Cardiovascular Effects of One year of Alagebrium and Endurance Exercise Training in Healthy Older Individuals

Fujimoto et al: Alagebrium and Exercise Training in Seniors

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Abstract

Background—Lifelong exercise training maintains a youthful compliance of the left ventricle (LV), while a year of exercise training started later in life fails to reverse LV stiffening, possibly because of accumulation of irreversible advanced glycation end-products (AGE). Alagebrium breaks AGE crosslinks and improves LV stiffness in aged animals. However, it is unclear whether a strategy of exercise combined with alagebrium would improve LV stiffness in sedentary older humans.

Methods and Results—62 healthy subjects were randomized into 4 groups: Sedentary+placebo; Sedentary+Alagebrium (200mg/day); Exercise+placebo; and Exercise+Alagebrium. Subjects underwent right heart catheterization to define LV pressure-volume curves; secondary functional outcomes included cardiopulmonary exercise testing and arterial compliance. Fifty seven/62 subjects (67±6 yrs; 37f/20m) completed one year of intervention followed by repeat measurements. Pulmonary capillary wedge pressure and LV end-diastolic volume were measured at baseline, during decreased and increased cardiac filling. LV stiffness was assessed by the slope of LV pressure-volume curve. After intervention, LV mass and end-diastolic volume increased and exercise capacity improved (by ~8%) only in the exercise groups. Neither LV mass nor exercise capacity was affected by Alagebrium. Exercise training had little impact on LV stiffness (Training×Time effect p=0.46), while Alagebrium showed a modest improvement in LV stiffness compared to placebo (Medication×Time effect p=0.04).

Conclusions—Alagebrium had no effect on hemodynamics, LV geometry, or exercise capacity in healthy, previously sedentary seniors. However it did show a modestly favorable effect on age-associated LV stiffening.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01014572.

Key Words: alagebrium, exercise training, diastolic function, aging, cardiac function, hemodynamics
Aging is associated with stiffening of the cardiovascular system\(^1\). For example, in healthy sedentary humans, aging leads to left ventricular (LV) stiffening and atrophy, which may contribute to the substrate for syndromes such as heart failure with preserved ejection fraction (HFpEF)\(^2,3\). Life-long intensive endurance exercise training prevents these age-associated changes in LV morphology and stiffness\(^4\). However, these benefits were not observed when exercise training was started later in life\(^5\), suggesting the need for an adjunctive therapy to improve LV stiffness in previously sedentary older individuals.

Advanced glycation end-products (AGEs) are stable non-enzymatic crosslinks between glucose and amino groups\(^6\). AGEs accumulate slowly on long-lived proteins such as collagen and elastin in the arterial wall and ventricles, contributing to arterial and ventricular stiffening with sedentary aging and diabetes\(^7-9\). AGEs may also increase oxidative stress and inflammation, leading to endothelial dysfunction and modification of the extracellular matrix\(^10,11\).

A thiazolium derivative, alagebrium, breaks AGE crosslinks and prevents accumulation of collagen and AGEs in the LV\(^12\), resulting in improved LV stiffness and LV-arterial coupling in animals\(^9,13\). In humans, less dramatic effects of alagebrium on LV function have been reported. For example, relatively short duration alagebrium use had little effect on LV size and estimated LV filling pressure in HFpEF\(^14\), as well as on Doppler derived LV early diastolic function in heart failure with reduced ejection fraction\(^15\). These findings suggest that short term use of alagebrium alone might not be sufficient to alter LV diastolic function in hearts with decades of accumulation of AGEs. However, there has been no study which invasively evaluated the effect of alagebrium on LV stiffness in healthy aged individuals. Moreover, it is unclear whether a concurrent pharmacological therapy is required to observe an exercise effect in
LV stiffness when significant AGE accumulation and AGE cross-links are likely to have occurred.

Thus, we hypothesized that a combination of alagebrium and exercise training for one year would be the optimal strategy to reverse age-associated LV stiffening and atrophy compared to alagebrium or exercise alone in healthy older individuals. To investigate this hypothesis, we performed comprehensive and detailed measurements of hemodynamics and LV structure and function in healthy older individuals before and after one year of alagebrium combined with exercise training.

