Impact of an Exercise Program on Arterial Stiffness and Insulin Resistance in Hemodialysis Patients

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Abstract. Cardiovascular disease remains the primary cause of mortality in patients who are maintained on hemodialysis. Arterial stiffness and insulin resistance are independent risk factors for cardiovascular mortality in this population. In healthy individuals, higher physical conditioning is associated with reduced arterial stiffness. Exercise reduces insulin resistance and glucose intolerance in sedentary, overweight individuals and diabetic patients. The purpose of this study was to determine the impact of an exercise program on arterial stiffness and insulin resistance in a group of patients on hemodialysis. The effect of exercise training on arterial stiffness and insulin resistance in 11 patients who were on chronic hemodialysis was evaluated. Exercise classes of 1-h duration were conducted twice weekly for 3 mo. Arterial stiffness was assessed using the radial artery pressure waveform analysis. Aerobic exercise improved arterial stiffness from 17 ± 3 u at baseline to 12.2 ± 3 u at the end of the intervention ($P = 0.01$). After 1 mo of detraining, arterial stiffness reverted to pre-exercise levels (17.3 ± 3 u). Pulse pressure paralleled arterial stiffness changes, and the correlation between them was statistically significant ($r = 0.725$, $P = 0.012$). Insulin resistance was calculated using the homeostatic model assessment formula. Exercise at the intensity and duration used in our study had no impact on insulin resistance ($P = 0.38$). These findings suggest that 3 mo of aerobic exercise training improves arterial stiffness, an independent risk factor for cardiovascular mortality in patients who are on hemodialysis, and has no impact on insulin resistance. The beneficial effect on arterial stiffness dissipates within 1 mo of detraining. To obtain therapeutic benefits, an exercise program for patients who are maintained on hemodialysis should be designed to promote regular long term exercise, >3 h/wk.

Despite significant advances in the technique and quality of their treatment, patients who are on hemodialysis (HD) continue to display high morbidity and mortality. Cardiovascular (CV) events account for up to 50% of deaths in this population (1). Recent studies have demonstrated that both arterial stiffness and insulin resistance are independent risk factors for CV mortality in patients with ESRD (2,3).

In patients who are on HD, arterial stiffness is associated with increased left ventricular afterload, left ventricular hypertrophy, decreased subendocardial perfusion, and increased mechanical fatigue of the arteries. Moreover, uremic patients are universally insulin resistant. Insulin resistance may be involved in the pathogenesis of atherosclerosis, hypertension, and dyslipidemia.

Rehabilitation programs, focusing on exercise, benefited patients after myocardial infarction, bypass surgery, chronic lung disease, rheumatologic disorders, strokes, and other neurologic conditions. Central effects of exercise training in patients who are on HD include improved left ventricular function, a beneficial effect on coronary risk factors (*e.g.*, hypertension, lipid profile), an increased cardiac vagal activity, and a decrease in the incidence of cardiac arrhythmias (4–6). Peripheral changes include an improvement in muscle structure, function, and strength, as well as an increase in red blood cell mass, hematocrit, and hemoglobin (7–9). These central and peripheral adaptations to exercise training may cause an increase in the functional capacity of patients who are on HD, thereby offering them a better quality of life.

Our group has shown that a supervised exercise program benefits the aerobic capacity, clearance (Kt/V), and quality of life in patients who are on HD (10). Exercise during HD seems to be associated with improved hemodynamic stability, possibly by maintaining plasma levels of norepinephrine (11).

It has been well established that arterial stiffness increases with advancing age. Moreover, patients with ESRD have premature aging of the vascular tree. Higher physical conditioning status is associated with reduced arterial stiffness, both within a healthy predominantly sedentary population and in endurance-trained older men relative to their less active age-peers (12). These findings suggest that exercise may mitigate the stiffening of the arteries that accompanies normative and, possibly, premature aging.

