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Applications of the Autonomic Nervous System in Clinical Practice

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Academic Teaching Text

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Ladislav Kočan

CONTENTS

ABBREVATIONS

α2-AR	Alpha-2 adrenergic receptors
A-P	Antero-posterior projection
AR	Adrenergic receptors
ASIPP	American Society of Interventional Pain Physicians
AV	Atrioventricular node
CGRP	Calcitonin gene-related peptid
CLTI	Chronic limb threatening ischemia
CNS	Central nervous system
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CRBS	Complex regional pain syndrome
CRT	Cardiac resynchronization therapy
EBM	Evidence based medicine
EDV	End-diastolic volume
ESC	European Society of Cardiology
ESV	End-systolic volume
FPP	Fossa pterygopalatina
G12/13	G-protein variant
Gaq/11	G-protein variant
Gaq	G-protein variant
Gi	G-protein variant
GRK	G-protein-coupled receptor kinase
Gs	G-protein variant
Gq	G-protein variant
HF	Heart failure
HR	Heart rate
HRV	Heart rate variability
IHS	International Headache Society
IL	Interleukin
ILC2s	Innate lymphoid cells type 2
INS	International Neuromodulation Society
M	Muscarinic acetylcholine receptors
MSNA	Muscle sympathetic nerve activity
n. X	Vagus nerve
NO	Nitric oxide
NYHA	New York Heart Association
PaCO2	Partial pressure of carbon dioxide
PAD	Peripheral arterial disease
PaO2	Partial pressure of oxygen
PNS	Peripheral nervous system
PPG	Ganglion pterygopalatinum , ganglion sphenopalatinum
RAP	Refractory angina pectoris

RF	Radiofrequency ablation
SA	Sinoatrial node
SCM	Sternocleidomastoid muscle
SCS	Spinal cord stimulator
SDNN	Standard deviation of intervals between normal beats
TENS	Transcutaneous electrical nerve stimulation
TLR4	Toll-like receptor 4
TAR	Trigeminal autonomic reflex
VATS	Video-assisted thoracoscopic splanchnicectomy
VIP	Vasoactive intestinal peptide
WIP	World Institute of Pain

PREFACE

MUDr. Ladislav Kočan PhD., FIPP

The autonomic nervous system (ANS) constitutes a vital component of the peripheral nervous system, responsible for maintaining homeostasis and regulating internal processes within the body. Unlike the voluntary control exerted by the central nervous system, the autonomic nervous system operates involuntarily, innervating smooth organs, vessels, skin glands, and even exerting some influence over skeletal muscles in connection with vegetative functions such as breathing, digestion, and the urinary and gonadal systems. Its impact extends crucially to the cardiac muscles of the heart and plays a significant role in endocrine and metabolic functions, thermoregulation, as well as emotional and behavioral responses, including adaptive reactions to stressors.

The autonomic nervous system consists of three parts: the sympathetic, parasympathetic, and enteric nervous systems. The sympathetic nervous system is the most extensive component of the autonomic nervous system. It becomes activated during stressful situations and states such as 'fight or flight,' typical for organism mobilization. The sympathetic system activates catabolic processes, leading to energy depletion necessary for individual sustenance.

The parasympathetic nervous system is a visceromotor component of the autonomic nervous system responsible for maintaining anabolic processes. Its primary function is to conserve and store energy, essential for maintaining organismal homeostasis. This system is active during calm conditions and relaxation, often referred to as 'rest and digest' states. Both systems essentially function as antagonists. The sympathetic system acts in the short term to protect the individual against potential dangers, while the parasympathetic system affects functions associated with the long-term survival of the individual. The third component of the autonomic nervous system is the enteric system, which comprises large intramural plexuses located in the gastrointestinal tract. Its function is to control muscle tension, movements, wall movements of the digestive tract, and its secretion activity.

Given the intricate functions of the autonomic nervous system, therapeutic interventions targeting this aspect of the nervous system have posed a challenge for medical professionals throughout history. In his 1917 article "The Vegetative Nervous System from the Clinical Viewpoint," published in the Boston Medical and Surgical Journal,

Malcolm Woodbury delves into the recent advancements in such treatments and their outcomes. The first surgical transection of sympathetic nerve fibers, known as "rami communicantes," was performed in 1924 in Australia by surgeons Royle and Hunter. Concurrently, Surgeon Adson in the United States and J. Diezes in Argentina independently conducted lumbar sympathetic chain resections for the treatment of Thromboangiitis obliterans, also known as Burger's disease.

Sympathetic nerve blocks have since become a widely utilized treatment for visceral, ischemic, neuropathic, and sympathetically mediated pain, as well as for conditions associated with microcirculation disruptions in the limbs. Modern interventions, including sympathetic nerve blocks, ablations, and surgical resections, can be performed through various approaches. Previously, these procedures were typically conducted via open laparotomy, but this approach has become obsolete due to its extensive tissue damage and diminished efficacy. Presently, surgical laparoscopic techniques or minimally invasive procedures guided by ultrasound or fluoroscopy are preferred.

The majority of sympathetic ganglia and plexuses are anatomically segregated into prevertebral and paravertebral regions, rendering them more accessible for percutaneous procedures. Based on current outcomes from sympathetic treatment procedures, we have observed their positive impact, notably in pain management, alleviating patient suffering, and promoting tissue regeneration.

The parasympathetic nervous system has also been the subject of past research, particularly regarding the treatment of certain diseases. Historical records highlight investigations into the primary parasympathetic nerve, the vagus nerve. Early studies explored vagal nerve stimulation for antiarrhythmic therapy, with the first experiments conducted on dogs by Einbrodt in 1859. These experiments demonstrated a reduction in mortality from ventricular tachycardia following direct vagal ventricular stimulation. Subsequent studies in 1973 and 1978 further validated the potential for reduced mortality from acute myocardial infarction with vagal stimulation. Myers, in 1991, elucidated the protective effect of vagal stimulation-induced bradycardia against ventricular fibrillation, indicating a direct influence of the vagus nerve on the heart's ventricles. In contemporary clinical practice, vagal nerve stimulation has been employed in the treatment of refractory epilepsy and severe psychiatric depressive disorders. Other procedures targeting the parasympathetic system include blockades of cranial parasympathetic ganglia, such as the pterygopalatine ganglion, for resistant headaches. Additionally, research into complex

sacral parasympathetic nerve stimulation is ongoing for treating patients with spinal cord injuries, aiming to alleviate symptoms like urinary retention.

The aim of this publication is to provide a comprehensive and objective exploration of the anatomical and physiological intricacies of the autonomic nervous system, offering insights into its clinical applications. Within these pages, we meticulously delineate various interventional therapeutic procedures tailored to specific diagnoses related to the autonomic nervous system, aligning each intervention with the anatomical framework of the autonomic system. The efficacy of these procedures is evaluated based on the level of evidence, as per the current recommendations of Evidence-Based Medicine.

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General section

1 THE AUTONOMIC NERVOUS SYSTEM

MUDr. Dušan Rybár, PhD.

The autonomic nervous system (ANS) is a vast neural network that innervates the majority of organs and organ systems within the human body, particularly smooth muscle (internal organs, blood vessels, and skin), cardiac muscle, and glandular tissue. It regulates processes typically beyond voluntary control, such as cardiac function, vascular constriction, smooth muscle tone and movement within organs, glandular secretion, among others. Similar to the somatic nervous system, it comprises an afferent component conveying signals into the system and an efferent component innervating effector organs. However, the ANS doesn't neatly adhere to simple textbook illustrations. Its complexity lies in the extensive branching connections, the variety of neurotransmitters involved, and the intricate organization within peripheral tissues, surpassing that found in central nervous system (CNS) structures.

The initial anatomical observations of a nerve resembling structures with ganglia in the neck and along the spinal cord, emitting delicate, unmyelinated branches to all internal organs, sparked the concept of an intrinsic "sympathy" between the central and distant parts of the nervous system. This notion birthed the name "sympathetic" for this system (SNS). Conversely, the term "vagus nerve" (n. vagus) derives from the trajectory of its myelinated fibers, emanating from the brainstem and then the skull, akin to a "vagus" leading to almost every part of the body. In areas it does not directly innervate, such as the lower abdomen and pelvic region, its function is assumed by myelinated nerves stemming from the sacral segments of the spinal cord.

Functionally and anatomically, both the sympathetic and vagus nerves exhibit a characteristic shared by the autonomic nervous system (ANS): no target organ receives direct innervation from the central nervous system (CNS). The nerve signal, originating from the "first" neuron within the CNS, always synapses with the "second" neuron outside the CNS, typically within a ganglion. The axons of the first neuron, connecting in the ganglion, are termed "preganglionic" fibers, while those of the second neuron, termed "postganglionic," no longer directly innervate the target organ. The vagus nerve's interconnection within ganglia often went unnoticed for some time, as ganglion cells are typically found very close to target organs, often within their walls. This proximity led to

the naming of the parasympathetic nervous system (PNS), with the prefix "para-" indicating "near" or "next to."

It took considerable time for the ANS to differentiate into two functionally distinct systems. The SNS comprises the larger portion of the autonomic nervous system, serving as the prototypical "fight-or-flight" response system, activated during organismal mobilization, stress, and threat. Its broader distribution results in more extensive and less targeted responses compared to the PNS. The SNS activates the cardiovascular and respiratory systems, ensuring adequate nutrient and oxygen supply, particularly to vital organs such as the brain and heart. These events are energy-consuming (catabolic effect). In contrast, the PNS primarily facilitates "rest and recovery," evident in actions such as heart rate reduction, increased glandular secretion, and pupil constriction. These actions conserve energy (anabolic effect), and unlike the SNS, PNS responses are typically localized. The PNS is vital for maintaining hemodynamic homeostasis and counteracts sympathetic activity antagonistically.

Both components of the ANS are present in most organs, where they interact and participate in regulating visceral functions. Despite their cooperative roles, they often exhibit antagonistic effects, with one system exerting inhibitory influence while the other stimulates activity. In addition to the SNS and PNS, the enteric nervous system (ENS) functions as a distinct autonomic system, modulated by the CNS but not under direct control. This combination of sympathetic, parasympathetic, and enteric control provides intricate regulation of individual bodily functions within a tightly integrated framework.

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2 GENERAL NEUROANATOMY OF THE AUTONOMIC NERVOUS SYSTEM

MUDr. Dušan Rybár, PhD.

The anatomical distribution of the autonomic nervous system (ANS) is complex, involving multiple regions of both the central and peripheral nervous systems.

2.1 The Central Autonomic Nervous System

Distinguishing autonomic neural structures from somatic ones at higher levels of the central nervous system poses a significant challenge, typically feasible only for didactic purposes. The highest integrative centers for somatic functions are inseparable from those governing autonomic functions. These centers not only ensure the harmonization of internal organ functions or adaptation to somatic activities but also facilitate adjustments in response to changes in the external environment. Central neurons, responsive to a diverse array of afferent signals, regulate the activity of the autonomic nervous system. Once integrated, this afferent information modulates autonomic efferent activity, facilitating appropriate responses of organ systems to the organism's overall needs. Connections between autonomic forebrain and brainstem centers coordinate the coupling of autonomic efferent signals with higher mental functions.

The central ANS comprises interconnected regions of the forebrain, brainstem, and spinal cord. In the spinal cord, preganglionic sympathetic neurons within the thoracolumbar segments (Th1 to L2) regulate blood pressure, thermoregulation, and vascular flow redistribution during movement or stress. Conversely, parasympathetic neurons in the sacral segments (S2 to S4) govern urination, defecation, and sexual function, while coordinating with thoracolumbar sympathetic signals. The inferior brainstem (bulbopontine) oversees circulation, respiration, gastrointestinal function, and urination, whereas the upper brainstem (pontomesencephalic) integrates autonomic function control with pain and behavioral responses to physiological stress.

The forebrain system includes the hypothalamus, responsible for homeostasis and adaptation, and anterior limbic circuits encompassing the insula, anterior cingulate cortex, and amygdala. These systems integrate bodily sensations with emotionally and goal-directed autonomic outputs. Sympathetic and parasympathetic responses often oppose

each other, reflecting highly coordinated interactions within the CNS. Simultaneous coordination of sympathetic and parasympathetic control enables more precise regulation of target effector systems than stimulation of either system alone would achieve

2.2 The Peripheral Autonomic Nervous System

The peripheral ANS is anatomically more discrete than the central ANS, allowing for its division into the sympathetic, parasympathetic, and enteric nervous systems. Autonomic preganglionic fibers of the first neuron are myelinated (white) and establish connections with the second neuron in the autonomic ganglion. Postganglionic "second" neurons, located in ganglia outside the CNS, send postganglionic unmyelinated (gray) autonomic nerves to innervate organs and tissues throughout the body.

2.2.1 The Peripheral Sympathetic Nervous System

The preganglionic peripheral sympathetic nervous system (SNS) originates from the cell bodies of preganglionic neurons in the thoracolumbar region of the spinal cord. From here, efferent preganglionic fibers, generally short, extend to connect with postganglionic neurons localized in the sympathetic ganglia, collectively forming the sympathetic trunk (truncus sympaticus) with a rope-like alignment of ganglia bilaterally along the paravertebral and prevertebral regions. The paravertebral ganglia are further divided into 3 cervical ganglia (upper, middle, and variable lower or ganglion stellatum), 11 thoracic ganglia, 4 lumbar ganglia, and 4-5 sacral ganglia. Prevertebral ganglia, situated anterior to the aorta and spine, include the celiac, aortico-renal, superior, and inferior mesenteric ganglia. Additionally, there are several previsceral (terminal) ganglia located near target organs throughout the body. Within the sympathetic ganglia, postganglionic neurons receive preganglionic fibers and subsequently send thin, gray, unmyelinated efferent postganglionic fibers to innervate target organs. These postganglionic sympathetic fibers are notably long compared to preganglionic fibers, rendering them susceptible to metabolic and structural damage.

The anatomical distribution and innervation of ganglia generally follow a cranio-caudal order in the organism. For instance, the head and neck receive innervation from cervical ganglia, primarily supplied by preganglionic fibers from the upper thoracic segments of the spinal cord, while the lower limbs are innervated from lower spinal cord segments as well as lumbar and sacral ganglia.

In cases where central command from higher brain centers necessitates autonomic system activation, particularly involving sympathetic pathways, signals must pass through the spinal cord to reach the ganglia, where signal transformation into commands for peripheral organs occurs. This sometimes results in signal pathways deviating unexpectedly, such as when a signal for pupil dilation originating from the hypothalamus travels caudally to the spinal cord before returning via sympathetic fibers to the head to innervate the muscles responsible for dilating the pupils (pupillary reflexes are consensual, occurring equally in both eyes).

A notable feature of the sympathetic trunk is the adrenal medulla, consisting primarily of chromaffin cells capable of oxidizing adrenaline, resulting in a distinct dark brown coloration under chromium influence. These cells, modified ganglion cells lacking their own axons extending to effector organs, secrete adrenaline directly into the venous system, facilitating widespread dissemination of information throughout the body.

Acetylcholine serves as the preganglionic neurotransmitter in the peripheral sympathetic nervous system, acting on nicotinic receptors located on postganglionic neurons. Postganglionic neurotransmission primarily involves norepinephrine, which acts on adrenergic receptors of end effector organs. However, there are exceptions to this neurotransmission pattern: sweat gland fibers release acetylcholine, acting at muscarinic receptors, except in specific areas of hairless skin (palms and soles) where norepinephrine serves as the neurotransmitter. Additionally, acetylcholine acts as the neurotransmitter for postganglionic transmission to chromaffin cells in the adrenal medulla, while postganglionic sympathetic fibers innervating the kidneys release dopamine.

2.2.2 The Peripheral Parasympathetic Nervous System

The efferent fibers of preganglionic neurons in the peripheral nervous system (PNS) exit the central nervous system through the third (III), seventh (VII), ninth (IX), and tenth (X) cranial nerves (vagus nerve) as well as the second, third, and fourth sacral nerves. Unlike

the sympathetic nervous system (SNS), the peripheral PNS lacks a continuous chain of ganglia along the spine. Instead, numerous small ganglia are situated near the terminal target organs, often within their walls. Consequently, preganglionic fibers are considerably longer, while postganglionic fibers tend to be much shorter than those of the SNS.

Parasympathetic fibers originating from the sacral spinal cord arise from the S2-S4 region. These preganglionic fibers extend into the pelvic viscera, where they connect with local ganglia to innervate corresponding effector organs. Sacral parasympathetic fibers play a role in controlling the distal colon, urogenital tract, and sexual function. In contrast to the SNS, acetylcholine in the PNS acts as both a preganglionic and a postganglionic neurotransmitter. Preganglionic receptors are nicotinic, while postganglionic receptors are muscarinic.

2.2.3 The Enteric Autonomic Nervous System

The gastrointestinal tract has traditionally been regarded as one of the many organs innervated by the autonomic nervous system. However, due to its unique characteristics, the gastrointestinal system is now recognized as a distinct component of the ANS, often referred to as the enteric or intrinsic ANS. Unlike other organs, the enteric nervous system possesses its own distinctive ganglionic plexus within the walls of the gastrointestinal tract, which plays a crucial role in modulating its autonomic activity. While receiving both parasympathetic and sympathetic input, the enteric system operates independently with its own intricate network of autonomic ganglia.

Parasympathetic innervation of the gastrointestinal system originates from the craniospinal nerves (vagus nerve and nerves S2 - S4), while sympathetic supply arises from the thoracolumbar region. The enteric system comprises a complex network of autonomic ganglia, forming various plexuses housing millions of cells, roughly equivalent to the cell count of the entire spinal cord. Key plexuses within the enteric nervous system include Meissner's (submucosal) plexus, Auerbach's (myenteric) plexus, Cajal's (deep muscle) plexus, mucosal plexus, and submucosal plexus. Numerous neurotransmitters have been identified within the enteric nervous system, contributing to its intricate regulatory functions.

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3 PHYSIOLOGY OF AUTONOMIC NERVOUS SYSTEM

MUDr. Dušan Rybár, PhD.

Neuroanatomy provides the structural foundation from which the fundamental functions of the ANS are derived; neuroanatomy and ANS physiology are closely intertwined. An overview of the effector functions of the ANS on organs is presented in Table 1.

Organ		**Stimulation of the sympathetic nerve**	**Stimulation of the parasympathetic nerve**
Eye	pupilla m. ciliaris eyelids	mydriasis (m.dilatator pupillae) relaxation (distant view) widely open	miosis (m.sphincter pupillae) constriction (close-up view) closed
Glands	salivary sweaty	mild secretion (thick saliva) ↑ secretion	↑ secretion sweating palms
Heart	myocardium sinus node coronary arteries	↑ strength of contraction ↑ frequency dilatation	↓ strength of contraction ↓ frequency Ø
Vessels	smooth muscles of blood vessels	constriction	Ø
Lungs	bronchi- muscles - glands bronchial arteries	dilatation constriction	constriction ↑ secretion dilatation
GIT	wall muscle	↓ peristalsis constriction	↑ peristalsis dilatation

	sphincters – smooth muscles glands	↓ secretion	↑ secretion
Liver		glycogenolysis	glycogenesis
Adipose tissue		lipolysis	Ø
Gall bladder	muscle bile	constriction ↓ production	dilatation ↑ production
Kidney	urine	↓ production	Ø
Urinary bladder	m. detrusor m. sphnicter vesicae	relaxation constriction	constriction relaxation
Genitals		contraction of blood vessels, ejaculation; secretion of gl. vestib. major; contraction of the uterus; fallopian tube; ductus deferens; glandulae vesiculosae; prostate	vasodilation erection
Skeletal muscles	arterioly metabolism muscle spindles	dilatation increased ↓ sensitivity	Ø Ø Ø
Body temperature		increase	decrease
Immune system		suppression	activation
Piloerection		contraction	Ø

Table 1 Overview of effector functions of the autonomic nervous system (adapted from Schmidtová and Rybárová, 2006; Karemaker, 2017).

3.1 Regulation of Body Temperature

Thermoregulation is a complex process in humans. The hypothalamus regulates body temperature through preoptic and anterior hypothalamic neurons, which are sensitive to cold and heat. Additionally, hypothalamic neurons integrate skin temperature information. These neurons tightly regulate the desired temperature setpoint, but certain situations can alter the body temperature setpoint. For example, the release of pyrogen decreases the sensitivity of neurons to perceive heat while increasing the activity of neurons to perceive cold, leading to an upward shift in the body temperature setting. Conversely, thyrotropin-releasing hormone increases the activity of heat-sensing neurons while decreasing the activity of cold-sensing neurons, causing a downward shift in the body temperature setpoint. If hypothalamic neurons detect a thermal deviation from the setpoint, they initiate a series of actions to stabilize body temperature.

In humans, non-autonomous behavior, such as dressing or undressing and seeking shelter, is one of the primary methods of thermal regulation. Autonomous control of thermal regulation is provided by shivering, non-shivering thermogenesis, modulation of blood flow through the skin, modulation of sweating, and piloerection. Shivering, controlled by the posterior hypothalamus, involves autonomously controlled skeletal muscle contractions that increase heat production despite being mediated by somatic motor nerve fibers. Non-shivering thermogenesis occurs via activation of the sympathetic and sympathoadrenal systems, increasing metabolic activity. Direct sympathetic stimulation of brown fat induces thermogenesis, traditionally considered a neonatal phenomenon; however, recent findings suggest brown fat preservation and functionality even in adults. Control of blood flow through the skin serves as an effective mechanism of thermal regulation. High basal sympathetic tone exists in the limbs; inhibition of this tone leads to extensive peripheral vasodilation. In cold environments, high sympathetic tone causes vasoconstriction of arteriovenous anastomoses and contraction of superficial veins, minimizing heat loss. Conversely, in warm environments, reduced sympathetic tone leads to dilation of arteriovenous anastomoses and superficial veins, facilitating heat loss.

Millions of sweat glands throughout the body, functioning as eccrine glands involved in thermoregulation, release sweat according to the body's needs in response to postganglionic sympathetic cholinergic activation.

3.2 Pupillary Function and Visual Accommodation

The aim of the system is to adjust the size of the pupils according to the amount of light required for proper image formation on the retina. To achieve this, two functionally opposed smooth muscles exist within the opaque iris: the parasympathetic pupillary sphincter and the sympathetic pupillary dilator. This process involves a feedback system, not from the rod and cone feedback system of the retina, but rather from the inner retinal photosensitive ganglion cells. These cells send an integrating signal with information about the strength of illumination to the midbrain, along with signals to two effector muscles. The fastest of these muscles is the sphincter, with its motor nucleus likely located nearby (probably the Edinger-Westphal nucleus within the midbrain oculomotor complex).

The illumination signal operates independently of the connection to the optical cortex in the forebrain, meaning subjective awareness of the signal is unnecessary to elicit a pupillary response to bright light. The parasympathetic function extends beyond pupillary constriction to include innervation of the ciliary muscle, which induces bulging of the lens for near vision. Part of the oculomotor complex, in addition to the entire system of accommodation and pupil constriction, includes the convergence of the eyeballs. Collectively, these functions—miosis, lens accommodation, and convergence—are termed the accommodative reflex.

The parasympathetic nerve pathways responsible for pupillary constriction are fairly well understood. Parasympathetic preganglionic fibers from the Edinger-Westphal nucleus connect to the ciliary ganglion, from where postganglionic fibers travel via short ciliary nerves to the pupillary sphincter muscle. An increase in parasympathetic tone leads to sphincter constriction and subsequent pupil constriction.

The sympathetic pathway governing pupillary dilation is less clear. Sympathetic preganglionic innervation from the cervical truncus sympathicus connects to the superior cervical ganglion. Postsynaptic fibers then emanate from the carotid plexus through the optic nerve and continue through the long ciliary nerve to innervate the iris dilator muscles. The dilator signal inhibits parasympathetic (contractile) fibers and simultaneously stimulates dilator fibers, resulting in pupil dilation. Additionally, the parasympathetic signal can be inhibited at the midbrain level via the adrenergic pathway. The primary impulse for pupil dilation remains uncertain. Lack of light as a stimulus for

dilation is considered, or it may result from relaxation of the sphincter muscle. The maximum pupil size in darkness may be due to central sympathetic tone, reflecting mental excitation or rest.

Pupil diameter thus reflects the activity of the feedback system, regulated by the parasympathetic efferent pathway, with the ability to adapt to internal and external environments (such as escape, fight, and fear) under sympathetic control.

3.3 Heart and Heart Rate Variability

The heart receives innervation from both the sympathetic and parasympathetic nervous systems, primarily through the cardiac plexus located around the atria. These sites serve as integrative centers, where efferent autonomic signals and afferent cardiac signals (related to contraction and interstitial status) converge to regulate heart rate and cardiac function. Parasympathetic innervation, mainly responsible for regulating heart rate, acts swiftly and dominantly. The sinoatrial node alone generates an intrinsic heart rate of approximately 100 excitations per minute. Thus, for most of the day, the heart is primarily under parasympathetic control, maintaining a heart rate (HR) within the range of 60 to 100 beats per minute. During exercise, however, heart rate increases, reaching a maximum value of around 208 - 0.7 x age.

In a healthy individual, the primary determinants of heart rate variability are blood pressure, mediated through the baroreflex pathway, and respiration. The nervous system exhibits ubiquitous activity induced by pulse pressure, whereby mechanoreceptors in the walls of large arteries respond to the pulse wave, triggering baroreceptor afferent nerves (Figure 1). This leads to immediate vagal efferent responses aimed at dampening heart rate. The average resting heart rate results from repetitive vagal modulation, alongside sympathetic and hormonal activity. Changes in pulse rate or mean pressure are quickly reflected in vagal efferent activity, affecting heart rate within the same beat at resting rates below about 75 beats/min.

Parasympathetic activity not only influences heart rate but also significantly reduces atrial contractility, and to a lesser extent, ventricular contractility. It also decreases excitation conduction rates through the AV node, atria, and ventricles. This effect can be beneficial in conditions like reentry tachycardia, where vagal stimulation, such as carotid sinus massage, can slow conduction velocity and halt tachycardia.

The sympathetic nervous system innervates the entire heart, including the atria, sinoatrial and atrioventricular nodes, and ventricles. Activation of β-adrenergic receptors by circulating adrenaline and locally released noradrenaline increases heart rate and contraction force, but also elevates metabolic demands. Consequently, sympathetic activation may exacerbate conditions with impaired coronary circulation.

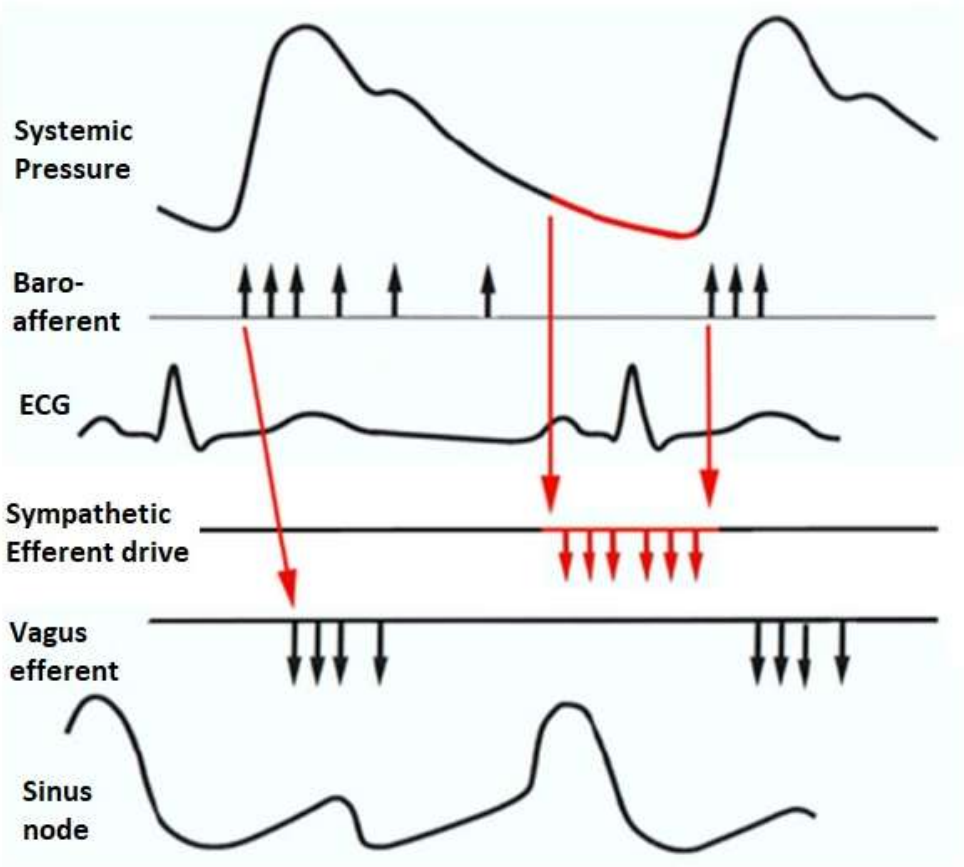

Figure 1 Feedback Effect of Pulse Pressure Wave on Heart Rate (adapted from Karemaker, 2017).

