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Cardiac autonomic neural remodeling and susceptibility to sudden cardiac death: effect of endurance exercise training

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Billman GE. Cardiac autonomic neural remodeling and susceptibility to sudden cardiac death: effect of endurance exercise training. *Am J Physiol Heart Circ Physiol* 297: H1171–H1193, 2009. First published August 14, 2009; doi:10.1152/ajpheart.00534.2009.—Sudden cardiac death resulting from ventricular tachyarrhythmias remains the leading cause of death in industrially developed countries, accounting for between 300,000 and 500,000 deaths each year in the United States. Yet, despite the enormity of this problem, both the identification of factors contributing to ventricular fibrillation as well as the development of safe and effective antiarrhythmic agents remain elusive. Subnormal cardiac parasympathetic regulation coupled with an elevated cardiac sympathetic activation may allow for the formation of malignant ventricular arrhythmias. In particular, myocardial infarction can reduce cardiac parasympathetic regulation and alter β -adrenoceptor subtype expression enhancing β_2 -adrenoceptor sensitivity that can lead to intracellular calcium dysregulation and arrhythmias. As such, myocardial infarction can induce a remodeling of cardiac autonomic regulation that may be required to maintain cardiac pump function. If alterations in cardiac autonomic regulation play an important role in the genesis of life-threatening arrhythmias, then one would predict that interventions designed to either augment parasympathetic activity and/or reduce cardiac adrenergic activity would also protect against ventricular fibrillation. Recently, studies using a canine model of sudden death demonstrate that endurance exercise training (treadmill running) enhanced cardiac parasympathetic regulation (increased heart rate variability), restored a more normal β -adrenoceptor balance (i.e., reduced β_2 -adrenoceptor sensitivity and expression), and protected against ventricular fibrillation induced by acute myocardial ischemia. Thus exercise training may reverse the autonomic neural remodeling induced by myocardial infarction and thereby enhance the electrical stability of the heart in individuals shown to be at an increased risk for sudden cardiac death.

sympathetic nervous system; parasympathetic nervous system; β -adrenergic receptors; myocardial infarction; ventricular fibrillation

THE EFFECTIVE MANAGEMENT OF cardiac arrhythmias, either of atrial or ventricular origin, remains a major challenge for the cardiologist. Sudden cardiac death [due to ventricular tachyarrhythmias (20, 71, 114, 126)] remains the leading cause of death in industrially developed countries, accounting for between 300,000 and 500,000 deaths each year in the United States (1, 71, 298, 302). In a similar manner, atrial fibrillation is the most common rhythm disorder contributing to a substantial mortality, as well as a reduction in the quality of life, among these patients (146, 159). Atrial fibrillation currently accounts for about 2.3 million cases in the United States and has been projected to increase by 2.5-fold over the next half century (10). Indeed, the prevalence of this arrhythmia increases with each decade of life (0.5% patient population between the ages of 50 and 59 yr climbing to almost 9% at age 80–89 yr) and contributes to approximately one quarter of ischemic strokes in the elderly population (146, 159). In addition to the obvious emotional distress, the morbidity and

mortality resulting from cardiac arrhythmias places a substantial financial strain on the health delivery system [incremental cost per quality-adjusted life-year as much as US \$558,000 (63A)]. Despite the enormity of this problem, both the identification of the mechanisms responsible for these arrhythmias as well as the development of safe and effective antiarrhythmic agents remain elusive.

Alterations in cardiac autonomic regulation (cardiac autonomic remodeling) induced by cardiac disease, particularly during myocardial ischemia and infarction, may contribute significantly to the induction of ventricular fibrillation (39, 64, 65, 68, 80, 233, 244). As such, interventions that favorably improve cardiac autonomic balance [e.g., aerobic exercise conditioning by increasing parasympathetic and/or decreasing sympathetic activity (15, 38, 53, 60, 100, 179, 182, 206, 232, 258)] could provide safe and effective means to reduce the incidence of lethal ventricular arrhythmias. It is, therefore, the purpose of this review to evaluate the antiarrhythmic potential of aerobic (endurance) exercise conditioning. First, the relationship between alterations (remodeling) in cardiac autonomic regulation induced by cardiac disease and an enhanced susceptibility to ventricular fibrillation will be investigated. Clinical

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and experimental evidence that endurance (aerobic) exercise conditioning can restore a more normal cardiac autonomic regulation (reverse cardiac autonomic remodeling), thereby protecting against malignant arrhythmias, will then be analyzed.

Cardiac Autonomic Neural Remodeling and Sudden Cardiac Death

Changes in both the parasympathetic and sympathetic regulation of the heart, particularly as a consequence of myocardial ischemia or infarction, can contribute significantly to the induction of ventricular fibrillation (39, 64, 65, 68, 80, 233, 244). The following sections will first review the clinical and experimental evidence linking changes in cardiac parasympathetic regulation to an increased risk for malignant arrhythmias and then provide a similar analysis for the relationship between cardiac sympathetic activity and ventricular fibrillation.

Cardiac parasympathetic nervous system. It is now widely accepted that reductions in cardiac parasympathetic control are associated with an increased risk for sudden death (39, 64, 65, 68, 80, 233, 244). Eckberg et al. (97) were among the first to demonstrate that the patients with the most advanced disease states also exhibited the greatest impairment in parasympathetic activity. Billman and coworkers (39, 46, 249) reported that baroreceptor-mediated reductions in heart rate (baroreceptor reflex sensitivity) were impaired by myocardial infarction,

with the greatest impairment noted in animals particularly susceptible to sudden death (Fig. 1). In this canine model, susceptibility to sudden cardiac death was defined as ventricular tachyarrhythmias (ventricular tachycardia, ventricular flutter, or ventricular fibrillation) that were induced by acute myocardial ischemia during submaximal exercise (39). Conversely, this exercise plus ischemia test either failed to induce any arrhythmias or provoked only single premature ventricular extrasystoles in resistant dogs (39). Heart rate variability (beat-to-beat variations in R-R interval that correspond to respiration), a widely used index of cardiac vagal activity (11, 24, 28–31, 95, 270), was also reduced to a greater extent in animals susceptible to ventricular fibrillation compared with animals resistant to these malignant arrhythmias (39, 42, 76, 249). In particular, the susceptible animals exhibited a much greater reduction (withdrawal) of cardiac vagal regulation in response to either submaximal exercise (39, 42, 117, 131) or acute myocardial ischemia (39, 76, 117, 131). The heart rate recovery following exercise was also depressed (slower reactivation of cardiac parasympathetic regulation) in dogs susceptible to ventricular fibrillation compared with animals resistant to these malignant arrhythmias (65, 259).

As previously noted, heart rate variability has gained widespread acceptance as a clinical tool for the evaluation of cardiac autonomic changes in patients. The term heart rate variability yields nearly 12,000 hits when placed in the

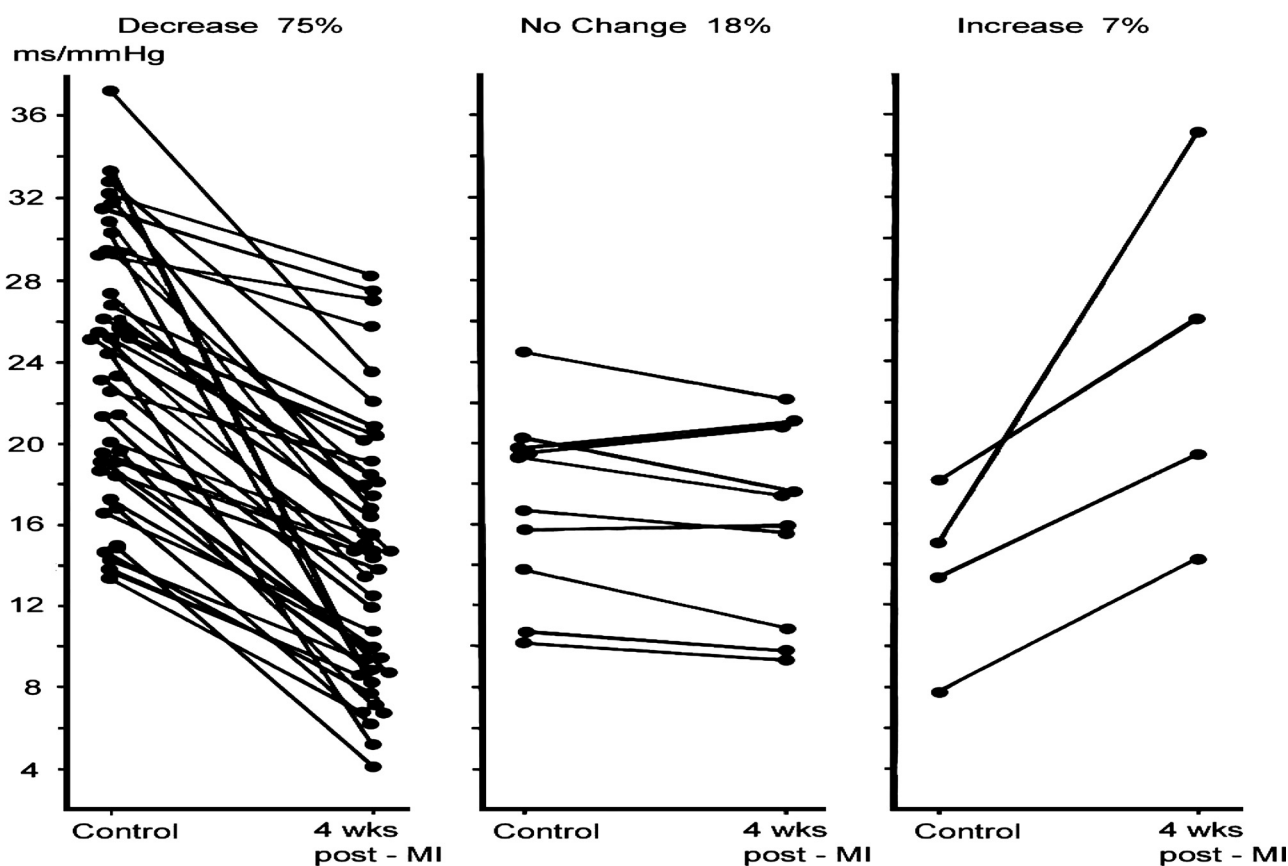


Fig. 1. Cardiac parasympathetic remodeling induced by myocardial infarction (MI) as measured by changes in baroreceptor reflex sensitivity (BRS). The individual plots of BRS for 55 dogs before and after MI are shown. BRS was considered to be unchanged if the difference before and after infarction was <3 ms/mmHg. Note that vast majority (75%) of the dogs exhibited a decrease in BRS following the infarction. [Reprinted with permission from Schwartz et al. (249).]

PubMed search engine. A variety of cardiovascular risk factors and disease states have all been shown to reduce heart rate variability, including diabetes (230, 281), smoking (147, 178), obesity (257), hypertension (183A, 210), and heart failure (2, 47, 76). Of particular interest, heart rate variability is reduced in patients recovering from a myocardial infarction and, furthermore, those patients with the greatest reduction in this variable also have the greatest risk for sudden death (11, 24, 28–31, 97, 153, 270). Kleiger and coworkers (153) found that in patients recovering from myocardial infarctions, those with the smallest heart rate variability (standard deviation of R-R interval) had the greatest risk of dying suddenly. The relative risk of mortality was 5.3 times greater in patients with R-R interval variability <50 ms compared with patients with variability >100 ms. This finding has been subsequently confirmed by numerous more recent clinical studies (11, 24, 28, 29, 31, 95, 129, 158A, 158C, 160, 270). To cite just one example, La Rovere et al. (158C), reporting for the Autonomic Tone and Reflexes After Myocardial Infarction group, found that post-myocardial infarction patients with either low heart rate variability or a small heart rate response to an increase in blood pressure (i.e., baroreceptor reflex sensitivity) had a much greater risk of sudden death than those with well preserved cardiac vagal tone. The greatest risk for mortality was observed in patients with a large reduction in both markers of cardiac vagal regulation (158C). As was previously noted in animals susceptible to ventricular fibrillation (45, 259), heart rate recovery after exercise has also been shown to be an independent predictor of mortality across substantial and diverse population groups (73, 74, 143, 193, 194, 200, 201). Cole et al. (74) demonstrated in a multicenter study of 5,234 individuals that abnormal heart rate recovery after submaximal exercise predicted death, even after adjustment for various confounding factors; Nishime et al. (200) published similar results from a total of 9,454 patients.