Methods

Subject population and study design
This study was a prospective, controlled, randomized (for all subjects), double-blind placebo (Alagebrium only) study over one year evaluating the efficacy of the combination of alagebrium or placebo (200 mg daily) and aerobic exercise training or contact control in healthy older individuals (≥ 60 years of age). Sixty two healthy sedentary adults (40 female, 22 male; 67.1±6 years) were recruited from the Dallas Heart Study[^16], the Cooper Center Longitudinal Study[^17] and a random sample of all employees of Texas Health Resources[^2]. Subjects were randomly assigned to 4 groups: a) Sedentary+placebo (Controls); b) Sedentary+Alagebrium (Alagebrium alone); c) a year of aerobic exercise at modest intensity + placebo (Exercise alone); and d) exercise training and alagebrium (Exercise&Alagebrium). Subjects who were randomized into the sedentary group underwent non-aerobic yoga or balance training as contact control for the year period. Subjects were excluded if they were exercising for >30 minutes 3 times/wk. All subjects were rigorously screened for comorbidities, including obesity, lung disease, diabetes
mellitus, hypertension (24-hour blood pressure (BP) >140/90 mmHg or on medical treatment for hypertension), coronary artery disease or structural heart disease at baseline and post-exercise transthoracic echocardiograms. All subjects signed an informed consent form approved by the institutional review boards of the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas. All procedures conformed to the standards set by the Declaration of Helsinki.

**Exercise testing**

All the subjects performed maximal exercise testing to measure maximal oxygen uptake (VO$_2$max) as previously reported. A modified Astrand-Saltin incremental treadmill protocol was used. Measures of ventilatory gas exchange were made by use of the Douglas bag technique. Gas fractions were analyzed by mass spectrometry (Marquette MGA 1100) and ventilatory volumes were measured with a Tissot spirometer. The heart rate at the ventilatory threshold was defined as the heart rate at maximal steady state (MSS), which was generally equivalent to ~80-85 % of the maximal heart rate. Exercise testing was repeated at the end of the 6th month and after one year of the intervention.

**Exercise training program**

Subjects who were randomized into the exercise group participated in a 1-year training program with the goal of increasing duration and intensity. Initially, the subjects walked or jogged, 3 times/wk for 25 min/session, at the “base pace” which targets heart rates equivalent to ~70-80 % of maximal heart rate. From the 3rd month, “base pace” was gradually prolonged to 35 min/session. At the 4th month, a 30 min/session of higher intensity MSS, was added monthly and
the frequency of MSS was increased to twice/month from the 5th month. From the 6th to 12th month, subjects exercised 4 sessions/wk (3 “base pace” for 35-40 min and 1 MSS for 40 min). The sedentary group underwent yoga or balance training 3-4 times/wk in order to control for the increased contact associated with monitoring the exercise training sessions18.

**Cardiac magnetic resonance imaging**

Cardiac MRI images were obtained using a 1.5-tesla Philips NT scanner19. LV mass and volumes were measured using QMass software (Medis, The Netherlands) as previously reported4. LV mass was computed as the difference between epicardial and endocardial areas multiplied by the density of heart muscle, 1.05 g/ml20. Papillary muscle mass was regarded as a fraction of LV mass.

**Echocardiography**

LV images were obtained by three-dimensional echocardiography (iE33; Philips Medical System) at all loading conditions during the invasive study. LV end-diastolic volume (EDV) was analyzed offline with Qlab software (3DQA; Philips). Consistent with a previous report from our laboratory21, LVEDV resulted in a good correlation with MRI values in this study, with a typical error expressed as a coefficient of variation of 10% (95% confidence interval 8-12).

**Experimental protocol**

Right heart catheterizations were performed before and after exercise training. A 6Fr Swan-Ganz catheter was placed to measure pulmonary capillary wedge (PCWP) and right atrial pressures during end expiration. After the baseline measurements, lower-body negative pressure
(LBNP) was used to decrease cardiac filling\textsuperscript{4,5,22}. Measurements including heart rate, PCWP, BP, LVEDV, and cardiac output (and therefore stroke volume) by acetylene rebreathing\textsuperscript{23} were performed after 5 minutes each of -15 and -30 mmHg LBNP. The LBNP was then released. After repeat measurements confirmed a return to a steady state, cardiac filling was increased by rapid infusion (~200 ml/min) of isotonic saline. Measurements were repeated after 10-15 and 20-30 ml/kg of saline infusion. Total arterial compliance was determined by the ratio of stroke volume and pulse pressure to evaluate central aortic function\textsuperscript{24}. Effective arterial elastance was defined as brachial systolic BP×0.9 divided by stroke volume\textsuperscript{25,26}.

**Assessment of cardiac catheterization data**

To evaluate LV stiffness, LV pressure-volume curves were constructed by relating LVEDV and PCWP\textsuperscript{4,5,21}. To characterize LV pressure-volume curves, we modeled the data obtained at baseline and during cardiac unloading and loading according to an exponential equation\textsuperscript{27}:

\[ P = P_\infty (\exp(a(V - V_0)) - 1) \]