Insulin resistance is a characteristic feature of uremia, irrespective of the type of renal disease, with muscle tissue insensitivity being the primary cause (13). Regular physical exercise improves insulin sensitivity in both normal individuals and patients with lifestyle-related diseases (*e.g.*, type 2 diabetes,

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hypertension, hyperlipidemia, ischemic coronary artery disease) (14).

We hypothesized that exercise training, by decreasing BP, improving blood flow to the skeletal muscle, and stimulating myocyte glucose uptake and metabolism, may have a beneficial effect on arterial stiffness and insulin resistance in patients who are on HD. An improvement in arterial stiffness and/or insulin resistance may translate into a superior risk factor profile (*e.g.*, left ventricular hypertrophy, hypertension, dyslipidemia), enhanced coronary perfusion, decreased number of CV events, and a better survival of patients who are on HD.

Materials and Methods

Patients

We studied 11 chronic HD patients (7 women and 4 men), with a mean age of 55.5 ± 4 yr (range, 31 to 78). Their HD treatment consisted of 3.5 to 4 h, three times a week. The causes of ESRD included diabetes (three cases), hypertension (three cases), glomerulonephritis (two cases), bilateral nephrectomy for renal cell carcinoma (one case), polycystic kidney disease (one case), and lupus nephritis (one case).

Exclusion criteria were active, symptomatic CV or respiratory disease; uncontrolled hypertension; and musculoskeletal abnormalities that limited exercise ability. All patients were on a stable medication regimen, and doses were not adjusted during the study. The study protocol was approved by the University Health Network Research Ethics Board, and informed consent was obtained from all study participants.

Study Protocol

Exercise test. Patients underwent a cardiac stress test, using a Chung protocol, in the Cardiac Rehabilitation Center of our hospital, under the supervision of an exercise physiologist and a qualified internist. During the test, in addition to recording BP and heart rate (HR) responses to exercise, patients were monitored for symptoms (leg fatigue, tiredness, dizziness, chest pain, or shortness of breath) and for electrocardiogram changes. Each patient was subsequently provided with an individualized exercise prescription. This prescription was based on a target HR, which ranged between 60 and 80% of the maximal HR documented during the stress test.

Exercise classes. One-hour exercise classes were conducted twice weekly for 3 mo at the Cardiac Rehabilitation Center of the University Health Network. Under the supervision of a qualified internist and two HD nurses, patients trained on treadmills and/or recumbent bikes. A typical class consisted of a 5- to 10-min warm-up period, 40 to 50 min of conditioning exercise, and a 5- 10-min cool-down.

HR was measured at baseline and every 10 to 15 min thereafter until the end of the class. The date of each session, times and values of HR, length of time spent on a treadmill or bike, and any additional comments were recorded.

Analytic Methods

Arterial stiffness was assessed using the SphygmoCor System and Program (Sydney, Australia). This system has the ability to derive the central aortic pressure waveform noninvasively from the pressure pulse recorded at a peripheral site (radial artery) (15). The result provides an augmentation index expressed in units (u). A pencil-type hand-held probe with the sensing element at the tip was used to obtain the radial pulse waveform of the nonvascular access arm. Arterial stiffness was measured at baseline, after 3 mo of exercise classes, and 1 mo after detraining. Each value represented the average of three consecutive determinations. These measurements were obtained 2 min apart, midweek, predialysis, and, when applicable, pre-exercise. The mean values were calculated, and the results were compared. Brachial BP was measured in the nonvascular access arm before each arterial stiffness determination.

Insulin resistance was evaluated in nondiabetic patients by the homeostasis model assessment method (HOMA-IR) using fasting glucose (FG) and fasting insulin (FI) levels (16). After 12 h of overnight fasting, two predialysis samples were obtained, 5 min apart, midweek, for glucose and insulin levels. Their mean values were calculated and used to estimate insulin resistance in the formula HOMA-IR (mmol/L × μU/ml) = FG (mmol/L) × FI (μU/ml)/22.5. Insulin resistance determinations after 1, 2, and 3 mo of exercise were obtained and results were compared with baseline values.

