ganglion-blocking drug such as trimetaphan reversibly eliminates the activity,
- changes in the intensity of the nerve activity are followed within a few seconds by sympathetically mediated responses, such as blood pressure, leg or forearm blood flow (mainly MSA), skin blood flow (SSA) and skin electrical resistance (SSA).

Microneurographic findings

The old view of a generalized sympathetic tone has been rejected by, for instance, studies of MSA and SSA which have shown pronounced differentiation[56,59,61,62]. Short lasting emotional excitement and mental stress evoked by arithmetic problems have been associated with strong SSA responses without changes in MSA[59]. SSA is important for temperature regulation and has been shown to increase both at ambient temperatures below (vasoconstrictor impulses) and above (sudomotor impulses) thermoneutral conditions[63]. Thiopentone and halothane anaesthesia have been associated with dose-dependent reductions of SSA[64].

MSA, in contrast to SSA, is an efferent part of the baroreceptor reflex and is therefore modulated by changes in blood pressure[65]. A decrease in arterial blood pressure evokes MSA bursts (fig. 5) aiming to restore blood pressure by an increase in skeletal muscle vascular resistance. The sensitivity and speed of this response is illustrated by the large burst evoked by the prolonged diastole after an extrasystolic heart beat (fig. 5). The response delay of approximately 1.3 s between the ventricular depolarisation in the ECG and the MSA burst inhibition in the peroneal nerve represents to a large extent the C-fibre conduction velocity[57,66].

The characteristic pulse synchrony in MSA is due to baroreflex modulation: each systolic blood pressure peak causes a short-lasting inhibition of sympathetic

outflow. The importance of the inhibitory afferent nerve activity from the arterial baroreceptors for the pulse synchrony has been illustrated by the effects of bilateral local anaesthesia of the glossopharyngeal and vagal nerves in the neck[67]. This procedure evoked a pronounced increase in MSA (and arterial blood pressure) and the pulse synchrony was replaced by a fast and irregular burst rhythm. Changes in MSA and arterial blood pressure have been shown to be positively correlated to diastolic but not to systolic blood pressure[65]. At a given blood pressure, the sympathetic discharges are stronger when pressure is decreasing than when it is increasing[65], i.e. the direction of the pressure change is important for the MSA response. The MSA responses due to dynamic arterial baroreflex function buffer short-term blood pressure changes, whereas preload changes affecting cardiopulmonary low-pressure baroreceptors exert more tonic reflex effects on MSA. The importance of these low pressure baroreceptors has been shown when central venous pressure (CVP) but not arterial pressure has been decreased by applying subatmospheric pressure around the lower body[68]. Arterial pressure and CVP often change in the same direction, for example during a Valsalva manoeuvre, and the MSA response is therefore due to a combination of arterial and low-pressure baroreflex effects. When changing posture from the supine to the upright position, the arterial baroreflex contributes to the initial MSA increase whereas the persisting higher level of MSA is due to unloading of cardiopulmonary baroreceptors.

During resting conditions, the MSA burst frequency shows large inter-individual differences (from less than 10 to more than 90 bursts/100 heart beats)[69]. However, in the same individual, simultaneous recordings from different nerves and repeated recordings also after several months show similar burst frequency[69]. Interindividual comparisons of burst frequency have shown a weak positive correlation to age but no correlation to the blood pressure level in normotensive subjects.

Nerve signal processing and data analysis

The nerve signal was amplified with a gain of 50000 and the signal-to-noise ratio was improved by using a 700-2000 Hz bandpass filter and an amplitude discriminator (fig. 6). An RC-integrating network with a time constant of 0.1 sec was used to obtain a mean voltage display of the multi-unit nerve activity (fig. 6). MSA can be presented as burst frequency (per minute or per 100 heart beats)(III,IV,V) or as "total MSA", i.e. the product of burst frequency/minute and either the burst mean amplitude (III,IV) or area (V). The MSA burst detection and quantification can be done manually with computer support (III,IV) or by computer only after setting detection criteria (V). The computer program[70] 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 rise and fall with a local maximum occurring in the MSA signal within 1000-1800 ms from a preceding R-wave in the ECG. 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. All recorded circulatory parameters in the respective study protocol were stored on tape and subsequently analysed by computer. For

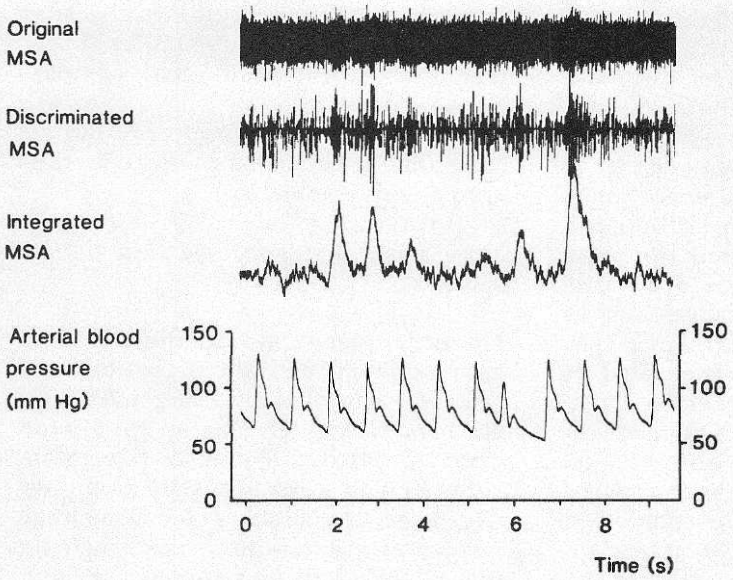


Figure. 6. Original, discriminated and integrated neurogram of muscle nerve sympathetic activity (MSA) and arterial blood pressure. The recording is from the same sequence as in figure 5 but here shown at a faster speed.

further analysis, all data in relation to each corresponding heart beat were exported to Excel spreadsheets (Microsoft, USA).

Recording equipment and success rate

All microneurographic recordings were performed in the operating room. Besides a nerve amplifier, tape recorder and ink-jet recorder for measuring and storing MSA, the recording set-up also included equipment for continuous measurements of ECG, invasive arterial blood pressure, laser Doppler skin blood flow, finger pulse amplitude, respiratory movements, end-tidal CO_2 concentration, F_iO_2, end-tidal isoflurane concentration (paper IV) and intermittent plethysmographic measurements of leg blood flow (fig. 7). The patients rested as comfortably as possible on the operating table and had extra blankets if needed to prevent cooling and discomfort. The ambient temperature in the room was kept constant during the experiment. Due to the complexity of the microneurographic technique when recordings are made during general anaesthesia, the number of patients included in the studies was lower than the total number of patients investigated (table 1).

CUSUM-technique

To clarify the time relations between the start of changes in MSA and MAP after

Table 1.

Total number of patients investigated	41
Failure to find sympathetic activity with adequate signal-to-noise ratio	7
Adequate SSA but no MSA	3
Loss of recording site during induction of anaesthesia	2
Remaining number of patients with MSA	29
Number of patients included in study III	18
Number of patients included in study IV (also included in III)	8
Pilot patients preceding study V	2
Number of patients included in study V	9

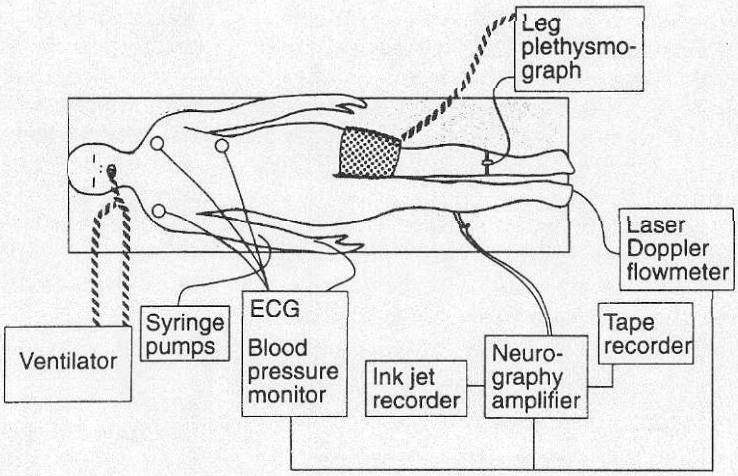


Figure. 7. The recording set-up in the operation room during the microneurographic studies.

injection of a drug, a cumulative sum-technique (CUSUM)[71] was used (III). Total MSA and MAP were averaged for every 5 heart beats. During a 25-50 sec control period before the manoeuvre (for example the induction of anaesthesia) averaged values of MSA and MAP were set to 100%. The differences between the values for each period of 5 heart beats and the respective average control value were then cumulated during the control period and the initial period after the injection. Taking a reference level equal to the mean of a control period gives a CUSUM of zero slope. With the cumulation, the onset of a change in MSA or MAP was magnified and thus easy to detect.

Baroreflex tests

In humans, cardiac baroreflex sensitivity is usually determined by plotting arterial blood pressure against the corresponding RR-interval after intravenous injection of a pressor drug such as phenylephrine or angiotensin. The baroreflex sensitivity is represented by the slope when the x-y-plot has been subjected to linear regression analysis. This "slope method" was originally described by Smyth et al. 1969[72]. Later, depressor drugs such as nitroprusside (SNP) or nitroglycerine have also been used in a corresponding way[73]. During anaesthesia MSA is low. A pressor test therefore reduces MSA below the detection limit. Consequently, in our anaesthesia-related studies, we used only depressor tests, which activate MSA. The depressor test period used by us for analysis was delimited by the start of the SNP-induced decrease in MAP and the point within 60 s when the lowest MAP was achieved (fig. 8). Since not all heart beats are associated with MSA bursts, it is not possible to plot the individual MSA burst area against the corresponding blood pressure value for every heart beat and therefore the x-y-plot method had to be slightly modified. The approach used was to perform several depressor tests under the same experimental condition and to utilize all heart beats from all tests to construct the diagram. The heart beats were sorted according to blood pressure values. The blood pressure range was divided in ten equal intervals each comprising an equal number of heart beats and the mean of all blood pressure values in each interval was plotted against corresponding values of MSAA and RR-interval, respectively. DAP was used for plotting against MSAA[65]

whereas MAP was used for plotting against RR-intervals. Regression lines with a correlation coefficient below 0.5 were excluded. This limit is slightly lower than a correlation coefficient of 0.63, which corresponds to $p<0.05$, originally used by Smyth. In a recent paper, Sleight has discussed whether or not slopes with lower correlation coefficients also ought to contribute to the average slope value. Sleight proposes weighting of the slopes by their correlation coefficients [74]. This procedure is, however, not useful for a group of patients if statistical comparisons are to be made, since standard deviations cannot be determined. If all slopes (irrespective of correlation coefficients) had been included in study V, the results would not have been different from those presented in the paper.

