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Swimming Exercise, Arterial Stiffness, and Elevated Blood Pressure

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Swimming Exercise, Arterial Stiffness, and Elevated Blood Pressure

By

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Dedication

To my family, who have continuously nurtured my curiosity, challenged my philosophies and encouraged me to follow my own destined path.

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Swimming Exercise, Arterial Stiffness, and Elevated Blood Pressure

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Age is the major risk factor for cardiovascular diseases (CVD) and this is attributable in part to stiffening of large elastic arteries and development of vascular endothelial dysfunction. In contrast, regular aerobic exercise is associated with reduced risk of CVD. Swimming is an attractive form of aerobic exercise and always recommended for health promotion as well as prevention and treatment of risk factors for CVD. However, there is little scientific evidence to date indicating that swimming is equally efficacious to land-based exercise modes in reducing cardiovascular risks. Accordingly, the aim of the research was to determine the role of regular swimming exercise on both CVD traditional risk factors and vascular functions. To comprehensively address this aim, 2 different approaches were used: Study 1 (cross-sectional study) was designed to determine the potential benefit of regular swimming exercise in the primary prevention of age-related decreases in vascular function. Key measurements of vascular function were performed in middle-aged and older swimmers, runners, and sedentary controls. Central arterial compliance was higher in swimmers and runners than in sedentary controls. Study 2 (intervention study) was designed to determine whether

regular swimming exercise could reverse the age-associated decline in vascular function. Middle-aged and older subjects completed either a 12-week swim training program or relaxation/ stretching exercise (attention control) program. Short-term swim training improved arterial blood pressure and vascular functions. In summary, regular swimming exercise can attenuate reductions in and partially restore the loss of vascular function including central arterial compliance and endothelial function in middle-aged and older adults. Swimming exercise exhibited typical central arterial compliance and endothelial function phenotypes that are often displayed in land-based exercise.

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Chapter 1: General Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in modern society.[1] "Vascular aging" has recently been emphasized as one of the most important risk factors for CVD. Two vascular changes that are believed to be among the most important are increased stiffness of large elastic arteries and dysfunction of the vascular endothelium.[2] Arterial stiffness is characterized by a progressive loss of buffering capacity of the central arteries in response to ejection of blood from the heart. Increases in arterial stiffness can cause increased left ventricular afterload, increased myocardial oxygen demand, and decreased coronary blood flow. Eventually, this process leads to coronary ischemia.[3, 4] Furthermore, the vascular structure of the carotid sinus determines the deformation of, and strain on, the arterial baroreceptor endings during changes in arterial baroreflex regulation of heart rate.[5] Based on cross-sectional observations, large elastic artery stiffness becomes progressively greater (compliance is lower) with advancing age even in healthy men and women.[6-8]

The vascular endothelium plays a primary role in the modulation of vascular tone and structure through production of the vasorelaxing factor nitric oxide (NO), which acts to protect the vascular wall from the development of atherosclerosis and thrombosis.[9] Endothelial dysfunction in general and impaired endothelial-dependent vasodilation in particular have been linked to the classic manifestations of established coronary artery disease.[10]

Several epidemiological studies have found that regular aerobic exercise is associated with a reduced risk of atherosclerotic vascular disease and acute cardiovascular events, particularly in middle-aged and older adults.[11, 12] In addition to favorably modifying traditional risk factors such as blood pressure, a novel mechanism by which regular exercise may confer this protection is through improved vascular function including arterial compliance[8, 13], endothelial function.[14, 15]

Swimming is widely promoted and recommended as a mode of exercise by national and international organizations.[16-18] However, there is evidence to suggest that cardiovascular risk profiles of regular swimming exercises may not be as favorable as that of land-based exercises. For instance, swimmers tend to have higher body fat level, and blood pressure, as well as lower maximal aerobic power than runners.[19] So far, the only epidemiological study that assessed the relationship between regular swimming and cardiovascular risk factors failed to find a significant association.[20] Whether regular swimming exercise can prevent the age-related loss in vascular function and/or restore lost function in previously sedentary middle aged and older adults is unknown. No randomized controlled intervention study has determined an influence of regular swimming on cardiovascular risk profiles. In spite of the fact that little is known about the effects of regular swimming for health promotion and disease prevention, regular swimming has been widely promoted and prescribed without the underpinning of firm scientific support from clinical studies. *Therefore, the overall goal of this dissertation is to determine the role of regular swimming exercise on arterial blood pressure, vascular function and other cardiovascular risk factors.*

The specific aims of this project were to determine (1) whether the decline in key vascular function (i.e., central artery compliance, arterial baroreflex sensitivity and endothelial-dependent vasodilation) observed with sedentary middle-aged and older adults is absent in individuals who regularly perform swimming exercise and (2) if a program of swimming training improves vascular function and CVD risk factors in previously sedentary middle aged and older adults.

To systematically address these aims, two different but related approaches were utilized: Study # 1 (cross-sectional study) was designed to determine the potential benefit of regular swimming exercise in the age-related decreases in vascular function. Study # 2 (intervention study) was designed to determine whether regular swimming exercise could lower blood pressure and reverse the age-associated decline in vascular function in previously sedentary middle-aged and older adults with elevated blood pressure.

Study 1 Hypotheses:

1. Swimmers will demonstrate higher levels of key vascular function measurements (i.e., central artery compliance, arterial baroreflex sensitivity, and endothelial-dependent vasodilation) than sedentary controls
2. Levels of such vascular measurements will be different from runners who are matched of age and exercise training status.
3. The higher arterial compliance in runners and swimmers than in sedentary controls will be associated with greater cardiovagal baroreflex sensitivity (BRS)

Study 2 Hypotheses:

1. Regular moderate-intensity swimming exercise will decrease arterial blood pressure in previously sedentary middle-aged and older adults with elevated blood pressure.
2. Regular swimming exercise will restore the age-associated loss of vascular function in previously sedentary middle-aged and older adults.

