The Effects of Aerobic, Resistance and Combination Training on Insulin Sensitivity and secretion in Overweight Adults from STRRIDE AT/RT: A Randomized Trial

Running Head: Aerobic, Resistance, and Combination Training & Insulin Sensitivity

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Most health organizations recommend a combination of aerobic training (AT) and resistance training (RT), yet few studies have compared their acute (within 24 hours of the last exercise bout) and sustained (after 14 days of no exercise training) effects alone and in combination on glucose metabolism. The present study, (Studies Targeting Risk Reduction Interventions through Defined Exercise – Aerobic Training and/or Resistance Training (STRRIDE-AT/RT)) compared the effects of AT, RT and the combination (AT/RT) on insulin action at both acute and sustained phases. Subjects (N=196) were 18 to 70 years old (mean age = 50), overweight (mean BMI = 30), sedentary with moderate dyslipidemia and were randomized into one of three eight-month exercise groups: 1) RT: 3 d/wk, 8 exercises, 3 sets/exercise, 8-12 repetitions/set, 2) AT: equivalent to ~19.2 km/wk (12 miles/wk) at 75% peak VO2, 3) AT/RT: the combination of AT and RT; 144 subjects completed the intervention. Eighty-eight subjects completed all pre- and post-intervention testing visits. Insulin sensitivity, glucose effectiveness and disposition index were measured via a frequently sampled, intravenous glucose tolerance test (IVGTT) with subsequent Minimal Model analyses. AT/RT resulted in greater improvements in insulin sensitivity, beta cell function (disposition index) and glucose effectiveness than either AT or RT alone (all P<0.05). Approximately 52% of the improvement in insulin sensitivity by AT/RT was retained 14 days after the last exercise training bout. Neither AT or RT led to acute or chronic improvement in Si. In summary, only AT/RT (which required twice as much time as either alone) led to significant acute and sustained benefits in insulin sensitivity.
INTRODUCTION

While the benefits of being physically active are clear, the optimal exercise mode, amount and intensity for specific, acute and sustained health benefits are poorly understood. Many organizations recommend both aerobic training (AT) and resistance training (RT) for adults. However, these recommendations are based on the evaluation of each modality separately, as few studies have investigated the acute and more chronic effects of combined AT and RT regimens compared to each modality. Understanding the effects of AT and RT is of critical importance if we are to apply evidence-based approaches to exercise recommendations.

STRRIDE-AT/RT (Studies Targeting Risk Reduction Interventions through Defined Exercise – Aerobic Training and/or Resistance Training), was designed to address three major questions relating to exercise recommendations for overweight, sedentary adults. First, what are the specific benefits of resistance training (RT) in this population? Second, how do these benefits compare with those that accrue when a similar amount of time is spent in aerobic training (AT)? Third, are there additive, synergistic or possibly antagonistic effects when both AT and RT are combined (AT/RT)? Answers to these questions should improve the ability of clinicians, exercise professionals and the lay public to more accurately understand the benefits of different exercise regimens and more efficiently utilize precious exercise time. Here we summarize the effects of AT, RT and AT/RT on insulin sensitivity as measured by the frequently sampled intravenous glucose tolerance test (IVGTT). Both the acute (within 24 hours of last exercise bout) and sustained (after 14 days of detraining) effects on insulin sensitivity were determined.
No other studies, to our knowledge, have looked at the effects of AT, RT and the combination of AT plus RT on IVGTT derived insulin sensitivity and insulin secretion. In addition, no other studies have looked at these interventions on both acute (16 to 24 hours after the last training bout) and more sustained (measured after 14 days without exercise) effects on insulin sensitivity and insulin secretion. Based on the consistent findings of improved insulin sensitivity with aerobic exercise, with consistent, but less data on resistance training(13-15, 21), we hypothesize that AT-only and RT-only will both improve insulin sensitivity, and that when added together the effects will be additive – as opposed to synergistic or antagonistic. Further, based on the findings of Houmard et al., (16) which showed that insulin action declined more dramatically in the endurance athletes, with almost no change in resistance trained athletes after 14 days without exercise, we hypothesize that RT will result in a great retention of the improvement in insulin sensitivity, after 14 days without exercise, and that this effect will be evident in both the RT only and AT/RT groups.

METHODS

Subjects (Screening, Inclusion and Exclusion Criteria). Subjects recruited for the STRRIDE-AT/RT study were used in this analysis. The protocol was approved by the institutional review boards at Duke University and East Carolina University. Subjects (n=3,145) responded to local advertisements and were screened by phone. Of these, 234 met inclusion criteria and were recruited into the study. Inclusion criteria were: age 18 to 70 years, sedentary (dedicated leisure time physical activity less than two times per week), body mass index 26-35 kg/m², and mild to moderate dyslipidemia (LDL cholesterol 130-190 mg/dL; and/or HDL cholesterol ≤40...
mg/dL for men or ≤45 mg/dL for women). Subjects were nonsmokers without a history of diabetes, hypertension, or coronary artery disease. Use of statin drugs was an exclusion criteria. After informed written consent, subjects were asked to maintain their current lifestyle during a four month run-in period followed by randomization into one of three exercise training groups. The purpose of the run-in period was to discourage individuals who were not serious about the study commitment and thus reduce the dropout rate that may occur after randomization. Of the 234 recruited, 38 subjects dropped out during the run-in period, leaving 196 subjects for randomization. Of the subjects who were randomized, 73.5% (n=144) completed the study. Eighty-eight subjects of these had complete IVGTT data.

