

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



*Learn and Live*SM

The Impact of Exercise Training on Conduit Artery Wall Thickness and Remodeling in Chronic Heart Failure Patients

Andrew J. Maiorana, Louise H. Naylor, Anne Exterkate, Anne Swart, Dick H.J. Thijssen, Kaitlyn Lam, Gerry O'Driscoll and Daniel J. Green

Hypertension 2011;57;56-62; originally published online Nov 8, 2010;

DOI: 10.1161/HYPERTENSIONAHA.110.163022

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2011 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/cgi/content/full/57/1/56>

Subscriptions: Information about subscribing to Hypertension is online at
<http://hyper.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

The Impact of Exercise Training on Conduit Artery Wall Thickness and Remodeling in Chronic Heart Failure Patients

Andrew J. Maiorana, Louise H. Naylor, Anne Exterkate, Anne Swart, Dick H.J. Thijssen, Kaitlyn Lam, Gerry O'Driscoll, Daniel J. Green

Abstract—Exercise training is an important adjunct to medical therapy in chronic heart failure, but the extent to which exercise impacts on conduit artery remodeling is unknown. The aim of this study was to evaluate the impact of aerobic and resistance exercise training modalities on arterial remodeling in patients with chronic heart failure. We randomized 36 untrained subjects with chronic heart failure to resistance training (58.8 ± 3.5 years), aerobic training (61.3 ± 2.8 years), or an untrained control group (64.4 ± 2.4 years). Peak oxygen consumption during cycle ergometry increased after 12 weeks in both the resistance and aerobic training ($P < 0.001$) groups, but not in controls, whereas leg strength only increased after resistance training ($P < 0.05$). Brachial artery wall thickness decreased in the resistance training group (475 ± 10 versus 443 ± 13 μm ; $P < 0.01$), whereas no changes were apparent in the aerobic or control groups. Brachial diameter increased by $\approx 6\%$ and $\approx 5\%$ in the aerobic training and resistance training groups ($P < 0.01$), with no change evident in the control group. The wall:lumen ratio consequently declined in the resistance training group at 12 weeks (0.121 ± 0.004 versus 0.107 ± 0.004 ; $P < 0.01$) and increased in the control group (0.111 ± 0.006 versus 0.121 ± 0.009 ; $P < 0.05$). No wall:lumen change was evident in the aerobic training group. Our findings suggest that exercise has a systemic impact on remodeling of conduit arteries in humans and that resistance exercise training may be advantageous in subjects with chronic heart failure in this regard. (*Hypertension*. 2011;57:56-62.)

Key Words: exercise ■ arteries ■ heart failure ■ remodeling ■ vasculature

Exercise training in chronic heart failure (CHF) patients is associated with improved prognosis,^{1,2} functional capacity,^{2,3} and quality of life.⁴ In addition, aerobic training (AT) results in beneficial effects on some measures of vascular function.⁵ Recent studies have assessed the impact of resistance training (RT), designed to specifically target peripheral limitations to function in CHF. Such studies have observed improvements in peak oxygen consumption ($\dot{V}O_2$ peak), muscular strength and endurance, and vascular function.^{3,6-9} However, few previous studies have directly compared the effects of resistance and aerobic exercise training in CHF patients.¹⁰

Wall thickness and wall:lumen ratio have been used in peripheral conduit arteries to reflect arterial remodeling,¹¹⁻¹³ a process that may depend on exercise-mediated changes in systemic hemodynamics and arterial shear stress.¹⁴⁻¹⁸ We recently reported important differences in the impact of different exercise modalities on systemic changes in shear

stress during bouts of exercise,¹⁹ a finding which raises the possibility that distinct forms of exercise may induce differential changes in arterial size and wall thickness in humans. Although it has been suggested previously that exercise training can induce systemic changes in conduit and resistance artery size,²⁰ less attention has been focused on the impact of exercise training on remodeling and thickness of the wall, per se. Reduced wall thickness of the brachial artery is associated with reduced risk of cardiovascular events,²¹ whereas a progressive increase in wall thickness of the brachial artery parallels increasing severity of CHF.²² Exercise training-induced improvement in wall thickness may, therefore, have prognostic implications.

The purpose of this randomized, controlled trial of patients with stable CHF was to directly compare the effects of RT and AT on the wall thickness, diameter, and wall:lumen ratio of the brachial artery, a conduit vessel that is not prone to atherosclerosis and that reflects the impact of repeated bouts

Received September 20, 2010; first decision October 5, 2010; revision accepted October 14, 2010.

