

Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention

GEORGE E. BILLMAN

Department of Physiology and Cell Biology, The Ohio State University, Columbus, Ohio 43210

Billman, George E. Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention. *J Appl Physiol* 92: 446–454, 2002; 10.1152/japphysiol.00874.2001.—Sudden, unexpected cardiac death due to ventricular fibrillation is the leading cause of death in most industrially developed countries. Yet, despite the enormity of this problem, the development of safe and effective antiarrhythmic therapies has proven to be an elusive goal. In fact, many initially promising antiarrhythmic medications were subsequently found to increase rather than to decrease cardiac mortality. It is now known that cardiac disease alters cardiac autonomic balance and that the patients with the greatest changes in this cardiac neural regulation (i.e., decreased parasympathetic coupled with increased sympathetic activity) are also the patients at the greatest risk for sudden death. A growing body of experimental and epidemiological data demonstrates that aerobic exercise conditioning can dramatically reduce cardiac mortality, even in patients with preexisting cardiac disease. Conversely, the lack of exercise is strongly associated with an increased incidence of many chronic debilitating diseases, including coronary heart disease. Because it is well established that aerobic exercise conditioning can alter autonomic balance (increasing parasympathetic tone and decreasing sympathetic activity), a prudently designed exercise program could prove to be an effective and nonpharmacological way to enhance cardiac electrical stability, thereby protecting against sudden cardiac death.

cardiovascular disease; ventricular fibrillation; sudden cardiac death; exercise training; myocardial infarction; sympathetic nervous system; parasympathetic nervous system

SUDDEN DEATH, DEFINED AS UNEXPECTED death from cardiac causes that occur within 1 h of onset of symptoms (116), remains the major cause of death in most industrially developed countries (1, 14, 46, 127). In the United States alone, between 300,000 and 500,000 people die suddenly each year (1, 14, 46, 127). Holter monitoring studies have demonstrated that sudden death was most frequently caused by ventricular tachyarrhythmias (10, 56). For example, Hinkle and Thaler (56) and Bayes de Luna et al. (10) found that ventricular tachyarrhythmias were responsible for 93 and 83% of the deaths, respectively. Studies of cardiac

arrest in Seattle demonstrated that ventricular fibrillation accounted for 75% of deaths, asystole for 20%, and electromechanical dissociation for 5% (49). Only a minority of these patients had a known history of heart disease before collapse, yet up to 90% of all sudden death patients were subsequently shown to have underlying coronary artery disease (1). Sudden death is often the first and only manifestation of this illness. Unfortunately, “only about 1% of the victims of cardiac arrest are resuscitated and survive to leave the hospital” (14). However, despite the enormity of this problem, the development of safe and effective antiarrhythmic agents remains elusive. For example, the cardiac arrhythmia suppression trial study (38) demonstrated that, although class I antiarrhythmic drug (i.e., drugs that block sodium channels) effectively suppressed premature ventricular contractions, some of these com-

Address for reprint requests and other correspondence: G. E. Billman, Dept. of Physiology and Cell Biology, The Ohio State Univ., 304 Hamilton Hall, 1645 Neil Ave., Columbus OH 43210-1218 (E-mail: billman.1@osu.edu).

pounds (flecainide and encainide) increased the risk for arrhythmic cardiac death. In other words, these drugs increased rather than decreased overall cardiac mortality. In a similar manner, many class III antiarrhythmic drugs (drugs that prolong refractory period, most likely via modulation of potassium channels) have been shown to prolong QT interval, to promote the life-threatening tachyarrhythmia *tosades de pointes* (i.e., polymorphic ventricular tachycardia in which the QRS waves seem to “twist” around the baseline), and to increase cardiac mortality in some patient populations (100, 122). There are, in fact, relatively few drugs that have been proven to reduce cardiac mortality in high-risk patients such as those recovering from myocardial infarction. To date, only β -adrenergic receptor antagonists and amiodarone, a class III antiarrhythmic drug that also blocks β -adrenergic receptors, have been shown to reduce sudden cardiac death (4, 53, 54, 66, 127). Mortality following myocardial infarction remains high among patients with substantial ventricular dysfunction, even with β -adrenergic receptor antagonist therapy. The 1-yr mortality is 10% or higher with sudden death, accounting for approximately one-third of the deaths in these high-risk patients (27). In a similar manner, the long-term use of amiodarone is limited due to adverse side effects, including pulmonary fibrosis and thyroid toxicity (84). Given the adverse side effects of many antiarrhythmic drugs, as well as the partial protection afforded by even the best agents (i.e., drugs that block β -adrenergic receptors), nonpharmacological interventions should be examined to determine whether they might provide a better therapeutic option.