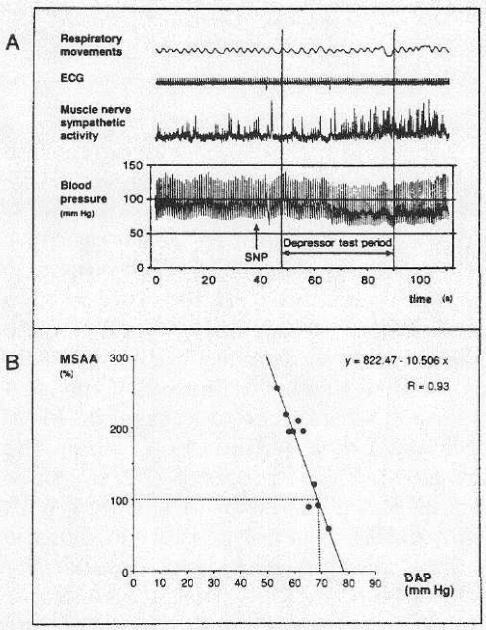


Figure. 8. (A) Original recording. Muscle sympathetic neurogram and haemodynamic recordings from a typical depressor test in the awake state in one patient (intravenous injection of sodium nitroprusside, SNP, 2 $\mu g \cdot kg^{-1}$ marked with an arrow). The depressor test period as delimited by start of decrease in MAP and the lowest achieved MAP is marked with lines. Note the single large MSA bursts caused by a sudden decrease in DAP after two spontaneous extrasystolic heart beats. (B) Baroreflex slope. X-y-plot of MSAA vs. DAP and linear regression analysis of pooled data from four depressor tests before anaesthesia in the same patient. MSAA is expressed as percent of basal MSAA value during the awake control period. The MSAA set point, which corresponds to the preSNP reference blood pressure is marked with a dotted line.

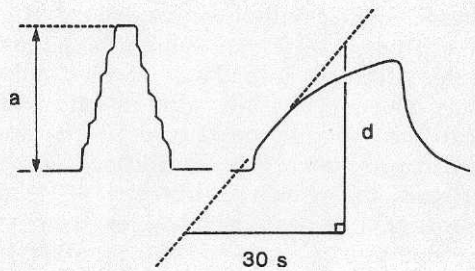
In 2 of the 9 patients in study V some depressor tests during anaesthesia and surgery increased the baseline of the integrated neurogram. Reintegration of the original neurograms using a shorter time constant (0.05 s) eliminated only part of the baseline elevation. This indicates that the sympathetic nerve activity had become continuous and systolic baroreflex inhibitions were incomplete. Since the continuous nerve activity was not included when calculating MSAA, sympathetic baroreflex sensitivity was somewhat underestimated in these patients, especially during surgery, when the elevations of baseline were most marked.

Other manoeuvres used in study III were ventilator-induced sighs, valsalva-like manoeuvres and transitory increases of PEEP. These ventilatory manoeuvres induce combined responses from both arterial and cardiopulmonary baroreceptors as well as mechanical stretch receptors in the lungs.

Strain gauge plethysmography

Venous occlusion plethysmography for measurements of arterial blood flow in a limb was first presented by Brodie and Russell in 1905[75] and during the first decades of the 20th century the technique was further developed. The recorded limb was sealed in a solid jacket and the sealed space was filled

with air or water and connected to a volume recorder. Some disadvantages of the original technique were reduced by Whitney when he, in 1949, introduced the mercury-in-rubber strain gauge plethysmograph. This improved method was fully described by Whitney in 1953[76]. The silicon rubber tube (bore diameter 0.5 mm and wall thickness 0.8 mm) is placed around the thickest part of the calf or forearm and slightly extended. A Wheatstone bridge circuit (50 mA) is connected to the tube ends which are closed with metal plugs and thus in electrical contact with the mercury. A change in electrical resistance between the ends of the tube is directly proportional to the change in length of the tube. Calibration of the strain gauge is performed by a 3 mm extension. To reduce artefacts, the forearm or calf must be positioned slightly above heart level and not in contact with any surface. In order to estimate the arterial blood flow in the limb, the venous return is temporarily stopped by an occlusion cuff (40 mm Hg) placed proximal to the strain gauge. During the first 5-10 s the increase in electrical resistance represents the arterial blood flow (fig. 9). During longer venous occlusion the arterial blood flow decreases due to gradually increased venous blood pressure. Plethysmography of the forearm and calf mainly represents skeletal muscle blood flows. Influences of skin blood flow from the hand or the foot can be eliminated by an arterial occlusion cuff at the wrist or ankle. Distal occlusion of the hand is most important due to the relatively small muscle volume in the forearm[77].



$$\text{Blood flow} = \frac{3 \cdot d \cdot 2 \cdot 2 \cdot 100}{a \cdot \text{limb circumference}}$$

Figure. 9. Strain gauge plethysmography. The left part of the figure shows calibration of electrical resistance corresponding to 3 mm extension of the mercury-filled silicon rubber tube. The right part of the figure shows the effect on electrical resistance of sudden venous occlusion.

In the formula used for calculation of blood flow "a" represents the calibration change in electrical resistance, corresponding to 3 mm extension. The slope expressed by "d" is related to extrapolation of the first linear part of the curve (5-10 s) to a period of 30 s. A factor 2 is added to the numerator in order to obtain flow/minute and another factor 2 in order to transform the change in circumference to a change in volume. The factor 100 is added to obtain flow/100 ml tissue. Leg (calf) blood flows were in our studies based on the average of 2-5 measurements. Reference values of leg blood flow range from 1.4 to 3.6 $ml \cdot min^{-1} \cdot 100$ ml tissue^{-1}[78]. Although, there is a high correlation between the different plethysmography techniques, the strain gauge method will give a 9% underestimation compared with water plethysmography[79]. We have therefore only expressed our data in terms of relative changes related to measurements during a control period in each patient.

Impedance cardiography

Impedance cardiography for measurements of cardiac stroke volume was developed by Kubicek et al during the early 1960s[80]. This noninvasive method was originally developed for space research but later it has also been used in clinical research and for routine

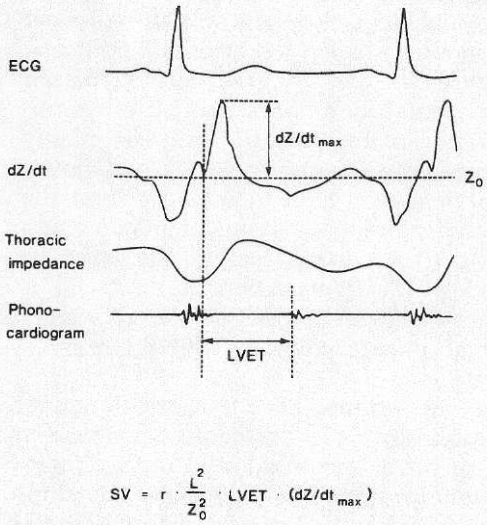


Figure 10. Impedance cardiography. The maximum value of the first derivative of thoracic impedance (dZ/dt_{max}) and left ventricular ejection time (LVET) are used in Kubiceks formula for calculation of stroke volume (SV).

haemodynamic monitoring. Two circular electrodes (metal tape, 3M) are placed around the neck and two around the lower chest. The two outer electrodes are connected to a constant current source providing a 100 kHz sinusoidal current. The resulting voltage is monitored from the two inner electrodes by a high impedance amplifier and a detection circuit. The method is based on the assumption that the chest is a cylinder. When a rapid sinusoidal current is transmitted across this cylindrical distensible fluid, an increase of fluid in the cylinder causes a decrease in impedance which is directly proportional to the increase in cylinder volume. The change in impedance and its first derivative (dZ/dt), ECG and phonocardiogram (in order to detect the aorta valve closure) in relation to the cardiac cycle are shown in figure 10.

In Kubicek's formula for calculation of stroke volume the electrical resistivity of blood (r) is positively correlated to the haematocrit value. Since no changes in haematocrit values were expected during the recording period in our patients, the resistivity value was set to 127 (ohm·cm), which refers to a haematocrit value of 40% at 37.5° C[81,82]. L is the mean distance between the two inner electrodes (cm). Z_0 is the basic impedance across the chest. LVET is the left ventricular ejection time (s) measured from the shift in the derived impedance curve indicating the start of the ejection to the start of the second heart sound. dZ/dt (ohm·cm·s^{-1}) is the difference between the basic impedance level and the maximum value in the derived impedance curve.

We used an impedance cardiograph model 400 (Instrumentation for Medicine Inc, Greenwich, Ct, USA). The impedance waves, ECG and phonocardiogram were presented on a Mingograph (Siemens-Elema) ink chart recorder. The ejection time (LVET) and dZ/dt were manually derived from the recorded tracings. The recordings were made during relaxed apnoea and each stroke volume was calculated from mean values of 6 consecutive heart beats. Cardiac output was calculated from the product of stroke volume and heart rate. Although impedance cardiography has shown a high agreement with cardiac output measured with dye dilution[83] and thermodilution[84] techniques, the results in our study (I) are presented as relative changes from an initial control period before start of anaesthesia.

Laser Doppler flowmetry

Laser Doppler flowmetry measures the flux of erythrocytes, that is the product of the number of erythrocytes and their velocity. The use of this method for blood flow measurements was first

presented in 1972 by Riva[85]. The first studies concerned blood flow in retinal vessels. In 1975 measurements of skin blood flow were presented and in 1977 the first equipment for clinical use was available[86]. Further development and evaluation of the technique was done by Tenland and Nilsson[87-89]. The technique uses laser light with a wavelength of 632.8 nm in vacuum (red light) to illuminate the examined tissue. Light beams scattered in moving erythrocytes undergo a frequency shift according to the Doppler effect. These frequency fluctuations in reflected light are measured by a photodetection unit. The output signal has been shown to be directly proportional to the flux of erythrocytes in an experimental model. A decrease in oxygen tension from 15 to 5 kPa has been shown to decrease the flowmetry output by 5%. The measuring depth in skin is assumed to be about 1 mm. Since large local variations in skin blood flow have been observed, it is important that repeated recordings are made from the same site.

In our studies, we have used PeriFlux 1d (IV) and 2B (V), Perimed AB, Stockholm, Sweden. The model 2B has improved linearity to overcome the disadvantage of a slight underestimation at high flow rates. The laser Doppler probe was placed on the plantar side of the right big toe and not moved during the experiment. Before the initial control period, the zero level was checked and recorded on tape for subsequent quantification. In some experiments the gain was changed when the output signal exceeded the maximal range. Since these values are relative and not absolute measurements of the blood flow, data were presented as percentage changes of the awake control period value (= 100%).

Laser Doppler flowmetry has been compared with heat and isotope washout techniques, dynamic capillary microscopy, occlusion and photopulse plethysmography with good qualitative correlation[87,90,91].