When considered together, these clinical and experimental studies clearly suggest that reductions in cardiac parasympathetic regulation play an important role in the development of sudden cardiac death. Thus one would predict that interventions that alter cardiac parasympathetic control should also alter susceptibility to malignant arrhythmias. Several experimental studies have shown that electrical stimulation of the vagus nerves can reduce ventricular fibrillation threshold, antagonize the effects of sympathetic stimulation, and decrease the incidence of ventricular fibrillation (67, 80, 150, 155, 304). As early as 1860, Einbrodt demonstrated that electrical stimulation of the vagus nerves increased the amount of current that was required to induce ventricular fibrillation (99). This observation was subsequently confirmed by Garrey in 1908, who further reported that vagal stimulation could terminate ongoing ventricular fibrillation in a few animals (111). More recently, acute vagal stimulation has been shown to improve cell-to-cell electrical coupling [i.e., attenuate ischemically mediated increases in myocardial electrical impedance (89)] and to prevent reperfusion arrhythmias in anesthetized cats (304) or ventricular fibrillation in a conscious canine model of sudden death (277). In the latter study, ventricular fibrillation was only induced in 12% of the dogs that received vagal nerve stimulation compared with 92% of the animals that were not so treated (277). Furthermore, this protection occurred independently of heart rate reductions in about half of the protected

dogs. Similar findings have been reported in the clinic. Reflexively mediated increases in cardiac vagal activation terminated ventricular tachycardia in patients (288). In a similar manner, anesthetized cats that exhibited the largest increase in cardiac efferent vagal nerve activity in response to phenylephrine injections (i.e., activation of the baroreceptor reflex) had the best preserved vagal efferent activity during myocardial ischemia and were resistant to the induction of ventricular fibrillation (67). Long-term continuous vagal nerve stimulation has also been shown to reduce arrhythmias, decrease mortality, and improve cardiac function in animal models of heart failure (8, 168, 234). A multicenter study is currently investigating the potential beneficial effects of continuous long-term right cervical vagal stimulation in human patients with heart failure (87, 252).

Pretreatment with drugs that increase cholinergic receptor activation has also been shown to protect against ischemically induced ventricular fibrillation in animal models (32, 86, 296). Antiarrhythmic actions have been reported for cholinesterase inhibitors [prostigmine (192) and edrophonium (122)], muscarinic receptor agonists [carbachol (32), oxotremine (86), and methacholine (86)], and the muscarinic second messenger cGMP (32). This protection was noted even when heart rate was held constant by ventricular pacing (32), suggesting an important protective role for the direct activation of muscarinic receptors on ventricular cardiomyocytes. Conversely, bilateral vagotomy or the cholinergic antagonist atropine can increase arrhythmia formation (79, 85).

Unfortunately, many cholinergic agonists exert profound gastrointestinal actions, thereby limiting their therapeutic potential. The observation that low doses of cholinergic antagonists paradoxically increased the level of cardiac vagal activity (156) led to the proposal that this treatment could provide an acceptable means of enhancing cardiac parasympathetic activity in patients (66). Several independent clinical studies (66, 84, 213, 284), in fact, demonstrated that low doses of scopolamine augmented markers of cardiac vagal activity in post-myocardial infarction patients. However, Halliwill et al. (117) and Hull et al. (134) independently demonstrated that, although low doses of cholinergic antagonists increased baseline cardiac vagal activity (as measured by R-R interval variability), this treatment failed to alter the incidence of ventricular fibrillation induced by myocardial ischemia. Halliwill et al. (117) further demonstrated that the enhanced baseline vagal activity was not maintained when the heart was stressed by either exercise or myocardial ischemia. As such, it is not surprising that this therapy did not protect against ventricular fibrillation. To be an effective antiarrhythmic therapy, an intervention must not only increase baseline vagal activity but must also maintain this enhanced activity when the heart is stressed.

Although it is beyond the scope of the present review to analyze extensively the strengths and weaknesses of the various indexes used to measure heart rate variability, a brief discussion of some of the limitations with these techniques is merited. For a more detailed presentation the reader is encouraged to read one or more of the review articles that eloquently address the technical issues concerning the heart rate variability and its relationship to cardiac autonomic regulation (11, 24, 95, 212, 270). First and foremost, it must be emphasized that heart rate variability only provides an indirect assessment of cardiac autonomic activity and does not provide a direct

measurement of either cardiac parasympathetic or sympathetic nerve activity. Furthermore, there is considerable debate as to the exact relationship between changes in cardiac autonomic activity and a particular branch of the autonomic nervous system. For example, frequency domain analysis of heart rate variability usually reveals two or more peaks, a low frequency (<0.15 Hz) and a higher frequency peak (>0.15 Hz), that are often assumed to correspond to cardiac sympathetic and cardiac parasympathetic neural activity, respectively (11, 24, 95, 212, 270). However, accumulating evidence clearly demonstrates this assumption is naïve and greatly oversimplifies the complex nonlinear interactions between the sympathetic and the parasympathetic divisions of the autonomic nervous system (212). This is particularly true with regards to the relationship between low frequency power and cardiac sympathetic regulation. Low frequency power was found to be reduced by selective parasympathectomy and also was not totally eliminated when the denervation was combined with β -adrenoceptor blockade (224). Furthermore, interventions that would be expected to increase cardiac sympathetic activity, such as acute exercise or myocardial ischemia, not only failed to increase low frequency power but actually provoked significant reductions in this variable (131). Sympathetic activity has also been shown to modulate the high frequency component of heart rate variability (271), albeit to a lesser extent than the parasympathetic influences on low frequency power. As noted above, the vast majority of the clinical and the experimental studies demonstrate a strong association between high frequency power and cardiac parasympathetic activity (11, 24, 28, 29, 31, 39, 40, 42, 44, 45, 95, 129, 158A, 158C, 160, 270); however, this relationship is qualitative rather than quantitative in nature. In other words, a low or high amount of heart rate variability may reflect a decreased or increased cardiac parasympathetic regulation but does not provide a quantification of the actual cardiac nerve firing rate. Thus heart rate variability data should be interpreted with appropriate caution.

Cardiac sympathetic nervous system. Several lines of evidence demonstrate that any intervention that elicits an increase in cardiac sympathetic activity also enhances the development of lethal cardiac arrhythmias (39, 64, 65, 68, 80, 233, 244). Psychological stress or acute bouts of exercise, interventions known to increase sympathetic activity, also increase arrhythmia formation during ischemia (4, 81, 107, 280, 282, 301). Indeed, an excessively large heart rate increase at the onset of exercise (a marker of cardiac sympathetic activation) has been linked to an increased susceptibility to ventricular fibrillation in patients with ischemic heart disease (105). For example, patients with documented coronary artery disease that exhibited the largest increase in heart rate at exercise onset also had a greater risk for cardiac events (cardiac deaths and nonfatal myocardial infarctions) than did those subjects with a more modest heart rate increase (105). Similar results have been obtained in animal studies. Billman (40) found that dogs with healed myocardial infarctions that exhibited the greatest heart rate increases during exercise onset developed ventricular fibrillation during myocardial ischemia more frequently than those animals that proved to be resistant to malignant arrhythmias. The elevated heart rate response to exercise onset was abolished by prior treatment with the β -adrenoceptor antagonist propranolol (40). β_2 -adrenoceptor activation may be particularly arrhythmogenic in these animals (see below).

Because pharmacological agents often have actions at multiple sites in addition to those on the tissue of interest, more direct evidence for a role of enhanced cardiac sympathetic nerve activity in the genesis of malignant arrhythmias is provided by nerve stimulation and by nerve recording studies in animal models (80, 135A, 138, 177, 233, 244, 300). The pioneering studies of Schwartz and colleagues established nearly 40 years ago that myocardial ischemia provokes a powerful increase in cardiac sympathetic efferent activity (a cardiocardiac reflex) that can directly precipitate ventricular tachycardia (177, 248). More recently, Peng Chen and coworkers (300) demonstrated that increased sympathetic nerve activity (whole nerve recordings) often preceded the onset of ventricular tachyarrhythmias in conscious dogs. Furthermore, the direct electrical stimulation of cardiac sympathetic nerves, particularly those originating from the left stellate ganglion, decreases ventricular fibrillation threshold, can produce heterogeneities in ventricular refractory period or action potential restitution, and also induces ventricular arrhythmias (80, 135A, 138, 198, 233, 244). Finally, sympathetic nerve sprouting and compensatory reinnervation following myocardial infarction alters regional electrical properties of the heart, thereby facilitating the formation of ventricular arrhythmias (64, 65, 68, 299).

If an enhanced cardiac sympathetic activity is critical for the development of lethal arrhythmias, then interventions that reduce or disrupt cardiac sympathetic nerve activation should also exert beneficial actions on cardiac rhythm. Conversely, interventions that enhance cardiac sympathetic activation should increase arrhythmia formation. Indeed, interventions that reduce cardiac sympathetic activity have been shown to protect against arrhythmias (80, 123, 124, 149, 233, 244), whereas those that enhance cardiac sympathetic activity provoke malignant arrhythmias (34, 39, 43, 80, 135A, 138, 233, 244). For example, the sympathomimetic drug cocaine augmented the autonomic response to acute myocardial ischemia and induced malignant arrhythmias 76.4% (42 of 55) of conscious dogs that had been previously shown to be resistant to the induction of ventricular fibrillation (34–37, 39, 41, 43). Conversely, and as has been previously noted, β -adrenoceptor blockade has been shown to reduce cardiac mortality in patients recovering from myocardial infarction (123, 124, 149). In these patients, β -adrenoceptor antagonists reduced overall mortality by 20% and mortality due to sudden death by 30–50% (127, 128, 203, 236, 254). β -adrenoceptor blockers were most effective in reducing early (1 h to 7 day) cardiac mortality during myocardial infarction (127, 128, 203, 236). Similar results have been reported in animal studies (3, 39, 86, 278). β -adrenoceptor blockade with propranolol HCl protected 11 of 18 dogs susceptible to ventricular fibrillation (39). Although propranolol also decreased heart rate, it was not possible to differentiate between the cardioprotection that results from direct effects on the ischemic myocardium from indirect effects due to reductions in heart rate. Similar results have been reported using the same canine model of sudden death. Adamson et al. (3) and Vanoli et al. (278) reported that propranolol suppressed ventricular fibrillation in 8 of 11 and 5 of 9 susceptible dogs, respectively. These studies also did not control for the β -adrenoceptor blockade-mediated reductions in heart rate. If the data from these three studies are combined, then the nonselective β -adrenoceptor antagonist propranolol

protected 63.2% (24 of 38) of the susceptible dogs from malignant arrhythmias. However, it must be emphasized that β -adrenoceptor blockers did not provide a complete protection in either human or animal models. For example, the mortality following myocardial infarction remains high among patients with substantial ventricular dysfunction, even when placed on optimal β -adrenergic receptor antagonist therapy (63). The 1-yr mortality is 10% or higher, with sudden death accounting for approximately one-third of the deaths in these high-risk patients (63).