Insulin action measures. Insulin action was determined with a three-hour intravenous glucose tolerance test (4). Glucose (50%) was injected at time zero, through an intravenous catheter placed in the antecubital space at 0.3 g per kg body mass and insulin (0.025 U per kg body mass) was injected at minute 20. Twenty-nine blood samples (at minutes 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180) were obtained centrifuged, and stored at –80°C. Insulin was measured by immunoassay (Access Immunoassay System, Beckman Coulter, Fullerton, CA) and glucose with an oxidation reaction (YSI 2300, Yellow Springs, OH). Insulin sensitivity index (Si), glucose effectiveness (Sg – the ability of glucose to cause its own uptake into the cell at basal insulin levels), acute insulin response to intravenous glucose (AIRg – calculated as area under the insulin curve during the first 10 minutes; is a measure of insulin secretion) and disposition index (DI = AIRg x Si; is considered a measure of beta cell function) were calculated using Bergman’s minimal model (4). The IVGTT was performed after an overnight fast at baseline at the end of exercise training.
(16 to 24 hrs after the last exercise bout) and also 14 days after the cessation of exercise training.

**Body Composition.** At Duke, body composition was determined using the BOD POD™ air displacement plethysmography method (Life Measurement, Inc., Concord, CA) on all subjects at all time-points. At ECU, body composition was measured by dual energy X-ray absorptiometry machine (DEXA). As previously reported, measurements with BOD POD and DEXA are highly correlated (0.94) with one another(2). Furthermore, the focus of this analysis was on pre-post intervention change scores, thus, any differences between the study sites due to the techniques used to assess body composition did not affect the data interpretation.

**Computed Tomography, Waist Circumference, Cardiopulmonary Exercise Testing, and Strength Evaluations.** Body mass was measured in light clothing without shoes to the nearest 0.1 kg on a digital scale. The average of three weights taken over two weeks, on different days, was used for each time point. Height was measured once, to the nearest 0.5 cm. CT data included here have been presented previously(30). They are included in this paper again as they were used in multivariate analyses and because they are variables of interest with regard to insulin sensitivity. CT scans were performed by a radiological technologist who was blinded to the subject’s group assignment. With subjects in the supine position, a single, 10 mm axial image was taken of the abdomen at the level of the L-4 pedicle. A second, single 10 mm axial image was taken at the best visual location of the liver (determined by a scout image frontal radiograph taken prior to the liver scan). A mid-thigh scan (taken midway between the mid-acetabulum and the superior border of the patella) was used to determine the surface area for the thigh muscles and for adipose tissue areas. The CT images were analyzed using OsiriX™ imaging software, an advanced open-source PACS workstation DICOM viewer (OsiriX
Foundation; Genève, Switzerland), to determine the area of the visceral, subcutaneous, and
total abdominal adipose tissue in the obtained images. With this program, once the
parameters are set (e.g., definition of adipose tissue density range was set at -30 to -190
Hounsfield Units) the program is largely automated. Test-retest reliability correlations for
surface areas obtained are generally between $r = 0.98$ and $0.99$ as the methodology is extremely
reproducible. To obtain liver density, in the liver image, three, $3.0 \, \text{cm}^2$ circular regions of
interest (ROI’s) were manually selected, avoiding visible vessels, bile ducts, bordering surfaces
and motion artifact, and averaged to estimate liver density. One hundred and seventeen
subjects had two CT tests done prior to the beginning of the exercise interventions and the test
retest correlation for liver density values was $0.910 \, (P < 0.0001)$ with no significant difference
between test and re-test means ($P = 0.79$).

Waist circumference was measured at the minimal waist (the lowest circumference
measurement above the umbilicus and below the xiphoid. Minimal waist was used as we
previously showed that it was more highly correlated with metabolic health than umbilical
waist measures.(34)

A maximal exercise test with a 12-lead EKG and expired gas analysis were performed on
a treadmill using a TrueMax 2400 Metabolic Cart (ParvoMedics; Sandy, UT) before and after the
exercise interventions – as described previously(10).

In RT and AT/RT subjects, the total amount of weight lifted during a single resistance
training session was recorded each week, either by a supervising personal trainer at the ECU
site or electronically by the FitLinxx Strength Training Partner™ system (FitLinxx; Norwalk, CT) at
the Duke site. The total amount of weight lifted in pounds from a typical single session during
Week 5 or 6 was used as the baseline measure of overall strength and the total from a typical, single session at the end of training was used as the end of training measure of overall strength.

**Exercise Training (Protocols, Ramp period, Duration, Modes, Verification, and Adherence).** The exercise groups were as follows: 1) Resistance Training (RT) [3 days/wk, 3 sets/day, 8-12 repetitions/set, 8 exercises], 2) Aerobic Training (AT) [equivalent to roughly 19.2 km/wk (~12 miles/wk) at 75% peak VO₂], and 3) Aerobic Training plus Resistance Training (AT/RT) i.e., the full AT plus the full RT regimens.