Photoelectric pulse plethysmography

The use of photoelectric plethysmography for blood volume measurements started in the 1930s. Pioneer methodological work was done by Hertzman[92]. The principle of the technique is illumination of, for example, a skin area and photodetection of the light modulated by blood volume changes. The light source and the photodetector can be arranged on either side on, for example, a finger (transillumination) or positioned side by side on virtually any skin area. With both arrangements, the light undergoes scattering, absorption, reflection and refraction as it passes through the skin. Nowadays, both the light source and the photodetector are made with semiconductor technology, as the modified van Gough type ILP/7A used by us (III,IV,V), and can therefore be placed side by side in a small-sized probe head[93]. The light emitting diodes (LED) generate light in the IR-wave range (800-900 nm) without heating the skin. Use of IR-light has decreased errors due to influence of ambient light and temperature changes. The potential error in relation to haemoglobin oxygenation which occurs at lower light waves (below 800 nm) is negligible in the IR-wave range used.

The pulse amplitude is used as an index of blood flow. Although the pulsations mainly represent changes in blood volume, it has also has been proposed that orientation and packing of erythrocytes contribute to the pulse amplitude. This was shown by Challoner and recently also by Lindberg in experiments with peristaltic blood flow through a system of closed glass tubes[93,94].

Although the glass tubes did not allow volume changes, a photoelectric pulse plethysmograph recorded a pulsative flow in the tubes. The photoelectric method has been used for blood flow measurements on the surfaces of the kidneys, liver, brain, mesenterium and nasal septum, but the most common use is for skin blood flow measurements. Comparative studies between photoelectric pulse plethysmography and occlusion plethysmography[95], impedance plethysmography[96], piezoelectric plethysmography[97] and laser Doppler flowmetry[98] have shown good qualitative correlations.

Unfortunately, the depth of measurement in the skin is unknown. Blood flow in all vessels contributes to the output signal (i.e. both flow through arteriovenous anastomoses and through the capillary network). Since it is difficult to obtain reliable absolute flow values with the photoelectric pulse plethysmographic method, all values in our studies (III,IV,V) are presented as relative values related to the awake control period.

Catecholamine, propofol and methohexitone concentration measurements

For catecholamine analysis (I) 5 ml of arterial blood was sampled in iced tubes containing 1.4 mg heparin and 50 µl of a 0.4 M glutathione solution. The samples were stored in ice-water and immediately after terminating the anaesthesia they were centrifuged at 4°C and 3000 rpm for 10 minutes. The plasma was removed and stored at -70°C until analysed. The levels of adrenaline, noradrenaline and dopamine were determined by electrochemical detection after high-performance liquid chromatography (HPLC)[99,100]. The minimum detection level was 0.03 $ng \cdot ml^{-1}$.

Blood samples for measurements of propofol concentrations (I, II) were stored in heparin tubes at 4°C before analysis. Samples for analysis of methohexitone (I, II) were centrifuged and plasma were stored at -70°C. Both concentrations of propofol in blood[101] and methohexitone in plasma[102] were analysed by HPLC-technique.

Statistics

In general, parametric statistical tests were used. Analysis of variance (ANOVA) was used in all studies to detect overall statistical significance before further multiple comparisons were made (I-V). Statistical comparisons between groups were performed with one- or two-factor ANOVA with the Tukey Compromise post-hoc test (I,II,V). Within group comparisons were made with either one-factor ANOVA with Fisher's protected least significant difference (PLSD) comparative test (III,IV) or multiple paired Student's T-tests with Bonferroni correction for multiple comparisons (I,V). In some cases nonparametric tests were used (I,II,III), for example in the analysis of recovery data which were not assumed to be normally distributed. Then Kruskal-Wallis test was used for overall statistical analysis and Mann-Whitney U with Bonferroni correction was used for statistical comparisons (I). P-values <0.05 were considered to be significant. The computer software used for statistical analysis was StatView and SuperANOVA (Abacus Concepts Inc, Berkeley, CA, USA).

4. Résumé of papers

Paper I:

Anesthetic modulation of the cardiovascular response to microlaryngoscopy.
A comparison of propofol and methohexital with special reference to leg blood flow, catecholamines and recovery.

Thirty-five (ASA physical status 1-2) patients (22-68 years) scheduled for microlaryngoscopy were studied. One patient participated twice but in different groups. Invasive arterial blood pressure, heart rate, stroke volume (impedance cardiography), leg blood flow (LBF; occlusion plethysmography) and catecholamine concentrations were measured. The patients were randomized with Pocock and Simons method for sequential allocation[103], according to age and sex, to four groups receiving either a low or a high maintenance dose of propofol or methohexitone (9 patients in each group). The infusion rates of propofol were 6 or 12 $mg \cdot kg^{-1} \cdot h^{-1}$ and of methohexitone 5 or 10 $mg \cdot kg^{-1} \cdot h^{-1}$. These infusion rates were assumed to be equianaesthetic, based on studies defining ED50 and ED95 of the two drugs[104,105]. After a preanaesthetic dose of atropine (5 $\mu g \cdot kg^{-1}$) and fentanyl (2 $\mu g \cdot kg^{-1}$), the anaesthesia was induced with either propofol (2.0 $mg \cdot kg^{-1}$) or methohexitone (1.5 $mg \cdot kg^{-1}$) depending on to which group of anaesthetic infusion during maintenance the patient was randomized. The patients were muscle relaxed with suxamethonium (bolus followed by an infusion), intubated with a naso-tracheal insufflation catheter and ventilated artificially with high frequency positive pressure ventilation (HFPPV). With the laryngoscope fixed to a frame mounted on the operating table, the microlaryngoscopy started exactly 4 minutes after the initial injection of propofol or methohexitone. Measurements were made before injection of atropine (control), before intubation with the naso-tracheal ventilation catheter (-2 min) and 1, 5, 10 and 15 min after the start of microlaryngoscopy. Blood was also sampled for analysis of arterial catecholamines and drug concentrations, and arterial blood-gases. During the postoperative phase, various recovery parameters were noted.

Results

The groups were similar concerning haemodynamic data in the control state before anaesthesia. The low methohexitone infusion dose was insufficient to control MAP, which increased 41% ($p<0.05$) during the first 15 minutes of the microlaryngoscopy compared with the awake state (fig. 11). In the other groups, the corresponding increases were 11-22% (n.s.). The HR increased in all groups but the increase was most prominent in the low-dose methohexitone group.

There were no significant changes in cardiac output (CO) during microlaryngoscopy. Nor were significant differences in CO or systemic vascular resistance (SVR) found between the groups. However, compared with the control period, significant increases in SVR by 25-39% were noted at some points of measurements in the low-dose

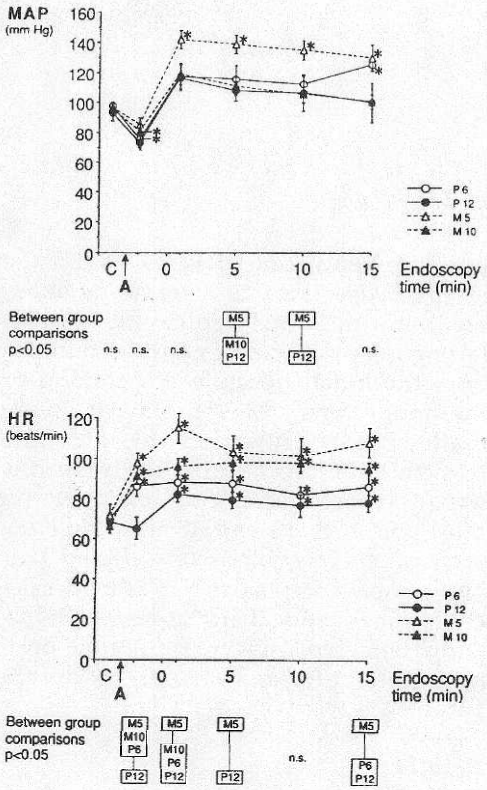


*Figure. 11. Mean arterial blood pressure (MAP) and heart rate (HR) (mean ± SEM) at awake control (C), after induction of anaesthesia (A) and during endoscopy (starts at 0) with infusion of propofol 6 or 12 mg·kg^{-1}·h^{-1} (represented by P6 and P12) or methohexitone 5 or 10 mg·kg^{-1}·h^{-1} (M5, M10). Significant changes (p<0.05) compared to awake control are depicted by *. Significant differences (p<0.05) between groups are shown below each graph.*

methohexitone and the low-dose propofol groups. LBF increased consistently in all groups, except in patients anaesthetized with the low dose of methohexitone (fig. 12). In the high-dose methohexitone group, on the other hand, LBF increased 300%, which was more than in the other groups. In contrast to methohexitone, the increases in LBF were similar with the low and high doses of propofol (110% above control values). During endoscopy, changes in LVR were essentially reciprocal to those in LBF (fig. 12). The methohexitone low-dose group was the only group which did not show a decrease in LVR. The methohexitone low-dose group showed increases in noradrenaline levels compared with awake values and in adrenaline levels compared with the other groups.

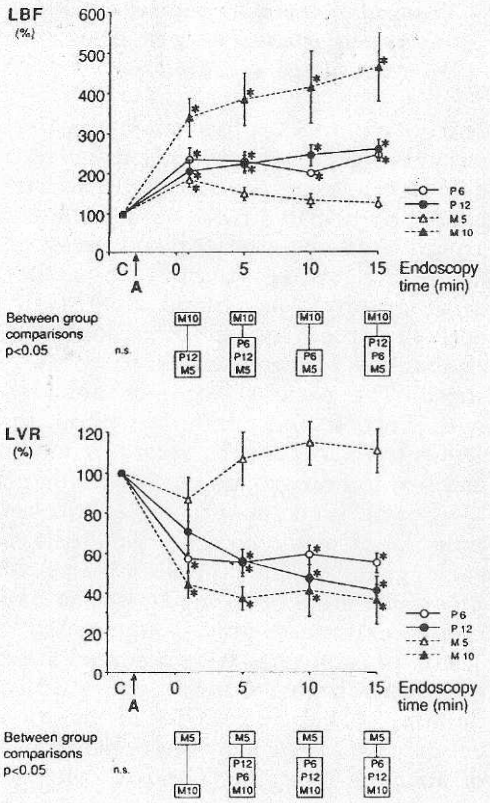


*Figure. 12. Leg blood flow (LBF) and leg vascular resistance (LVR) (mean ± SEM in percent of control values = 100) at awake control (C) and during endoscopy (starts at 0) with infusion of propofol 6 or 12 mg·kg^{-1}·h^{-1} (P6, P12) or methohexitone 5 or 10 mg·kg^{-1}·h^{-1} (M5, M10). Induction of anaesthesia is illustrated by A. Significant changes (p<0.05) compared to awake control are depicted by *. Significant differences (p<0.05) between groups are shown below each graph.*

	Eyes open on command		Breathing easily		Orientation in time and location		Recall of telephone nr		Leaving operating room		Leaving recovery room	
	mean	range	mean	range	mean	range	mean	range	mean	range	mean	range
Propofol 6 mg·kg^{-1}·h^{-1}	3,6 *	(2-7)	4,1 *	(2-10)	4,4 *	(3-6)	4,4 *	(3-6)	9,1 *	(7-14)	13,3 *	(6-22)
Propofol 12 mg·kg^{-1}·h^{-1}	7,4	(2-13)	7,4	(2-15)	8,1	(3-13)	8,2	(3-13)	12,7	(9-18)	26,0 *	(10-50)
Methohexital 5 mg·kg^{-1}·h^{-1}	3,8 *	(0-8)	4,3 *	(1-10)	9,9	(2-40)	5,2 *	(2-9)	9,7 *	(6-14)	31,7	(12-114)
Methohexital 10 mg·kg^{-1}·h^{-1}	11,3	(4-18)	13,6	(3-30)	18,6	(5-40)	23,3	(5-60)	18,2	(10-25)	47,4	(16-71)

*Table 2. Recovery parameters (min). Significant differences compared to the methohexitone high dose group (10 mg·kg^{-1}·h^{-1}) are depicted by *.*

Recovery was significantly prolonged after high-dose methohexitone anaesthesia compared with the other groups (table 2).