Surgical interventions that remove the cardiac sympathetic nerves provide a more complete protection from arrhythmias in both animal models and human patients. Schwartz (241, 242) has written an excellent historical overview of the development of left cardiac sympathetic denervation for the treatment of ventricular arrhythmias. As early as 1899, it was proposed that the removal of cervicothoracic sympathetic nerves might provide pain relief for patients with angina (106). In 1916, Jonnesco (also spelled Jonnesco) tested this hypothesis in a single patient with incapacitating angina and concomitant cardiac arrhythmias (141). Both the angina attacks and the arrhythmias were alleviated by the transection of the left stellate ganglion. This observation was subsequently confirmed in larger groups of patients (62, 82, 142, 169). Although sympathectomy for the management of angina has been supplanted by pharmacological approaches, experimental (39, 83, 121, 186, 243, 245–247) and clinical (103, 250, 251, 291, 303) studies illustrate the antiarrhythmic potential of cardiac sympathetic denervation therapies. For example, the removal of the left stellate ganglion increased the threshold of ventricular fibrillation and reduced arrhythmias induced by myocardial ischemia in animal models (243, 245–247). In fact, left stellectomy completely suppressed ventricular fibrillation induced by myocardial ischemia in a canine model of sudden death, protecting all 11 so tested (39, 247). Similar results have been reported in humans (78, 250, 251). Left cardiac sympathetic denervation has been used successfully to reduce arrhythmias in high risk patients following myocardial infarction (250), patients with long QT syndrome (78, 251), and patients with catecholaminergic polymorphic ventricular tachycardia (78, 291).

β_2 -Adrenoceptor Activation and Susceptibility to VF

As previously noted, enhanced sympathetic activation can reduce cardiac electrical stability and induce ventricular fibrillation. Presumably, the activation of adrenoceptors (both pre- and postsynaptic receptors) mediates the arrhythmogenic effects of catecholamines released from the sympathetic nerve terminals. The mammalian myocardium contains both β_1 - and β_2 -adrenoceptors (6). In the normal heart, the β_1 -adrenoceptor is the dominant receptor subtype and mediates the inotropic response to the activation of sympathetic nerves. Under certain pathological conditions, however, the activation of β_2 -adrenergic receptors may become particularly important (6, 56). It is now well established that β_1 -adrenoceptor sensitivity decreases substantially during heart failure, whereas the β_2 -adrenoceptor number remains relatively constant (6, 56). As a consequence, the failing heart becomes more dependent upon the activation of β_2 -adrenoceptors for inotropic support. The activation of these receptors may help maintain cardiac function in diseased hearts but not without potentially adverse consequences. β_2 -

adrenoceptor activation promotes an increase in the calcium current without altering calcium reuptake by the sarcoplasmic reticulum (7). The resulting elevation in intracellular calcium could provoke oscillations in membrane potential that, in turn, could trigger arrhythmias (33). Thus β_2 -adrenoceptor activation would tend to reduce the cardiac electrical stability and increase the propensity for the formation of malignant arrhythmias in the diseased heart. In addition to these direct effects on ventricular myocytes, presynaptic actions of catecholamines may also indirectly modify adrenergic responses. Although the synaptic autoreceptor regulation hypothesis has been challenged (145), a number of reports suggest that adrenergic receptors located on the nerve terminals can regulate the amount of neural transmitter released by a given nerve impulse (57, 58). As such, the activation of these presynaptic receptors could either enhance (β_2 -adrenoceptor promote transmitter release) or attenuate (α_2 -adrenoceptor decrease transmitter release) the postsynaptic sympathetic response (57, 58). Therefore, alterations in the presynaptic autoreceptor regulation in response to myocardial infarction or acute ischemia could also contribute to an abnormal cardiac autonomic regulation.

Billman and coworkers (50, 132) demonstrated in dogs with healed myocardial infarctions that the nonselective β -adrenoceptor agonist isoproterenol provoked significantly larger increases both in heart rate, fractional shortening, and in the velocity of circumferential fiber shortening (an index of contractility) in those animals that were susceptible to ventricular fibrillation induced by myocardial ischemia compared with those animals that were resistant to these malignant arrhythmias (132). The selective β_2 -adrenoceptor antagonist ICI 118,551 reduced the isoproterenol response to a much greater extent in the susceptible animals, eliminating any differences noted between the groups (50). Interestingly, isoproterenol elicited similar responses in both the resistant and susceptible animals before myocardial infarction (Fig. 2), data that further implicate cardiac β -adrenoceptor remodeling to an enhanced susceptibility to ventricular fibrillation in this canine model of sudden death. In a similar manner, the calcium transient amplitude and the single-cell isotonic shortening response to either the selective β_2 -adrenoceptor agonist zinterol or isoproterenol was larger in myocytes obtained from the hearts of susceptible compared with resistant dogs, differences that were also eliminated by β_2 -adrenoceptor but not by β_1 -adrenoceptor blockade (50, 132) (Fig. 3). Interestingly, isoproterenol often induced calcium after-transients (cellular arrhythmias) in myocytes from susceptible but not from cells obtained from the hearts of resistant dogs. These after-transients were also suppressed by β_2 -adrenoceptor blockade but were unaffected by β_1 -adrenoceptor antagonists.

In the intact dog, β_2 -adrenoceptor blockade also almost completely suppressed ventricular fibrillation (VF) induced by acute myocardial ischemia, protecting 10 of 11 susceptible animals (50). In agreement with these findings, zinterol infusion provoked ventricular tachyarrhythmias in rabbits with heart failure induced by myocardial infarction (90). Furthermore, zinterol elicited aftercontractions and calcium after-transients in 88% of heart failure compared with 0% of control myocytes (90). β_2 -adrenoceptor stimulation also induced aftercontractions, after-transients, increased calcium transient amplitude, and sarcoplasmic reticular calcium load in myocytes from patients with heart failure (90). When considered

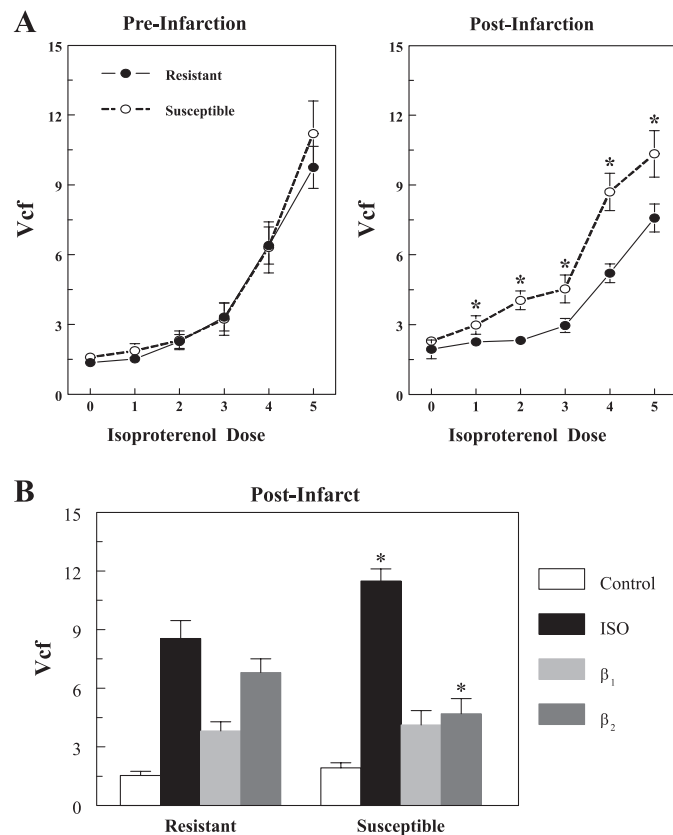


Fig. 2. β -adrenoceptor remodeling induced by myocardial infarction. *A*: inotropic response to increasing doses of the nonselective β -adrenoceptor agonist isoproterenol (Iso) before and after myocardial infarction in dogs that were subsequently shown to be either resistant ($n = 12$) or susceptible ($n = 16$) to ventricular fibrillation. Note that isoproterenol provoked a larger response in the susceptible animals after myocardial infarction. There were no differences between the groups before the myocardial infarction. *B*: effects of selective β -adrenoceptor antagonists on the maximum isoproterenol induced velocity of circumferential fiber shortening (Vcf) responses in dogs susceptible ($n = 12$) or resistant ($n = 15$) to ventricular fibrillation. Isoproterenol elicited a greater increase in the susceptible compared with the resistant dogs. The β_2 -adrenoceptor antagonist ICI 118,551 (0.2 mg/kg iv) elicited a significantly greater reduction in the isoproterenol response in the susceptible compared with the resistant animals. β_1 -adrenoceptor antagonist, bisoprolol (0.6 mg/kg iv); isoproterenol, $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Control, predrug Vcf, i.e., the values before the isoproterenol infusions began. [Reprinted with permission from Houle et al. (132).] * $P < 0.01$, susceptible vs. resistant dogs for a given treatment.

together these data demonstrate that enhanced β_2 -adrenoceptor responsiveness is associated with an increased propensity for ventricular fibrillation due to a calcium overload-induced spontaneous calcium release from the sarcoplasmic reticulum and resulting afterdepolarizations of the cardiac membrane. One would predict that interventions that restore a more normal β_1 - to β_2 -adrenoceptor balance should also protect against ventricular fibrillation.

Clinical studies have not extensively evaluated the contribution of β_2 -adrenoceptors to cardiac mortality. A small clinical trial found that the β_2 -adrenoceptor agonist salbutamol increased episodes of ventricular tachycardia in patients with congestive heart failure (187). In a similar manner, there are case reports in which β_2 -adrenoceptor agonists have precipitated sudden death as a consequence of the cardiac actions of these agents in patients with asthma (227, 228). More compelling, but indirect, evidence in support of the β_2 -adrenoceptor

hypothesis is provided by analysis of the numerous β -adrenoceptor antagonist trials. There is overwhelming evidence that β -adrenoceptor antagonists can protect against arrhythmia formation induced by myocardial ischemia and infarction (123, 124). Indeed, this marked reduction in cardiac mortality has been verified in at least 32 trials involving ~29,000 patients (123, 124). However, if one carefully examines the clinical studies cited above, it then becomes apparent that not all β -adrenoceptor antagonists offer the same level of protection, particularly during acute myocardial infarction. The majority of the studies using the β_1 -adrenoceptor antagonist metoprolol failed to report significant reductions in the incidence of ventricular fibrillation during acute myocardial infarction (127, 128). Furthermore, although atenolol did reduce overall mortality by 15%, the number of patients who died as the result of malignant arrhythmias was not altered (9A). In contrast, propranolol therapy elicited large reductions in both overall mortality (65% decrease) and sudden cardiac death (41% decrease) in post-myocardial infarction patients with persistent ST-segment depression (254), a group of patients known to be at a particularly high risk for subsequent cardiac events (292). Thus a better antiarrhythmic protection can be achieved with complete (i.e., β_1 - and β_2 -adrenoceptor), rather than selective (i.e., β_1 -), β -adrenoceptor blockade.

Effect of Exercise Conditioning on Cardiac Autonomic Regulation

Endurance exercise training is well established to alter autonomic nervous system activity, resulting in an apparent increase in cardiac parasympathetic tone coupled with decreases in sympathetic activity (39, 53, 60, 232). For example, in both the human and animals, the heart rate at submaximal workloads was reduced in trained individuals compared with sedentary controls (15, 38, 53, 60, 61, 112, 113, 175, 179, 258, 260). A resting bradycardia is a well-established consequence of exercise training and is, in fact, used as a marker that the exercise-trained state has been achieved (38, 60, 91, 113, 175, 206, 232, 240, 260). Both acetylcholine content and cholinesterase were increased in the hearts of trained rats compared with control animals (91, 269). In humans, exercise training during recovery from myocardial infarction has been reported to increase heart rate variability (93, 158B, 158D, 167, 176, 185, 208, 264, 275). In a similar manner, exercise training has been shown to attenuate reductions in heart rate variability in patients with either hypertension (75) or heart failure (93, 108, 151). Thus these data suggest that endurance exercise training can elicit changes in cardiac autonomic control that attenuate the cardiac autonomic remodeling induced by myocardial infarction.

