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Cardiorespiratory coupling in health and disease

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ABSTRACT

Cardiac and respiratory activities are intricately linked both functionally as well as anatomically through highly overlapping brainstem networks controlling these autonomic physiologies that are essential for survival. Cardiorespiratory coupling (CRC) has many potential benefits creating synergies that promote healthy physiology. However, when such coupling deteriorates autonomic dysautonomia may ensue. Unfortunately there is still an incomplete mechanistic understanding of both normal and pathophysiological interactions that respectively give rise to CRC and cardiorespiratory dysautonomia. Moreover, there is also a need for better quantitative methods to assess CRC. This review addresses the current understanding of CRC by discussing: (1) the neurobiological basis of respiratory sinus arrhythmia (RSA); (2) various disease states involving cardiorespiratory dysautonomia; and (3) methodologies measuring heart rate variability and RSA.

1. Introduction

The neuronal control of breathing and heart rate (HR) are closely linked, functionally as well as anatomically. Cardiorespiratory coupling (CRC) is perhaps best typified by the occurrence of respiratory sinus arrhythmia (RSA). As early as 1936, Anrep, Pascual and Rössler proposed that the heart rate sinus arrhythmia is caused by the regulation of cardiac vagal outflow involving the same neuronal processes that generate the respiratory rhythm and reside within the brainstem (Anrep et al., 1936). Indeed, extensive overlap has been confirmed between brainstem areas that control breathing and those that control cardiovascular functions. In addition to a potential role of the pons in controlling CRC (Dick et al., 2009), there are well defined medullary interactions including those between the so-called pre-Bötzinger complex (preBötC) and the cardiac vagal neurons located within the nucleus ambiguus (NA) (Spyer and Gilbey, 1988; Mendelowitz, 1996; Dergacheva et al., 2010). The close interaction between cardiac and respiratory control synergizes these autonomic functions that are critical for survival. This coupling is not only important for the homeostatic regulation of blood gases, but a tight coupling of cardiorespiratory control is also critical for regulating central nervous functions, such as arousal. There is increased evidence that cortical and brainstem arousal is linked to the generation of the sigh, an augmented breath which is associated with a characteristic biphasic HR change. The magnitude of the sigh-linked HR change is predictive for the degree and type of arousal (Thach and Lijowska, 1996; Thach, 2002). However, the mechanisms that link the sigh, heart rate change and the arousal remain unknown. Thus, it is currently also unclear why a larger heart rate change is associated with a decreased arousal threshold. Altered cardiovascular function is commonly associated with respiratory diseases and dysautonomias (Trang et al., 2003; Lin et al., 2004; Weese-Mayer et al., 2008a, 2008b; Cazzola et al., 2012). Respiratory dysfunction can negatively impact cardiovascular health and vice versa. However, at the same time there are potential benefits associated with proper CRC (Hayano et al., 1996; Ben-Tal et al., 2012). In this review we will discuss the importance and basis of CRC in health and disease. The review centers around three specific aspects: (1) the neurobiological basis of CRC and particularly, respiratory sinus arrhythmia (RSA); (2) dysautonomia states associated with the decline of CRC and function; and (3) computational approaches examining heart rate variability (HRV).

2. The neurobiological basis of RSA

RSA occurs during both normal breathing (i.e., eupnea) and augmented breathing patterns (i.e., sighs). It is characterized by a heart rate (HR) increase during inspiration and a HR decrease during expiration. RSA is believed to represent a healthy form of HRV and is hypothesized to improve energetic efficiency of gas exchange (Hayano et al., 1996) or alternatively, to assist in reducing cardiac work while maintaining healthy blood gas levels (Ben-Tal et al., 2012). Sighs and concomitant

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RSA commonly occur at the onset of arousal and are hypothesized to contribute to the mechanistic process of recovering airway patency following occlusion (Remmers et al., 1978; Roberts et al., 1986; Wulbrand et al., 2008). RSA is normally measured and assessed in young healthy individuals as high frequency heart rate variability (HRV). Both sympathetic and parasympathetic activities are responsible for the generation of RSA.