From the Advanced Heart Failure and Cardiac Transplant Service (A.J.M., K.L., G.O.), Royal Perth Hospital, Perth, Western Australia, Australia; School of Physiotherapy and Curtin Health Innovation Research Institute (A.J.M.), Curtin University, Perth, Western Australia, Australia; School of Sport Science, Exercise, and Health (L.H.N., D.J.G.), University of Western Australia, Perth, Western Australia, Australia; Department of Physiology (A.E., A.S., D.H.J.T.), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Research Institute for Sport and Exercise Science (D.H.J.T., D.J.G.), Liverpool John Moores University, Liverpool, United Kingdom; School of Medicine (G.O.), University of Notre Dame, Fremantle, Western Australia, Australia.

Correspondence to Andrew J. Maiorana, Advanced Heart Failure and Cardiac Transplant Service, Royal Perth Hospital, GPO Box X2213, Perth, Western Australia 6847, Australia. E-mail Andrew.Maiorana@health.wa.gov.au

© 2010 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.110.163022

Table 1. Subject Characteristics at Baseline and 12-Week Follow-Up

Characteristic of Subjects	Control (n=12)		Aerobic Trained (n=12)		Resistance Trained (n=12)	
	Pre	12 wk	Pre	12 wk	Pre	12 wk
Age, y	64.4±2.4	...	61.3±2.8	...	58.8±3.5	...
Male gender	11	...	11	...	10	...
Weight, kg	86.5±4.0	87.6±4.1	89.2±4.5	88.4±4.5	81.2±5.1	82.4±4.8
BMI, kg/m ²	30.1±1.3	30.5±1.3	30.4±1.1	30.1±1.0	28.4±0.8	28.9±0.6
SBP, mm Hg	123±6	121±8	127±4	127±5	125±6	123±5
DBP, mm Hg	69±3	67±4	70±2	74±2†	71±4	69±4
Rest HR, bpm	63±4	62±3	65±3	63±2	67±4	62±3
EF, %	37±3*	38±3	29±3	32±3	26±3	29±3
NYHA class						
I	4		3		3	
II	6		8		6	
III	2		1		3	
Etiology						
IHD	9		7		7	
ICM	3		3		5	
NC	0		1		0	

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; EF, ejection fraction; NYHA, New York Heart Association; IHD, ischemic heart disease; ICM, idiopathic dilated cardiomyopathy; NC, noncompaction cardiomyopathy. Data are mean±SEM.

*Data are significantly different from resistance-trained group at baseline (*P*<0.05).

†Data are significantly different from preintervention (*P*<0.05).

of exercise on systemic changes in hemodynamics and wall shear stress.

Methods

Subjects

Thirty-six untrained subjects (32 men and 4 women; 61.5±1.7 years) completed the study after screening, consisting of medical history and examination and hematologic and biochemical profile, including measurement of serum electrolytes, urea and creatinine, uric acid, liver function, and serum lipids. The following were excluded: smokers, those with renal impairment or proteinuria, hepatic impairment, hyperuricemia, hypercholesterolemia, exercise-induced ischemia, or hypertension. The study complied with the Declaration of Helsinki. The study protocol was approved by the Royal Perth Hospital Ethics Committee, and subjects provided written informed consent.

Subjects were randomized to 12 weeks of RT, AT, or control. All of the patients were stratified to New York Heart Association class I to III with an ejection fraction <50% and without congestive cardiac failure. Twenty-four subjects had coronary heart disease, 11 idiopathic dilated cardiomyopathy, and 1 noncompaction cardiomyopathy. Subject characteristics are presented in Table 1. Baseline medications (Table 2) were maintained for the duration of the study.

Experimental Measurements

Arterial wall thickness and diameter measurements, leg strength, and aerobic capacity were assessed at entry, with follow-up at 6 and 12 weeks. Ejection fraction and body mass index were obtained at entry and 12 weeks.

Brachial Artery Diameter and Wall Thickness Analysis

A 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (Aspen, Acuson) was used to visualize the brachial artery proximal to the cubital fossa. Perpendicular

incidence of the B-mode imaging ultrasound beam in relation to the orientation of the vessel provided clearly demarcated intima-medial boundaries, which were optimized using contrast controls on the ultrasound machine. The analog video output from the ultrasound machine was converted into a digital DICOM 3.0 file by DICOM Encoder software described by Potter et al.²³⁻²⁵ Heart rate and blood pressure were determined on the contralateral arm from an automated sphygmomanometer (Dinamap 8100, Critikon).