where \( P \) is PCWP, \( P_\infty \) is pressure asymptote of the curve, \( V \) is LVEDV and \( V_0 \) is the equilibrium volume at which \( P \) is assumed to be 0 mmHg. For the purposes of this study, we characterized and explicitly define four, different but related mechanical properties of the heart during diastole: 1) LV chamber stiffness, from here on called “LV stiffness” was assessed from the LV stiffness constant “a” that describes the shape of the exponential pressure-volume curve, and which comprises the functional stiffness of the entire LV chamber within the range of pre-load studied; 2) as LV volume and pressure are influenced by external constraints\textsuperscript{28}, LV transmural filling pressure (TMP) was calculated as PCWP - right atrial pressure\textsuperscript{29} and used to construct LV TMP-volume curves to evaluate “myocardial stiffness”\textsuperscript{4,5,21}; 3) “Operating stiffness,” reflecting the functional stiffness of the LV chamber at the baseline, supine, LVEDV
was assessed by the changes in PCWP relative to those in LVEDV during cardiac unloading and loading\(^3\); 4) “LV distensibility” was defined as the absolute value of LVEDV for any given distending pressure (PCWP) independent of LV stiffness\(^3\), independent of the overall shape of the p/v curve.

The PCWP and stroke volume were used to construct Starling (stroke volume index/PCWP) curves. LV stroke work was calculated as (mean BP-PCWP)\(\times\)stroke volume. LVEDV/stroke work relationships were constructed, and the slopes of the relationship were used to assess LV systolic function\(^30\).

**Assessment of overall cardiovascular function**

The primary outcome in the present study was a change in LV stiffness assessed by the LV stiffness constant derived from the pressure-volume curves, which reflects LV static diastolic function. Secondary outcomes included: a) functional responses during exercise as assessed by VO\(_2\)\text{max}; b) LV morphology by cardiac MRI to document the cardiac adaptation to the exercise training; c) global LV performance assessed from Starling curves and preload-recruitable stroke work; d) myocardial stiffness assessed from LV TMP-volume curves; e) operating stiffness; f) LV distensibility; and g) global arterial function and ventricular-arterial coupling.

**Sample size calculation**

Sample size was estimated (\(\alpha=0.05, \beta<0.20\)) based on previous data in aged animals\(^9\), suggesting that Alagebrum may improve LV stiffness by as much as 24 units, with a standard deviation of 13. Thus, assuming the effect was equivalently potent in humans in an unpaired comparison, this effect could be detected with 13 subjects per group. Extrapolating this
difference to humans, we expected the same effect could be detected with 13 subjects per group. With an expected drop-out of 2 subjects in each group over one year, we planned to enroll 15 subjects per group.

**Statistical analysis**

Measurements of LV volume by cardiac MRI and echocardiography, and VO$_2$max were performed by investigators blinded to the group assignment (Alagebrium or placebo). After all the measurements and data analyses were completed, drug codes were broken and made available for statistical analysis. Statistical analyses were performed using SAS version 9.2 (Cary, NC). Continuous data were expressed as mean±SD except for graphics, in which SEM was used. Baseline data in 4 groups before intervention were compared by using a one-way ANOVA with post hoc analysis or nonparametric Kruskal-Wallis test depending on the outcome of tests for normality. A Linear Mixed Model was used as the primary statistical analysis tool. Based on our study design, the main effects of Alagebrium (Medication×Time) or exercise training (Training×Time) over one year were first assessed, followed by an interaction effect of Alagebrium and training (Medication×Training×Time) as the primary analysis. As a secondary analysis, differences in least square means were used for pre-post multiple comparisons where either the main time effect of Alagebrium or training, or an interaction containing time achieved a P value <0.05. For pressure-volume curves, a multivariate regression analysis was conducted on the repeated measures data, modeling pressure by use of the covariates volume and subject group. A two-way repeated measures ANOVA was used to evaluate the effects of intervention on variables at multiple loading conditions. A p value <0.05 was considered significant.
Results

Subject characteristics

As shown in Figure 1, 58 subjects out of 62 (94%) completed a year of intervention. One subject in the Exercise alone group had no catheterization after intervention for technical reasons. Thus, hemodynamic data were analyzed in the remaining 57 subjects. There were no differences in clinical variables including age, gender, heart rate, supine systolic BP, or VO$_2$max among the 4 groups before intervention, Table 1. Resting heart rate tended to decrease in the exercise groups after 1 year of intervention (Training×Time p=0.06). Body weight was unaffected by the intervention in both exercise and non-exercise groups (Training × Time p=0.34, and Training × Medication × Time p= 0.18). The 1 year of intervention had little impact on systolic BP, pulse pressure, cardiac index or HbA1c, Table 2.

Tolerability and Safety

Two subjects on alagebrium had gastrointestinal symptoms and dropped out at the 3rd and 6th months. No other adverse events were observed in the alagebrium groups.

Effects of exercise training and alagebrium on exercise capacity

By the end of a year of training, subjects in the two exercise groups achieved a similar duration of training (∼150 min/wk, p=0.91). As shown in Table 2, exercise training increased VO$_2$max (Training×Time p<0.001) by 8-9 % (Exercise alone: 23.0±4.7 vs. 24.8±5.7 ml/kg/min, p<0.001; Exercise&Alagebrium: 24.1±5.0 vs. 26.3±6.0 ml/kg/min; p<0.001). Conversely, no change in VO$_2$max was observed in Controls (p=0.46) or Alagebrium alone (p=0.19). Compliance for
Alagebrium was > 90% (pill counts), and all the subjects participated in > 85% of training sessions.