Sympathetic activity depends on the activity of presympathetic neurons that originate in the rostral ventrolateral medulla and that are modulated by respiratory activity (Pilowsky, 1995; Zoccal et al., 2008; Costa-Silva et al., 2010; Moraes et al., 2012). Coupling of the sympathetic nervous system to respiratory activity is readily observed in splanchnic, cardiac, renal and adrenal nerves all exhibiting peak activity during phrenic nerve discharge (Numao et al., 1987). Specifically, this pattern of sympathetic activity ramps up during inspiration and reaches a peak during late-inspiration and the beginning of post-inspiratory activity (Miyawaki et al., 1996; Zoccal et al., 2008; Costa-Silva et al., 2010).

In addition to these sympathetic interactions, baseline HR changes can also be attributed to the cardioinhibitory influence of the parasympathetic nervous system (Kunze, 1972; Pickering et al., 1972; Stornetta et al., 1987; Dergacheva et al., 2010), which as will be discussed in the subsequent sections depends on the interactions between the preBötC and the NA. The balance between sympathetic and parasympathetic control is dependent on the developmental and behavioral state of the organism.

RSA is already observed prenatally at a time when lungs still do not participate in gas exchange. Fetal RSA has been recorded at gestational week 36 (Groome et al., 1994a, 1994b; Gustafson et al., 2011) and it is likely one of the first signs of autonomic CRC. At this time, parasympathetic activity appears to dominate CRC as heart rate decreases and high frequency HRV increases during episodes of fetal breathing (Gustafson et al., 2012). After parturition, the autonomic nervous system continues to mature at which point the sympathetic system will also contribute to changes in HRV, this is most obvious during the regulation of the sleep wake cycle. It has been suggested that an increased sympathetic tone contributes to decreased high frequency HRV during wakefulness, while decreased sympathetic activity during slow wave sleep (Van de Borne et al., 1994) may lead to an increased HRV (Harper et al., 1978; Trelease et al., 1981). The postnatal increase in sympathetic tone may in part be due to the development of oxygen sensitivity in the carotid bodies (Carroll et al., 1993; Sovik et al., 1999; Carroll and Kim, 2005; Donnelly et al., 2009; Gauda et al., 2009) and may contribute to the gradual stabilization of cardiorespiratory activity. Thus, the strength of RSA is determined by a cardiorespiratory network involving both the peripheral and central nervous system.

While the degree of peripheral input contribution (including both baroreceptors and chemoreceptors) to RSA is still debated (Eckberg, 2009; Karemaker, 2009a, b), lung inflation is not essential for sigh generation (Lieske et al., 2000) and its accompanying RSA (Wulbrand et al., 2008). Moreover, HR remains coupled to brainstem respiratory rhythms when subjects are artificially ventilated at different rates (Spyer and Gilbey, 1988; Daly, 1991; Shykoff et al., 1991). Thus, although peripheral receptor input may modulate the strength of RSA as postulated by Anrep et al. (1936), RSA is sufficiently coordinated within the central nervous system to function without peripheral inputs (Anrep et al., 1936).