A series of recent studies have comprehensively examined the effects of exercise training both on the parasympathetic (39, 44, 47, 157) and on the β -adrenoceptor (39, 51, 130) regulation of cardiac function in dogs susceptible or resistant to ventricular fibrillation induced by acute myocardial ischemia. The susceptible ($n = 20$) and resistant ($n = 13$) dogs were randomly assigned to either a 10-wk exercise program (susceptible, $n = 9$; and resistant, $n = 8$) or an equivalent sedentary period (susceptible, $n = 11$; and resistant, $n = 5$). Heart rate variability was evaluated at rest, during exercise, and during a 2-min occlusion at rest, before, and after the 10-wk period. As

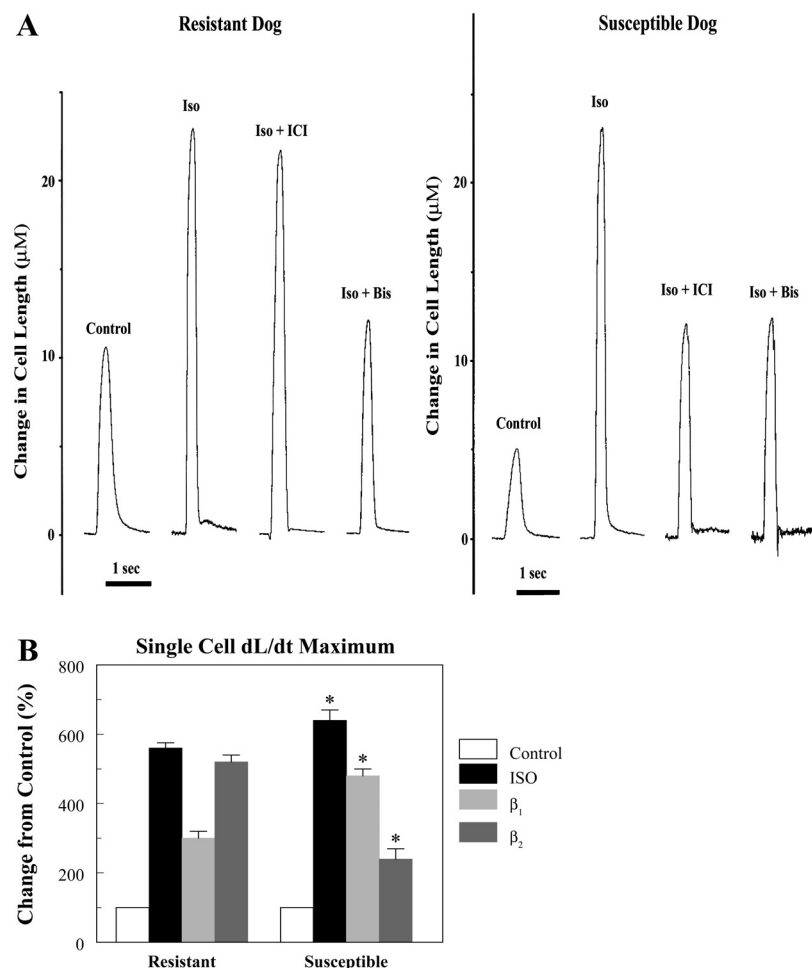


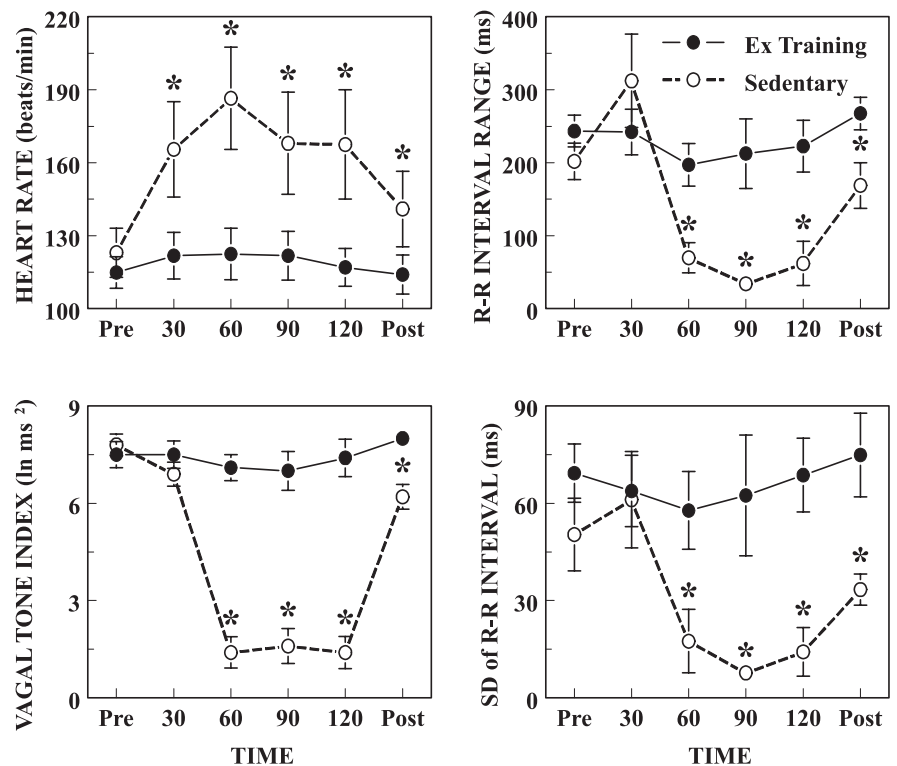
Fig. 3. β -adrenoceptor remodeling in isolated canine ventricular myocytes. **A**: representative recordings of the unloaded single-cell shortening of a ventricular myocyte obtained from 1 susceptible and 1 resistant dog. The recordings were made during electrical field stimulation at 0.5 Hz with bicarbonate buffer (control), 100 nM isoproterenol (Iso), and isoproterenol in the presence of either the β_2 -adrenoceptor antagonist ICI 118,551 (ICI; 100 nM) or the β_1 -adrenoceptor antagonist bisoprolol (Bis; 200 nM). Note the large effects of the β_2 -adrenoceptor blockade in the susceptible animal. A single tracing represents the average of 16 individual tracings. **B**: effect of isoproterenol on the rate of change (dL/dt maximum, cellular inotropic response) in the unloaded single-cell shortening in ventricular myocytes obtained from susceptible and resistant dogs. Note that isoproterenol (100 nM) elicited a larger increase in the velocity of shortening in the susceptible dogs compared with resistant dogs. This larger increase was attenuated by treatment with the β_2 -adrenoceptor antagonist ICI 118,551 (100 nM). In contrast, the β_1 -adrenoceptor antagonist bisoprolol (200 nM) provoked larger reductions in the resistant dogs. * $P < 0.01$ susceptible vs. resistant animal for a given treatment. [Reprinted with permission from Houle et al. (132).]

in previous studies (39, 73, 114), pretraining, the coronary occlusion provoked significantly greater increases in heart rate (susceptible, 54.9 ± 8.3 vs. resistant, 25.0 ± 6.1 beats/min) and greater reductions in heart rate variability (susceptible, -6.3 ± 0.3 vs. resistant, -2.8 ± 0.8 ln ms^2) in the susceptible dogs compared with the resistant animals. Similar response differences between susceptible and resistant dogs were noted during submaximal exercise. Exercise training significantly reduced the magnitude of the tachycardia and heart rate variability reduction elicited by either coronary artery occlusion (Fig. 4) or submaximal exercise (Fig. 5) to a greater extent in the susceptible animals compared with the resistant dogs. In contrast, these variables were not altered in the sedentary susceptible dogs (Figs. 4 and 5). In a similar manner, exercise training attenuated the heart rate increase provoked by exercise onset and enhanced (accelerated) the heart rate return toward baseline values (heart rate recovery) following the termination of exercise (45). Correspondingly, heart rate variability (indexes of cardiac vagal regulation) was also enhanced following exercise training. In marked contrast, neither the heart rate nor the heart rate variability responses to exercise onset or following the termination of exercise were altered in sedentary (time control) animals (45). Atropine pretreatment eliminated the differences in the indexes of cardiac vagal activity and the heart rate response to the termination of exercise noted between the sedentary and exercise-trained dogs (45). These data

suggest that exercise training enhanced cardiac parasympathetic activity.

Regular endurance exercise has also been shown to improve β -adrenoceptor responsiveness in normal animals (18, 262), aged animals (184), and animals with hypertension (174), despite either a reduction (18) or no change in the β_1 -adrenoceptor density (119, 184). MacDonnell et al. (174) demonstrated that exercise training could improve the inotropic response to β -adrenoceptor stimulation in spontaneously hypertensive rats. The effects of exercise training on β_2 -adrenoceptor responsiveness in dogs with damaged hearts that were susceptible to ventricular fibrillation have been recently evaluated (51). Before exercise training, the β_2 -adrenoceptor antagonist ICI 118,551 (0.2 mg/kg) significantly reduced the peak contractile (by echocardiography) response to isoproterenol more in the susceptible animals (susceptible, $-45.5 \pm 6.5\%$ vs. resistant, $-19.2 \pm 6.3\%$) compared with the resistant dogs. After exercise training, the resistant and the susceptible dogs exhibited similar responses to the β_2 -adrenoceptor antagonist (susceptible, $-12.1 \pm 5.7\%$ vs. resistant, $-16.2 \pm 6.4\%$; Fig. 6). In contrast, ICI 118,551 provoked even greater reductions in the isoproterenol response in the sedentary susceptible dogs ($-62.3 \pm 4.6\%$; Fig. 6). The β_2 -adrenoceptor agonist zinterol (1 μM) elicited significantly smaller increases in isotonic shortening in ventricular myocytes (Fig. 7) obtained from exercise-trained susceptible dogs ($n = 8$; $7.2 \pm 4.8\%$) compared with cells from sedentary (i.e.,

Fig. 4. Exercise training induced reverse remodeling of cardiac parasympathetic regulation: response to acute myocardial ischemia. The effect of the 10-wk exercise training (Ex training; $n = 9$) or 10-wk sedentary ($n = 7$) period on the heart rate and the heart rate variability responses to a 2-min coronary occlusion in animals susceptible to ventricular fibrillation is shown. The coronary occlusion elicited significantly smaller increases in heart rate and smaller reductions in the various indexes of cardiac vagal regulation in the exercise-trained dogs compared with animals that received a similar sedentary period. The post-training response in the susceptible exercise-trained animals was no longer different from that noted for the resistant (either exercise trained or sedentary) dogs. $*P < 0.01$, exercise trained vs. sedentary. Pre, last 30 s before the coronary occlusion; Post, 1 min following coronary occlusion release (i.e., average over 30 to 60 s postrelease). [Reprinted with permission from Billman and Kukielka (44).]

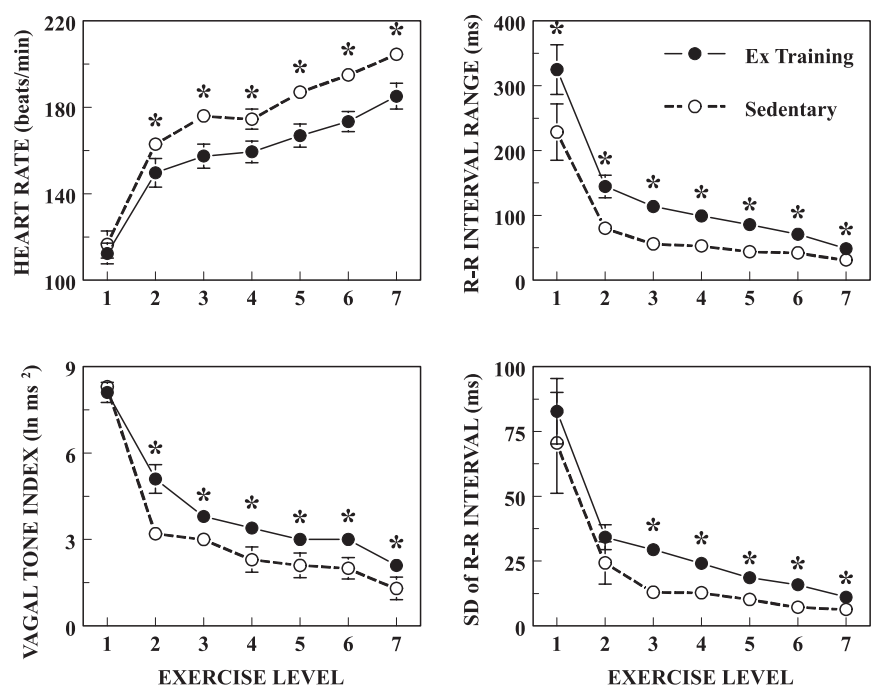


nontrained) susceptible dogs ($n = 7$; $42.8 \pm 5.8\%$). In fact, the contractile response of the myocytes from the exercise-trained dogs was not different from the response noted for cells from either exercise-trained ($n = 6$; $3.0 \pm 1.4\%$) or sedentary ($n = 5$; $3.2 \pm 1.8\%$) resistant dogs. In a similar manner, exercise training normalized the β -adrenoceptor expression and content (130). Thus exercise training can improve cardiac β -adrenoceptor balance (by reducing β_2 -adrenoceptor responsiveness) and could, thereby, decrease the risk for ventricular fibrillation.

