# Autonomic dysfunction in critically ill patients

***Essay*** for partial fulfillment of the Master

Degree in General Intensive Care

*Submitted by*

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**Karim Mohamed Yakout**

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**Ach** : Acetylcholine
**ACPA** : anti-citrullinated protein antibodies
**AD** : Autonomic dysfunction
**AF** : Atrial fibrillation
**ALT** : Alanine transaminase
**ANS** : Autonomic nervous system
**APD** : Action potential duration
**AST** : Aspartate transaminase
**ATP** : Adenosine tri-phosphate
**BAT** : Baroreflex activation therapy
**BMI** : Body mass index
**BP** : Blood pressure
**BRS** : Baroreceptor reflex sensitivity
**CAN** : Cardiovascular autonomic neuropathy
**CB** : Carotid body
**CHD** : Coronary heart disease
**CHF** : Congestive heart failure
**CKD** : Chronic kidney disease
**CN** : Cranial nerve
**CNS** : Central nervous system
**COPD** : Chronic obstructive pulmonary disease
**CPP** : Cerebral perfusion pressure
**CRP** : C-reactive protein
**CSBs** : Carotid sinus baroreceptors
**CVD** : Cardiovascular disease
**CVLM** : Caudal ventroateral medulla
**DAN** : Diabetic autonomic neuropathy
**ECG** : Electro-cardiogram
**eGFR** : estimated glomerular filteration rate
**ENS** : Enteric nervous system
**GBS** : GuillianBarre syndrome
**GI** : Gastro-intestinal
**GU** : Gastrourinary

**HCM** : Hypertrophic obstructive cardiomyopathy
**HF** : High frequency
**HFrEF** : Heart failure with reduced ejection fraction
**HR** : Heart rate
**HRV** : Heart rate variability
**ICP** : Intracranial pressure
**ICU** : Intensive care unit
**IL** : Interleukin
**LBNP** : Lower body negative pressure
**LF** : Low frequency
**LVEF** : Left ventricular ejection fraction
**MAPs** : Mono-phasic action potentials
**MI** : Myocardial sclerosis
**MODS** : Multiple organ dysfunction syndrome
**M-RSA** : Respiratory sinus arrhythmia maneuver
**MS** : Multiple sclerosis
**MSA** : Multisystem atrophy
**NAFLD** : Non-alcoholic fatty liver disease
**NASH** : Non-alcoholic steato-hepatitis
**NIHSS** : National institutes of health stroke scale
**NTS** : Nucleus tractus solitaries
**OH** : Orthostatic hypotension
**OS** : Overall survival
**OSA** : Obstructive sleep apnea
**PD** : Parkinson disease
**PNS** : Peripheral nervous system
**PSNS** : Parasympathetic nervous system
**RA** : Rheumatoid arthritis
**RF** : Rheumatoid factor
**ROS** : Reactive oxygen species
**RRMS** : Relapsing remitting multiple sclerosis
**RVLM** : Rostral ventrolateral medulla
**SAECG** : Signal averaged ECG
**SAS** : Sleep apnea syndrome

**SBP** : Systolic blood pressure
**SCI** : Spinal cord injuries
**SNS** : Sympathetic nervous system
**SSW** : Stimulated skin wrinkling
**$T_1$DM** : Type 1 diabetes mellitus
**$T_2$DM** : Type 2 diabetes mellitus
**TNF** : Tumor necrosis factor
**ULF** : Ultra low frequency
**VLF** : Very low frequency

# Introduction

The autonomic nervous system enables the body to adjust its circulation and respirationto maintain an appropriate oxygen delivery to the tissues. It is therefore, necessaryto continuously restore the very sensitive symmetry between the two efferent-limbs of the autonomic nervous system - the sympathetic and the parasympathetic.

Acute or chronic disturbances of this sympathetic/parasympathetic balancecontribute to the pathogenesis of the cardinal symptoms of various disease states;e.g., to the dyspnea and exercise intolerance in chronic heart failure or to tachycardia, hypertension and hyperventilation during acute hypoxia in bronchial asthma.

The physiological interplay of cardiovascular and ventilatory mechanisms in regulatingoxygen delivery to the tissues is well known and described, but our knowledge. of the cardiorespiratory reflex behavior in disease states is limited.

Though disorders, requiring treatment on the intensive care unit (lCU), are accompaniedby disturbances of the sympathetic/vagal balance, there are only a fewstudies describing the autonomic tone and the interference of the cardiorespiratoryreflexes in ICUpatients.**(Haensch, CA and Isenmann, S., 2012 )**

Assessment of impaired autonomic nervous system function could not only behelpful in explaining the pathogenic origin of these disorders; it provides the ICUphysician with a potent tool for evaluation of disease prognoses, for the introductionof new therapeutic strategies and for the differentiation between chronic adaptiveprocesses of the nervous system,

such as occur in chronic heart failure patients, oracute processes, such as in hypovolemic shock.**(Keith L. Moore et al; 2014 )**

# Aim of the work

The aim of this work is to highlight the role of autonomic nervous system in clinical presentation of different diseases especially in critically ill patients, and its importance in diagnosis and prediction of prognosis.