Arterial diameter and wall thickness were measured using DICOM-based intima-medial thickness measurement software, after an overnight fast, as described previously.²³ This custom-designed software performs edge detection and wall tracking that is independent of investigator bias. The software is written in an icon-based

Table 2. Cardiac Medication Use by Subject Grouping

Class of Medication	Control	Aerobic Trained	Resistance Trained
ACE inhibitor	9 (75)	12 (100)	9 (75)
Angiotensin II inhibitor	3 (25)	1 (8)	0
Furosemide	9 (75)	10 (83)	12 (100)
Spironolactone	5 (42)	6 (50)	9 (75)
Digoxin	1 (8)	5 (42)	3 (25)
Amiodarone	1 (8)	1 (8)	0
Aspirin	10 (83)	7 (58)	7 (58)
Warfarin	3 (25)	5 (42)	3 (25)
Clopidogrel	3 (25)	2 (17)	3 (25)
HMG-COA reductase inhibitor (statin)	10 (83)	6 (50)	7 (58)
β-blocker	10 (83)	12 (100)	11 (92)
Antianginal	5 (42)	4 (33)	0

ACE indicates angiotensin-converting enzyme; HMG-COA, 3-hydroxy-3-methylglutaryl-coenzyme A. Data are n (%).

Table 3. The Influence of Resistance and Aerobic Training on Aerobic Capacity and Leg Strength

Parameter	Control			Aerobic Trained			Resistance Trained		
	Pre	6 wk	12 wk	Pre	6 wk	12 wk	Pre	6 wk	12 wk
$\dot{V}O_2$ peak, mL · min ⁻¹ · kg ⁻¹	15.1±1.3	14.5±1.2	14.1±1.1†	14.5±1.3	15.7±1.8	17.2±1.6‡	13.7±1.2	15.8±1.3†	16.4±1.1‡
Exercise time, s	570±62	568±61	543±60†	589±47	666±65*	716±64‡	587±67	621±70	680±82*
Peak HR, bpm	117±7	118±5	111±8	130±6	128±8	128±8	120±8	117±6	117±6
Limiting symptom, CPET									
Dyspnea	6	8	7	3	1	3	3	3	3
Leg fatigue	5	3	4	4	7	7	8	7	8
Exhaustion	1	1	1	2	3	2	1	1	1
Other	0	0	0	2	0	0	0	0	0
Leg strength, kg	62±7	61±8	63±7	57±4	61±4	65±6	60±7	64±7	68±8*

HR indicates heart rate; CPET, cardiopulmonary exercise testing, primary symptom at volitional exhaustion. Data are mean±SEM.

*Significantly different from pretraining at $P<0.05$.

†Significantly different from pretraining at $P<0.01$.

‡Significantly different from pretraining at $P<0.001$.

graphical programming language (LabVIEW 7.0) and uses an IMAQ vision toolkit for image handling and analysis routines. Briefly, the observer initially chooses a frame from a DICOM file in which the intima-medial thickness and diameter are visually optimal. The observer then selects a region of interest around the B-mode ultrasound calibration marks. The software automatically detects the calibration marks and calculates a pixel:centimeter ratio. A rectangular region of interest is then drawn over the B-mode image that includes both walls of the artery. Within this region of interest, an edge-detection algorithm finds the near and far wall lumen edges and the far-wall media-adventitia interface. The software then marks the interfaces and calculates lumen diameter and the intima-medial thickness. To adjust for individual differences in lumen diameter, intima-medial thickness:lumen ratio was calculated. We have published a detailed account of the methodology, identifying an intraobserver error of $\approx 2\%$ associated with this operator-independent software package.²³

Assessment of Exercise Tolerance

Cardiopulmonary exercise testing was undertaken on a cycle ergometer (Corival, Lode), with initial workload set at 25 W and 25 W increments every 3 minutes. Heart rate and rhythm were continuously recorded by 12-lead ECG, and blood pressure was measured manually during the last 30 seconds of each stage by sphygmomanometry. Time to volitional fatigue (seconds) was recorded, and $\dot{V}O_2$ peak was determined by indirect calorimetry using the Vmax metabolic analysis system (Sensormedics).

Assessment of Muscular Strength

Maximal voluntary contractile strength was assessed using dual leg extension exercise using the 1 repetition maximum technique on a pin-loaded weight stack resistance machine (Pulsestar), with minimum 2.5-kg increments. Subjects were instructed in correct lifting technique and to avoid a Valsalva maneuver.

