Role of the Autonomic Nervous System in Ventricular Arrhythmias During Acute Myocardial Ischemia and Infarction

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Richard L. Verrier and Alex Y. Tan

Contents

Abstract

Significant advances have been made in recent years to elucidate the neural mechanisms involved in the genesis of cardiac arrhythmias during acute myocardial ischemia and infarction. The cellular and molecular processes whereby the sympathetic nervous system serves as a trigger for arrhythmia, and those responsible for the protective effect of vagus nerve activity, have been extensively characterized. Mounting evidence supports the importance of neural remodeling following myocardial infarction, which has provided valuable clues regarding factors that impact risk for sudden cardiac death. Promising nerve stimulation strategies including vagus nerve activation and spinal cord stimulation have progressed from animal testing to clinical trials.

R.L. Verrier, PhD, FACC (✉) • A.Y. Tan, MD
Division of Cardiovascular Medicine, Harvard Medical School,
Beth Israel Deaconess Medical Center, Harvard-Thorndike Electrophysiology Institute,
99 Brookline Avenue, RN-301, Boston, MA 02215-3908, USA
e-mail: rverrier@bidmc.harvard.edu

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Abbreviation

ICD Implantable cardioverter defibrillator

4.1 Introduction

Neural influences play a major role in determining whether an acute myocardial ischemic event or myocardial infarction culminates in ventricular fibrillation, the arrhythmia responsible for sudden cardiac death. It has been argued that, in many cases, malignant ventricular arrhythmias in patients with coronary artery disease are in fact the consequence of heterogeneous neural remodeling or "frayed nerves."

During acute myocardial ischemia, powerful cardio-cardiac reflexes are activated that are adaptive with respect to maintaining contractility but have deleterious consequences because of the highly arrhythmogenic impact of heightened catecholamine levels (Malliani et al. 1969). The facts that sudden cardiac death exhibits a circadian pattern of heightened risk in the early morning hours (Muller et al. 1987), that β-adrenergic blockade (Olsson et al. 1992) and left stellectomy (Schwartz et al. 1992, 2004; Wilde et al. 2008; Coleman et al. 2012) reduce sudden cardiac death risk, and that, in 20–30 % of events, intense emotions, particularly anger, have been linked to myocardial infarction (Mittleman et al. 1995) and life-threatening arrhythmias as evidenced by implantable cardioverter defibrillator (ICD) discharge (Lampert et al. 2002) attest to the pivotal role of neural factors in malignant arrhythmias.

New evidence suggests that myocardial infarction profoundly disrupts, or "frays," cardiac nerves, setting the stage for heterogeneous reinnervation, which is conducive to sustained reentrant ventricular arrhythmias (Zhou et al. 2004; Verrier and Kwaku 2004). Thus, the concept has emerged that neural remodeling following myocardial infarction should be considered an important element in risk for sudden cardiac death along with remodeling of the myocardial substrate.

The main goal of this review is to discuss both the enduring and the new concepts that underlie our current understanding of the role of neural influences in myocardial ischemia- and infarction-induced ventricular tachycardia and fibrillation.

4.2 Adrenergic Influences on Cardiac Arrhythmia Vulnerability

Adrenergic inputs constitute an important trigger for ventricular arrhythmias during acute myocardial ischemia and infarction. Demonstration of the triggering role of sympathetic nerve discharge in spontaneous ventricular tachycardia and fibrillation was provided by direct recording of left stellate ganglion nerve activity in ambulatory dogs with chronic myocardial infarction (Fig. 4.1) (Zhou et al. 2008). Such striking surges in sympathetic nerve activity also occur within a few

