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## REFERENCES

1. Medical Information Brochure. Titusville, NJ: Janssen Pharmaceutica Products, LP, 2003.

## IMPROVEMENT OF HEART RATE RECOVERY AFTER EXERCISE TRAINING IN OLDER PEOPLE

*To the Editor:* Heart rate recovery (HRR), defined as the fall in heart rate during the first minute of recovery after exercise, is a marker of vagal tone, which is a powerful predictor of mortality in patients with coronary artery disease[1] and in elderly subjects.[2] Exercise training has been associated with improvement in cardiovascular capacity in older people,[3] but whether exercise training influences HRR in older people is still unknown. Therefore, in this study, the effect of exercise training on HRR was evaluated in elderly subjects with no cardiac disease.

Twenty-four subjects aged 70 and older were retrospectively selected from our archives and screened for symptoms of cardiovascular disease. Baseline exercise test was negative for myocardial ischemia in all subjects. All subjects had completed an 8-week program, performed for a variety of indications and consisting of an aerobic physical training program including 30 minutes of cycling three times per week at 65% to 75% of maximum heart rate achieved at peak exercise test performed at enrollment, an educational intervention, dietary advice, and psychological support. All subjects underwent a cardiopulmonary exercise test (CPX) before and at the end of exercise training. At the end of each CPX, peak oxygen uptake ($VO_{2peak}$), the rate of increase of ventilation per unit of increase of carbon dioxide production ($VE/VCO_{2slope}$), and HRR were recorded.

Twenty-five healthy subjects younger than 60 with no evidence of exercise-induced myocardial ischemia and not enrolled in any exercise training program were also retrospectively selected from our archives and used as a control group for analyzing HRR. These patients performed two exercise tests several weeks apart.

After exercise training, in elderly subjects, an increase in $VO_{2peak}$ from $12.3 \pm 3.0$ to $13.9 \pm 2.7$ mL/kg per minute ($P < .001$), a decrease in $VE/VCO_{2slope}$ from $31.1 \pm 3.3$ to $29.1 \pm 2.7$ ($P < .005$) and an increase in ventilatory aerobic threshold from $8.3 \pm 1.8$ to $9.5 \pm 2.1$ mL/kg per minute was observed ($P < .01$). HRR improved from $18.7 \pm 1.9$ beats/min to $23.6 \pm 3.4$ beats/min ($P < .001$). The mean value of HRR at the end of exercise training was higher than the value observed in younger control subjects ($P < .002$). In these subjects, the HRR on serial testing was $22.0 \pm 3.2$ beats/min and $22.0 \pm 5.3$ beats/min ($P = .71$). In elderly subjects, the improvement of HRR after exercise training was inversely correlated with the change of $VE/VCO_{2slope}$ ($P < .001$; $r = -0.739$) (Figure 1) but not with $VO_{2peak}$ ($r = 0.362$) or ventilatory aerobic threshold ($r = 0.317$).

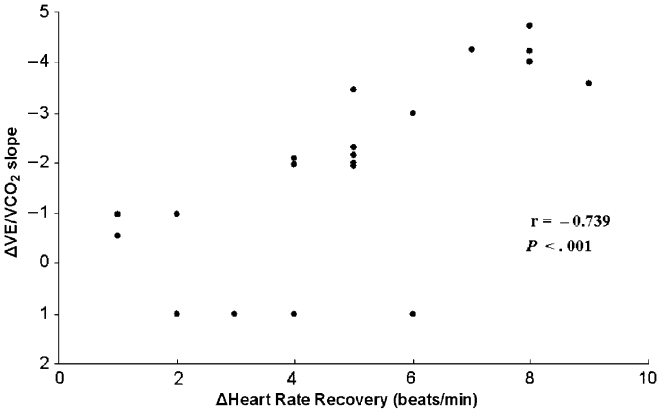


**Figure 1.** Relationship between changes in heart rate recovery (beats/min) and the rate of increase of ventilation per unit of increase of carbon dioxide production ($VE/VCO_{2slope}$) after exercise training in elderly subjects.

Several studies have shown that changes in vagal tone can be used as an outcome tool that helps identify patients or subjects with or without cardiovascular disease at risk for a cardiovascular event,[1,4–6] although the evidence of a prognostic value of HRR in older subjects without cardiovascular disease is rather poor.

Physical exercise is an important component of a standard cardiac rehabilitation program after a cardiac event.[7] In subjects without cardiovascular disease, exercise is an independent predictor of long-term survival[8] in young and elderly subjects, but the mechanisms involved in exercise-induced reduction in mortality are unclear and probably multifactorial, including a favorable effect of exercise training on autonomic tone. Several studies have shown that, in patients with heart disease, exercise training favorably modulates parasympathetic/sympathetic balance.[9]

In this study, exercise training resulted in HRR improvement in healthy elderly subjects, suggesting that exercise training improves vagal/sympathetic balance in older subjects without cardiovascular disease as well. Whether the observed improvement in HRR may have long-term beneficial prognostic effects was not the aim of the study, although a beneficial effect might be postulated, in light of the Framingham data.[5]

In addition, a significant correlation was observed between HRR and changes in $VE/VCO_{2slope}$, a parameter adding prognostic significance to the value of $VO_{2peak}$.[10] The significance of this finding may be due to improved cardiovascular fitness and ventilation at peak exercise at the end of training. Whether in this clinical context this parameter may bear prognostic significance, as in patients with congestive heart failure, is uncertain and should be assessed in future researches.