Chapter 2. Comparison of Central Artery Elasticity in Swimmers, Runners, and the Sedentary

ABSTRACT

Despite the fact that swimming is one of the most popular, most practiced, and most recommended forms of physical activity, little information is available regarding the influence of regular swimming on vascular disease risks. Using the cross-sectional study design, key measures of vascular function were determined in middle-aged and older swimmers, runners, and sedentary controls. There were no group differences in age, height, dietary intake, and fasting plasma concentrations of glucose, total cholesterol, and LDL-cholesterol. Runners and swimmers were not different in their weekly training volume. Brachial systolic blood pressure and pulse pressure were higher ($p<0.05$) in swimmers than in sedentary controls and runners. Both runners and swimmers had lower ($p<0.05$) carotid systolic blood pressure and carotid pulse pressure than sedentary controls. Carotid arterial compliance was higher ($p<0.05$) and β-stiffness index was lower ($p<0.05$) in runners and swimmers than in sedentary controls. There were no significant group differences between runners and swimmers. Cardiovagal baroreflex sensitivity (BRS) was greater ($p<0.05$) in runners than in sedentary controls and swimmers and BRS tends to be higher in swimmers than in sedentary controls ($p=0.07$). Brachial artery FMD was significant greater ($p<0.05$) in runners compared with sedentary controls and swimmers. Our present findings are consistent with the notion that habitual swimming

exercise may be an effective endurance exercise for minimizing the loss in central arterial compliance with advancing age.

INTRODUCTION

A decrease in compliance of large elastic arteries in the cardiothoracic circulation and a generalized endothelial dysfunction [6, 21, 22] are regarded as a surrogate marker of cardiovascular disease with advancing age. The age-related reduction in arterial compliance leads to elevations in systolic blood pressure and pulse pressure [23] and contributes to left ventricular hypertrophy and ischemia.[4] Furthermore, because arterial baroreceptors are located within the wall of the carotid sinus and aorta arch, stiffening of the central arteries plays a role in reductions in the ability of reflexogenic regions to transduce signals generated by acute changes in intravascular pressure. [5]

There is accumulating evidence indicating that regular aerobic exercise enhances central arterial compliance and improves nitric oxide (NO) mediated endothelial function.[13, 14] Moreover, aerobic exercise is associated with the attenuation of age-related increases in arterial blood pressure [24] as well as a decline in cardiovagal baroreflex sensitivity (BRS).[25] Most, if not all, of the available studies to date have utilized land-based exercises (e.g., walking, running, cycling) as the modes of physical activity. [6, 13]

Swimming is an attractive form of exercise as it is easily accessible, inexpensive, and isotonic.[26] Because of the buoyancy of water, compressive stress on joints is small, and orthopedic injury rate is low. [27] Furthermore, due to cold temperature and increased thermoconductibity of surrounding water, heat-related illness is extremely low. [28] Thus, swimming can be an ideal mode of exercise for those at elevated risks of vascular disease, including the elderly, obese, and patients with arthritis. Although swimming is widely promoted and recommended as a mode of aerobic exercise by national and

international organizations [16-18], research focusing on the influences of swimming on vascular disease risks is lacking. [26] In fact, no study has addressed whether swimming is equally efficacious to land-based exercises in enhancing vascular function.

Accordingly, the aims of the present investigation were to determine (1) whether swimmers would demonstrate greater levels of key vascular function measures (i.e., central artery compliance, arterial baroreflex sensitivity, and endothelial-dependent vasodilation) than sedentary controls; and (2) if the levels of such vascular measures are different from runners who are matched for age and exercise training status.

METHODS

Subjects. We studied a total of 75 apparently healthy middle-aged and older adults (37-75 yr). They were either swimmers (17 men and 8 women), runners (17 men and 8 women) or sedentary controls (16 men and 9 women). All subjects were nonobese, nonsmoking, normotensive (<140/90 mmHg), normolipidemic, and free of overt cardiovascular and other chronic diseases as assessed by medical history questionnaire and blood chemistry and hematological evaluation. None of the subjects were taking cardiovascular-acting medications, including hormone replacement therapy. Physical activity status was verified by a modified Godin physical activity questionnaire (Appendix B) [29] and maximal oxygen consumption. In average, runners and swimmers had been exercising 4.1±2.2 times/wk for 9±2 years and 4.8±1.1 times/wk for 9±2 years, respectively. Sedentary participants had been sedentary at least for the past 12 months. Before participation, a verbal and written explanation of the procedures and potential

risks was provided. All subjects gave their written informed consent to participate. The study was reviewed and approved by the Institutional Review Board.

Measurements. All laboratory procedures were performed at rest under comfortable laboratory conditions. Before they were tested, subjects abstained from food, alcohol, and caffeine for at least 4 hours. An overnight 12-h fast was required before the measurement of metabolic risk factors. Premenopausal women were tested during the early follicular phase of the menstrual cycle.

Body composition. Body composition was assessed using dual-energy X-ray absorptiometry (Lunar DPX, GE Medical Systems, Fairfield, CT) with subject in the supine position.

Dietary intake. A 3-day dietary intake record was obtained and analyzed by a registered dietitian using the Nutritionist Pro software (Axxya Systems, Stafford, TX). Carbohydrate, fat, protein, and alcohol intake were presented as percentage of the total caloric intake.