Exercise Training Interventions

Exercise trained subjects performed 3 supervised sessions per week at the Royal Perth Hospital Cardiac Gymnasium.

For the first 6 weeks of RT, weights were maintained at 50% to 60% 1 repetition maximum, and subjects worked on a 2:1 (60:30 seconds) work:rest ratio. For the second 6 weeks, weights were increased to 60% to 70% 1 repetition maximum with a 1:1 (45:45 seconds) work:rest ratio. Work:rest ratios were guided by an external auditory cue. After the first few sessions, subjects performed 3 sets of 9 exercises, with a 3-minute rest period between each set, for a total of 46.5 minutes per session.

AT commenced at 50% to 60% of baseline $\dot{V}O_2$ peak and progressed to 60% to 70% of the $\dot{V}O_2$ peak after 6 weeks, so that the relative intensity was consistent with the RT group. Exercise intensity was determined using the American College of Sports Medicine metabolic equations for walking and cycling and heart rate regression equations derived from the exercise tests at baseline for weeks 1 to 6 and at 6 weeks for weeks 7 to 12. After the first few sessions, each session involved 20 minutes of cycling and 20 minutes of treadmill walking separated by a 6.5-minute rest period to match the total duration of the RT group conditioning phase (46.5 minutes per session).

All of the exercise sessions were closely supervised by an experienced clinical exercise physiologist to ensure compliance with the exercise prescription. Control subjects were required to maintain their usual activities for the 12-week study period, but no formal exercise training was provided.

Statistical Analyses

Statistical analyses were performed using Excel (Windows Excel 2007) and SPSS version 15.0. All of the data are reported as mean±SEM, and statistical significance was assumed at $P<0.05$. All of the variables were analyzed using 2-factor general linear models with repeated measures. The factors were training status and group. Post hoc analysis was performed with the least significant difference test to correct for multiple comparisons.

Results

Impact of Exercise Training on Subject Characteristics

Of the initial 38 subjects who entered the study, 2 subjects dropped out, both from the RT group, 1 because of work commitments and the other because of a noncardiac illness. For subjects who completed the study, attendance at exercise training was similar between the AT (85±3%) and RT (89±3%) groups. Table 1 presents selected characteristics of the 36 subjects who completed the study. Baseline ejection fraction and lumen diameter were slightly lower for the RT compared with the control group ($P<0.05$), but there were no differences between groups for other parameters. Subjects were taking usual cardiac medications, and this was similar for all of the groups (Table 2).

Body weight and body mass index did not change in any of the groups across the 12-week intervention period

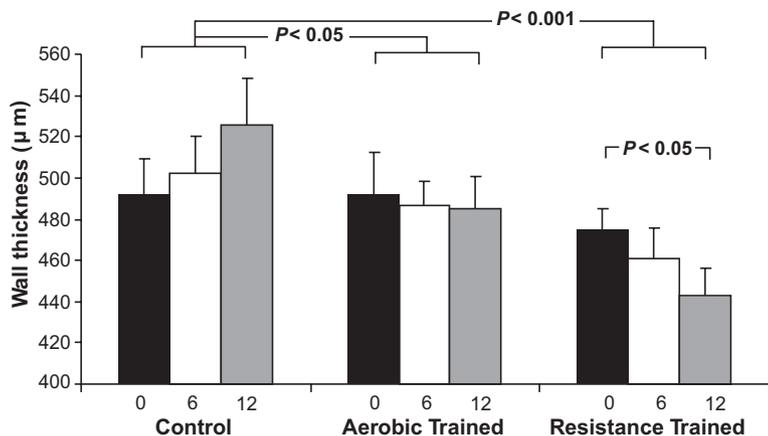


Figure 1. Influence of RT and AT on brachial wall thickness compared with the control group. Data are mean ± SEM. Black, pre; white, 6 weeks; gray, 12 weeks.

(Table 1). Peak oxygen consumption increased after 12 weeks of AT ($P < 0.001$) and 6 ($P < 0.01$) and 12 weeks ($P < 0.001$) of RT but decreased in controls ($P < 0.01$) at 12 weeks. Leg strength only increased after 12 weeks of RT ($P < 0.05$; Table 3).