A ramp period of eight to ten weeks, designed to gradually increase the amount of aerobic exercise over time, was prescribed to all subjects in the AT and AT/RT groups. Details about the prescribed and actual exercise training amounts, intensity, and frequency are provided in Table 1. The aerobic exercise modes included treadmill, elliptical trainers, cycle ergometers or any combination of these. As the intensity of the AT program was based on and maintained by using heart rate zones, subjects in the AT/RT group performed the AT exercise first, followed by the RT program. For aerobic exercise amount, the total number of minutes that needed to be obtained was determined by fitness level, as all subjects were prescribed a specific amount of exercise per unit body weight (i.e. 14 kcal per kilogram of body weight per week). Higher fit individuals required less time to expend the prescribed number of calories per week. Exercise frequency was not prescribed, however subjects were encouraged not to exceed 60 minutes per day. For example, a 100 kilogram person would be prescribed to expend 1400 kcal per week (100 x 14). If their maximal oxygen consumption was 4 liters per minute and they exercise at 75% of that value, they consumed 3 liters of oxygen per minute. Consuming one liter of oxygen requires approximately 5 kcal of energy expenditure(35). So
exercise at a rate that requires 3 liters of oxygen consumption per minute is equivalent to
expending 15 Kcals per min. Therefore this 100 kg person who has an exercise prescription of
1400 kcals per week would need to exercise 93.3 minutes per week (1400 kcals per week
divided by 15 kcals expended per minute = 93.3 minutes per week). This subject could choose
to do 2 sessions per week of 46.7 minutes or 3 sessions of 31.1 minutes. Subjects were
encouraged to exercise at least 3 times per week.

For subjects randomized to RT, the ramp period began with one set during Weeks 1-2,
two sets during Weeks 3-4, building up to the prescribed three sets on Week 5. RT subjects
were prescribed three sessions per week (on non-consecutive days) of three sets of 8-12
repetitions on eight Cybex weight lifting machines designed to target all major muscle groups.
Throughout the training intervention, the amount of weight lifted was increased by five pounds
each time the participant performed 12 repetitions with proper form on all three sets on two
consecutive workout sessions to insure a progressive resistance training stimulus.

All aerobic exercise sessions were verified by direct supervision and/or with a heart rate
monitor that provided recorded, downloadable data (Polar Electro, Inc; Woodbury, NY).
Aerobic compliance was equal to the number of minutes completed within the prescribed heart
rate range, divided by the number of total weekly minutes prescribed. All resistance training
sessions were verified by direct supervision and/or the FitLinxx Strength Training Partner™.

Exercise Detraining. All subjects were instructed to discontinue exercise training for 14
days after their last bout of exercise. Sixteen to 24 hours after their last training session an
IVGTT was obtained to assess the acute responses to the last bout plus the accumulated affect
of exercise training. An IVGTT was again preformed after 14 days of no exercise training to
determine the longer lasting (i.e. more sustained) effects of exercise training.

Statistical Analyses. Data were analyzed using Statview (SAS Institute, Cary, NC). Two-
tailed, paired t-tests were used to determine if the post minus pre change score within each
group was significant. A P-value of <0.05 was considered significant. Analysis of co-variance
(ANCOVA), with baseline values used as the covariate, to control for baseline differences, was
used to determine if there were significant differences between groups. When the ANCOVA
was significant, a Fisher’s post hoc analysis was performed to determine differences between
groups. A post hoc P-value <0.05 was considered significant. To explore possible mechanisms
responsible for the observed effects, multivariable modeling was performed using linear
models with backward stepwise variable selection.

RESULTS

Baseline characteristics and the exercise programs are described in Table 1. There were no
differences in age, gender, BMI or race distribution between groups. Participants in the AT
group were more adherent to the aerobic regimen as compared to the participants in the
AT/RT group (P = 0.002). No other group differences in adherence were observed.

In Table 2, baseline and change scores are presented for each group, as well as the P values
for the two-tailed t-tests that indicate which within group change scores were significant.
There was a significant increase in Si post-training in AT/RT, but not in AT or RT. The change in
Si in AT/RT was significantly greater than the change in Si in AT (P = 0.006) and in the RT group
(P = 0.001) (Figure 1). BMI decreased significantly in AT and AT/RT, and there was a tendency
towards an increase in RT. All three training programs led to significant increase in peak VO₂, although improvements in response to the aerobic training programs were significantly higher. As expected, the RT stimulus elicited significant increases in the total weight lifted per session in RT (increased by 49.5%) and AT/RT (43.5%). Fat mass decreased significantly in AT and AT/RT, with no significant change in RT. Lean body mass increased significantly only in RT. Thigh muscle adipose tissue decreased significantly in all three groups but most markedly in AT/RT. Abdominal subcutaneous adipose tissue decreased significantly in AT and AT/RT but not RT. Visceral adipose tissue decreased significantly only in AT.

Fasting insulin concentrations decreased in the AT and AT/RT groups. HOMA-IR decreased significantly only in the AT group. The acute insulin response to glucose (AIRg) decreased significantly 24 hours after training only in AT. There were no differences between groups for the change in AIRg. Disposition Index (DI), a measure of pancreatic beta cell function, increased significantly only in AT/RT. However, given that DI = AIRg x Si, and AIRg was not changed significantly in AT/RT, this increase was driven primarily by the large increase in Si.

