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From exercise training to sudden death prevention via adrenergic receptors

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THE DAUNTING PROBLEM of sudden cardiac death has many facets. One of these has revolved around the triggering role of sympathetic activation on one hand and around the seemingly protective effect of exercise training on the other. In their recent article in the *American Journal of Physiology-Heart and Circulatory Physiology*, Holycross et al. (9) add an important and novel piece of information that contributes to approach the solution of the puzzle.

A quantum leap for the understanding of sudden arrhythmic death during acute myocardial ischemia was provided in a previous issue of the Journal in 1969, when—by using the technique of single-fiber recording—Malliani et al. (13) demonstrated that myocardial ischemia elicits within seconds an excitatory cardio-cardiac sympathetic reflex. This reflex is independent of blood pressure changes and of baroreceptive reflexes, because it is present also at the spinal level, and is directly associated with the onset of ventricular tachyarrythmias as demonstrated by their disappearance following dorsal root section, a beautifully selective intervention that eliminates the sensory traffic from the heart while leaving intact the efferent cardiac-bound sympathetic activity (19). The consequent abrupt release of norepinephrine in the ischemic myocardium obviously provides an important arrhythmogenic milieu. Indeed, when the physiological sympathetic reflex was mimicked by direct electrical stimulation of the left stellate ganglion, either after a coronary artery occlusion or during a transient myocardial ischemia, it led to the frequent occurrence of ventricular fibrillation (VF) (7, 23). These findings and the related concept did contribute to the initial and successful use of β-blockers for the reduction of sudden death among patients surviving a myocardial infarction (MI) (2) and explain the impressive and significant reduction in sudden death (from 21% to 3.5%) produced by left cardiac sympathetic denervation in a high-risk subgroup of post-MI patients (20).

Despite the numerous limitations inherent in clinical studies based on exercise training, in which randomization and adherence to therapeutic protocols are especially difficult to implement and monitor, there has been multiple and growing evidence indicating that—among post-MI patients—exercise training is associated with decreases in cardiac mortality and in sudden cardiac death (16). A wealth of hypotheses have been proposed to explain this beneficial effect, but the underlying mechanisms are not yet fully elucidated. It is nonetheless fair to say that significant evidence points to an important role for exercise training-induced modulation of the neural control of the heart. The aspect initially considered had stemmed from the well-known association between exercise and increases in vagal activity. Using a valid methodology for a reliable quantification of autonomic reflexes, predominantly vagal, as that known as baroreflex sensitivity (BRS) (12, 25), Billman et al. (3) provided the first evidence that exercise training can improve a depressed BRS present in high-risk post-MI dogs and at the same time reduce the probability of VF during a transient myocardial ischemia occurring during submaximal exercise, used as a means to physiologically increase sympathetic activity. This animal model for sudden cardiac death (18) is the same as that used by Holycross et al. in the study under discussion (9).

Multiple findings have pointed to vagal activation being a major player in the antifibrillatory protective effect of exercise training. Numerous experiments in anesthetized preparations (for a review, see Ref. 6) and clear evidence in the same postinfarction conscious dog model (28) have demonstrated that vagal stimulation at the onset of acute myocardial ischemia can effectively prevent VF. These experimental findings have been successfully translated to the clinical level. La Rovere et al. (11) have done—with the appropriate differences—in post-MI patients something very similar to what Billman et al. (3) had done in their dogs. They identified 95 patients with a first and recent MI and, after careful matching for several variables (including age, sex, site of MI, left ventricular ejection fraction, extent of coronary artery disease, and BRS) they were randomized to either 30 days of exercise training or 30 days of rest. BRS increased significantly in the exercise group and remained unchanged in the other group (11). The focus of the analysis was on those patients who had shown an increase in BRS $\geq$3 ms/mmHg, regarded as a sign of adequate increase in reflex vagal activity. At 10-yr follow-up there was a striking difference in mortality (23% vs. 0; $P < 0.04$) patients with insufficient increase in BRS (including also several of those randomized to exercise) to those with clear-cut BRS increases. This study showed that exercise training per se is not sufficient for a statistically significant reduction in cardiac mortality, which also requires a meaningful shift in autonomic balance. This finding dovetails perfectly with the report by Holycross et al. (9).

