

Autonomic Nervous System Disturbances in Cardiovascular Disorders



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Abstract

The autonomic nervous system is a crucial component in regulatory responses of the cardiovascular system. There has been increasing evidence of research demonstrating that dysregulation of this system has an important role in the pathogenesis of common cardiovascular disorders, including hypertension, heart failure, atrial fibrillation, cardiac sudden death or neurally-mediated syncope. This paper focuses the clinical perspective of the role of autonomic activity in various pathological states and introduces the potential impact of targeting autonomic modulation as an option in cardiovascular therapies.

Experimental and clinical evidence has shown that autonomic nervous system (ANS) dysfunction has an important role in the pathophysiology of common cardiovascular disorders [1-3]. In fact, ANS is a crucial component in the responses of the cardiovascular system to routine daily stimuli, and, therefore, an imbalance in the sympathetic-vagal outflow may result in a dysregulation of cardiovascular function. Thus, the sympathetic and/or parasympathetic branches of the ANS may have a determinant contribution in cardiovascular pathology, including hypertension, heart failure, arrhythmias (supraventricular and ventricular) and reflex syncope, often with a significant impact in outcomes [4]. In the recent years, a variety of reports have proposed a new paradigm to be considered as a different approach in various cardiovascular pathologic states. The term autonomic modulation therapy, a treatment option that uses autonomic nerve stimulation, denervation or different training programs (tilt training, exercise rehabilitation) to achieve a better autonomic balance in these conditions has been used as a promising non-pharmacological measure with clinical benefits [2,5,6].

Inappropriate sympathetic overactivity is consistently observed in patients with essential hypertension. Abnormalities of the afferent and efferent sympathetic function are associated with sustained hypertension, not only because of its hemodynamic effects (increased cardiac output and vascular resistance), but also by altering water handling by the kidney and by inducing cardiac and vascular remodeling [7-9]. The adrenergic overdrive also has a role in the pathophysiological mechanisms underlying the complex alterations known as target organ damage that characterizes the clinical course of hypertension [9,10]. The modifications of sympathetic and vagal activation obtained by non-pharmacological and pharmacological interventions are considered to be part of an antihypertensive strategy in order to correct elevations in blood pressure and restore the normotensive state [10].

The pathophysiology of chronic heart failure (CHF) is characterized by cardiovascular signs of an increased sympathetic and a decreased parasympathetic activity, with sympathetic overdrive, increased heart rate and depressed baroreflex being considered independent predictors of poor long-term outcome [3,6,10]. Modulation of ANS activation as a potential therapy for CHF is receiving investigational and clinical attention, with a potential future role to optimize effectiveness of standard intervention modalities in the treatment of CHF [6,11]. Prospective studies are needed to reach a consensus on how modulation of ANS should be incorporated into the treatment of patients with this syndrome.

Neurally mediated syncope, the most common cause of recurrent syncope, is an acute hemodynamic reaction produced by a sudden change in the normal pattern of ANS tonus that maintains blood pressure in the standing posture. The occurrence of excessive autonomic reflex activity (sympathetic activity suddenly decreases while parasympathetic acutely increases) results in an abrupt fall in blood pressure and/or slowing of the heart rate prior to syncope [2,12,13]. Modulation of the autonomic function, elicited by a head-up tilt training program, that appears to increase vasoconstrictor reserve combined with a reduction in its variance, may be an effective therapeutic option, with long-term benefits [12,13]. A novel technique based on radiofrequency catheter ablation of cardiac vagal ganglia, known by cardioneuroablation, has been utilized in selected patients presenting with cardioinhibitory type of reflex syncope, as a potential alternative therapy [14]. Data indicate that this option could be effective, but the results still limited, observational and based on small-scale studies.

Compelling evidence links ANS disturbances and sudden cardiac death, with heightened sympathetic activity favoring the development of ventricular arrhythmias and the increased vagal thought to be protective, particularly in survivors of myocardial infarction and in patients with left ventricular systolic dysfunction [15]. Heart rate variability (HRV) and arterial baroreflex sensitivity, non-invasive techniques obtained from signal processing of heart rate and blood pressure are currently used as tools to evaluate ANS activity and, when presenting reduced values,

are considered independent markers that predispose to the occurrence of ventricular tachyarrhythmias and sudden death [16]. Therefore, interventions designed to either augment parasympathetic activity and/or reduce cardiac adrenergic activity would also protect against ventricular fibrillation [15,16].

In a different perspective, patients with a type-1 Brugada ECG pattern show the highest incidence of arrhythmic events and sudden unexplained death during sleep, when the vagal tone is dominant, with studies demonstrating the presence of cardiac autonomic neuropathy [17]. Recent publications identified a more rapid restoration of the parasympathetic and a smaller level of sympathetic activation after exercise, and an abnormal sympathetic innervation of the heart in Brugada patients, resulting in a dominance of the parasympathetic tone and subsequent autonomic imbalance [17,18]. Also, analyses of 24h Holter recordings revealed altered HRV in Brugada subjects with ventricular fibrillation compared to controls [19]. Although the full extent of these changes has not been elucidated, autonomic remodeling mechanisms have been accepted to contribute to an arrhythmogenic substrate.

Regarding atrial fibrillation (AF), the most common sustained arrhythmia in clinical practice, ANS is recognized as a modulator in the pathogenesis of paroxysmal AF, but the mechanisms linking ANS activity with the arrhythmia are incompletely understood. Studies have demonstrated that there is an interaction between sympathetic and parasympathetic nervous systems in developing AF, with both branches of the ANS being proarrhythmic in the atria (through atrial refractory periods shortening and increased heterogeneity of repolarization) [20,21]. However, further investigation is required to understand whether intervention aiming at the specific components of the cardiac autonomic innervation could lead to improve AF management, especially using therapies able to achieve clinical benefits via ANS modulation.

ANS dysfunction has been regarded as one of the putative mechanisms involved in various common cardiovascular disorders. Ongoing research has to further test autonomic activity as a complex pathway underlying the pathophysiology of these diseases, but also as a therapeutic target using both pharmacologic and intervention techniques to obtain benefits from adequate autonomic modulation.

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