Exercise as a Physiologic Intervention to Counteract Hypertension
Can a Good Idea Go Bad?

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Various treatment strategies have been developed to treat hypertension and affect its clinical outcome. These include early lifestyle modifications such as weight loss, nutritional changes, and exercise as well as pharmacological interventions that are based on diuresis, inhibition of the renin-angiotensin system, calcium channel blockade, central and peripheral sympatolysis, as well as α- and β-receptor blockade. In individuals with prehypertension and patients with established hypertension, initial treatment, before the administration of pharmacological therapies, focuses on lifestyle changes targeting nutrition and exercise. In particular exercise is an intervention that is widely prescribed and recommended. Multiple clinical trials have shown effects of exercise on blood pressure with an average reduction of −10 mm Hg systolic and −8 mm Hg diastolic. Unfortunately, exercise is notoriously difficult to observe, evaluate, and dose in an outpatient population with hypertension.

Exercise as a Physiological Cardiovascular Intervention

Exercise is a physiological intervention with a broad variety of positive cardiovascular effects that include changes in lipid metabolism, insulin resistance, weight, arterial hypertension, inflammation, endogenous anabolism, and mood. It seems, in fact, reasonable to hypothesize that metabolic abnormalities associated with the primarily sedentary lifestyle in modern Western civilizations are not only counteracted but normalized by physical activity. Therefore, regular exercise would be a physiological correction rather than a medical treatment intervention.

Exercise programs distinguish between primarily aerobic dynamic (eg, running and cycling) and resistance (eg, strength training) exercises. Dynamic exercise with alternating muscle contraction and relaxation results in a steady rise of systolic blood pressure when intensity increases, whereas the diastolic pressure varies minimally. In contrast, resistance exercise is characterized by prolonged isometric muscle contraction before relaxation with high interstitial pressure that causes collapse of arterioles and capillaries. Blood pressure increases in relation to intensity and duration of the contraction.

Effects of exercise on the myocardium have been well established. Regular dynamic exercise increases stroke volume and cardiac output and reduces β-adrenergic stimulation. Exercise training increases myocardial mass, left ventricular dimensions, and stroke volume in healthy subjects. In chronic heart failure, exercise has been shown to improve exercise tolerance and symptoms, which is attributed to peripheral adaptations such as improved endothelial function and skeletal muscle strengthening. Moreover, exercise training has been associated with reversal of molecular and structural changes in the myocardium of hypertensive animals.

Cardiac Hypertrophy and Failure

A number of experimental studies have investigated the pathways underlying cardiac hypertrophy. Although cardiac hypertrophy is thought to be an initially supportive adaptation of the myocardium in response to increased load and wall stress, it has been well established that continued myocardial strain leads to maladaptive changes in the myocardium and ultimately cardiac failure.

Cardiac hypertrophy is a response of the myocardium to increased load. Assessments of wall stress are based on Laplace law which describes spherical wall stress as a function of diameter, wall thickness, and internal pressure. This relationship has been modified to reflect biophysical specifics of ventricular strain patterns where wall stress is a function of intraventricular pressure, myocardial thickness, and ventricular diameter. Therefore, increased afterload leads to elevated end-systolic intraventricular pressure which is balanced by increased myocardial wall thickness to keep myocardial wall stress constant. If increased afterload persists because of an uncontrolled elevation of arterial pressure, myocardial growth reaches a limit and ventricular dilatation develops which, in turn, further increases myocardial wall stress. This stage is accompanied by a decrease in cardiac function defined by measures of cardiac contractility and relaxation and defines the transition from compensated cardiac hypertrophy to cardiac failure.

Myocardial abnormalities during the development of cardiac hypertrophy and failure are accompanied by changes in the expression of structural, metabolic, signaling, and inflammatory genes. Notably, these transcriptional changes also result in a switch from adult to embryonic isoforms of several genes such as the transition
from α-myosin heavy chain to β-myosin heavy chain. Further, patterns of physiological hypertrophy such as cardiac hypertrophy in response to exercise are characterized by a selective activation of the PI3K/Akt cascade which is thought to be a “healthy” adaptation to increased myocardial load. In contrast, increased activation of the p38/MAPK cascade has been demonstrated in pathologic hypertrophy such as prolonged myocardial wall stress. Notably, spatial and temporal patterns have been identified in the progression of cardiac hypertrophy, and the increased frequency of programmed cell death (apoptosis) in the myocardium has been linked to pathologic hypertrophy. Further, changes in extracellular matrix composition and volume occur in cardiac hypertrophy and result in the development of myocardial fibrosis. Altogether, the progression of maladaptive myocardial changes ultimately leads to the transition from cardiac hypertrophy to cardiac failure.