Another interesting finding of this study was a significant inverse relationship between HRR and $VE/VCO_{2slope}$. With all the limitations outlined above about the prognostic

implications of the change of each of these two parameters in older subjects without cardiovascular disease, it can be hypothesized that exercise training improves functional cardiovascular capacity and vagal/sympathetic balance and that this effect is proportional to an improvement in lung ventilation. Future researches should investigate the significance of this correlation.

*Francesco Giallauria, MD*
*Domenico Del Forno, PhD*
*Francesco Pilerci, MD*
*Anna De Lorenzo, MD*
*Athanasio Manakos, MD*
*Rosa Lucci, MD*
*Carlo Vigorito, MD*
*Department of Clinical Medicine*
*Cardiovascular and Immunological Science*
*University of Naples Federico II*
*Naples, Italy*

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## REFERENCES

1. Watanabe J, Thamilarasan M, Blackstone EH et al. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality. Circulation 2001;104:1911–1916.
2. Messinger-Rapport B, Pothier Snader CE, Blackstone EH et al. Value of exercise capacity and heart rate recovery in older people. J Am Geriatr Soc 2003;51:63–68.
3. Marchionni N, Fattirolli F, Fumagalli S et al. Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: Results of a randomized, controlled trial. Circulation 2003;107: 2201–2206. Epub 2003, April 21.
4. Imai K, Sato H, Hori M et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol 1994;24:1529–1535.
5. Tsuji H, Venditti FJ, Manders ES et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 1994;90:878–883.
6. Cole CR, Foody JM, Blackstone EH et al. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med 2000;132:552–555.
7. Ades PA. Medical progress. Cardiac rehabilitation and secondary prevention of coronary artery disease. N Engl J Med 2001;345:892–902.
8. Myers J, Prakash M, Froelicher V et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
9. Lucini D, Milani RV, Costantino G et al. Effects of cardiac rehabilitation and exercise training on autonomic regulation in patients with coronary artery disease. Am Heart J 2002;143:977–983.
10. Corrà U, Mezzani A, Bosimini E et al. Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. Am Heart J 2002;143:418–426.

## ETIDRONATE AMELIORATES PAINFUL SOFT-TISSUE CALCIFICATION IN WERNER SYNDROME

*To the Editor:* Bisphosphonates, chemical compounds widely used as antiosteoporotic agents, were originally brought into clinical practice to treat ectopic calcification.[1] Their application for this purpose has been almost forgotten because the therapeutic dose may also affect normal bone formation. Here, we report that etidronate, a first-generation bisphosphonate, ameliorated soft-tissue calcification and improved performance in a patient with progeroid Werner syndrome without apparent adverse effects.

A 47-year-old woman visited our hospital because of intolerable pain in the left knuckle, bilateral elbows, and ankles. She had graying and loss of hair, peripheral soft tissue atrophy, a skin ulcer on the right ankle, marked insulin resistance, and a history of cataract at the age of 30. Werner syndrome was suspected; peripheral blood deoxyribonucleic acid (DNA) analysis confirmed homozygous type 4 mutations in the causative WRN helicase gene.[2]

Pain in the left knuckle was due to a hard subcutaneous nodule (Figure 1, left panel), which turned out to be an ectopic calcification (Figure 1, middle panel). Similar calcification was also found in the elbows and Achilles tendons; all of them coincided with the positions of pain. Her hands, elbows, and left ankle were free of ulcers. X-rays of the lumbar and thoracic spines showed no sign of osteoporosis. Serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone were in the normal range.

The patient could hardly clench her left fist or walk more than 1 m because of pain in the knuckle and ankles. Etidronate at a dose of 20 mg/kg per day was started orally in an attempt to suppress the ectopic calcification.

Clinical symptoms improved dramatically after 3 months of treatment. She was now able to walk for more than 6 m, was free of pain in the elbows, and felt remarkably less pain in her knuckle. The size of the nodule became smaller (Figure 1, right panel), indicating the effectiveness of etidronate in reversing calcification. No adverse effects were described at this point, but etidronate was stopped to avoid possible inhibition of bone formation.

Bisphosphonates, first synthesized in the 1860s, was originally used in industry to prevent scaling or precipitation of calcium carbonate.[1] Their biological effect of inhibiting ectopic calcification in vivo, as inspired by the structural similarity to inorganic pyrophosphate, was initially reported in 1968,[3] but clinical use of bisphosphonates for this purpose has not developed further, because they also interfere with mineralization of normal bone. Instead, they are now established as drugs against osteoporosis because of their property of preventing bone resorption when given at lower doses.

Werner syndrome, an autosomal recessively inherited progeroid disorder caused by homologous mutations in a RecQ family DNA helicase, often accompanies soft-tissue calcification for unknown reasons.[4,5] It can be asymptomatic but often results in severe pain and may promote skin ulcer formation. These symptoms limit patients' daily activity, threaten their quality of life, and facilitate development of overt diabetes mellitus due to inactivity on the base of insulin resistance.