We were very interested in determining if people with dysglycemia respond differently to the interventions? For the AT/RT group and for the RT only group fasting glucose status did not make a difference. That is, the AT/RT group had a very robust improvement in insulin sensitivity whether the subjects had normal or impaired fasting glucose. The RT only group also responded the same regardless of fasting glucose status, i.e no change in insulin sensitivity with RT intervention. However, for the AT only exercise intervention, there was a significant correlation (r = -0.42) between baseline fasting glucose and change in insulin sensitivity (P<0.05). Subjects with fasting glucose below 100 mg/dL (i.e. normal fasting glucose) experienced an improvement in insulin sensitivity (mean Si change was 1.1 with SD of 2.4, N=15). However, the subjects with impaired fasting glucose experienced a decrease in insulin...
sensitivity with AT exercise (mean Si change was -0.92 with SD of 3.0, N=12). Albeit the subjects
numbers were small, the difference in the changes in insulin sensitivity between subjects with normal
fasting glucose and impaired fasting glucose trended toward significance (P<0.08). Interestingly, the
detraining responses were similar. That is, no difference based on fasting glucose status for RT and
AT/RT groups, but a trend (P<0.061) towards a significant difference between subjects with normal
glucose and impaired fasting glucose after 14 days of no exercise.

We were very interested in this finding and, fortunately, we had nearly identical data from our
first STRRIDE study(17), so we went back and looked at those data. We had an identical exercise group
(AT only – with same intensity and same amount of exercise) with nearly identical subject population
(mild to moderate dyslipidemia – same as in the current study) and with complete IVGTT data.

However, in this study we saw no effect of glucose status on the change in insulin sensitivity (impaired
fasting glucose subjects, N=12 Si change was 0.84 with SD of 1.6; and in normal fasting glucose subjects,
N=38, Si change was 0.88 with SD of 1.9.

Detraining/Sustained effects: A little over half (52%) of the acute improvement in Si observed 24 hours after the last training bout in the AT/RT group persisted after 14 days of
detraining (see Figure 2, see also Table 3). As a result, it would appear that half of the overall
total training effect measured at 24 hours after the last exercise bout was acute and half was
sustained/chronic. However, it is important to point out that positive change in Si only trended
toward significance after 14 days of no exercise (P= 0.056; Table 3). Although with fewer
subjects (N=15 for AT/RT detraining data, compared to N=23 for 24 hour post training data)
there is decreased power to detect a significant difference. Similarly, we see that DI showed a
trend towards significant improvement after 14 days in the AT/RT group (P= 0.071; Table 3).

Interestingly, there was also a trend for change in DI for the AT only group, however, in this
case the trend was for a negative change, i.e. DI (Disposition Index, a marker of beta cell function) trended toward a decrease below beginning baseline values.

Finally, in most, but not all cases, the variations (as indicated by the standard deviations of the changes) in the change scores for detraining changes (Table 3) were somewhat larger than the variation observed for change scores from Table 2 indicating a slightly larger variation in detraining responses than training responses. This would seem to indicate that the detraining effects (i.e. the rate at which the training effects deteriorate after training cessation) vary more from individual to individual than the training effects.

Multivariate analyses and possible mechanisms: To explore possible mechanisms responsible for the observed effects, multivariable modeling was performed using linear models with backward stepwise variable selection. We included variables describing change in cardiorespiratory fitness (peak VO₂), regional adiposity (liver fat, thigh muscle adipose tissue, subcutaneous abdominal adipose tissue, visceral adipose tissue (VAT), waist circumference and body composition (lean body mass, fat mass, BMI). None of these variables explained the acute effect of AT/RT on Si, although change in VAT approached statistical significance (p=0.07). With detraining, the final regression model included VAT, fat mass and lean body mass as significant predictors of change in Si (R²=0.32, p=0.007).

Outlier Analyses – for the key variable of insulin sensitivity (Si) from the IVGTT test, we removed three subjects who had very high baseline measures, as they were greater than three standard deviations from the mean. We also removed one subject who had a change in Si with training which was > 4 SD from the mean. Removing these outliers had no appreciable effect on the overall findings or interpretation with regard to statistical significance. Leaving the
outliers in had large effects on the means and standard deviations of Si and change in Si. Therefore we removed these outliers.

In Figure 3 we show the raw glucose and insulin data obtained from the 180 minute IVGTT (in addition to the major outcome variables obtained through minimal model analyses shown in earlier tables and figures). The three graphs on the left side of Figure 3 are of the glucose values during the IVGTT for the AT, RT and AT/RT groups. The three graphs on the left side are of the insulin values during the IVGTT for these groups. Inserts for each graph show expanded views for the 19 minute through 80 minutes time periods and emphasize the larger decrease in glucose values (for the graph inserts on the left) for the post exercise training versus pre training curves, over this time period, observed in the AT/RT group compared to AT and RT only groups. The inserts on the right (insulin graphs) show virtually no pre versus post training difference in insulin responses for the AT and RT only groups compared to a noticeable reduction in the insulin curve observed after training versus before training in the AT/RT group. These data support the minimal model results which showed robust improvement in Si for the AT/RT group, compared to no significant difference in pre versus post data for either the AT or the RT only groups.