Indeed, in the article under discussion (9), Billman and associates have continued in their tireless exploration of the underlying mechanisms that may shed light on the protective effect of exercise training. Using the animal model described together with Schwartz in 1984 (18), they have investigated the effects of endurance exercise on the expression of β_1- and β_2-adrenergic receptors in dogs known to be at high risk for VF (the so-called "susceptible" dogs). The main findings of the

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study were that *1*) the high-risk dogs show a decrease in β_1-adrenergic receptors, thus creating an imbalance with relative dominance of β_2-adrenergic receptors; *2*) exercise training restores the β_1-adrenergic receptors in these animals; *3*) there was no difference in β_2-adrenergic receptors between high- and low-risk animals; and, finally, *4*) among the low-risk dogs the β_2-adrenergic receptors appear to reside in the caveolae, where they are less exposed to activation by catecholamines, whereas the opposite seems to be true in high-risk animals.

These data, as carefully discussed in the article, are consistent with the hypothesis that β_2-adrenergic receptor activation could play a particularly important role in the onset of VF during acute myocardial ischemia. This intriguing concept has been recently supported by an important genetic finding. Sotoodehnia et al. (26) have investigated a possible relationship between specific polymorphisms of the β_2-adrenergic receptor gene and occurrence of sudden cardiac death in a large population (26). They found that individuals homozygous for Gln27Glu had a significantly higher risk for sudden cardiac death (hazard ratio 1.56; 95% confidence interval 1.17–2.09) and concluded that their results demonstrate an association between functionally significant genetic variants and sudden cardiac death. In turn, this finding is supported by—and supports—the previous observation by Altschuld and Billman (1) that selective blockade of the β_2-adrenergic receptors prevents VF in the canine model for sudden death.

Do these data translate into the results of clinical trials? To a certain extent, yes. Trials with metoprolol (8, 27) and with atenolol (10), both β_1-adrenergic receptor blockers, have failed to reduce the incidence of VF despite reductions in total mortality, whereas propranolol and carvedilol have reduced both total mortality and sudden deaths (14, 24). This picture is somewhat more blurred in heart failure, another condition in which there is a downregulation of β_1-adrenergic receptors (4), where clinical trials showed that the prevention of sudden death is similar when using selective (metoprolol and bisoprolol) and nonselective (carvedilol) β-blockers (5, 15, 17). But sudden death after MI and in heart failure are different cups of tea.

The finding by Holycross et al. (9) that among dogs at high risk for VF the expression and protein content of β_1-adrenergic receptors are decreased and that endurance exercise training restores the original ratio between β_1- and β_2-adrenergic receptors is important. When coupled with the previous evidence that these high-risk dogs show signs of impaired ability to reflexly increase cardiac vagal activity (22), the picture that emerges is that whenever, and for whatever reason, there is a shift in autonomic balance such that sympathetic activity becomes relatively dominant and there is also a shift toward a relative dominance of β_2-adrenergic receptors an arrhythmogenic milieu is created that may facilitate the occurrence of sudden cardiac death. Initial evidence also suggests that these alterations in the neural control of cardiac function might be under at least partial genetic control (21).