It is well established that exercise conditioning can favorably alter cardiac autonomic regulation (25, 98) and as such may represent a nonpharmacological means of preventing lethal ventricular arrhythmias. It is, therefore, the purpose of this review to evaluate the antiarrhythmic potential of aerobic exercise conditioning. First, the role that the autonomic nervous system may play in the genesis of malignant arrhythmias will be briefly discussed. Then, the effects of aerobic exercise conditioning on cardiac autonomic regulation and susceptibility to ventricular arrhythmias will be analyzed.

CARDIAC AUTONOMIC NEURAL ACTIVITY AND SUDDEN DEATH

Alterations in cardiac autonomic control, particularly during myocardial ischemia, play a critical role in the induction of ventricular fibrillation (for reviews, see Refs. 32 and 104). Several lines of evidence demonstrate that any intervention that elicits an increase in cardiac sympathetic activity also enhances the development of lethal cardiac arrhythmias (32, 104). The direct electrical stimulation of cardiac sympathetic nerves, particularly those originating from the left stellate ganglion, decreases ventricular fibrillation threshold, can produce inhomogeneities in ventricular refractory period, and induces ventricular arrhythmias

(32, 104). Psychological stress or acute bouts of exercise, interventions known to increase sympathetic activity, also increase arrhythmia formation during ischemia (45, 119, 120). Conversely, interventions that reduce cardiac sympathetic activity have been shown to protect against arrhythmias (32, 53, 54, 66, 102, 104). β -Adrenergic-receptor blockade, in particular, has been shown to reduce cardiac mortality in patients recovering from myocardial infarction (53, 54, 57, 64, 66, 99). Pooled data from more than 29,000 patients during long-term treatment after myocardial infarction indicated that β -adrenergic-receptor antagonists reduced overall mortality by 20% and mortality due to sudden death by 30–50% (57–59, 86, 101, 107). In perhaps the best study, propranolol therapy elicited large reductions in overall mortality (61%) and sudden cardiac death (41%) in postmyocardial infarction patients with persistent ST-segment depression (107), a group of patients known to be at high risk for subsequent cardiac events (124). β -Adrenergic-receptor antagonists also reduced early (1 h to 7 day) cardiac mortality during myocardial infarction (58, 59, 86, 101) and were particularly effective in suppressing arrhythmias induced by myocardial ischemia (97). Similar results have been reported in animal studies (17, 34).

Alterations in cardiac parasympathetic control also contribute significantly to the risk for sudden death (32, 104). Eckberg et al. (40) 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 co-workers (21, 103) further 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. Heart rate variability, an index of cardiac vagal tone (18, 39, 47, 52, 96, 114), was also reduced to a greater extent in animals susceptible to ventricular fibrillation compared with animals resistant to these malignant arrhythmias (19, 21, 30, 60, 103). In particular, the susceptible animals exhibited a much greater reduction (withdrawal) of vagal tone coupled with a greater increase in sympathetic activity in response to either submaximal exercise (19, 20, 50, 60) or acute myocardial ischemia (30, 50, 60).

Clinical studies have largely confirmed these canine studies. In particular, it has been shown that myocardial infarction will reduce heart rate variability and, furthermore, that the patients with the greatest reduction in this variable also have the greatest risk for sudden death (14, 69, 114). Kleiger and co-workers (70) found that, in patients recovering from myocardial infarction, 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 a R-R interval variability <50 ms compared with patients with a variability >100 ms. Similar findings have been reported in numerous, more recent clinical studies (14, 15, 59, 63, 75, 77). To cite just one example, La Rovere

et al. (75) reporting for the Autonomic Tone and Reflexes After Myocardial Infarction Group found that postmyocardial infarction patients with either low heart rate variability or a small heart rate response to an increase in blood pressure (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 tone (75).