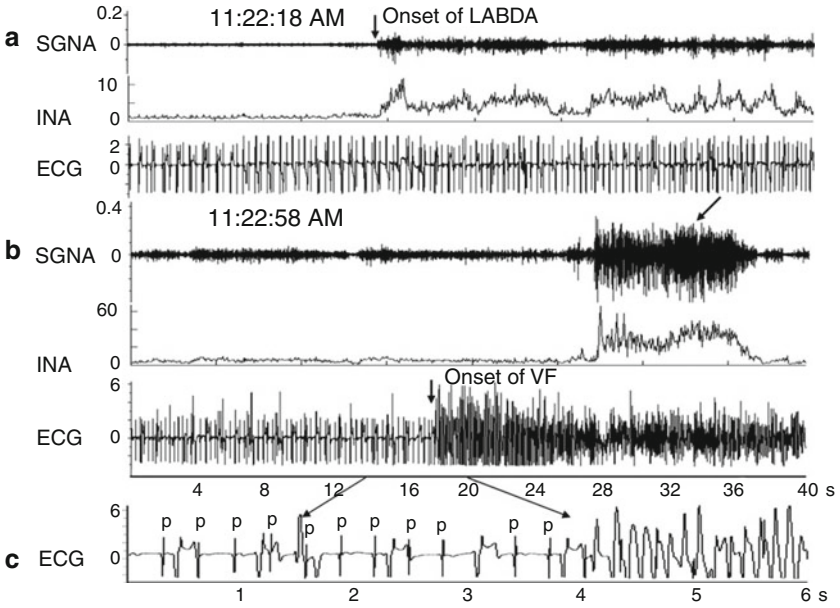

Fig. 4.1 Example of increased left stellate ganglion nerve activity (*SGNA*) preceding ventricular fibrillation (*VF*) and sudden cardiac death (Zhou et al. 2008). (**a**) Increased low-amplitude burst discharge activity (*LABDA*) resulted in accelerated idioventricular rhythm. (**b**) VF occurred approximately 40 s later. Panels (**a**) and (**b**) are continuous. (**c**) A 6-s recording from panel (**b**). *INA* integrated nerve activity in millivolts, *P* P wave, which is dissociated from ventricular activation due to complete AV block (Reprinted with permission from Elsevier)

seconds of experimental left anterior descending coronary artery occlusion (Malliani et al. 1969) and are associated with a fall in ventricular fibrillation threshold (Lombardi et al. 1983), as well as by a marked increase in spontaneous occurrence of ventricular tachycardia and fibrillation and correlated increase in T-wave alternans magnitude (Nearing et al. 1991, 1994). With reperfusion, a second peak in ventricular arrhythmia vulnerability and T-wave alternans occurs, likely provoked by washout of by-products of cellular ischemia (Lombardi et al. 1983; Nearing et al. 1991, 1994; Corbalan et al. 1976). Left stellate ganglionectomy significantly attenuates the surge in vulnerability to ventricular fibrillation during occlusion but enhances its magnitude during reperfusion (Schwartz et al. 1976; Nearing et al. 1991).

4.3 Role of Adrenergic Receptor Activation

Enhanced sympathetic nerve activity increases vulnerability to ventricular arrhythmias in the ischemic heart by complex processes. Multifold direct arrhythmogenic effects on cardiac electrophysiologic function are primarily mediated through β_1-adrenergic receptors. They include derangements in impulse formation, conduction,