3.4 Regulation of Blood Pressure

To ensure efficient nutrient flow through microvessels, a pressure higher than the colloid osmotic pressure of plasma (approximately 28mmHg) is required. Considering pressure losses in supply arteries and draining venules and veins, the mean driving arterial pressure should be at least 50mmHg. This figure must be higher when accounting for the needs of the kidneys, which require higher driving pressure due to the ultrafiltration process in the glomeruli. Thus, in the supine position, the minimum mean blood pressure required is at

least 65 mmHg. Additionally, in the upright position, the hydrostatic pressure difference between the head and the heart must be added, resulting in a minimum required mean pressure of about 75 mmHg at heart level.

The autonomic nervous system (ANS) plays an active role in maintaining this pressure. Ohm's law for circulation states that pressure equals cardiac output multiplied by resistance, where cardiac output equals pulse volume multiplied by heart rate. Therefore, vascular resistance, heart rate, and pulse volume are the determinants of blood pressure control. Blood vessels, except for a few specialized systems, are richly innervated only by sympathetic nerves, making the sympathetic nervous system the major regulator of blood pressure. It cooperates closely with local mechanisms to distribute blood flow to meet oxygen and nutrient demands.

Smooth muscle cells in the vessel wall's media are the active components that modulate vessel diameter. Depending on vessel localization, the walls have varying amounts of smooth muscle cells. α- or β-receptors and purinergic receptors occur in different blood vessel subtypes depending on tissue. Sympathetic activity can lead to vasoconstriction or dilation, depending on the tissue's needs.

Central blood pressure control mechanisms require afferent signals mainly from baroreceptive areas sensitive to arterial stretching. These signals respond not only to pressure but also to perfusion efficiency. Postural changes from lying to upright posture cause fluid transfer from the chest to the lower limbs due to gravity, resulting in increased hydrostatic pressure in the lower limbs and splanchnic vessels. This leads to a reduction in venous return, cardiac output, and blood pressure.

Changes in arterial blood pressure activate baroreceptors in the sinus caroticus and the aortic arch, which are mechanoreceptors located in blood vessel adventitia. These baroreceptors signal to the central nervous system through excitatory pathways to regulate peripheral vascular resistance and cardioinhibitory action, ultimately modulating blood pressure. Efferent signals from the central nervous system lead to sympathetic vasoconstriction and parasympathetic control of heart rate. However, an increase in heart rate alone may not suffice to maintain adequate cardiac output as blood pressure falls.

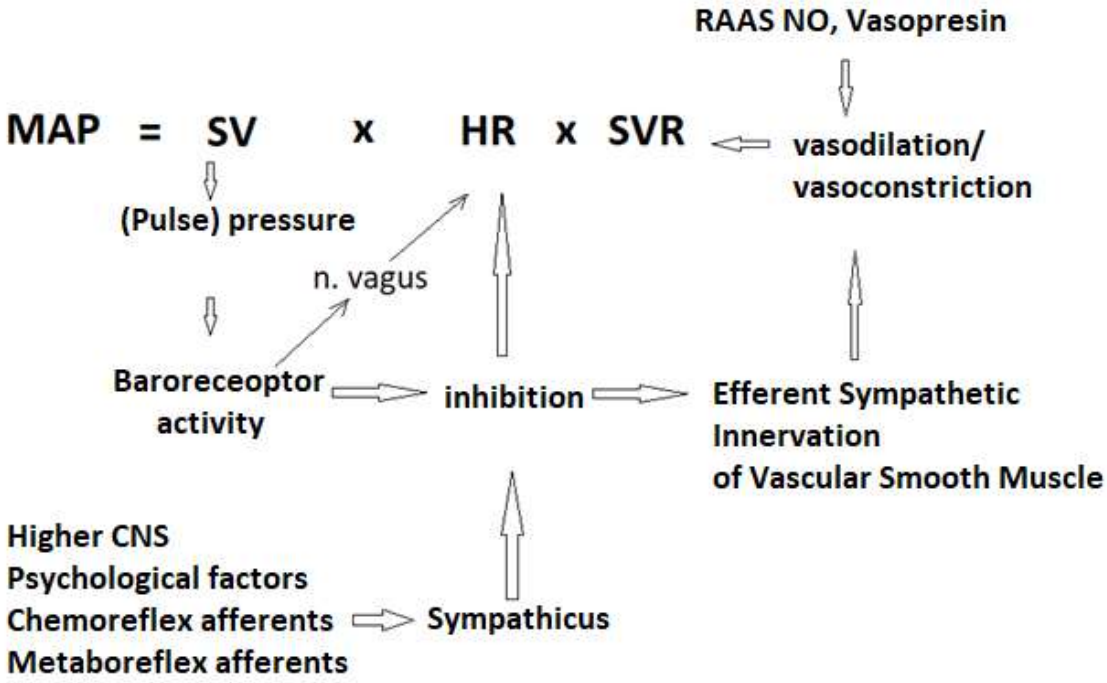

Figure 2 Autonomous Control of Circulation and Its Main Parameters (adapted from Karemaker, 2017).

3.5 The Lungs and Ventilation

The functional pulmonary circulation is a low-pressure system not involved in nutritional circulation; rather, its goal is to saturate flowing blood with oxygen and remove carbon dioxide. Nutritional circulation is provided by the systemic circulation through the tracheal and bronchial arteries. Therefore, the action of the autonomic nervous system (ANS) on the lungs is twofold, depending on whether it regulates the functional circulation or the lungs themselves.

The lungs are autonomously innervated by both sympathetic and parasympathetic (via the vagus nerve) nerves. Their primary influence is on airway diameter regulation, but they also innervate the pulmonary vasculature. Diseases characterized by increased airway resistance, such as bronchial asthma or chronic obstructive pulmonary disease, are well known, while an increase in pulmonary vascular resistance leading to pulmonary hypertension occurs late in disease progression.

During the normal respiratory cycle, sympathetic and parasympathetic efferent signals act in counter-phase: sympathetic activity during inspiration dilates the airway, while parasympathetic activity during expiration likely stiffens the airway, preventing collapse.

However, this activity may also relate to glandular function. Recent studies have implicated vagal nerve activity in the development of postoperative acute respiratory distress syndrome (ARDS) as a factor increasing airway resistance.

Respiration rate and depth adapt to momentary needs and are regulated by a system where chemoreceptors (peripheral carotid and aortic bodies and central ones on the ventrolateral surface of the medulla oblongata) provide afferent signals, and the diaphragm and intercostal muscles act as effectors for inspiration. Breathing also involves voluntary control, such as using exhaled air compression to produce voice.

Respiratory rate variability (RRV) and heart rate variability (HRV) resemble each other due to feedback delay and changes in central nervous system (CNS) tone, despite operating at different basal frequencies. The "natural frequency" of RRV may be around 30-60 s, similar to the frequency of recurrent sleep apnea or breathing patterns in Cheyne-Stokes breathing.

During inhalation, alveoli expand, left atrial pressure decreases, and pulmonary microcirculation compliance increases, resulting in decreased left ventricular output and blood pressure, triggering a baroreflex-mediated increase in heart rate. Conversely, during exhalation, left ventricular output and blood pressure increase, leading to a decrease in heart rate under the influence of respiratory centers. This synchronization between breathing and heart rate can become mutually dependent, particularly during sleep when the coupling is tight and varies during waking hours depending on volitional activities.

3.6 Gastrointestinal Functions

The gastrointestinal tract ensures the digestion, absorption, and transport of nutrients and metabolic products within the body. Several systems are involved in the digestive process. The entire process of digestion commences with the secretion of saliva. Taste and smell activate afferent nerves that transmit signals to the secretory centers of the medulla oblongata. Efferent preganglionic parasympathetic fibers run through the facial nerve to the submaxillary and sublingual glands and through the glossopharyngeal nerve to the parotid gland. Parasympathetic fibers connect in local ganglia near the glands, from which postganglionic fibers directly stimulate the salivary glands. Sympathetic fibers originating from the medulla oblongata connect in the cervical truncus sympatheticus,

from where postganglionic sympathetic fibers directly innervate the myoepithelial cells of the salivary glands. Parasympathetic fibers stimulate saliva secretion, while sympathetic fibers stimulate myoepithelial cell contraction and saliva secretion. Gastric secretion triggers oral and gastric vagal afferent signals that reach the medulla oblongata, from where efferent vagal activity stimulates neurons of the intestinal submucosal plexuses, leading to the activation of secretory intestinal cells. Similarly, reflex autonomic pathways stimulate the secretion of pancreatic juices and bile. Intestinal peristalsis is under the control of the enteric nervous system, which is, however, modulated by parasympathetic efferent signals (vagus nerve and sacral parasympathetic pathways) and the thoracolumbar sympathetic system. Parasympathetic signals are primarily excitatory, while sympathetic signals are primarily inhibitory (though excitatory to the sphincters). Efferent signals to the enteric nervous system provide information for local gastrointestinal plexuses where motor or secretory function is integrated. For example, parasympathetic signals stimulating contractions are transmitted along the transverse and longitudinal axis of the intestine by interstitial Cajal cells to coordinate them. This creates efficient intestinal motility in the oral-aboral direction. Smooth muscle coordination during eating and gastrointestinal function is modulated by the sympathetic and parasympathetic pathways, but local control is maintained through the enteric nervous system. Even in cases of complete efferent denervation, local control of peristalsis by the autonomous cells of the intestine is preserved. During swallowing, the lower esophageal sphincter opens and remains open for approximately 8 seconds until the food bolus passes into the stomach. The sphincter then closes to prevent reflux. The enteric nervous system also coordinates cyclic patterns of contractility to maintain normal intestinal function, comprising a period of rest (also known as phase 1), a period of intermittent contractility (phase 2), and a period of maximal contractility (phase 3). Defecation occurs through a coordinated series of sympathetic and parasympathetic signals to the intestinal system. Sacral parasympathetic efferent fibers inhibit the anal sphincter and increase intra-intestinal pressure. Lumbar sympathetic fibers cause contraction of the internal and external anal sphincters to maintain continence.

3.7 Bladder Regulation

Bladder function involves two general scenarios: retention of urine without incontinence and timely voiding. Parasympathetic stimulation promotes urination, while sympathetic activity causes urinary retention. Urinary retention is modulated by sympathetic and pudendal nerve reflexes from the lumbosacral spinal cord. The sympathetic pathways originate from the preganglionic fibers of the thoracolumbar segments, which pass to the truncus sympatheticus, then to the prevertebral ganglia in the hypogastrium, and finally to the pelvic plexuses. Postganglionic sympathetic fibers innervate the smooth muscle of the urethra and the base of the bladder, contracting the urethra and external urethral sphincter to prevent incontinence. Inhibitory sympathetic impulses also inhibit urination by innervating the rest of the bladder and vesicular parasympathetic ganglia. As urine collects in the bladder, afferent signals decrease, stimulating sympathetic innervation of the bladder outlet and the external urethral sphincter. Afferent signals from the bladder to the periaqueductal gray ensure voluntary initiation of micturition. This activates the spinobulbar pathways, resulting in parasympathetic stimulation of the bladder (excitatory) and inhibitory stimulation of the urethral smooth muscle. Urine emptying begins with a decrease in intraurethral pressure, relaxation of the pelvic floor, detrusor contraction, and increased intravesicular pressure until the bladder is emptied.

3.8 Sexual Functions

Male and female sexual functions differ in many ways, but the autonomic pathways and physiology are similar in both sexes. Sexual arousal, blood flow in clitoral and penile tissue, detumescence, gland secretion, and muscle contraction are similar in men and women. The central nervous system, with its paraventricular nucleus and limbic system, is involved in sexual arousal and tissue perfusion, while afferent pathways from the spinothalamic tract transmit sensation, which is then integrated into the CNS to achieve and modulate resulting arousal. Tissue perfusion depends on vasomotor activity, which relaxes the smooth muscle walls via NO as the primary neurotransmitter. NO is released from nonadrenergic, noncholinergic parasympathetic nerves and from the endothelium lining cavernous sinusoids and blood vessels (mediated by cholinergic stimulation). Noradrenergic nerve fibers release noradrenaline, which, by acting on alpha-1 receptors,

causes contraction of arterioles and smooth muscle, maintaining tissue flaccidity, while cessation of noradrenaline secretion aids in tissue erection. Contraction of smooth muscles in the epididymis, vas deferens, vesiculae seminales, and prostate causes the emission of semen (mediated by sympathetic fibers), while ejaculation consists of rhythmic contractions of bulbocavernous, ischiocavernous, and periurethral striated muscles mediated by parasympathetic fibers.

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Special section

1 EVIDENCE-BASED MEDICINE

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When determining a patient's treatment method in clinical practice, decisions are made based on our own clinical experience, the best scientific medical knowledge, and the patient's needs and wishes. These three pillars form the basis of evidence-based medicine (EBM), and all three aspects must be taken into account when treating the patient.

Scientific evidence and knowledge are distinguished based on their relevance to the treatment of a given disease and are crucial for minimizing erroneous decisions by medical personnel in providing healthcare. Individual levels of evidence are represented using the so-called Haynes' pyramid, which depicts the strength of given claims in ascending order based on the methodology of collected and evaluated data.

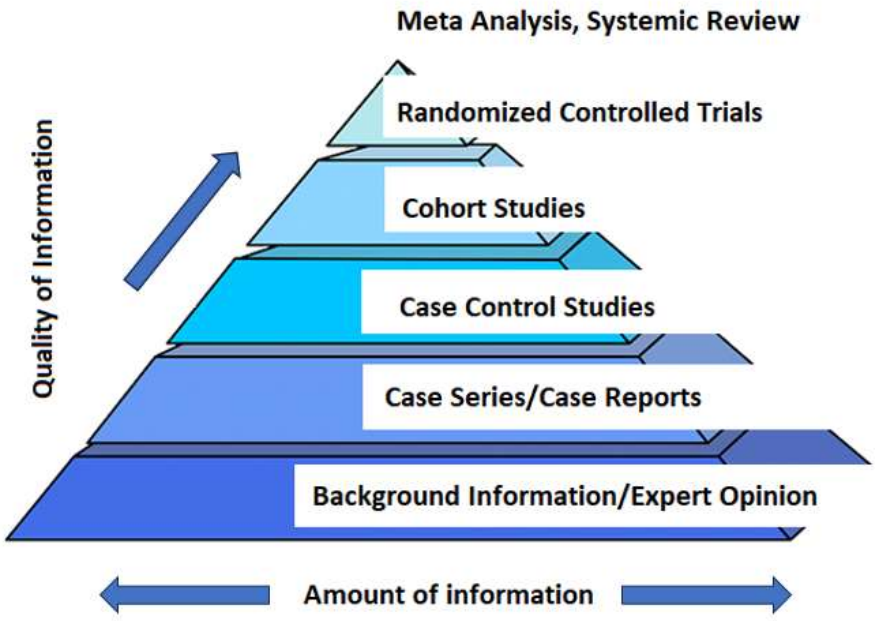

Figure 3 Haynes' Pyramid of the Strength of Medical-Based Evidence (Kočan, 2015).

At the lowest level are expert opinions, case reports, and case series. Expert opinions and individual experiences bring new perspectives to medical problems, which may warrant further research. However, their initial conclusions cannot be generalized in common practice. Case reports highlight unique cases, such as rare diseases, unconventional treatments, or intriguing outcomes that may offer valuable insights or considerations for treatment.

Cross-sectional (population) studies point to potential correlations between different factors, but they do not establish causality (cause-effect relationship). Retrospective studies suggest possible correlations between outcomes and past influencing factors, but causality cannot be established.

Cohort studies (prospective) compare groups of individuals with and without specific characteristics, behaviors, or interventions. These observational studies help assess potential associations but do not establish causality.

Randomized controlled clinical trials are considered the gold standard of clinical research. They involve dividing a group of participants into two groups through random selection. One group receives the active treatment or intervention, while the other serves as the control group, receiving a placebo or sham intervention. Randomization ensures that any resulting differences can be attributed to the phenomenon under study.

Systematic reviews and meta-analyses represent the highest level of evidence. They synthesize and evaluate the findings of multiple studies, both randomized trials and observational studies, to provide a comprehensive overview of the evidence. Systematic reviews offer greater accuracy and statistical reliability by summarizing studies with similar methodologies.

The evaluation of evidence within EBM can be interpreted using different systems, such as "hierarchies of evidence" or "evidence grading systems." These frameworks help assess the quality and strength of evidence from scientific studies and guide decision-making in clinical practice, policy development, and guideline formulation. Two commonly used systems are the **GRADE System and the Benefit/Risk Assessment System.**

1.1 GRADE System

The GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation) is often used to evaluate the quality of evidence and the strength of recommendations in clinical guidelines. It classifies evidence as: high (A), moderate (B) or low (C) quality based on study design, risk of bias, inconsistency, indirect evidence, imprecision and publication bias.

In general:

Level of Evidence A Data derived from multiple randomized clinical trials or analyses.

Level of evidence B Data derived from a single randomized clinical trial or large non-randomized studies.

Level of evidence C Expert consensus and/or data derived from small studies, retrospective studies, registries.

Furthermore, this system, behind the level of proof, refers to the so-called classes (I, IIa, IIb, III). These classes indicate the strength of the recommendation. Class I represents strong evidence and a high level of certainty, while classes IIa, IIb, and III indicate decreasing levels of certainty and strength of evidence.

In general:

Class I Evidence and/or general agreement that a given treatment or intervention is beneficial, useful and successful.

Class II Conflicting evidence and/or differing opinions on the usefulness/efficacy of a treatment or intervention.

Class IIa The preponderance of evidence/opinion is on the side of usefulness/ of effectiveness

Class IIb Usefulness/effectiveness is less well supported by evidence/opinion.

Class III Evidence or general agreement that a given treatment or intervention is not useful/effective and in some cases may be harmful.

1.2 Benefit/risk Assessment System

Scales (A, B, C): Similar to the GRADE system, these scales represent the quality of evidence, with A representing the highest quality and C the lowest.

To express the "benefit/risk" value, the system assigns a numerical value of 1 if the benefit due to the effectiveness of the treatment was greater than the risk associated with possible complications. A value of 2 is assigned by the system when the benefit of the effect has been closely balanced with the risk of potential side effects.

Evaluation of results (positive, negative, ±): This system additionally determines the level of treatment benefit through symbols by categorizing results as positive, negative, or a combination of both (±). The symbol (±) is used when both positive and negative studies are considered.

1A+	One or more RCTs with methodological weaknesses demonstrate effectiveness. The benefits clearly outweigh the risks and burdens.	Positive recommendation
1B+	The effectiveness demonstrated in various Randomized Controlled Clinical Trials (RCTs) is of good quality. The benefits clearly outweigh the risks.	
2B+	One or more RCTs with methodological weaknesses demonstrate effectiveness. However, the benefits are closely balanced with the risks and burdens.	
2B±	Multiple RCTs, with methodological weaknesses, yield contradictory results, either better or worse than the control treatment. Benefits are closely balanced with risks and burdens, or there is uncertainty in the estimates of benefits, risks, and burdens.	Considered, preferably study-related
2C+	Effectiveness is only demonstrated in observational studies. Since there is no conclusive evidence of the effect, the benefits are closely balanced with risks and burdens.	
0	There is no literature available, or there are only case reports, but these are insufficient to prove effectiveness and/or safety. These treatments should only be applied in studies.	Only study-related
2C-	Observational studies indicate no effectiveness or only short-lived effectiveness. Given the lack of positive effect, the risks and burdens outweigh the benefits.	Negative recommendation
2B-	One or more RCTs with methodological weaknesses, or large observational studies, do not indicate any superiority to the control treatment. Given the absence of a positive clinical effect, the risks and burdens outweigh the benefits.	

Table 2 Benefit/risk assessment system (Van Zundert, 2011).

In the following text, we will describe intervention procedures for selected clinical diagnoses in which the autonomic nervous system plays an important role. Considering that the given diagnostic-therapeutic method often has an adjuvant, complementary character, the level of evidence and its class taking into account the resulting effect within the general recommendations of evidence-based medicine will be expressed in the

description of the selected procedures, either using the GRADE system or the Benefit/Risk Assessment System.

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2 THE AUTONOMIC SYSTEM OF CERVICO-THORACIC REGION IN CLINICAL PRACTICE

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The autonomic nervous system in the cervico-thoracic region comprises the sympathetic part, which includes three pairs of cervical sympathetic ganglia, twelve pairs of thoracic ganglia, sympathetic nerve fibers accompanying the spinal nerves, and separate sympathetic nerves. Its counterpart is the parasympathetic nervous system, which consists of the innervation of the paired vagus nerve (nervus vagus, n.X.) and its branches. Branches of both nervous systems form common mixed nerve plexuses near the target organs, such as the heart, lungs, and esophagus. The function of the autonomic system is highly complex, involving regional regulatory mechanisms such as vasomotor regulation and the conduction of sympathetic-mediated pain in pathological conditions. Simultaneously, the autonomic nervous system plays a role in controlling global regulatory functions involving vital organs and organ systems, such as the adaptation of the cardiovascular and respiratory systems to stress responses.

An example showcasing the versatility and interconnection of various adjacent and distant anatomical structures is the inferior cervico-thoracic sympathetic stellate ganglion, which is involved in controlling many systems. Dysfunction or abnormal activity of this ganglion can lead to sympathetic hyperactivity, potentially contributing to conditions such as tachycardia and cardiac arrhythmias. Additionally, the ganglion regulates the vasomotor function of blood vessels and innervates tissues in the upper limb, playing a crucial role in the development of pathological conditions following trauma.

2.1 Stellate Ganglion

Peripheral innervation originating from the sympathetic cervical trunk, which accompanies major blood vessels along with parasympathetic nerve fibers, forming the internal and external carotid plexus, is clinically significant. These branches play a crucial role in transmitting impulses from the carotid sinus to the glomus caroticum. Additionally, branches from the C1-C7 spinal nerves innervate the skin, vessels, neck musculature, upper limb, and hand. Nerve branches from the middle and inferior ganglia,

which descend to the cardiac plexus and, together with parasympathetic branches, mediate autonomic innervation of the heart, are also important.

From a therapeutic standpoint, the stellate ganglion, also known as the cervicothoracic ganglion, holds significance. Due to its unique connection with the visceral and somatic systems of the body, interventions targeting this anatomical structure are valuable from diagnostic, prognostic, and therapeutic perspectives across medical disciplines such as interventional pain management (a specialty focused on treating chronic pain), cardiology, and arrhythmology.

Stellate ganglion blockade is employed for diagnosing and treating clinical conditions such as complex regional pain syndrome, ventricular tachycardia, and refractory angina. It is also used to assess the prognosis of the treatment effect before implanting a spinal cord stimulator.

2.2 Ventricular Tachycardia

Interventions targeting the stellate ganglion are employed during what are known as arrhythmogenic storms. These storms entail persistent runs of ventricular tachycardia, despite exhaustive antiarrhythmic drug therapy and defibrillation attempts. Ventricular tachycardia is considered one of the most severe cardiac rhythm disorders and is typically evaluated as an emergent clinical condition, often diagnosed via EKG. The severity of ventricular tachycardia and its clinical impact on the patient depend on its duration. During ventricular tachycardia, ventricular contractions during systole occur very rapidly and ineffectively.

A brief episode may be asymptomatic, but with prolonged duration, clinical manifestations such as hypotension and decreased tissue perfusion can occur, potentially leading to syncope or even death. Further deterioration can occur if ventricular tachycardia transitions into ventricular fibrillation or asystole. Most patients with ventricular tachycardia have significant underlying cardiac abnormalities such as myocardial infarction or cardiomyopathy. Possible triggers of ventricular tachycardia include electrolyte abnormalities (especially hypokalemia or hypomagnesemia), acidosis, hypoxemia, and side effects of certain drugs that prolong the QT interval and may contribute to its development. Prolonged QT interval syndrome (whether congenital or

acquired) is associated with a specific form of ventricular tachycardia known as "Torsades de pointes."

Ventricular tachycardias can be classified based on the possible foci in the myocardium into monomorphic or polymorphic. Monomorphic ventricular tachycardia originates from a single abnormal focus, resulting in regular occurrence of identical QRS complexes. Polymorphic ventricular tachycardia, on the other hand, arises from several different foci in the myocardium, leading to irregular QRS complexes of varying shapes. In general, ventricular tachycardia can lead to hemodynamic collapse and often progresses to ventricular fibrillation followed by cardiac arrest.

Treatment of ventricular tachycardia, aside from very brief episodes, typically involves cardioversion and antiarrhythmic drugs depending on the symptoms. After successful stellate ganglion blockade with a local anesthetic, procedures such as radiofrequency ablation of the ganglion or chemical lysis with 6% phenol may be performed. Patients are often considered for long-term treatment with an implantable cardioverter-defibrillator.

2.3 Refractory Angina Pectoris

Dysfunction of the autonomic nervous system is implicated in the pathogenesis of cardiovascular diseases, including congestive heart failure, cardiac arrhythmias, and plays a pivotal role in the cascade of pathophysiological events leading to coronary artery disease.

The treatment strategy for cardiovascular diseases aligns with the current recommendations of the European Society of Cardiology (ESC). For refractory angina pectoris (RAP), one of these nosological entities, interventions aimed at sympathetic nervous system blockade are recommended directly in the diagnostic and therapeutic process.

RAP is a clinical entity associated with chronic coronary artery disease, characterized by myocardial ischemia that cannot be adequately managed by a combination of drug therapy, angioplasty, or coronary artery bypass grafting. Despite advancements in revascularization procedures and pharmacotherapy, RAP remains a significant medical challenge with a high incidence and prevalence, even in developed countries.

Its prevalence in the population is estimated at 6%, representing 2.5-8% of patients with coronary artery disease. Patients with RAP experience significantly reduced quality of

life due to anginal pain, limitation of normal daily activities, and psychosocial stress. Most RAP patients are relatively young, predominantly male, without severely reduced left ventricular ejection fraction, 3-vessel coronary involvement, or post-MI status. Paradoxically, they exhibit low annual cardiac mortality rates (5-7%), primarily due to the low incidence of malignant arrhythmias. Therefore, while none of the current RAP therapies have demonstrated a positive impact on mortality, the relatively low cardiac mortality and the age of the patients emphasize the importance of improving quality of life.

Several non-pharmacological treatments have been proposed for RAP, but only three have relevant medical evidence according to current recommendations: external counterpulsation, and two neurostimulation methods - transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS). SCS, an advanced therapeutic method, involves implanting electrodes in the epidural canal connected to an electrical impulse generator. Its mechanism of action is complex and involves modulation of the autonomic nervous system. Prior to SCS implantation, bilateral stellate ganglion blockade is typically performed as a prognostic measure. The therapy for RAP using SCS is assessed in the 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes, with a **class IIB recommendation** and **level of evidence B**. A more detailed explanation of the mechanism of action of SCS will be provided in the chapter on neuromodulation techniques.

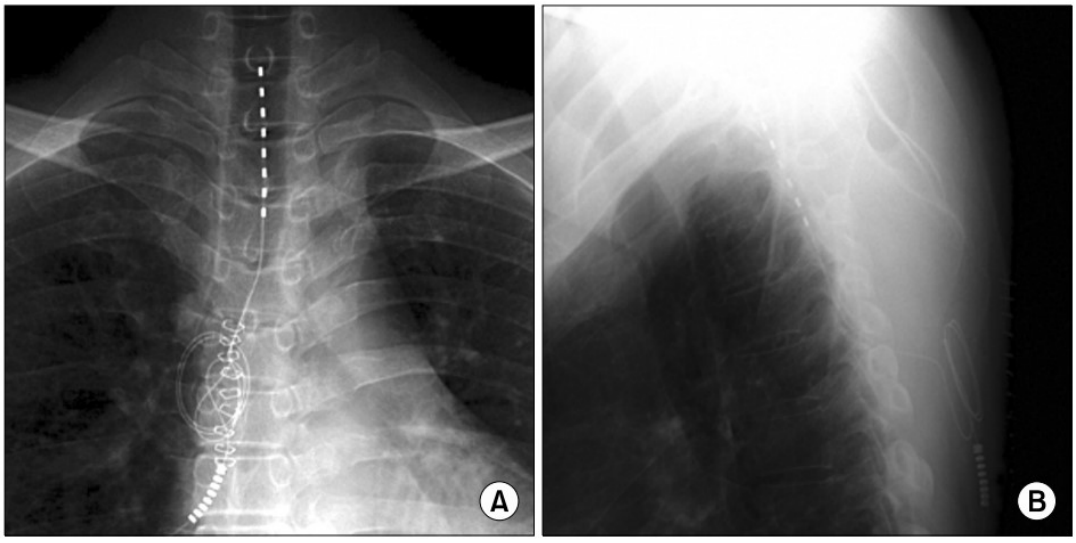

Figure 4 X-ray demonstrating the position of implanted thoracic SCS electrodes in a refractory angina patient (A) AP projection and (B) lateral projection (Lee, 2012).

2.4 Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a chronic progressive painful disease that affects the skin, muscles, joints, and bones. It can develop in the injured part of a limb as a severe complication after trauma or following a surgical procedure. Type I and Type II CRPS are distinguished by their association with tissue and nerve damage in the limb.

Type I CRPS typically develops after initial damage to a limb and is not confined to the area of a single peripheral nerve. Symptoms of Type II CRPS are similar to those of Type I, but with the presence of peripheral nerve damage and subsequent focal deficit, along with autonomic manifestations in the innervation area of the damaged nerve.

Generally, burning pain of constant or variable intensity is present, along with allodynia (non-painful stimulus causing unpleasant pain) triggered by light touch or movement, and hyperalgesia (weak painful stimulus causing intense pain). Changes in temperature on the affected limb and alteration in limb color due to differences in blood supply may also occur, along with swelling.