Paper II:

The effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in the cat.

In an experimental open-loop model in the cat (n=14), the effects on the baroreceptor reflex were studied during administration of either isoflurane (n=8), methohexitone (n=8) or propofol (n=8). Data during basal chloralose anaesthesia alone, obtained before administration of each additional anaesthetic, were used as control values. The order of administration of the three anaesthetics - isoflurane, propofol and methohexitone - was randomized. The anaesthetics were administered in a low and a high dose (table 3) corresponding to 0.5 and 1.0 MAC (minimum alveolar concentration) or assumed equipotent intravenous infusion rates. The baroreflex was tested by artificially changing the carotid sinus pressure from 50 to 200 mm Hg in steps of 25 mm Hg. This procedure was performed before the administration of each anaesthetic and repeated after 20-30 minutes at each dose level. An elimination period of 2 hours was allowed after the intravenous anaesthetics and 1 hour after isoflurane. A normalized baroreceptor reflex response was a prerequisite before introducing the next anaesthetic. Because of this requirement, many experiments had to be discontinued after one or two anaesthetics. Two cats had a maintained baroreflex reactivity before the administration of the third anaesthetic.

	Low dose	High dose
Propofol	4.5 mg·kg^{-1}·h^{-1}	9.0 mg·kg^{-1}·h^{-1}
Methohexitone	3.75 mg·kg^{-1}·h^{-1}	7.5 mg·kg^{-1}·h^{-1}
Isoflurane	0.80 %	1.6 %

Table 3. Maintenance doses of propofol, methohexitone and isoflurane.

Results

Increases in carotid sinus pressure from 50 to 200 mm Hg were associated with decreases in MAP and HR. In the control state, the average baroreflex sensitivity, in terms of MAP response, was 74.9±6.2 mm Hg/mm Hg (mean±SEM), which corresponds to a gain of 3.0. The effects of the baroreceptor reflex tests on systemic MAP and HR before and during maintenance with low and high doses of the three anaesthetics are shown in figure 13. In the isoflurane and methohexitone groups, reflex sensitivity expressed either as MAP or HR responses was significantly depressed at the high dose level of the anaesthetic (fig. 14). In the isoflurane group, reflex sensitivity in terms of MAP response was also depressed with the low isoflurane dose. In the propofol group, there were no significant differences compared with the control state. With the high dose of the

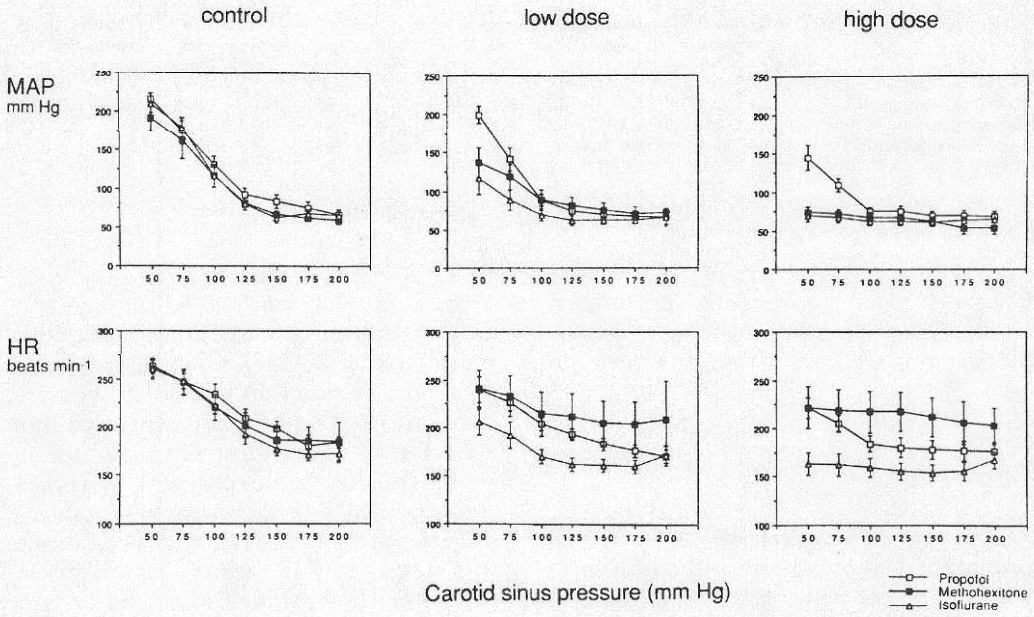


Figure. 13. Effects on systemic MAP and HR (means and SEM) of artificial unloading and overloading of the carotid sinuses (baroreceptor reflex test) before (=control) and during low and high doses of propofol, methohexitone and isoflurane.

anaesthetics, reflex sensitivity in terms of either MAP or HR responses was significantly lower during isoflurane and methohexitone than during propofol anaesthesia. With the low dose, only reflex sensitivity in terms of MAP was significantly lower during isoflurane compared with propofol anaesthesia. During isoflurane and methohexitone anaesthesia, the capacity of the baroreflex was attenuated in a similar way as the baroreflex sensitivity. The baroreflex set point for MAP was significantly higher during methohexitone than during propofol anaesthesia and the set point for HR was significantly decreased for isoflurane compared with control values. In a subgroup of the animals, baroreflex sensitivity concerning MAP and HR substantially recovered within 10 minutes after discontinuation of the anaesthetics.

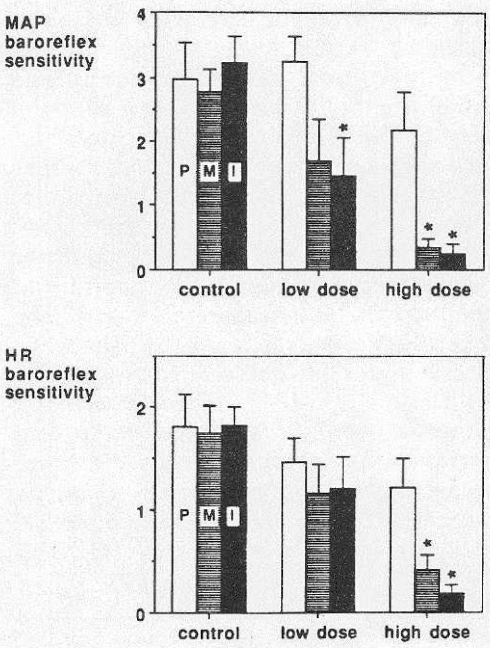


*Figure. 14. Baroreceptor reflex sensitivity - in systemic MAP and HR before (=control) and during low and high doses of propofol (P), methohexitone (M) and isoflurane (I). Means and SEM. Significant changes compared to control: * = $p<0.05$.*

Paper III:

Characteristics of muscle nerve sympathetic activity during general anaesthesia in humans.

Eighteen patients (ASA physical status 1-2), aged 30-70 (mean 51) years, scheduled for elective otorhinolaryngeal surgery participated in this descriptive study investigating the effects of various anaesthetics, baroreflex stimuli and surgical stress on muscle nerve sympathetic activity (MSA), arterial blood pressure, heart rate and skin blood flows (laser Doppler flowmetry and finger pulse plethysmography).

Results

In the 6 patients who received a bolus injection of fentanyl (3 μg/kg) before the start of anaesthesia, mean arterial pressure decreased gradually from 112±6 (mean±SEM) to 106±9 mm Hg ($p<0.05$) during the first 90 sec after the injection. Total MSA (defined as the product of mean burst amplitude and bursts/min) was unaltered apart from a transient increase in 5 of 6 patients one minute after the fentanyl injection.

During induction of anaesthesia with propofol (n=16) or methohexitone (n=2) MSA and blood pressure decreased in all patients (fig. 15). In a subgroup of 7 propofol patients the MSA burst frequency decreased to about 50% and total MSA to one-third of the control values, but the pulse-synchronous burst character was always maintained. An initial transient increase in MSA before the decrease started was confirmed in two of five patients by the cumulative sum (CUSUM) technique, which visualized the time relationship between changes of MSA and MAP.

Laryngoscopy and tracheal intubation initiated an immediate strong increase

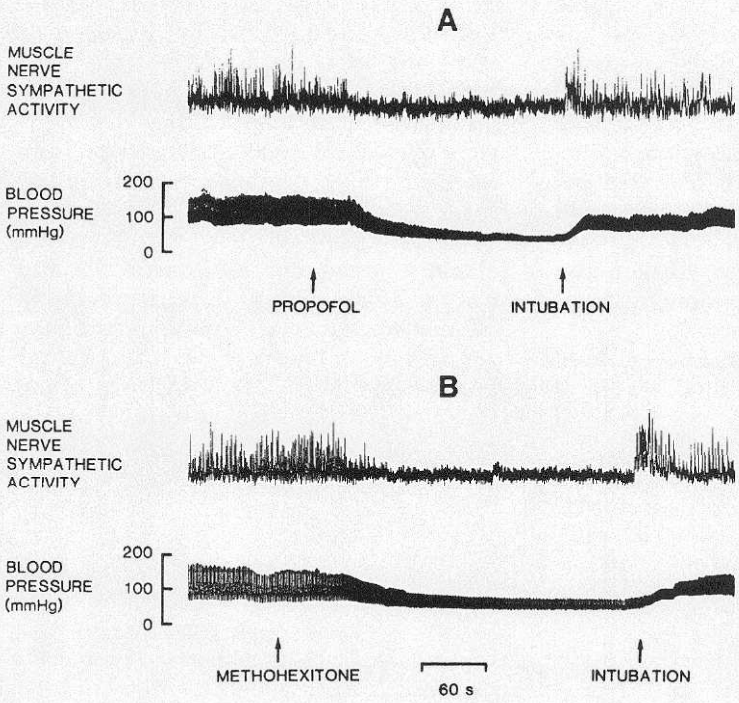


Figure. 15. Examples of changes of MSA and arterial blood pressure during induction of anaesthesia with bolus doses of propofol (upper panel, A) and methohexitone (lower panel, B). Note the drug-induced progressive decreases of MSA and arterial blood pressure and the sudden increases of nerve traffic with tracheal intubation.