# Autonomic nervous system anatomy & physiology

The autonomic nervous system (ANS) is a very complex, multifaceted neural network that maintains internal physiologic homeostasis. This network includes cardiovascular, thermoregulatory, gastro-intestinal (GI), genitourinary (GU), and ophthalmologic (pupillary) systems (fig. 1-1). ***(Haensch CA and Isenmann S, 2012 )***

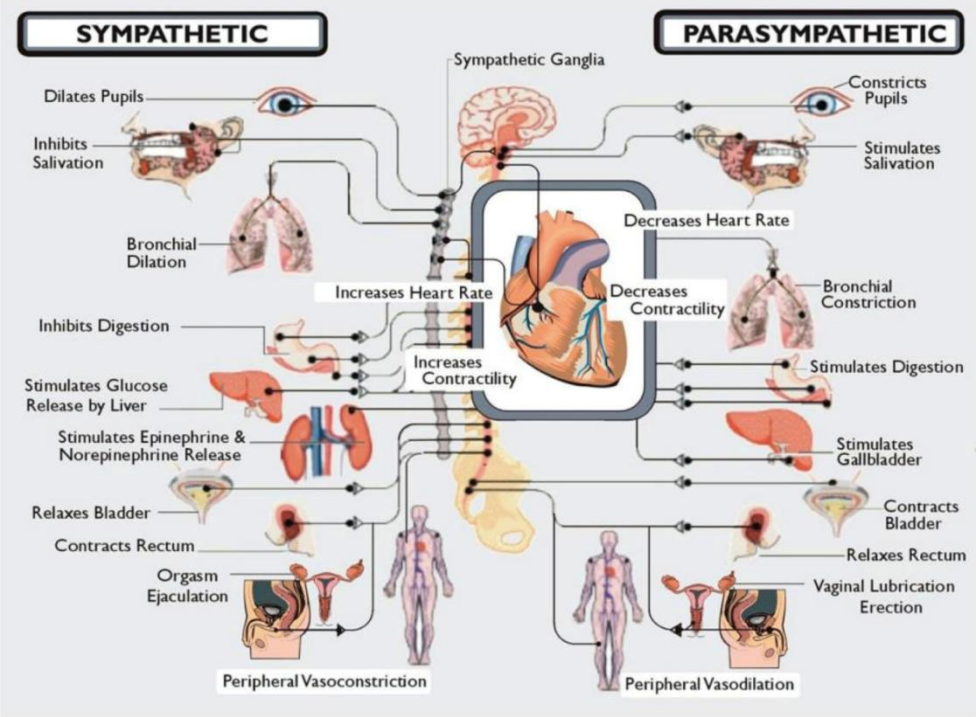


**Fig.( 1-1 ):** Organs supplied by autonomic nervous system. ***(Haensch CA and Isenmann S, 2012 )***

## 1- Sympathetic nervous system (SNS)

The **sympathetic nervous system** (**SNS**) is one of the two main divisions of the autonomic nervous system, the other being the parasympathetic nervous system. The autonomic nervous system functions to regulate the body's unconscious actions. The sympathetic nervous system's primary process is to stimulate the body's fight-or-flight response. It is, however, constantly active at a basic level to maintain homeostasis. ***(Romanov A et al., 2017)***

### Structure

There are two kinds of neurons involved in the transmission of any signal through the sympathetic system: pre-ganglionic and post-ganglionic. The shorter preganglionic neurons originate from the thoracolumbar region of the spinal cord specifically at T1 to L2-L3, and travel to a ganglion, often one of the paravertebral ganglia, where they synapse with a postganglionic neuron. From there, the long postganglionic neurons extend across most of the body.

At the synapses within the ganglia, preganglionic neurons release acetylcholine, a neurotransmitter that activates nicotinic acetylcholine receptors on postganglionic neurons. In response to this stimulus postganglionic neurons—with two important exceptions—release norepinephrine, which activates adrenergic receptors on the peripheral target tissues. The activation of target tissue receptors causes the effects associated with the sympathetic system (fig. 1-2). ***(Gulqun M, 2017)***

The two exceptions mentioned above are postganglionic neurons of sweat glands and chromaffin cells of the adrenal medulla. Postganglionic neurons of sweat glands release acetylcholine for the activation of

muscarinic receptors, except for areas of thick skin, the palms and the plantar surfaces of the feet, where norepinephrine is released and acts on adrenergic receptors. Chromaffin cells of the adrenal medulla are analogous to post-ganglionic neurons; the adrenal medulla develops in tandem with the sympathetic nervous system and acts as a modified sympathetic ganglion. Within this endocrine gland, pre-ganglionic neurons synapse with chromaffin cells, stimulating the chromaffin to release norepinephrine and epinephrine directly into the blood. ***(Keith L Moore et al ; 2014 )***