Treatment is complex and involves a multidisciplinary approach utilizing complex pharmacotherapy, interventional procedures, physical therapy, and psychological support. Interventional procedures play a crucial role, including selective nerve blockades, neuraxial blockades, and sympathetic blockades (stellate ganglion blockade for CRPS in upper limbs, and lumbar sympathetic blockade for CRPS in lower limbs). In cases where individual therapeutic procedures fail, spinal cord stimulator (SCS) implantation may be considered. The mechanism of action of SCS will be described in more detail in the chapter on neuromodulation techniques.

According to evidence-based medicine (EBM) publications, recommendations for individual interventions in the treatment of CRPS are based on a benefit/risk rating system:

Stellate ganglion block: **Recommendation class 2B+**

Brachial plexus block: **Recommendation class 2C+**

Epidural infusion analgesia: **Recommendation class 2C+**

Spinal cord stimulation (SCS): **Recommendation class 2B+**

Peripheral nerve stimulation: **Recommendation class 2C+**

2.5 Stellate Ganglion Block

A stellate ganglion block can be performed under ultrasound (USG) or X-ray control. The procedure is conducted under aseptic conditions, with the injection site cleaned using a disinfectant and covered with a sterile drape. The physician performing the blockade has the necessary instruments stored on a sterile table. Throughout the procedure, the patient maintains intravenous access, while basic monitoring of EKG, oxygen saturation, and blood pressure is conducted. For ultrasound-guided blockade, a high-frequency linear probe is the most suitable.

When the procedure is conducted under X-ray control, it adheres to principles of occupational safety in an environment with ionizing radiation. Lateral access is preferred in this approach. A sign of successful blockade following the application of local anesthetic or ganglion ablation is the development of Horner's syndrome.

Horner's syndrome, also known as Claude-Bernard-Horner syndrome, is characterized by a triad of miosis, ptosis of the eyelid, and apparent monopthalmos (referred to as the Horner triad). It arises due to disruption of the sympathetic nervous system, which, in the case of a blockade, occurs at the postganglionic level (interrupting nerve excitations in the region of the carotid plexus). Horner's syndrome can also occur at the central level (damage to Budge's ciliospinal center) or the preganglionic level (compression of the cervical sympathetic nerve).

During ultrasound-guided control, the procedure can be conducted using "in-plane" or "out-of-plane" imaging. In "in-plane" imaging, the entire needle course under the probe is visible, while in "out-of-plane" imaging, only the cross-section of the needle under the probe is visible. The positioning of the needle and probe depends on optimal visualization of structures in the ultrasound image. Knowledge of external landmarks significantly facilitates the procedure and reduces its duration.

Due to the presence of numerous nerve structures and vessels in the area, "in-plane" imaging is preferred when advancing the needle through tissue. Typically, nerve blockade is performed with the patient in the supine position. The ultrasound probe is usually placed behind the clavicular head of the sternocleidomastoid muscle (SCM) and above the external jugular vein. In this technique, the needle is advanced from lateral to medial, targeting the musculus longus coli, located inferomedially from the internal carotid artery.

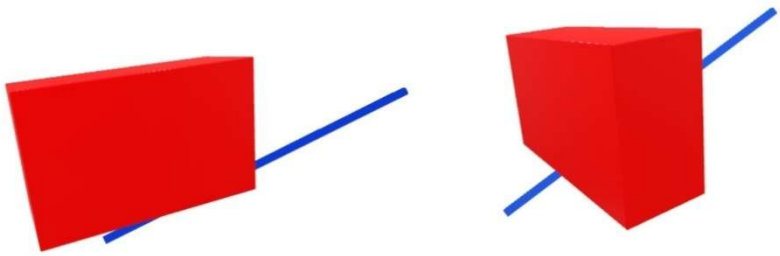

Figure 5 Illustration of the probe position and the needle in “in-plane” imaging (A) and (B) “out of plane” imaging (Author's archive).

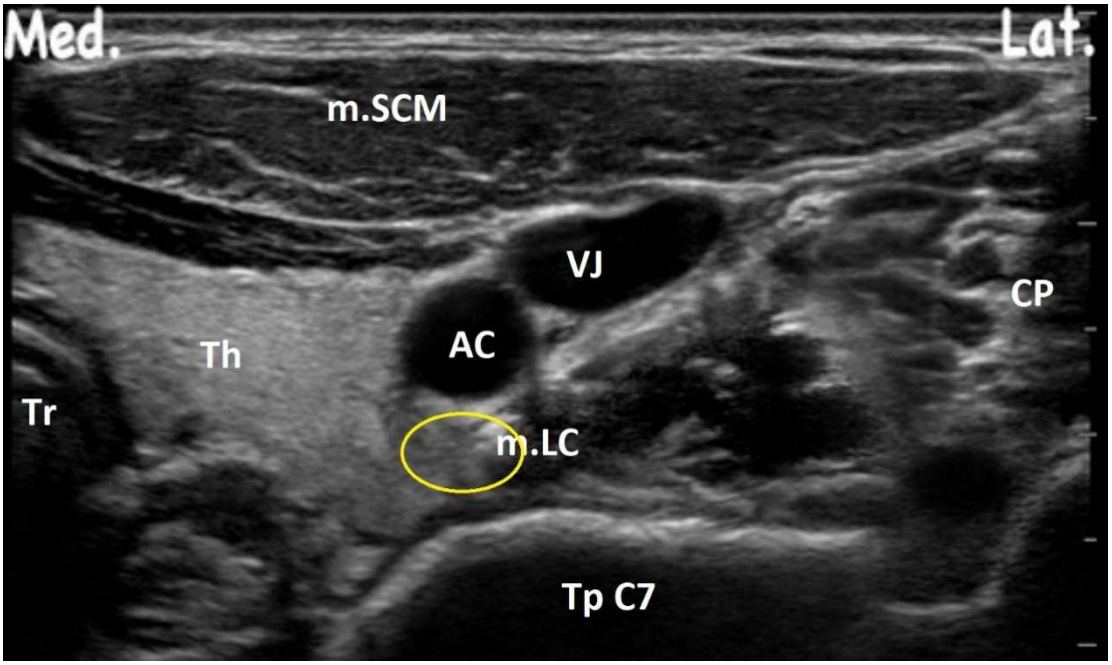

Figure 6 Ultrasound image of visualizing the cervical tissues during a stellate ganglion blockade, Med. Medial side, Lat.-lateral side, AC-internal carotid artery, VJI - internal jugular vein, m.LC - musculus longus coli, m.SCM - sternocleidomastoid muscle, Tr-Trachea, Th - thyroid gland - Tp C7 - transverse process of C7, CP - cervical plexus, yellow circle - target site of tissue infiltration (Author's archive).

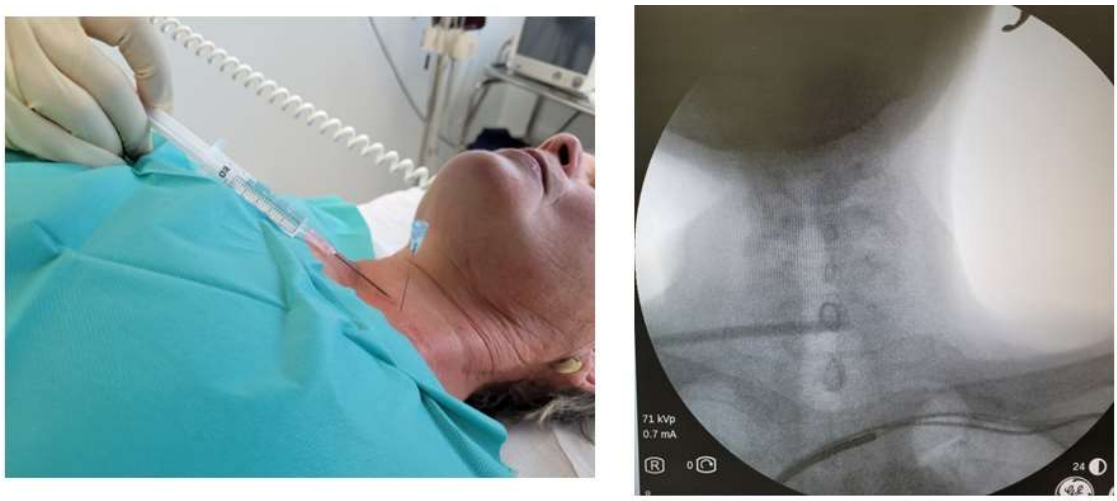

Figure 7 Localization of the needle placement during a stellate ganglion blockade under X-ray control, infiltration of the area with local anesthesia (Author's archives).

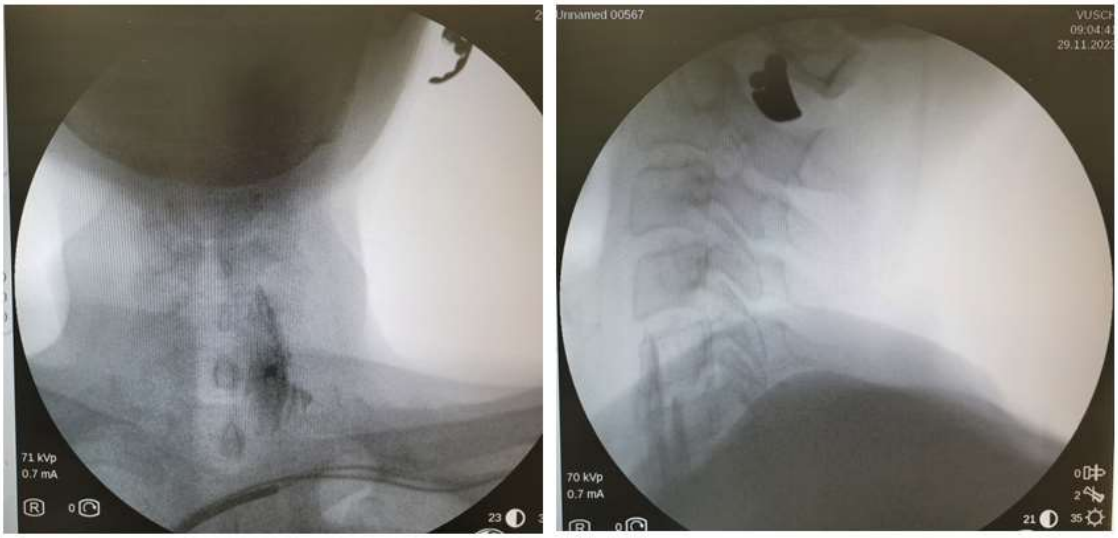

Figure 8 Spread of the contrast in the stellate ganglion area, X-ray control AP and lateral projections (Author's archives).

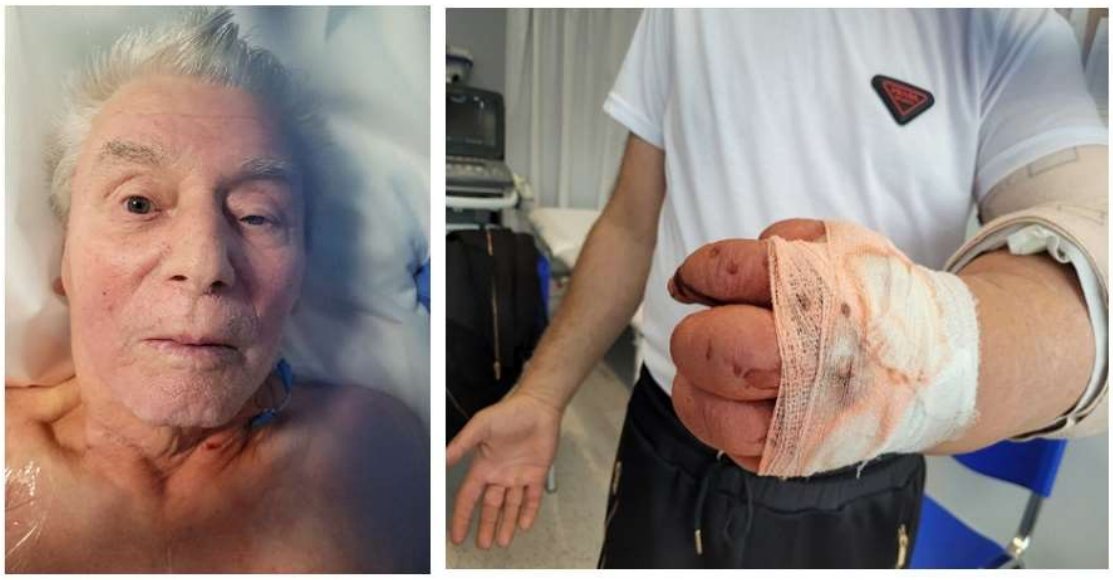

Figure 9 **A**. Horner's syndrome following a stellate ganglion blockade, **B**. patient with complex regional pain syndrome after upper limb trauma (Author's archives published with patient's permission).

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3 AUTONOMOUS CONTROL OF THE CARDIOVASCULAR SYSTEM VIA BARORECEPTORS

MUDr. Ladislav Kočan PhD., FIPP

Baroreceptors are specialized nerve endings sensitive to changes in arterial pressure. They are part of the autonomic nervous system's sensory afferent pathway, monitoring real-time changes in blood pressure. Baroreceptors are activated during blood pressure elevation, causing vessel dilation.

Tissues containing baroreceptors are associated with both sympathetic and parasympathetic components. Vegetative fibers communicate with cardiovascular centers through nuclei in the medulla oblongata, pons, and hypothalamus, maintaining autonomic regulation of the heart and vessels. The brain responds to these signals by initiating adjustments to maintain or restore blood pressure within a normal range.

When blood pressure is too high, the baroreceptor reflex induces a decrease in heart rate (negative chronotropic effect) and vasodilation, both of which lower blood pressure. Conversely, if blood pressure is too low, the baroreceptor reflex increases heart rate (positive chronotropic effect) and induces vasoconstriction to raise blood pressure. Key anatomical locations with a high concentration of baroreceptors include the carotid sinus and the aortic arch.

The carotid sinus, a widening of the common carotid artery, contains a high concentration of baroreceptors that monitor blood pressure. Mechanical stimulation of the carotid sinus, such as during compression, can lead to bradycardia and decreased blood pressure, potentially causing syncope. This condition, known as carotid sinus syndrome, can occur due to external pressure on the neck, such as during shaving or wearing tight clothing.

Another location with a high concentration of baroreceptors is the aortic arch. Baroreceptors play a key role in the short-term regulation of blood pressure through the baroreceptor reflex, which quickly reacts to changes in blood pressure. Dysfunction of baroreceptors and the baroreceptor reflex can contribute to conditions such as orthostatic hypotension or hypertension.

Therapeutic options include carotid sinus massage, a simple bedside maneuver used to diagnose various arrhythmias. Carotid sinus massage is contraindicated in patients with diseased carotid arteries due to the risk of stroke. In some cases, stimulating baroreceptors in the carotid sinus can be used to treat resistant hypertension by activating the baroreflex.

Additionally, a pacemaker-like device can be implanted to chronically stimulate receptors, reducing blood pressure.

However, stimulation treatment of baroreceptors is not recommended for routine use in the treatment of hypertension, according to recommendations of the European Cardiological Society, classified as **recommendation class III**, **level B**.

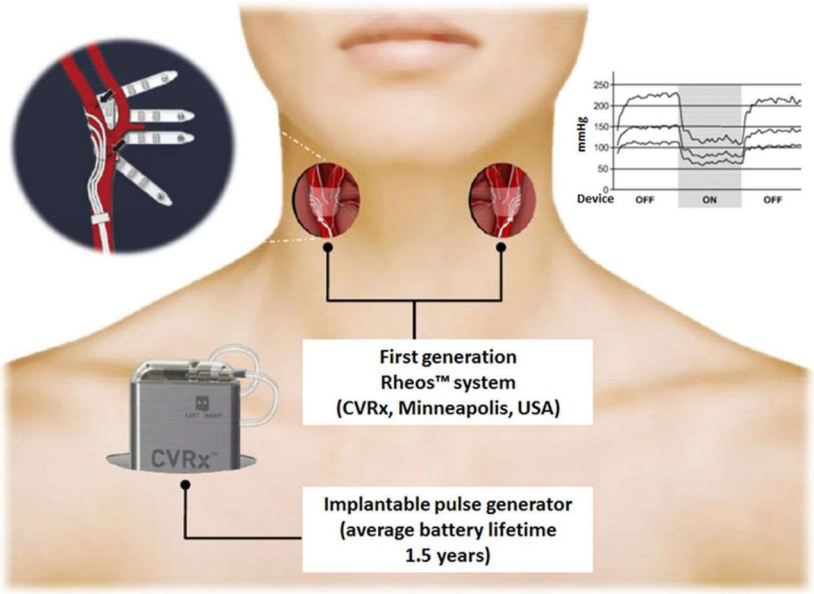

Figure 10 Stimulation of the baroreceptors in the common carotid artery (Ewen, 2017).

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4 AUTONOMIC REGULATION OF THE HEART IN HEART FAILURE

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Heart failure (HF) is a syndrome characterized by enhanced sympathetic nerve activity and dysregulation of the parasympathetic nervous system. This dysregulation is supported by abundant evidence in patients with HF, including increased levels of catecholamines in urine and elevated plasma levels of norepinephrine, all of which correlate with prognosis according to the New York Heart Association (NYHA) classification.

In the 1980s and 1990s, a new hypothesis emerged focusing on the neurohumoral effects on cardiac failure, which underscored the importance of the renin-angiotensin-aldosterone axis. It was discovered that inhibition of this system by inhibitors of the renin-angiotensin-aldosterone axis improves symptoms and reduces mortality in patients with heart failure with systolic dysfunction. The recognition of exhausted sympathetic activity has sparked new discussions regarding the treatment of chronic heart failure with beta-blockers.

The aim of this chapter is to describe the main autonomic system-regulated mechanisms in the myocardium during physiological states induced by a stress reaction, as well as states originating from pathological conditions and cell interactions during heart failure.The aim of this chapter is to describe the main autonomic system-regulated mechanisms in the myocardium during physiological states induced by a stress reaction, as well as states originating from pathological conditions and cell interactions during heart failure.

4.1 Hemodynamic Response to Stressful Situations

During a stress reaction, the autonomic nervous system becomes stimulated, activating the sympathetic nervous system, which plays a regulatory role. The primary mechanisms of sympathetic activation during a stress reaction include stimulation of heart receptors, vessel vasoconstriction, and sodium retention by the kidneys. The activated sympathetic system acts on the heart through three main mechanisms: a positive inotropic effect

(improving muscular contraction), a lusitropic effect (improving diastolic function), and a chronotropic effect (increasing heart rate).

Physiologically, the increase in cardiac output occurs by decreasing end-systolic volume (ESV) and increasing end-diastolic volume (EDV) and heart rate (HR). The equation for calculating cardiac output is CO = (EDV - ESV) × HR. Cardiac output is increased by a positive lusitropic effect, which facilitates ventricular relaxation, thus enhancing diastolic filling of the heart. Other mechanisms that increase cardiac output include increasing heart rate (positive chronotropic effect). Although the heart significantly contributes to adapting to physical strain or shock, this compensatory effect can only be sustained for a brief period.

An essential mechanism of the cardiovascular system is the baroreceptor response to hypotension, which leads to an increase in heart rate. This response occurs during physical exertion, hemorrhagic states, and heart failure. Regulatory centers in the brainstem can be stimulated by peripheral tissues and specifically by receptors monitoring blood pressure. Neural mechanisms may enhance the sensitivity of arterial baroreceptors. Metabolic changes such as hypoxia, hypercapnia, and acidosis result in sympathetic stimulation. These mechanisms are relevant in prolonged bleeding and heart failure.

4.2 Heart Failure: Involvement of the Autonomic System

The pathophysiology of heart failure (HF) is characterized by hemodynamic abnormalities that lead to neurohormonal activation and an imbalance in the autonomic system, specifically an increase in sympathetic activity and a decrease in parasympathetic activity. Activation of the sympathetic nervous system and inhibition of the parasympathetic system have long been considered manifestations of the clinical syndrome of heart failure. The autonomic nervous system fundamentally participates in both acute and long-term hemodynamic events and plays a crucial role in changes in cardiac function and the pathophysiology of heart failure.

A theory describing the involvement of the autonomic system in the pathophysiology of heart failure was formulated in the 1990s. The main evidence supporting this theory was the finding that inhibition of sympathetic stimulation of the heart through β-receptor blockade had a positive effect on the course of cardiac disease. Subsequently, numerous drugs and interventions that could potentially positively influence or activate protective

mechanisms and positively affect the course of heart failure have been studied experimentally.

The cardiac autonomic nervous system consists of sympathetic and parasympathetic systems, which work harmoniously together but exert opposing effects. The principal neurotransmitter of both preganglionic sympathetic and parasympathetic neurons is acetylcholine, while the neurotransmitter of postganglionic sympathetic neurons is norepinephrine (acting on adrenergic receptors). The postganglionic parasympathetic neurotransmitter is acetylcholine (acting on muscarinic receptors). Neurotransmission results in either a stimulatory or inhibitory effect on a given cell. The sympathetic and parasympathetic systems comprise numerous afferent and efferent fibers between the central nervous system and peripheral tissues, with abundant interneuronal connections between the two systems. Sympathetic ganglia innervating the heart mainly arise from the right and left stellate ganglion. These fibers travel along coronary arteries, penetrating the myocardium to the endocardium. Sympathetic terminal fibers end in the myocardial tissue of the atria and ventricles, passing through the sinoatrial (SA) and atrioventricular (AV) nodes and Purkinje fibers. Sympathetic stimulation increases contractility, heart rate, and the speed of electrical activation through the AV node and Purkinje fibers.

Parasympathetic innervation predominantly targets the atria, specifically the SA and AV nodes, with a smaller concentration of fibers in the ventricles, around the coronary arteries, and in Purkinje fibers. Activation of parasympathetic fibers slows the heart rate, the progression of electrical activation through the AV node and Purkinje fibers, and decreases atrial contractility. Parasympathetic effects are mediated by the right and left vagus nerves (nervus vagus, n. X) arising from the brainstem, further divided into superior and inferior cardiac rammi, which connect with postganglionic sympathetic neurons to form the cardiac plexus.

The site of norepinephrine interaction is adrenoreceptors, which produce central and peripheral effects. Adrenoreceptors are connected to G-proteins, exerting their effect through a complex mechanism involving a second messenger in a cascade of intracellular interactions. Alpha-2 receptors typically have inhibitory effects, many being located presynaptically, reducing the release of norepinephrine. Alpha-1 receptors and major types of cardiac beta receptors (β1, β2-receptors) generally have excitatory effects. Adrenoreceptors (ARs) are divided into three groups: α1-AR, α2-AR, and β-AR, each further subdivided into several subtypes. In the heart, β-ARs and α1-ARs are the major

adrenoreceptors, accounting for approximately 90% and 10% of the total number of cardiac adrenoreceptors, respectively.

Evidence from preclinical and clinical studies suggests that α1-ARs mediate adaptive and protective effects in the heart, activating pleiotropic signals that prevent pathological cardiac remodeling in heart failure. These effects may be particularly important in chronic heart failure when catecholamine levels are elevated and β-AR receptors are dysfunctional or inactivated (down-regulated). Subsets of β1- and β2-receptors coexist and functionally cooperate in the heart, with β1-receptors predominant in the myocardium, accounting for 75% to 80% of the total β-ARs. Activation of cardiac β-adrenergic receptors increases heart rate, myocardial contractility, impulse conduction through the AV node, and sinus node activity in the heart.

The primary mediator of the parasympathetic system is acetylcholine, stored in vesicles in presynaptic nerve endings and released upon stimulation. It activates postsynaptic muscarinic and preganglionic nicotinic receptors, with its action terminated by the enzyme acetylcholinesterase. Parasympathetic stimulation decreases cardiac conduction of excitations in the sinoatrial node and AV node without significantly affecting cardiac contractility.

Experimental evidence suggests that stimulation of muscarinic receptors in the heart inhibits the release of norepinephrine from adrenergic nerve endings, potentially modulating cardiac sympathetic activity in heart failure. One of the first responses to myocardial stress or damage is sympathetic nervous system activation, leading to increased norepinephrine release and decreased uptake at adrenergic nerve endings.

These mechanisms in heart failure are centrally controlled and affect other systems and organs besides the heart, such as peripheral circulation and subsequent tissue and organ perfusion. The clinical response is primarily manifested by declining renal function, leading to decreased diuresis and progressive increases in blood urea and creatinine levels. In the acute phase, catecholamines induce increased ventricular contractility and heart rate, aiding in maintaining cardiac output. Systemic vasoconstriction and tonicity of the venous system increase in the initial phase, contributing to maintaining blood pressure by increasing systemic vascular resistance and cardiac overload.

In the kidneys, renal vasoconstriction is induced by angiotensin II action, allowing relatively good maintenance of glomerular filtration despite decreased renal blood flow. Noradrenaline and angiotensin II stimulate sodium reabsorption in the proximal tubule, contributing to fluid accumulation characteristic of cardiac failure. The heart responds to

increased venous return by increasing end-diastolic volume and ejection volume via the Frank-Starling mechanism. Chronic sympathetic stimulation leads to myocyte enlargement, interstitial tissue thickening, and heart chamber remodeling, potentially resulting in left ventricular enlargement.

The activated sympathetic nervous system increases noradrenaline and adrenaline levels during chronic heart failure, resulting in chronic persistent β-AR receptor stimulation, which is significant in heart failure. Cardiomyocyte β-AR receptor function, including mediated signaling, is continuously impaired during heart failure, leading to long-term depletion of cardiac adrenergic reserves. Cardiac β-receptor dysfunction in heart failure is characterized at the molecular level by selective reduction of β1-receptor density at myocyte plasma membranes (downregulation) and disconnection of β1- and β2-receptor links from their coupled G-proteins (functional desensitization). The protective mechanism during long-term β-receptor stimulation is the response provided by GRK (G-protein-coupled receptor kinase) enzyme activity.

GRK is involved in the desensitization process, mediated by the phosphorylation of activated β-adrenergic receptors, which leads to their separation from G-protein, thereby reducing their ability to respond to further stimulation. This process helps regulate the cellular response to catecholamines and maintain homeostasis. Most importantly, in this process, are the subpopulations of GRK2 and GRK5 kinases, predominantly found in the myocardium.

The current consensus is that excessive amounts of catecholamines, originating from the sympathetic nervous system, are produced in chronic heart failure. Catecholamines extracellularly stimulate cardiac β-adrenergic receptors, resulting in intracellular up-regulation of GRK2 in cardiomyocytes. This action ultimately leads to a decrease in the density and sensitivity of cardiac β-receptors and depletion of the cardiac inotropic reserve. The increase in GRK2 likely functions as a homeostatic protective mechanism designed to protect the heart from excessive catecholamine toxicity. In summary, increased sympathetic nervous system activity in chronic heart failure causes increased desensitization of cardiac β1- and β2-adrenergic receptors and down-regulation of β1-ARs, leading to a progressive loss of cardiac adrenergic and inotropic reserves, characteristic molecular abnormalities of this disease.

Less understood is the role of the parasympathetic nervous system in heart failure pathophysiology. It is known that in patients with heart failure, the activity of the parasympathetic system is reduced, contributing to tachycardia and reduced heart rate

variability, factors associated with higher mortality in heart failure. Stimulation of muscarinic receptors in cardiac muscle has a demonstrable negative lusitropic effect and an antagonizing effect on β-adrenergic stimulation. In individuals with hypertension, increased sympathetic nervous system activity may play a role in the development of left ventricular diastolic dysfunction, thereby increasing the risk of heart failure. Numerous preclinical and clinical studies have demonstrated an association between increased sympathetic nervous system activity and diastolic dysfunction.

In addition to pharmacological therapy, which is the standard of practice in heart failure treatment, several clinical trials are currently investigating the potential of unilateral and bilateral thoracic sympathectomy on the course of heart failure, with preliminary results suggesting bilateral sympathectomy as a promising therapy. Another option to influence the sympathetic system in heart failure patients is cardiac resynchronization therapy (CRT), which improves sympathetic function in patients with HF accompanied by reduced systolic function. Biventricular stimulation has been shown to reduce muscle sympathetic nerve activity more effectively than right ventricular or right atrial stimulation alone.

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5 CHEMORECEPTORS

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Chemoreceptors are specialized sensory cells that detect changes in the chemical composition of the body's internal environment. In the human body, chemoreceptors are distributed across various organs and tissues and play a pivotal role in regulating physiological processes, especially those related to gas exchange and pH balance. Two main types are distinguished based on their localization: peripheral and central.

Peripheral chemoreceptors are primarily found in the carotid bodies, situated near the bifurcation of the common carotid artery, also known as the Glomus caroticum. These clusters of chemoreceptor cells are highly sensitive to fluctuations in partial oxygen (PaO_2), carbon dioxide ($PaCO_2$), and pH levels in arterial blood. The Glomus caroticum is interconnected with sympathetic fibers from the cervical sympathetic nerve and parasympathetic fibers from the vagus nerve. This system operates on the basis of the high metabolic activity of sensory cells, which consume oxygen at high rates. In case of inadequate oxygen supply (such as a decrease in SaO_2, hemoglobin levels, or microcirculation perfusion), these cells promptly signal these changes to the respiratory center, providing a rapid response to pathological alterations.

Another significant cluster of peripheral chemoreceptors, known as aortic bodies, is localized in the aortic arch. They play a vital role in regulating respiratory and cardiovascular functions in response to changes in blood gases and pH levels.