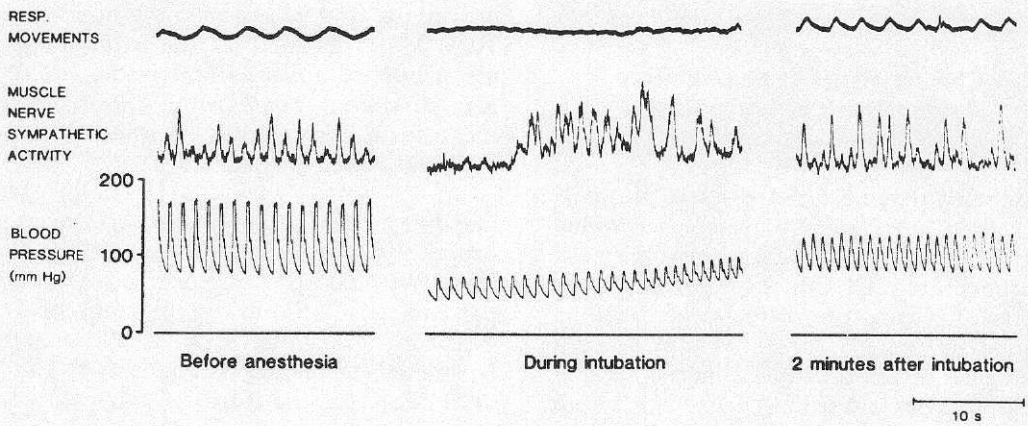


Figure. 16. Change of pattern of MSA during intubation. MSA was pulse-synchronous before anaesthesia and immediately before intubation (although with low burst amplitudes). Intubation caused an instant increase in MSA and the activity became continuous (pulse-synchrony was lost and baseline elevated). Two minutes after intubation arterial blood pressure had increased to a stable level and the pulse-synchrony of MSA had returned.

in MSA, followed by a slower gradual increase of blood pressure (fig. 16). In 9 of 13 patients the normal pulse-synchronous burst pattern was lost and replaced by an irregular burst pattern and in 12 of 13 patients the activity became continuous and the neurogram baseline was elevated. These changes gradually disappeared and normal pulse-synchrony and baseline levels re-occurred in all patients within 45 s after intubation. External manipulation of the tracheal tube or pharyngeal suction evoked effects similar to those evoked by the intubation procedure, but weaker and without loss of cardiac rhythmicity.

The anaesthetics in this study were used alone or in combinations. Table 4 summarizes the effects on MSA of these anaesthetics.

Surgical stimulation as such (n=13) was always associated with an increase in MSA followed by increases in arterial blood pressure and heart rate. Ventilator-induced sighs induced a transient increase of MSA (fig. 17). Repeated every 5th minute during maintenance of anaesthesia, the sighs were used as an index of baroreflex/lung receptor reflex response. This response was most clear-cut during administration of 70% nitrous oxide alone, whereas the addition of 0.3 and 0.6% isoflurane (n=8) dose dependently seemed to reduce all components of the response. During undisturbed anaesthesia with 1.0 MAC isoflurane (1.2% end-tidal concentration) sigh-

Anaesthetics	Effect on MSA	n
fentanyl	–	6
methohexitone (bolus/infusion)	↓	2/2
propofol (bolus/infusion)	↓	14/3
isoflurane	↓	8
halothane	↓↑	3
nitrous oxide	↑	12

Table 4. The effects on MSA of different anaesthetics used in study III.

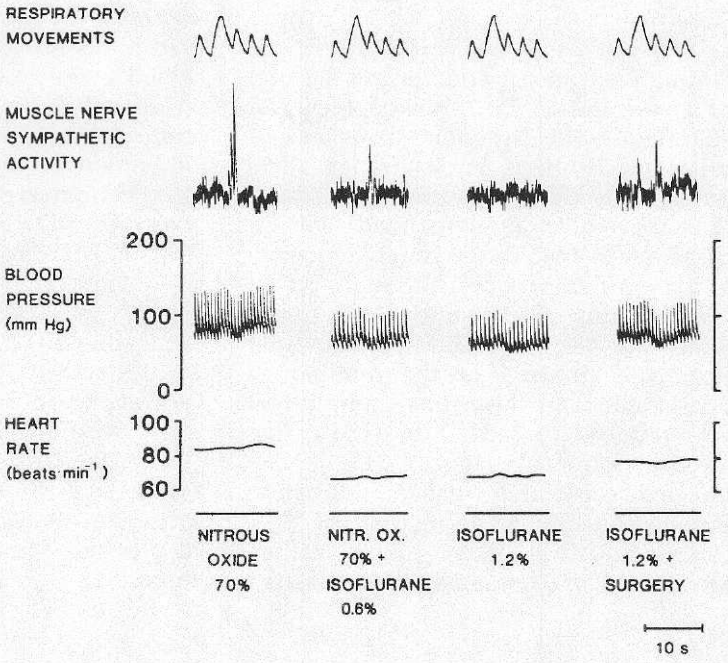


Figure. 17. Effects of ventilator induced sighs during 70% nitrous oxide alone, with addition of 0.6% (end-tidal conc) isoflurane and 1.2% (end-tidal conc) isoflurane alone. The MSA response was successively reduced but reappeared during surgery with 1.2% (end tidal conc) isoflurane anaesthesia. The panels shown were obtained after at least ten minutes administration of each anaesthetic.

induced changes were minimal or abolished, whereas surgery at this isoflurane dose caused an increased basal MSA and a restored reflex response.

Paper IV:

Percutaneous recording of muscle nerve sympathetic activity during propofol, nitrous oxide and isoflurane anesthesia in humans.

Muscle nerve sympathetic activity (MSA), arterial blood pressure, heart rate (HR) and skin blood flows (laser Doppler flowmetry and finger pulse plethysmography, respectively) were recorded before and during anaesthesia in 8 ASA physical status 1 patients (31-70 yrs) scheduled for otorhinolaryngeal surgery. After preanaesthetic medication with rectal diazepam (0.25 mg/kg) the patients arrived at the operating room. Recordings of all parameters were established before the start of anaesthesia. After induction with propofol and vecuronium, tracheal intubation and mechanical ventilation (F_iO_2 0.30) were performed. Anaesthesia was maintained according to the following protocol:

- 10 min with N_2O/O_2
- 10 min with N_2O/O_2 + 0.3% isoflurane (end-tidal concentration)
- 10 min with N_2O/O_2 + 0.6% isoflurane (end-tidal concentration)
- 10 min with O_2/air + 0.6% isoflurane (end-tidal concentration)
- 10 min with O_2/air + 1.2% isoflurane (end-tidal concentration)

Results are presented as means ± SEM from a 5-min control period before induction of anaesthesia, during the minute before and the minute after intubation, and during the last 3 min of each anaesthetic period.

Results:

During the control period before the start of anaesthesia, MSA showed its usual character with irregular sequences of pulse-synchronous bursts (range 18-63 bursts/min). Bolus injection of propofol (2.6 mg/kg) was associated with a decrease in both MSA burst frequency and burst amplitude, although pulse-synchronous rhythmicity was maintained (fig. 18). The total MSA (calculated from the product of the number of bursts/min and mean burst amplitude) was reduced to 34±2% ($p<0.05$) of the awake control level (fig. 19). Laryngoscopy and tracheal intubation initiated an immediate increase in MSA (total MSA 151±23% of control value), which in 4 of 7 patients was associated with a temporary loss of pulse-synchrony (during 13-37 s). Mean arterial blood pressure (MAP), which decreased from 99±16 mm Hg during awake control to 73±10 mm Hg ($p<0.05$) after induction of anaesthesia, increased to 109±15 mm Hg after intubation. Heart rate (HR) showed gradual increases from 68±8 to 78±8 beats/min before and 86±10 beats/min after intubation. Skin blood flows increased after induction of anaesthesia to 700-1000% of control values ($p<0.05$), whereas intubation did not evoke additional changes. After 10 min ventilation with nitrous oxide alone, total MSA was increased to the same level as during the first minute after intubation, while MAP was decreased from 109±5 to 84±4 mm Hg ($p<0.05$).

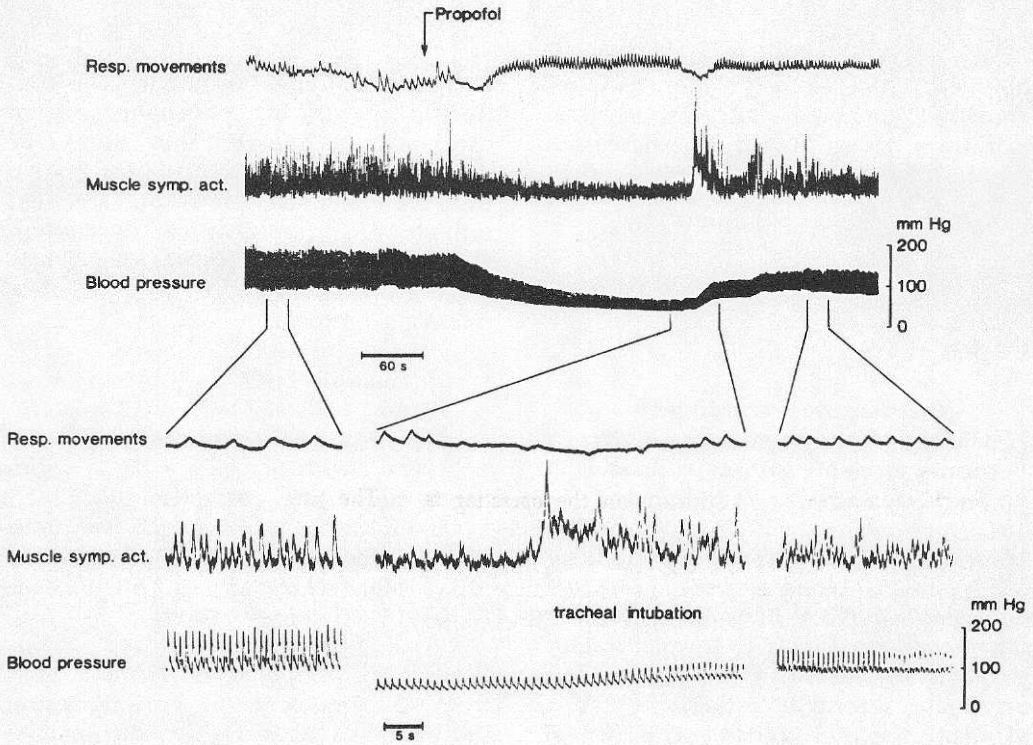


Figure. 18. Experimental records from one patient during induction of anaesthesia with propofol. The upper part of the figure shows a condensed recording (time scale 60 sec). In the lower part, selected periods have been displayed at a faster speed (time scale 5 sec).