Effect of Exercise Training on Ventricular Repolarization and Myocyte Calcium Regulation

The mechanisms by which alterations in cardiac autonomic regulation could protect against ventricular fibrillation remain to be fully elicited. Abnormal repolarization (due to altered potassium currents) or intracellular calcium regulation could act individually or in concert to decrease cardiac electrical stability and increase the propensity for sudden cardiac death.

Fig. 5. Exercise training induced reverse remodeling of cardiac parasympathetic regulation: response to submaximal exercise. The effect of the 10-wk exercise training ($n = 9$) or 10-wk sedentary period ($n = 7$) on the heart rate and the heart rate variability responses to submaximal exercise in animals susceptible ventricular fibrillation is shown. Exercise elicited significantly smaller increases in heart rate and smaller reductions in the various indexes of cardiac vagal activity in the exercise-trained dogs compared with animals that received a similar sedentary period. The post-training response in the susceptible exercise-trained dogs was no longer different from that noted for the resistant (exercise trained or sedentary) dogs. $*P < 0.01$, exercise trained vs. sedentary. Exercise levels: 1 = 0 kph/0% grade, 2 = 4.8 kph/0% grade, 3 = 6.4 kph/0% grade, 4 = 6.4 kph/4% grade, 5 = 6.4 kph/8% grade, 6 = 6.4 kph/12% grade, and 7 = 6.4 kph/16% grade. [Reprinted with permission from Billman and Kukielka (44).]



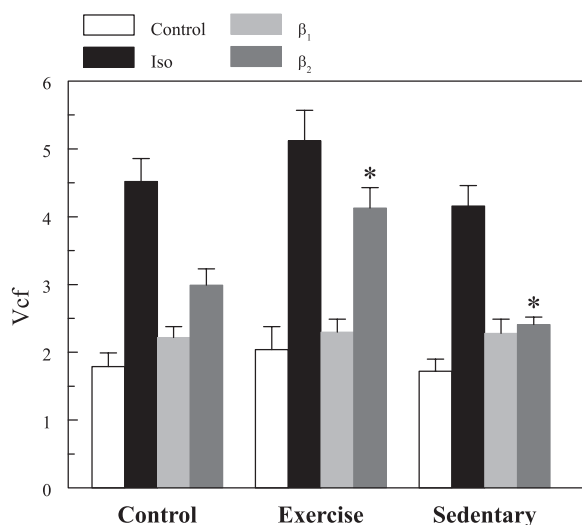


Fig. 6. Exercise training (Ex training) induced reverse remodeling of cardiac β -adrenoceptor regulation. Effects of selective β -adrenoceptor antagonists on the maximum isoproterenol (Iso) induced velocity of circumferential fiber shortening (Vcf) responses in susceptible dogs before (control, $n = 18$) and after either a training ($n = 8$) or a sedentary ($n = 10$) time period. The β_2 -adrenoceptor antagonist ICI 118–551 (0.2 mg/kg iv) elicited a significantly greater reduction in the isoproterenol response in the sedentary dogs. In contrast, the β_2 -adrenoceptor response was significantly reduced in the exercise-trained dogs. β_1 -adrenoceptor antagonist = bisoprolol (0.6 mg/kg iv); isoproterenol = $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. * $P < 0.01$, control drug treatment response compared with the corresponding drug treatment response for either the 10-wk exercise-trained or the 10-wk sedentary group. [Reprinted with permission from Billman et al. (51).]

It is well established that myocardial ischemia induces repolarization abnormalities that can provide an electrophysiological substrate for ventricular arrhythmias (92, 137, 172, 197, 217, 229, 263). In intact animals, these repolarization abnormalities are expressed as changes in the QT interval duration and/or the T-wave morphology that may become particularly obvious during myocardial ischemia. Indeed, coronary artery occlusion provoked significantly greater increases in the QT interval corrected for heart rate in dogs that were susceptible to ventricular fibrillation compared with animals that were resistant to malignant arrhythmias (39). The T-wave morphology also differed in the two groups of animals. The ischemia induced a notching or bifurcation in the T wave (i.e., a biphasic T wave) in more susceptible dogs (22 of 45 animals, 48.9%) than in resistant animals (5 of 31 animals, 16.1%). The duration of the T wave also increased to a greater extent in the susceptible animals. In particular, the descending portion of the T wave (T peak – T end), an index of the transmural dispersion of repolarization (205, 295), increased to a much greater extent in the susceptible animals (preocclusion, 29.1 ± 1.6 ms; and occlusion, 44.2 ± 2.0 ms) than in the resistant dogs (preocclusion, 29.0 ± 1.3 ; and occlusion, 30.6 ± 1.3 ms) (39). In fact, a marked heterogeneity of left ventricular repolarization has been recorded in susceptible dogs, whereas resistant animals displayed no such regional differences in repolarization (268).

Studies performed in isolated myocytes have identified abnormalities in ion currents that are likely responsible for repolarization deficits induced by myocardial infarction (92, 137, 172, 197, 217, 229, 263). For Example, Sridhar et al.

(263) recently demonstrated that multiple repolarizing potassium currents (I_{Kr} , I_{to} , and inward I_{K1}) were attenuated in myocytes obtained from dogs susceptible compared with cells from the hearts of dogs either resistant to ventricular fibrillation or from control (noninfarcted) animals. Action potential duration (APD), the beat-to-beat APD variability (a marker for the temporal dispersion of repolarization), and spontaneous oscillations in the membrane potential (early afterdepolarization) were also significantly increased in the susceptible compared with either the resistant or the control cells (263) (Fig. 8). These data suggest that a loss of repolarization reserve via reductions in multiple repolarizing currents leads to action potential prolongation, repolarization instability, and afterdepolarizations in myocytes from animals susceptible to sudden cardiac death. These abnormalities may provide a substrate for initiation of ventricular tachyarrhythmias following myocardial infarction (33).

The effects of endurance exercise training exercise on repolarization abnormalities have not been extensively investigated. Aerobic conditioning has been shown to reduce QT interval in patients with long QT syndrome (215) and in both healthy young and elderly women (112, 244). In a similar manner, myocardial ischemia provoked significantly greater increases in both QT interval and $T_{\text{peak}}-T_{\text{end}}$ in sedentary compared with exercise-trained dogs that had been previously shown to be susceptible to ventricular fibrillation (48) (Fig. 9). Preliminary data (11 cells obtained from 2 dogs) indicate that exercise training can also decrease APD in susceptible animals to such an extent that it no longer differed from animals without infarction. Finally, aerobic exercise training reduced the regional difference in ventricular repolarization in patients with heart failure (5) and increased ventricular effective refractory in rabbits (267). When considered together, these data suggest that endurance exercise training can reduce ischemically induced heterogeneities in repolarization and thereby could protect against ventricular fibrillation.

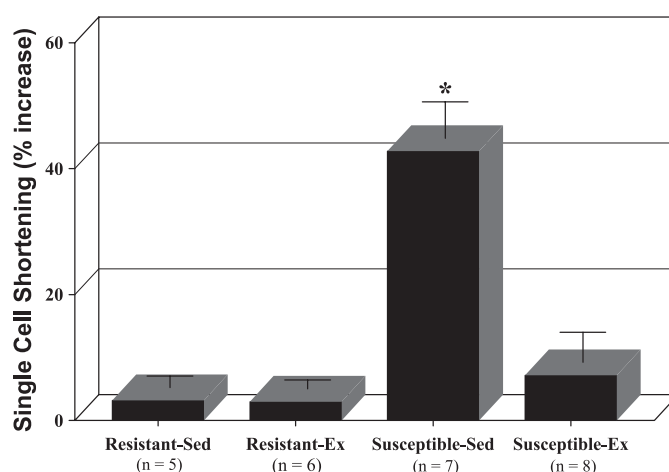
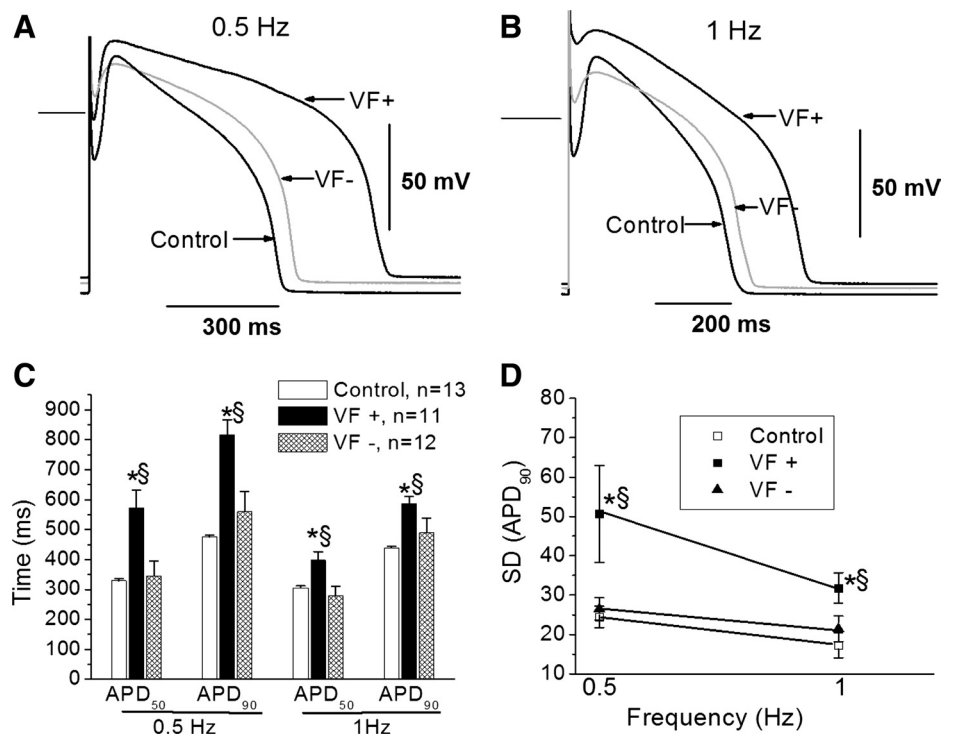


Fig. 7. Exercise training (Ex training) induced reverse remodeling of β -adrenoceptor regulation of isolated canine ventricular myocytes. The effect of exercise training on the single-cell shortening (percent change from control) response to the selective β -adrenoceptor agonist (zinterol; $1 \mu\text{M}$) is shown. The responses were compared between ventricular myocytes (6–15 cells/dog) obtained from susceptible [sedentary (Sed), $n = 7$; trained, $n = 8$] and resistant (sedentary, $n = 5$; trained, $n = 6$) animals. Note the much larger response in the sedentary susceptible animals. * $P < 0.01$, sedentary vs. trained. [Reprinted with permission from Billman et al. (51).]

Fig. 8. Repolarization abnormalities induced by myocardial infarction recorded in isolated canine ventricular myocytes. Action potential duration and action potential variability in myocytes obtained from control (no infarction), susceptible (VF+), and resistant (VF-) dogs are shown. The VF+ myocytes exhibited prolonged action potential duration at 50% repolarization (APD₅₀) and action potential duration at 90% repolarization (APD₉₀) and increased variability in APD₉₀. A and B: representative action potential tracings from control, VF+, and VF- recorded at 0.5 and 1 Hz, respectively. The line indicates 0 mV potential. C: summary APD₅₀ and APD₉₀ values at the 2 stimulation rates in the 3 groups. D: averaged SD in APD₉₀ measured from each myocyte in the 3 groups plotted as the function of stimulation frequency. **P* < 0.05 vs. control; §*P* < 0.05 vs. VF-. [Reprinted with permission of Sridhar et al. (263).]