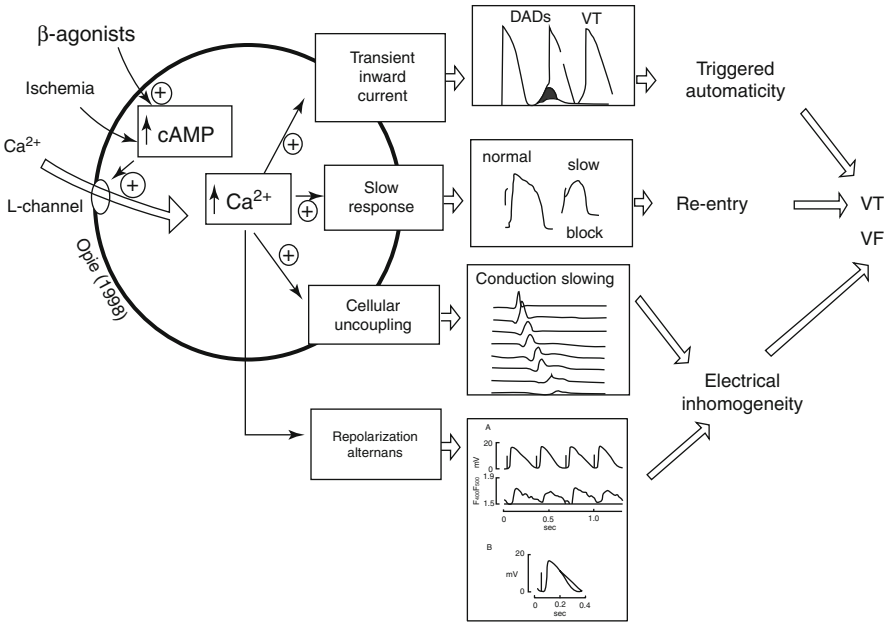

Fig. 4.2 The cardiac β-adrenergic signaling system mediating ventricular arrhythmogenesis. The central pathways include links between cyclic adenosine 3′,5′-monophosphate (*cAMP*), cytosolic calcium, and specific calcium-mediated electrophysiologic abnormalities that predispose to ventricular tachycardia (*VT*) and ventricular fibrillation (*VF*) (Modified from Opie (2004) and used with his permission). The lowest panel is based on Lee et al. (1988), indicating that simulated ischemia results in alternation in calcium transients, which appears to underlie action potential alternans (Reprinted with permission from Lippincott Williams & Wilkins)

repolarization alternans, and heterogeneity of repolarization, with the potential for culmination in ventricular tachycardia and fibrillation (Fig. 4.2) (Opie 2004; Lee et al. 1988). Indirect effects include impairment of oxygen supply–demand ratio resulting from increased cardiac metabolic activity, alpha-adrenergically mediated coronary vasoconstriction, especially in vessels with damaged endothelium, and changes in preload and afterload.

Increased levels of catecholamines stimulate β-adrenergic receptors, which in turn alter adenylate cyclase activity and intracellular calcium flux. These effects are probably mediated by the cyclic nucleotide and protein kinase regulatory cascade, which can alter spatial heterogeneity of calcium transients and consequently provoke T-wave alternans and heterogeneity of repolarization (Verrier et al. 2011).

In the setting of myocardial ischemia, α-adrenergic blockade may alleviate coronary vasoconstriction and reduce platelet aggregability, but in the normal heart, α-adrenergic receptor stimulation or blockade does not appear to affect ventricular electrical stability, as evidenced by the fact that administration of an α-adrenergic agonist such as phenylephrine or methoxamine does not influence excitable properties when the pressor response is controlled to prevent reflex changes in autonomic tone (Verrier et al. 1974; Kowey et al. 1983).

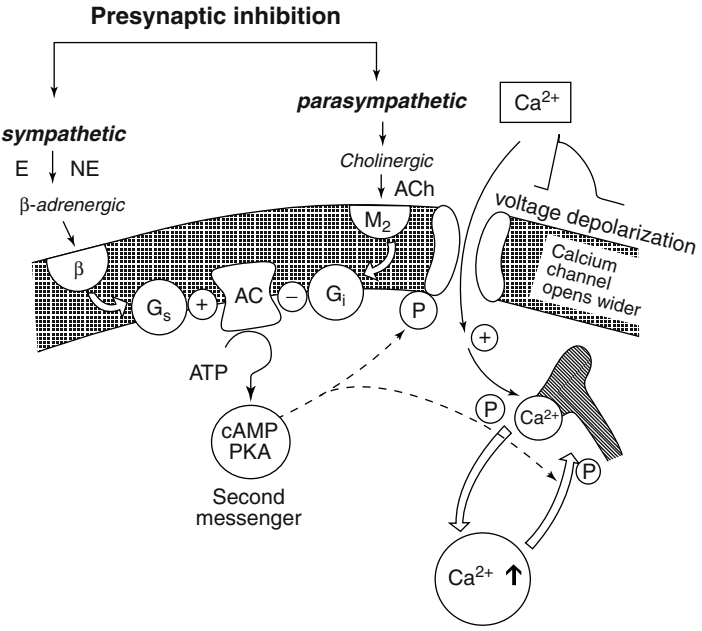

Fig. 4.3 Interaction between parasympathetic and sympathetic systems at a cellular level may involve two opposing cyclic nucleotides, cyclic adenosine 3′,5′-monophosphate (*cAMP*) and cyclic guanosine 3′,5′-monophosphate. Many effects of vagal stimulation can best be explained by the inhibitory effect on the formation of cAMP, including formation of the inhibitory G protein G_i in response to M_2-receptor stimulation (Reprinted from Opie (2004) and used with his permission)