**Cardiac size and vascular function**

As shown in Table 3, exercise training increased LV mass index (Training×Time p=0.02) and LVEDV index (Training×Time p=0.04) with no changes in mass-volume ratio. Alagebrium did not affect LVEDV or mass assessed by cardiac MRI (Medication×Time p≥0.13). Neither total arterial compliance nor effective arterial elastance was improved by alagebrium or exercise training after one year of intervention.

**Catheterization data**

As shown in Figure 2A, the Starling curves were superimposable in all groups after the intervention. Stroke volume (p≥0.42) and PCWP (p≥0.09) were unaffected across all loading conditions in all 4 groups. The slopes of preload-recruitable stroke work relations after intervention were similar to those before intervention, suggesting unaltered LV systolic function in all 4 groups, Figure 3. There were no time effects of alagebrium and exercise training, or an interaction effect of alagebrium, training and time for measures of LV systolic function.

**LV pressure-volume curves**

The group mean LV pressure-volume curve in Exercise &Alagebrium was modestly flattened suggesting improved LV stiffness after the intervention, Figure 4. In Alagebrium alone, LVEDV was unaffected at baseline and during saline infusion, but decreased slightly during -30 mmHg LBNP. No improvement in LV stiffness was observed in Controls or Exercise alone; however,
the pressure-volume curve in Exercise alone shifted rightward towards increased LV distensibility.

An improvement in LV stiffness by alagebrium was observed after one year of intervention (Medication×Time \( p=0.04 \)). After adjustment for gender, the effect of alagebrium on LV stiffness was still observed (Medication×Time \( p=0.02 \)). Conversely, exercise training had no favorable effect on LV stiffness (Training×Time \( p=0.46 \), Medication×Training×Time \( p=0.86 \)), Table 3.

Given the significant main effect of Alagebrium, further analysis showed that this effect was most prominent in the Exercise&Alagebrium group, which demonstrated a trend towards an improvement in LV stiffness (LV stiffness constant: 0.127±0.071 vs. 0.102±0.031, \( p=0.07 \)). Conversely, Controls (placebo + yoga) tended to increase LV stiffness after one year of intervention (0.114±0.059 vs. 0.128±0.055, \( p=0.12 \)). No significant improvement in LV stiffness was observed in Alagebrium alone (\( p=0.21 \)) or Exercise alone (\( p=0.94 \)). Operating stiffness during cardiac loading tended to decrease only in Exercise&Alagebrium (2.4±1.4 vs. 1.7± 0.4 mmHg·ml\(^{-1}\)·m\(^2\), \( p=0.06 \)), Table 3.

As shown in Figure 5, no changes in the slopes of LV TMP-volume curves were observed in any of the 4 groups after intervention. Myocardial stiffness was not improved in any of the 4 groups (Medication×Time \( p=0.68 \), Training×Time \( p=0.08 \), Medication×Training×Time \( p=50 \), Table 3.

**Discussion**

We report for the first time in healthy seniors that one year of alagebrium had no effect on LV hemodynamics and geometry, or exercise capacity. However, alagebrium produced a modest
improvement of LV stiffness, assessed directly by the LV stiffness constant of invasively measured LV pressure-volume curves compared to placebo which was most prominent when combined with exercise training.

*Effects of a year of Alagebrium and exercise training on LV compliance*

Healthy aging is characterized by a gradual increase in cardiovascular stiffness, which may be caused by collagen accumulation and/or AGE cross-links in the interstitial space of the myocardium9. Consistent with our previous report in mostly men5, trained with longer duration and higher intensity exercise sessions, we observed that one year of exercise did not improve LV stiffness in our older subjects. These results confirm that exercise training started later in life is unlikely to exert favorable effects on LV stiffness in both men and women.

In animal models, alagebrium at the doses used in this study has been shown to decrease AGE deposition12, lower LV end-diastolic pressure, and reverse age-associated LV stiffening 9. In aged rats, a combination of alagebrium and exercise training had a greater impact on LV stiffness than alagebrium or exercise training alone and essentially reversed many cardiovascular effects of sedentary aging31. In the present study, alagebrium exerted only a modest effect on LV stiffness, mainly due to the improvement of operating stiffness during cardiac loading in the Exercise&Alagebrium group. As we did not measure AGE deposition in the interstitial space of the LV, we cannot be certain whether alagebrium broke down established AGE cross-links.