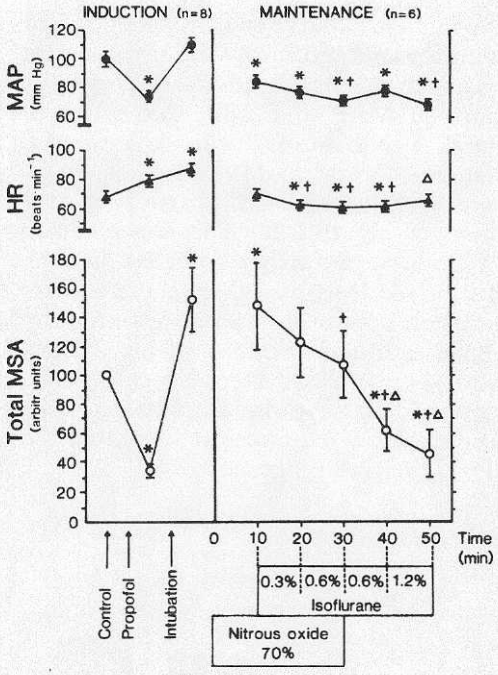


*Figure. 19. Mean values ± SEM of mean arterial blood pressure (MAP), heart rate (HR) and total MSA (bursts/minute x mean burst amplitude) of the whole material. Total MSA expressed in % of the awake control value (=100). Symbols *, † and Δ indicate statistical significance (p<0.05) for comparisons with the awake control period (*), with 70% nitrous oxide (†) and with 0.6% isoflurane + 70% nitrous oxide (Δ), respectively. MSA data immediately before and after intubation include measurements from 7 patients.*

Supplementation of 70% of increasing doses of isoflurane (0.3% and 0.6% end-tidal concentration) to nitrous oxide was associated with gradual decreases in total MSA and MAP ($p<0.05$ at 0.6%)(fig. 19). Withdrawal of nitrous oxide, which implied a decrease in depth of anaesthesia from 1.0 MAC to 0.5 MAC, was associated with a substantial decrease in total MSA (from 107±56 to 61±42 % of control level; $p<0.05$) while MAP increased from 71±6 to 78±5 mm Hg (ns). Increase of isoflurane from 0.6% to 1.2% did not significantly change MSA. Skin blood flows were stable during nitrous oxide and/or isoflurane anaesthesia, with laser Doppler blood flows of 1100-1300% and finger pulse amplitudes of 1600-1900% of the respective control values.

Paper V:

Sympathetic muscle nerve activity, peripheral blood flows and baroreceptor reflexes in humans during propofol anesthesia and surgery.

Nine (ASA physical status 1-2) patients, aged 26-59 yrs, scheduled for elective microlaryngoscopy were studied. Muscle nerve sympathetic activity, arterial blood pressure, heart rate, leg blood flow (occlusion plethysmography) and skin blood flows (laser Doppler flowmetry and finger pulse plethysmography) were recorded before and during undisturbed propofol anaesthesia (0.1 $mg \cdot kg^{-1} \cdot min^{-1}$) and during microlaryngoscopy when the propofol infusion dose was individually adjusted so that mean arterial blood pressure was kept at the awake control level. The patients were muscle relaxed with atracurium and artificially ventilated through a tracheal tube. During the microlaryngoscopy the laryngoscope was fixed to a frame mounted on the operating table. The sensitivity of the muscle sympathetic and cardiac limbs of the baroreflex were tested by measuring the compensatory responses to the blood pressure reduction induced by bolus injections of sodium nitroprusside (SNP). The baroreflex sensitivity was represented by the linear regression slope when blood pressure values were plotted against MSA-area (MSAA) or cardiac RR-intervals.

Results

Induction of anaesthesia with propofol (on average 2.4 mg/kg including supplementary doses) reduced both the number of MSA bursts and their mean areas in all subjects. Four minutes after induction, total MSA (MSAA/min) was 39% of the awake control value ($p<0.05$). This reduction was similar to the decrease in MSA noted during undisturbed steady-state propofol infusion 15-20 minutes later (fig. 20). However, during microlaryngoscopy when MAP was controlled close to the awake control level MSA was restituted. HR increased both during anaesthesia and during microlaryngoscopy compared with the awake control state (fig. 21). Leg vascular resistance (derived from the ratio of MAP and LBF) decreased in parallel with MSA during anaesthesia, but in contrast to MSA the resistance remained decreased during microlaryngoscopy (fig. 20). This was reflected in part by a further increase in LBF during endoscopy when the propofol infusion dose was increased more than three-fold. The increase in blood flow also seen in laser Doppler skin blood flow and finger pulse amplitude during anaesthesia remained unchanged during microlaryngoscopy.

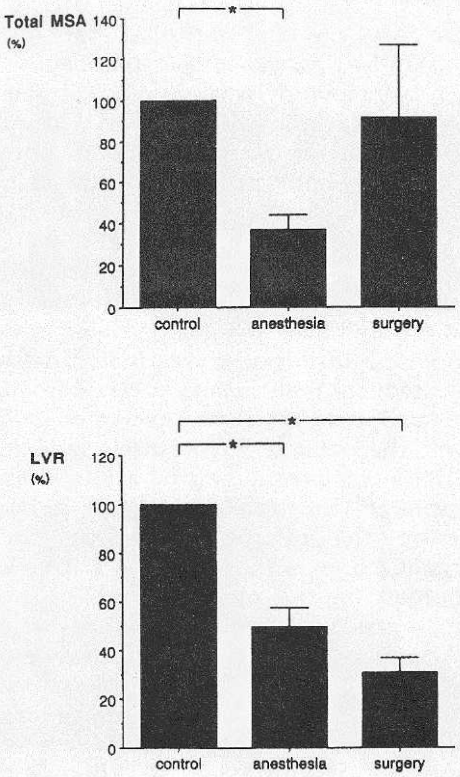


*Figure. 20. Mean values ± SEM (in percent of control = 100) of "total MSA" and leg vascular resistance (LVR) in the awake state (control), during undisturbed anaesthesia and microlaryngoscopy (surgery). Significant changes ($p<0.05$) are depicted by *.*

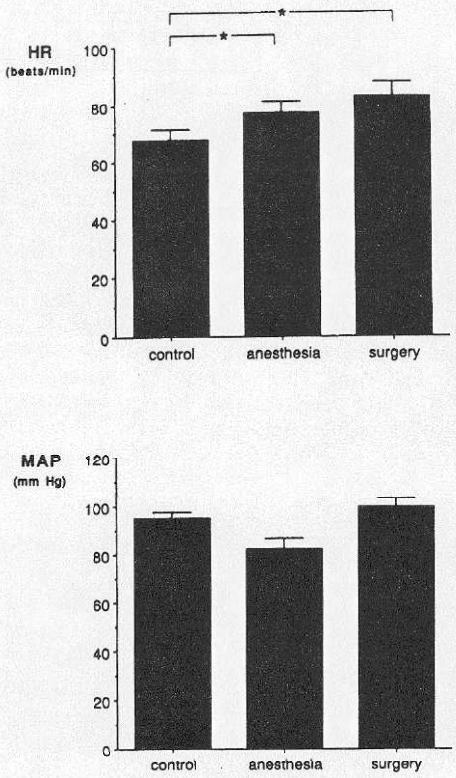


*Figure. 21. Mean values ± SEM of HR and MAP in the awake state (control), during undisturbed anaesthesia and microlaryngoscopy (surgery). Significant changes ($p<0.05$) are depicted by *.*

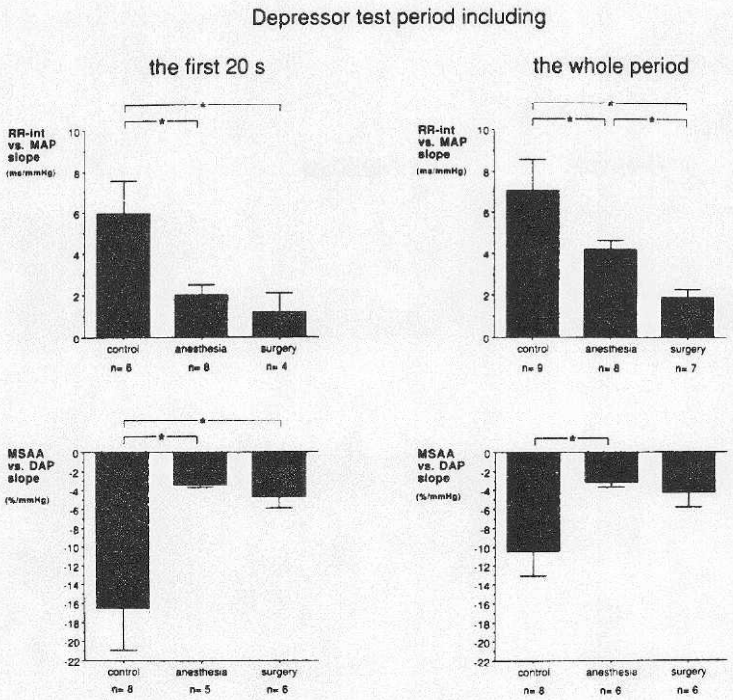


*Figure. 22. Mean values ± SEM of slope values (i.e. regression coefficients) from RR-interval vs. MAP-slopes (upper panels) and MSAA vs. DAP-slopes (lower panels) calculated from individual baroslopes with correlation coefficient exceeding 0.5. Slope values from depressor test periods only including the first 20 s are shown in the left panels and tests including the whole period are shown in the right panels. MSAA is expressed as percent of basal MSAA value during the awake control period. Significant changes ($p<0.05$) are depicted by *.*

During undisturbed anaesthesia, the sensitivity was depressed in both the cardiac and muscle sympathetic limb of the baroreflex (fig. 22). During micro-laryngoscopy the cardiac baroreflex sensitivity was further depressed, while the muscle sympathetic limb was unchanged. These baroreflex changes were also obvious when the analysis of the depressor tests was restricted to the first 20 sec of fall in blood pressure, although the cardiac baroreflex sensitivity in general was weaker (fig. 22).

5. Discussion

Induction of anaesthesia and tracheal intubation

Induction of anaesthesia is usually associated with a decrease in arterial blood pressure. All patients in the present studies had anaesthesia induced with propofol or methohexitone. Decreases in blood pressure induced by these agents are usually ascribed to both decreased cardiac output and vasodilation[106,107]. The decrease in blood pressure is often more pronounced during induction of anaesthesia with propofol than with methohexitone. The heart rate usually increases during methohexitone anaesthesia[106] whereas propofol is associated with varying heart rate changes[107]. With both drugs, we found that induction of anaesthesia is followed by a decrease in postganglionic sympathetic nerve activity to the skeletal muscle vasculature. This decrease was closely associated with the concomitant decrease in arterial blood pressure. The reductions in total MSA found during propofol induction (IV,V) are similar to those recently observed by Ebert after induction with propofol[108] and thiopentone[109]. In contrast, etomidate did not seem to affect either MSA or blood pressure[108].