2.1. Neurobiological origins of RSA

Several in vivo studies have demonstrated respiratory modulation of brainstem neurons involved in autonomic cardiac and cardiovascular control (Gilbey et al., 1984; Guyenet and Koshiya, 1995; Mandel and Schreihofer, 2006). Cardiac vagal motoneurons in the NA discharge during expiration, and silenced during inspiration. In cats, Gilbey et al. (1984) demonstrated that these cardiac neurons discharge primarily during the period of post-inspiration. These authors also demonstrated that the neuronal discharge followed central respiratory activity and not lung inflation. But, the neuronal control of CRC is not limited to a local control of NA neurons. Neurons located more rostrally to the NA, within the rostral ventrolateral medulla (RVLM), also exhibited respiratory-related changes in membrane potential (Lipski et al., 1996; Granata and Cohen, 2004), but these activities were more diverse. Bulbospinal and barosensitive RVLM neurons showed either peak or nadir activity during inspiration (McAllen and Blessing, 1987), and similar discharge patterns were described for the caudal ventrolateral medulla (Mandel and Schreihofer, 2006) indicating that complex interactions exist throughout the brainstem. The use of the in situ working heart-brainstem preparation suggested that input from the pons is important for the CRC (Dick et al., 2009). One possible role is that pontine-mediated excitation generates post-inspiratory activity in cardiac vagal neurons (Dick et al., 2009), while the inspiratory-related inhibition of these neurons may originate within the medulla (Mendelowitz and Kunze, 1991). Yet, while the pons clearly plays a role in modulating CRC, NA neurons can also exhibit inspiratory inhibition as well as post-inspiratory activation as can be demonstrated in isolated medullary slices – i.e. in the absence of the pons (Fig. 1; AJ Garcia III, and JM Ramirez unpublished data). Thus, while the final neural pathway by which vagal tone is expressed on HR resides not only within the medullary brainstem in preganglionic cardiac vagal neurons of the NA (CVN_{NA}), this medullary area seems to contain sufficient neuronal circuitry to exhibit the basic activation pattern that characterizes these neurons also under in vivo conditions as already postulated by Gilbey et al. (1984).

2.2. Neuromodulation of pre-Bötzinger complex neurons and CVN_{NA}

Critical for understanding the medullary mechanisms underlying cardiorespiratory coupling is the so called preBötC (Smith et al., 1991), a brainstem area that in vivo (Smith et al., 1991; Ramirez et al., 1998; Gray et al., 2001; Schwarzacher et al., 2011) and in isolation generates not only inspiratory, but also post-inspiratory activity (Ramirez et al.,

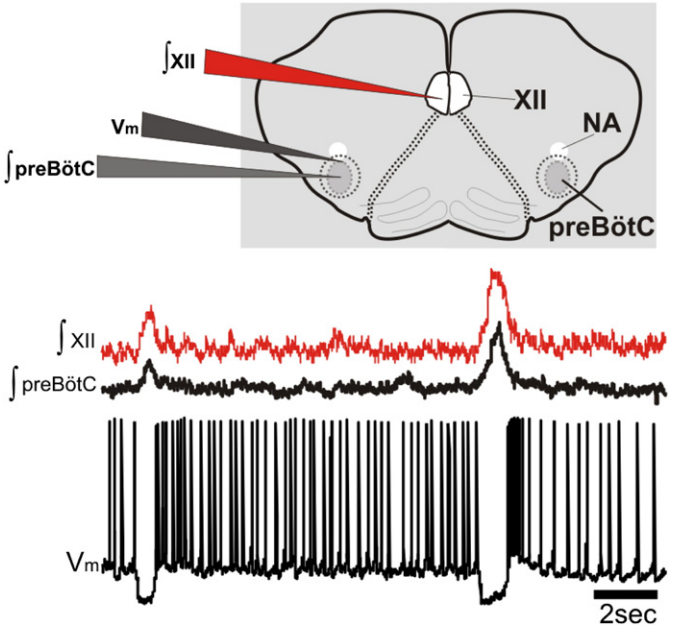

Fig. 1. In vitro intracellular recording from a NA neuron within the rhythmic preBötC slice. As shown in the membrane potential trace (V_m), this putative NA neuron is phasically inhibited during inspiratory bursts from both the preBötC and hypoglossal nucleus (XII). This blind patch recording was made from a rhythmically active preBötC slice (600 μm) prepared from a 7 day old mouse using procedures described in Ramirez et al. (1996) and approved by the Institutional Animal Care and Use Committee at Seattle Children's Research Institute. This neuron was identified as a choline acetyltransferase positive neuron located ventrally in the external formation of the NA.