Statistical Analyses

All results are expressed as mean ± SEM. In the case of arterial stiffness, results were analyzed using a paired *t* test to assess the change between baseline and the end of the intervention. In the case of insulin resistance, within-subject responses to exercise were analyzed using paired *t* test between baseline and the final value and a repeated measure ANOVA for results over time. The relationship between arterial stiffness and pulse pressure was analyzed using correlation coefficients. All statistical analyses were performed using the statistical package SAS (SAS Institute Inc., Cary, NC).

Results

A total of 16 patients who were on chronic HD were tested. For personal reasons, four of them elected not to attend exercise classes and were not included in the study. An additional patient was excluded from the data analysis, as he attended classes sporadically and exercised for only 10 to 15 min at a time, without reaching the target HR. As a result, 11 patients completed 3 mo of supervised exercise classes for 1 h twice weekly. The overall attendance was 80%. Baseline clinical characteristics of all patients are summarized in Table 1. During each class, patients were able to reach the target prescribed by the exercise physiologist at the time of the stress test, increasing the mean HR values by 34%, from 79 ± 6 beats/min pre-exercise to 106 ± 6 beats/min at peak.

Arterial stiffness was 17 ± 3 u at baseline (normal values ~10 u) and decreased to 12.2 ± 3 u after 3 mo of exercise ($P = 0.01$). One month after detraining, arterial stiffness reverted to pre-exercise levels (17.3 ± 3 u; Figure 1). Pulse pressure decreased significantly from 64 ± 7 mmHg at baseline to 57 ± 6 mmHg after 3 mo of exercise. One month after detraining,

Table 1. Baseline clinical characteristics of the cohort

No. of patients	11
Age (yr)	55.5 ± 4
Gender (male/female)	4/7
Duration of hemodialysis treatment (yr)	3.18 ± 1
Presence of hypertension (%)	91
Presence of diabetes (%)	27
Antihypertensive medications (%)	64

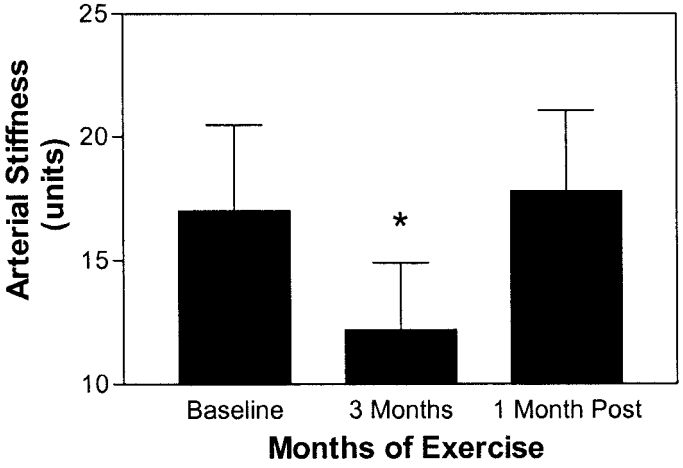

Figure 1. Arterial stiffness (AS) at baseline, after 3 mo of exercise, and after 1 mo of detraining. *$P < 0.05$ *versus* baseline.

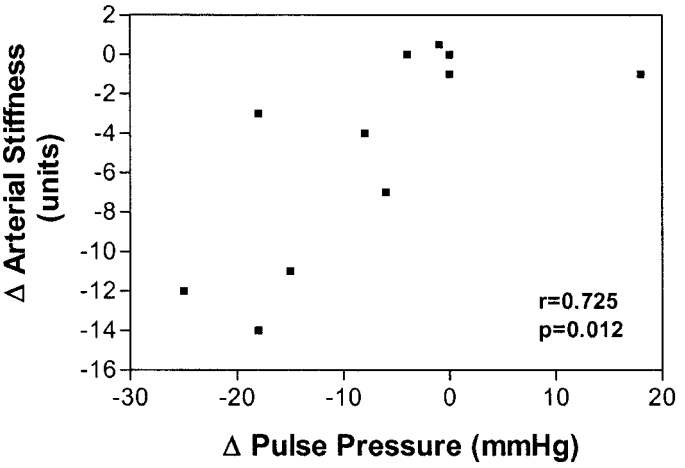

Figure 3. Correlation between AS and PP changes as measured after 3 mo of the exercise program.