Impact of Exercise Training on Wall Thickness, Arterial Diameter, and Wall:Lumen Ratio

Two-way ANOVA revealed significant interaction effects for change in wall thickness when both the control and RT ($P < 0.001$) and control and AT groups were compared ($P < 0.05$). Post hoc *t* tests revealed significantly decreased wall thickness in the RT group at 12 weeks (0.44 ± 0.01 versus 0.49 ± 0.01 mm; $P < 0.05$), no change in the AT group (0.49 ± 0.02 versus 0.485 ± 0.02 mm; $P = 0.59$), and a slight increase in the control group (0.49 ± 0.17 versus 0.53 ± 0.02 mm; $P < 0.05$; Figure 1).

Brachial artery diameter (Figure 2) significantly increased by ~6% (AT 4.30 ± 0.19 versus 4.56 ± 0.2 mm; $P < 0.05$) and ~5% (RT 3.98 ± 0.16 versus 4.17 ± 0.16 mm; $P < 0.01$) after 12 weeks of training. No changes were evident in the control group (4.51 ± 0.19 versus 4.52 ± 0.24 mm; $P = 0.94$).

Significant interaction effects for change in wall:lumen ratio (Figure 3) were evident when both the control and RT ($P < 0.001$) and control and AT groups were compared ($P < 0.05$). Subsequent *t* tests indicated that wall:lumen ratio declined significantly in the RT group at 12 weeks (0.121 ± 0.004 versus 0.107 ± 0.004 mm; $P < 0.01$) and

increased significantly in the control group at 12 weeks (0.111 ± 0.006 versus 0.121 ± 0.009 mm; $P < 0.05$). No significant change was evident in the AT group ($P = 0.20$).

Discussion

The purpose of the present study was to compare the impact of AT versus RT on remodeling of the brachial artery in subjects with CHF. Our principal finding was that RT increased artery diameter, decreased wall thickness, and consequently decreased the wall:lumen ratio of the brachial artery, whereas AT increased artery diameter without modifying wall thickness or wall:lumen ratio. This suggests that RT may be superior to AT in inducing remodeling of the brachial artery wall. In contrast to these benefits of exercise training, the control group exhibited an increased wall:lumen ratio and a trend for increased wall thickness across the 12 weeks of the study.

We contend that changes in brachial artery wall thickness, diameter, and wall:lumen ratio are indicative of systemic vascular remodeling, given that the upper limbs were not heavily involved in the exercises undertaken. It is likely, therefore, that systemic hemodynamic responses to bouts of exercise, which, in turn, modulate shear stress, a known stimulus to arterial wall remodeling,^{14–16,18,26} may have mediated these changes. In this sense, changes in the brachial artery provide an index of systemic arterial remodeling in response to exercise training, and RT may be a more

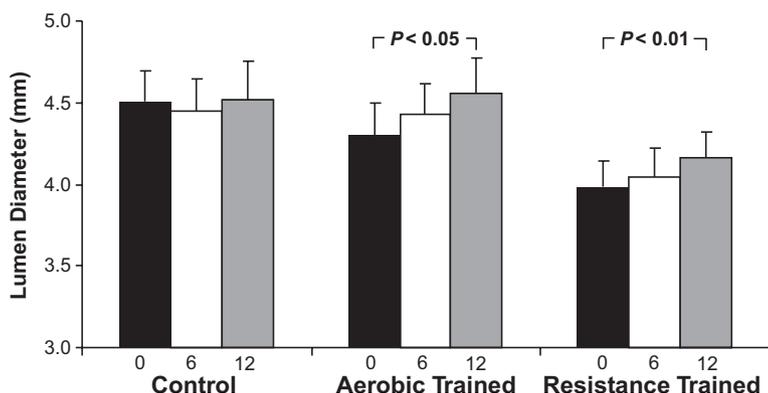


Figure 2. Influence of RT and AT on brachial lumen diameter compared with the control group. Data are mean ± SEM. Black, pre; white, 6 weeks; gray, 12 weeks.

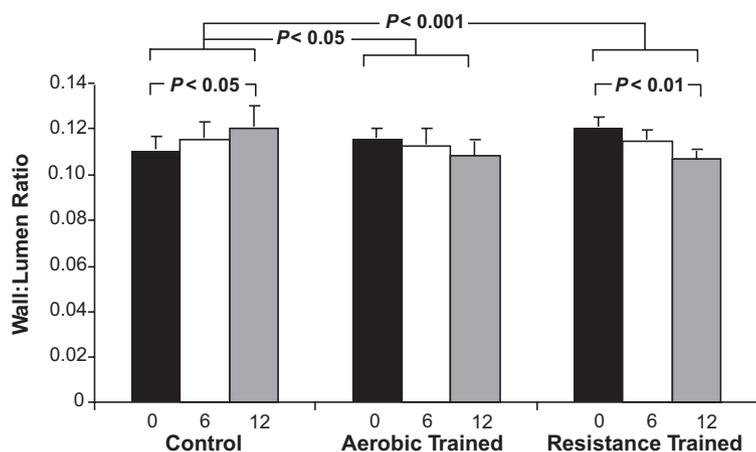


Figure 3. Influence of RT and AT on brachial wall:lumen ratio compared with the control group. Data are mean \pm SEM. Black, pre; white, 6 weeks; gray, 12 weeks.