In the present study, the Exercise&Alagebrium group demonstrated a trend towards improved LV stiffness by ~20% after one year of intervention. To put these data into a physiologically relevant context, we recently reported in healthy sedentary humans that LV stiffening occurs during the transition between youth and early middle-age (42±4 yrs), and
becomes manifest during late middle-age (57±4 yrs)\(^2\). In these healthy sedentary subjects, the LV stiffness constant obtained using exactly the same techniques as in the present study was greater in late middle-age than that in early middle-age by ~ 20 % although this difference was not statistically significant\(^2\). If age-associated LV stiffening develops continuously during the aging process, the one year of intervention with alagebrium and exercise training might have reversed the age-associated LV stiffening by the equivalent of ~10-15 years.

Although a small favorable effect of Alagebrium on age-associated LV stiffening was observed, myocardial stiffness-assessed from LV TMP-volume curves was not improved. Consequently we speculate that alagebrium may have a more favorable effect on the pericardium than the myocardium in healthy older humans; this hypothesis is supported by the observation that operating stiffness was most prominently reduced during cardiac loading (when pericardial constraint is most prominent) in the Exercise&Alagebrium group.

In the present study, the small increase in LV distensibility (increase in volume for a given pressure without a change in LV stiffness) seen in Exercise alone did not seem to be present in Exercise&Alagebrium. We speculate that alagebrium may have had a modifying effect on the physiological eccentric remodeling induced by this dose of exercise training.

*Effects of a year of Alagebrium and exercise training on hemodynamics and LV size*

A previous study reported in older hypertensive patients with systolic BP of 159±12 mmHg that 2 months of alagebrium (210 mg once daily) decreased pulse pressure and systolic BP, resulting in an improved arterial compliance\(^3\). In older hypertensive patients with lower systolic BP (146±5 mmHg), the same duration of alagebrium at a higher dose (210 mg twice daily) had no effects on systolic BP or pulse pressure\(^3\). Thus, the magnitude of the reduction in systolic BP
seems to be greater in patients with a higher baseline BP than those with a lower baseline BP\textsuperscript{34}. In the present study, we observed no effect of alagebrium on supine systolic BP, pulse pressure or arterial compliance. In contrast to previous studies in hypertensives, we carefully enrolled subjects with no cardiovascular diseases including hypertension. These findings suggest that AGE accumulation might be smaller in the hearts of our healthy older subjects compared to previously examined hypertensive patients.

There has been little information about the effects of alagebrium on LV geometry in humans. In a small, open label pilot study in HFpEF and concentric LV hypertrophy, Little et al. reported that alagebrium for 4 months had no impact on the primary (exercise capacity) or the secondary (aortic distensibility) study outcomes. However, LV mass decreased and LV early diastolic function assessed by Doppler echocardiography improved with no change in LV volumes\textsuperscript{14}. They concluded that alagebrium might induce regression of LV hypertrophy and lower estimated LV end-diastolic pressure. Conversely, we did not observe a reduction of directly measured PCWP in either of our Alagebrium groups. Moreover, neither LV mass nor LVEDV was affected by alagebrium alone or a combination of alagebrium with exercise training.

\textit{Effects of a year of Alagebrium and exercise training on exercise performance}

We observed significant and similar increases in VO\textsubscript{2}max in the two exercise groups, suggesting that alagebrium does not have a unique effect on VO\textsubscript{2}max. The increases in VO\textsubscript{2}max after training in the present study were significantly smaller than that observed previously in another study of older individuals after one year of exercise training (19\%, 22.8±3.4 vs. 27.2±4.3 ml/kg/min)\textsuperscript{5}. In addition, in contrast to the previous study\textsuperscript{5}, neither total arterial compliance nor arterial elastance improved after training, resulting in no change in arterial function or stroke
volume at least in the resting supine position during catheterization. In the present study, to maximize compliance with the training program, we did not prescribe interval training, which is reported to significantly increase VO_{2max}^{35}; we also did not include any long duration of activities >40 minutes. Therefore, the average duration of exercise training was shorter by ~50 min/wk in the present study. We speculate that the discrepancy of the results between these two studies may be related to the lack of interval training and/or a lack of longer training sessions in this study.