4.4 Sympathetic–Parasympathetic Nerve Interactions

Vagus nerve influences are contingent on the prevailing level of adrenergic tone (Lown and Verrier 1976). When sympathetic nerve activity is augmented by thoracotomy, sympathetic nerve stimulation, myocardial ischemia, or catecholamine infusion, vagus nerve activation exerts a protective effect on ventricular vulnerability. But, vagus nerve stimulation alone is without effect on ventricular vulnerability during β-adrenergic blockade. Levy and Blattberg (1976) termed this phenomenon "accentuated antagonism" (Fig. 4.3) (Opie 2004). The basis for this antagonism of adrenergic effects is presynaptic inhibition of norepinephrine release from nerve endings and muscarinically mediated action at the second messenger level, attenuating the response to catecholamines at receptor sites (Levy and Blattberg 1976). Vagus nerve influences also provide indirect protection against ventricular fibrillation during both myocardial ischemia and reperfusion by reducing excess heart rates, which can otherwise critically compromise diastolic perfusion time to increase the ischemic insult (Zuanetti et al. 1987). However, the beneficial effects of vagus nerve activity may be annulled if profound bradycardia and hypotension ensue.

4.5 Nerve Degeneration and Regrowth in Response to Myocardial Infarction

Myocardial infarction can elicit extensive damage to the afferent and efferent innervation of the heart (Minardo et al. 1988) (Fig. 4.4). The resulting heterogeneous reinnervation, supersensitivity to catecholamines, and loss of antiarrhythmic effects of vagus nerve activity converge to enhance susceptibility to ventricular arrhythmias during the acute phase of myocardial infarction (Table 4.1) (Zipes and Miyazaki 1990).

Chen and coworkers (2001) demonstrated a significant correlation between increased sympathetic nerve density as reflected in immunocytochemical markers and history of ischemia in native hearts of human transplant recipients. In a canine model, they documented increased incidence of ventricular tachycardias and sudden cardiac death following induction of nerve sprouting with nerve growth factor. Episodes of T-wave alternans also occurred (Tsai et al. 2002), consistent with this parameter's capacity to track arrhythmia vulnerability in humans as well as animal models (Verrier et al. 2011). The predisposition to arrhythmias was also linked to immunocytochemical evidence of a heterogeneous pattern of sympathetic nerve reinnervation (Zhou et al. 2004; Verrier and Kwaku 2004) (Fig. 4.5), prompting the

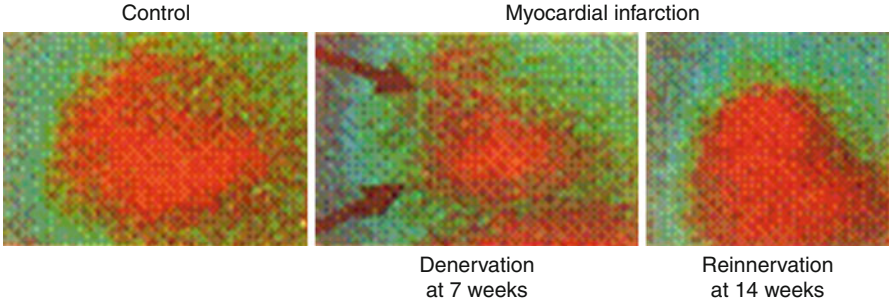

Fig. 4.4 MIBG scintigraphic images of sympathetic innervation before and after myocardial infarction in dogs (Minardo et al. 1988). Left panel: Left lateral preoperative metaiodobenzylguanidine (MIBG) image showing homogeneous uptake. Middle panel: MIBG images obtained 7 weeks after latex injection showing anteroapical defect (*arrow*). Right panel: MIBG images at 14 weeks after latex injection showing homogeneous uptake (Reprinted with permission from Lippincott Williams & Wilkins)

Table 4.1 Autonomic effects of myocardial infarction

Hours: Damage to efferent and afferent autonomic nerve supply
Days, weeks:
Heterogeneous re-innervation (14 weeks)
Denervation supersensitivity (>17 weeks)
Risk for arrhythmias
Desensitization to cardiac pain, due to damage to afferent fibers

From Zipes and Miyazaki (1990)