Metabolic risk factors for atherosclerosis. A blood sample was collected by venapuncture after an overnight fast. Fasting plasma concentration of glucose, lipids, and lipoproteins were determined using a Vitros DT60 analyzer (Ortho-Clinical Diagnostics, Raritan, NJ).

Pulse wave velocity (PWV), arterial blood pressure, and augmentation index. Bilateral brachial and ankle blood pressure, carotid and femoral pulse waves, and heart rate were measured by an automated vascular testing device (VP-2000, Omron

Healthcare Bannockburn, IL) [30] after the subject had been lying in a supine position for at least 15 minutes. Ankle-brachial pressure index (ABI) was calculated as ankle systolic blood pressure divided by brachial systolic blood pressure and was used to screen for peripheral artery disease. Carotid and femoral artery pulse waves were recorded by arterial applanation tonometry incorporating an array of 15 micro-piezoresistive transducers placed on the carotid and femoral arteries. The time delay was measured automatically with the foot-to-foot method, and pulse wave velocity was subsequently calculated. Augmentation index was obtained using the arterial tonometry placed on the carotid artery as previously described. [6]

Arterial compliance. Arterial compliance and β-stiffness index were measured noninvasively by a combination of ultrasound imaging on the carotid artery with simultaneous applanation tonometry on the contralateral artery. [13] A longitudinal image of the common carotid and femoral artery were acquired 1-2 cm proximal to the bifurcation using an ultrasound machine equipped with a high-resolution linear array transducer (Philips iE33 Ultrasound System; Bothel, WA). All the ultrasound-derived images of carotid and femoral arteries were analyzed by the same investigator, who was blinded to the group assignment, using the image analysis software (Vascular Research Tool Carotid Analyzer, Medical Imaging Applications, Coralville, IA). Time points that corresponded with maximal systolic expansion and basal diastolic relaxation were selected. The pressure waveform and amplitude were obtained from the contralateral artery using arterial applanation tonometry (VP-2000, Omron Healthcare) and analyzed by waveform browsing software (WinDaq 2000, Dataq Instruments, Akron, OH).

Because the baseline levels of carotid blood pressure are subjected to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial and diastolic blood pressure to the brachial artery value as previously described [13].

Flow-mediated dilation (FMD). Brachial FMD was measured using standard procedure as described previously. [31] A pneumatic blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa. Brachial diameter and blood flow velocity was acquired from a Doppler ultrasound machine equipped with a high-resolution linear array transducer (Philips iE33 ultrasound). After baseline images were obtained for 2 minutes, the cuff was inflated to 100 mmHg above individual subject's systolic blood pressure for 5 minutes. Brachial artery blood flow was measured from 10 sec before to 20 sec after the blood flow occlusion to capture peak reactive hyperemia. Then, the transition from blood flow to diameter measurements was made, and brachial artery diameter was subsequently recorded for 2 min. All ultrasound-derived blood flow and diameter data were analyzed by the same investigator using the image analysis software (Vascular Research Tool Brachial Analyzer, Medical Imaging Applications, Coralville, IA). Flow-mediated dilation was calculated as (maximal artery diameter-baseline artery diameter)/baseline artery diameter x 100 [32]. The average of at least 10 end-diastolic brachial artery diameters was used for baseline diameters, and the mean of 3 peak end-diastolic diameters during reperfusion phase was used for maximum artery diameter.

Cardiovagal BRS. Cardiovagal BRS was determined using Valsalva's maneuver as previously described. [5, 33] After 15 min in the seated upright position, subjects performed Valsalva's maneuver by forcibly exhaling against a closed airway. Subjects were asked to maintain an expiratory mouth pressure of 40 mmHg for 10 seconds. The R-R interval of the ECG and beat-by-beat blood pressure were measured continuously. Subjected performed 3 Valsalva's maneuver at 5 min intervals during which heart rate and BP returned to baseline levels. Data for cardiovagal BRS were recorded and analyzed by waveform browsing software (Windaq 2000) during the phase IV overshoot. Systolic blood pressure values were linearly regressed against corresponding R-R intervals from the point where the R-R intervals began to lengthen to the point of maximal systolic blood pressure elevation.[25]

Maximal oxygen consumption. Graded exercise testing was undertaken using a metabolic cart during a modified-Bruce protocol. After a five-minute warm up, subjects walked or ran while the treadmill slope was gradually increased 2% every 2 minutes until volitional exhaustion.

Statistical analyses. ANOVA was used for statistical analysis to determine significant group differences. Univariate correlation and regression analyses were performed to determine the relation between carotid arterial compliance and cardiovagal BRS. All the variables were expressed as mean±SEM.

RESULTS

As presented in Table 2.1, there were no group differences in age, height, and dietary intakes. Body mass and body mass index were lower ($p<0.05$) in runners than in sedentary controls and swimmers. Body fat percentage of swimmers was lower ($p<0.05$) than sedentary controls but higher ($p<0.05$) than runners. As expected, physical activity scores were greater ($p<0.01$) in runners and swimmers than sedentary controls. Maximal oxygen consumption of swimmers was greater than sedentary controls but lower than runners. Fasting plasma concentrations of glucose, total cholesterol, and LDL-cholesterol were not different among groups. Runners had significantly lower plasma triglyceride and higher HDL-cholesterol concentrations than sedentary controls.

Heart rate at rest was lower ($p<0.05$) in runners than in sedentary controls and swimmers (Table 2.2). Brachial systolic blood pressure and pulse pressure were higher ($p<0.05$) in swimmers than in sedentary controls and runners. Both runners and swimmers had lower ($p<0.05$) carotid systolic blood pressure and carotid pulse pressure than sedentary controls. Brachial ankle PWV was significantly lower in runners than in swimmers and sedentary controls. There were no group differences in carotid artery augmentation index.