When considered together, these clinical and experimental studies clearly suggest that reductions in cardiac parasympathetic tone 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 ventricular fibrillation. 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 (29, 32, 67, 73, 128). For example, vagal stimulation has been shown to prevent reperfusion arrhythmias in anesthetized cats (128) and ventricular fibrillation in a conscious canine model of sudden death (118). Cholinergic agonists have also been shown to prevent ischemically induced ventricular fibrillation (16, 34), even when heart rate was held constant by ventricular pacing (16). These data suggest that the activation of muscarinic receptors on ventricular cardiomyocytes may be responsible for this cardioprotection. Conversely, bilateral vagotomy or the cholinergic antagonist atropine can increase arrhythmia formation (31, 35).

It is unlikely that electrical stimulation will become an acceptable therapeutic option in patients, and 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 (74) led to the proposal that this treatment could provide an acceptable means of enhancing cardiac parasympathetic activity in patients (28). Several independent clinical studies (28, 33, 92, 121), in fact, demonstrated that low doses of scopolamine augmented markers of cardiac vagal tone in postmyocardial infarction patients. However, Halliwill et al. (50) and Hull et al. (61) both demonstrated that, although low doses of cholinergic antagonists increased baseline cardiac vagal tone, as measured by heart rate variability, this treatment failed to prevent ventricular fibrillation induced by myocardial ischemia. Halliwill et al. further demonstrated that the enhanced baseline vagal tone was not maintained when the heart was stressed by either exercise or myocardial ischemia. As such, it is not surprising that this therapy failed to prevent ventricular fibrillation. To be an effective antiarrhythmic therapy, an intervention must be designed so that it not only increases baseline vagal activity but also maintains this enhanced activity when the heart is stressed.

EFFECT OF EXERCISE CONDITIONING ON CARDIAC AUTONOMIC TONE AND SUSCEPTIBILITY TO SUDDEN DEATH

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 (for reviews, see Refs. 25 and 98). For example, in both humans and animals, the heart rate at submaximal workloads was reduced in trained individuals compared with sedentary controls (22, 25, 62, 98, 108, 115). 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 (22, 36, 41, 48, 62, 81, 88, 108). Both acetylcholine content and cholineacetyl transferase were increased in the hearts of trained rats compared with control animals (37). In humans, exercise training during recovery from myocardial infarction has been reported to increase heart rate variability (76, 80, 82, 89). Thus these data suggest that endurance exercise training can elicit changes in cardiac autonomic control that could, in turn, protect against ventricular fibrillation.

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 (13, 42, 43, 65, 79, 87, 90, 93, 105). Paffenbarger and Hall (90) 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. Recently, the Harvard Alumni Health Study (79, 105) clearly demonstrated that physical activity was associated with a decreased risk of coronary heart disease and death. Fitness, as measured by the heart rate response at a given level of exercise, has also been linked to cardiac mortality (42). Ekelund et al. (42), for example, found that individuals with the lowest levels of fitness had a 6.4- to 8.5-times greater risk of cardiac disease and death compared with individuals with the highest levels of fitness. Furthermore, Bartels et al. (9) 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 per 10^5 person-years), whereas those in the most active group had the lowest (0.9 deaths per 10^5 person-years).

The effects of exercise in patients recovering from myocardial infarction also strongly suggest that this treatment may reduce mortality in this high-risk group (13, 65, 76, 80, 82, 89, 111). A significant reduction in cardiac death has been reported for patients in multifactorial intervention programs that included daily physical exercise (65). The decreased cardiovascular mortality resulted primarily from a reduction in the incidence of sudden death (5.8% in the exercise group vs. 14.4% in the control group). Because exercise was

but one factor among many, the effects of the daily exercise program per se on sudden death cannot be addressed. More recently, meta-analysis of 22 randomized trials of rehabilitation with exercise after myocardial infarction found that exercise training elicited significant reductions in both the reinfarction rate and the incidence of sudden death (13). 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 -adrenergic-receptor antagonists (53, 54, 66). Exercise training has also been shown to improve cardiac function and to reduce arrhythmia frequency in congestive heart failure patients (12, 44, 68), a patient population with a high risk for sudden death (6, 94, 110). Hertzeanu et al. (55) found that both the frequency and severity of the arrhythmias were reduced after a 6-mo exercise program in postmyocardial infarction patients with ejection fractions $<30\%$. Exercise training also improves autonomic balance (i.e., increased heart rate variability) in heart failure patients (68) and may thereby reduce the risk for sudden death. Furthermore, aerobic exercise training reduced the regional difference in ventricular repolarization in patients with heart failure (3), thereby removing the substrate for the formation of reentrant arrhythmias. Thus these clinical data suggest that regular physical exercise can protect against sudden death, as well as improve autonomic balance in patients with cardiac disease.