pulse pressure reverted to pre-exercise levels (65 ± 6 mmHg; Figure 2). The effect on pulse pressure was largely attributed to a significant decline in the systolic BP.

A significant correlation was observed between Δ Arterial Stiffness_1 (the negative change in arterial stiffness after training) and Δ Pulse Pressure_1 (the negative change in pulse pressure after training; $r = 0.725$, $P < 0.012$; Figure 3) and also between Δ Arterial Stiffness_2 (the positive change in arterial stiffness after detraining) and Δ Pulse Pressure_2 (the positive change in pulse pressure after detraining; $r = 0.677$, $P < 0.022$; Figure 4).

Exercise training had no effect on insulin resistance. HOMA-IR values actually increased at 1, 2, and 3 mo compared with baseline, indicating a numerical but nonsignificant increase in insulin resistance over time (Table 2).

Monthly blood work was obtained as per our HD unit standard of care. The levels of hemoglobin, potassium, albumin, calcium, phosphorus, and urea clearance were unaffected by exercise (Table 2). There was no significant change in predialysis and postdialysis weights, as well as interdialytic weight gain throughout the study period (Table 2).

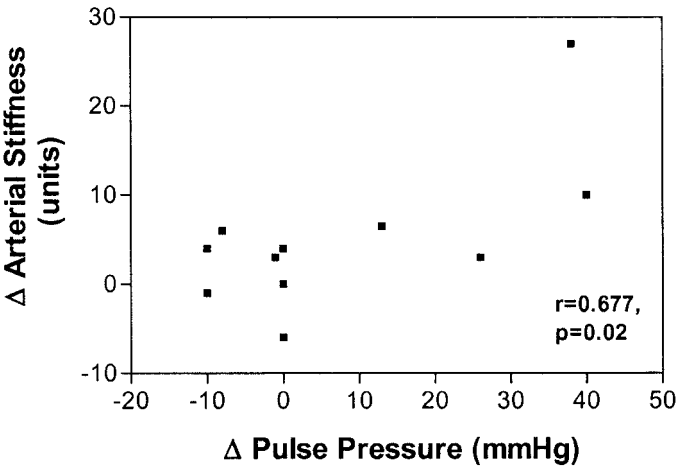

Figure 4. Correlation between AS and PP changes as measured 1 mo after the end of the exercise program (detraining).

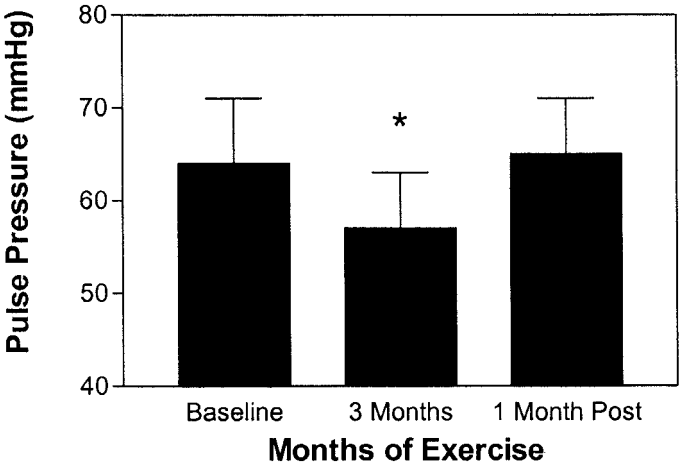

Figure 2. Pulse pressure (PP) at baseline, after 3 mo of exercise, and after 1 mo of detraining. *$P < 0.05$ *versus* baseline.