Carotid arterial compliance was higher ($p<0.05$) and β-stiffness index was lower ($p<0.05$) in runners and swimmers than in sedentary controls (Figure 2.1). There were no significant group differences between runners and swimmers. Unlike the measures of central artery stiffness, measures of peripheral artery stiffness, femoral artery compliance and β-stiffness index, were not different among the 3 groups (Figure 2.2). Cardiovagal

BRS was greater ($p<0.05$) in runners than in sedentary controls and swimmers (Figure 2.3). Cardiovagal BRS of swimmers tends to be higher than sedentary controls but this did not achieve statistical significance ($p=0.07$). Cardiovagal BRS was positively associated with carotid arterial compliance ($r=0.44$, $P<0.01$).

Brachial artery FMD was significant greater ($p<0.05$) in runners compared with sedentary controls and swimmers (Figure 2.4). Baseline brachial artery diameter was not different among groups (sedentary controls = 4.2±1.9 mm, runners = 4.2±1.8 mm, and swimmers = 4.6±1.8 mm). Peak blood flow and the calculated shear rate were not different among the 3 groups so FMD values were not adjusted for shear rate.

DISCUSSION

Despite the fact that swimming is one of the most popular, most practiced, and most recommended forms of physical activity, little information is available regarding the influence of regular swimming on vascular disease risks. This is the first study, to our knowledge, to determine whether swimmers would exhibit similar phenotype of vascular function to runners. The salient finding of the present study is that central artery compliance was greater in swimmers than in age-matched sedentary controls, and the level of arterial compliance was not different from runners, suggesting that high levels of regular swimming exercise may prevent arterial stiffening similar to land-based exercises.

In the present study, middle-aged and older swimmers demonstrated higher levels of brachial systolic and pulse pressures than runners and sedentary controls. Our findings

are consistent with previous cross-sectional studies showing that cardiovascular risk profiles, in particular arterial blood pressure, of swimmers are less favorable than those of runners. [34, 35] Interestingly, "central" blood pressures were significantly lower in swimmers than in sedentary controls. Central blood pressure is determined by a number of factors, including aortic diameter, arterial wave reflection, and left ventricular ejection characteristic [36] and is a better predictor of cardiovascular disease risks than brachial blood pressure. [37] The lower central blood pressure in swimmers was associated with a greater arterial compliance. Taken together, these results are consistent with the notion that regular swimming exercise plays an important role in preventing arterial stiffening.

It remains unclear how regular aerobic exercise improves arterial compliance. One possibility is that regular physical activity may act on the elasticity of artery through endothelium-dependent vasodilation. [14] Flow-mediated dilation (FMD) serves as an index of nitric oxide-mediated endothelium-dependent vasodilator function in humans. In the present study, a greater arterial compliance in swimmers was not associated with a higher FMD. These results in swimmers are consistent with our previous pharmacological study showing that nitric oxide does not appear to play a role in increasing arterial compliance through regular walking exercise. [38] Other possibilities to explain the beneficial effects of regular exercise on macrovascular function include reductions in vascular vasoconstrictor tone [38], endothelin-1 [39], and collagen cross-linking.

In contrast to the central arteries, the compliance of peripheral arteries does not appear to change much with a variety of interventions or states, including aging and endurance training. [6, 13] Consistent with this, we found that femoral arterial compliance is

not different among the 3 groups. A lack of influence of regular exercise on peripheral arterial compliance is attributed to the fact that peripheral arteries do not exhibit same extent of pulsatile changes in diameter compared with central arteries.

Accumulating evidence indicates that habitual aerobic exercise favorably modulates age-associated declines in cardiovagal BRS. [5, 25] Consistent with the previous findings, results from present study showed that cardiovagal BRS is enhanced in middle-aged and older endurance-trained runners compared with sedentary controls. Cardiovagal BRS was ~25% greater in swimmers than in sedentary controls, and there was a trend ($p=0.07$) for the difference to be significant. Moreover, cardiovagal BRS was significantly associated with arterial compliance. Thus, regular swimming appears to be associated with a greater level of cardiovagal BRS, presumably through increased carotid arterial compliance.

Is regular swimming associated with reduced risk of cardiovascular and all-cause mortality? Only 2 studies are available to answer this question. In one epidemiological study, swimming was not associated with reduced risk of cardiovascular disease although walking and running examined in the same study demonstrated significant associations. [20] A more recent epidemiological study, however, reported the smaller relative risk of developing CVD in swimmers than sedentary populations [40], and the relative risk of swimmers were lower than those of walkers and runners. Thus, at present, it remains highly controversial as to whether swimming is equally cardioprotective to land-based exercise modes. Similar to these epidemiological studies, our findings are somewhat divergent as well. Central arterial compliance was greater in swimmers than in sedentary

controls. However, endothelium-dependent vasodilation, as assessed by FMD, was not different between swimmers and sedentary controls. Clearly, more research effort should be directed toward the influence of swimming exercise on vascular disease risks.

In addition to the use of a cross-sectional study design, the present study has other limitations that should be discussed. Although swimmers and runners are matched well for exercise training volume, maximal oxygen consumption was significantly lower in swimmers than in runners. However, based on the principles of specificity of training, this is an expected finding as maximal oxygen consumption was assessed on treadmill. Transfer of cardiovascular training benefits is very limited for VO_2max on treadmill when swimming exercise is performed as a training modality. [41]

CONCLUSION

In summary, central arterial compliance was greater in middle-aged and older swimmers than in age-matched sedentary controls and the level of arterial compliance was not different between runners and swimmers. Higher arterial compliance in swimmers was associated with greater arterial baroreflex sensitivity. As such, habitual swimming exercise may be an effective endurance exercise for minimizing the loss in central arterial compliance and its sequela that occur with advancing age. Future studies involving swimming exercise intervention are warranted.

