

Aerobic exercise training reduces blood pressure, angiotensin II and oxidative stress of patients with resistant hypertension: the EnRiCH trial

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Introduction: Resistant hypertension is a major challenge of modern cardiovascular medicine, as it is a puzzling problem without a clear solution. Exercise training clearly reduces blood pressure (BP) and oxidative stress in patients with hypertension, however evidence is limited regarding resistant hypertension.

Purpose: To determine the effect of an aerobic exercise training program in BP, angiotensin II and oxidative stress in patients with resistant hypertension.

Methods: EnRiCH is a prospective, two-center, single-blinded, randomized controlled trial with a parallel two-arm group. Sixty patients with resistant hypertension were randomly assigned in a 1:1 ratio to undergo a 12-week aerobic exercise training program (exercise) or usual care (control). The powered primary efficacy measure was 24-hour ambulatory systolic BP change from baseline. Secondary outcome measures included daytime and nighttime ambulatory BP, office BP, cardiorespiratory fitness, and oxidative stress and inflammatory biomarkers: Interferon-gamma (IFN- γ), Angiotensin II, vascular endothelial growth factor (VEGF), and superoxide dismutase (SOD).

Results: Fifty-three patients (exercise n=26, control n=27) completed the study. Patients were mainly women (54.7%), with an office BP of 140.7 \pm 15.9/84.2 \pm 9.4 mm Hg and taking an average of 4.6 antihypertensive medications (median, 5; range, 3 to 7). At baseline, no differences

were found between groups for the study outcomes and patient characteristics. Ambulatory systolic BP was reduced -7.1 mm Hg (95% CI, -12.8 to -1.4 ; $P=0.015$) in the exercise group (127.4 \pm 12.2 to 121.2 \pm 12.2, $p=0.007$) compared to control group (126.1 \pm 17.2 to 126.9 \pm 15.2, $p=0.514$) over 24-hour. In addition, 24-hour ambulatory diastolic BP (-5.1 mm Hg, -7.9 to -2.3 , $P=0.001$), daytime ambulatory systolic (-8.4 mm Hg, -14.3 to -2.5 , $P=0.006$), and diastolic BP (-5.7 mm Hg, -9.0 to -2.4 , $P=0.001$) were also reduced in the exercise group compared to the control group. There were no differences in the change of nighttime ambulatory BP between groups. Cardiorespiratory fitness improved in the exercise group by 14% (4.7 ml.kg $^{-1}$.min $^{-1}$, $P<0.001$), while it remained unchanged in the control group (-0.37 ml.kg $^{-1}$.min $^{-1}$, $P=0.442$). A significant between-group difference in favor of exercise group was found for IFN- γ (-4.3 pg/mL, 95% CI: -7.1 to -1.5 ; $P=0.003$), Angiotensin II (-157.0 pg/mL, 95% CI: -288.1 to -25.9 ; $P=0.020$), VEGF (10.53 pg/mL, 95% CI: 0.60 to 22.54; $P=0.035$), and SOD (0.35 pg/mL, 95% CI: 0.10 to 0.58; $P=0.009$).

Conclusions: A 12-week moderate intensity aerobic exercise program reduced ambulatory BP, angiotensin II and oxidative stress in patients with resistant hypertension. The antihypertensive effects of exercise in patients with resistant hypertension may be mediated by positive changes in oxidative stress and inflammatory biomarkers.