No major complications or side effects were recorded. A transient episode of symptomatic hypotension was observed in one patient during one exercise class. This patient attended the class immediately after an HD session, during which >3 liters of fluid were ultrafiltered.

Discussion

This study evaluated the effect of an exercise training program on arterial stiffness and insulin resistance, two independent risk factors for CV mortality in patients who are on HD. We hypothesized that exercise training, by decreasing BP levels, improving the blood flow to the skeletal muscle, and stimulating myocyte glucose uptake and metabolism, might have a beneficial effect on arterial stiffness and insulin resistance in this population. Long term, this may translate into a better risk factor profile (*e.g.*, left ventricular hypertrophy,

Table 2. Monthly predialysis measurements[a]

Variables	Baseline	1 Month	2 Months	3 Months
Hemoglobin (g/L)	126 ± 5	120 ± 2	120 ± 5	118 ± 6
Potassium (mmol/L)	5.2 ± 0.3	4.6 ± 0.2	4.6 ± 0.2	4.5 ± 0.2
Albumin (g/L)	39 ± 0.4	38 ± 0.5	38 ± 0.6	39 ± 0.8
Calcium (mmol/L)	2.33 ± 0.09	2.39 ± 0.04	2.39 ± 0.07	2.36 ± 0.07
Phosphorus (mmol/L)	1.47 ± 0.10	1.41 ± 0.10	1.51 ± 0.20	1.36 ± .10
PRU (%)	73 ± 2	72 ± 3	75 ± 2	76 ± 3
HOMA-IR	2.64 ± 0.6	4.00 ± 1.4	4.47 ± 1.6	2.88 ± 0.55
Predialysis weight	75.8 ± 4.2	75.9 ± 4.2	75.8 ± 4.1	75.6 ± 4.0
Postdialysis weight	73.6 ± 4.0	73.8 ± 4.1	73.1 ± 4.0	73.6 ± 4.0
Interdialytic weight change	2.2 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	2.0 ± 0.2

[a] PRU, percent reduction in urea; HOMA-IR, homeostasis model assessment, insulin resistance.

hypertension, dyslipidemia), a decreased number of CV events, and a better survival of patients who are on HD.

The major finding of this study is that 3 mo of aerobic exercise training significantly improved arterial stiffness in 11 patients who are on chronic HD. The effect is transient (*i.e.*, arterial stiffness values reverted to baseline levels 1 mo after detraining). The potential consequences of a sustained improvement in arterial stiffness are a decreased left ventricular afterload and hypertrophy, an increased subendocardial perfusion resulting in a better myocardial supply/demand balance, and an improvement in the mechanical stress of the large arteries. Three months of aerobic exercise was not sufficient to have an impact on insulin resistance, as assessed by HOMA-IR.

Damage to large (elastic type) arteries is common in patients with ESRD. Increased arterial stiffness and intima-media thickness and increased pulse pressure are the principal arterial alterations. In our study, exercise had no impact on calcium and phosphate levels, fasting glucose and insulin, or urea clearance, factors that can, potentially, influence arterial structure and arterial stiffness in patients who are on HD.

Exercise training improves BP levels and decreases the use of antihypertensive medications in patients who are on HD (17) and patients with predialysis renal failure (18). An increased systolic BP and widening of pulse pressure are common in patients who are on HD. Epidemiologic studies in the general and hypertensive populations have identified pulse pressure as a strong predictor of CV mortality (19,20). In patients who are on HD, higher systolic BP, lower diastolic BP, and wider pulse pressure all conferred greater CV and total mortality risk. Pulse pressure was independent of and more robust than both systolic and diastolic BP (21). Our results show that exercise improved both pulse pressure and arterial stiffness, and the correlation between them was significant. To our knowledge, this is the first study to demonstrate that exercise can be used, as a nonpharmacologic intervention, to improve not only BP but also arterial stiffness in patients who are on HD.