There are also experimental studies that demonstrate that aerobic exercise conditioning can reduce the susceptibility to ventricular fibrillation. Billman and co-workers (22) were the first to demonstrate that daily exercise could prevent ventricular fibrillation induced by acute ischemia in dogs with healed anterior wall myocardial infarctions. A 6-wk daily exercise program (treadmill running) prevented 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 also improved in these animals after daily exercise, data consistent with an improved parasympathetic regulation of the heart. More recently, Hull et al. (62) confirmed and extended these findings using the same canine model of sudden death. They also found that daily exercise protected against ischemically induced ventricular fibrillation and, furthermore, that baseline heart rate variability (an index of cardiac parasympathetic activity) increased after training. The electrical current necessary to induce a repetitive ventricular response (i.e., the ventricular fibrillation threshold) also increased as a consequence of daily exercise (62). In a similar manner, Opie and co-workers (85, 95) 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 fi-

brillation 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, which may reflect a reduction in β -adrenergic-receptor activity. Swim training of rats was also reported either to reduce (11) or to not alter (5) the susceptibility to ventricular fibrillation induced by coronary artery occlusion. However, Hamra and McNeil (51) reported that, although exercise training reduced the arrhythmias induced by ischemia in isolated canine purkinje fibers, it enhanced the arrhythmia response to isoproterenol or phenylephrine. In contrast, Bakth et al. (8) 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 (8). Recently, even a single bout of exercise was found to preserve cardiac autonomic control, as well as to reduce the incidence of ventricular fibrillation induced by acute myocardial ischemia and reperfusion in anesthetized dogs for at least 24 h after completion of the exercise (7). These data further indicate the potential beneficial effects of even modest exercise on cardiac rhythm.

FUTURE DIRECTIONS

The specific mechanisms by which aerobic exercise conditioning can reduce cardiac mortality remain to be fully elucidated. It is well established that habitual exercise can favorably alter many known risk factors for cardiovascular disease (106), including reducing obesity (23, 126), lowering the incidence of non-insulin-dependent diabetes (123), lowering arterial blood pressure (72, 91), improving myocardial perfusion (78, 83), increasing fibrinolytic enzyme activity (112, 113), and altering blood lipid profile by increasing high-density lipoprotein cholesterol and decreasing low-density lipoprotein cholesterol (117, 126). However, the beneficial effects of regular exercise do not result solely from risk factor modification. It is now known that the association between exercise and reductions in mortality can occur independent of changes in these other risk factors (24). Thus other factors must also contribute to the protections induced by aerobic exercise conditioning. The data cited in the preceding sections strongly suggest that exercise-induced changes in the autonomic neural regulation of the heart may protect against sudden cardiac death. In particular, an exercise-induced increase in cardiac parasympathetic activity could enhance the electrical stability of the heart, thereby preventing malignant arrhythmias during myocardial ischemia. It should be emphasized that a direct causal link between exercise-induced alterations in the cardiac autonomic regulation on a reduced cardiac mortality has yet to be established.