Table 2.1. Selected subject characteristics

	Sedentary	**Runners**	**Swimmers**
Male/Female, n	16/9	17/8	17/8
Age, years	54 ± 2	52 ± 2	56 ± 2
Height, cm	170 ± 2	173 ± 2	173 ± 2
Body mass, kg	74 ± 2	67 ± 2*	76 ± 2†
BMI, kg/m^2	26 ± 1	22 ± 1*	25 ± 1†
Body fat percentage, %	30 ± 2	18 ± 2*	24 ± 2*†
VO_2max, ml/kg/min	31 ± 2	50 ± 2*	41 ± 2*†
Physical activity score, U	11 ± 4	58 ± 3*	57 ± 4*
Total caloric intake, kcal/day	2370 ± 212	2343 ± 169	2160 ± 150
Carbohydrate intake, %	46 ± 3	49 ± 3	47 ± 2
Fat intake, %	36 ± 2	32 ± 2	33 ± 2
Protein intake, %	13 ± 1	14 ± 1	16 ± 1
Alcohol intake, %	5 ± 2	4 ± 1	3 ± 1
Sodium intake, mg/day	3472 ± 348	2968 ± 278	3014 ± 246
Total cholesterol, mg/dl	193 ± 9	179 ± 9	194 ± 11
LDL-cholesterol, mg/dl	120 ± 8	105 ± 8	123 ± 9
HDL-cholesterol, mg/dl	47 ± 3	61 ± 3*	52 ± 4†
Triglyceride, mg/dl	125 ± 14	70 ± 14*	97 ± 15
Plasma glucose, mg/dl	94 ± 3	95 ± 3	99 ± 3

Values are mean±SEM. *$p<0.05$ vs. Sedentary, † $p<0.05$ vs. Runners

BMI = body mass index, VO_2max = maximal oxygen consumption

Table 2.2. Hemodynamic measures at rest

	Sedentary	**Runners**	**Swimmers**
Heart rate, beats/min	60 ± 2	50 ± 2*	58 ± 2†
Systolic BP, mmHg	119 ± 3	119 ± 3	128 ± 3*†
Mean BP, mmHg	89 ± 2	88 ± 2	93 ± 2
Diastolic BP, mmHg	71 ± 1	72 ± 1	74 ± 2
Pulse pressure, mmHg	48 ± 2	47 ± 2	54 ± 2*†
Carotid systolic BP, mmHg	116 ± 3	104 ± 3*	104 ± 3*
Carotid pulse pressure, mmHg	47 ± 2	36 ± 2*	37 ± 2*
baPWV, cm/sec	1336 ± 36	1230 ± 35*	1334 ± 36†
Carotid AI, %	15 ± 5	13 ± 4	13 ± 5

Values are mean±SEM. *p<0.05 vs. Sedentary, † p<0.05 vs. Runners.

BP=blood pressure, baPWV=brachial ankle pulse wave velocity, AI=augmentation index.