REFERENCES

1. **Altschuld RA, Billman GE.** β_2-Adrenoceptors and ventricular fibrillation. *Pharmacol Ther* 88: 1–14, 2000.
2. **Beta-Blocker Heart Attack Study Group.** The beta-blocker heart attack trial. *JAMA* 246: 2073–2074, 1981.
3. **Billman GE, Schwartz PJ, Stone HL.** The effects of daily exercise on susceptibility to sudden cardiac death. *Circulation* 69: 1182–1189, 1984.
4. **Bristow MR, Ginsburg R, Umans V, Fowler M, Minobe W, Rasmussen R, Zera P, Menlove R, Shah P, Jamieson S, Stinson EB.** Beta-1 and beta-2 adrenergic receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1 receptor down-regulation in heart failure. *Circ Res* 59: 297–309, 1986.
5. **CIBIS II Investigators and Committees.** The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 353: 9–13, 1999.
6. **De Ferrari GM, Vanoli E, Schwartz PJ.** Vagal activity and ventricular fibrillation. In: *Vagal Control of the Heart: Experimental Basis and Clinical Implications*, edited by Levy MN and Schwartz PJ. Armonk, NY: Futura, 1994, p. 613–636.
7. **Harris AS, Otero H, Bocage AJ.** The induction of arrhythmias by sympathetic activity before and after occlusion of a coronary artery in the canine heart. *J Electrocardiol* 4: 34–43, 1971.
8. **Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Málek I, Nyberg G, Rydén L, Swedberg K, Vedin A, Waagstein F, Waldenström A, Waldenström J, Wedel H, Wilhelmsen L, Wilhelmsson C.** Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet* 2: 823–827, 1981.
9. **Holycross BJ, Kukielka M, Nishijima Y, Altschuld RH, Carnes CA, Billman GE.** Exercise training normalizes β-adrenoceptor expression in dogs susceptible to ventricular fibrillation. *Am J Physiol Heart Circ Physiol* (August 24, 2007). doi:10.1152/ajpheart.00763.2007.
10. **ISIS-1 (First International Study of Infarct Survival) Collaborative Group.** Mechanisms for the early mortality reduction produced by beta-blockade started early in acute myocardial infarction: ISIS-1. *Lancet* 1: 921–923, 1988.
11. **La Rovere MT, Bersano C, Gnemmi M, Specchia G, Schwartz PJ.** Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. *Circulation* 106: 945–949, 2002.
12. **La Rovere MT, Schwartz PJ.** Baroreflex sensitivity. In: *Cardiac Electrophysiology. From Cell to Bedside* (3rd ed.), edited by Zipes DP and Jalife J. Philadelphia, PA: Saunders, 2000, p. 771–781.
13. **Malliani A, Schwartz PJ, Zanchetti A.** A sympathetic reflex elicited by experimental coronary occlusion. *Am J Physiol* 217: 703–709, 1969.
14. **McMurray J, Køber L, Robertson M, Dargie H, Colucci W, Lopez-Sendon J, Remme W, Sharpe DN, Ford I.** Antiarrhythmic effect of carvedilol after acute myocardial infarction. Results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) Trial. *J Am Coll Cardiol* 45: 525–530, 2005.
15. **MERIT-HF Study Group.** Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 353: 2001–2007, 1999.
16. **O'Connor GT, Buring JE, Yusuf S, Goldhaber SZ, Olmstead EM, Paffenbarger RS Jr, Hennekens CH.** An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 80: 234–244, 1989.
17. **Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH.** The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 334: 1349–1355, 1996.
18. **Schwartz PJ, Billman GE, Stone HL.** Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. *Circulation* 69: 790–800, 1984.
19. **Schwartz PJ, Foreman RD, Stone HL, Brown AM.** Effect of dorsal root section on the arrhythmias associated with coronary occlusion. *Am J Physiol* 231: 923–928, 1976.
20. **Schwartz PJ, Motolese M, Pollavini G, Lotto A, Ruberti U, Trazzi R, Bartorelli C, Zanchetti A, Italian Sudden Death Prevention Group.** Prevention of sudden cardiac death after a first myocardial infarction by pharmacologic or surgical antiadrenergic interventions. *J Cardiovasc Electrophysiol* 3: 2–16, 1992.
21. **Schwartz PJ, Vanoli E, Crotti L, Spazzolini C, Goosen A, Heradien M, Bacchini S, Turco A, La Rovere MT, Bartoli A, George AL Jr, Brink PA.** Neural control of heart rate modifies arrhythmia risk in congenital long QT syndrome. *J Am Coll Cardiol*. In press.
22. **Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD.** Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 78: 969–979, 1988.

23. **Schwartz PJ, Vanoli E, Zaza A, Zuanetti G.** The effect of antiarrhythmic drugs on life-threatening arrhythmias induced by the interaction between acute myocardial ischemia and sympathetic hyperactivity. *Am Heart J* 109: 937–948, 1985.
24. **Shivkumar K, Schultz L, Goldstein S, Gheorghiade M.** Effects of propranolol in patients entered in the Beta-Blocker Heart Attack Trial with their first myocardial infarction and persistent electrocardiographic ST-segment depression. *Am Heart J* 135: 261–267, 1998.
25. **Smyth HS, Sleight P, Pickering GW.** Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity. *Circ Res* 24: 109–121, 1969.
26. **Sotoodehnia N, Siscovick DS, Vatta M, Psaty BM, Tracy RP, Towbin JA, Lemaitre RN, Rea TD, Durda JP, Chang JM, Lumley TS, Kuller LH, Burke GL, Heckbert SR.** Beta2-adrenergic receptor genetic variants and risk of sudden cardiac death. *Circulation* 113: 1842–1848, 2006.
27. **The MIAMI Trial Research Group.** Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. *Eur Heart J* 6: 199–226, 1985.
28. **Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ.** Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res* 68: 1471–1481, 1991.