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## Fundamental aspects of cardiovascular regulation in predisposition to atrial fibrillation

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### Abstract

**Background:** Atrial fibrillation is the most common sustained arrhythmia in cardiology. The structural factors leading to atrial fibrillation are well known, but there should be also regarded the functional factors. In 2014, the Task Force published guidelines for atrial fibrillation describing the importance of the vegetative nervous system in creating predisposition to atrial fibrillation although it describes that the mechanism is not completely clear. Furthermore, it is important to understand this mechanism, regarding the increasing number of patients affected by atrial fibrillation without any structural heart diseases. The aim of this work is to understand the physiological background of the predisposition to the appearance and recurrence of atrial fibrillation regarding the role of neural regulatory systems of the heart, especially when no structural heart diseases are present. Therefore, the following is a fundamental analysis of the neural regulation of heart rhythm, including the vegetative nervous system at its medullar and central levels and also the cerebral cortex input in heart regulation.

**Conclusions:** The predisposition to atrial fibrillation regarding the neural regulatory systems of the heart can be pinpointed to three key factors: 1. Central over-activity; 2. Sympathetic efferent overflow towards the heart in rest state; 3. Parasympathetic exhaustion and break-down of the parasympathetic protective function.

**Key words:** atrial fibrillation, neural heart rhythm regulation, central over-activity.

### Introduction

Atrial fibrillation is the most common sustained arrhythmia in cardiology, which affects about six million people in the European Union [1]. The “Worldwide Epidemiology of Atrial Fibrillation: Global Burden of Disease” study in 2013 revealed, that 33.5 million people around the world have atrial fibrillation, which results in around 0.5 percent of the world’s population. Though the influence of structural factors of the heart on the arrhythmogenesis of atrial fibrillation is well known [2], it is important to understand the conditions for occurrence of atrial fibrillation in patients without any eminent structural changes in the heart [3]. Thus, the state of the regulatory mechanisms of the heart should also be taken into consideration [4]. The vegetative nervous system plays a key role in the neural regulation of the heart [5]. In 2014, the Task Force published guidelines for atrial fibrillation describing the importance of the vegetative nervous system in creating predisposition to atrial fibrillation [6].

The aim is to understand the physiological background of this predisposition and in addition to analyze the role of the cerebral cortex input on the heart regulation in creating the predisposition to atrial fibrillation. Therefore, the following is a fundamental analysis of the neural regulation of heart rhythm.

### The neural regulation of the heart

Regarding the neural regulation of the heart it is predominantly regulated by the vegetative nervous system at the level of the medulla oblongata [7]. There is a pressor center (cardio-accelerator center) and a depressor center (cardio-inhibitory center). The first is driven by nervi sympathici cordis and the second is driven by nervus vagus [7]. At this level, the vegetative regulation of the heart is non-stop and also it is modulated by breathing, by the central part of the vegetative nervous system and by the cerebral cortex impulses [7, 8, 25]. Regarding the central efferent impulses, these are impulses that reach the heart via passing through the pressor center of the hemodynamic center in the medulla oblongata [9]. These impulses fulfill their action on the heart by utilizing the sympathetic fibers [9]. It is the first key moment in understanding the mechanism of neural predisposition to atrial fibrillation [10, 11]. This means that the primary reaction of the heart on all central efferent impulses is sympathicotonic [9, 12]. The secondary reaction is the vagal counteractivation at medullar level and the parasympathetic counteractivation at the central level [12, 5]. This reaction is important and will be explained further in detail below.

### The protective function of parasympathetic counteractivation at medullary level and the central input

Usually the parasympathetic part of the vegetative nervous system is regarded as the one which is responsible for vasodilation and for the known effects on the heart (negative bathmotropic, dromotropic, inotropic, tonotropic, and chronotropic) [5, 7], however, there is another very important function. It functions also to protect the heart from an increase in central efferent impulsatory activity [12]. It is imperative to analyze in detail what occurs during an increase in impulsatory activity and what kind of protective mechanisms the parasympathetic vegetative nervous system has. The pressor center always has an inhibitory influence on the depressor center [5, 7]. This is also important in order to protect the heart when the central regulation of the heart increases during rest state [12]. It is a necessary protective mechanism because when the central regulation increases, the intensity of the sympathetic efferent impulses to the heart in rest state also increases [9, 12]. As it was already mentioned above it occurs due to the fact that the central regulatory input exerts its influence via the sympathetic fibers passing through the pressor center [9]. When the regulation of the heart works physiologically, the sympathetic activation driven by the central regulatory impulses is com-