It has also been proposed that abnormal calcium regulation in diseased hearts contributes not only to contractile dysfunction but also to the development of malignant arrhythmias (25, 26, 33, 233, 255, 256). It is well established that elevated cytosolic calcium (calcium overload) can provoke oscillations in membrane potential (delayed afterdepolarizations) that, if of sufficient magnitude to reach threshold, can trigger extrasystoles (33, 233). These afterdepolarizations have been shown to result primarily from an inward current associated with the activation of the sodium/calcium exchanger (NCX) in the reverse mode (i.e., 1 Ca²⁺ out of the cell in exchange with 3 Na⁺ into the cell) (26, 216, 237, 255, 256). As such, an overexpression of NCX1 [the predominate isoform in the mammalian heart (165, 199, 216)], particularly in a setting of elevated cytosolic calcium as could occur during myocardial ischemia (33, 233), would prove to be particularly arrhythmogenic. Several investigators reported both an increased NCX1 expression (protein and/or mRNA) and an increase in lethal arrhythmia development (triggered by delayed afterdepolarizations) in animal models of heart failure (13, 218, 219). In a similar manner, heart failure provoked increases in NCX1 expression coupled with decreases in sarco(endo)plasmic reticulum Ca²⁺-ATPase (SERCA) levels in both patients and animals (13, 171, 207, 218, 219, 222, 239, 289, 293). It is well established that patients with the greatest left ventricular dysfunction following myocardial infarction also have the greatest risk for sudden death (30). Thus changes in calcium regulatory proteins that accompany cardiac disease could provoke abnormalities in myocyte calcium homeostasis that would reduce cardiac electrical stability, enhancing the risk for lethal cardiac rhythm disorders.

As was previously noted, exercise training results in a more favorable cardiac autonomic balance (enhanced cardiac vagal and reduced cardiac β_2 -adrenoceptor sensitivity) (39, 44, 45,

130). Since changes in intracellular calcium play a critical role in the neural signal transduction process (parasympathetic activation reduces, whereas sympathetic activation increases myocyte calcium), exercise training could also facilitate a more normal myocyte calcium handling. Therefore, exercise-induced changes in calcium regulatory proteins could represent a link between the autonomic nervous system and susceptibility to ventricular fibrillation. In particular, exercise training-induced changes in NCX1 expression could contribute to an improvement in cardiac myocyte calcium regulation and thereby decrease the risk for arrhythmias.

There have been relatively few studies that have examined the effects of exercise training on calcium regulatory proteins, often yielding conflicting results. For example, both increases (69, 274, 293) and decreases (69, 211) in NCX1 activity have been reported following exercise training in rats with healthy hearts. In contrast, exercise training elicited beneficial changes in NCX1 levels in models of cardiovascular disease. Zhang et al. (297) reported that high intensity sprint training reduced NCX1 activity and decreased sarcoplasmic reticular calcium contents in myocytes obtained from the hearts of rats with a moderate-sized left ventricular infarct. In a similar manner, exercise training reversed the increased expression of NCX1 and decreased SERCA activity (i.e., SERCA and NCX1 protein levels following training were similar to values for the normal hearts) in a canine model of tachycardia-pacing-induced heart failure (171). Sedentary hypertensive rats that were prone to arrhythmia development exhibited an increased NCX1 expression and decreased phospholamban expression compared with normotensive rats (77). Daily exercise (voluntary wheel running) both reduced arrhythmia formation and normalized phospholamban and NCX1 expression in the hypertensive rats (77). In contrast, myocardial infarction decreased (rather than increased) NCX1 expression by 30% in infarcted

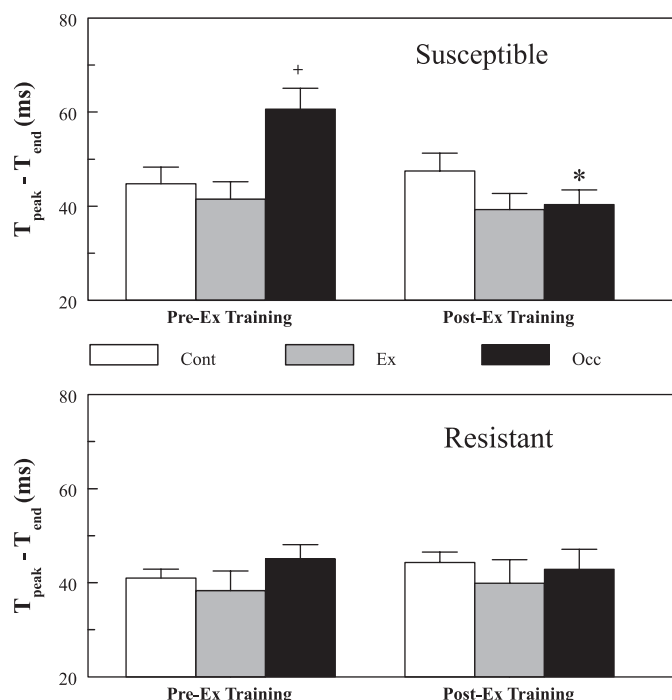


Fig. 9. Exercise training induced reverse remodeling of repolarization abnormalities in dogs susceptible to ventricular fibrillation. The effect of exercise training on the descending portion of the T wave [$T_{\text{peak}}-T_{\text{end}}$; an index of ventricular repolarization (172, 247)] response to the exercise plus ischemia test in susceptible and resistant animals before (Pre) and after (Post) either a 10-wk exercise training or 10-wk sedentary period is shown. Note that ischemia provoked a greater $T_{\text{peak}}-T_{\text{end}}$ increase in susceptible compared with resistant dogs. Note further that exercise training eliminated this $T_{\text{peak}}-T_{\text{end}}$ increase. $+P < 0.05$ occlusion (Occ) vs. exercise; $*P < 0.05$ Pre vs. Post.

rats compared with sham-treated animals. Interestingly, exercise training elicited beneficial changes even in this study (293). NCX1 expression increased in trained rats with or without infarction (293) such that, after training, NCX1 levels in the infarcted rats no longer differed from the values observed in the sedentary sham group (293). Following myocardial infarction, NCX1 levels were higher in dogs that were susceptible, compared with those animals that were resistant, to ventricular fibrillation (158). In contrast, NCX1 levels were similar in both exercise-trained resistant and susceptible animals (158). Thus exercise training can restore NCX expression, thereby improving myocyte calcium handling and reducing the risk for malignant arrhythmia.

Exercise and Susceptibility to Sudden Death

As reviewed in the previous sections, cardiac autonomic neural remodeling that arises as a consequence of myocardial infarction can play a crucial role in the induction of ventricular fibrillation. Furthermore, aerobic exercise conditioning can favorably alter cardiac autonomic balance (by increasing parasympathetic and decreasing cardiac β -adrenoceptor activity) in these patients. As such, exercise training could thereby provide a safe and effective nonpharmacological therapy for the prevention of lethal ventricular arrhythmias. The following section will evaluate the clinical and experimental evidence that exercise conditioning can reduce the risk for ventricular arrhythmias.

Clinical Studies

The effects of daily exercise on the incidence of cardiac arrhythmias and sudden death have not been extensively investigated. However, there are a number of epidemiological studies that indicate that high levels of physical activity may protect against coronary artery disease and reduce cardiac mortality (23, 100, 102, 144, 166, 178A, 204, 209, 214, 253). Paffenbarger and Hall (209) found that longshoreman with the highest energy output at work had the lowest incidence of myocardial infarction and other manifestations of ischemic heart disease, including sudden death. A meta-analysis of 32 studies confirmed this initial finding, demonstrating that the risk of death from coronary disease was significantly lower in individuals with active compared with sedentary occupations (23). In a similar manner, both the Harvard Alumni Health Study (166, 253) and the Nurse Health Study (178A) found that physical activity was associated with a decreased risk (over 30% reduction) for coronary heart disease and death (166, 178A, 253). Fitness, as measured by the heart rate response at a given level of exercise, has also been linked to cardiac mortality (101). Ekelund et al. (101), for example, found that individuals with the lowest levels of fitness had a 6.4 to 8.5 greater risk of cardiac disease and death when compared with individuals with the highest levels of fitness. Meyers et al. (188) further reported that subjects with cardiovascular disease who had the highest exercise capacity also exhibited the lowest mortality rate during a 14-yr follow-up period. Furthermore, Bartels et al. (19) found that the incidence of sudden cardiac death was inversely related to the level of regular physical activity; that is, sedentary individuals had the highest rate of sudden death (4.7 deaths/10⁵ person-yr), whereas those in the most active group had the lowest (0.9 deaths/10⁵ person-yr). It should be emphasized that even very modest levels of exercise were associated with significant reductions in mortality. Hakim and coworkers (115, 116) found that, in elderly men, low intensity exercise (walking 2 miles or more per day) was associated with a much lower mortality rate (23.8%) during the 12-yr follow-up period than was noted in those men that walked less than a mile per day (40.5%). It is interesting to note that walking has also been shown to reduce the incidence of atrial fibrillation in older (>65 yr) adults (196).

The effects of exercise in patients recovering from myocardial infarction strongly suggest that this treatment may reduce mortality in this high-risk group (144, 158B, 158D, 167, 176, 204, 208, 266). A significant reduction in cardiac death has been reported for patients in multifactorial intervention programs that included daily physical exercise (144). The decreased cardiovascular mortality resulted primarily from a reduction in the incidence of sudden death (5.8% vs. 14.4% in the control group), a trend that has been maintained for 15 yr after the initial study (118). Since exercise was but one factor among many, the effects of the daily exercise program per se on sudden death cannot be addressed. Meta-analysis of 22 randomized trials of rehabilitation with exercise after myocardial infarction found that exercise training elicited both significant reductions in the reinfarction rate and in the incidence of sudden death (204). There was an overall reduction in cardiac mortality of 20% (due largely to the reduction in sudden death), a reduction that is comparable to the mortality reductions noted for β -adrenoceptor antagonists (123, 124, 149).

Exercise programs have also been shown to improve cardiac autonomic regulation and ventricular function in patients with cardiovascular disease (93, 135, 185, 264, 275). Exercise training improved baroreceptor sensitivity (BRS; the heart rate response to changes in arterial blood pressure that largely reflect cardiac parasympathetic function) in patients recovering from myocardial infarction (135, 158D). Furthermore, the group of patients that exhibited the greatest change in BRS (increase, ≥ 3.0 ms/mmHg) exhibited the lowest mortality during a 10-yr follow-up period. Indeed, no deaths were reported among the patients with a BRS change > 3.0 ms/mmHg, whereas more than 20% of the patients with smaller changes in BRS died during the follow-up period (158D). In a similar manner, exercise training improved autonomic balance (i.e., increased heart rate variability, increased baroreceptor reflex sensitivity, or decreased muscle sympathetic nerve activity) in heart failure patients (21, 108, 151, 189, 231) and may thereby reduce the risk for sudden death. Furthermore, exercise training improved cardiac function and reduced arrhythmia frequency in congestive heart failure patients (2, 22, 72, 104, 151, 223), a patient population with a high risk for sudden death (220, 265). For example, Hertzeanu et al. (125) found that both the frequency and severity of the arrhythmias were reduced after a 6-mo exercise program in post-myocardial infarction patients with ejection fractions $< 30\%$. Finally, aerobic exercise training reduced the regional difference in ventricular repolarization in patients with heart failure (5), thereby removing the substrate for the formation of re-entrant arrhythmias. Thus the limited clinical data suggest that regular physical exercise may protect against sudden death, as well as improve autonomic balance, in patients with cardiac disease.