DISCUSSION

Determining how much exercise, what intensities, and what types of exercise (modes) are most beneficial for acquiring specific health benefits, realizing that not any one amount or type of exercise is likely to be best for every health benefit, is of great interest to public health (10, 17, 18, 20, 22, 31, 32). Determining the effects of these different exercise programs on
their ability to sustain health benefits when exercise is interrupted (i.e. during brief periods of
detraining) can provide important information as to durability and provide insights as to the
possible biologic mechanisms underlying training-induced improvements in health parameters
(1, 22, 31, 33). That is, both the magnitude of the health benefit of regular exercise and the
ability to sustain the health benefit are important factors in determining optimal exercise
prescriptions for specific health benefits. To our knowledge this is the first randomized trial to
directly compare the acute and sustained effects induced by comparable amounts of time spent
doing resistance training (RT), or aerobic training (AT), and the combination of the RT plus AT
programs on insulin action in overweight/obese middle- to older-aged adults.

There were three major findings from the current study. First, the combination of eight
months of resistance training plus aerobic training (which required approximately twice as
much exercise training time as either alone) resulted in significantly greater improvements in
insulin sensitivity than did either AT or RT alone (Figure 1). Second, the combination of AT and
RT also resulted in significantly larger improvements in the disposition index (a measure of beta
cell function; DI = Si x AIRg) and glucose effectiveness (a measure of how well glucose can cause
its own cellular uptake) than did either AT or RT (Figure 1). Neither AT or RT resulted in
improvements in insulin sensitivity, disposition index, or glucose effectiveness. All three
exercise programs resulted in reduced AIRg (acute insulin response to glucose), and while this
reduction was only significant in AT, there was no significant difference in change scores among
the groups. Third, in addition to the robust improvement in insulin sensitivity observed in
AT/RT 24 hours after the last training bout, approximately 52% of this improvement in insulin
sensitivity was retained up to 14 days after the last bout of exercise (Figure 2), an effect that
appears to be associated with changes in body composition. This is not surprising as we have previously shown that, fat, particularly visceral fat, is significantly correlated to variables of metabolic risk.\(^\text{29, 34}\) The acute improvements in disposition index and glucose effectiveness were not sustained over the more prolonged detraining period. Importantly, the participants in AT/RT exercised for approximately double the time of either the participants in RT or AT. Thus, while it is tempting to suggest that the synergistic effect was due to combining the two different modes of exercise, we cannot rule out the possibility that the effect was due to a greater total amount of exercise.

The finding that effects of combined AT/RT were superior to either AT or RT alone is consistent with previous reports on glucose control (HbA1c) in patients with type 2 diabetes (6, 28) and physical function in non-diabetic humans (9). This is particularly true when the AT/RT group is the additive combination of the AT and RT programs as was the case in the present study and in prior work by Sigal et al. (28) By comparison, both Church et al. (6), and Davidson et al. (9), controlled for total time such that the AT group and the AT/RT groups had approximately equal training times each week. While Church et al., did not observe their AT/RT to be significantly better than their AT group in reducing HbA1c, only AT/RT was significantly better than control. Interestingly, both the AT and the AT/RT groups were similarly effective when comparing the effects for the subgroup of diabetic humans with elevated baseline HbA1c values \(\geq 7.0\%\). In contrast, while Davidison et al., observed that AT/RT was significantly better than AT for improving measures of physical function in non-diabetic humans, improvements in insulin action determined with hyperinsulinemic-euglycemic clamps were not different between AT and AT/RT groups. Thus, in general, when the amount of exercise training
exposure time is equal, there do not appear to be large differences among AT/RT and AT.

However, when the total time for AT/RT is the linear combination of the AT and RT, i.e. twice as much time, the differences are more robust.

It was surprising that neither AT or RT improved insulin sensitivity while the combination of the two had a very robust effect. Exercise training is consistently reported to improve insulin sensitivity(13-15, 21) (reviews are cited for brevity), especially when insulin action is measured within 24 to 48 hours after the last training bout. The strong training stimuli of AT and RT are reflected in robust improvements in peak VO2 for AT, and improvements in strength and lean body mass for RT. One difference between our study and most studies that have found increased insulin sensitivity with AT and/or RT, is that most other studies measured insulin sensitivity with either an oral glucose tolerance test or the hyperinsulinemic-euglycemic clamp. It is possible that these more straightforward methods are more sensitive to exercise effects. Although the IVGTT, OGTT, and clamp are all validated techniques for assessing insulin sensitivity, methodological differences may at least partially explain discordance between our study and others. Specifically, neither the clamp or the OGTT require complex mathematical modeling. On the other hand, the raw results from an IVGTT must undergo minimal model analyses – a model that is based on a great deal of research and numerous complex assumptions. Importantly, we have previously observed and reported significant improvements in Si measured via IVGTT in response to the same AT stimulus employed in the current study. However, it should be noted that baseline Si was lower in the previous study (3.4 mU/L*min versus 4.5 in the current study), indicating that the relatively high baseline Si in the present study may explain, at least in part, why no statistically significant improvements in
Si were observed in the current study. It is also important to point out that of the three different exercise training interventions tested in STRRIDE (17), the intervention used in the present study showed the smallest improvement in of the three. 