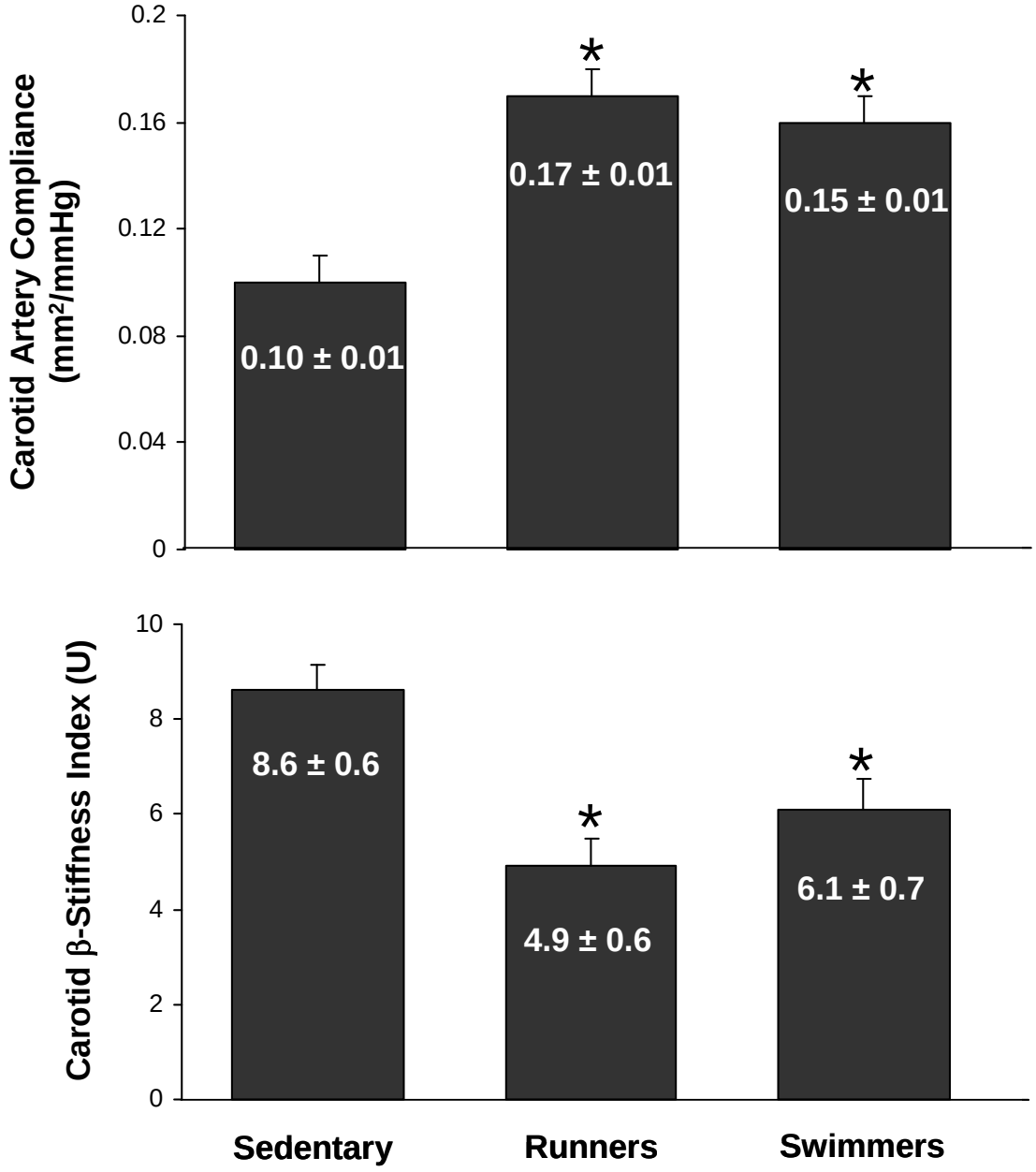

Figure 2.1. Central artery compliance and β-stiffness index.

Values are mean±SEM. *p <0.05 vs. sedentary.

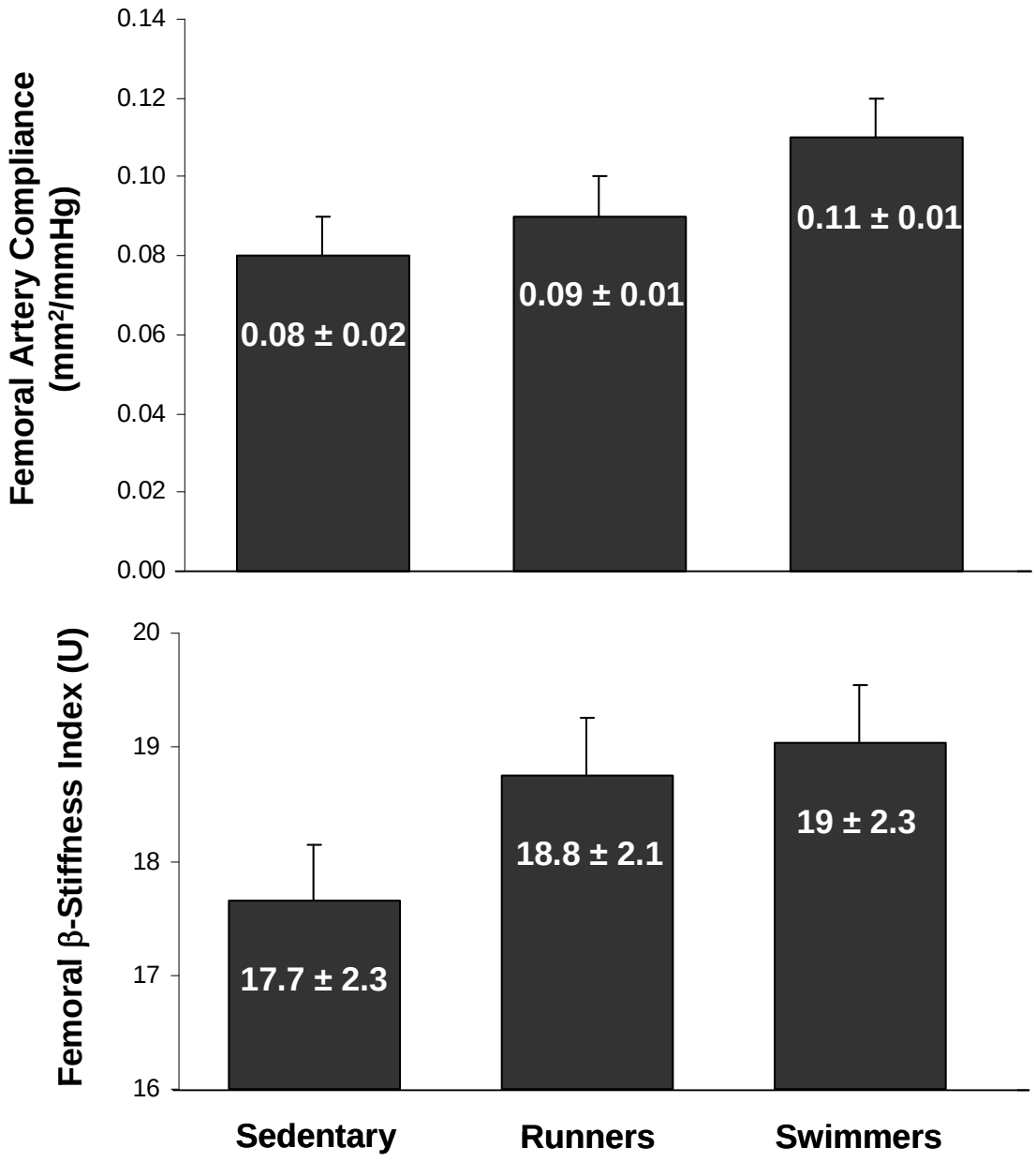

Figure 2.2. Femoral artery compliance and β-stiffness index.

Values are mean±SEM.