Central chemoreceptors are situated in the brainstem within the medulla oblongata and are part of a complex sensory network. These receptors primarily respond to fluctuations in carbon dioxide levels via pH changes in the cerebrospinal fluid surrounding the medulla oblongata and the fourth ventricle of the brain. Unlike peripheral chemoreceptors, the central receptor system operates with a time delay and inertia, sometimes spanning several hours. Together, this complex system of chemoreceptors contributes to the fine-tuned regulation of respiratory and cardiovascular processes, ensuring the body's adaptation to chemical changes in the environment.

The interaction between chemoreceptors and the autonomic nervous system is a crucial element in the body's regulatory mechanisms. These specialized sensory cells are sensitive to changes in the chemical composition of the blood and cerebrospinal fluid, significantly influencing the activity of the autonomic nervous system. Activated

chemoreceptors modulate the balance between the sympathetic and parasympathetic nervous systems.

The sympathetic system responds to specific stimuli detected by chemoreceptors. For instance, when low oxygen levels (hypoxia) or elevated carbon dioxide levels (hypercapnia) are detected in the bloodstream, the sympathetic nervous system accelerates heart rate, respiration, and blood flow to vital organs.

Conversely, in certain scenarios, the parasympathetic nervous system may be activated to counterbalance or mitigate the effects of the sympathetic response. An illustrative example is the parasympathetic response following the detection of physiological blood gas levels by chemoreceptors, resulting in a reduction in heart rate and respiration.

The primary objective of the interaction between the autonomic nervous system and chemoreceptor processing is to maintain homeostasis in the body. This is achieved through dynamic fine-tuning of autonomic functions in response to the body's chemical needs, ensuring that essential physiological parameters, such as blood gases and pH, are carefully maintained within an optimal range.

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6 AUTONOMIC INNERVATION OF THE LUNGS AND ITS INVOLVEMENT IN THE PATHOGENESIS OF SELECTED DISEASES

MUDr. Ladislav Kočan PhD., FIPP

The autonomic regulation of the lungs is crucial for the body's ability to adapt to sudden changes, during which the respiratory system must adjust adequately. The lungs are endowed with a rich supply of sensory, sympathetic, and parasympathetic fibers. The mechanisms of local innervation during respiration are well-documented, and in recent years, there has been increasing evidence of the involvement of the autonomic innervation component in the control of immune events.

6.1 Autonomic Control of Pulmonary Function

Sympathetic nerves constitute a minor component of the autonomic nervous system in the lungs, originating in the upper segments of the thoracic spinal cord (Th1-Th6) and emitting nonadrenergic signals to the bronchial blood vessels and submucosal glands. When stimulated, sympathetic nerves induce bronchodilation (expansion of bronchial diameter) and reduce mucus secretion. The neurotransmitter of the sympathetic fibers is norepinephrine, and its target sites of action in the respiratory tract are the Alpha-adrenergic and Beta-adrenergic receptors.

Alpha-1 receptors (α1) are found on smooth muscle cells in the airways (bronchioles) and blood vessels. Activation of alpha-1 receptors leads to smooth muscle contraction, vasoconstriction, and decreased blood flow.

Alpha-2 receptors (α2) are also present in the lungs, but their effects are more complex. Activation of alpha-2 receptors generally inhibits the release of norepinephrine and other neurotransmitters, leading to smooth muscle relaxation.

Beta-2 receptors (β2) are primarily found on the smooth muscle cells of the bronchioles in the lungs. When activated, beta-2 receptors cause relaxation of bronchial smooth muscle, leading to bronchodilation. This effect is important to facilitate increased airflow and improve breathing.

The parasympathetic nerves, which play a major role in the respiratory system, originate from the vagus nerve. The mediator released is acetylcholine. Vagus divides into two

branches in its course, namely: the superior laryngeal nerve and the recurrent laryngeal nerve.

The vagus nerve, acting through muscarinic receptors, controls important lung functions such as the cough reflex, mucus production, and changes in bronchial diameter. It also plays a key role in the regulation of local and systemic inflammatory responses. It is involved in the pathogenesis of autoimmune diseases, such as bronchial asthma, where excessive vagus nerve stimulation and an inflammatory response likely contribute to the development of the disease.

Muscarinic receptors, through which their effects are exerted in the lungs, belong to the G-protein coupled receptor family and are activated by the neurotransmitter acetylcholine. The name 'muscarinic receptor' implies that they can be selectively activated by muscarine, a substance found in some fungi.

There are five subtypes of muscarinic receptors, M1 to M5, distributed in various tissues in the body, including the respiratory system. In the lungs, the main subtypes of muscarinic receptors are M2 and M3.

M3 receptors are coupled to the G-protein, a particular subgroup referred to as Gq. To further explain the G-protein issue, four major groups (families) of G-proteins (Gi, Gs, G12/13, and Gq) have been identified so far. The Gq family, divided into four subgroups (subfamilies), is crucial for the function of muscarinic M3 receptors in the lungs. Among these, the most important and ubiquitously expressed isoforms are Gaq and Gaq/11, which are nearly 88% similar in their amino acid sequence and are highly abundant in airway smooth muscle. The M3 receptor is associated specifically with the Gq subfamily of G-proteins.

Muscarinic M2 receptors are primarily coupled to G-proteins of the Gi/o subtype. Activation of M2 receptors leads to the inhibition of adenylate cyclase, reduction of cyclic adenosine monophosphate (cAMP) levels, and modulation of ion channels, contributing to a variety of physiological effects such as the negative feedback regulation of acetylcholine release. The inhibitory action of M2 receptors on adenylate cyclase is a hallmark sign of G-proteins of the Gi/o subtype. M2 receptors are primarily found on presynaptic nerve endings and certain postsynaptic cells in the lungs.

Activated M2 receptors inhibit the release of acetylcholine, representing a negative feedback mechanism regulating parasympathetic tone. Activation of M2 receptors may lead to the contraction of airway smooth muscle, but their overall effect is considered negligible compared to M3 receptors. Activation of M2 receptors produces the opposite

effect to that described for the activation of M3 receptors, resulting in the inhibition of acetylcholine release. This inhibition serves to limit cholinergic-induced bronchoconstriction.

In recent years, research focusing on the influence of the autonomic nervous system on immune processes during viral infections has gained attention. It has been discovered that lung macrophages express M2 and M3 receptors on their biological membranes. This finding suggests a direct influence of acetylcholine on macrophage activity and the course of the inflammatory response. Furthermore, cytokines such as IFNs, TNF, and IL-1β have been found to influence the expression and activity of M2 receptors.

Building upon previous descriptions of autonomic innervation of the lungs, later investigations have revealed a complex pathway involving the participation of neurotransmitters secreted from autonomic nerve fibers innervating the airways. These neurotransmitters engage in intricate interactions after binding to their target receptors. Specifically, detailed knowledge of neurotransmitters such as 5-hydroxytryptamine, acetylcholine, calcitonin gene-related peptide (CGRP) group peptides, substance K, substance P, nitric oxide, and their respective receptors has been obtained.

Ensuring a balance between sympathetic and parasympathetic activity is crucial for optimal lung functioning. Sympathetic activation enables increased airflow and decreased mucus secretion during situations that demand heightened respiratory capacity, such as exercise or stress. Conversely, parasympathetic activation restricts airflow and increases mucus secretion during periods of rest or low physical activity.

M3 receptors are found predominantly on the surface of smooth muscle cells in the bronchi and bronchioles, as well as on glandular cells in the respiratory system.

Activation of M3 receptors leads to smooth muscle contraction, glandular secretion, and mucus production. In the airways, this leads to bronchoconstriction and increased mucus production, contributing to increased airway resistance.

The effects of muscarinic receptor activation are opposite to those of beta-adrenergic receptors in the lungs. While sympathetic stimulation (beta-adrenergic activation) leads to bronchodilation and increased airflow, parasympathetic stimulation (muscarinic activation) causes bronchoconstriction and mucus secretion.

Drugs that interact with muscarinic receptors are called anticholinergics or antimuscarinics. In the context of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), anticholinergic drugs are often used to block the

bronchoconstrictive effects of acetylcholine, promoting bronchodilation, and improving airflow.

6.2 Lung Autonomic Regulation and Its Impact on Immune Processes

The lungs, as vital organs, are constantly exposed to damage due to direct contact with the external environment. Therefore, local immune processes must be highly efficient and strictly controlled. Dysregulation of the local immune response in the lungs could lead to fatal infections, asthma, and other severe diseases. Studies have concluded that disruption of sympathetic innervation of the lung, whether caused by genetic factors, pharmacotherapy, or surgical ablation, enhances the responsiveness of innate immunity to lipopolysaccharides. Innate immunity serves as the body's first line of defense against infection and involves nonspecific immune responses. Lipopolysaccharides are part of the cellular membrane of predominantly Gram-negative bacteria and act as endotoxins. LPS is recognized by immune cells via TLR4 receptors (Toll-like receptor 4). Once the endotoxin binds to TLR4 receptors on the surface of macrophages and other immunocompetent cells, signaling cascades are triggered, resulting in the activation of various immune responses aimed at eliminating the pathogen. Simultaneously, loss or attenuation of local sympathetic innervation in the lungs leads to amplification of type II innate immunity, induced by interleukin 33 (IL-33). IL-33 is released into the circulation in response to tissue damage, infection, or other inflammatory signals. It plays a crucial role in promoting and regulating type 2 innate immunity, characterized by the activation of immunocompetent cells such as innate lymphoid cells type 2 (ILC2s), eosinophils, and mast cells. Subsequently, these cells produce other inflammatory cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). On the other hand, norepinephrine or specific β2-adrenergic receptor antagonism may inhibit the immune esponse elicited by lipopolysaccharide in primary alveolar macrophages or the immune response elicited by IL-33 in innate lymphoid cells type 2 (ILC2) in the lungs.

6.3 Autonomic Dysfunction's Impact on the Development and Progression of Bronchial Asthma

Asthma, a chronic inflammatory disease of the airways, is complex and thought to arise from a combination of genetic and environmental factors. Common triggers include allergens like pollen and dust mites, respiratory tract infections, and exposure to irritants such as tobacco smoke. The condition manifests with recurrent or chronic wheezing and/or coughing, alongside variable airway obstruction amidst bronchial hyperactivity and inflammation.

Increased bronchial airway irritability in asthmatics arises from several pathophysiological mechanisms, among which autonomic imbalance plays a pivotal role. This imbalance stems from decreased β2-adrenergic activity, leading to an augmented cholinergic and α-adrenergic response to various triggers like allergens, dust, stress, cold, and other irritants.

In addition to cholinergic and adrenergic mediators, numerous other signaling molecules (such as NO - nitric oxide, bradykinin, tachykinin, prostaglandins, neuropeptide Y, and others) regulate airway function. These mediators contribute to asthma pathogenesis not only by modulating airway smooth muscle tone but also by influencing pulmonary blood flow, endothelial permeability, and airway secretion.

Autonomic nervous system imbalance is a key pathophysiological mechanism in asthma, characterized by increased bronchial sensitivity to cholinergic mediators inducing bronchoconstriction and potential decreased sensitivity to β2-adrenergic dilators. (As mentioned, only a subset of β2-receptors is represented in the bronchial tree from β-receptors).

While stimulation of α1-receptors can induce bronchoconstriction under specific conditions, cholinergic neurotransmission can be inhibited by the α2-receptor pathway.

β2-receptors are crucial in asthma treatment; their stimulation leads to bronchodilation, increased mucociliary clearance, and decreased vascular permeability, acetylcholine release, inflammatory mediators, and neuropeptides.

6.4 Dysregulation of the Autonomic Nervous System in Chronic Obstructive Pulmonary Disease Patients

Chronic obstructive pulmonary disease (COPD) is characterized by permanent airflow limitation, usually progressive, and accompanied by an increased inflammatory response of the airways and lungs to inhaled pollutants. It is estimated to affect up to 10% of the world's population and includes:

1. Chronic bronchitis: Manifested as a chronic productive cough.
2. Emphysema: an irreversible enlargement of the airways peripheral to the terminal bronchiole.
3. Chronic airway obstruction: The common feature is a slowly progressive, irreversible obstruction with slowing of lung emptying on effortful expiration.

COPD risk factors are multifactorial. Smoking is a clearly documented risk factor, and its effects only become apparent after prolonged exposure to cigarette smoke, even in non-smokers (passive exposure). In addition, environmental pollution from coal, silica, cement dust, and fossil fuel exhalates may also contribute. Genetic risk factors include, for example, low levels of alpha1-antitrypsin.
Symptoms of COPD include shortness of breath, persistent cough, excessive mucus production and expectoration, and shortness of breath with light exertion, with diagnosis consisting of spirometric confirmation of airway obstruction.
Expiratory flow limitation in COPD patients results from progressive airway inflammation, with histologic findings including destruction of lung parenchyma, presence of mucosal edema, and airway remodeling. Patients exhibit exaggerated mucus production and increased airway smooth muscle tone due to excessive cholinergic stimulation.
The current understanding of COPD pathogenesis reveals its complex nature, resulting from multiple factors leading to progressive airway obstruction. It is a systemic disease that adversely affects multiple organ systems, including the cardiovascular and autonomic nervous systems. Autonomic dysfunction plays a crucial role in COPD pathophysiology, as several mechanisms under the control of the autonomic nervous system are impaired in this condition.

In COPD patients, autonomic nervous system activity may be affected by recurrent episodes of hypoxia, hypercapnia, increased intrathoracic pressure fluctuations (arising due to airway obstruction), increased respiratory effort, systemic inflammation, as well as treatment strategies involving betamimetics. Experimental findings suggest that autonomic dysfunction characterized by sympathetic predominance may significantly modulate inflammatory responses, potentially influencing the development of other diseases, including the increased incidence of cardiovascular disease in COPD patients.

Although several studies have demonstrated limited ventilatory response to exercise stress in COPD patients, the role of autonomic dysfunction in exercise stress intolerance is still a subject of clinical research. Increased sympathetic activity has been monitored in clinical studies primarily by heart rate variability, blood pressure variability, determination of plasma catecholamine levels, and assessment of muscle sympathetic nerve activity (MSNA). MSNA involves the transmission of signals from the sympathetic nervous system to blood vessels in the muscles, regulating blood flow and playing a key role in the body's response to various physiological demands such as exercise or stress.

COPD patients with increased sympathetic activity have also developed chronic heart failure concurrently, exhibiting muscle wasting and impaired exercise tolerance.

The exact relationship between autonomic dysfunction and pathophysiological mechanisms in COPD development has not yet been precisely described, but circumstantial evidence suggests a correlation. Treatments aimed at restoring autonomic neural balance towards reduced resting sympathetic activity may modulate the inflammatory state and likely contribute to improved health status in COPD. Treatment of COPD is complex and includes bronchodilators and anti-inflammatory therapy, aiming to slow disease progression.

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7 THORACIC SYMPATHETIC INNERVATION

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The hyperactivity of the sympathetic nervous system is associated with numerous pathological conditions. Blocking the thoracic sympathetic ganglia using local anesthetics and ablative techniques is employed in treating pain mediated by the sympathetic nervous system. Such conditions include complex regional pain syndrome, postherpetic neuralgia, phantom breast amputation pain, and upper limb peripheral vascular disease.

7.1 Thoracic Sympathetic Nerve Blockade

The truncus sympathicus is a bilateral chain of interconnected adjacent ganglia that communicate with each other and participate in the innervation of adjacent and distant tissues. The inferior cervical ganglion is connected to the superolateral thoracic ganglion, and together they form the cervicothoracic ganglion (ganglion stellatum) described above, which is important for the innervation of tissue structures located in the neck, upper extremity, and sympathetic innervation of the heart.

The distally deposited ganglia send postganglionic fibers to the autonomic nerve plexuses around the heart, bronchi, and esophagus, and are part of the spinal nerves that form the intercostal nerves. Distally, they form into splanchnic nerves which autonomically innervate the organs of the abdominal cavity.

In clinical practice, interventions targeting the thoracic sympathetic nervous system are also performed in the thoracic anatomical region. These include sympathetic blockade, chemical, and thermo/radiofrequency (RF) ablations aimed at treating pathological conditions such as hyperhidrosis, complex regional pain syndrome, and peripheral vascular disease. Clinical research is also underway to monitor the benefit of this therapy in patients with heart failure.

Thoracic sympathetic interventions can be performed by the surgical thoracoscopic method or by the minimally invasive interventional method under skiascopic navigation. Sympathetic blockade represents a test intervention in which a local anesthetic is applied to the thoracic sympathetic trunk. In radiographically navigated blockade, the patient is conscious, lying in the prone position, and a thin needle is inserted through a posterior

approach at two levels along the body of the thoracic vertebra at the level of the Th2 and Th3 vertebrae. The procedure is reviewed in AP, lateral, and oblique projections. The needle in the lateral projection must not cross the border in the middle of the thoracic vertebra, due to the risk of pneumothorax. After confirming the correct position of the needle in all three aforementioned projections and administration of the contrast agent, a local anesthetic is administered to provide nerve blockade. Most commonly, 2 ml of 1% lidocaine or 2 ml of 0.5% bupivacaine is injected during diagnostic blockade or before radiofrequency ablation.

After the drug application, the effect is monitored, according to the result of which it is possible to deduce the expected effect of chemical lysis or thermal/radiofrequency ablation. After a positive test blockade, chemical ablation can be performed, in which 96% alcohol, 6% phenol, or radiofrequency ablation of nerves with RF electrodes is applied to the target nerve structures. Radiofrequency denervation uses thermal energy at +75°C to +90°C that is precisely applied to sympathetic nerves, creating a controlled lesion to more effectively interrupt nerve signals. The method is performed with the patient in the prone position, using a so-called posterior approach. The patient is fully conscious during the procedure, communicates with the surgeon, and the entry site is infiltrated with local anesthetic. The procedure requires vascular access and monitoring of blood pressure, pulse rate, and oxygen saturation.

Another option for performing sympathectomy is surgical video-assisted denervation. It is one of the procedures performed by a thoracic surgeon in a lateral approach, under general anesthesia. The procedure is controlled by optical visualization, which allows a safer and more precise realization of sympathetic nerve severance.

Video-assisted thoracoscopic method and interventional radiofrequency/thermoablation techniques are among the sophisticated interventions where more precise and durable therapeutic effects can be achieved. Future advances in the technical level of interventional techniques make it possible to combine the benefits of both treatment modalities and to create a hybrid procedure in which a thin and rigid endoscope can be introduced under ultrasound or stereoscopic navigation through a posterior approach and ablative techniques can be performed under optical control.

Figure 11 Ultrasound-guided endoscope. (Source: EvoTouch+7StarScope: Ultrasound guided Micro-Endoscopy - Quantel Medical - Interventional Imaging - PDF Catalogs | Technical Documentation (medicalexpo.com).

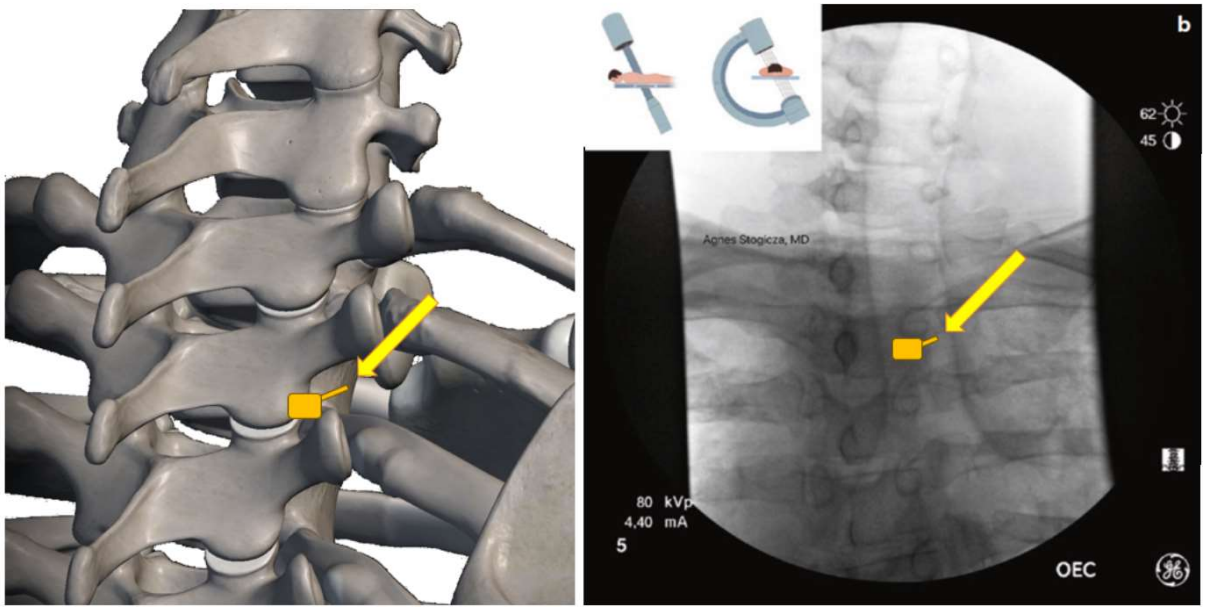


Figure 12 Skiascopic needle navigation in thoracic sympathetic blockade, oblique projection (adapted from Stogicz A, 2020).

According to evidence-based medicine publications, the following recommendations apply to thoracic sympathetic blockade in the treatment of KRBS: **Class IIb recommendation, Level of Evidence B.**

7.2 Intercostal Neuralgia

The intercostal nerves are part of the somatic nervous system. Motor fibers innervate the intercostal muscles, while sensory afferent branches conduct information from the skin and parietal pleura. Anatomically, they branch off from the anterior roots of spinal nerves Th1 to Th12, located beneath the adjacent eponymous rib. The twelfth thoracic nerve is positioned below the 12th rib and enters the abdominal wall, also known as the subcostal nerve.

Abundant connections exist between the intercostal nerves and the sympathetic nervous system, originating from the thoracic sympathetic trunk. Therefore, a role for the sympathetic nerve in the perception and transduction of painful stimuli in various pathologies leading to intercostal neuralgia can be hypothesized.

Various factors can provoke intercostal neuralgia, such as intercostal nerve compression syndrome, postoperative pain following thoracotomy procedures, breast surgery, rib fractures, pleuritis, diabetic polyneuropathy, acute herpes zoster, and others.

Interosseous blockade can be performed under ultrasound or skiascopic control with the assistance of an X-ray machine. The neurovascular bundle runs subcostally, under the adjacent rib, and the procedure is conducted with the patient in the prone position. A 6-13 MHz linear ultrasound probe is most suitable for the ultrasound-guided procedure. Imaging of two adjacent ribs is best displayed in the short-axis scanning plane, with the ribs easily identifiable by their typical oval shadow. In addition to the ribs, the key stationary structures are the internal and external intercostal muscles. Other visible structures in the ultrasound image are the pleura and the lungs, distinguishable during motion excursions of the thorax during inspiration and expiration. The skiascopic procedure is also performed with the patient in the prone position, with control during needle insertion in the antero-posterior and lateral projections, and verification of the final needle position with contrast agent being crucial.

Selective intercostal nerve blocks provide reliable unilateral analgesia in the dermatome of the nerve on which the block is performed. They consistently improve respiratory

function in patients with chest wall pain and facilitate early recovery after thoracic surgery. Intercostal blockade offers a technically simpler alternative to paravertebral nerve blocks or thoracic epidural anesthesia. However, there is an increased risk of intravascular drug application, potentially leading to systemic toxicity induced by the local anesthetic, as well as a higher risk of pneumothorax.

A potential drawback compared to paravertebral nerve blockade or thoracic epidural blockade is the necessity of performing multiple blockades if more than one level or bilateral analgesic coverage is required. Intercostal blockades do not provide complete surgical analgesia for thoracic surgery, so they must be integrated into a multimodal postoperative analgesia plan if used for perioperative analgesia.

A therapeutically beneficial, long-lasting alternative to intercostal blockade is intercostal nerve cryoablation, which can be performed directly under visual control perioperatively as prophylaxis for postoperative pain after thoracotomy procedures or as an outpatient procedure under scanscopic and ultrasound guidance.

The level of evidence, based on the American Society of Interventional Pain Physicians (ASIPP) literature review, indicates a level IV level of evidence for intercostal block in the treatment of intercostal neuralgia. The evidence obtained to date relies solely on case reports and small clinical trials. However, this treatment appears highly promising.

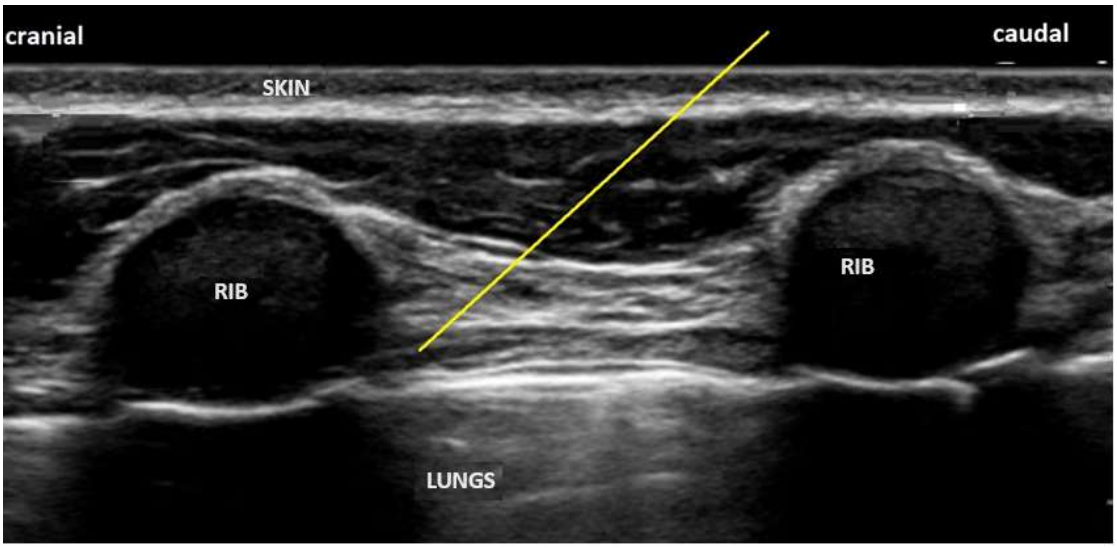


Figure 13 Ultrasound visualization of the intercostal space. The yellow line shows the needle guidance during blockade (from the author's archive).

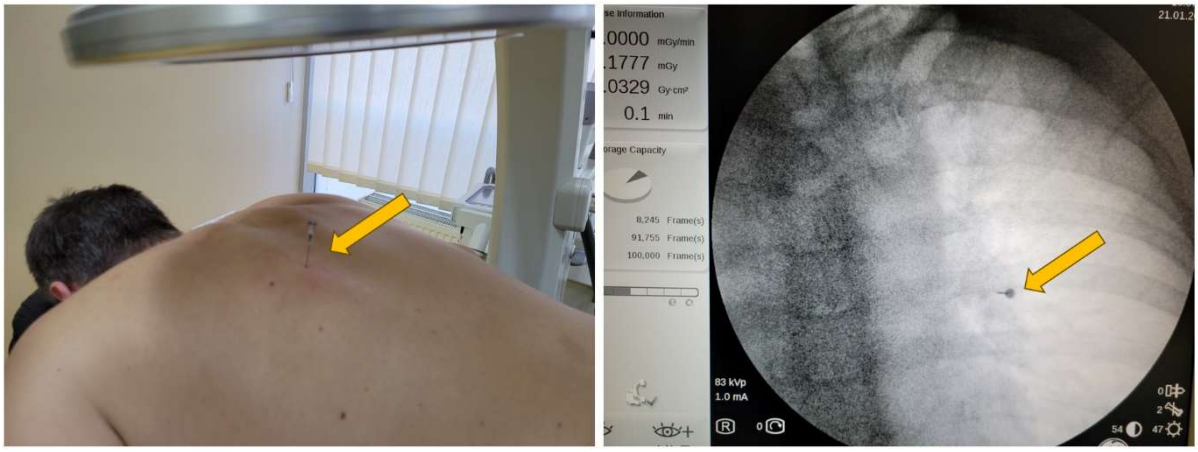
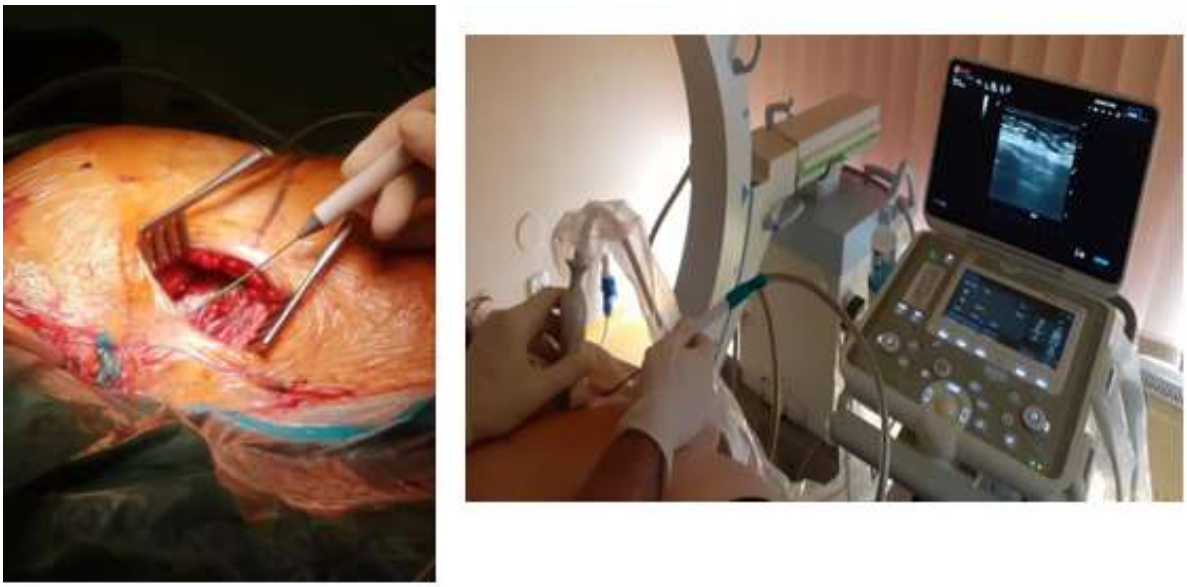


Figure 14 Skiascopically navigated interosseous nerve block in posterioanterior projection (from the author's archive).