Patients with ESRD have an increased activity of the sympathetic nervous system (22) and limited endothelium-dependent vasodilation (23). It is our speculation that exercise improved arterial stiffness and BP by acting mainly on the dynamic mechanism represented by endothelium and smooth muscle.

Our findings have another potential implication. One study concluded that arterial stiffness reversibility in response to BP lowering had a beneficial impact on survival of patients who were on HD (24), and this finding emphasized the need to test alternative therapies in patients in whom antihypertensive drugs are unable to alter arterial stiffness. We propose that exercise, by improving both arterial stiffness and BP, is an adjunct to antihypertensive drugs and should become a standard of practice for patients who are on HD.

Patients with ESRD are known to have insulin resistance, multiple risk factors, advanced atherosclerosis, and high CV mortality rate (25). Although the cellular basis for insulin resistance in uremic patients is not completely understood, the main mechanism seems to be muscle tissue insensitivity to insulin. Many factors have been implicated in the pathogenesis of insulin resistance in chronic renal failure, including exercise intolerance. Recently, insulin resistance, as assessed by HOMA-IR, was found to be an independent predictor of CV mortality in a cohort of nondiabetic, chronic HD patients (3). Physical activity, in addition to its own direct metabolic effects, markedly affects the ability of insulin to stimulate a range of metabolic processes. Exercise elicits effects on processes such as insulin-induced muscle glucose uptake and glucose metabolism, which influence systemic glucose homeostasis (26). These phenomena are probably responsible for the improvement in glucose homeostasis and metabolic control that typically occur with exercise in people with insulin resistance and probably contribute to the reduced risk for development of type 2 diabetes in individuals who engage in regular exercise.

The duration of most studies that focused on the effect of exercise on insulin resistance was 4 to 6 mo, whereas our training program consisted of 3 mo only. Some of the effects attributed to training are actually acute effects of recent exercise and not a chronic metabolic adaptation. Results of one study suggested that training had a transient effect, and just a few days of physical inactivity led to a marked reduction in

insulin action (27). Our patients exercised only twice a week, which may be inadequate from a frequency point of view. Recent data conclude that total exercise duration should be considered when designing training programs to improve insulin resistance, and ~3 h of exercise per week improved insulin resistance more substantially than 2 h (28), which was our prescription. In addition, the uremic environment may make patients who are on HD even more refractory to the effects of exercise on insulin resistance. To our knowledge, the only study that showed a benefit of exercise on insulin resistance in this population used a training program that consisted of 3 to 5 classes weekly for 12 mo (5). Thus, to benefit from it, patients who are on HD should exercise more frequently and for a prolonged period.

Limitations of the Study

Because we did not perform a structural analysis of the aorta and large arteries and did not measure endothelial function and sympathetic nervous system activity, we can only speculate that our findings are a result of an effect of exercise on endothelium-dependent vasodilation in patients who are on HD. In addition, we used a pre-/postintervention design without a control group. Our rationale was that finding a suitable comparison group is exceptionally difficult in this population, considering the many differences in medications, exercise tolerance, and comorbidities. The pre-/postintervention design allowed us to use each patient as his or her own control, thereby reducing the variability that would be inherent in an unpaired design. As mentioned previously, the exercise prescription and duration were inadequate to have an impact on insulin resistance in this population.

Conclusion

Three months of exercise training improved arterial stiffness, an independent risk factor for CV mortality in patients who are on HD. The effect dissipates within 1 mo of detraining, which supports the idea that, to benefit from it, patients should exercise life-long on a regular basis. At the intensity and duration used in our study, exercise had no effect on insulin resistance. More studies are needed to clarify the effects and mechanisms of action of exercise on arterial stiffness and insulin resistance, as well as on other risk factors (*e.g.*, left ventricular hypertrophy, BP, lipid profile), CV morbidity, and mortality in patients with ESRD.

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