IVGTT derived measures of insulin sensitivity are considered to be reflective of muscle or peripheral insulin sensitivity, while HOMA, a fasting insulin sensitivity measure, is thought to reflect hepatic insulin sensitivity. It is interesting, therefore, that the AT group showed improvement in HOMA and fasting insulin, but not Si (IVGTT derived insulin sensitivity measure), which would suggest that aerobic exercise training, in this population, improved hepatic, but not muscle insulin sensitivity. That both visceral fat and liver fat were also reduced in this group, adds support to the idea that hepatic insulin sensitivity was improved. Further, that the AT-only and the AT/RT groups did not have a significant reductions in HOMA and also did not experience significant reductions in visceral and/or liver fat, is consistent with this hypothesis, i.e. that visceral and liver fat changes are associated with changes in hepatic insulin sensitivity.

That said, the minimal effects of AT or RT, and the robust effects of AT/RT on insulin sensitivity in the present study were quite similar to the independent results we obtained for metabolic syndrome(3), which is, conceptually, highly related to insulin resistance(19). In our previous report we observed that combined AT/RT significantly improved both the ATP III metabolic syndrome score (a sum of five dichotomous scores from fasting glucose, blood pressure, waist circumference, triglycerides and HDL-cholesterol) and the more sensitive z-score of the metabolic syndrome measures (P<0.005 for both change scores). However, AT had no effect on the ATP III metabolic syndrome score and RT actually resulted in a borderline
significant (P=0.054) deterioration in this score. For the metabolic syndrome z-score, the RT program had no effect and the AT program trended toward a significant improvement (P=0.07). Taken together, these changes in metabolic syndrome scores are very similar to the change in insulin sensitivity and give confidence about the observed changes in Si using the IVGTT.

Another possible explanation exists. It is possible that obese subjects and/or subjects with metabolic syndrome may have a more blunted change in insulin sensitivity in response to resistance exercise training. Malin et al., (24) recently found showed that non-diabetic obese women experienced blunted improvements in post-prandial insulin sensitivity compared to lean controls after a resistance training program. In another study, Layne et al. (23) found that subjects with metabolic syndrome have blunted improvements in insulin sensitivity after resistance training. They attributed this to impaired muscle AMPK activation. The subjects in the present study had a prevalence of metabolic syndrome of approximately 45%. These factors may explain our findings of no significant effect of RT alone or AT alone on insulin sensitivity.

Whether the effects of exercise training on insulin sensitivity are almost completely a result of acute effects (lasting for 24-72 hours) or more sustained has not been investigated often. In the current study we observed that 52% of the total improvement in insulin sensitivity seen 24 hours after the last training bout in the AT/RT group was still evident 15 days after training had stopped. Previously, we reported that 36% of the total improvement in insulin sensitivity was still evident 30 days after the last training bout of an intense period of aerobic training(33). More recently, in a much larger study, we observed that with the AT exposure used in this study, that there was no significant difference between insulin sensitivity measured after 15 days detraining and baseline insulin sensitivity.(1) However, with a larger exposure (by 50%) at the same intensity, we observed that insulin sensitivity was still significantly greater
than baseline values at 15 days of detraining (approximately 70%) which was associated with a
reduction in fat mass obtained during training(1) For the present study, the final regression
model included changes in visceral adipose tissue, total body fat mass and lean body mass ($R^2 =
0.32, p = 0.007$), suggesting that changes in body composition explain 32 percent of the chronic
effect(5, 25).

Important strengths of this study include: 1) the randomized study design; 2) the
inclusion of three training programs in the same study; 3) direct verification of exercise amount,
intensity and therefore, exposure, of the AT, RT, and AT/RT interventions; 4) the inclusion of a
substantial resistance training program that reduces the likelihood that negative findings are
due to an inadequate RT stimulus; 5) a significant proportion of women and minorities in the
study population; and 6) the additive nature of the combination program, permitting the
assessment of additive or interacting effects of AT and RT. A limitation of this study is that the
participants were motivated men and women who volunteered to exercise in a semi-supervised
setting, limiting generalizability of the findings to the general population. This was an efficacy
study, not an intent-to-treat study, which has known strengths and limitations.

SUMMARY The major findings here were that a linear combination of AT and RT
robustly improved insulin sensitivity and that approximately half of the beneficial effect was
maintained over 14 days of detraining. When examining the results of the STRRIDE AT/RT trial
over many health-related variables, it is clear that AT/RT had the largest (albeit not always
significantly larger) improvements in insulin sensitivity, disposition index, glucose effectiveness,
body composition (reflecting both reductions in fat mass and increases in lean mass), waist
circumference, blood pressure, peak VO$_2$, and metabolic syndrome. As individuals in the AT/RT
group trained for approximately twice as much time each week, we cannot determine whether
greater improvements were due to qualitative synergistic effects of the two very different
exercise modes, or whether the effects were due to a greater amount of exercise, or a
combination of both. Previous studies that have shown only minimal differences between
AT/RT and AT when total training time is equal, suggest that the more robust effects observed
in the present study were likely due to the greater total training time.
Figure 1. The values are post minus pre training (means with SEM). These parameters are all derived from the IVGTT with Minimal Model analyses. Si, i.e. insulin sensitivity, (units are: mU/L/min). AIRg acute insulin response to glucose infusion (units are: mU/L/min) = area under the insulin curve during first 10 minutes of test. Sg – glucose effectiveness (units are: per minute), which is defined as the ability of glucose to cause its own uptake. DI, disposition index (no units for this term as the units for Si and AIRg cancel each other out) = AIRg X Si; and is considered a measure of beta cell function. All P-values refer to significant differences between the group indicated (AT or RT) versus the combination AT/RT based on post hoc tests for significant difference between groups. That is, AT/RT was significantly different from both AT and RT for insulin sensitivity, Sg, and disposition index.