One would predict that, if enhanced cardiac parasympathetic activity does, in fact, mediate the exercise-

induced protection from malignant arrhythmias, then interventions that disrupt or prevent these changes in cardiac vagal tone should produce corresponding changes in the susceptibility to ventricular fibrillation. Several different approaches (pharmacological, surgical, or transgenic) could be used to test this hypothesis in experimental animals. For example, the intravenous injection of pharmacological agents that block cardiac muscarinic receptors such as atropine or scopolamine would eliminate the exercise-induced enhancement in cardiac parasympathetic activity, thereby reinstating the lethal arrhythmias that were eliminated by exercise training. In a similar manner, selective cardiac parasympathectomy of the heart (96) when performed before exercise training may both reduce any training bradycardia and prevent exercise-induced reductions in the incidence of ventricular fibrillation. Finally, animals engineered to overexpress cardiac muscarinic receptors may mimic the effects of exercise training and should be less prone to arrhythmias induced by myocardial ischemia than the wild-type control animals. Conversely, animals in which the muscarinic receptors have been genetically eliminated (i.e., gene knockout) should be more prone to arrhythmias than the wild-type animals. Furthermore, one would predict that the beneficial effects of exercise conditioning would be greatly attenuated or eliminated in these animals (that is, exercise training could not improve cardiac electrical stability in animals lacking cardiac muscarinic receptors). It must be noted, however, that mice provide a poor model for the investigation of ventricular fibrillation. It is extremely difficult to induce and sustain ventricular fibrillation in these animals. Mice have a small ventricular mass and exhibit a rapid resting heart rate (with a correspondingly short action potential duration). As a consequence, repolarization is relatively uniform throughout the murine myocardium (i.e., little or no dispersion of refractory period can occur) and as such the reentrant pathways that are necessary for propagation of ventricular fibrillation (125) do not form in these animals. Therefore, the use of transgenic approaches in the investigation of the mechanisms responsible for ventricular fibrillation should employ species with a larger heart and slower resting heart rates such as the rabbit.

SUMMARY AND CONCLUSIONS

As previously noted, sudden cardiac death due to ventricular tachyarrhythmias is the most common cause of death in industrially developed countries (5, 14, 46, 127). Most currently available antiarrhythmic drugs (with the notable exception of β -adrenergic-receptor antagonists and amiodarone; Ref. 127) have largely been proven to be ineffective in preventing these untimely deaths. Indeed, many initially promising, novel antiarrhythmic compounds were found to induce lethal arrhythmias in some patients, leading to an increase rather than a decrease in overall cardiac mortality (38, 100, 122). It is now well established that cardiac autonomic balance is altered in patients with

cardiac disease and, furthermore, that the patients with the greatest alteration in the cardiac autonomic balance (i.e., decreased parasympathetic and/or increased sympathetic activity) are at the greatest risk for lethal cardiac arrhythmias (14, 69, 75, 114). The studies described above demonstrate that aerobic exercise conditioning can improve cardiac autonomic balance by both increasing cardiac parasympathetic tone and decreasing cardiac sympathetic activity. A growing body of epidemiological data clearly indicates that exercise conditioning can dramatically reduce cardiac mortality (13, 42, 43, 65, 79, 87, 90, 93, 105), even among high-risk patients (patients with heart failure or previous myocardial infarction; Refs. 12, 44, 55, 68). Conversely, the lack of exercise is strongly associated with an increased incidence of many chronic diseases, including coronary artery disease (26). Finally, daily exercise prevented ventricular fibrillation induced by myocardial ischemia in experimental models of sudden cardiac death (22, 62). It therefore seems reasonable to conclude that aerobic exercise conditioning could prove to be a nonpharmacological means of altering cardiac autonomic control, thereby enhancing cardiac electrical stability and preventing sudden cardiac death.

It should be noted, however, that strenuous exercise may itself pose a risk for sudden death in high-risk populations: e.g., patients recovering from myocardial infarction (45, 71, 109, 120). There are numerous anecdotal accounts of individuals (including trained athletes) who died suddenly during a bout of exercise. Therefore, exercise training may not be completely without risk. However, systematic studies of this paradox have been limited. Bartels et al. (9) 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. 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 (2) found that, although the incidence of sudden death significantly increased during or shortly after exercise, the "absolute risk of 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 sudden death, even during exercise, was significantly reduced in those physicians that exercised regularly compared with more sedentary individuals. Several authors (9, 45, 71, 109), after reviewing existing literature, also concluded that the potential benefits of regular exercise even in high-risk populations of patients greatly exceeded the small risk associated with exercise. Furthermore, it must be emphasized that the small risk associated with an acute bout of exercise is still considerably less than the proarrhythmic potential of many pharmacological interventions. Thus, with

appropriate monitoring and prudently designed exercise programs, even high-risk patients can benefit from regular physical exercise.

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