The fact that the onset of the decrease in MSA is normally followed by a blood pressure decrease (III) illustrates the role of the sympathetic activity in maintenance of vascular tone. However, with the aid of the CUSUM technique[71], we found that before the marked reductions in MSA and MAP occurred, some patients showed an initial transient increase in MSA. This initial augmentation of MSA may be caused by a central excitation during the induction of anaesthesia or a baroreflex response to a blood pressure reduction evoked by the direct vasodilatory effects of methohexitone or propofol before anaesthesia had caused depression of central sympathetic outflow and baroreflex sensitivity. The occurrence of transient increases of MSA during induction of anaesthesia has also been illustrated by unpublished data in two out or four pilot patients who received a subanaesthetic bolus dose of propofol (1 mg/kg) followed by infusion of 10 $mg \cdot kg^{-1} \cdot h^{-1}$ during the first 10 minutes (fig. 23).

Although the decrease in MSA after induction of anaesthesia with propofol or methohexitone was pronounced, MSA retained its pulse-synchronous pattern, indicating that baroreceptor reflex control of MSA was still operative.

The fact that stimulation of the pharynx and larynx increases sympathetic activity was demonstrated in the cat by Tomori and Widdicombe[110]. We found that laryngoscopy and tracheal intubation not only increased MSA but also induced short periods of continuous sympathetic activity (i.e. elevated mean voltage baseline) with or without loss of pulse synchrony in the neurogram. Pulse synchrony is caused by recurrent inhibitory influence from arterial baroreceptors and normally the inhibitory effect of each systolic pulse wave is strong enough to cause a short pause in the sympathetic neurogram[65]. In theory, continuous sympathetic activity and

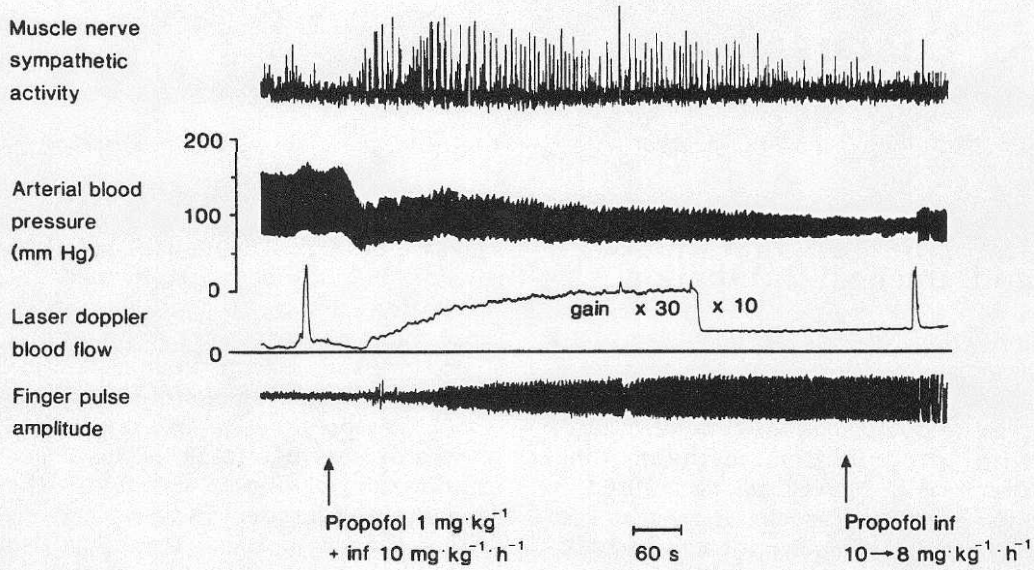


Figure. 23. Induction of anaesthesia with a subanaesthetic bolus dose of propofol (1 mg/kg) followed by an infusion (10 mg·kg⁻¹·h⁻¹). Note the increase of MSA during the first part of the induction sequence and the gradual decrease in sympathetic outflow when anaesthesia is established. Due to technical reasons, the blood pressure amplitude fades during the late part of the recorded sequence but is re-established before the sequence is ended.

lack of pulse synchrony should occur if baroreceptor inhibition is too weak in relation to the central sympathetic drive. The effects of temporary baroreceptor deafferentiation with bilateral blockade of the glossopharyngeal and vagal nerves by local anaesthetics support this view[67]. In the present studies, blood pressure was low after induction of anaesthesia and therefore the baroreceptor inhibitory influence was probably too weak to induce significant pulse rhythmicity in the strong sympathetic outflow evoked by intubation. This agrees with our finding that preintubation blood pressure was lower in subjects who lost MSA cardiac rhythmicity during intubation. We found that the increase in arterial blood pressure had a longer duration than the increase in MSA (fig. 24). The results suggest that the initial response to tracheal intubation is neurogenic and that increases in blood pressure lasting more than 5 minutes after the start of intubation are likely to be maintained by humoral substances.

Maintenance of anaesthesia

Propofol

Compared with the awake control level, the decrease in arterial blood pressure during undisturbed steady-state propofol anaesthesia was associated with a decrease in MSA and increases in skin and skeletal muscle blood flows. The corresponding decrease in leg vascular resistance is consistent with a reduced afterload, which has been proposed as one of several possible mechanisms causing propofol-induced hypotension[111,112]. In our studies, measurements

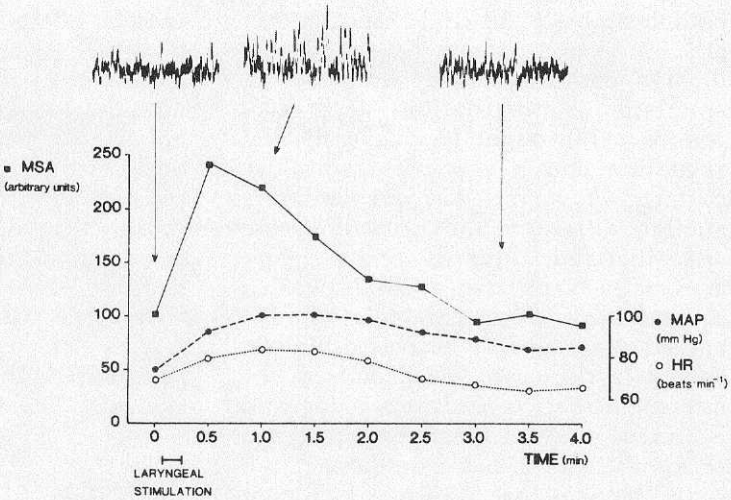


Figure. 24. Muscle nerve sympathetic activity (MSA), mean arterial blood pressure (MAP) and heart rate (HR) during laryngeal stimulation by external manipulation of the larynx and gentle movements of the tracheal tube for 10-15 sec in one patient anaesthetized with 70% nitrous oxide.

of cardiac output were performed only after the start of microlaryngoscopy. It is, however likely that undisturbed propofol anaesthesia induced a decrease in cardiac output[41,113-115]. It has been discussed whether this decrease in cardiac output is caused by myocardial depression[41,113] or whether venodilation and decreased preload are mainly responsible for the decrease in stroke volume[112,114-119].

Isoflurane

The haemodynamic response to isoflurane anaesthesia is usually characterized by a reduction of total peripheral resistance[120-122]. The inhibitory effect of isoflurane on sympathetic nerve activity has been demonstrated indirectly in humans, for instance by low levels of plasma catecholamines[123], and directly in animals by decreases in postganglionic activity in renal and cervical nerves[22,124,125]. Our findings show that MSA is inhibited already at relatively low doses of isoflurane and provide a contributory explanation for the decrease of vascular resistance.

Halothane

The effects of halothane on sympathetic outflow have been disputed since Millar and Biscoe[126] found an increase in sympathetic activity during halothane anaesthesia in the rabbit. Later, several studies in the cat led to the opposite conclusion[27,30,127,128]. However, large interindividual variations may occur[30]. Our observations are few and thus difficult to interpret. It is possible that in some patients administration of halothane causes an initial baroreflex-mediated increase in MSA when direct cardiovascular depression by halothane precedes the depression of baroreceptor reflex sensitivity.

Nitrous oxide

Most anaesthetics cause various degrees of inhibition of the sympathetic outflow but nitrous oxide is an exception. The concept that nitrous oxide is a centrally acting stimulant of sympathetic activity[127,129-133] is now supported by percutaneous recordings of increased MSA during nitrous oxide administration

both in studies by us (III,IV) and Ebert et al[134,135]. It can be argued that the increase in MSA demonstrated by Ebert during spontaneous ventilation with 40% nitrous oxide might be due to mental excitation and a changed respiratory pattern. However, our results were similar although the patients were anaesthetized, muscle relaxed and artificially ventilated. Withdrawal of nitrous oxide during stable isoflurane anaesthesia markedly decreased MSA in spite of a decreased MAC. Indeed, the interaction between nitrous oxide and isoflurane on MSA illustrates one aspect of so-called "balanced anaesthesia"[136]. It is also obvious that MSA may be a poor monitor of depth of anaesthesia during "balanced anaesthesia".

Fentanyl

Clinically, opiates have an important role in a balanced anaesthesia. We studied fentanyl, which as a sole agent is known to have only minor cardiovascular effects[137]. No significant change in MSA was observed after pre-anaesthetic administration of small doses of fentanyl (3 μg/kg). A lack of opiate interference with MSA during undisturbed conditions may seem consistent with the finding that the opiate antagonist naloxone at rest does not seem to affect haemodynamics or MSA[24]. However, during general anaesthesia and surgery the sympathetic effects of opiates may be more pronounced. This question remains to be studied.

Surgical stress

Propofol and methohexitone

We have shown that surgical stimuli increase MSA (fig. 25)(III,V). This is not surprising since it is well known that arterial blood pressure and plasma catecholamines can increase promptly during surgery[138]. The restitution of

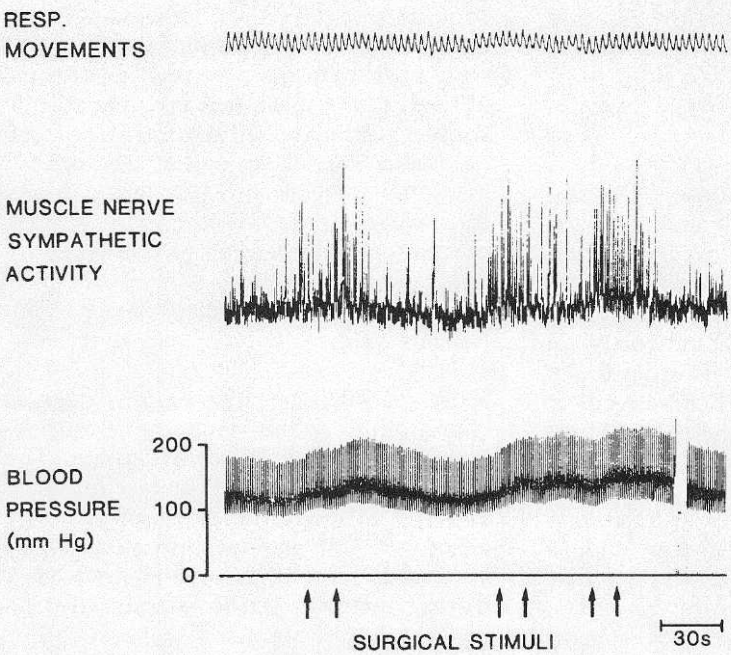


Figure. 25. Effects of muscle nerve sympathetic activity (MSA) and arterial blood pressure (MAP) of repeated reposition attempts of a zygomatic bone fracture in a patient anaesthetized with methohexitone (4 mg·kg^{-1}·h^{-1}).