Figure 2. Retention of the improvement in insulin sensitivity (Si) 14 days after the last exercise training bout. Of the 23 subjects in AT/RT with insulin sensitivity measured before training and 24-hour after the last training bout, only 16 of these subjects also IVGTT data at the 14 day detraining time point. To determine the percentage of the improvement in Si that was sustained after 14 days of no exercise, we used only subjects that had IVGTT data at all three time points. Just over half of the effect was sustained after 14 days. This amount trended toward significance (P = 0.092). The other two groups (AT & RT) did not have a significant improvement in Si at 24 hours, and there was no change at 14 days.

Figure 3. IVGTT raw data figures for each group for glucose values and insulin values over the 180 minutes of the IVGTT. The three graphs on the left side are of the glucose values during the IVGTT for the AT (top), RT (middle) and AT/RT (bottom) groups. The three graphs on the
left side are of the insulin values during the IVGTT for the AT (top), RT (middle) and AT/RT (bottom) groups. Inserts for each graph show expanded views for the 19 minute (just prior to the insulin infusion at 20 minutes) through 80 minutes time periods. These inserts emphasize the much larger decrease in glucose values (for the graph inserts on the left) for the post exercise training versus pre training curves, over this time period, observed in the AT/RT group compared to AT and RT only groups. The inserts on the right (insulin graphs) show virtually no difference in insulin responses for the AT and RT only groups compared to a noticeable reduction in the insulin curve observed after training versus before training in the AT/RT group.


Insulin Sensitivity Change

AIRg Change

Disposition Index Change

Sg Change

P < 0.0001

P < 0.0003

P < 0.0007

P < 0.0005

RT AT AT/RT

RT AT AT/RT

RT AT AT/RT

RT AT AT/RT
Insulin Sensitivity Change

AT/RT Group

24-hrs Post - Pre Training

100%
P < 0.02
N = 16

14 days Post - Pre Training

51.9%
P = 0.092
N = 16
## Table 1. Baseline Demographics and Exercise Prescription

<table>
<thead>
<tr>
<th>Variables</th>
<th>Resistance Training (n = 38)</th>
<th>Aerobic Training (n = 27)</th>
<th>Aerobic + Resistance (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>51.1 (11)</td>
<td>51.4 (10)</td>
<td>46.9 (11)</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
<td>30.0 (3.0)</td>
<td>30.5 (3.0)</td>
<td>30.6 (3.6)</td>
</tr>
<tr>
<td>Race</td>
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</tr>
<tr>
<td>Caucasian</td>
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</tr>
<tr>
<td>Other</td>
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<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Female</td>
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<td>14</td>
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</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>13</td>
<td>10</td>
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<tr>
<td>RESISTANCE Exercise</td>
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</tr>
<tr>
<td>Intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rx Amount (sets/wk)</td>
<td>72</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Rx Time (min/wk)</td>
<td>180</td>
<td>180</td>
<td></td>
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<tr>
<td>Adherence (%)</td>
<td>83.2 (14)</td>
<td>79.2 (16)</td>
<td></td>
</tr>
<tr>
<td>Actual Frequency (sessions/wk)</td>
<td>2.5 (0.4)</td>
<td>2.4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Actual Amount (sets/wk)b</td>
<td>59.9 (10)</td>
<td>56.7 (11)</td>
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<tr>
<td>AEROBIC Exercise</td>
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<td></td>
</tr>
<tr>
<td>Intensity (% peak VO₂)</td>
<td>65-80</td>
<td>65-80</td>
<td></td>
</tr>
<tr>
<td>Rx Amount (kcal·kg⁻¹·wk⁻¹)c</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Rx Time (min/wk)</td>
<td>132 (24)</td>
<td>134 (27)</td>
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<tr>
<td>Adherence (%)*</td>
<td>91.9 (9)</td>
<td>79.3 (18)</td>
<td></td>
</tr>
<tr>
<td>Actual Frequency (sessions/wk)</td>
<td>3.2 (0.5)</td>
<td>2.9 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Actual Time (min/wk)d</td>
<td>121 (20)</td>
<td>106 (32)</td>
<td></td>
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</tbody>
</table>