**Study limitations**

First, our study might be underpowered by the small number of subjects in each group. As mentioned in the methods section, sample size was estimated based on previous data in aged animals^{9}. We planned to enroll 15 subjects per group with an expected drop-out of 2 subjects in each group over one year and had excellent compliance for Alagebrium and exercise training. However, the change in LV stiffness with alagebrium was smaller in healthy humans than reported previously in animal models. Given the small number of the subjects and large variability observed, we were powered to detect a true minimal difference of ±0.045 in LV stiffness constant with a probability of type II error at less than 20% in Exercise&Alagebrium. The difference of LV stiffness observed in Exercise&Alagebrium was 0.0249 (n=14; standard deviation, 0.0555; 95% CI, -0.0071 to 0.0570; power, 0.32) in the present study. These results allow us to exclude with a high degree of confidence, a large, clinically meaningful effect of Alagebrium on LV stiffness in otherwise healthy elderly men and women. Second, LV pressure-volume curves were evaluated by use of mean PCWP as a surrogate for LV end-diastolic pressure. We performed a rigorous screening for cardiovascular disease and excluded
subjects who had valvular abnormalities such as mitral regurgitation or pulmonary disease which might alter the relationship between PCWP and LV end-diastolic pressure. Third, no myocardial biopsy was performed to measure AGEs or AGE-induced collagen cross-linking because of possible risks related to the procedure; therefore we cannot be certain that alagebrium had the desired effect in our population. However, the basic science underpinning alagebrium is robust, and we used doses that have been well tolerated and documented to be effective in animal and human studies.

Conclusions
Alagebrium had no effect on LV hemodynamics and geometry, or exercise capacity, but produced a modest favorable effect on LV stiffness particularly when combined with exercise training in healthy, previously sedentary seniors.

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Disclosures
None.
References


Table 1. Baseline subject characteristics

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<th>Alagebrium alone</th>
<th>Exercise alone</th>
<th>Alagebrium + Exercise</th>
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<td>14 (64)</td>
<td>14 (71)</td>
<td>14 (57)</td>
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<tr>
<td>Age (age range), yrs</td>
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<td>65 (61-72)</td>
<td>65 (62-80)</td>
<td>67 (60-80)</td>
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<td>Height, cm</td>
<td>166 (154-184)</td>
<td>167 (157-184)</td>
<td>165 (157-182)</td>
<td>168 (156-188)</td>
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<td>Body weight, kg</td>
<td>67 ± 13</td>
<td>74 ± 10</td>
<td>73 ± 11</td>
<td>73 ± 11</td>
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<tr>
<td>Body surface area, m²</td>
<td>1.76 ± 0.21</td>
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<td>1.84 ± 0.18</td>
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<td>Heart rate, beat/min</td>
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<td>63 ± 7</td>
<td>65 ± 9</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>118 ± 11</td>
<td>114 ± 11</td>
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<td>VO₂max, ml·kg⁻¹·min⁻¹</td>
<td>21.5 ± 4.5</td>
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<td>23.0 ± 4.7</td>
<td>24.1 ± 5.0</td>
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Values are mean ± SD. VO₂max indicates maximal oxygen uptake during a maximal exercise test. *Non-parametric analyses were employed and median values were shown.
Table 2. Resting hemodynamics

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<td><strong>Pulse pressure, mmHg</strong></td>
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<td>pre</td>
<td>51 ± 12</td>
<td>44 ± 9</td>
<td>48 ± 8</td>
<td>46 ± 9</td>
<td>0.73</td>
<td>0.23</td>
<td>0.72</td>
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<td>post</td>
<td>51 ± 13</td>
<td>47 ± 16</td>
<td>46 ± 10</td>
<td>48 ± 15</td>
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<td><strong>Cardiac index (reb), L·m⁻²</strong></td>
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<td>pre</td>
<td>2.72 ± 0.42</td>
<td>2.56 ± 0.24</td>
<td>2.77 ± 0.52</td>
<td>2.68 ± 0.46</td>
<td>0.41</td>
<td>0.68</td>
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<td>post</td>
<td>2.72 ± 0.47</td>
<td>2.58 ± 0.21</td>
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<td>2.65 ± 0.30</td>
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<td><strong>SV index (reb), ml·m⁻²</strong></td>
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<td>pre</td>
<td>43.0 ± 10.6</td>
<td>41.5 ± 7.1</td>
<td>42.6 ± 6.1</td>
<td>43.6 ± 5.7</td>
<td>0.61</td>
<td>0.76</td>
<td>0.94</td>
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<tr>
<td>post</td>
<td>42.7 ± 7.6</td>
<td>41.9 ± 7.4</td>
<td>43.4 ± 8.0</td>
<td>45.3 ± 7.0</td>
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<td><strong>VO₂max, ml/kg/min</strong></td>
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<td>pre</td>
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<td>26.3 ± 6.0*</td>
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<td><strong>PCWP, mmHg</strong></td>
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<td>11.2 ± 2.2</td>
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<td>7.4 ± 2.1</td>
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<td>7.7 ± 1.8</td>
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<td>7.2 ± 2.0</td>
<td>6.7 ± 2.0</td>
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<td>7.7 ± 1.8</td>
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<td>8.6 ± 1.9</td>
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<td>7.7 ± 2.2</td>
<td>6.7 ± 2.0</td>
<td>0.19</td>
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<td>3.8 ± 1.1</td>
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<td>3.4 ± 1.0</td>
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<td>0.84</td>
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<td>5.4 ± 0.3</td>
<td>5.7 ± 0.2</td>
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<td>5.6 ± 0.2</td>
<td>5.7 ± 0.2</td>
<td>5.6 ± 0.3</td>
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<td>0.17</td>
<td>0.73</td>
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<td>0.17</td>
<td>0.73</td>
<td>0.28</td>
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Values are mean ± SD. Training*Medication*Time indicates the interaction effects between exercise training and alagebrium; Training*Time, individual effect of exercise training; Medication*Time, individual effect of alagebrium; (reb), by acetylene rebreathing technique; SV, stroke volume; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; TMP, left ventricular transmural pressure. *p < 0.01 vs. before training.
Table 3. Ventricular and vascular function