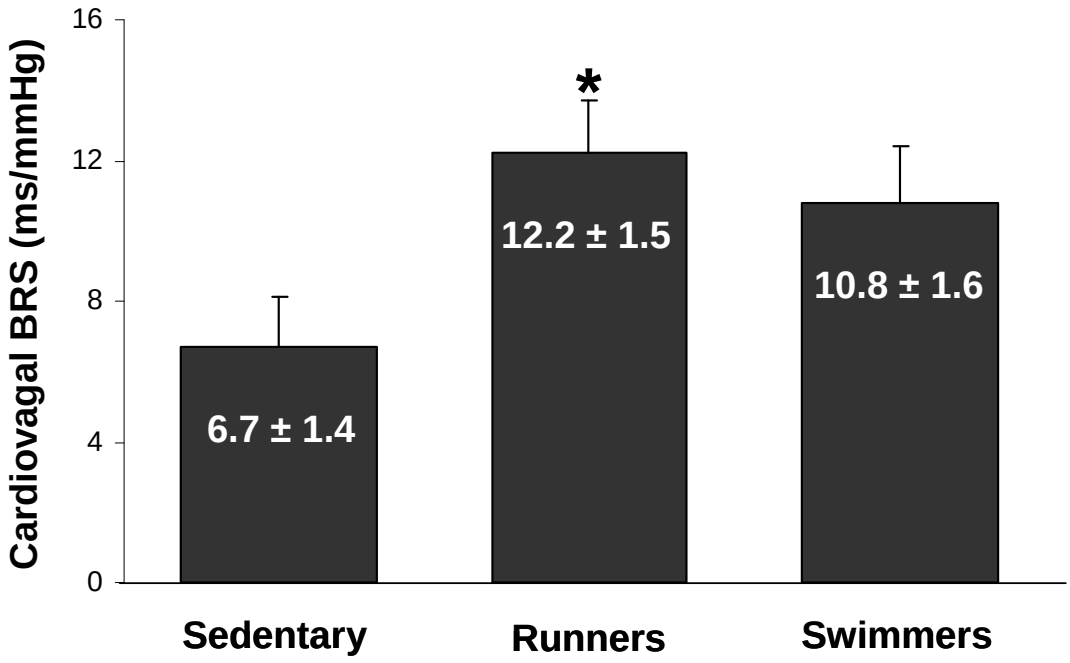

Figure 2.3. Cardiovagal baroreflex sensitivity.

Values are mean±SEM. *p <0.05 vs. sedentary.

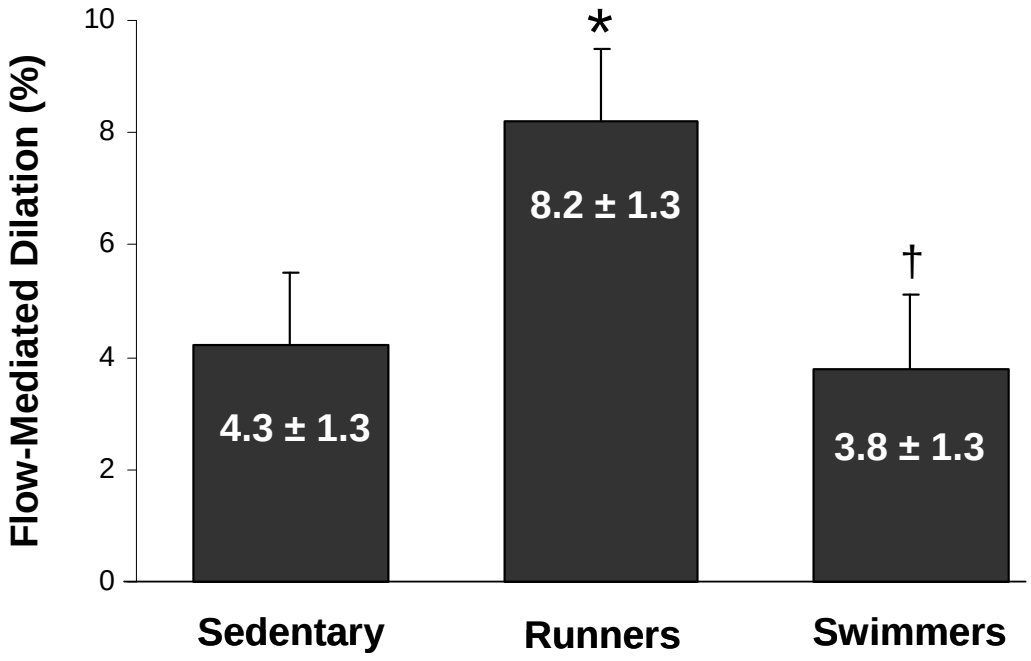

Figure 2.4. Flow-mediated dilation.

Values are mean±SEM. *p <0.05 vs. sedentary. †p <0.05 vs. runners.

Chapter 3: Swimming training reduces blood pressure and improves vascular function in middle-aged and older adults

ABSTRACT

The benefit of aerobic exercise training on blood pressure and vascular function are well established. However, the available evidence was derived exclusively from the data obtained using land-based exercises (walking, cycling). There is little scientific evidence to date indicating that swimming is equally efficacious to land-based exercises. The purpose of this study was to determine if regular swimming exercise would decrease arterial blood pressure and improve arterial compliance and endothelial function. Otherwise healthy middle-aged and older adults (age: 60±2) with pre-hypertension or stage-1 hypertension, not on any medication, were recruited and randomly assigned to either 12 weeks of swimming exercise or attention time controls. Before and after the intervention, arterial blood pressure, carotid arterial compliance, flow-mediated dilation (FMD), and cardiovagal baroreflex sensitivity (BRS) were measured. Before the intervention period, there were no significant differences in any of the variables between the swimming intervention and the attention control groups. Systolic blood pressure decreased significantly ($p<0.05$) from 131±3 to 122 ± 4 mmHg. Regular swimming exercise increased carotid arterial compliance ($p<0.05$) to levels similar to those of the middle-aged and older trained swimmers (Data presented in study#1). FMD and cardiovagal BRS improved significantly after swim training program ($p<0.05$). In conclusion, swimming exercise decreased arterial blood pressure at rest and improved

vascular function in previously middle-aged and sedentary individuals. This is a clinically important finding since swimming can be a highly useful alternative to land-based exercise for health promotion and disease prevention.

