The Autonomic Nervous System of the Heart

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Abstract

The *autonomic nervous system* (ANS) is the part of the nervous system that controls the visceral functions of the body, which are totally or largely independent of voluntary control of the individual. This part of the nervous system consists of autonomic regions in the central nervous system and of peripheral nerves. According to anatomical and functional characteristics, the ANS is classically divided into two main sections: the sympathetic and the parasympathetic systems. The former division promotes a so-called "fight-or-flight" response, while the parasympathetic autonomic system promotes a "rest and

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digest" response of the organism. The heart receives nerve fibers from both the sympathetic and the parasympathetic divisions, which variably contribute to the control of heart rate (chronotropism), contractile strength of the heart (inotropism), conductivity (dromotropism) and excitability (bathmotropism) of myocardial cells, as well as of coronary vascular tone and myocardial blood flow. The sympathetic system promotes an increase in heart rate and a positive inotropic response in order to increase cardiac output. On the contrary, the parasympathetic (vagal) system induces bradycardia and reduces myocardial contractile strength, thus resulting in decreased cardiac output.

Abbreviations

ANS	Autonomic nervous system
CNS	Central nervous system
GI	Gastrointestinal
MBF	Myocardial blood flow
nTS	Nucleus of the solitary tract
PET	Positron emission tomography
SNC	Sympathetic nerve chain

The *autonomic nervous system* (ANS) plays an outstanding role in the regulation of heart function. In this chapter, we will briefly review the anatomy and basic function of the cardiac ANS. A full understanding of the topic, however, presumes a sufficient knowledge of the whole structure of the ANS.

1.1 Overview of the ANS

The ANS is the part of the nervous system that controls the visceral functions of the body, which are usually below the level of consciousness, and therefore totally or largely independent of the voluntary control of the individual, including heart activity, respiratory function, digestion, gland secretory activity, organ and vessel motility, pupillary dilation, micturition, and sexual arousal.

The ANS is constituted by autonomic regions in the central nervous system and by peripheral nerves. The former consist of brainstem nuclei and bundles of visceral nerve fibers in the spinal cord, which have motor (efferent) and sensory (afferent) functions; the latter are represented by nerve fibers and ganglia.

The transmission of efferent autonomic impulses occurs through a sequential two-neuron pathway: a preganglionic (or presynaptic) neuron and a postganglionic (or postsynaptic) neuron. Preganglionic neurons origin from autonomic centers in the brain or spinal cord and synapse onto postganglionic neurons, which are located in peripheral ganglia, from where they innervate the target organ (Burt 1993).

According to anatomical and functional characteristics, the ANS is classically divided into two main sections: the sympathetic and the parasympathetic ANS.

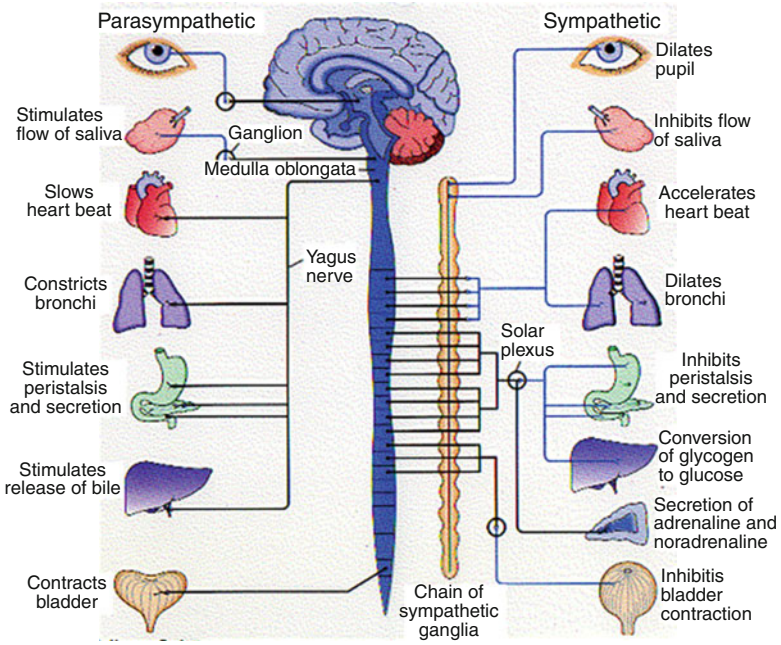

Fig. 1.1 Scheme of the sympathetic and parasympathetic nervous system (see text for description)