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<tr>
<th></th>
<th>Controls</th>
<th>Alagebrium alone</th>
<th>Exercise alone</th>
<th>Alagebrium + Exercise</th>
<th>Training *Time</th>
<th>Medication *Time</th>
<th>Training<em>Medication</em>Time</th>
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<tr>
<td><strong>Ventricular function</strong></td>
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<tr>
<td>LV mass index (mri), g·m⁻²</td>
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<tr>
<td>pre</td>
<td>47.9 ± 7.2</td>
<td>50.4 ± 6.5</td>
<td>48.7 ± 9.8</td>
<td>50.6 ± 9.9</td>
<td>0.02</td>
<td>0.13</td>
<td>0.94</td>
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<tr>
<td>post</td>
<td>46.8 ± 6.2</td>
<td>50.3 ± 6.4</td>
<td>49.2 ± 10.1</td>
<td>52.1 ± 10.4*</td>
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<td>Mass-volume ratio, g·ml⁻¹</td>
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<tr>
<td>pre</td>
<td>0.85 ± 0.09</td>
<td>0.86 ± 0.14</td>
<td>0.84 ± 0.13</td>
<td>0.82 ± 0.12</td>
<td>0.63</td>
<td>0.10</td>
<td>0.41</td>
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<tr>
<td>post</td>
<td>0.85 ± 0.12</td>
<td>0.88 ± 0.10</td>
<td>0.82 ± 0.13</td>
<td>0.85 ± 0.12</td>
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<td><strong>LVEDV index (echo), ml·m⁻²</strong></td>
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<td>pre</td>
<td>42.9 ± 5.5</td>
<td>42.8 ± 8.4</td>
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<td>44.9 ± 7.1</td>
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<td>45.8 ± 7.0</td>
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<td><strong>Ventricular function</strong></td>
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<td>LV stiffness constant</td>
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<td>pre</td>
<td>0.114 ± 0.059</td>
<td>0.122 ± 0.057</td>
<td>0.103 ± 0.043</td>
<td>0.127 ± 0.071</td>
<td>0.46</td>
<td>0.04</td>
<td>0.86</td>
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<tr>
<td>post</td>
<td>0.128 ± 0.053</td>
<td>0.105 ± 0.045</td>
<td>0.104 ± 0.056</td>
<td>0.102 ± 0.031</td>
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<td>V₀, ml·m⁻²</td>
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<td>17.9 ± 5.5</td>
<td>18.0 ± 10.1</td>
<td>21.9 ± 10.5</td>
<td>23.7 ± 9.4</td>
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<td><strong>Pressure asymptote, mmHg</strong></td>
<td>1.7 ± 1.7</td>
<td>1.7 ± 1.9</td>
<td>2.6 ± 2.2</td>
<td>1.7 ± 2.1</td>
<td>1.4 ± 1.9</td>
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<td>0.6 ± 0.2</td>
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<td><strong>Operating stiffness during unloading, mmHg·ml⁻¹·m²</strong></td>
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<td>2.1 ± 0.7</td>
<td>2.2 ± 1.0</td>
<td>2.4 ± 1.4</td>
<td>2.4 ± 1.4</td>
<td>2.4 ± 1.4</td>
<td>2.7 ± 1.8</td>
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<td>0.072 ± 0.026</td>
<td>0.084 ± 0.040</td>
<td>0.069 ± 0.021</td>
<td>0.098 ± 0.059</td>
<td>0.079 ± 0.044</td>
<td>0.077 ± 0.040</td>
<td>0.089 ± 0.044</td>
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<td><strong>LV stiffness constant (TMP)</strong></td>
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<td>20.7 ± 7.3</td>
<td>25.6 ± 9.3</td>
<td>21.5 ± 15.0</td>
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<td>24.1 ± 8.7</td>
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<td><strong>TAC index, ml·mmHg⁻¹·m²</strong></td>
<td>2.9 ± 1.4</td>
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<td><strong>Ea index, mmHg·ml⁻¹·m²</strong></td>
<td>2.7 ± 0.7</td>
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</table>
LVEDV(mri) indicates left ventricular end-diastolic volume by cardiac MRI; ESV, end-systolic volume; EDV(echo), end-diastolic volume by three dimensional echocardiography; TMP, LV transmural pressure, V₀, equilibrium volume; (TMP), by use of LV transmural pressure; TAC, total arterial compliance; Ea, effective arterial elastance. * P < 0.05 vs. before training.
Figure Legends

Figure 1. Enrollment, randomization, and retention of the study participants
Exercise&Alagebrium indicates subjects in this group had exercise training and alagebrium (200 mg/day) during the one year of intervention. GI indicates gastrointestinal.