A **B**

Figure 15 **A**. Perioperative interosseous nerve cryoablation after minithoracotomy. **B**. Percutaneous interosseous nerve cryoablation performed with the hybrid technique. Localization of the insertion site under combined ultrasound and skiascopic visualization (from the author's archive).

7.3 Splanchnic Nerves

The thoracic splanchnic nerves are sympathetic nerves that contribute to the autonomic supply to the abdomen and pelvis. Although they innervate anatomical structures in the abdominal cavity and pelvis, their nerves predominantly arise from the thoracic segments of the spinal cord and the cranial segments of the lumbar spinal cord, the Th1 - L2 region. Their preganglionic fibers (rami communicantes albi) pass through the thoracic sympathetic ganglia. They continue as three groups of paired sympathetic nerves: n. splanchnicus thoracicus major from Th5(6)-9, n. splanchnicus thoracicus minor from Th10, 11, and splanchnicus thoracicus imus from Th12.

Clinically, interventions aimed at blocking the great splanchnic nerve are beneficial in treating chronic pain in serious diseases such as pancreatic cancer and chronic pancreatitis. Other clinical conditions mentioned in the literature where splanchnic nerve blockade has been used include functional gastrointestinal tract diseases associated with persistent paralytic ileus. However, these are only published case reports.

The first surgical operation involving resection of the distal subphrenic splanchnic nerves was performed by the French surgeon Pierre Mallet-Guy in 1943. Splanchniectomies in the thoracic cavity via open thoracotomy have been described since 1990. The first reports of minimally invasive thoracoscopic interventions on the splanchnic nerves have been described since 1993. Since the mid-1990s, thoracic surgery has been performed via the minimally invasive approach. The advantages of surgery conducted via the mini-invasive approach are less operative trauma, lower likelihood of adhesions, and a smaller postoperative scar.

Video-assisted thoracoscopic splanchnic splenectomy (VATS) has become a common surgical method for approaching the splanchnic nerves. The surgery involves insufflation of the thoracic cavity with an inert gas, typically carbon dioxide. Guided selective intubation achieves lung collapse on the desired side of the chest, enabling the insertion of surgical instruments and creating the necessary space to work in the operative field. A 2008 systematic review of clinical trials investigating the outcomes of thoracoscopic splanchnic splenectomies highlighted the debate over the efficacy of unilateral versus bilateral splanchnic nerve transections.

Most patients who undergo splanchniectomy experience a significant reduction in observed pain scores, and many patients reduce their consumption of opioid analgesics

post-splanchniectomy. However, the effectiveness of this treatment depends on anatomic variations in the course of the splanchnic nerves, which may result in refractory pain in some cases of procedure failure.

Relatively common side effects in the early post-splanchniectomy period include increased bowel motility and orthostatic hypotension. These symptoms typically resolve within 18 months of the procedure.

For patients with unresectable tumors, surgery is justified. Two-thirds of patients report that they would undergo splanchniectomy again.

A less invasive alternative to surgical denervation is interventional blockades targeting the splanchnic nerves, which are performed under skiascopic control. After a positive blockade, radiofrequency ablation is performed, with bilateral blockade preferred for oncologic pancreatic pain.

During the procedure, the patient lies on their abdomen (in the prone position), and basic vital signs (blood pressure, ECG, SpO2) are monitored, with the patient provided intravenous access. The interventionalist visualizes the Th11 thoracic vertebral body on the X-ray image (center of the image). Three projections are used to navigate and insert the needle: the AP (anterio-posterior) projection, the oblique projection, and the lateral projection. During the block, a 15 cm 20-22G needle is introduced along the vertebral body, with the target needle position being the interface located between the posterior 2/3 and anterior 1/3 of the vertebral body in the lateral projection. After verification of the needle position in all imaging projections and application of the contrast agent, local anesthetic is injected, mostly bupivacaine 0.25% 5-10 ml. After a positive clinical response to blockade, radiofrequency (RF) ablation can be performed after several days to weeks. The implementation of the RF lesion consists of ablation at a temperature of 80°C and a lesion duration of 60-90 seconds, followed by a 180° rotation of the RF needle and performing a repeat lesion. The procedure is performed bilaterally.

According to evidence-based medicine publications, the following recommendations apply to thoracic sympathetic blockade in the treatment of KRBS**: class IIb recommendation, level of evidence B.**

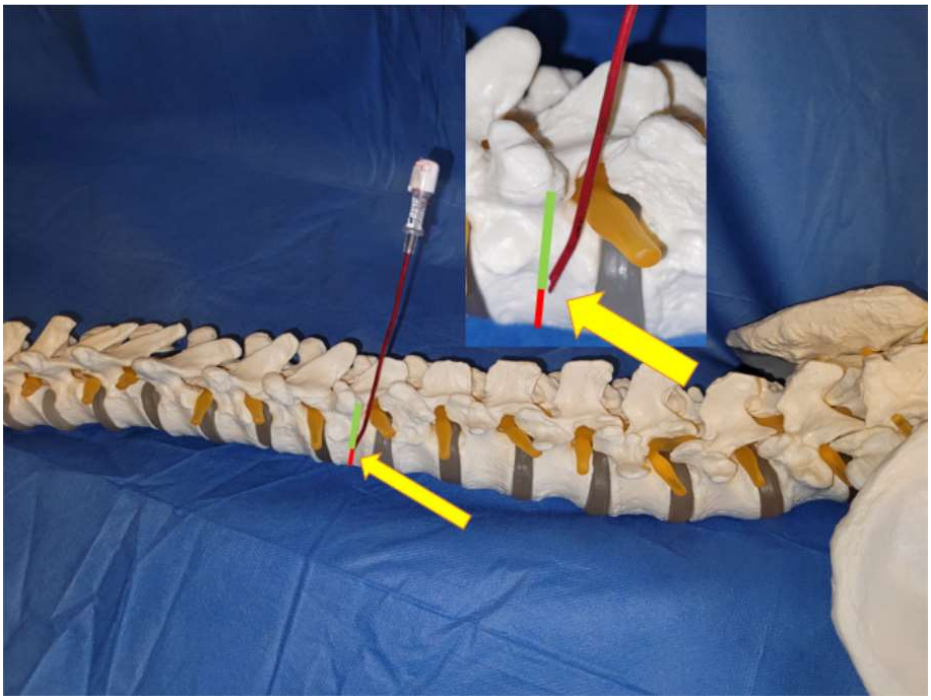


Figure 16 Oblique projection showing needle placement during splanchnic blockade (from author's archive).

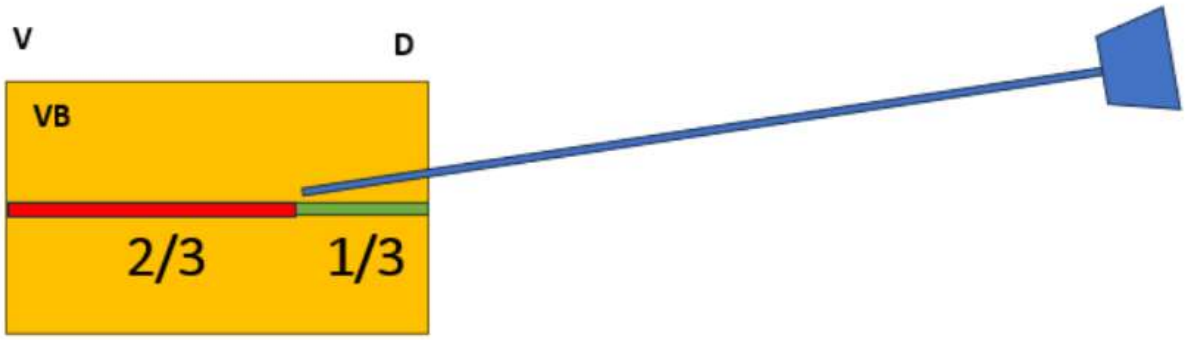


Figure 17 Schematic of safe needle placement in the lateral projection in splanchnic blockade. VB- vertebral body, V- ventral side, D- dorsal side (from author's archive).

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8 ONCOLOGICAL ABDOMINAL PAIN

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The issue of treating oncological pain is a current concern. The World Health Organization (WHO) has prioritized pain management in oncology, considering pain as the most prevalent symptom associated with oncological diseases and one of the most dreaded symptoms, particularly in advanced stages. Oncological pain adversely affects the progression of the disease and significantly diminishes the patient's quality of life. The neurophysiology of cancer pain is multifaceted, involving inflammatory, neuropathic, ischemic, and compressive mechanisms, often acting synergistically. Pain management encompasses combined pharmacotherapy and the utilization of various interventional algology techniques aimed at peripheral nerve blockades, nerve plexuses, and sympathetic nerve structures.

8.1 Thoracic Sympathetic Blockade

Neurolytic sympathetic blockades are highly effective therapeutic tools in managing challenging-to-control malignant visceral pain. In oncology patients, they serve as vital adjuncts to comprehensive analgesic therapy. It is essential to emphasize that treating oncological pain is a multidisciplinary endeavor.

Despite their positive analgesic effects, sympathetic nerve blockades cannot completely eradicate pain because cancer-related pain is multifaceted. In addition to the role of autonomic nerves in nociception (the perception of potentially harmful stimuli), oncological pain typically comprises somatic, visceral, and neuropathic components (known as total pain). Managing pain necessitates ongoing pharmacotherapy even after successfully performing sympathetic nerve blockades, although it is likely to reduce the overall dosage of analgesics. This approach, alongside decreasing opioid and non-opioid analgesic consumption, diminishes the occurrence of adverse drug effects and enhances patients' quality of life.

8.2 Celiac Plexus Blockade

The celiac plexus represents a network of sympathetic and parasympathetic fibers originating from the splanchnic nerves, the nerve fibers of the thoracic truncus sympatheticus, and the vagus nerve. It can consist of one to five larger ganglia and is situated retroperitoneally in front of the aorta at the level of the truncus coeliacus, surrounding the coeliac artery and the superior mesenteric artery. It autonomously innervates various organs including the liver, pancreas, gall bladder, stomach, spleen, kidneys, intestines, adrenal glands, and blood vessels.

An indication for celiac plexus blockade is both malignant and non-malignant pain originating from organs in the epigastrium. The most common indication is intense pain in malignant diseases of the pancreas, gallbladder, bile ducts, liver cancer, or painful metastases in the liver. Another indication is painful conditions in chronic pancreatitis, although this blockade is relatively infrequent in this condition. However, performing a blockade in oncological diseases is limited by the presence of metastases, which can mechanically impede access to the nerve structures of the celiac plexus. Hence, evaluating the extent of the metastatic process before the procedure is crucial.

In principle, this blockade can be implemented using three techniques based on imaging technology: CT, X-ray, or USG-guided technique. In the past, the posterior approach, which is more technically demanding, was preferred. When performing the procedure through a posterior approach, bilateral blockade is usually necessary. Currently, the front approach through the abdominal wall is more commonly used, often performed under CT navigation, although X-ray and USG navigation are also feasible. Even with technically correct execution, complete relief is not always guaranteed, and sometimes repeated applications are necessary. Similarly, the duration of relief varies, ranging from a few weeks to a year. Before each procedure, it is essential to individually evaluate the cost/benefit ratio of the given therapy, i.e., the risks and benefits. The procedure itself is typically performed in patients with an unfavorable prognosis, where complex pharmacological therapy fails. Blockade is performed with a local anesthetic, and definitive lysis is achieved with the application of 98% alcohol or 6% phenol.

Studies comparing oncology patients with malignancy of the abdominal parenchymal organs on opiate treatment (representing the control group) versus patients after chemical lysis of the celiac plexus have shown a significant reduction in pain after the application of the block, although there was no difference in survival length between the groups.

These results have been confirmed in prospective observational studies as well as randomized prospective studies.

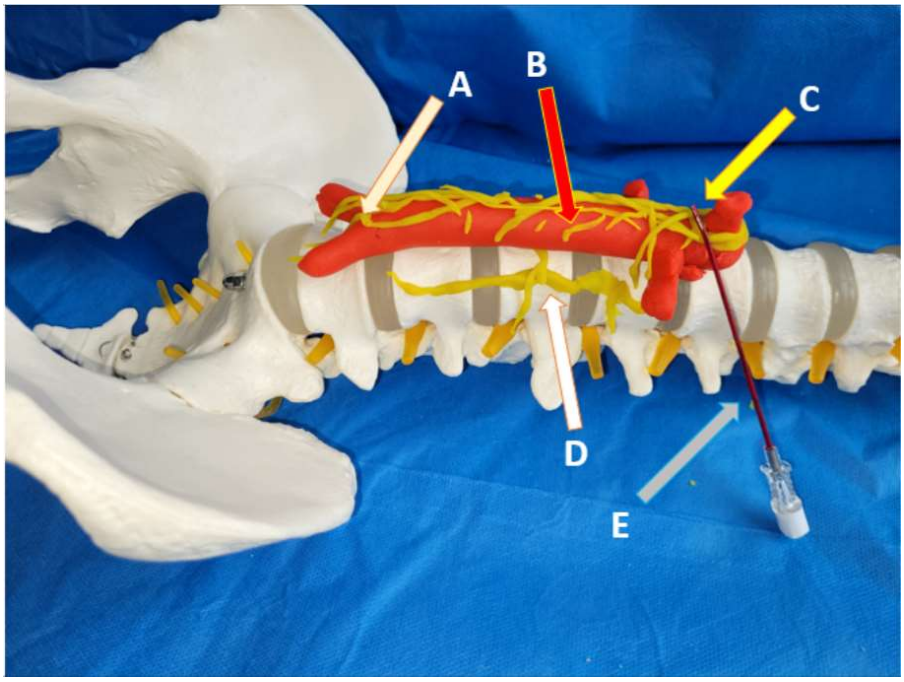


Figure 18 Ventral view of needle position during celiac plexus blockade. **A**: plexus hypogastricus, **B**: abdominal aorta, **C**: plexus coeliacus, **D**: truncus sympaticus in the lumbar region, **E**: needle (from the author's archive).

The occurrence of certain complications associated with this blockade depended to a certain extent on the methodology used, while some complications occurred independently of the methodology and imaging technique employed. The most common complications of the procedure include transient orthostatic hypotension lasting several days, which gradually subsides after the activation of compensatory vascular reflexes. Another relatively common complication is diarrhea related to sympathetic intestinal blockade. With proper treatment (hydration and antidiarrheals), it does not pose a serious problem for the patient and usually resolves on its own. Other complications include back pain, which can be caused by local trauma during needle insertion, retroperitoneal hematoma, irritation of retroperitoneal structures by the lytic agent used (alcohol), lumbar plexus injury, or kidney injury. Paraplegia and transient motor paralysis, probably caused by spasm of the lumbar segmental arteries, have also been described in the literature.

According to published EBM evidence, the following recommendations apply to the interventional treatment of oncological abdominal pain located in the epigastrium, based on the benefit/risk assessment system:
Neurolytic blockade of the celiac plexus, **recommendation class 2A+**
Neurolytic blockade of splanchnic nerves **recommendation class 2B+**

8.3 Superior Hypogastric Plexus Blockade

Among other interventional techniques used in the symptomatic treatment of oncological and non-cancerous pelvic pains is the blockade of the superior hypogastric plexus. Situated in the retroperitoneum, this plexus extends bilaterally from the lower third of the anterior aspect of L5 to the upper third of the anterior part of S1. It serves as a conduit for the afferent fibers of the pelvic organs. Similar to other sympathetic blocks, this procedure targets visceral pain, while somatic pain originating from the sacral spine area, muscles, and neuropathic pain caused by nerve compression or infiltration remain unaffected. Therefore, the primary indication is pain arising from the pelvic organs, with common indications including pain in cervical carcinomas, colorectal and urogenital tumors located in the small pelvis. While there are some reports of non-malignant pain treatment, these cases are largely anecdotal.
Procedure Description:
The intermesenteric plexus lies before the bifurcation of the abdominal aorta, continuing caudally as the upper hypogastric plexus. Blockade is typically performed under fluoroscopic control, most commonly through a posterolateral needle-guiding approach. Another approach is the posterior transdiscal approach, where the needle is passed through the intervertebral disc from the lumbosacral region under aseptic conditions and an antibiotic curtain. Some authors prefer this technique due to its simpler implementation. An anterior, transabdominal approach is also documented in the literature. The objective of the hypogastric plexus block is to insert the needle in front of the L5/S1 intervertebral disc or in front of the upper part of the L5 vertebra. This procedure must be carried out bilaterally, with neurolytic blockades using 6% phenol or 98% alcohol preferred.
Complications may include retroperitoneal hematoma and acute ischemia of the leg if an atherosclerotic plaque is released from the iliac vessels. Serious neurological

complications have not been widely reported in the literature concerning this block. With the transdiscal approach, risks of the procedure include infectious complications of the intervertebral disc and discitis.

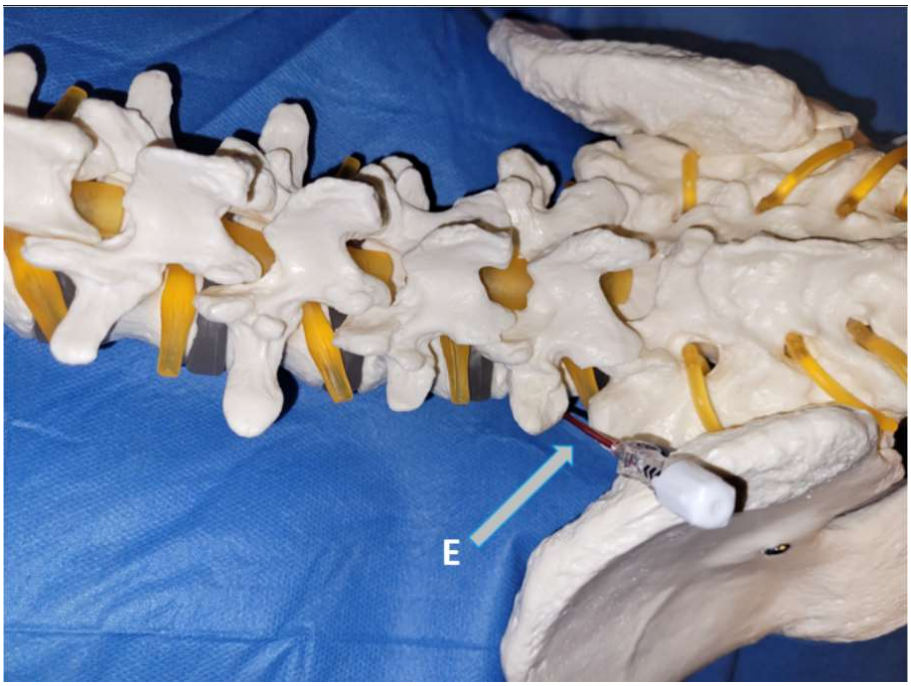


Figure 19 Dorsal view of needle position during hypogastric plexus blockade. **E**: needle (from the author's archive).

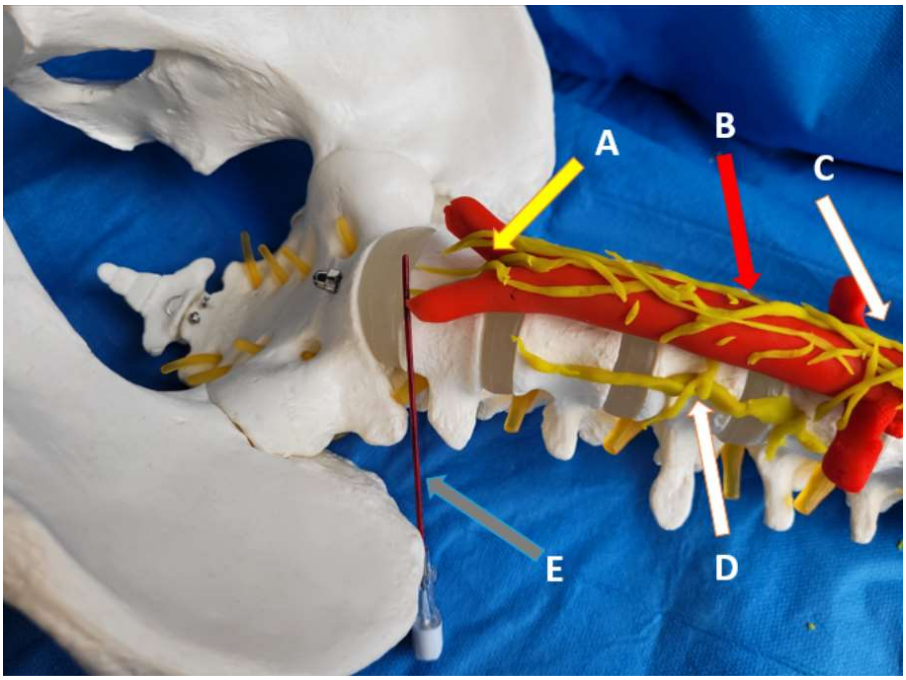


Figure 20 Ventral view of needle position during hypogastric plexus block. **A**: plexus hypogastricus, **B**: abdominal aorta, **C**: plexus coeliacus, **D**: truncus sympaticus in the lumbar region, **E**: needle (from the author's archive).

According to published EBM evidence, the following recommendations apply to the interventional treatment of localized oncological pain in pelvic tumors, according to the benefit/risk assessment system:
Neurolytic blockade of the plexus hypogastricus **recommendation class 2C+**
The level of evidence based on the review of the literature of the American Society of Interventional Pain Physicians (ASIPP) indicates **a level of evidence III** for neurolytic blockade of the superior hypogastric plexus in the treatment of oncological pain in pelvic tumors.
The recommendation according to the EBM evidence according to the benefit/risk assessment system for lumbar sympathetic blockade in the treatment of the disease - complex regional pain syndrome, is expressed as a **recommendation of class 2B+**

8.4 Chronic Pelvic Pain

Chronic pelvic pain is characterized by pain lasting longer than 6 months and located in the anatomical region of the pelvis. It is a multifactorial condition that affects more women than men. Due to its various underlying causes, this syndrome represents a complex health issue. Pain can be constant or intermittent throughout the day, and depending on its location, it may manifest as vulvodynia and/or perianal pain, bladder pain, or non-specific pelvic pain. It can also be associated with oncological pain from tumors in the pelvis or post-surgical conditions, such as after colorectal surgery. In some cases, a single disease may be the cause, while in others, pain may stem from multiple medical conditions.
Peripheral causes contributing to chronic pelvic pain include connective tissue diseases, pathologies in the pubic joint area, chronic inflammatory pelvic diseases often associated with sexually transmitted infections, residual ovarian tissue after extensive gynecological procedures, fibroids, endometriosis, varices in the uterine area and ovaries, as well as conditions such as irritable bowel syndrome, fibromyalgia, and urogenital tract diseases like interstitial cystitis. In men, the syndrome is often linked to chronic prostatitis. Risk factors include depression, mental stress, a history of sexual abuse, among others. Emotional stress exacerbates pain and affects the prognosis of the disease.

Treatment involves comprehensive pain management, with options including pharmacotherapy, hypogastric plexus blockade or ablation as an interventional technique, and consultation with specialized pain treatment centers regarding the possibility of spinal cord stimulator implantation.

8.5 Ganglion Impar Blockade

The Ganglion Impar (also known as the ganglion of Walther) is a solitary retroperitoneal ganglion formed by the fusion of terminal bilateral sympathetic ganglia into one. Positioned caudally in the midline at the junction of the last sacral vertebra and the first coccygeal vertebra, its blockade holds therapeutic value in addressing "sympathetically maintained" pain in the pelvic and perineal region, stemming from malignant intrapelvic pathology (e.g., prostate, cervical, and colon cancer) or non-malignant conditions (such as coccygodynia). Before proceeding with the blockade, it's imperative to investigate the underlying cause of new-onset pelvic pain, including screening for potential pelvic malignancies.

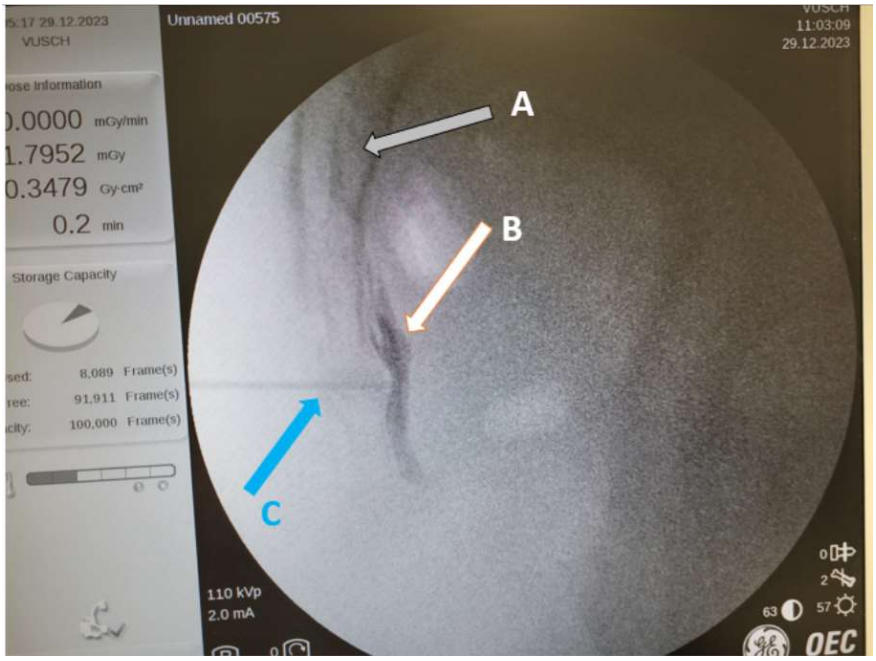
The Ganglion Impar blockade can be executed through a lateral approach via the anococcygeal ligament or a transdiscal approach, typically at the S5/Co1 level. Transdiscal blockade is the more common approach. Following a positive blockade with a local anesthetic, lytic or radiofrequency ablation procedures can be pursued for a prospective long-term effect.

Procedure Summary:

Transdiscal Ganglion Impar blockade is typically performed with the patient in the prone position under fluoroscopic guidance, often at the S5/Co1 level. After identifying the S5/Co1 intervertebral disc, a thin needle is inserted through the disc in a lateral projection, extending slightly beyond the ventral edge of the disc in the final position. An alternative, although not universally proven, approach involves entering from the region of the coccyx's end through the recto-coccygeal space.

Contrast material is then applied, distributing to outline the ventral outline of the vertebral bodies. Following confirmation of proper contrast distribution, a local anesthetic is administered during the ganglion blockade, while neurolysis involves the application of 6% phenol or 98% alcohol.

Indications for ganglion Impar blockade and neurolysis include burning, neuropathic pain of unknown etiology localized in the perineal region. It can be considered in cases of idiopathic coccygodynia (coccydynia) and tumor-related pains originating from the rectum, perineum, and external genitalia. In specific cases, combined neurolysis of the Ganglion Impar along with the hypogastric plexus may be beneficial..



Figrue 21 Lateral view (lateral projection) of needle position and contrast spread during ganglion impar blockade. **A**: coccyx, **B**: contrast spread, **C**: needle (from the author's archive).

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9 LUMBAR SYMPATHETIC CHAIN

MUDr. Ladislav Kočan PhD., FIPP

Similar to the thoracic region, a portion of the postganglionic sympathetic fibers of the lumbar sympathetic nervous system, after exiting the ganglia, accompany the course of the lumbar spinal nerves to target anatomical structures such as skin and muscles. Other postganglionic nerve fibers separate from the common nerve bundle in the course and connect to blood vessels, around which they form rich nerve plexuses.
Perivascular localization has an important influence on the regulation of vasoconstriction of the accompanying vessels and their branches supplying the lower limbs. Interventions targeting the lumbar sympathetic trunk are important in the diagnosis and treatment of various pathologies associated with sympathetic-mediated pain and conditions associated with disturbances in perfusion of lower body tissues, in which impaired microcirculation is the main pathophysiological phenomenon.
The majority of the lumbar sympathetic ganglia are found in the area of the second and third lumbar vertebrae and are, therefore, the target of blockades, ablation, and lytic procedures.