1.1.1 The Sympathetic ANS

A scheme of the sympathetic ANS is illustrated in Fig. 1.1. The sympathetic ANS division has a thoracolumbar "outflow," i.e., the cell bodies of the efferent preganglionic neurons are located in the intermediolateral columns of the thoracic and lumbar segments (from T1 to L2–L3) of the spinal cord. Preganglionic neurons are type B myelinated nerve fibers (<3 μm) that leave the spinal cord through the anterior roots of the respective thoracic and lumbar spinal nerves and reach the *sympathetic nerve chain* (SNC) through small white rami communicantes (Fig. 1.2).

The SNC runs on either side of the anterior face of vertebral bodies, extending from the cranium base to the coccyx and includes paravertebral ganglia along its course, specifically, 3 cervical ganglia, 11 or 12 thoracic ganglia, and 5 lumbar, 4 sacral, and 1 coccyx ganglia, which are interconnected by intermediate cords and contain the bodies of postganglionic sympathetic neurons (Fig. 1.1).

Preganglionic axons coming from a given spinal segment and nerve may terminate onto a postganglionic neuron located in the corresponding segmental ganglion or may instead travel either up or down along the SNC, synapsing onto a postganglionic neuron located in another SNC paravertebral ganglion.

Some sympathetic preganglionic fibers do not synapse in paravertebral ganglia but from SNC arrive to some specific *prevertebral ganglia* in the lumbar region (celiac, aorticorenal, and mesenteric ganglia) or ganglia located very proximal to

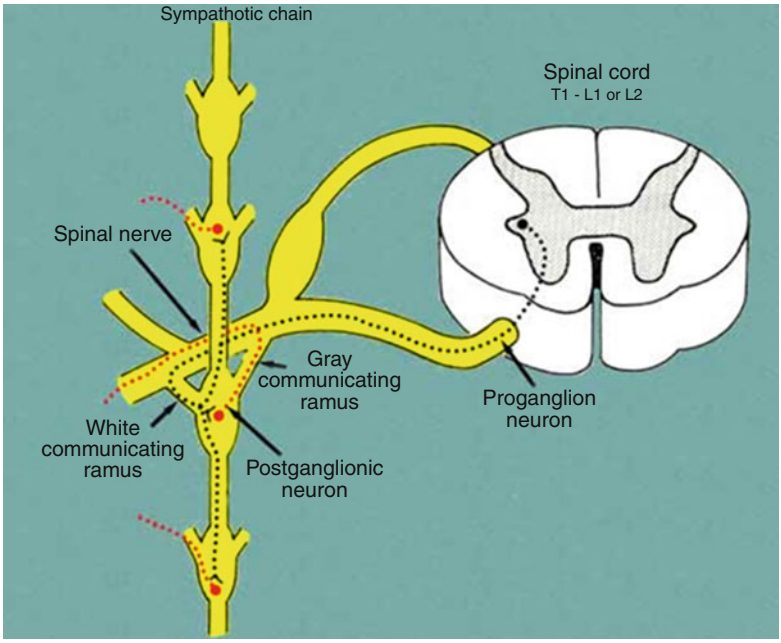

Fig. 1.2 Nerve connections between the spinal cord, spinal nerves, sympathetic nervous chain, and peripheral sympathetic nerves

target organs (*peripheral ganglia*). Finally, the SNC also sends out peripheral nerves that reach the target organs following the course of vessels (*perivascular branches*).

Postganglionic neurons are small nonmyelinated C fibers (0.3–1.2 μm) that reach the target organs by various ways. Some achieve somatic structures of the body (skin, muscles, bones) through spinal nerves that they reach from the SNC by gray rami communicantes (Fig. 1.2); some from cervical and high thoracic ganglia directly achieve cranial structures through peripheral nervous branches; similarly, visceral thoracic and abdominal organs receive sympathetic innervation from postganglionic fibers originating from sympathetic (cervical, thoracic, and splanchnic) ganglia.

1.1.2 The Parasympathetic ANS

A scheme of the parasympathetic ANS is illustrated in Fig. 1.1. The parasympathetic ANS division has craniosacral "outflow," i.e., the preganglionic efferent neurons leave the central nervous system through cranial nerves (III, VII, IX, X) or together with the anterior roots of sacral spinal nerves (mainly S2–S3, but also S1 and S4). Cell bodies of cranial parasympathetic preganglionic neurons are located in some nuclei of the brainstem, whereas those of sacral neurons are located at the

base of the intermediolateral portion of the anterior horns of the gray substance of the respective spinal segments.

