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Review

Cardiac sympatho-vagal balance and ventricular arrhythmia☆

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ABSTRACT

A hallmark of cardiovascular disease is cardiac autonomic dysregulation. The phenotype of impaired parasympathetic responsiveness and sympathetic hyperactivity in experimental animal models is also well documented in large scale human studies in the setting of heart failure and myocardial infarction, and is predictive of morbidity and mortality. Despite advances in emergency revascularisation strategies for myocardial infarction, device therapy for heart failure and secondary prevention pharmacotherapies, mortality from malignant ventricular arrhythmia remains high. Patients at highest risk or those with haemodynamically significant ventricular arrhythmia can be treated with catheter ablation and implantable cardioverter defibrillators, but the morbidity and reduction in quality of life due to the burden of ventricular arrhythmia and shock therapy persists. Therefore, future therapies must aim to target the underlying pathophysiology that contributes to the generation of ventricular arrhythmia. This review explores recent advances in mechanistic research in both limbs of the autonomic nervous system and potential avenues for translation into clinical therapy. In addition, we also discuss the relationship of these findings in the context of the reported efficacy of current neuromodulatory strategies in the management of ventricular arrhythmia.

Contents

1. Introduction

A hallmark of cardiovascular disease (hypertension, myocardial infarction, heart failure and malignant ventricular arrhythmia) is cardiac autonomic dysregulation (Floras, 2003). The phenotype of impaired parasympathetic responsiveness and sympathetic hyperactivity in experimental animal models (Ma et al., 1997; Ishise et al., 1998; Sun et al., 1999; Motte et al., 2005) is also well documented in large scale

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human studies in the setting of heart failure and myocardial infarction, and is predictive of morbidity and mortality (La Rovere et al., 1998; Nolan et al., 1998). Despite advances in emergency revascularisation strategies for myocardial infarction, device therapy for heart failure and secondary prevention pharmacotherapies, mortality from malignant ventricular arrhythmia remains high. Patients at highest risk or those with haemodynamically significant ventricular arrhythmia can be treated with implantable cardioverter defibrillators (ICD) (AVID, 1997; Moss et al., 2002; Bardy et al., 2005), but the morbidity and reduction in quality of life due to the burden of ventricular arrhythmia and shock therapy persists. Therefore, future therapies must aim to target the underlying pathophysiology that contributes to the generation of ventricular arrhythmia. Emerging evidence now suggests that modulation of the autonomic nervous system with neuro-axis targeting is gaining utility as a novel therapy in this patient group (Ardell et al., 2016; Shivkumar et al., 2016).

2. The integrated heart-brain neuro-axis

The autonomic nervous system functions to tightly regulate cardiac excitability and contractile function (Habecker et al., 2016). The interconnected architecture has been elegantly explored and described by Ardell and Armour (Armour, 2008) based upon physiological data from multiple studies across varying spatial domains. This system is considered as a manifestation of three levels of neural hierarchy, moving away from the historical reciprocal thesis of cardiac control where the two arms of the ANS acted as 'accelerator and brake' on cardiac function. Instead, the excitability of cardiac parasympathetic pathways or sympathetic pathways depends on tonic inputs to synaptic junctions at several stages in the brain, spinal cord and in the extrinsic and intrinsic cardiac ganglia (Gebber et al., 1996; Kember et al., 2011; Fukuda et al., 2015). Level 1 encompasses the spinal cord and medulla with higher centre modulation (McAllen et al., 2011; Harper et al., 2013). Level 2 incorporates extracardiac neurons such as the stellate ganglia (Armour, 1986a, 1986b; Ardell et al., 2009) and level 3 includes all the intrinsic cardiac ganglia and nerves (Armour, 2008). Cardiac afferents and extracardiac circulatory receptors serve to transmit beat to beat sensory information to levels 1 and 2 and processing at these levels allows feedback loops which maintain physiological electrical and contractile stability in normal and stressed states (Ardell et al., 2016).

In the setting of cardiovascular disease or cardiac injury such as myocardial infarction, neurophysiological changes take place at distinct levels in the neural circuitry (Rubart and Zipes, 2005; Vaseghi and Shivkumar, 2008). Effects at the level of the organ such as scar formation and fibrosis contribute to heterogeneities in electrical activation and may contribute to the creation of fixed and functional substrate for re-entrant arrhythmia (Stevenson, 2009). There is also afferent mediated activation of neurohumoural systems and increased sympathetic stimulation and reduced vagal tone (Wang et al., 2014). In the short term, this is an adaptive response to maintain cardiac output (Kember et al., 2013), although at the cost of increased myocardial oxygen demand. However, following the acute injury phase, there is continued abnormal cardiac afferent signalling resulting in a maladaptive environment of persistent sympathetic activity (Zucker et al., 2012) that contributes to remodelling and the progression of cardiac disease that can ultimately lead to fatal arrhythmia.