9.1 Microcirculation

Microcirculation constitutes the terminal vascular network of the systemic circulation, comprising vessels with a diameter of less than 20 μm. These microvessels include arterioles, postcapillary venules, capillaries, and their subcellular components. Technically, it serves as the terminal site of the cardiovascular system where oxygen is transferred from erythrocytes to target cells, thereby fulfilling the energy needs of tissue cells to carry out their functional activity. Microcirculatory dysfunction (MVD) is characterized by impaired autoregulation of blood flow and vascular tone, resulting in compromised oxygen delivery to tissues, elevated oxidative stress, and capillary reduction. The autonomic sympathetic nervous system appears to play a significant role at the microcirculation level, as indicated by numerous papers detailing the effectiveness of sympathetic blockade in conditions involving impaired tissue perfusion, such as critical limb ischemia.

Interventions targeting the lumbar sympathetic system have a broad range of applications, including supportive therapy for patients with critical limb ischemia. These interventions primarily aim to enhance the microcirculation of peripheral tissues. The efficacy of treatment is particularly evident in patients with responsive vessels. The effectiveness of lumbar sympathetic blockade, ablative procedures, and lytic methods can be evaluated by measuring changes in skin temperature or tissue oxygen values. Long-term treatment outcomes are best assessed using techniques focused on oxygen delivery to peripheral tissues.

9.2 Lumbar Sympathetic Ganglion Blockades

Lumbar sympathetic ganglion blockades are employed for both diagnosis and treatment of conditions associated with sympathetically maintained pain, primarily localized in the lower extremities. The sympathetic nervous system plays a significant role in regulating the vasomotor mechanisms of blood vessel microcirculation.

Typically, the lumbar sympathetic chain lies over the anterolateral aspect of the first to fourth lumbar vertebrae. Axons of lumbar sympathetic preganglionic neurons exit the spinal cord through the ventral roots of the first four lumbar spinal nerves and extend their fibers through the rami communicantes albi to the respective lumbar sympathetic ganglion. Postganglionic fibers then depart from the sympathetic chain, connecting either to the vascular plexus or to the spinal nerves via the gray rami communicantes. The majority of lumbar sympathetic ganglia are situated around the second and third lumbar vertebrae. Consequently, single-level blockade or chemical lysis, typically performed at the lower third of the L2 vertebra or the upper third of the L3 vertebra, is usually adequate. Radiofrequency ablation is conducted at three levels: L2, L3, and L4 vertebral bodies.

Sympathetic blockade is indicated in painful conditions where autonomic system involvement in pain processing is suspected or evident, such as sympathetic overactivity. Laboratory evidence suggests that sympathetic postganglionic neurons serve not only as efferent terminal nerve fibers (conducting impulses from the nerve center to the periphery) but also transmit excitations back to the nerve centers as primary afferent fibers. The autonomic nervous system forms a complex interconnection system with other motor and sensory nerve fibers. Sympathetic system blockade presumably results in a twofold effect:

1. Interruption of preganglionic and postganglionic sympathetically transmitted efferent nerve impulses, thereby blocking the transmission of sensory impulses from the central nervous system (CNS) to visceral organs and peripheral tissues.
2. A presumed second effect is the blockade of visceral afferent signals from limb organs and tissues to the CNS.

Indications for lumbar sympathetic blockade can be categorized into three groups:
1. Circulatory insufficiency of the extremities, including atherosclerotic vascular disease, diabetic gangrene, Buerger's disease, Raynaud's phenomenon, and conditions following reconstructive vascular procedures, as well as conditions following arterial embolic occlusions.
2. Renal colic pain, complex regional pain syndrome type I and II, intractable urogenital pain, post-amputation phantom pain, and frostbite.
3. Other clinical conditions such as phlegmasia alba dolens, erythromelalgia, acrocyanosis, among others.

Methodology of sympathetic blockade and sympathetic lysis:
Before conducting sympathetic lysis or ablation, a test blockade of the lumbar autonomic system is necessary to determine the expected benefit of lysis or ablation. The principle of the test nerve blockade is to temporarily (for 12 to 48 hours) prevent the transmission of nerve signals caused by sodium channel blockade following the application of local anesthetic.

Lumbar sympathetic blockade is conducted under X-ray guidance with the patient positioned prone:
1. The first step involves visualizing the L3 vertebra in the anteroposterior (AP) projection and aligning the upper endplate of the L3 vertebra. This projection ensures the correct tilt of the C-arm in the cranial direction (Figure A).
2. The second step is to obtain an oblique projection, where the transverse process of L3 overlaps with the body of the L3 vertebra (Figure B).
3. The third step entails inserting the needle in the "tunnel view" along the body of the L3 vertebra. In the tunnel view, we visualize the needle's course as if looking through it, displaying the needle as a small point (Figure C).

4. The needle position is sequentially checked in lateral and AP projections while confirming with a small amount of contrast (Figure D).

5. Following contrast imaging of the lumbar sympathetic structures, medications (6% Phenol), radiofrequency (RF) ablation, or cryoablation can be applied (Figure E and F). Note: in our hospital setting, we prefer using 6% Phenol in a 5ml volume.

6. The efficacy of the blockade can be assessed based on regional temperature changes over time and by evaluating changes in tissue oxygenation. Subjective assessment of changes in pain intensity and quality of life questionnaires before the procedure and at various time points after the procedure are appropriate.

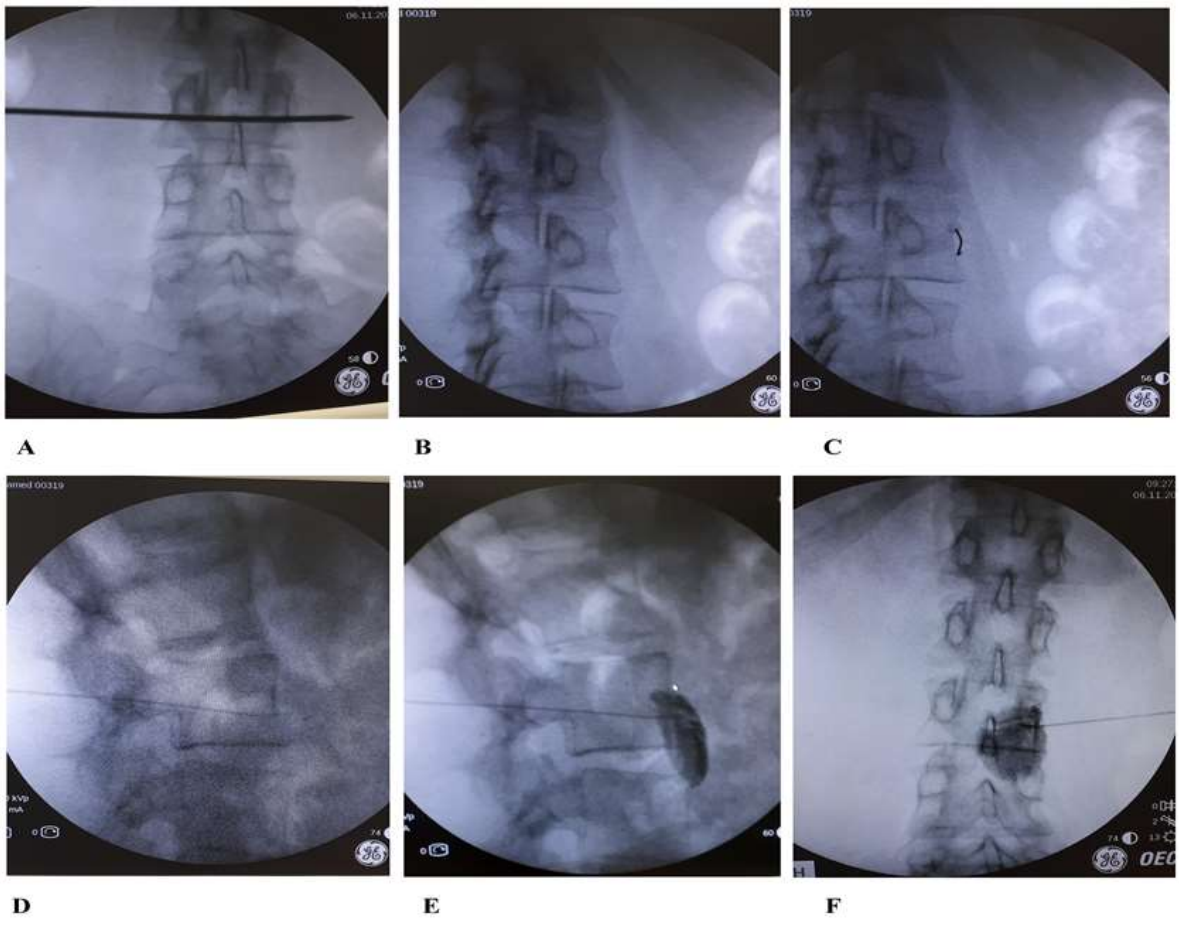

Figure 22 X-ray navigated lumbar sympathetic blockade in P-A projection, oblique projection and lateral projection **A**: endplate alignment of the target vertebra, **B**: C-arm rotation into oblique projection, **C**: needle insertion, **D**: needle control in lateral projection, **E**: contrast propagation in lateral projection, **F**: contrast propagation in A-P projection (from the author's archive).

Changes in limb temperature and dynamic tissue oxygenation are employed to monitor the impact of sympathetic blockade on microcirculation. Transcutaneous tissue oxygen partial pressure monitoring ($tcpO_2$) is a method that accurately measures the partial pressure of oxygen based on the polarographic principle. It detects diffusing oxygen from the capillary nutritive flow through the tissues to the superficial layers of the skin.

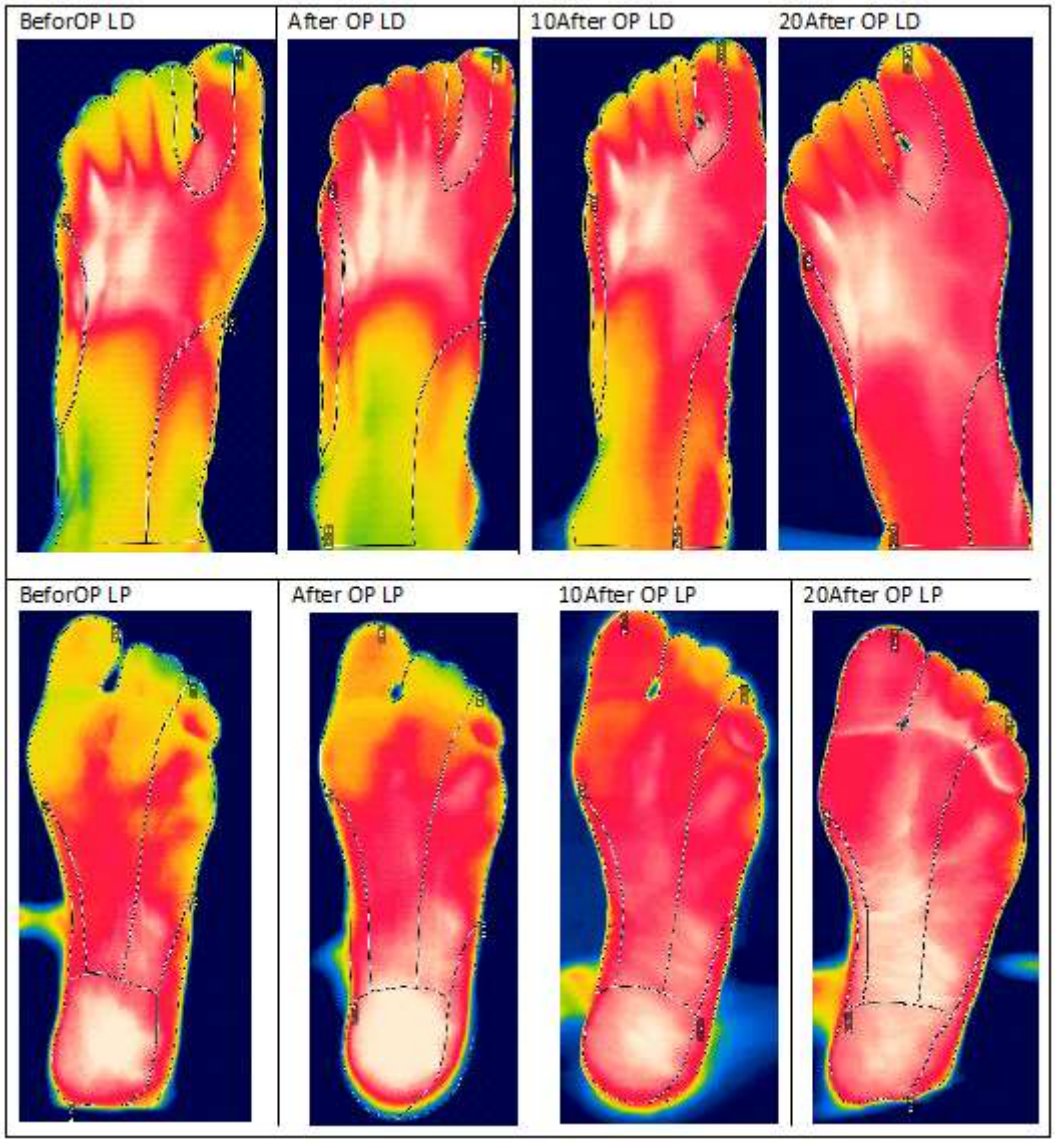

Figure 23 Imaging of the lower limbs with the FLIR SC660 high resolution infrared thermal imaging camera in the long wave spectral range. Left leg before left-sided sympathetic blockade, 5, 10 and 20 minutes after sympathetic blockade (from the author's archive).

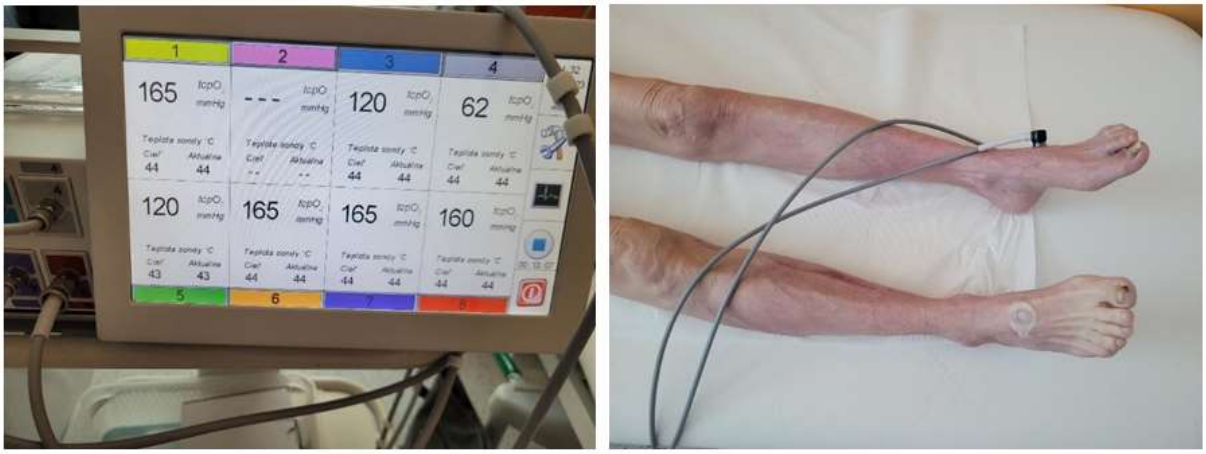

Figure 24 Tissue oxygen testing, monitoring and attachment of the Clark probe (from the author's archive).

9.3 Critical Lower Limb Ischemia

Critical lower limb ischemia (CLTI) represents the final stage of peripheral arterial disease (PAD). Current statistical data indicate an increasing prevalence of CLTI in society. It is a clinical syndrome defined by the presence of PAD combined with resting lower limb pain lasting more than 2 weeks, often accompanied by gangrene or ulceration of the lower limbs and abnormalities in monitored hemodynamic parameters. The prognosis for patients with CLTI is alarming, with significant mortality rates and frequent lower limb amputations, resulting in pain and impaired quality of life. A meta-analysis of untreated CLTI subgroups revealed a median mortality rate of 22% over 12 months, with previous limb amputation being a prognostically adverse factor associated with increased mortality.

The primary treatment for CLTI is revascularization of the affected vasculature, which has seen remarkable advancements in recent decades. However, the risk of amputation remains high, even after successful revascularization. Baubet et al. reported a 12% amputation rate within the first 6 months post-revascularization. Literature reviews indicate a high amputation rate of 15-20% within 1 year post-revascularization, despite uncomplicated procedures. Ongoing microcirculatory dysfunction may contribute to these unavoidable amputations.

Vascular revascularization surgery and endovascular techniques aim to improve tissue perfusion and oxygen delivery to the extremities. Additionally, minimally invasive interventions targeting the lumbar sympathetic system, such as lumbar sympathetic

blockade, sympatholysis, or ablation, can reduce sympathectomy, leading to vasodilation and improved perfusion in peripheral arterial vasculature, thereby reducing pain perception and enhancing wound healing in the lower limbs.

While therapeutic strategies for saving lower limbs from amputation have historically focused on revascularization of major vessels, the role of microcirculation in amputation risk has gained attention. Studies have shown that microvascular dysfunction significantly increases the risk of amputation, with approximately one in six below-knee amputations occurring solely due to microvascular dysfunction.

Lumbar sympathectomy or sympatholysis is a supportive treatment option for CLTI, performed following a positive test targeting the lumbar autonomic system. It involves permanently disrupting or disabling neural transmission in the lumbar sympathetic trunk, consisting of interconnected lumbar sympathetic ganglia L1-L5. Complication rates for the procedure are low, with temperature changes on the lower extremity skin, assessed via thermographic measurements, often showing increased vasodilation post-sympathectomy. Cohort studies have demonstrated subjective symptom improvement and objective parameters indicating enhanced tissue perfusion in 60% to 70% of patients post-procedure.

Evidence-based medicine recommends individual interventions for ischemic vascular disease based on a benefit/risk assessment system:

Sympathetic blockade **recommendation class 2B±**
Spinal cord stimulation (SCS) **recommendation class 2B±**

The level of evidence, based on the American Society of Interventional Pain Physicians (ASIPP) literature review, indicates a **level of evidence IV** for lumbar sympathetic blockade in the treatment of ischemic vascular disease.

The EBM evidence-based recommendation according to the benefit/risk rating system for lumbar sympathetic blockade in the treatment of disease-complex regional pain syndrome is expressed as a **grade 2B+ recommendation**

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10 DYSFUNCTION OF THE CRANIAL PARASYMPATHETIC SYSTEM

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Autonomic parasympathetic cranial innervation is provided by four cranial nerves: the oculomotor nerve, facial nerve, glossopharyngeal nerve, and vagus nerve. This innervation plays a crucial role in the complex control of physiological functions, including autonomic functions of the eyes, the function of lacrimal and salivary glands, and various defensive reflex arches. Additionally, this nerve system is implicated in the pathophysiology of certain diseases and symptoms, with headaches being one of the most common manifestations.

10.1 Cranial Parasympathetic System

The cranial parasympathetic nervous system, an integral part of the autonomic nervous system, comprises visceromotor and viscerosensory fibers that contribute to visceral pain perception and are involved in important reflexes such as the cough reflex and peristalsis. These fibers originate from four nuclei located in the brainstem and contribute to the formation of the oculomotor, facial, glossopharyngeal, and vagus nerves.

These cranial nerves contain motor, sensory, and parasympathetic fibers. After exiting the brain, preganglionic parasympathetic fibers synapse in ganglia (ciliary, otic, pterygopalatine, and submandibular) with postganglionic neurons, which then innervate target organs such as the eyes and salivary glands. The oculomotor, facial, and glossopharyngeal nerves predominantly provide parasympathetic innervation to the head, while the vagus nerve innervates organs in the thoracic and abdominal regions.

Parasympathetic innervation of the cranial nerves regulates functions such as eye accommodation, pupil size, lacrimal gland secretion, and salivary gland secretion. It also plays a role in certain types of headaches, including migraine, cluster headache, tension headache, and persistent idiopathic facial pain. Headaches involving the parasympathetic nervous system are characterized by unilateral autonomic symptoms such as miosis, ptosis, lacrimation, salivation, nasal congestion, rhinorrhea, cheek or forehead sweating, and eyelid swelling.

The parasympathetic function in the cranial region is counterbalanced by the sympathetic nervous system, which originates from the superior cervical sympathetic ganglion and supplies various target organs including the eyeball, face, pharynx, glands of the palate and nasal cavity, salivary and lacrimal glands, pineal gland, arterial smooth muscle, dilator of the pupil, upper eyelid muscle, carotid bodies, and heart.
Nociception and pain perception involve complex interactions between visceromotor, somatosensory nerves, and the autonomic nervous system. Trigeminal nerve activation triggers parasympathetic activity, leading to the release of vasoactive peptides that affect cerebral tissue perfusion, illustrating the interconnectedness of neural pathways in pain perception.

10.2 Headache

Due to their varied etiopathogenesis and diverse clinical manifestations, headaches pose a significant and intricate challenge in terms of differentiation. The International Headache Society (IHS) has undertaken the study of headaches and has developed and published the third update of the headache classification, which is based on new scientific evidence. This classification officially came into effect in January 2018 after a five-year period of its beta version. It categorizes headaches into three major groups: primary headache, secondary headache, and neuropathies associated with pain in the facial region. Each of these categories is further divided into groups and subgroups. In the following section, we provide a concise overview of the basic classification, outlining the categories, groups, and subgroups. However, due to their extensive nature, we do not delve into the sub-subgroups here. Interested readers can refer to the cited literature for more detailed information.

10.3 Headaches Associated with Autonomic Nervous System Disorders

10.3.1 Migraine

The clinical course of a migraine can be divided into 4 phases. In the first phase, which occurs about 24 hours before the actual pain attack, some patients may experience non-specific prodromes such as difficulty expressing themselves, increased appetite,

excessive yawning, irritability, etc. In the second phase, aura may appear, characterized by phenomena like photopsia (flickering lights, scintillation scotoma) and sensory symptoms (pins and needles in the hands, numbness, or dysphasia).

In stage 3, the headache emerges as the most regular and bothersome symptom. The pain is typically unilateral but may also occur on both sides of the head or alternate sides. Stage 3 can last from 2 to 72 hours. Accompanying symptoms include nausea, vomiting, photophobia, phonophobia, as well as cold hands and feet.

Phase 4 consists of postdromes. These may persist for up to 24 hours after the migraine attack subsides, characterized by feelings of emptiness, fatigue, muscle pain, or, paradoxically, euphoria.

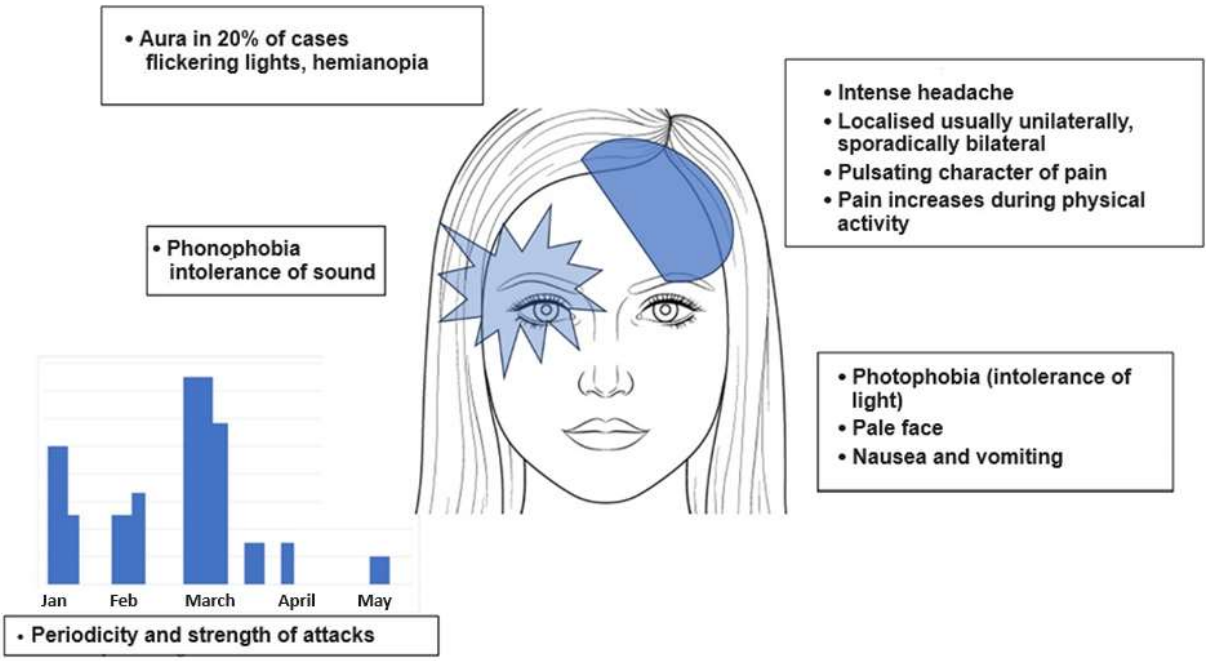

Figure 25 Schematic representation of symptoms, periodicity of attacks and migraine course (adapted from Kulichová, 2006).

10.3.2 Tension-type Headache

Tension-type headache, also known as a contraction-muscle headache, is characterized by dull or squeezing sensations, typically affecting both sides of the head and ranging from mild to moderate in intensity. Accompanying symptoms may include vomiting, visual disturbances, and focal neurological symptoms. Tension headaches are categorized

based on frequency, with episodic episodes occurring less than 15 days per month and chronic cases happening more than 15 days per month. The duration of pain varies, lasting from 30 minutes to 7 days, often starting later in the day and gradually intensifying.
Tension headaches can also occur alongside other primary or secondary headaches. Some individuals experience tension headaches in conjunction with increased cranial and cervical muscle tension.
In differential diagnosis, the primary clinical distinction between tension-type headaches and migraines lies in the absence of sensitivity to triggering factors such as light or movement in tension pain.

10.3.3 Trigeminal Autonomic Headache

Trigeminal autonomic cephalalgia (TAC) comprises a group of primary headaches characterized by unilateral headache in the trigeminal distribution accompanied by ipsilateral autonomic manifestations. TACs, although relatively rare, are often overlooked in initial diagnoses, including in pediatric cases. Accurate diagnosis is crucial for effective treatment.

This group of disorders includes:

- Cluster headache
- Paroxysmal hemicrania
- Short-duration unilateral neuralgiform headache (SUNCT/SUNA)
- Hemicrania continua
- Probable trigeminal autonomic headache

(In the appendix, you'll find The International Classification of Headache Disorders by the Headache Classification Committee of the International Headache Society)

These conditions present with an unpleasant, stabbing headache of moderate to severe intensity, along with unilateral autonomic facial symptoms such as lacrimation, conjunctival redness, eyelid swelling, ptosis, miosis, rhinorrhoea, and nasal mucosal congestion. Trigeminal autonomic headache syndromes vary in the duration and frequency of pain attacks.

In differential diagnosis, TAC must be distinguished from trigeminal pain, which is localized to the face and occurs without autonomic symptoms.

The pathognomonic features of TAC include (1) involvement of the trigeminovascular system, (2) periodicity (often sleep-related), and (3) autonomic symptoms. TACs are believed to be centrally mediated pain rather than peripherally mediated (central pain originates in the central nervous system, while peripheral pain stems from the peripheral nervous system). This assertion is supported by evidence such as gender association, circadian rhythmicity, and the prominent role of the trigeminovascular system, similar to migraine. The hypothalamus plays a critical role in these central mechanisms.

Due to the localization of pain, involvement of the ophthalmic part of the trigeminal nerve with adjacent perivascular autonomic nervous system activation is assumed. Horner's syndrome manifests as dysfunction of the sympathetic part, while increased parasympathetic nervous system activity results in lacrimation and rhinorrhea. These autonomic facial manifestations persist beyond the resolution of pain and are attributed to trigeminoparasympathetic reflex activation (TPR).

The TPR reflex arc involves the superior salivatory nucleus and the sphenopalatine ganglion, with postganglionic effects on glands, mucous membranes, and blood vessels in the area. Parasympathetic system activation leads to increased release of mediators such as vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and nitric oxide (NO).

10.3.4 Chronic Paroxysmal Hemicrania

Chronic paroxysmal hemicrania is a primary headache more prevalent in women and characterized by the following symptoms:

At least 20 attacks of severe pain occurring with a frequency of 5 attacks per day (or less), localized unilaterally in the orbit, supraorbital, or temporal regions and lasting 2-30 minutes. The headache is accompanied by at least one of the following symptoms:

- Ipsilateral conjunctival injection, lacrimation, or both
- Ipsilateral nasal congestion, rhinorrhoea, or both
- Ipsilateral eyelid swelling

• Ipsilateral sweating on the forehead and face
• Ipsilateral miosis, ptosis, or both

The drug of choice for therapy is Indomethacin, typically administered at a dose of 75-150 mg/day in multiple doses. If there is intolerance to Indomethacin, acetylsalicylic acid or verapamil may be considered as prophylactic alternatives. Chronic paroxysmal hemicrania may either resolve spontaneously or persist for life.