It should be noted that strenuous exercise itself might pose a risk for sudden death in high-risk populations: for example, patients recovering from myocardial infarction (19, 107, 154, 261, 273, 283). There are numerous anecdotal accounts of individuals (including trained athletes) who died suddenly during a bout of exercise (182). Therefore, exercise training may not be completely risk free. However, systematic studies of this paradox have been limited. For example, an examination of 1,180 (of which 304 met the inclusion criteria) sudden deaths that occurred in Oregon between 2002 and 2005 revealed that the vast majority (80%) of the cardiac arrests occurred during either light activity or sleep; only a minority of the deaths ($< 5\%$) were associated with vigorous physical activity (226). The history of regular exercise for these victims of sudden death was not reported. Bartels et al. (19) demonstrated that the incidence of sudden death increased during a bout of exercise for both sedentary and regular exercisers with the greatest incidence in the sedentary group (Table 1). As noted above, the overall incidence of sudden death was much lower in the fit group. Thus the authors concluded that the protective effect of regular physical activity far exceeded the very modestly increased risk for sudden death during exercise. In a similar manner, a large prospective study of male physicians (4) found that although the incidence of sudden death increased during and shortly after exercise (Table 2), the absolute risk for sudden death during any particular episode of rigorous exertion was extremely low (1 sudden death per 1.51 million episodes of exertion). These investigators further reported that a history of regular exercise reduced the relative risk for sudden death. In other words, the probability for

Table 1. Risk of sudden death during exercise: effect of regular physical activity

Activity Level	VF, Death/10 ⁵ Person Years	Relative Risk for VF During Exercise)
1 (Sedentary)	4.69	389.5
2	4.25	150
3	2.63	—
4 (Highest)	0.92	4.0

Data were collected from two districts in Berlin (population = 219,251). During an 18-mo period, there were 77 confirmed deaths due to ventricular fibrillation (VF). The activity level was determined. The authors concluded that “the protective effects of regular physical exercise for scd” (sudden cardiac death) “by far exceeds the risk increase of the actual strenuous situation” (19).

sudden death, even during exercise, was significantly reduced in those physicians that exercised regularly compared with their more sedentary colleagues. Corrado et al. (81) found that young athletes had a greater relative risk for death from cardiovascular causes than nonathletes. However, Viskin (282) examined these, together with other reports, and concluded that arrhythmic death among athletes was very rare, with an estimated range from 0.4 to 2.3 per 100,000 person-years. Furthermore, the deaths for truly asymptomatic athletes were even lower, since half of the athletes who died suddenly were found to have a history of syncope. Several authors (4, 19, 38, 107, 154, 261, 273), after reviewing the existing literature, concluded that the potential benefits of regular exercise, even in high-risk populations of patients, far exceeded the small risk associated with exercise. Thus, with appropriate monitoring and prudently designed exercise programs, even high-risk patients can benefit from regular physical exercise.

Experimental Studies

There is also limited experimental evidence that aerobic exercise conditioning may reduce the susceptibility to ventricular fibrillation. A summary of the results of these studies may be found in Tables 3 and 4. Billman and coworkers (47) were the first to demonstrate that daily exercise could protect against ventricular fibrillation induced by acute ischemia in dogs with healed anterior wall myocardial infarctions. A 6-wk daily exercise program (treadmill running) completely suppressed ventricular fibrillation in all eight animals previously shown to be susceptible to sudden death. In contrast, sedentary animals (6-wk cage rest period) were not protected. If the animals were placed on a cage rest program ($n = 2$) after the training (i.e., deconditioning), the susceptibility to arrhythmias returned. The heart rate response to an increase in arterial pressure (i.e., BRS) improved in these animals after daily exercise (Fig. 10), suggesting that the protection may result, in part, from improved cardiac autonomic regulation (as discussed in a previous section). This initial observation was subsequently confirmed (44, 45, 47, 51, 130, 133). Hull et al. (133) found that a similar 6-wk exercise protected all seven dogs susceptible to ventricular fibrillation that completed the training program, whereas Billman and coworkers more recently found that a 10-wk exercise training program protected dogs ($n = 8$) from tachyarrhythmias induced by ischemia (44, 45, 51, 130). In contrast, four of eleven sedentary susceptible dogs died during the 10-wk control period, and the remaining seven animals still had malig-

Table 2. Risk of sudden death during exercise: effect of regular physical activity (Harvard Physician Study)

Frequency of Habitual Vigorous Exercise	Sudden Deaths <i>n</i> = 122	Sudden Deaths Related to Vigorous Exercise <i>n</i> = 23	Relative Risk 95% Cardiac index
<1 time/wk	32	3	74.1 (22.0–249)
1–4 times/wk	67	13	18.9 (10.2–35.1)
≥5 times/wk	23	7	10.9 (4.5–26.2)

The authors found that the relative risk for sudden death increased during or following vigorous exercise. "However, the absolute risk for sudden death during a particular episode of vigorous exertion was extremely low (1 sudden death per 1.51 million episodes)." They further reported that habitual exercise significantly decreased even this small risk for sudden death (4).

nant arrhythmia when tested at the end of this 10-wk sedentary period (44, 51, 130). Thus far, a total of 57 susceptible dogs have been assigned to either an exercise training program (10 wk of progressively increase treadmill running; *n* = 32) or an equivalent sedentary (*n* = 25) period. Seven sedentary (7 of 25, 28%), but only two exercise training animals (2 of 32, 6.2%), died spontaneously during this 10-wk period. It should be emphasized that both dogs died before the third week of training and well before a trained state had been achieved. To date, exercise training completely suppressed malignant arrhythmias in all 30 susceptible dogs that have completed the exercise training. In marked contrast, ventricular fibrillation was still induced in 17 of 18 sedentary dogs at the end of the study. As noted in a previous section, heart rate variability (a marker of cardiac parasympathetic regulation) (44, 133, 157) and the electrical current necessary to induce a repetitive ventricular response (i.e., the ventricular fibrillation threshold) also increased after training (133).

In a similar manner, Opie and coworkers (202, 221) found that exercise training increased the ventricular fibrillation threshold during a coronary occlusion in isolated rat hearts with and without previous myocardial infarction. The amount of electrical current necessary to induce ventricular fibrillation was much greater in hearts obtained from exercise-trained rats as opposed to those obtained from untrained animals. They attributed these differences to reductions in myocardial cAMP levels that may reflect a reduction in β -adrenoceptor activity (202, 221). Swim training of rats either reduced (21) or did not affect (12) the susceptibility to ventricular fibrillation induced by coronary artery occlusion. More recently, Collins and coworkers (77) demonstrated that the time to arrhythmia onset induced by myocardial ischemia was significantly increased in exercised (voluntary wheel running) spontaneously hyperten-

sive compared with sedentary rats. Lujan et al. (173) further reported that rats bred for a high aerobic capacity exhibited a lower incidence (3 of 11 rats) of ventricular tachyarrhythmias during myocardial ischemia compared with low aerobic capacity rats (6 of 7 rats). In the dog, Hamra and McNeil (120) reported that although exercise training reduced the arrhythmias induced by ischemia in isolated purkinje fibers, it enhanced the arrhythmia response to isoproterenol or phenylephrine. In contrast, Bakth et al. (16) demonstrated that exercise conditioning increased ventricular fibrillation threshold in both diabetic and normal dogs. The reduction in ventricular fibrillation threshold induced by epinephrine was attenuated after exercise training, data that once again suggest that exercise alters the autonomic control of the heart (16). The role that these apparent changes in the autonomic control of the heart play in the exercise conditioning-induced prevention of ventricular fibrillation remains to be determined.

If enhanced cardiac parasympathetic activity was solely responsible for the antiarrhythmic action of exercise training, then one would predict that interventions that disrupt cardiac parasympathetic actions should also eliminate the beneficial actions of exercise training on cardiac electrical stability (i.e., restore the inducibility of arrhythmias). As previously noted (39, 44, 46, 51, 130), a 10-wk exercise training program completely abolished ventricular fibrillation that was induced by acute myocardial ischemia in dogs shown to be susceptible to malignant arrhythmias, whereas a similar 10-wk control (sedentary) period failed to protect any animal. To evaluate the cardiac parasympathetic contribution to the antiarrhythmic effects of exercise training, studies were repeated after the injection of atropine to abolish any exercise training-induced enhancement of cardiac vagal regulation. This intervention increased heart rate (44) and provoked reductions in the various indexes of heart rate variability but only induced ventricular fibrillation in one of eight trained susceptible dogs (44). Thus exercise training-induced increases in cardiac vagal activity were not solely responsible for the training-induced protection from ventricular fibrillation. Other factors must also have contributed to the exercise training-induced protection from ventricular fibrillation.

Future Direction: Unanswered Questions

Although much progress has been made toward delineating the role that alterations in cardiac autonomic activity play in the genesis of ventricular arrhythmias, there are many questions that remain to be answered. Some of these unanswered questions will be highlighted in this section of the review.

Table 3. Effect of exercise training on ventricular arrhythmias: animal studies

Study (Reference)	Model	Results
Noakes et al. (202)	Rat: isolated heart, ischemia	↑ VF threshold
Bakth et al. (16)	Dog: diabetic and normal, with and without epinephrine	↑ VF threshold
Posel et al. (221)	Rat: isolated heart post-MI, ischemia	↑ VF threshold
Arad et al. (12)	Rat: isolated heart (swim training)	No Δ VF threshold
Belichard et al. (21)	Rat: ischemia (swim training)	↓ arrhythmias
Hamra and McNeil (120)	Dog: purkinje fibers	↓ arrhythmias, ischemia
	Ischemia or catecholamines	↑ arrhythmias, catecholamines
Collins et al. (77)	Rat: hypertensive, ischemia	↑ time to arrhythmias
Lujan et al. (173)	Rat: bred for high aerobic capacity, ischemia	↓ arrhythmias

MI, myocardial infarction.

Table 4. *Exercise training and ventricular arrhythmias: canine model of sudden cardiac death*

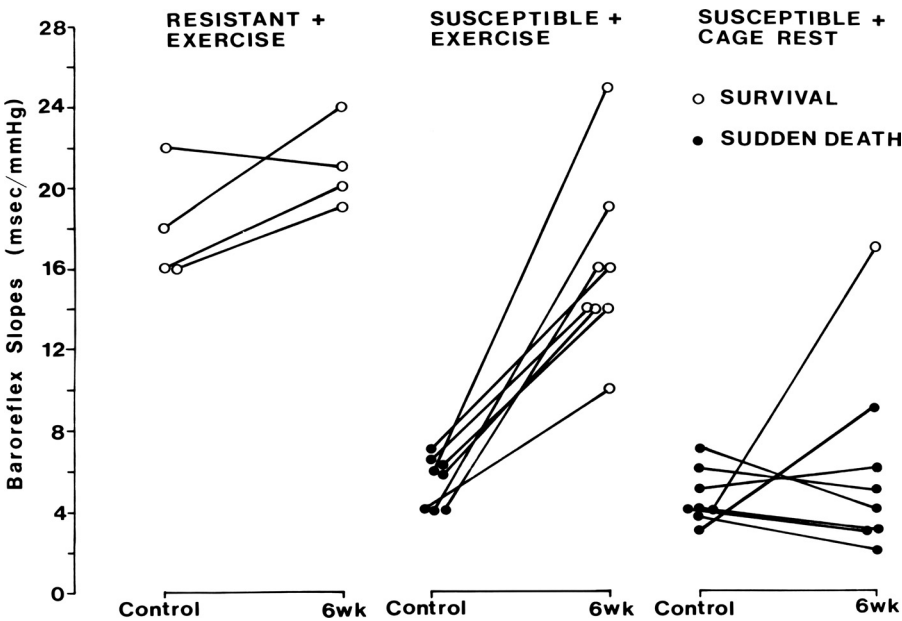
Study (Reference)	Results
Billman et al. (46)	↑ baroreflex sensitivity, protected against VF
Hull et al. (133)	↑ baroreflex sensitivity, ↑ heart rate variability (at rest), ↑ VF threshold, protected against VF
Billman and Kukielka (44)	↑ heart rate variability (during exercise or ischemia), protected against VF
Billman et al. (51)	↓ β ₂ -adrenoceptor responsiveness, protected against VF
Billman and Kukielka (45)	↑ heart rate variability (during recovery from exercise), ↓ heart rate response to exercise onset, protected against VF