Parasympathetic postganglionic neurons have cell bodies located in parasympathetic ganglia, which are always found peripherally, next to, or also within, the target organs, and are always reached by preganglionic parasympathetic fibers through somatic nerves.

It is worth noting that 75 % of all parasympathetic nerve fibers are situated in the vagus nerve (X cranial nerve). Vagal fibers mostly originate from the *dorsal motor nucleus* and, in part, from the *ambiguous nucleus*. The vagus nerve sorts out of the central nervous system through the jugular foramen at each side and travels down until the abdomen, giving branches to thoracic and upper abdominal organs.

1.1.3 Afferent ANS Fibers

As for the somatic sensitive system, signals from visceral organs are transmitted by *primary sensory neurons*. The afferent fibers originated from visceral organs travel in sympathetic and parasympathetic nerves and transmit information to the central nervous system about activities of the organ or the occurrence of tissue injury, the latter through nociceptive fibers. These signals also generate autonomic reflexes which allow regulation of organ functions. Some of these signals (e.g., pain signals) can be transmitted to cortical centers and become conscious.

Nociceptive fibers are mainly associated with sympathetic nerves. Their cell bodies are located in spinal ganglia, achieved through the SNC and rami communicantes, and they end in the posterior roots of the spinal cord, where they synapse on "second-order" nociceptive neurons. Nociceptive visceral fibers are much less numerous than nociceptive somatic fibers and usually end at more levels in the spinal cord, thus generating less specific and localized pain sensation.

Afferent primary sensory fibers associated with parasympathetic nerves are more involved in regulatory reflexes of system/organ activities. Again, they are mainly associated with the vagus nerve, but several visceral cranial afferent fibers travel with the glossopharyngeal or facial nerves and pelvic fibers with pelvic nerves. The cell bodies of these afferent fibers are located in ganglia associated with these parasympathetic nerves. Primary sensory neurons then project onto "second-order" visceral sensory neurons located in the medulla oblongata, in the *nucleus of the solitary tract*, and other nuclei.

1.1.4 The Enteric ANS

It is worth noting that enteric ganglia diffused inside the wall of the digestive tube collectively contain as many neurons as the entire spinal cord, including local sensory neurons, motor neurons, and interneurons, and is able to act as a largely autonomous part of the ANS. For this reason, the enteric ANS is often considered as a third, independent part of the ANS.

1.2 Function of the ANS

A description of the functions of the ANS is beyond the scope of this chapter, and therefore some general concepts only are discussed here.

The sympathetic and parasympathetic systems are generally thought to act in opposition to each other. However, their effects in most organs should be better considered as complementary in nature rather than antagonistic, with most visceral functions resulting from the balance of the influence of the two ANS branches (Guyton and Hall 2006). Furthermore, some viscera (e.g., visceral vessels, liver, spleen) only receive sympathetic innervations, and in other cases sympathetic and parasympathetic nerves have synergic effects (e.g., increase of salivary gland secretion).

Overall, however, the sympathetic ANS is typically activated in conditions of stress and is responsible for the so-called "fight-or-flight" response, which is characterized by enhanced heart rate and contractility, dilation of coronary vessels, bronchiole dilation and increased alveolar oxygen exchange, increased blood flow to skeletal muscles, and reduction of blood flow to the gastrointestinal tract and skin.

The parasympathetic ANS, instead, predominates in basal conditions, defining the so-called "rest and digest" status, which is characterized by dilation of blood vessels and accelerated peristalsis of the gastrointestinal tract, together with reduction of cardiac and respiratory activities.

The peripheral effects of sympathetic and parasympathetic systems are mediated by the release from nerve endings of specific chemical neurotransmitters, which act on specific receptors on cell membranes of target organs.

The neuromediator released by peripheral sympathetic fibers and therefore responsible for their effects is *norepinephrine*, while *acetylcholine* is the neuromediator released by parasympathetic nerve fibers (Fig. 1.3). Together with these primary neuromediator, both sympathetic and parasympathetic nerve fibers can variably release other substances, mainly neuropeptides, which can contribute to the final effects of nerve stimulation. Examples of these substances include neuropeptide Y, galanin, and dynorphin in noradrenergic fibers, and vasoactive intestinal peptide, calcitonin gene-related peptide, and substance P in cholinergic fibers (Jänig 2006). The exact role of most of these co-released substances, however, remains to be defined.