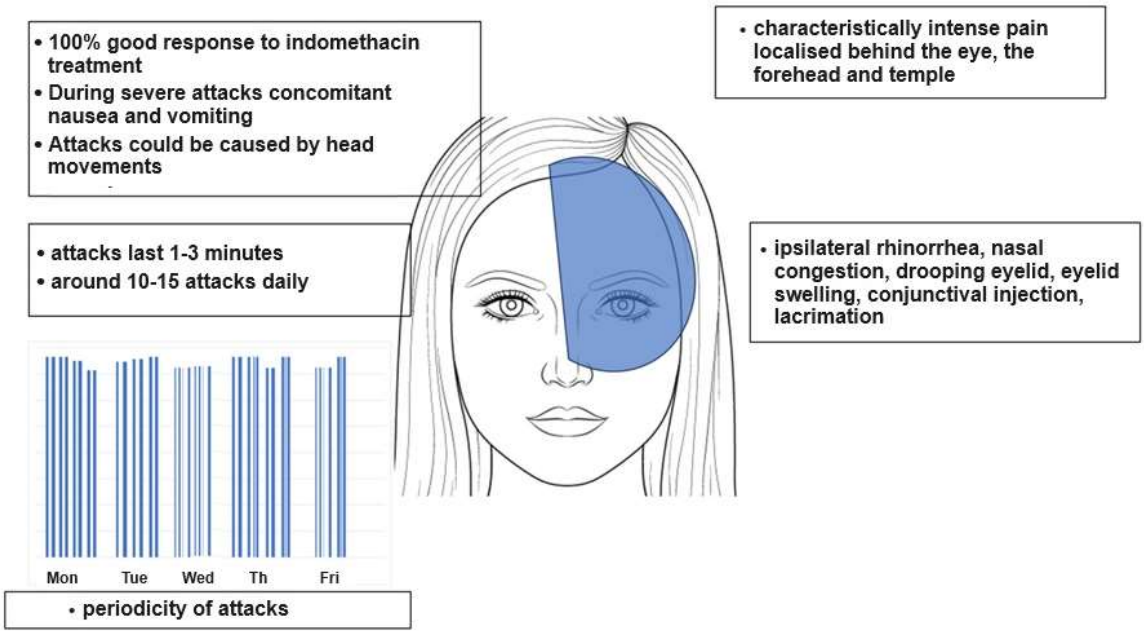

Figure 26 Schematic representation of the symptoms, periodicity of attacks and the course of chronic paroxysmal hemicrania (adapted from Kulichová, 2006).

10.3.5 Cluster Headache

Cluster headaches are characterized by unilateral pain predominantly around the eye and temples. The term "cluster" indicates the nature of the pain, as cluster headaches occur regularly. They often last for several weeks or months and may occur seasonally (spring, autumn). They may also be absent during certain periods or months. The pain is concentrated around the eye, may radiate to the jaw or the back of the head.

These headaches also affect the eye, causing redness and tearing, drooping of the eyelid, nasal congestion, increased secretion, and increased sweating of the face. The presence of partial Horner's syndrome indicates suppression of the sympathetic nervous system passing over the region of the intracranial part of the internal carotid artery and increased activity of parasympathetic innervation.

The regularity of these headaches suggests a role of the hypothalamus in their pathogenesis. Episodes of pain typically last from 15 minutes to 3 hours, often occurring at night. The interval between attacks ranges from two days to several hours, and the interval of pain occurrence may last from several hours to several days.

Treatment options are limited, but migraine medications (triptans) are commonly used, and symptoms can be significantly relieved by inhaling oxygen.

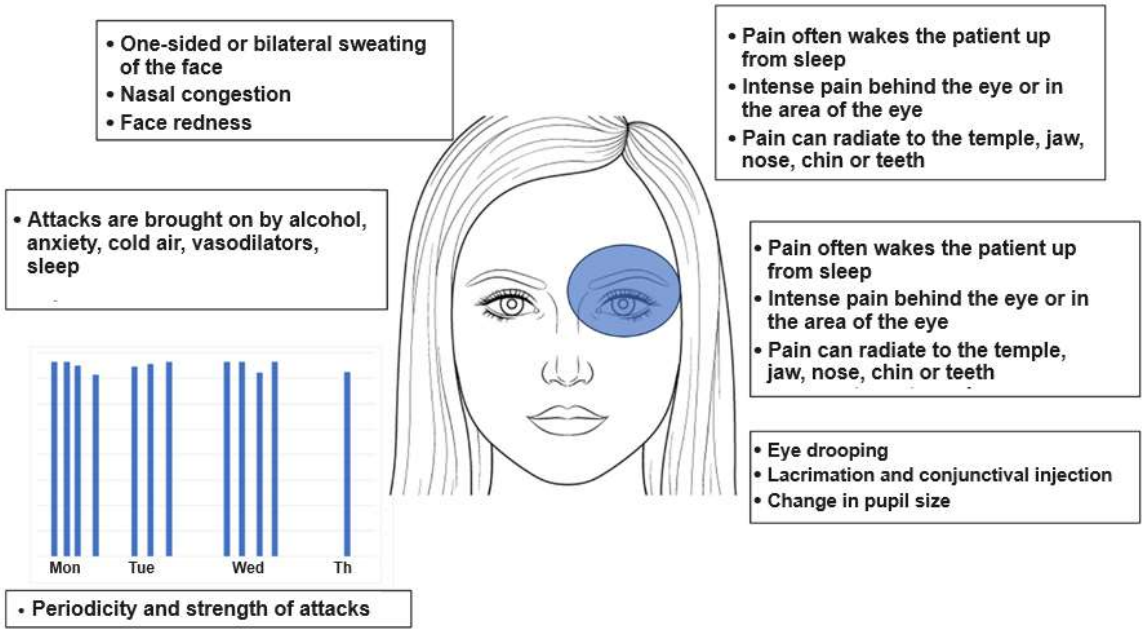

Figure 27 Schematic representation of the symptoms, periodicity of attacks and course of cluster headaches (adapted from Kulichová, 2006).

10.3.6 Hemicrania Continua

Hemicrania continua is a primary headache more common in women, lasting at least 3 months without relief. It is characterized by unilateral pain with a variable course of moderate to severe intensity. Concomitant symptoms include conjunctival hyperemia, lacrimation, nasal congestion, rhinorrhea, ptosis, and miosis.

This headache type is distinguished from migraine and cluster headache by findings on positron emission tomography (PET) imaging, which reveals evidence of mesencephalic changes in Hemicrania continua. Patients diagnosed with this condition typically respond well to treatment with indomethacin.

10.3.7 Treatment Options

The treatment of headaches relies on accurate diagnosis to determine the appropriate approach. Addressing pain with an autonomic component involves several strategies.

Symptomatic (abortifacient) treatment aims to alleviate pain and accompanying symptoms. Recommended drugs for migraine and cluster pain include ergotamine and triptans. For cluster pain specifically, inhaling 100% oxygen for 15-30 minutes at a flow rate of 7l/min is also recommended.

Prophylactic pharmacological treatment is prescribed for episodic pain, such as cluster pain, where verapamil, a calcium blocker, is commonly used prophylactically.

When conservative treatments fail, interventions targeting the parasympathetic ganglion—the pterygopalatine ganglion (PPG)—are considered. The PPG is situated within the pterygopalatine fossa (FPP), resembling an inverted pyramid about 2cm high with a 1cm wide base. Positioned posteriorly to the maxillary sinus's posterior wall, the FPP communicates laterally with the infratemporal fossa. Above the FPP, the foramen rotundum allows passage for the maxillary nerve (the second branch of the n.V). Anteriorly to the FPP lies the medial nasal concha.

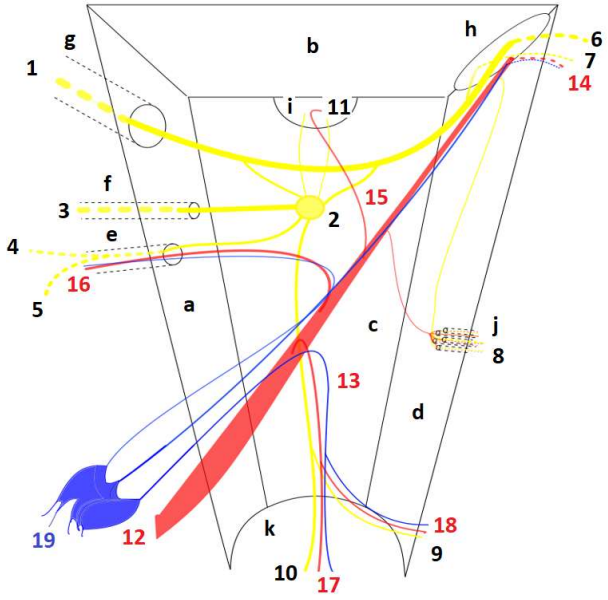

Figure 28 Schematic representation of the anatomy of the pterygopalatine fossa **a** – processus pterygoideus; **b** – facies maxillaris alae majoris o. sphenoidalis; **c** – lamina perpendicularis o. palatini; **d** – facies infratemporalis maxillae; **e** – canalis pterygoideus; **f** – canalis palatinovaginalis; **g** – foramen rotundum; **h** – fissura orbitalis inferior; **i** – foramen sphenopalatinum; **j** – foramina alveolaria; **k** – canalis palatinus major; **1** – n. maxillaris; **2** – ganglion pterygopalatinum; **3** – ramus pharyngeus; **4** – n. petrosus major; **5** – n. petrosus profundus; **6** – n. zygomaticus; **7** – n. infraorbitalis; **8** – nn. alveolares sup. post.; **9** – nn. palatini minores; **10** – n. palatinus major; **11**– nn. nasales posteriores; **12**– a. maxillaris; **13**– a. palatina descendes; **14**– vasa infraorbitalia; **15**– vasa sphenopalatina; **16**– vasa canalis pterygoidei; **17**– vasa palatina majora; **18**– vasa palatina minora; **19**– plexus pterygoideus (https://www.wikiskripta.eu/w/Fossa_pterygopalatina).

Interventions targeting the pterygopalatine ganglion (PPG) involve both diagnostic test blockades and therapeutic procedures. Following a successful blockade, radiofrequency denervation can be administered, all performed under X-ray guidance.

During the procedure, the patient lies in a supine position with the head immobilized, and intravenous access is established. Blood pressure, ECG, and pulse oximetry are continuously monitored. The patient remains conscious, breathing spontaneously, and receives oxygen via a mask while lightly sedated. Local anesthesia is applied to the injection site.

With the head position corrected in the lateral projection, the radiograph should depict both left and right FPP. The insertion needle is then guided just below the zygomatic bone arch. Throughout the procedure, the needle is advanced slightly cranially and anterio-posteriorly, with its progress regularly assessed by radiographic imaging in lateral and PA projections. Once in the final position, the needle should make contact with the lateral wall of the nasal fossa, adjacent to the medial nasal concha.

Subsequently, either local anesthetic is injected into the ganglion for a test blockade or an RF electrode is inserted through the RF needle for long-lasting ganglion lesioning. In RF procedures, motor and sensory stimulation are initially tested, followed by either pulsed radiofrequency denervation at 42°C or conventional radiofrequency denervation at 80°C for 60 seconds.

The primary risk associated with the RF procedure is complete destruction of the PPG, potentially leading to persistent dry eye. Other potential, albeit less severe, complications include temporary hypoesthesia of the soft palate, epistaxis, nasal swelling, and cheek hematoma.

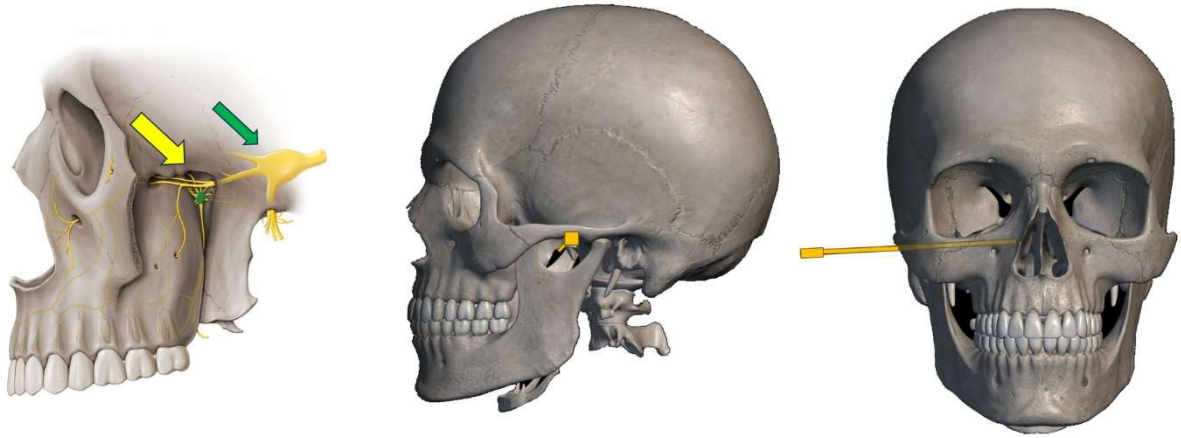

Figure 29 Schematic representation of the anatomy of the pterygopalatine fossa with the sphenopalatine ganglion (yellow arrow) trigeminal ganglion -ganglion gasseri (green arrow). Anatomical representation of needle insertion in sphenopalatine ganglion block in lateral and AP projection (adapted from Stogicza, 2020).

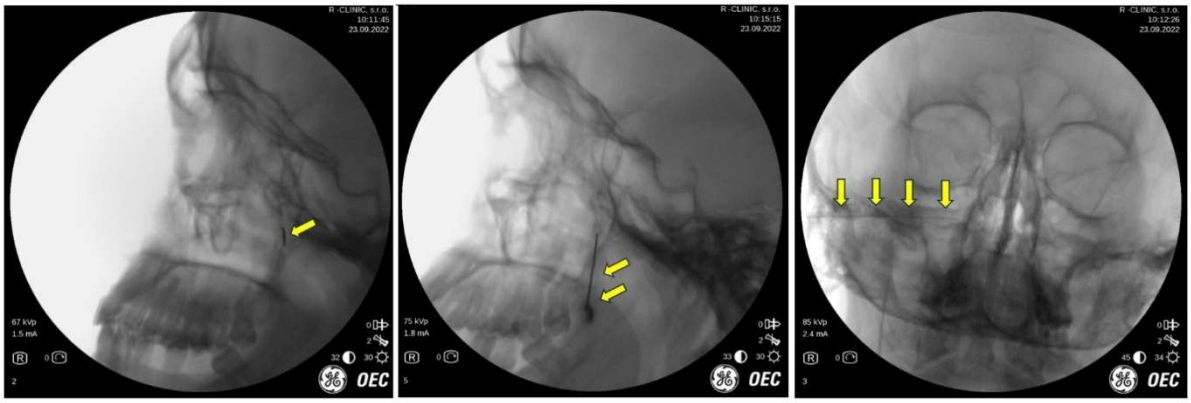

Figure 30 Interventional procedure of the sphenopalatine ganglion blockade under X-ray navigation in lateral and AP projection (from the author's archive).

As an outpatient procedure to alleviate intense headache and facial pain (such as migraine, cluster pain, or idiopathic facial pain), a brief ganglion blockade with a limited duration can be conducted. The procedure involves inserting a swab trans-nasally through the nasal passages. A local anesthetic is then injected through the hollow rod, absorbed by the mucosa, and infiltrating the PPG ganglion, thereby modulating its activity.

Local Anesthetics	
Type	Group
0,25% Bupivacaine	Amide Local Anesthetics
4% Lidocaine	

Figure 31 Infiltration of the sphenopalatine ganglion with local anesthetic. Material: swab, local anaesthetic (Kováčová, 2023).

Interventional headache from an EBM perspective

According to the EBM publication evidence, evaluated by the benefit/risk system, the following recommendations issued by the World Institute of Pain (Benelux section) are valid for the interventional treatment of headache and idiopathic facial pain:

Persistent Idiopathic Facial Pain - Pulsed RF of the sphenopalatine ganglion - **Recommendation 2C+**

Persistent Idiopathic facial pain - RF denervation of the sphenopalatine ganglion - **Recommendation 2C+**

Cluster facial pain - RF denervation of the sphenopalatine ganglion -

Recommendation 2C+

Level of evidence based on the American Society of Interventional Pain Physicians (ASIPP) literature review, for interventional procedures targeting the sphenopalatine ganglion:

Thermal Radiofrequency Surgery - Cluster Headache - **Level of Evidence IV**

Thermal radiofrequency procedure - PPG facial neuralgia - **Level of evidence IV**

Pulsed radiofrequency denervation - idiopathic facial pain - **Level of evidence IV**

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https://www.wikiskripta.eu/w/Fossa_pterygopalatina

11 CLINICAL SIGNIFICANCE OF THE VAGUS NERVE

MUDr. Ladislav Kočan PhD., FIPP

The vagus nerve is an important cranial nerve that contributes to the complex innervation of the autonomic structures of the neck, thoracic, and abdominal organs. Its activity is a crucial part of the physiological regulatory mechanisms in the body. On the other hand, it should be noted that the imbalance of the autonomic nervous system, involving innervation of the vagus nerve, plays a variable role in the pathogenesis of various diseases (positive versus negative effects of its action).

11.1 Vagus Nerve

The vagus nerve contains visceromotor, somatomotor, somatosensory, viscerosensory, and gustatory fibers. Viscerosensory fibers of the vagus nerve supply signals from the pharynx, larynx, and internal organs of the thoracic and abdominal cavities to the central nervous system. Somatosensory fibers of the vagus nerve, running in the auricular branch of the nerve, innervate a small area of the posterior and inferior wall of the external auditory canal and the upper part of the auricle adjacent to the auditory canal. Special sensory fibers of the vagus nerve transmit taste stimuli from the epiglottis region and the adjacent part of the root of the tongue. Visceromotor fibers of the vagus nerve terminate in the organ ganglia of the digestive tract (communicating with the enteric nervous system), and then in the intramural ganglia of the respiratory tract, heart, great vessels, and other organs. From these ganglia, short postganglionic fibers emerge to innervate the effector cells of organs such as the myocardium, glands, and smooth muscle. The somatomotor fibers of the vagus nerve, together with those of the glossopharyngeal nerve, innervate most of the muscles of the soft palate and pharynx, as well as the muscles of the larynx.

The vagus nerve is a major part of the parasympathetic nervous system, involved in controlling important body functions such as regulating lung function, heart function, vasomotor function of blood vessels, digestion, and immune responses. Its activity is involved in controlling psychological functions, including modulating feelings and mood.

Its function is also involved in some reflex actions such as coughing, sneezing, swallowing, and vomiting.

The vagus nerve conducts parasympathetic fibers to the organs of the thoracic and abdominal cavities, thus complementing the cephalic and sacral parasympathetic nerves. It supplies parasympathetic innervation to a large part of the body, including the anatomical structures of the neck, organs of the thorax, abdomen, and parts of the organs of the pelvis. The preganglionic fibers of the vagus nerve arise from the vagal nucleus, located in the medulla oblongata. These fibers leave the skull through the jugular foramen and follow the course of the common carotid artery and internal jugular vein, descending caudally to the target organs. The vagus nerve is formed by preganglionic fibers that are very long. Connection to the postganglionic fibers occurs only in the microscopic ganglia, which are embedded near or in the walls of the organs. On the other hand, the postganglionic fibers are very short and run only in the organ tissue.

The principal neurotransmitter of the preganglionic and postganglionic neurons of the vagus nerve is acetylcholine. Acetylcholine released from preganglionic neurons acts through nicotinic receptors to induce rapid postsynaptic changes in postganglionic neurons of the autonomic ganglia. Acetylcholine, released from nerve endings of postganglionic vagal neurons, acts mainly through 5 types of muscarinic receptors M1-M5, which are functionally coupled to G-proteins.

The parasympathetic activity of the vagus nerve influences the activity of the heart, lungs, gastrointestinal tract, exocrine and endocrine glands, and immune processes, related to autonomic processes associated with energy acquisition, such as digestion, nutrient resorption, and the storage of energy stores in macro-energy molecules. This continuous neuronal regulation of the expenditure and renewal of the body's energy resources is essential for maintaining homeostasis.

In the neck, the vagus nerve innervates the pharynx, larynx, trachea, esophagus, and thyroid gland. In the thorax, it supplies vital organs such as the heart and lungs with autonomic fibers, around which its fibers form the parasympathetic part of the cardiac plexus and pulmonary plexus. The cardiac nerves slow down the action of the heart, which is why they are also referred to as nerves retardantes. The vagus nerve has a close topographical relation to the thoracic part of the esophagus, around which it equally participates in the formation of the esophageal plexus. In the abdominal cavity, it innervates the stomach, small intestine, large intestine (up to the colic flexure), liver, gall

bladder, pancreas, spleen, kidneys, and the abdominal portion of the ureters. In the pelvis, it autonomically innervates the ovaries in females and the testes in males.

11.2 Treatment Options for the Vagus Nerve

Pharmacologically, it is possible to negatively affect (block) the effects of the vagus nerve with parasympatholytic agents. Parasympatholytics work as competitive antagonists of acetylcholine at the muscarinic receptor. The best known and most widely used parasympatholytic in clinical practice is atropine, which antagonizes the muscarinic effects of acetylcholine to varying degrees by blocking the M-receptors. Conversely, very small doses of atropine irritate the vagus nerve. Atropine has a spasmolytic effect on smooth muscle, reducing the secretion of salivary, sweat, and respiratory glands. The atropine group of parasympatholytics, in addition to atropine, includes homatropine (used in ophthalmology), scopolamine (which has antiemetic effects), benztropine, and biperiden, used in the treatment of parkinsonism. The second large group is synthetic parasympatholytics, which are used in clinical practice as antispasmodics and antiparkinsonics.

Conversely, the increased parasympathetic effect achieved by the pharmacological route occurs after the administration of parasympathomimetics. Parasympathomimetics are divided into two groups based on their action, either by direct interaction at the muscarinic M-receptor (acetylcholine and its derivatives) or indirectly, by inhibition of acetylcholinesterase (reversible and irreversible inhibitors).

In addition to pharmacological options to increase parasympathetic activity, vagus nerve function can also be influenced by neurostimulation techniques. Stimulation techniques targeting the vagus nerve are currently used in clinical practice in the treatment of some neurological diseases such as epilepsy, and further in the treatment of some psychiatric diseases such as depression.

11.3 The Vagus Nerve and the Immune Response

The immune system is one of the basic mechanisms for maintaining the homeostasis and integrity of the body. Its main function is to recognize its own and foreign cells, antigens, proteins, and other potentially harmful substances. This ability to distinguish self from

foreign is essential in protecting the body from invading pathogens and in eliminating damaged or otherwise altered cells of the body, such as malignant cells. The immune system consists of two major subdivisions, namely the innate (non-specific) and acquired (specific) immune systems. With innate immunity, the body's response is independent of the type of antigen, and the defensive reactions are general in nature. The acquired immune system responds to a specific antigen. The immune system is subject to complex regulatory mechanisms at multiple levels.

The regulation of immune processes involves, among other mechanisms, the humoral system via the hypothalamic-pituitary-adrenocortical axis and the central nervous system, also known as the cholinergic anti-inflammatory pathway, which is formed by the efferent pathways of the vagus nerve. The mediator of the cholinergic anti-inflammatory pathway is acetylcholine, which acts on target nicotinic acetylcholine receptors, with the specificity of regulation being local. On the other hand, the mediators of humoral regulation, activated via the hypothalamic-pituitary-adrenocortical axis, are corticosteroids, and the specificity of this control is global. The mechanisms involved in the anti-inflammatory action of the vagus nerve can be activated in two ways, either by activation of neuronal structures related to the anti-inflammatory pathway of the vagus nerve, or by directly affecting cholinergic transmission through activation of nicotinic receptors expressed on immune cells.

Activation can lead to a reduction in the extent of inflammatory processes with beneficial effects on the progression of septic and hemorrhagic shock, ischemia-reperfusion tissue injury, and other conditions where excessive activation of immune cells is detrimental. Preclinical studies suggest a possible influence of immune regulation via the descending pathways of the vagus nerve in the course of septic shock and reduction of the development of hypotension.

On the other hand, inhibition of immune functions may have a negative impact on the body's defense against invading pathogens, for example, in the first stages of bacterial peritonitis or in the period after a stroke.

Activation of the cholinergic anti-inflammatory pathway has been experimentally studied in ischemia-reperfusion tissue injury. Induced immune changes were monitored both at the local and organ system levels. Data from preclinical studies aimed at monitoring ischemia-reperfusion injury in the heart and liver suggest conclusions in which cholinergic activation leads to a decrease in blood free radicals and has a potential protective effect against the development of oxidative stress.

Another example related to the regulation of immune responses is traumatic brain injury, which is accompanied by increased activity of the vagus nerve. This results in a reduced immune response, which may contribute to increased susceptibility to infection. On the other hand, the immunosuppression induced as a result of CNS damage may limit any adverse immune system response during situations where CNS tissue epitopes are exposed to immune cells.

The vagus nerve is further implicated in the pathogenesis of autoimmune diseases that are associated with autonomic dysfunction and reduced activity of the vagus nerve. Such diseases include rheumatoid arthritis, systemic lupus erythematosus, and other chronic inflammatory diseases.

In bronchial asthma, the cholinergic anti-inflammatory pathway shows some specificity, characterized by increased release of acetylcholine from the endings of the vagus nerve. This factor has a negative effect on the course of the disease due to the bronchoconstrictive effect of acetylcholine.

The effect of vagal innervation on the respiratory system is multifaceted. It provides sensory and motor innervation of the trachea, sensitively innervates the bronchi and lungs. Vagal respiratory reflexes lead to increased respiratory effort, which is associated with expiration. Likewise, the cough reflex is activated by stimulation of the sensory endings of the vagus nerve. It is believed that there are at least two types of vagus nerves responsible for the activation of the cough reflex. The physiological regulation of the vagus nerve and its involvement in pathological conditions is described in Chapter 6, Autonomic Regulation of the Lung.

11.4 The Vagus Nerve and Oncology

In oncology, a possible role of the autonomic nervous system in tumor genesis and growth has been postulated. These hypotheses are based on facts including the proven innervation of human tumors, the expression of receptors on tumor cells for neurotransmitters, as well as the fact that neurotransmitters influence individual steps of carcinogenesis and metastasis formation. The progression of several tumor types is dependent on the intensity of the inflammatory response, which may be regulated through mediator pathways involving nuclear factor κB (NF-κB), which plays an important role in linking the progression of chronic inflammation and the eventual development of cancer. Disruption

of the NF-κB pathway leads to a marked reduction in tumor formation in models of colorectal and hepatocellular carcinoma.

Based on the above data, we hypothesize that activation of the cholinergic anti-inflammatory pathway may inhibit chronic inflammation and modulate the progression of tumor growth.

11.5 The Vagus Nerve and Cardiovascular Diseases

A decline in vagal activity is associated with an increased risk of cardiovascular morbidity and mortality. Vagal activity has been evaluated in clinical trials by parameters such as resting heart rate range, heart rate variability, and baroreflex sensitivity. This adverse phenomenon is independent of traditional risk factors.

At the same time, the autonomic system may also play a role in the development of underlying cardiovascular risk factors such as atherosclerosis and arterial hypertension, as well as obesity. In the etiopathogenesis of atherosclerosis, in addition to excessive stimulation of the sympathetic nervous system, dysfunction of the parasympathetic nervous system may also be involved in its development.

A negative correlation between vagal tone and plasma fibrinogen levels has been demonstrated, with this relationship being more pronounced in women than in men. These findings point to the potential involvement of the vagus nerve in atherosclerotic processes and their subsequent thrombotic complications.

Among other findings, there is a known positive correlation between increased vagal activity and slowing the development of arterial hypertension, cardiac hypertrophy, or the development of chronic heart failure.

11.6 The Vagus Nerve and Gastrointestinal Diseases

The extensive innervation of the gastrointestinal tract by sensory and motor fibers of the vagus nerve provides a bidirectional connection between the brain and the gastrointestinal tract. The central nervous system, through the vagus nerve, regulates physiological reactions and functions of the digestive tract such as digestion, secretion, motility, as well as sensation and gastrointestinal reflexes such as perception of discomfort in the epigastrium, nausea, sensation of early satiety, and vomiting. Sensations arising in the

gastrointestinal tract are transmitted by afferent pathways of the vagus nerve. Electrical stimulation of the abdominal afferent pathways of the vagus nerve does not produce pain; vagal afferent fibers can modulate nociception.

The most thoroughly studied role of the vagus nerve in the regulation of gastrointestinal tract activity during pathological situations is the emesis reflex. The selective antiemetic effect of 5-HT3 receptor antagonists has allowed the introduction of clinically effective drugs that also act through influencing the activity of abdominal vagus afferent pathways. The vagus nerve plays a role in the development of gastrointestinal clinical manifestations such as irritable bowel syndrome, gastroesophageal reflux, and postoperative ileus. Clinical evidence points to its involvement in pancreatitis, in the context of cholinergic regulation of the tone of the sphincter of Oddi. The vagus nerve is involved in the regulation of glucose homeostasis via innervation of the liver, pancreas, and small intestine.

11.7 Neurological and Psychiatric Disorders

Diseases associated with vagal innervation include certain neurological and psychiatric diagnoses such as epilepsy, Parkinson's disease, Alzheimer's disease, and depressive syndrome. Therapy for these diseases based on peripheral vagus nerve stimulation has a proven positive therapeutic effect. While it is standard in clinical practice for some diseases, for others it is still the subject of preclinical and clinical trials.