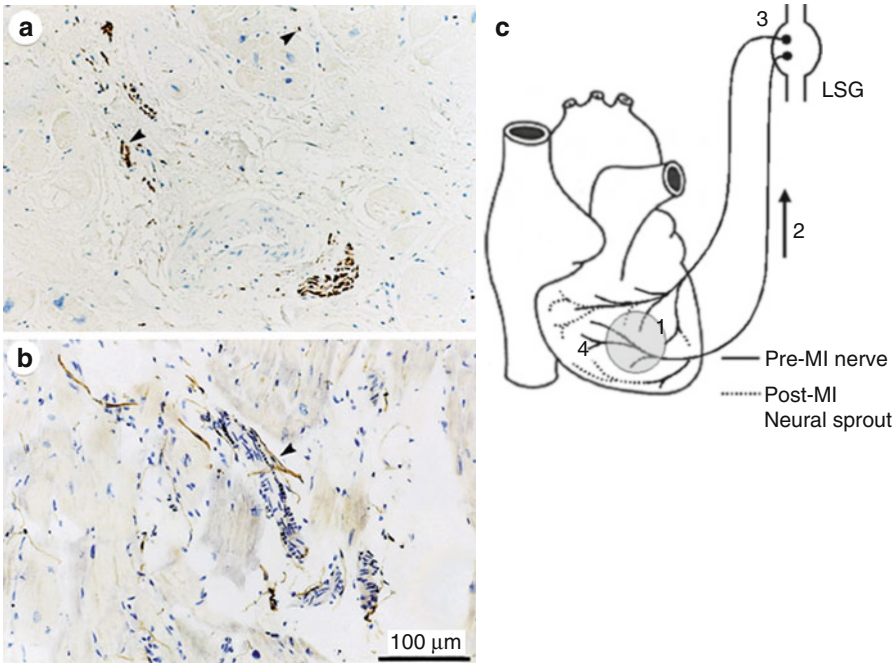

Fig. 4.5 Nerve sprouting after myocardial infarction. Panels (**a**) and (**b**) demonstrate TH-positive nerve fibers (*arrowheads*) in injured areas or around coronary arteries and in a patient with coronary artery disease (Cao et al. 2000). Panel (**c**) signaling of neural remodeling after myocardial infarction (Verrier and Kwaku 2004). Myocardial injury (*shaded area*) results in early local nerve growth factor (NGF) release, presumably from damaged cells, followed by upregulated NGF and growth-associated protein 43 (GAP43) expression, especially in the infarct area (*1*). These signal proteins are then retrogradely transported (*2*) to the nerve cell bodies in the ganglia (*3*) where they stimulate the sprouting of new cardiac nerve endings in the heart (*4*), predominantly in noninfarcted regions, leading to heterogeneous hyperinnervation (Reprinted with permission from Lippincott Williams & Wilkins)

suggestion that the term "neural remodeling" should be employed alongside "myocardial remodeling" in the conceptual framework of the pathophysiology of acute myocardial infarction.

4.6 Nerve Stimulation as an Antiarrhythmic Strategy

Electrical stimulation of the cardiac nerve supply has been reported to reduce ventricular tachyarrhythmias. Spinal cord stimulation, which is both sympatholytic and enhances cardiac vagus nerve tone, is capable of decreasing ischemia-induced arrhythmias in canines (Issa et al. 2005) and T-wave alternans in patients with ischemic cardiomyopathy (Ferrero et al. 2008). Chronic vagus nerve stimulation prevented ventricular fibrillation and sudden cardiac death in conscious dogs with a healed myocardial infarction (Vanoli et al. 1991). In humans, chronic vagus nerve

stimulation improves left ventricular function in patients with advanced heart failure (De Ferrari et al. 2011), suggesting the potential for concurrent improvement in mechanical function and reduction in arrhythmia risk.

Conclusion

Our comprehension of the role of the autonomic nervous system has continued to evolve in an intriguing and productive manner. Activation of the sympathetic nervous system is an important factor in the genesis of ischemia- and infarction-induced ventricular arrhythmias. Increased vagus nerve activity is protective by inhibition of norepinephrine release and cyclic nucleotide-mediated antagonism at the adrenergic receptor level. The pattern of local neurocircuitry critically influences heterogeneity of repolarization, a fundamental factor in arrhythmogenesis. Especially important is the neural remodeling that occurs in the post-myocardial infarction period. A number of promising therapeutic approaches based on pharmacologic and electrical targeted neuromodulation to decrease cardiac sympathetic while augmenting vagus nerve tone are being pursued.

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