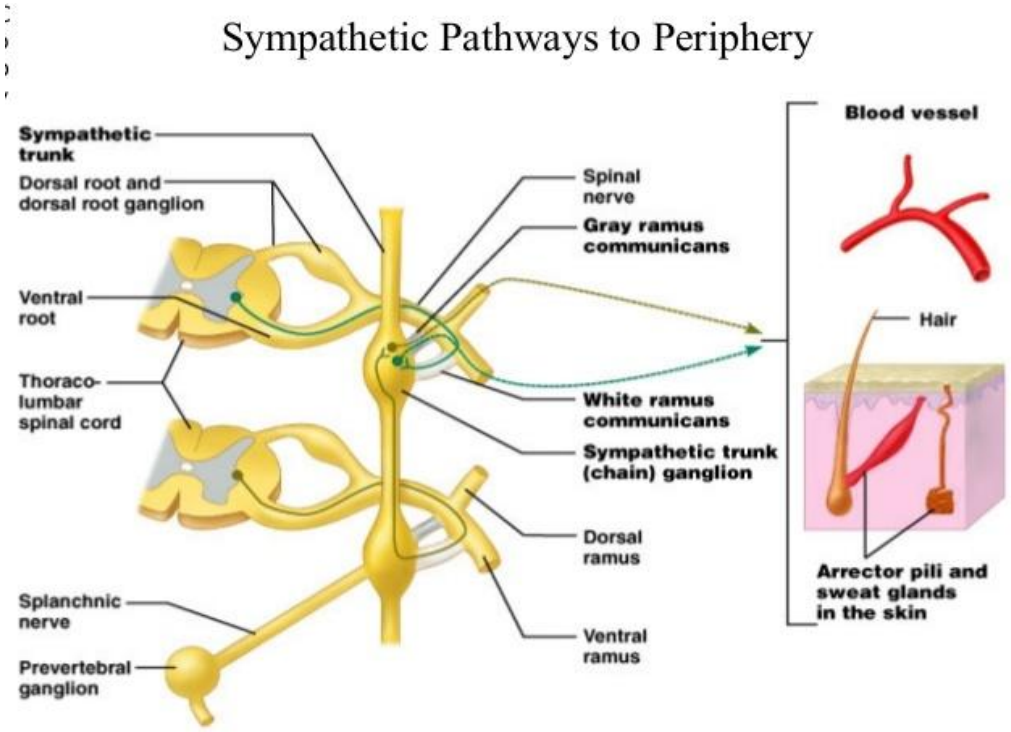


**Fig.( 1-2 ):** Sympathetic pathways. ***(Gulgun M, 2017)***

## Organization

Sympathetic nerves arise from near the middle of the spinal cord in the intermediolateral nucleus of the lateral grey column, beginning at the first thoracic vertebra of the vertebral column and are thought to extend to the second or third lumbar vertebra. Because its cells begin in the thoracic and lumbar regions of the spinal cord, the sympathetic nervous system is

said to have a *thoracolumbar outflow*. Axons of these nerves leave the spinal cord through the anterior root. They pass near the spinal (sensory) ganglion, where they enter the anterior rami of the spinal nerves. However, unlike somatic innervation, they quickly separate out through white rami connectors (so called from the shiny white sheaths of myelin around each axon) that connect to either the paravertebral (which lie near the vertebral column) or prevertebral (which lie near the aortic bifurcation) ganglia extending alongside the spinal column. ***(Watanabe N and Hotta H, 2017 )***

To reach target organs and glands, the axons must travel long distances in the body, and, to accomplish this, many axons relay their message to a second cell through synaptic transmission. The ends of the axons link across a space, the synapse, to the dendrites of the second cell. The first cell (the presynaptic cell) sends a neurotransmitter across the synaptic cleft where it activates the second cell (the postsynaptic cell). The message is then carried to the final destination.

Presynaptic nerves' axons terminate in either the paravertebral ganglia or prevertebral ganglia. There are four different ways an axon can take before reaching its terminal. In all cases, the axon enters the paravertebral ganglion at the level of its originating spinal nerve. After this, it can then either synapse in this ganglion, ascend to a more superior or descend to a more inferior paravertebral ganglion and synapse there, or it can descend to a prevertebral ganglion and synapse there with the postsynaptic cell. ***(Erica A. Wehrwein et al, 2016 )***

The postsynaptic cell then goes on to innervate the targeted end effector (i.e. gland, smooth muscle, etc.). Because paravertebral and prevertebral ganglia are relatively close to the spinal cord, presynaptic neurons are generally much shorter than their postsynaptic counterparts, which must extend throughout the body to reach their destinations.