It is also worth noting that postganglionic sympathetic fibers for sweat glands and for skeletal muscle vessels release acetylcholine and that acetylcholine is also

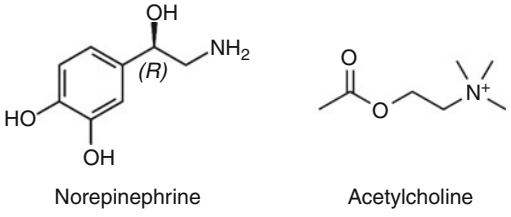

Fig. 1.3 Chemical structure of the sympathetic (norepinephrine) and parasympathetic (acetylcholine) neurotransmitters

the neurotrasnmitter of both sympathetic and parasympathetic signals by preganglionic neurons in the respective ganglia.

Norepinephrine exerts its effects through binding and activation of adrenergic receptors on target cells. Two main classes of adrenergic receptors have been described, the α- and β-receptors (Ahlquist 1948). The α-adrenergic receptors present two main types α1- and α2-receptors. Similarly, two main types of β-adrenergic receptors have been found, β1- and β2-receptors, although a third type (β3) has recently been found to also play some relevant physiological role (Bylund et al. 1994).

Acetylcholine binding (cholinergic) receptors are also divided into two main classes, based on their response to the alkaloids nicotine and muscarine. Nicotinic receptors can roughly be grouped in two main classes, muscular and neuronal receptors. Five different types of muscarinic receptors have been described, named M1 to M5, with M2 and M3 being the receptors mainly located in the heart and bronchi, respectively (Goyal 1989).

1.3 The ANS of the Heart

1.3.1 Anatomy

The heart receives abundant nerve fibers from both the sympathetic and the parasympathetic ANS.

Preganglionic sympathetic neurons for the heart have their cell bodies in the lateral horns of the spinal cord, at the level of the first 4–5 thoracic segments, and they synapse onto postganglionic nerve fibers located in paravertebral cervical and thoracic ganglia of the SNC, which give origin to *cardiac cervical nerves* (superior, medium, and inferior) and *cardiac thoracic nerves* (from the 2nd to the 4th–5th thoracic ganglia) (Fig. 1.4).

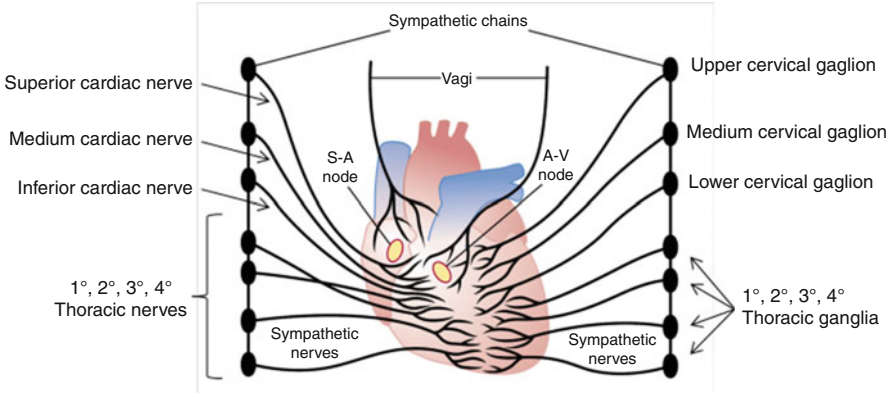

Fig. 1.4 Scheme of the sympathetic and parasympathetic (vagal) innervations of the heart (Modified from Guyton and Hall (2006))

The *superior cardiac nerves* origin, on each side, from the inferior portion of the superior cervical ganglia. They go down to the heart following a different way: the right nerve runs behind the anonymous artery and the aortic arch; the left nerve follows the left common carotid artery. The *medium cardiac nerves*, the biggest among cardiac nerves, derive from the medium cervical ganglia and can reach the cardiac plexus directly, without fusion with other nerve fibers. Finally, the *inferior cardiac nerves* derive from the stellate ganglia and directly arrive to the cardiac plexus.

The efferent parasympathetic preganglionic nerve fibers originate in the medulla oblongata and reach the heart through the two vagal nerves. The postganglionic efferent neurons reside in the inferior ganglia of the vagus nerves or in the cardiac plexus.