Understanding of this complex cardiac neural-axis has led to targeted autonomic modulation therapies for heart failure and arrhythmia aimed at the cervical cardiac vagus and sympathetic nervous system respectively (Ardell et al., 2016). This review explores recent advances in mechanistic research in both limbs of the ANS and potential avenues for translation into clinical therapy. In addition, we also discuss the relationship of these findings in the context of the reported efficacy of current neuromodulatory strategies in the management of ventricular arrhythmia.

3. Mechanisms of ventricular arrhythmia

An understanding of the mechanisms responsible for the initiation and maintenance of ventricular arrhythmia is critical if effective treatment strategies are to be investigated and developed. The principle contributing factor to the onset of arrhythmia is re-entry. Fibrillation occurs when an electrical wave-break induces re-entry and leads to a sequence of new wave-breaks (Garfinkel et al., 2000; Weiss et al., 2000, 2011). Wave-break is affected by static and dynamic factors and these influence the likelihood of local wave-break resulting in re-entry. Static factors are predominantly anatomical such as scar and fibrosis and lead to tissue heterogeneity and electrical remodelling that is fixed. Key components of dynamic factors are changes in membrane voltage and intracellular calcium, which are influenced by the autonomic nervous system and act synergistically with static factors to destabilise electrical activation (Weiss et al., 2000).

4. The effects of sympathetic stimulation on cardiac electrophysiology

Contemporary research has led to a spectrum of neuro-axial therapies in the setting of patients at high risk of malignant ventricular arrhythmia. This has been based on mechanistic evidence from models of sympathetic hyperactivity at the level of the organ in animals (Habecker et al., 2016), and more recently from human studies (Shivkumar et al., 2016).

The effect of sympathetic stimulation on global ventricular electrophysiology has been studied extensively in animal models (Mantravadi et al., 2007; Ng et al., 2009) and humans (Vaseghi et al., 2014). In the rabbit heart in-vitro, sympathetic stimulation using an electrode inserted in the spinal canal produces regional apex-base changes in restitution kinetics (Mantravadi et al., 2007; Ng et al., 2009). This is presumably mediated by regional differences sympathetic innervation and I_{Ks} distribution, potentially influencing the vulnerability to arrhythmia. The ability of local changes in sympathetic activity to trigger ventricular arrhythmias is well established (Nash et al., 2001). Epicardial injection of NE in the pig elicits triggered automaticity, and computational modelling implicated a Ca^{2+} overload mechanism, supporting the hypothesis that heterogeneity or gradients of activation are pro-arrhythmic. The functional effect of post myocardial infarction remodelling has been elegantly demonstrated in patients undergoing endocardial and epicardial mapping as part of therapeutic catheter ablation procedures (Vaseghi et al., 2012). The effect of direct adrenergic stimulation with isoproterenol or reflex sympathetic stimulation in response to baroreflex activation elicites regional changes in repolarisation dynamics. This includes abnormal neural control in remote areas where a lack of action potential duration (APD) shortening in response to baroreflex activation suggests functional denervation. These results were reproduced in a porcine model of myocardial infarction following direct stellate ganglia stimulation (Ajijola et al., 2013). Interestingly, histological and molecular analysis of stellate ganglia tissue from these animals also demonstrates remodelling with increased tyrosine hydroxylase staining (Rajendran et al., 2016). This has been replicated in studies on stellate ganglia tissue from patients undergoing sympathectomy for refractory ventricular arrhythmia (Ajijola et al., 2012b).

5. Efferent cardiac sympathetic neurotransmission in health and disease

A growing body of work has demonstrated that sympathetic hyperactivity associated with several cardiovascular diseases resides, at least in part, with dysregulation in post-ganglionic cardiac sympathetic neurons. This is of particular interest as this area is perhaps more easily accessible for therapeutic intervention compared to the brainstem. Emerging evidence suggests that impaired NO and intracellular calcium handling are key intermediaries in sympathetic dyautonomia, since