beneficial modality in subjects with CHF to improve artery wall thickness.

Several cross-sectional studies have assessed artery wall thickness responses to exercise training in the lower limbs. AT was independently associated with decreases in femoral wall thickness in postmenopausal women.¹² Similarly, healthy, aerobically trained men had larger femoral artery lumen diameter, smaller femoral wall thickness, and smaller wall:lumen ratio compared with sedentary men.¹¹ Although a recent study found that femoral wall thickness increased with age, even in habitually exercising adults, smaller wall thickness was observed in the femoral artery of middle-aged and older adults who performed regular aerobic exercise.¹³ In one of the few longitudinal studies, 3 months of lower limb AT developed larger common femoral artery lumen diameters, smaller femoral artery lumen diameters, and smaller wall:lumen ratios in healthy but sedentary middle-aged men.¹¹ Collectively these studies suggest that exercise may retard age-related wall thickening as a localized effect.

Studies of exercise training on carotid artery thickness have been equivocal. A decrease in carotid artery wall thickness occurred in overweight and obese children, after 6²⁷ and 12 months²⁸ of exercise training, suggesting a systemic effect; however, no change was evident after exercise training in healthy adults.^{29,30}

Our data indicate that exercise training predominantly involving the lower limbs can decrease brachial artery wall thickness and wall:lumen ratio in patients with existing cardiovascular disease. Limited previous evidence suggests that leg exercise training can increase peak vasodilator capacity, an index of resistance vessel remodeling, in the upper limbs following a training regimen specifically involving the legs²⁰ and changes in peak brachial artery diameter and flow in response to predominantly lower limb exercise training.³¹ Finally, we recently identified beneficial effects on conduit artery wall thickness and wall:lumen ratio in both upper and lower limbs of healthy sedentary subjects who undertook 24 weeks of exercise training.³² However, our present data are the first, to our knowledge, to suggest that arterial wall remodeling can occur as a systemic response to exercise training in CHF subjects and the first to compare the impact of exercise training modalities.

We observed a superior effect of RT to induce remodeling of the brachial artery wall compared with AT. The mechanisms responsible for changes in wall thickness in response to training were not specifically addressed in this study, but the similar magnitude of improvement in aerobic capacity in both training groups (19% versus 20%) suggests that change in fitness, per se, is not primarily responsible for arterial remodeling. Similarly, there were no differences between the AT and RT group in terms of change in body mass index or BP, arguing against a unique effect of RT on arterial remodeling mediated through changes in these cardiovascular risk indices. Exercise is known to increase arterial shear stress, a potent stimulus to increased endothelium-derived NO production and consequent arterial remodeling in animals.^{14–16,18} It is possible that exercise-mediated changes in hemodynamics and shear stress, which can occur in the brachial artery during leg exercise,^{26,33} may transduce systemic changes in arterial caliber and wall thickness. We recently observed differences in brachial artery shear stress with different forms of leg exercise¹⁹; similarly, RT may have elicited a different shear stress–transducing stimulus to AT in the present study.

Systemic conduit artery remodeling may have implications for changes in arterial compliance and atherosclerotic risk. Indeed, brachial artery wall thickness predicts cardiovascular events in patients with and without angiographic evidence of atherosclerosis²¹ and is associated with the severity of atherosclerosis in the carotid and coronary arteries.³⁴ In CHF, brachial wall thickness progressively increases with worsening disease severity.²² If remodeling is extrapolated to the resistance vessels responsible for determining afterload, our data may have implications for the optimal exercise management of patients with CHF. Our results, therefore, endorse the use of carefully prescribed and administered RT as a modality in this clinical population.