The *cardiac plexus* is situated at the base of the heart, in front of the tracheal bifurcation, and below and behind the aortic arch. It consists of the confluence of various, both sympathetic and vagal, cardiac nerves and of a variable number of little parasympathetic ganglia, among which the most remarkable and constant is Wrisberg's ganglion, which is located between the tracheal bifurcation and the pulmonary artery division. Some little parasympathetic ganglia are also located inside the myocardial walls, mainly at atrial level.

The cardiac plexus can be divided into a superficial part, which lies in the concavity of the aortic arch, and a deep part, situated between the aortic arch and the trachea. The two parts are closely connected and provide autonomic innervation to the sinoatrial node, atrioventricular node, atrial and ventricular myocardium, as well as large and small vessel walls.

Afferent nerve fibers from the heart mainly travel in sympathetic cardiac nerves. Many nervous sensory receptorial units, which may consist of either free ending terminations or encapsulated nervous endings, can easily be detected in the heart, especially at subendocardial level and at the level of vena cava and pulmonary veins mergers, interatrial septum, and atrioventricular valve limbs. Cell bodies of sympathetic-sensitive neurons are situated in the first 4–5 spinal thoracic ganglia. Second-order sympathetic sensory fibers originated in the spinal cord cross the median line and ascend in the ventral spinothalamic tract to end in the posteroventral nucleus of the thalamus.

Afferent vagal fibers have also been detected in the heart and play a role primarily in mediating some cardiac reflexes (Gibbins et al. 2003). Stretch receptors present in the atria contribute to minimize changes in arterial pressure following changes in blood volume (Di Carlo and Bishop 2001); their stimulation causes a reflex inhibition of vagal activity and an increase in heart rate (Bainbridge reflex). Stimulation of stretch receptors in the left ventricle can, instead, typically result in vagal-mediated hypotensive and bradycardic responses (Jarisch-Bezold reflex) (Guyton and Hall 2006).

1.3.2 Function of the ANS of the Heart

The autonomic innervation of the heart considerably contributes to the regulation and control of cardiac functions and activities, including heart beat rate

(chronotropism), conductivity of the electrical signal (dromotropism) and excitability (bathmotropism), and contractile strength (inotropism) of myocardial cells. Furthermore, the ANS also plays a relevant role in the regulation of coronary vascular motility and myocardial blood flow (MBF).

As in the whole body, the sympathetic and parasympathetic sections of the ANS have also antagonistic effects on most heart functions. Of note, however, they do not necessarily have comparable effects and influence on the various parts of the heart. Instead, some cardiac activities are mainly influenced by one of the two sections, depending on differences in their distribution to the heart.

Thus, sympathetic activation significantly increases myocardial contractility in all heart chambers, whereas vagal activation significantly inhibits atrial contractility, but has poor effects on ventricular cardiomyocytes, due to the poor distribution of vagal fibers to the ventricles. Vagal stimulation, however, can mitigate the increased inotropism resulting from increased β-stimulation of the heart.

1.3.2.1 Effects of the Sympathetic ANS

Overall, the sympathetic division has an excitatory effect on most heart function. The heart is indeed a major target organ in the "fight-or-flight" response associated with sympathetic activation in physical or stressful conditions, as well as in all conditions that require an increase in cardiac output.

Thus, the sympathetic ANS promotes an increase in heart rate (up to 200 bpm and more in young adults), by speeding up the depolarization current rate of the cells of the sinus node. This effect is accompanied by an increase in the velocity of conduction and a reduction of the functional refractory period in the conduction system of the heart, in particular of the AV junction, besides an increase in myocardial contractility to as much as double of normal, with a consequent increase of stroke volume. Furthermore, sympathetic activation also enhances cardiac electrical activation and contractility of both atrial and ventricular myocardial cells.

It is important to stress that conditions associated with activation of the adrenergic ANS also lead to catecholamine release by the adrenal gland (mainly adrenaline) which determines blood-borne-related adrenergic effects on the whole heart.

The effects of catecholamines on myocardial cells are mainly mediated by β1-receptors.

In the healthy human heart, indeed, β1-adrenoceptors are predominant (β1 to β2 ratio = 3:1) and are distributed in all cardiac regions. β2-Adrenoceptors are instead mainly concentrated in the ventricles and atria, where they are functionally linked to inotropic responses. The presence of β3-adrenoceptor in the human heart, on the other hand, is still a matter of debate (Lefkowitz et al. 1984). A summary of adrenergic receptors involved in mediating sympathetic effects on the heart is reported in Table 1.1.