pensated or counterbalanced by the parasympathetic part of the vegetative nervous system. At the medullary level, this means that the depressor center acts as a filter membrane [12]. By its permanent inhibitory action on the pressor center, the depressor center filters out a part of the central efferent regulatory impulses reaching the pressor center (fig. 1). In other words, not all efferent impulses of the central heart regulation reach the heart. This is the protective function of the parasympathetic part of the vegetative nervous system [13].

The central level includes the influence of cerebral cortex, limbic system, hypothalamus, reticular formation. It fulfills its action on the heart via the pressor center. So it acts always at the heart sympathicotonic. In order to avoid a sympathetic overflow of the heart driven by the central efferent impulses, there is a protective mechanism at the medullary level: the depressor center of the hemodynamic center always has an inhibitory influence on the pressor center. This means that the depressor center acts as a filter membrane, so it filters out a part of the central efferent regulatory impulses reaching the pressor center before they further stream to the heart. This is the protective function of the parasympathetic part of the vegetative nervous system.

### Pathological counterbalance at the medullary level

Described above is an overview of how the protective parasympathetic counterbalance works at the medullary level. When the parasympathetic vegetative nervous system does not function properly, the following occurs: the central modulation increases, which in turn stimulates its sympathetic action on the heart, but the parasympathetic inhibitory counteractivation on the pressor center is insufficient [14]. This means that the parasympathetic protective filtering of the central efferent impulses is not capable of inhibiting enough of these impulses [13]. Under such conditions, more central efferent impulses stream towards the heart than what is physiologically normal during the rest state [9, 15, 16]. This leads to an increase in sympathetic activity on the heart during this time. As the parasympathetic barrier becomes less active and effective, a large amount of efferent central impulses reach the heart [8]. As a consequence, this results in higher sympathicotony of the heart at rest [8, 17]. The conditions which provoke a permanent chronic decrease in functional activity of the parasympathetic part of the vegetative nervous system can lead to a permanent overflow of the heart in its rest state [12]. This is because under such conditions the efferent modulative impulses are hardly inhibited in the hemodynamic center by its depressive center. As a result, efferent modulatory impulses of high intensity pass through the pressor center to the heart. This is the sympathetic overflow of the heart during the rest state [12]. Such a state itself leads to an ongoing exhaustion of the parasympathetic part of the nervous system. The exhaustion leads to an ongoing decrease in the ability to inhibit the modulative impulses [14, 17, 11]. Thus, the amount that is streaming to the heart continues to in-