This study benefited from a longitudinal study design and randomization of subjects to exercise and inactive control groups. We also used custom-designed edge-detection and wall tracking software program that is operator independent and has been validated against an external phantom.²³ The exercise training that we undertook was individually prescribed and closely supervised. We made a concerted effort to ensure that forearm muscle

work was minimized during the exercise programs, so that brachial measures could be used as markers of systemic exercise effects. A limitation of the study was the lack of a combined AT and RT group, and it is possible that such an intervention may be associated with benefits exceeding those observed in the present study.³⁵ Our findings are limited to subjects with CHF, and we did not assess carotid or lower limb arterial wall changes, which may have provided information pertaining to the impact of localized exercise and the potential benefit in terms of cardiovascular risk. Finally, it is possible that AT may have induced wall changes if a longer program had been completed.

Perspectives

We assessed artery wall thickness, lumen diameter, and wall:lumen ratio in the brachial arteries of patients with CHF who undertook either RT or AT. Our rationale for studying the brachial artery was that this artery reflects systemic arterial remodeling, a process that may depend on episodic changes in hemodynamics and arterial shear stress. Our findings suggest that exercise has a systemic impact on the remodeling of conduit arteries in humans and that RT may be a more beneficial training modality in subjects with CHF in this regard.

Acknowledgments

We thank Fiona Beeck for assisting with data collection and exercise training and Leanne Campbell for supervising exercise training.

Sources of Funding

A.J.M., D.J.G., and G.O. were supported by the National Heart Foundation (Australia). D.H.J.T. was supported by the Dutch Heart Foundation (E. Dekker, stipend). D.J.G. was supported by the Australian Research Council.

Disclosures

None.

References

1. O' Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1439–1450.
2. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise trianing in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99:1173–1182.
3. Maiorana A, O' Driscoll G, Cheetham C, Collis J, Goodman C, Rankin S, Taylor R, Green DJ. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. *J Appl Physiol*. 2000; 88:1565–1570.
4. Willenheimer R, Erhardt L, Cline C, Rydberg E, Israelsson B. Exercise training in heart failure improves quality of life and exercise capacity. *Eur Heart J*. 1998;19:774–781.
5. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, Schoene N, Schuler G. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. *JAMA*. 2000;283:3095–3101.
6. Hare DL, Ryan TM, Selig SE, Pellizzer AM, Wrigley TV, Krum H. Resistance exercise training increases muscle strength, endurance, and