1.3.2.2 Effects of the Parasympathetic (Vagal) ANS

In opposition with sympathetic activity, the parasympathetic (vagal) division of the ANS has inhibitory effects on most heart function. Thus, the sinus node activity is

Table 1.1 Main effects of sympathetic and vagal ANS on the heart and coronary arteries

Target organs	Sympathetic effects		Vagal effects	
	Receptor type (adrenergic)	Effect	Receptor type (muscarinic)	Effect
Heart				
SA node	β1, β2	Heart rate increase	M2	Heart rate decrease
Atria	β1, β2	↑Contractility	M2	↓Contractility
		↑Conduction velocity		↑Conduction velocity
AV node and conduction system	β1, β2	↑Conduction velocity	M2	↓Conduction velocity: AV block
Ventricles	β1, β2	↑Contractility	–	
		↑Conduction velocity		
		↑Automatism		
		↑Ventricular foci excitability		
Coronary arteries	α1, α2	Constriction	M3	Mild dilation
	β2	Dilation		

slowed down, resulting in bradycardia and sinus pauses or blocks; similarly, electrical conduction through the AV node is significantly delayed and can even be blocked. On the other hand, vagal activation has no relevant effects on intraventricular conduction.

Vagal fibers are, indeed, mainly distributed to the atria and not much to the ventricles, even if a strong vagal stimulation can decrease the strength of heart muscle contraction by about 20 %. The effects of vagal activation on atrial cells, on the other hand, are characterized by a reduction of contractile activity but an increase in conduction speed due to a reduction in action potential duration, which can favor some reentrant tachyarrhythmias.

The effects of the vagus nerve on the heart are mediated by cholinergic M2 receptors, whereas its mild direct vasodilating effect on coronary arteries is mediated by M3 receptors (Table 1.1).

1.3.2.3 Sympatho-vagal Balance

As discussed about the general function of the ANS, in rest conditions the heart is mainly under the influence of vagal activity. Thus, sinus node discharge (i.e., heart rate) and AV nodal conduction are substantially determined by the level of vagal activation.

In fact, in rest conditions, the sympathetic nerve fibers to the heart discharge continuously at a slow rate, determining a pumping force just of 30 % above that without any sympathetic stimulation; accordingly, inhibition of sympathetic ANS activity at rest only induces a modest depression of myocardial contractility. Similar considerations apply to sinus node firing.

During exercise or stress arousal, instead, vagal activity is progressively suppressed and sympathetic drive enhances, thus resulting in a predominant sympathetic cardiac stimulation. Thus, adrenergic inhibition in these conditions may significantly blunt the increase in heart rate and contractile force.

1.4 ANS Regulation of Coronary Blood Flow

The ANS in the heart also considerably contributes to the regulation of coronary artery tone and, even more, of MBF, together with biochemical and physical factors.

The ANS influences MBF both in a direct and in an indirect way (Crea et al. 2013). The latter depends on the fact that, as discussed above, the activity of the ANS is a major determinant of heart rate and myocardial contractility, and therefore of myocardial oxygen consumption, which, in turn, is the fundamental determinant of MBF. Thus, any increase in sympathetic activity leads to an increase in cardiac metabolism, which results in a local release of vasodilator substances and, eventually, in MBF. The opposite is achieved through inhibition of adrenergic activity and/or increase in vagal activity.

The direct effect of sympathetic stimulation on coronary vascular tone and MBF depends on the balance between α- and β-adrenergic receptors located in coronary vessels walls. Specifically, smooth muscle cells of coronary vessels mainly contain α_1-receptors and β_2-receptors. Stimulation of α_1-receptors results in coronary vasoconstriction; instead, β_2-stimulation mediates coronary vasodilation. Smaller coronary arteries mainly contain β_2-adrenergic receptors, whereas epicardial larger coronary arteries mainly have α_1-adrenergic receptors. The final physiologic effect of sympathetic activation is a mild to moderate vasodilation and increase in MBF.

On the other hand, while the indirect effect of vagal stimulation of the heart is vasoconstriction, due to the reduced myocardial oxygen consumption, the very limited direct effect of parasympathetic stimulation on coronary vessels is a mild vasodilation, which is likely mediated by a release of NO from endothelial cells (Pelc et al. 1988).

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