Question 1: how do changes in atrial pacemaker activity as measured by heart rate variability or baroreceptor reflex sensitivity relate to changes in ventricular electrical properties that trigger lethal arrhythmias? As previously noted, there is a strong association between reductions in either heart rate variability or baroreceptor reflex sensitivity and an increased incidence of sudden cardiac death in patients recovering from myocardial infarction (11, 24, 28, 95, 129, 158A, 158C, 270). However, both heart rate variability and baroreceptor reflex sensitivity provide an index of changes in atrial parasympathetic activity (i.e., chronotropic function) (11, 39, 70, 270). Therefore, it is not immediately obvious how changes in parasympathetic regulation of atrial pacemaker activity are related to changes in the electrical stability of the ventricles (70) since the ventricular myocardium receives a relatively sparse parasympathetic innervation (80, 223A, 279). There are at least two possible explanations for this observation. First, the distribution of parasympathetic nerve fibers is not uniform throughout the ventricles; the Purkinje fibers receive more vagal efferent nerve fibers than the rest of ventricular myocardium (223A). As these muscle cells rapidly conduct electrical activity throughout the ventricular myocardium to coordinate ventricular activation, even small changes in parasympathetic activity would have disproportionate effects on the ventricular electrical properties. Indeed, both direct vagal nerve stimulation and baroreceptor reflex activation have been shown to delay impulse conduction and to prolong ventricular refractory period (70, 183, 290). Finally, the parasympathetic nerves can

also indirectly alter ventricular electrical activity via the pre-synaptic inhibition of sympathetic neural activity. The activation of muscarinic receptors located on sympathetic nerve terminal is known to inhibit the release of norepinephrine (276) and thereby attenuate the electrical and mechanical response to sympathetic nerve activation. For example, the effects of vagal stimulation are accentuated during simultaneous sympathetic activation such that parasympathetic nerve activation can completely counteract refractory period shortening induced by sympathetic stimulation (290). Thus a combination of both the direct and indirect actions of parasympathetic neural activation on the ventricular conducting tissue could enhance ventricular electrical stability. If these changes in ventricular parasympathetic activity parallel similar changes in atrial tissue, then changes in heart rate variability may accurately reflect parasympathetically mediated changes in the ventricular electrical properties. This hypothesis that explains the association between low heart rate variability (atrial event) and an increased risk for sudden cardiac death (ventricular event) remains to be tested.

Question 2: what mechanisms are responsible for the attenuation of baroreceptor reflex sensitivity following myocardial infarction? Do the changes in baroreceptor reflex sensitivity result from changes in sensory inputs, the central processing of the sensory information, efferent output, or the end organ response? This review has largely focused on autonomic efferent neural activity and the end organ responses to the autonomic remodeling. There is considerable evidence that myocardial

Fig. 10. Effects of exercise training on BRS and susceptibility to ventricular fibrillation. BRS (heart rate changes plotted against changes in arterial blood pressure) are shown before and after either a 6-wk daily endurance exercise program or an equivalent sedentary (cage rest) period. Ventricular fibrillation is indicated by the ●, while an incidence of no arrhythmias is indicated by the ○. Note that exercise training improved BRS (to levels similar to those noted for resistant dogs) and prevented ventricular fibrillation in the 8 of 8 exercise-trained susceptible dogs. In contrast, only 1 of 8 sedentary dogs was protected from sudden death. Interestingly, the sedentary dog that was protected from ventricular fibrillation also exhibited an increase in BRS. [Reprinted with permission from Billman et al. (47).]



infarction alters cardiac autonomic efferent regulation such that individuals with the greatest impairment in parasympathetic activity coupled with an enhanced β_2 -adrenoceptor responsiveness exhibit the greatest risk for malignant arrhythmias. Ultimately, the autonomic neural changes provoke changes in myocyte homeostasis (particularly calcium regulation) that decrease the electrical stability of the cells and culminate in ventricular arrhythmias. It is also possible that afferent nerve activity and the central neural processing of this sensory information could contribute significantly to the abnormal autonomic regulation following myocardial infarction. Myocardial infarction provokes alterations in ventricular mechanical properties that lead to abnormalities in wall motion and reduced cardiac pump function that become more obvious when the heart is stressed (e.g., during exercise or increased afterload). This left ventricular dysfunction could provoke an apparent reduction in baroreceptor reflex function by at least three different mechanisms. First, the heart and major blood vessels are richly supplied by afferent nerves endings that have receptors that are particularly sensitive to mechanical stimuli (170). Abnormal ventricular wall motion that occurs as a consequence of myocardial infarction could directly activate these ventricular mechanoreceptors and thereby alter the central neural integration of cardiovascular afferent information such that an apparent inhibition of baroreceptor reflex regulation results. Consistent with this hypothesis, the activation of cardiopulmonary receptors by myocardial infarction, heart failure, or acute volume expansion has been shown to attenuate the baroreceptor reflex (49, 96, 140, 190, 191, 272). Furthermore, the removal of left ventricular afferent nerve fibers increased baroreceptor reflex sensitivity following myocardial infarction (190). Second, the hemodynamic consequences of myocardial infarction could indirectly alter baroreceptor reflex function. The carotid sinus baroreceptors, in addition to registering mean and pulsatile arterial pressure, respond to the rate of rise in pressure over time (dp/dt) (96, 152). A reduction in arterial dp/dt due to changes in ventricular contractile function could lead to a slower receptor firing rate and, thereby, reduced baroreceptor responsiveness. Finally, sympathetic efferent activity to the smooth muscle of the carotid sinus and other arterial afferent sites may reduce baroreceptor reflex activity (54). The sympathetically mediated contraction of the smooth muscle surrounding these mechanoreceptors could reduce the stretch on (i.e., unload) these receptors decreasing the afferent nerve firing rate. Thus sympathetic efferent activity would tend to reset the baroreceptors such that they would become less sensitive (i.e., reduced gain) to changes in arterial pressure (54).

Question 3: what are the contributions of central and/or peripheral neural integration to an enhanced risk for arrhythmias following myocardial infarction? As noted for *Question 2*, the activation of afferent pathways by myocardial infarction could contribute to the alterations cardiac in autonomic regulation that have been linked to an increased risk for malignant arrhythmias. It is likely that alterations in central (17, 279) or peripheral (14, 279) neural integration of this cardiovascular afferent information also contribute to changes in the efferent autonomic activity that are reflected in changes in heart rate variability and baroreceptor reflex sensitivity. Zucker and co-workers (109, 110, 286, 287) provide strong evidence that central neural processing is altered by heart failure and that

these alterations may be responsible for the enhanced sympathetic efferent activity associated with this disease. For example, Wang et al. (287) reported that an upregulation of glutamate receptors in the rostral ventrolateral medulla contributed the elevation in sympathetic tone in rats with congestive heart failure. An imbalance between angiotensin II type 1 (upregulated) and angiotensin II type 2 (downregulated) in the rostral ventrolateral medulla has also been implicated in the sympathetic overactivity associated with heart failure (110). An enhanced angiotensin II type 1 receptor activity also correlated with an increased sympathetic afferent processing in the nucleus of the tractus solitarius (286), the primary central neural sensory processing site (9). Interestingly, exercise training reduced sympathetic efferent activity and produced more normal angiotensin II type 1 receptor levels within the rostral ventrolateral medulla in rats with heart failure (195). In a similar manner, alterations within the autonomic ganglia may also be induced by either myocardial ischemia or heart failure (14, 279). Using a canine model, Bibevksi and Dunlap (27) report that defective cardiac parasympathetic ganglia contributed to the reduced parasympathetic regulation of heart rate in heart failure. It remains to be determined whether alterations in either central or peripheral neural processing provoked by myocardial infarction increase the risk for lethal arrhythmias.

Question 4: what are the mechanisms responsible for the autonomic changes induced by exercise training? A reduction in heart rate, both at rest and at a given level of exercise, is a hallmark of exercise training. As previously noted, this training-induced bradycardia largely reflects changes in autonomic regulation of atrial pacemaker cells (39, 53, 60, 206, 232, 238). However, the mechanisms that trigger this change in cardiac efferent activity have not been determined. It is possible that exercise-induced changes in afferent activity or central nervous system integration of this sensory information could contribute significantly to the training bradycardia, particularly in patients with compromised cardiac function. Exercise training has been shown to improve ventricular function following myocardial infarction (98, 148, 238, 294) and could, thereby, decrease the activation of the cardiopulmonary receptors (by reducing wall motion abnormalities). In a similar manner, exercise training has been shown to reduce sympathetic hyperactivity in rats with heart failure by improving the central nervous system angiotensin II receptors profile (195). The role that changes in central nervous system processing play in the induction of the training bradycardia in both healthy subjects and patients with cardiovascular disease merit further investigation.

Question 5: what are the cellular/molecular mechanisms that link alterations in cardiac autonomic regulation and increased risk for ventricular fibrillation and how does exercise training alter these cellular/molecular abnormalities to protect against malignant arrhythmias? It seems likely that autonomic neural dysfunction leads to regional changes in both ion channel (i.e., abnormal repolarization due to altered potassium currents) and intracellular calcium regulation (calcium entry, calcium release, and calcium removal) that could act individually or in concert to decrease cardiac electrical stability and to increase the propensity for sudden cardiac death. However, the precise intracellular and ion channel changes that provoke arrhythmias, as well as those cellular events that are modified by exercise training, remain largely to be determined. Several intracellular regulatory pathways could be disrupted by

myocardial infarction. In particular, cholinergic and adrenergic signal transduction pathways, as well as the regulation of intracellular calcium, merit further investigation. A better understanding of the cellular changes responsible for arrhythmia formation and how these regulatory pathways are altered by exercise training should provide novel targets for therapeutic interventions. The benefits of exercise may, therefore, become available for even those patients that are unable (or unwilling) to complete an exercise program. Perhaps the dream of exercise in a pill may someday become a reality.

And the list goes on! These are but a few of the many questions that remain to be answered. If these questions are satisfactorily answered, then novel therapies almost certainly will result.

Summary and Conclusions

Sudden cardiac death due to ventricular tachyarrhythmias is the most common cause of death in industrially developed countries (1, 71, 298, 304). Most currently available antiarrhythmic therapies [with the notable exceptions of β -adrenoceptor antagonists (123, 124, 149, 302)] have largely been proved to be ineffective in preventing untimely deaths. In fact, several initially promising antiarrhythmic compounds were found to induce lethal arrhythmias in some patients, leading to an increase rather than a decrease in overall cardiac mortality (94, 235, 285). Cardiac autonomic remodeling is induced in patients with cardiac disease, with the patients with the greatest autonomic impairment exhibiting the greatest risk for lethal ventricular tachyarrhythmias (11, 24, 28–31, 95, 153, 270). It is widely accepted that aerobic exercise training improves cardiac autonomic balance by enhancing cardiac parasympathetic regulation and reducing sympathetic activity, perhaps by restoring a more normal β -adrenoceptor balance (i.e., reducing abnormal β_2 -adrenoceptor expression and/or sensitivity) (53, 60, 100, 232). A growing body of clinical and epidemiological data clearly indicates that even modest daily physical activity can dramatically reduce cardiac mortality in both healthy individuals and in high-risk patients (patients with heart failure or a previous myocardial infarction) (19, 23, 102, 115, 116, 144, 158B, 158D, 166, 167, 176, 188, 204, 208, 209, 214, 253, 266). Conversely, the lack of exercise is strongly associated with an increased incidence of many chronic diseases, including coronary artery disease (55). Exercise training improved cardiac autonomic regulation (a reverse remodeling of cardiac autonomic regulation such that cardiac parasympathetic control is enhanced while myocardial β_2 -adrenoceptor sensitivity is reduced) and completely suppressed ventricular fibrillation induced by myocardial ischemia in a canine model for sudden death. In fact, exercise training has been proved to be the most effective antiarrhythmic therapy of any of the various treatments evaluated in this canine model of sudden death (39), protecting 100% of the animals (30 of 30 dogs) from ventricular fibrillation after the completion of endurance training (treadmill running) program. As such, aerobic exercise training could prove to be a safe and effective nonpharmacological means of maintaining an optimal cardiac autonomic balance, thereby enhancing cardiac electrical stability and reducing the risk for sudden cardiac death.

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