Figure 2. Frank Starling relationship
Systolic ventricular performance for Controls, Alagebrium alone, Exercise alone, and exercise and alagebrium (Exercise&Alagebrium) before and after the one year of intervention. Note no differences in stroke volume index for any given PCWP in any of the 4 groups before and after intervention.

Figure 3. Preload recruitable stroke work
Lines represent results of linear regression analyses for Controls, Alagebrium alone, Exercise alone, and Exercise&Alagebrium before and after the intervention. Stroke work was unaffected across all loading conditions in all 4 groups after intervention (p=0.24).

Figure 4. LV diastolic pressure-volume relationships
Pressure-volume curves before and after one year of intervention. In Exercise alone, LV pressure-volume curves were shifted rightwards with no changes in the slope of pressure-volume curves. In Exercise &Alagebrium, pressure-volume curves were modestly flattened after intervention.
Figure 5. LV diastolic transmural pressure-volume relationships

Transmural pressure-volume curves before and after one year of intervention. No changes were observed in the slopes of pressure-volume curves in the 4 groups.
Figure 1

124 individuals screened for eligibility

62 excluded
31 did not meet inclusion criteria
31 declined to participate

62 randomized

Controls
15 allocated
0 lost to follow-up
15 analyzed
0 excluded

Alagebrium alone
16 allocated
0 lost to follow-up
2 discontinued program
1 GI symptom
1 family reason
14 analyzed
2 excluded

Exercise alone
15 allocated
0 lost to follow-up
1 with no post cath
14 analyzed
1 excluded

Exercise & Alagebrium
16 allocated
0 lost to follow-up
2 discontinued program
1 GI symptom
1 family reason
14 analyzed
2 excluded
Figure 2

Starling curves

Controls

Alagebrium alone

Pre
Post

Pre
Post

SV index, ml/m²

PCWP, mmHg

Exercise alone

Exercise & Alagebrium

SV index, ml/m²

PCWP, mmHg

SV index, ml/m²

PCWP, mmHg

SV index, ml/m²

PCWP, mmHg

SV index, ml/m²

PCWP, mmHg

SV index, ml/m²

PCWP, mmHg

SV index, ml/m²

PCWP, mmHg
Figure 3

Preload-stroke work relations

- **Controls**
  - Pre
  - Post

- **Alagebrium alone**
  - Pre
  - Post

- **Exercise alone**
  - Pre
  - Post

- **Exercise & Alagebrium**
  - Pre
  - Post

![Graphs showing preload-stroke work relations for different groups](image-url)
**Figure 4**

LV pressure - volume curves

- **Controls**
  - Pre: Stiff cons 0.122, Vo 11.4, Pa 0.3
  - Post: Stiff cons 0.130, Vo 15.4, Pa 0.3

- **Alagebrium alone**
  - Pre: Stiff cons 0.125, Vo 16.2, Pa 0.4
  - Post: Stiff cons 0.114, Vo 11.2, Pa 0.3

- **Exercise alone**
  - Pre: Stiff cons 0.122, Vo 16.7, Pa 0.4
  - Post: Stiff cons 0.123, Vo 19.9, Pa 0.4

- **Exercise & Alagebrium**
  - Pre: Stiff cons 0.123, Vo 18.4, Pa 0.4
  - Post: Stiff cons 0.107, Vo 23.4, Pa 1.0

PCWP, mmHg vs. LV end-diastolic volume index, ml/m²
Figure 5

LV TMP - volume curves

Controls

Alagebrium alone

Exercise alone

Exercise & Alagebrium

LV end-diastolic volume index, ml/m²

LV end-diastolic volume index, ml/m²

Stiff cons     0.111    0.108
Vo             22.8    22.5

Stiff cons     0.109    0.119
Vo             24.0    23.9

Stiff cons     0.114    0.111
Vo             27.6    27.7
Cardiovascular Effects of One year of Alagebrium and Endurance Exercise Training in Healthy Older Individuals
Naoki Fujimoto, Jeffrey L. Hastings, Graeme Carrick-Ranson, Keri M. Shafer, Shigeki Shibata, Paul S. Bhella, Shuaib M. Abdullah, Kyler W. Barkley, Beverley Adams-Huet, Kara N. Boyd, Sheryl A. Livingston, Dean Palmer and Benjamin D. Levine

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http://circheartfailure.ahajournals.org/content/early/2013/10/15/CIRCHEARTFAILURE.113.000440