Electrical stimulation of the vagus nerve in the treatment of neurological and psychiatric disorders is one method that allows modulation of brain activity. The principle of treatment involves stimulation of the ascending and descending pathways running in the vagus nerve. While stimulation of the ascending pathways is mainly used in the treatment of epilepsy, stimulation of the descending pathways has thus far only been studied in experimental models, where it shows significant anti-inflammatory effects. Alternatively, the vagus nerve can be stimulated by applying a current to the external auditory canal.

Electrical stimulation of the vagus nerve was first approved in 1997 by the US Food and Drug Administration (FDA) for the treatment of pharmacoresistant epilepsy. Gradually, this treatment method began to be used in Europe as well. Currently, electrical stimulation of the vagus nerve is predominantly used in the treatment of epilepsy in several tens of

thousands of patients. VNS also shows a positive therapeutic effect in patients with depression, anxiety, Alzheimer's disease, and persistent hiccups.

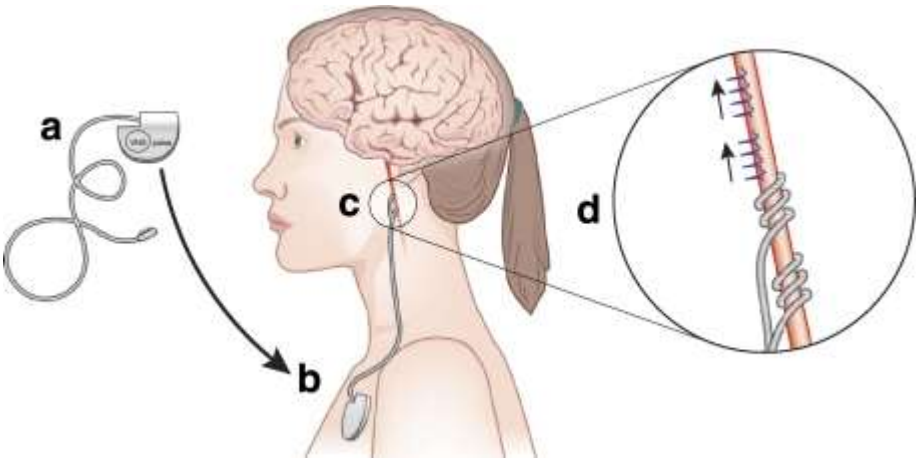

Figure 32 Illustration of the electrode placement and the vagus nerve stimulator. The spiral electrodes are placed around the left vagus nerve in the cervical region, the stimulator itself is implanted subcutaneously in the upper thoracic region (adapted from George and Aston-Jones, 2010).

According to EBM publication evidence, the American Epilepsy Society recommendations for the treatment of refractory epilepsy with peripheral stimulation of the vagus nerve, expressed according to a benefit/risk rating system, apply: **recommendation class 2C+**

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12 THERAPEUTIC APPROACHES TARGETING SACRAL PARASYMPATHETIC INNERVATION

MUDr. Ladislav Kočan PhD., FIPP

The sacral portion of the parasympathetic nervous system originates from spinal segments S2-S4. Efferent motor nerves, known as anterior spinal nerve roots, emerge from these sacral spinal segments, accompanied by parasympathetic fibers. Preganglionic parasympathetic nerve fibers, referred to as nervi splanchnici sacrales, branch off from the arising sacral spinal nerves S2-S4. These fibers either extend directly to target organs or contribute to the formation of mixed autonomic plexuses, such as the inferior hypogastric plexus, which encompasses both sympathetic and parasympathetic components.

In clinical practice, complex spinal stimulation of the anterior sacral nerve roots is utilized to alleviate unwanted symptoms following spinal cord injury. These injuries significantly impact patients' lives, leading to mobility limitations and impairments in key bodily functions such as urinary, sexual, and intestinal health. Unfortunately, direct treatment of the injured spinal cord remains elusive. Therefore, subsequent therapy focuses on enhancing the control of compromised physiological functions.

The primary objective of this treatment is to alleviate autonomic dysfunction and reduce the sensation of pressure in the urinary bladder. Standard therapy typically involves a combination of anticholinergic drugs and intermittent urinary catheterization. In more challenging cases, intravesical injections of botulinum toxin type A may be necessary. Additionally, augmentation procedures for the urinary bladder and other interventions aimed at maintaining the tone of the bladder sphincter muscles may be considered.

Alternative access involves neuromodulation of intact nerve pathways and their impact on effector organs, such as nerves supplying the urinary bladder and muscle sphincters. In 1976, stimulation of the anterior sacral spine roots was first applied for the treatment of urinary bladder dysfunction. This method was later complemented by selective dorsal rhizotomy of the spinal cord, which interrupts the reflex arc, thereby preventing reflex contractions of the urinary bladder. This approach significantly reduces urinary incontinence, increases bladder capacity, and improves compliance.

While the primary focus of anterior spinal root stimulation is on neurogenic dysfunction, it also affects the distal colorectal and anal sphincters due to their common innervation through sacral nerve roots (S2-S4). However, the clinical impact of sacral root stimulation on neurogenic bowel dysfunction has not been adequately explored.

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13 SPINAL CORD AND PERIPHERAL NERVE STIMULATION AND ITS IMPACT ON THE AUTONOMIC NERVOUS SYSTEM

MUDr. Róbert Rapčan, FIPP, MBA, PhD.

Neuromodulation, as defined by the International Neuromodulation Society (INS), involves affecting nerve activity through the action of electrical stimulation or chemical substances on specifically selected sites in the human body. Its aim is to normalize or modulate nerve function.

Neuromodulation techniques comprise a set of therapeutic modalities with various options for influencing pain pathways. These may involve the application of a selected drug or the application of an electrical signal near the peripheral (PNS) or central nervous system (CNS) to modulate pain perception. Despite many theories based on experimental results, the pathophysiological mechanism of action has not yet been clearly explained.

The dominant position among neuromodulation techniques in the management of chronic pain is represented by techniques based on the stimulation of spinal structures, dorsal ganglia, and peripheral nerves by applying electrodes to the posterior or, in specific indications, to the anterior epidural space. These therapeutic methods target chronic pain conditions such as complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS), as well as complicated ischemic pain. Patients are usually referred for this type of therapy only after other treatment options have been exhausted.

13.1 A Brief History of Neuromodulation

Electrical stimulation of the nervous system has a long history, dating back to ancient Rome. It progressed somewhat during the 19th century and began to gain real medical and clinical significance in the 20th century. The introduction of the gate control theory by Melzack and Wall, which proposed that stimulation of thick myelinated non-nociceptive fibers leads to a perceived closing of the "gate" for pain transmission by non-myelinated nociceptive fibers, can certainly be seen as a significant historical breakthrough. In 1997, Wall and Sweet pioneered therapeutic peripheral nerve stimulation, while Shealy and Mortimer introduced spinal cord stimulation for the treatment of chronic pain. In 1973, Hisobuchi performed the first thalamic stimulation, and four years later, Richardson and Akil reported the first use of periventricular

stimulation for somatic pain. Further advances in stimulation techniques, therapeutic protocols, and indication algorithms continue to be developed and refined. Spinal cord and brain stimulation are becoming standard practices in modern medicine in many countries around the world, including Slovakia.

13.2 Mechanism of Action of SCS

Electrical stimulation using implantable devices entered its modern phase of use in the 1980s, and new electrode designs, implanted pulse generators, and treatment protocols are continually being developed. Interestingly, despite approximately 50 years of technical innovation, there has been no significant improvement in the clinical effect of spinal cord stimulators. The actual mechanism of action is nowadays conceived in a very complex way and is explained by neurophysiological processes in the posterior spinal cord fascicles, subcortical, and cortical structures of the nervous system. This complex effect leads to a change in the balance of the descending inhibitory and excitatory mechanisms of the nervous system, in favor of inhibition. It is also very likely that endogenous opioids have some effect, although previous research suggests that kappa and delta receptors are more important in spinal cord stimulation, with mu receptors playing only a marginal role. The gate control theory of Wall and Melzak is now considered obsolete.

13.3 Conventional Percutaneous Spinal Cord Stimulation

Currently, spinal cord stimulation is the most acceptable method of choice in treating patients with FBSS. Patients in whom previous conservative therapy has not produced the expected pain relief are indicated for this form of treatment. These patients experience persistent lower limb pain and are not candidates for further surgical treatment due to unproven structural changes in the spine. Therefore, the goal of SCS in such patients is to cover at least 80% (ideally 100%) of the painful area through which the paresthesias are spreading and to achieve at least a 50% reduction in pain along with a significant improvement in their quality of life within 1-2 years of use.

SCS has a significant positive effect especially in neuropathic pain. Based on the evidence of several studies, it is clear that the sooner treatment of neuropathic back and leg pain

with SCS is initiated after the first failed surgery, the better results can be achieved. Clinical results support the gate control theory of pain as a fundamental concept that respects the selective recruitment and stimulation of low-threshold, large-diameter collateral nerve fibers when the transmission of neural pain signals to the brain is blocked. Implantation of an SCS consists of placing electrodes in the epidural space at the appropriate level of the spine under local anesthesia, as patient cooperation is required. Ideal placement is considered to be in the area of the attachment of the posterior horns to the spinal cord. The generator is placed in a subcutaneous pocket in the abdominal area to minimize strain on the patient while allowing comfortable operation. Fibrosis around the electrode occurs 6-8 weeks after surgery, improving its fixation. To maximize the success of SCS, the effectiveness of the electrodes should be tested during the trial period. To continue treatment, it is important that during this period the induced paresthesias cover at least 80% of the painful area and are pleasant, and the phenomenon of post-stimulation analgesia should be present - the analgesic effect should persist even after the stimulation is switched off.

Thanks to multipolar, multichannel, and multiprogram techniques, stimulation can be optimally adapted to the specific needs of each patient. Although the initial cost of the device is high, the treatment lasts for several years. Research has shown that after 3.2 years, SCS becomes cost-effective compared to conventional therapy. SCS has been shown to have a significant therapeutic effect that can lead to uninterrupted, long-term pain relief with a reduction in pain medication consumption, improved quality of life and functional status, and in some cases even the ability to return to work and everyday activities that the patient has been unable to pursue due to pain. Additionally, SCS is associated with minimal side effects.

13.4 High-Frequency Percutaneous Spinal Cord Stimulation

Traditional SCS generators normally operate at frequencies ranging from 2 to 1200 Hz, with the most commonly used frequencies being 40 to 60 Hz. At these frequencies, patients experience a tingling sensation (paresthesias), ideally covering the patient's pain distribution. This type of stimulation requires perioperative testing and positioning of the electrodes to ensure that the paresthesias cover the painful area as much as possible. Finding the possibility of coverage by paresthesias was and is very difficult, often

impossible, in cases of axial back pain. As such, SCS has long been limited to predominantly extremity pain.

High-frequency spinal cord stimulation uses short pulse duration (30 microseconds), high frequency (10 kHz), and low amplitude (1 to 5 mA) without generating paresthesias, with a good effect on axial back pain. The mechanism of action is not clearly explained, but it is hypothesized that the main effect of high-frequency electrical current stimulation is to stabilize WDR neurons in the posterior spinal cord fascicles and convert them from a pathological hyperexcited state to a physiological state, prior to the onset of chronic pain. Because the high-frequency system does not generate paresthesias, it does not require perioperative testing of the electrode position, and only anatomical placement is sufficient, saving operation time. Also, the absence of paresthesias does not disturb the patient's sleep, and this, together with the pain-reducing effect, increases the quality of sleep, which is a significantly positive factor in any complex pain syndrome.

13.5 Burst Stimulation

It is a long-term effort in neuromodulation therapy to achieve the highest quality pain control effect for each individual using a spinal cord stimulator. The standard is to work with parameters such as pulse width, frequency, and amplitude. We try to adjust these parameters according to the patient's needs. A very important, although often underestimated parameter, is the frequency of stimulation. Apart from the conventional frequency of up to 1200 Hz, a high-frequency stimulator is also used today, where the frequency of stimulation is up to 10 kHz. Another interesting pattern in stimulator frequency programming is the combination of high frequency with conventional, tonic stimulation - so-called "burst" stimulation. This stimulation uses a series of five high-frequency pulses of 500 Hz (500 Hz spike frequency). Each series is repeated 40 times per second (40 Hz burst frequency). The pulse width is fixed at 1 ms, and the amplitude is optimized for each patient individually.

13.6 Neuromodulation in the Treatment of Visceral Pain

Visceral pain has long been considered generalized pain with no clear direct correlation between visceral innervation and the location where the patient experiences pain

(Kapural, Cywinski, & Sparks, 2011). In reality, however, visceral innervation is essentially analogous to cutaneous dermatomes, which mimic the embryonic origin and position of the organ in question and are ultimately arranged into so-called viscerotomes. Painful visceral impulse conduction can be traced towards the spinal cord and the corresponding viscerotome, and it is also possible to subsequently link this to the corresponding dermatome. Visceral innervation is mediated by the sympathetic and parasympathetic nervous systems. Parasympathetic afferent fibers enter the vagal fascicles, whereas sympathetic afferent fibers enter the lower six thoracic and upper three cervical segments. It is the implantation of the SCS electrode into the epidural space at this level and the influence of neuromodulation treatment on these segments that should lead to a significant reduction in the perception of pain impulses from the abdominal visceral organs. The implantation of electrodes in the anterior epidural space to influence visceral pain is also being experimented with. The use of spinal cord stimulation in the treatment of visceral pain is still considered more or less experimental medicine, but year by year more and more facts are accumulating that support the idea of using this method also in this segment of advanced pain treatment.

13.7 Autonomic Nervous System and the Hypothesis of Its Influence by Spinal Cord Stimulation

The autonomic nervous system (ANS) is an important and self-regulating nervous system involved in maintaining homeostasis and regulating internal organs. This system autonomously provides vital functions, innervating the smooth muscles of internal organs, blood vessels, skin, heart, and glands through neurons of the central and peripheral nervous system. It also influences the striated musculature of organs related to autonomic functions such as respiratory and esophageal muscles.

The main function of the ANS is to maintain optimal vital organ functions, such as heart function and smooth muscle tone, to meet the body's momentary needs. Through its activity, the ANS regulates cardiovascular, respiratory, digestive, urinary, and reproductive systems, as well as endocrine and metabolic functions, thermoregulation, emotional and behavioral expressions, and adaptive responses to stress.

Considering all hypotheses related to the mechanism of action of SCS, it is likely that spinal cord stimulation also affects the autonomic nervous system, leading to changes in

skin conductance, heart rate, and respiratory rate. Prolonged pain disrupts the balance of the autonomic nervous system, reducing inhibitory parasympathetic mechanisms and potentially increasing heart rate. Heart rate variability may serve as a parameter for monitoring the clinical success of treatment in chronic pain patients.

Respiratory rate tends to increase in patients with chronic pain, but certain interventions like yoga practice may modify this parameter. Spinal cord stimulation appears to amplify the action of the parasympathetic nervous system, leading to modifications in heart rhythm and respiratory rate. In analyzing the mechanism of action of spinal cord stimulation, uncertainties remain, including its influence on the autonomic nervous system. The literature suggests interactions between peripheral and central systems regulating cardiovascular function and pain modulation, potentially mediated through the nucleus tractus solitarius (NTS). Afferent vagal effects in the NTS may interact with impulses from nociceptive pathways, affecting overall pain thresholds and autonomic functions. Several studies have observed changes in heart rate and respiratory rate with SCS, suggesting modulation of the sympathetic and parasympathetic nervous systems. Dysregulation of the sympathetic nervous system may manifest as increased skin conductance due to excessive sweating, although research on the effect of SCS on skin conductance has yielded inconclusive results. Further research is needed to elucidate the specific effects of SCS on autonomic function and to explore potential therapeutic implications.

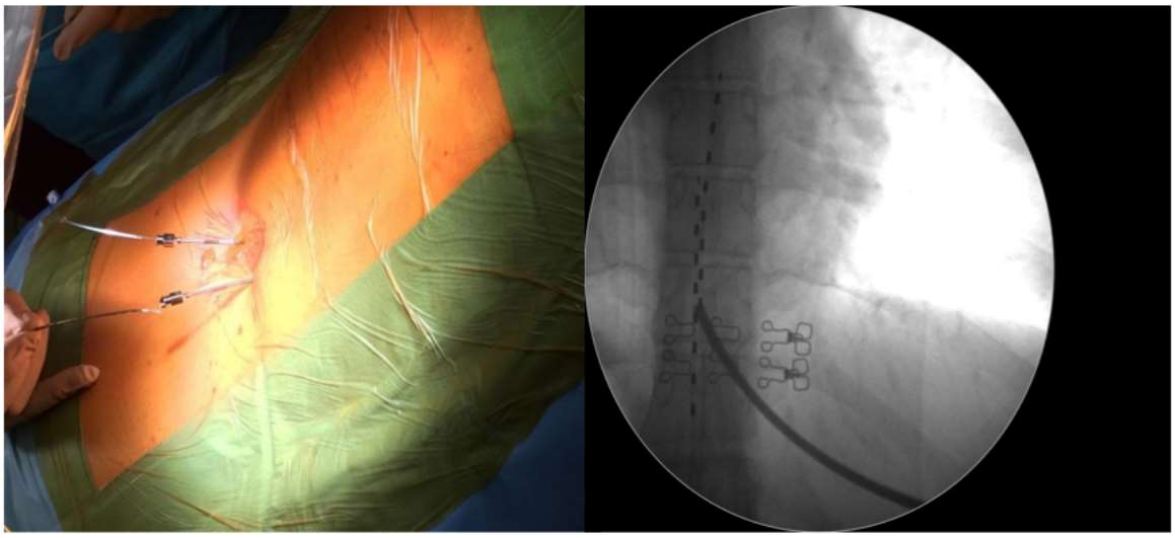
13.8 PNS and the Autonomic Nervous System

Peripheral nerve stimulation operates on the principle of directly affecting electrical activity in the peripheral nerve. A common indication is the bilateral stimulation of the great occipital nerve in certain types of headaches, as well as vagal stimulation. However, various other neuropathic pains involving peripheral nerves are also indications for this therapy for effective pain management (such as damage to the brachial plexus, intercostal neuralgia, among others). Despite the placement of electrodes in close proximity to the peripheral nerve, the likely mechanism of action is very complex. For instance, cervical stimulation of the vagus nerve operates on the principle of modulating peripheral and central nociceptive functions. It inhibits inflammatory cascades, reducing TNFA, IL - 1b, IL - 18, and other cytokinins. Simultaneously, the effect of vagal stimulation decreases

thalamic activity and the activity of neurons in the trigeminal nucleus caudalis region. This should explain the reduction of symptoms in trigeminal neuralgia and migraines. However, a positive effect has also been observed in rheumatoid arthritis and Crohn's disease.

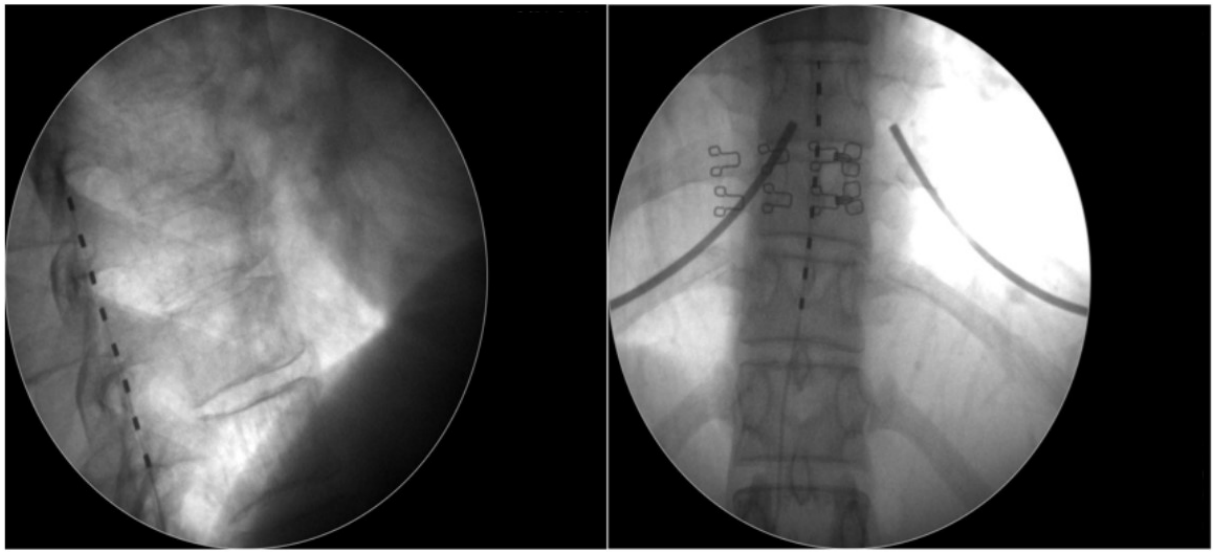
13.9 Conclusion

SCS most likely has the potential to influence the autonomic nervous system by increasing the activity of the parasympathetic nervous system, leading to a decrease in the dominance of the sympathetic nervous system. A direct effect on the sympathetic nervous system is unlikely. Although studies on patients with heart failure have been conducted, where SCS, acting at the level of Th1 - Th4 spinal segments, does not acutely improve heart rate variability (HRV) or baroreceptor sensitivity, in patients with low standard deviation of intervals between normal beats (SDNN), HRV may improve. This suggests that SCS has some effect on the autonomic nervous system in certain types of patients with acute heart failure. Animal experiments have shown a positive effect of SCS in myocardial infarction in terms of reducing the inflammatory response and myocardial fibrosis, suggesting the potential of SCS to improve the abnormal autonomic activity associated with acute myocardial infarction. It can be concluded that the biological effect of SCS as well as PNS on the autonomic nervous system is highly plausible, but further research is still needed to define a clear clinical application of SCS and PNS in the context of acting on the autonomic nervous system.



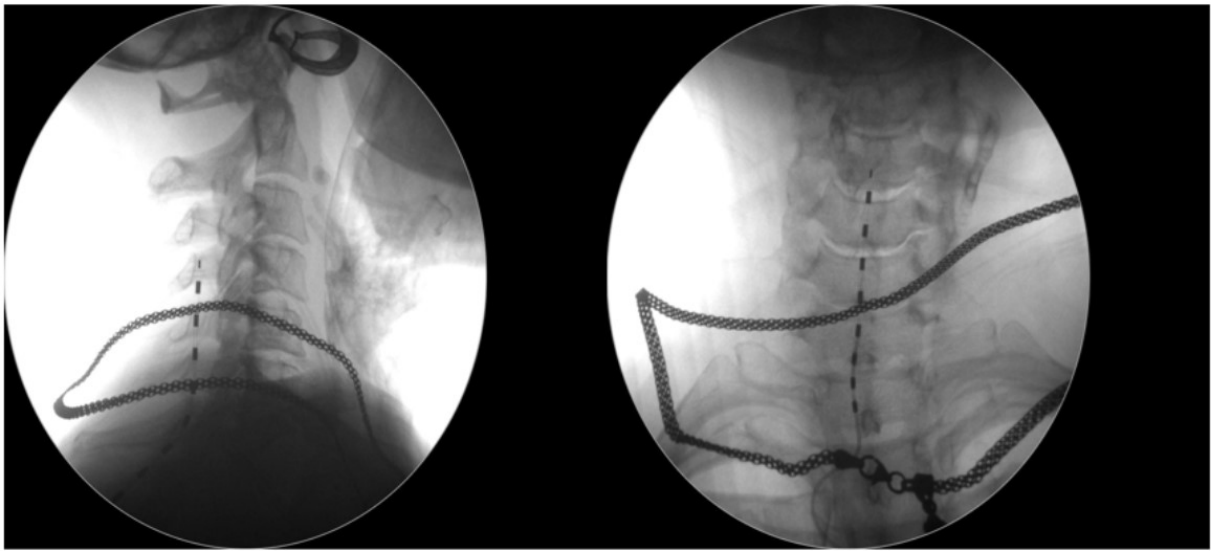
A **B**

Figure 33 **A** Implantation of the paired electrodes of the spinal cord stimulator, the patient is in the prone position. **B** placement of the paired electrodes of the spinal cord stimulator in the thoracic spine region, AP projection (Author's archive).



A **B**

Figure 33 **A** SCS, single lead placement, lateral view, thoracic level. **B** SCS, single lead placement, AP view, thoracic level. (Author's archive).



A **B**

Figure 34 **A** SCS, single lead placement in the cervical spine, lateral view. **B** SCS, single lead placement in the cervical spine, AP view (Author's archive)

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LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

Appendix

The International Classification of Headache Disorders by the Headache Classification Committee of the International Headache Society (IHS)

APPENDIX

The International Classification of Headache Disorders by the Headache Classification Committee of the International Headache Society (IHS) in 2023

I. PRIMARY HEADACHES
1. Migraine
1.1. Migraine without aura
1.2. Migraine with aura
1.3. Chronic migraine
1.4. Complications of migraine
1.5. Probable migraine
1.6. Episodic syndromes that may be associated with migraine

2. Tension-type headache (TTH)
2.1. Infrequent episodic tension-type headache
2.2. Frequent episodic tension-type headache
2.3. Chronic tension-type headache
2.4. Probable tension-type headache

3. Trigeminal autonomic cephalalgias (TACs)
3.1. Cluster headache
3.2. Paroxysmal hemicrania
3.3. Short-lasting unilateral neuralgiform headache attacks
3.4. Hemicrania continua
3.5. Probable trigeminal autonomic cephalalgia

4. Other primary headache disorders
4.1. Primary cough headache
4.2. Primary exercise headache
4.3. Primary headache associated with sexual activity
4.4. Primary thunderclap headache
4.5. Cold-stimulus headache
4.6. External-pressure headache
4.7. Primary stabbing headache
4.8. Nummular headache
4.9. Hypnic headache
4.10. New daily persistent headache

II. SECONDARY HEADACHES
5. Headache attributed to trauma or injury to the head and/or neck
5.1. Acute headache attributed to traumatic injury to the head
5.2. Persistent headache attributed to traumatic injury to the head
5.3. Acute headache attributed to whiplash
5.4. Persistent headache attributed to whiplash
5.5. Acute headache attributed to craniotomy
5.6. Persistent headache attributed to craniotomy

6. Headache attributed to cranial and/or cervical vascular disorder
6.1. Headache attributed to cerebral ischaemic event
6.2. Headache attributed to non-traumatic intracranial haemorrhage
6.3. Headache attributed to unruptured vascular malformation

6.4. Headache attributed to arteritis
6.5. Headache attributed to cervical carotid or vertebral artery disorder
6.6. Headache attributed to cranial venous disorder
6.7. Headache attributed to other acute intracranial arterial disorder
6.8. Headache and/or migraine-like aura attributed to chronic intracranial vasculopathy
6.9. Headache attributed to pituitary apoplexy

7. Headache attributed to non-vascular intracranial disorder
7.1. Headache attributed to increased cerebrospinal fluid pressure
7.2. Headache attributed to low cerebrospinal fluid pressure
7.3. Headache attributed to non-infectious inflammatory intracranial disease
7.4. Headache attributed to intracranial neoplasia
7.5. Headache attributed to intrathecal injection
7.6. Headache attributed to epileptic seizure
7.7. Headache attributed to Chiari malformation type I
7.8. Headache attributed to other non-vascular intracranial disorder

8. Headache attributed to a substance or its withdrawal
8.1. Headache attributed to use of or exposure to a substance
8.2. Medication-overuse headache
8.3. Headache attributed to substance withdrawal

9. Headache attributed to infection
9.1. Headache attributed to intracranial infection
9.2. Headache attributed to systemic infection

10. Headache attributed to disorder of homoeostasis
10.1. Headache attributed to hypoxia and/or hypercapnia
10.2. Dialysis headache
10.3. Headache attributed to arterial hypertension
10.4. Headache attributed to hypothyroidism
10.5. Headache attributed to fasting
10.6. Cardiac cephalalgia
10.7. Headache attributed to other disorder of homoeostasis

11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth,mouth or other facial or cervical structure
11.1. Headache attributed to disorder of cranial bone
11.2. Headache attributed to disorder of the neck
11.3. Headache attributed to disorder of the eyes
11.4. Headache attributed to disorder of the ears
11.5. Headache attributed to disorder of the nose or paranasal sinuses
11.6. Headache attributed to disorder of the teeth
11.7. Headache attributed to temporomandibular disorder
11.8. Head or facial pain attributed to inflammation of the stylohyoid ligament (Eaglesov syndróm)
11.9. Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth,mouth or other facial or cervical structure

12. Headache attributed to psychiatric disorder
12.1. Headache attributed to somatization disorder
12.2. Headache attributed to psychotic disorder

III. Neuropathies and Facial Pains
13. Painful lesions of the cranial nerves and other facial pain
13.1. Pain attributed to a lesion or disease of the trigeminal nerve
13.2. Pain attributed to a lesion or disease of the glossopharyngeal nerve
13.3. Pain attributed to a lesion or disease of nervus intermedius
13.4. Occipital neuralgia
13.5. Neck-tongue syndrome
13.6. Painful optic neuritis
13.7. Headache attributed to ischaemic ocular motor nerve palsy
13.8 Tolosa-Hunt syndrome
13.9 Paratrigeminal oculosympathetic (Raeder's) syndrome
13.10. Recurrent painful ophthalmoplegic neuropathy
13.11. Burning mouth syndrome
13.12. Persistent idiopathic facial pain
13.13. Central neuropathic pain

14. Other headache disorders
14.1. Headache not elsewhere classified
14.2. Headache unspecified

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Applications of the Autonomic Nervous System in Clinical Practice

Academic Teaching Text

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