### Unexpected Effects of Exercise in Hypertensive Animals

The current study by Schultz et al assessed whether long-term voluntary wheel running affects cardiac remodeling in experimental hypertension. Unexpectedly, the results of their study revealed that exercise in spontaneously hypertensive rats led to acceleration in the progression of cardiac failure as suggested by an enhanced dilatation of the left ventricle, increased myocardial fibrosis, and decreased cardiac function. Further, the authors found evidence that the hypertensive animals presented with more symptomatic heart failure in response to exercise. Although the authors also observed patterns of more physiological hypertrophy in response to exercise, the hypertensive animals did not show the expected preservation of cardiac function in response to exercise. Finally, the authors observed a significant effect of exercise on markers of myocardial structure in control animals with an increase in cell size, cross-sectional area, and volume.

These findings are results of an animal study and, therefore, cannot be simply extrapolated to human disease. In fact, the findings of the study are contradictory to the observed beneficial relationship between physical activity and overall cardiovascular mortality. Despite the variable quantification and categorization of physical activity among the trials, there appears to be a general trend toward improved cardiovascular mortality with increased energy expenditure. The benefit is seen even at low levels of exercise and physical activity.

However, it is not entirely clear how exercise improves cardiovascular outcomes. In a recent randomized trial of sedentary, hypertensive, postmenopausal women looking at dose-response changes in fitness by Church et al, low levels of exercise (50% of recommended physical activity by the NIH Consensus Development Panel) resulted in a 4.2% increase in VO2 max (peak absolute oxygen consumption) over 6 months but surprisingly, no significant changes were observed in blood pressure, lipid metabolism, or BMI with increasing levels of fitness. If exercise and increased fitness do not improve traditional cardiac risk factors, it is difficult to speculate a causal mechanism by which exercise exerts its effects. Thus, in the current study by Schultz et al, the correlation between exercise and increased symptomatic heart failure and hypertrophy in the hypertensive animals should be interpreted cautiously. Potential confounders include levels of exercise and purposely altered hypertensive adaptive mechanisms.

Human trials have looked primarily at low to moderate levels of intensity. Compared with the control animals, the hypertensive animals in the current study exercised significantly more for unknown reasons because the exercise protocol was based on voluntary activity. The excessive exercise pattern in hypertensive animals is a limitation of this study and cannot be explained at this point; however, in the hypertensive rats, exercise might have become a pathologic stimulus rather than the physiological stimulus that has been observed in other studies. This limitation might be crucial because the level of exercise seems critical in defining the specific effects of exercise on the heart.

Further studies are needed to compare well-defined exercise protocols at different intensity levels in hypertensive and control animals as well as hypertensive animals after therapeutic correction of arterial hypertension. Although a physiological growth pattern was detected in cardiac myocytes, it was clearly not enough to compensate for this level of stress. Notably, exercise in the hypertensive rats resulted in widespread fibrosis further suggesting abnormal myocardial stress. As shown in other studies, myocardial fibrosis is associated with diastolic dysfunction and a proarrhythogenic state.

The beneficial central and peripheral effects of exercise make it an intriguing option for a therapeutic intervention before and in addition to pharmacological therapies in hypertension and chronic heart failure. Although limited to an animal study, the findings of the current study indicate that uncontrolled and excessive exercise in the hypertensive state can have deleterious effects on cardiac remodeling and may, in fact, accelerate the progression to cardiac failure. This animal study should raise our awareness of potentially detrimental effects of high-intensity exercise in uncorrected hypertension, and its findings need to be evaluated in further studies. It would be interesting to see whether the correction of hypertension through pharmacological interventions might reverse the responsiveness of the myocardium to the positive effects of exercise in this animal model. On the other hand, it is possible that the structural and metabolic changes in hypertension cause abnormalities in the myocardium that are not reversible by simple pharmacological correction of arterial pressure. Defining the fine line between beneficial and detrimental effects of exercise requires further studies, although the current analysis adds valuable information in determining the effects of exercise as a supportive nonpharmacological intervention in hypertension.

### Disclosures

None.
References


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Hypertension. 2007;50:294-296; originally published online July 2, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.087718

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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