- blood flow in patients with chronic heart failure. *Am J Cardiol*. 1999;83:1674–1677.
7. Delagardelle C, Feiereisen P, Krecke R, Essamri B, Beissel J. Objective effects of a 6 months' endurance and strength training program in out-patients with congestive heart failure. *Med Sci Sports Exerc*. 1999;31:1102–1107.
8. Pu CT, Johnson MT, Forman DE, Hausdorff JM, Roubenoff R, Foldvari M, Fielding RA, Singh MA. Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. *J Appl Physiol*. 2001;90:2341–2350.
9. Selig SE, Carey MF, Menzies DG, Patterson J, Geerling RH, Williams AD, Bamroongsuk V, Toia D, Krum H, Hare DL. Moderate-intensity resistance exercise training in patients with chronic heart failure improves strenght, endurance, heart rate variability, and forearm blood flow. *J Card Fail*. 2004;10:21–30.
10. Feiereisen P, Delagardelle C, Vaillant M, Lasar Y, Beissel J. Is strength training the more efficient training modality in chronic heart failure? *Med Sci Sports Exerc*. 2007;39:1910–1917.
11. Dinunno FA, Tanaka T, Monahan KD, Clevenger CM, Eskurza I, DeSouza CA, Seals DR. Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. *J Physiol*. 2001;534:287–295.
12. Moreau KL, Donato AJ, Seals DR, Dinunno FA, Blackett SD, Hoetzer GL, DeSouza CA, Tanaka H. Arterial intima-media thickness: site-specific associations with HRT and habitual exercise. *Am J Physiol Heart Circ Physiol*. 2002;283:1409–1417.
13. Moreau KL, Silver AE, Dinunno FA, Seals DR. Habitual aerobic exercise is associated with smaller femoral artery intima-media thickness with age in healthy men and women. *Eur J Cardiovasc Prev Rehabil*. 2006;13:805–811.
14. Kojda G, Hambrecht R. Molecular mechanisms of vascular adaptation sto exercise: physical activity as an effective antioxidant therapy? *Cardiovasc Res*. 2005;67:187–197.
15. Langille BL, O'Donnell F. Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent. *Science*. 1986;231:405–407.
16. Tinken TM, Thijssen DHJ, Hopkins ND, Dawson EA, Cable NT, Green DJ. Shear stress mediates vascular adaptations to exercise training in humans. *Hypertension*. 2010;55:312–318.
17. Folkow B. Hypertension and endothelial function. *Blood Press Suppl*. 1992;1:11–12.
18. Tuttle J, Nachreiner R, Bhuller A, Condict K, Connors B, Herring B, Dalsing M, Unthank J. Shear level influences artery remodelling, wall dimension, cell density and eNOS expression. *Am J Physiol*. 2001;281: H1380–H1389.
19. Thijssen DHJ, Dawson EA, Black MA, Hopman MT, Cable NT, Green DJ. Brachial artery blood flow responses to different modalities of lower limb exercise. *Med Sci Sports Exerc*. 2009;41:1072–1079.
20. Silber D, McLaughlin D, Sinoway L. Leg exercise conditioning increases peak forearm blood flow. *J Appl Physiol*. 1991;71:1568–1573.
21. Frick M, Suessenbacher A, Alber H, Dichtl W, Ulmer H, Pachinger O, Weidinger F. Prognostic value of brachial artery endothelial function and wall thickness. *J Am Coll Cardiol*. 2005;46:1006–1010.
22. Poelzl G, Frick M, Huegel H, Lackner B, Alber H, Mair J, Herold M, Schwarzacher S, Pachinger O, Weidinger F. Chronic heart failure is associated with vascular remodelling of the brachial artery. *Eur J Heart Fail*. 2005;7:43–48.
23. Potter K, Green DJ, Reed CJ, Woodman RJ, Watts GF, McQuillan BM, Burke V, Hankey GJ, Arnolda LF. Carotid intima-media thickness measured on multiple ultrasound frames: evaluation of a DICOM-based software system. *Cardiovasc Ultrasound*. 2007;5:29.
24. Potter K, Hankey GJ, Green DJ, Eikelboom J, Jamrozik K, Arnolda LF. The effect of long-term homocysteine-lowering on carotid intima-media thickness and flow-mediated vasodilation in stroke patients: a randomized controlled trial and meta-analysis. *BMC Cardiovasc Disord*. 2008;8:24.
25. Potter K, Reed CJ, Green DJ, Hankey GJ, Arnolda LF. Ultrasound settings significantly alter arterial lumen and wall thickness measurements. *Cardiovasc Res*. 2008;6:6.
26. Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol*. 2004;561:1–25.

27. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *J Am Coll Cardiol*. 2006;48:1865–1870.
28. Woo KS, Chook P, Chung WY, Sung RYT, Qiao M, Leung SSF, Lam CWK, Metreweli C, Celermajer DS. Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation*. 2004;109:1981–1986.
29. Tanaka T, Seals DR, Monahan KD, Clevenger CM, DeSouza CA, Dineno FA. Regular aerobic exercise and the age-related increase in carotid artery intima-medial thickness in healthy men. *J Appl Physiol*. 2002;92:1458–1464.
30. Rakobowchuk M, Tanguay S, Burgomaster KA, Howarth KR, Gibala MJ, MacDonald MJ. Sprint interval and traditional endurance training induce similar improvements in peripheral arterial stiffness and flow-mediated dilation in healthy humans. *Am J Physiol Regul Integr Comp Physiol*. 2008;295:236–242.
31. Tinken TM, Thijssen DHJ, Black MA, Cable NT, Green DJ. Time course of change in vasodilator function and capacity in response to exercise training in humans. *J Physiol*. 2008;586:5003–5013.
32. Green D, Swart A, Exterkate A, Naylor L, Black M, Cable N, Thijssen D. Impact of age, sex and exercise on brachial and popliteal artery remodeling in humans. *Atherosclerosis*. 2010;210:525–530.
33. Tinken TM, Thijssen DHJ, Hopkins N, Black MA, Dawson EA, Minson CT, Newcorner SC, Laughlin MH, Cable NT, Green DJ. Impact of shear rate modulation on vascular function in humans. *Hypertension*. 2009;54:278–285.
34. Rohani M, Jogestrand T, Kallner G, Jussila R, Agewell S. Morphological changes rather than flow-mediated dilatation in the brachial artery are better indicators of the extent and severity of coronary artery disease. *J Hypertens*. 2005;23:1397–1402.
35. Maiorana AJ, O'Driscoll G, Dembo L, Cheetham C, Goodman C, Taylor R, Green DJ. Effect of aerobic and resistance exercise training on vascular function in heart failure. *Am J Physiol Heart Circ Physiol*. 2000;279:1999–2005.