MSA during microlaryngoscopy, in spite of a large increase of the propofol infusion rate (V), illustrates the balance between the stimulatory effect of somatosensory afferents on sympathetic outflow and the inhibitory effect of anaesthetics. Since leg blood flow increased and leg vascular resistance decreased compared with awake control values, the most likely interpretation is that propofol also has marked direct vasodilatory effects which override the neural vasoconstriction during surgery. The vasorelaxant effects of propofol have been demonstrated both in isolated rat aorta[112,116] and in capacitance vessels[116-118]. The effects on the capacitance vessels are already evident at low propofol concentrations and a dose relationship has been established in vitro for human vessels. These vascular effects of propofol which mimic the vasodilating effects of nitroglycerine may explain why very high propofol doses are sometimes needed to block the pressor response to surgical stress (V).

When methohexitone was compared with propofol in assumed equi-anaesthetic doses, the differences in leg blood flow between the low and high doses were large in the methohexitone but none in the propofol groups. Our observations concerning methohexitone, a barbiturate, are supported by studies on thiopentone in an isolated cat skeletal muscle preparation by Grände et al[139]. These authors showed that thiopentone at low concentrations increased vascular resistance, probably due to a decreased metabolic demand and a reduced local concentration of vasodilating metabolites[140,141], whereas higher concentrations decreased vascular resistance and myogenic vascular reactivity in a dose-dependent manner. The methohexitone effects on MSA may be similar to those of propofol, since two patients anaesthetized with methohexitone infusion showed a dose-related depression of MSA during surgery (III).

Catecholamine concentrations have often been used as an index of increased sympathetic nervous activity during tracheal intubation and surgical stress[138,142-144]. MSA has not previously been used as an index of perioperative stress, but stress induced by isometric hand grip elicits parallel increases in MSA and venous plasma noradrenaline concentrations[145]. Our material does not allow such comparisons but, compared with the awake state, we observed that as long as the pressor response to stress was blocked, there were no increases in arterial noradrenaline concentrations (I) or in MSA (V).

Baroreceptor reflexes

During anaesthesia, pharmacological effects of the anaesthetic drugs on baroreflex sensitivity influence the ability of the cardiovascular system to buffer sudden changes in blood pressure. In our studies, the baroreceptor reflex was evaluated in an experimental baroreflex open-loop model (II) and in humans through either ventilatory induced circulatory changes (III) or SNP-induced hypotension (V). The baroreflex tests were performed either during steady-state anaesthesia at undisturbed conditions or during surgical stress. The studies focused on the baroreflex effects of propofol, methohexitone and isoflurane.

Propofol

Propofol maintained the baroreflex sensitivity better than methohexitone and isoflurane at assumed equi-anaesthetic doses when tested in vagotomized cats (II). These results may seem surprising since in the clinical setting both propofol and isoflurane are often

associated with marked decreases in blood pressure[47,107]. However, our findings are in agreement with previous studies which showed that the response in heart rate to a change in arterial blood pressure was not affected by propofol in humans[146,147] and was less affected by propofol than by other anaesthetics (althesin, pentobarbitone and ketamine) in the rabbit[148]. However, extrapolation of the sensitivity diagram in our study (II) also indicates that propofol in higher doses than used in this study may cause significant depression of the baroreceptor reflex.

In the cat, the unchanged cardiac baroreflex sensitivity during propofol anaesthesia was assumed to be due to a relatively unaffected cardiac sympathetic response since the vagal influence, which is normally the most important heart rate modulating factor[9], was intentionally abolished. The vagal influence is therefore likely to explain why cardiac baroreflex sensitivity in our human study (V) was markedly depressed by propofol.

Concerning the muscle sympathetic limb of the baroreflex during undisturbed propofol anaesthesia, the sensitivity was significantly depressed both in Ebert's[108] and in our study (V). During microlaryngoscopy, the baroreflex remained depressed. We suggest that this is explained by the pharmacological effects of the high dose of propofol during this procedure. For instance, it is possible that direct relaxant effects of the very high propofol doses on the baroreceptor-harbouring vessels[112,116] change afferent baroreceptor nerve activity during baroreflex tests.

In contrast to muscle sympathetic baroreflex sensitivity, the sensitivity in the cardiac baroreflex limb was further depressed during surgery. This is consistent with observations of a selective inhibition of the cardiac baroreflex during hypothalamic defence area stimulation[13-15] which could mimic the cardiovascular response to intense pain[12].

Methohexitone

Barbiturates have previously been shown to depress the baroreceptor reflex[25-27,149]. This was confirmed in the cat study (II), in which the baroreflex sensitivity was significantly more depressed during methohexitone than during propofol anaesthesia. In a microneurographic study concerning the baroreflex sensitivity, MSA burst frequency was depressed by thiopentone[109]. Our MSA recordings in two patients with methohexitone infusion were not quantified but showed, at infusion rates of 4 $mg \cdot kg^{-1} \cdot h^{-1}$, an abolished baroreflex response to a valsalva-like manoeuvre or to 15 cm of positive end-expiratory pressure (PEEP).

Isoflurane

Experimentally, isoflurane anaesthesia was also associated with a depression of baroreflex sensitivity in terms of both heart rate and pressure responses (II). This is consistent with previous observations[22,32,34,35,125]. Isoflurane seems to act at multiple sites in the baroreceptor reflex arch. This includes both a dose-dependent sensitisation of the baroreceptors causing a decrease in efferent preganglionic sympathetic activity and a ganglionic depression causing a further decrease in efferent postganglionic sympathetic activity[22]. Our experimental findings in the cat are qualitatively consistent with our observations of MSA during isoflurane anaesthesia in patients (III). In patients, baroreflex responses evoked by ventilator-induced sighs were abolished at 1.2 % end-tidal concentration of isoflurane. With the influence of

surgical stress, however, baroreflex responses were restored.

Summary of baroreflex effects

When propofol is used as reference, human and animal data indicate that during undisturbed anaesthesia the sympathetic baroreflex will be less affected by etomidate[108] and nitrous oxide[135] and more depressed by methohexitone (II,III) and isoflurane (II,III). When the pressor response during microlaryngoscopy is controlled by high doses of propofol, the sympathetic baroreflex sensitivity shows about the same depression as during undisturbed anaesthesia. During surgical stress, the balance between different cardiovascular regulatory mechanisms in relation to anaesthetic interactions is complex and therefore not always recognized. Further investigations of these issues are thus of importance for anaesthetic management and care.

6. Conclusions

- Sympathetic activity to skeletal muscle (MSA) is depressed by propofol, methohexitone and isoflurane, whereas nitrous oxide is associated with an increase in MSA.

- Vasodilation during propofol anaesthesia may be caused both by an inhibition of sympathetic nerve traffic and by a direct vascular effect.

- In the cat, the arterial baroreceptor reflex is better maintained with propofol than with methohexitone or isoflurane in equianaesthetic doses.

- During anaesthesia, MSA retains its normal pulse-synchronous character, even when the activity is depressed. This indicates that arterial baroreceptor modulation is qualitatively operative.

- The cardiovascular response to microlaryngoscopy is better controlled by a low dose propofol infusion than by an equianaesthetic infusion of methohexitone. The recovery is more rapid after a high dose propofol infusion than after an equianaesthetic infusion of methohexitone.

- The depression of MSA during undisturbed propofol infusion is to a large extent restored during microlaryngoscopy in spite of a more than three-fold increase of the propofol infusion rate.

- Baroreflex sensitivities of both cardiac and muscle nerve sympathetic limbs are depressed by propofol. During surgery, a further depression of the cardiac baroreflex may be due to a central vagal inhibition similar to that found in animals during defence area stimulation.

- The baroreflex sensitivity is determined by a balance between an augmented central sympathetic outflow due to the intensity of surgical stimulation and inhibition due to the anaesthetic dose.

7. Acknowledgements

I wish to express my sincere gratitude to:

- **Johan Pontén**, my tutor and friend, for guiding me throughout this work with continual support and encouragement.
- **B Gunnar Wallin**, head of the Department of Clinical Neurophysiology, for introducing me to the microneurographic recording technique, and for excellent recourses and guidance.
- **Hengo Haljamäe**, head of the Department of Anaesthesiology, for support and encouragement.
- **Italo Milocco**, my chief, for stimulating interest and generous support.
- **Mikael Elam**, for microneurographic assistance, valuable criticism and pleasent collaboration.
- **Björn Biber, Beng-Åke Henriksson** and **Jan Martner**, experimental co-workers, for educative baroreflex discussions and valuable criticism.
- **Hans Ejnell** for standardized afferent stimulation and pleasant collaboration, and **Hans Sonander** for helpful criticism.
- **Tomas Karlsson** for invaluable technical help with neurographic recording equipment and **Marita Ahlqvist** for professional experimental and drawing assistance.
- **Sven Björkman, Jan Hedner** and **Jan Häggendal** for pharmacological analyses.
- **Stefan Lundin** for valuable discussions and unbiased advice.
- **Staff and colleagues** at the Department of Anaesthesia and Intensive Care for their support and friendship, which makes my work enjoyable every day.
- **Birgit Eriksson, Suzanne Manner-Winter** and all the staff of the ENT operation unit for invaluable co-ordination and patience.
- **Kalle Sandell** for excellent and rapid photographic work.
- **My family**, Marie-Louise, Anna, Erik and Fredrik, for their love, patience and support.

This study was supported by grants from the Swedish Medical Research Council (project no. 06575 and 03546), the Medical Faculty at the University of Göteborg, the Medical Society of Göteborg, "Förenade Liv" Mutual Group Life Insurance Company and the Swedish Society for Medical Research.

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9. Original papers

Anesthetic modulation of the cardiovascular response to microlaryngoscopy.
A comparison of propofol and methohexital with special reference to leg blood flow, catecholamines and recovery. I

The effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in the cat. II

Characteristics of muscle nerve sympathetic activity during general anaesthesia in humans. III

Percutaneous recording of muscle nerve sympathetic activity during propofol, nitrous oxide and isoflurane anesthesia in humans. IV

Sympathetic muscle nerve activity, peripheral blood flows and baroreceptor reflexes in humans during propofol anesthesia and surgery. V

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