Values are means (SD). aRx Amount (72 sets/wk) = 3 days/wk, 3 sets of 8-12 reps, on 8 different machines. bActual Amount (sets/wk) = Rx Amount X Adherence. cRx Amount (14 kcal·kg⁻¹·week⁻¹) is approximately calorically equivalent to 12 miles of jogging per week. dActual Time (min/wk) = Rx Time X Adherence.* Pvalue=0.002, otherwise there was no significant difference between groups.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Resistance Training (n = 38)</th>
<th>Aerobic Training (n = 27)</th>
<th>Aerobic + Resistance (n = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVGTT parameters</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Si (mU / L / min)</td>
<td>4.08 (1.9)</td>
<td>-0.21 (2.0)</td>
<td>0.50</td>
<td>4.46 (3.1)</td>
</tr>
<tr>
<td>AIRg (mU / L / min)</td>
<td>495 (322)</td>
<td>-35 (224)</td>
<td>0.35</td>
<td>471 (352)</td>
</tr>
<tr>
<td>DI</td>
<td>1794 (1204)</td>
<td>-114 (1107)</td>
<td>0.53</td>
<td>1813 (1341)</td>
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<tr>
<td>Sg (per minute)</td>
<td>0.0243 (0.011)</td>
<td>-0.001 (0.016)</td>
<td>0.82</td>
<td>0.0231 (0.014)</td>
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<tr>
<td>HOMA</td>
<td>2.15 (1.12)</td>
<td>0.05 (1.3)</td>
<td>0.83</td>
<td>2.43 (1.72)</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>99.3 (10.6)</td>
<td>-0.3 (9.0)</td>
<td>0.84</td>
<td>96.8 (13.5)</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>8.63 (4.0)</td>
<td>-0.22 (5.0)</td>
<td>0.79</td>
<td>9.66 (6.0)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>88.8 (16.0)</td>
<td>0.81 (2.4)</td>
<td>0.049</td>
<td>88.8 (11.5)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>30.0 (3.0)</td>
<td>0.24 (0.8)</td>
<td>0.08</td>
<td>30.5 (3.0)</td>
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<tr>
<td>Waist Circumference (cm)</td>
<td>96.5 (9.6)</td>
<td>0.15 (1.7)</td>
<td>0.59</td>
<td>97.1 (11.0)</td>
</tr>
<tr>
<td>Peak VO2 (mL/kg/min)</td>
<td>27.3 (6.1)</td>
<td>1.40 (2.9)</td>
<td>0.005</td>
<td>27.1 (5.6)</td>
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<tr>
<td>Strength (kg/session)</td>
<td>20130 (8031)</td>
<td>9956 (5798)</td>
<td>&lt;0.0001</td>
<td>NA</td>
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<tr>
<td>Fat Mass (Kg)</td>
<td>25.1 (6.9)</td>
<td>-0.22 (2.0)</td>
<td>0.51</td>
<td>26.7 (5.5)</td>
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<tr>
<td>Lean Body Mass (Kg)</td>
<td>63.6 (14.6)</td>
<td>1.04 (1.8)</td>
<td>0.001</td>
<td>61.0 (10.2)</td>
</tr>
<tr>
<td>Thigh muscle AT (cm²)</td>
<td>876 (398)</td>
<td>-43 (111)</td>
<td>0.04</td>
<td>780 (337)</td>
</tr>
<tr>
<td>Abdominal SAT (cm²)</td>
<td>302 (101)</td>
<td>-6.9 (32)</td>
<td>0.23</td>
<td>330 (100)</td>
</tr>
<tr>
<td>Visceral AT (cm²)</td>
<td>169 (80)</td>
<td>0.6 (21)</td>
<td>0.87</td>
<td>187 (114)</td>
</tr>
<tr>
<td>Liver Fat (HU)</td>
<td>58.3 (8.3)</td>
<td>0.70 (5.1)</td>
<td>0.46</td>
<td>57.4 (9.8)</td>
</tr>
</tbody>
</table>

Values are means (SD). There were no significant baseline differences between groups. IVGTT (intravenous glucose tolerance tests with Minimal Model analyses): Si - is insulin sensitivity index from IVGTT. AIRg = Acute Insulin Response to infused glucose (Area Under the curve during 1st 10 minutes). DI = Disposition Index, a measure of pancreatic beta cell function = Si x AIRg. These are no units for this measure. AT - adipose tissue. Sg - Glucose effectiveness - ability of glucose to cause its own uptake into cells. SAT - subcutaneous adipose tissue, Liver fat is estimated from liver density with Hounsfield Units (HU). NOTE: ONLY the IVGTT variables presented here are new and have not been published previously and they are the focus of this paper. The additional data provided are helpful for interpreting the IVGTT data within the context of the other variables presented.
Table 3. Baseline frequently sampled intravenous glucose tolerance test (IVGTT*) values plus 14-day detraining changes scores with significance of detraining change scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Resistance Training (n = 27)</th>
<th>Aerobic Training (n = 21)</th>
<th>Aerobic + Resistance (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>P value</td>
</tr>
<tr>
<td>Si (mU/L/min)</td>
<td>4.30 (1.8)</td>
<td>-0.55 (2.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>AIRg (mU/L/min)</td>
<td>525 (324)</td>
<td>-17 (288)</td>
<td>0.77</td>
</tr>
<tr>
<td>DI</td>
<td>2114 (1237)</td>
<td>-318 (1428)</td>
<td>0.26</td>
</tr>
<tr>
<td>Sg (per minute)</td>
<td>0.024 (0.011)</td>
<td>0.002 (0.015)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Values are means (SD). There were no significant baseline differences between groups. Frequently sampled (29 blood samples over 180 minutes) IVGTT (intravenous glucose tolerance tests with Minimal Model analyses): Si - is insulin sensitivity index from IVGTT. AIRg = Acute Insulin Response to infused glucose (Area Under the curve during 1st 10 minutes). DI = Disposition Index, a measure of pancreatic beta cell function = Si x AIRg. Sg - Glucose Effectiveness - ability of glucose to cause its own uptake into cells. NOTE: the values per group in this table include only subjects who have both baseline and detraining data and therefore are a different/lower number than those from Table 2, who have baseline and end of exercise data only.