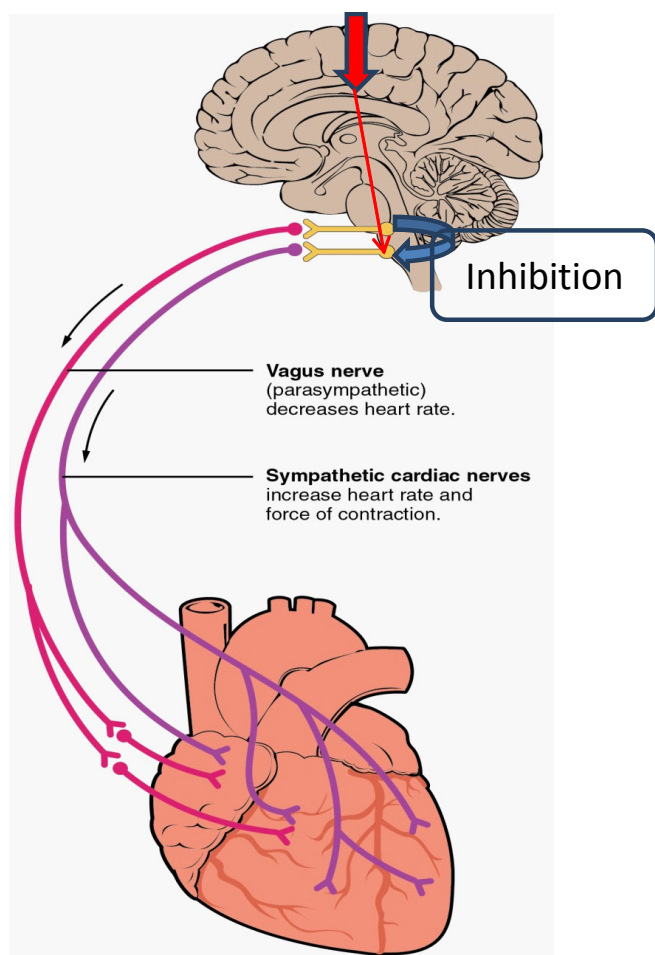


Fig. 1. The central and the medullary levels of heart regulation.

crease. This is *circulus vitiosus*. Under these conditions, the modulative regulation of the heart becomes dominant versus the medullary one [18]. This is a pathological situation which creates predisposition for the appearance or recurrence of atrial fibrillation [12, 18].

### The central regulation of the heart

Under normal conditions, the heart is regulated by the medullary level and modulated by the central level [5, 7, 18]. This explains why heart regulation occurs autonomously and why the central level has a modulative function. Autonomic heart regulation is ensured by the baroreflex. Normally under central regulation is understood the hypothalamus which represents the highest vegetative center [7]. In this article the central regulation is regarded in a large sense. It includes cerebral cortex, motor cortex, limbic system, hypothalamus, reticular formation [7, 10, 13]. It should be noted that both groups of pathways were taken into account: the group of pathways from the reticular formation to the hemodynamic center and the group of pathways via hypothalamus to the hemodynamic center [19, 20]. So, the cerebral cortex impulses pass through cardiovascular control center in medulla oblongata. The central modulative influence of the heart also occurs in a calm state because the heart always has to supply effectively with blood every action and state of an organism. Even in a calm state, the heart receives many central impulses necessary to maintain the muscle tonus, the position of the body in space, as well the basic vital functions [7, 20]. It is essential that all this information is received by the heart in order to properly respond by regulating frequency and blood pressure.

Of course the question arises whether there are conditions that can increase the central regulation of the heart in calm state. There are both physiological and pathological conditions that can increase the central regulation of the heart. An example of physiological condition is observed during increased mental activity or during psychoemotional stress [17, 26]. This increase of central regulation is transitory, occurring only during stress or mental activity [17, 18]. After its action stops, the physiological counter-balance switches. As a consequence, the central regulation decreases until its physiological level, so no sympathetic overactivity occurs [17]. A pathological increase of the central heart regulation is characterized by a permanent increase, even in a calm state when the person is relaxed [12, 17, 18, 22]. This leads to a permanent sympathetic overactivity of the heart and can result in permanent positive bathmotropy [26]. This is a dangerous state because it creates favorable conditions to atrial fibrillation [11, 12, 23]. Such a mechanism could explain the appearance of atrial fibrillation and the recurrence of atrial fibrillation in patients without any structural heart diseases identified by an echocardiogram [6, 11, 21, 24].

By advance analysis of heart rate variability, the physiological and pathological central heart modulation can be detected [12, 24, 25, 27]. This can also be used to identify

the level of sympaticotony in a calm state as well as the level of activity of the parasympathetic part of the vegetative nervous system [16, 25]. Our future aim is to research possible factors which can lead to an increase in central heart modulation during a rest state, when the person is relaxed.

### Conclusions

1. The predisposition towards atrial fibrillation appearance and recurrence can be pinpointed to three key factors:
  - a) Central overactivity.
  - b) Sympathetic efferent overflow towards the heart in rest state.
  - c) Parasympathetic exhaustion and break-down of the parasympathetic protective function.
2. The parasympathetic part of the vegetative nervous system has not only the well-known functions of vasodilation and the known effects on the heart (negative bathmotropic, dromotropic, inotropic, tonotropic, and chronotropic), but also the very important function of protecting the heart from an increase in central efferent impulsatory activity.
3. An increase of central modulative influence on the heart in rest state could be regarded as a possible mechanism in creation of the neural predisposition for atrial fibrillation.

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