INTRODUCTION

Age is the major risk factor for cardiovascular diseases (CVD) and this is attributable in part to decreased arterial compliance and development of vascular endothelial dysfunction. In sedentary healthy humans, the compliance of the large elastic arteries in the cardiothoracic circulation decreases with advancing age.[6, 13] The age-related reduction in carotid compliance is associated with functionally and clinically important physiological and pathophysiological consequences within the cardiovascular and autonomic nervous systems including increases in systolic blood pressure[7], left ventricular hypertrophy [4], and a decrease in cardiovagal baroreflex sensitivity (BRS).[42] Via these effects, reduced carotid arterial compliance is thought to play a critical role in the development of cardiovascular and autonomic disorders.

In contrast to age, regular aerobic exercise is associated with enhanced vascular function and reduced risk of CVD. Cross-sectional findings show that measures of large artery compliance [6, 13] and endothelial function [14, 22, 43] are consistently higher in middle-aged and older adults who perform habitual endurance exercise than in their sedentary peers. The short-term exercise intervention studies demonstrated improvements in arterial compliance [13, 44] and endothelial function. [14, 15] Moreover, exercise training appears to decrease blood pressure.[45, 46]

Swimming is often recommended as a form of exercise for prevention and treatment of hypertension and cardiovascular disease as it is easily accessible, inexpensive and isotonic. However, regular swimming has been widely promoted and prescribed without the underpinning of firm scientific support from clinical studies. The

recommendations have arisen from extrapolation of data from other forms of exercise (i.e., walking and cycling). Therefore, the purpose of this study was to determine the effects of swim training on arterial blood pressure, arterial compliance and endothelial function in pre- or stage-1 hypertensive middle-aged and older individuals.

METHODS

Subjects. Male and female middle-aged and older adults, age 50-80 years, were recruited from Austin, TX and surrounding communities. Prior to baseline measurements, every subjects had systolic blood pressure at rest between 140-159 mmHg (stage 1 systolic hypertension) or 120-139 mmHg (pre-hypertension) with diastolic blood pressure of less than 99 mmHg [47]. All of the participants had their medical history assessed and were subjected to a physical examination and treadmill exercise stress tests by a licensed physician to ensure that the study would not be dangerous for them. If the participants develop symptoms other than fatigue, they were excluded from the study. No subjects had clinical or electrocardiographic evidence of coronary artery disease. They also had no orthopedic complications that would have prohibited them from swimming. Prior to participation, verbal and written explanations of procedure and its potential risks were provided. Each participant then gave their written consent to participate in the investigation. The experimental procedures were reviewed and approved by the Institutional Review Board at The University of Texas at Austin. After the baseline measurements had been completed, subjects were assigned to either swimming exercise or relaxation/stretching exercise (attention control). Group assignments were made as

randomly as possible, with some regard given to individual preference when subjects strongly objected to their group assignment. About 20% of subjects chose the group preference. The mean ages of subjects in the training and control groups were 58±2 and 61±2 years, respectively. Prior to the study, there were no significant differences ($p > 0.05$) in age and physical characteristics between the groups (Table 3.1). During the course of this investigation, subjects in both groups were instructed to maintain their usual lifestyle and dietary habits.

Training protocols. Subjects in the swimming exercise group participated in a supervised 12-week swimming training program of 45 min sessions, 3 days per week on alternate days. The swimming training was performed in various swimming pools in the city of Austin and the surrounding communities, including two swimming pools on the campus of The University of Austin (University Aquatic Center or Gregory Gym pool) that are open to the public/community. For the first few weeks of swimming training program, subject swam 15-20 minutes/day, 3-4 days/week at a relatively low intensity of exercise (~60% of the individually-determined maximal heart rate from their maximal oxygen consumption test). As their overall level of fitness and exercise skill improve, the intensity and duration of exercise increased to 40-45 minutes/day, 3-4 days/week at a moderate intensity of 70-75% of maximal heart rate. The target heart rate during swimming was adjusted on the basis of the observation that the maximal heart rate during swimming is approximately 10-13 beats/min lower than that during running. [51] The water temperature of the swimming pool was held constant at 27–28 °C during this

investigation. Each subject was instructed to swim continuously during the 45 min swimming workout, except during the time needed for checking a 10 s target heart rate. Adherence to the exercise training will be documented through the use of physical activity logs and heart rate monitors.

The attention time control group visited the laboratory at the same frequency as the subjects assigned to the swimming training intervention, and underwent general progressive relaxation/stretching exercise. In the proposed study, we used the approach taken by van Montfrans et al.[48] Briefly, a mixture of Jacobson's method of progressive relaxation (a systemic distal-to-proximal progression of conscious contraction and relaxation of musculature)[49] and Schultz's autogenic relaxation (progressive conscious control and relaxation of muscle and body tension)[50] were used. In addition static stretching exercise for the entire body was used in alternate with relaxation exercise. Subjects followed the instruction from stretching DVD. The stretching program included neck, chest, shoulder, arm, back, hip and leg stretches.

Measurements. All tests were conducted in the Cardiovascular Aging Research Laboratory and the Fitness Institute of Texas in Bellmont Hall on the University of Texas at Austin campus. Testing was conducted before and after the 12-week training and control periods. Subjects did not receive any feedback about the results of the testing until the conclusion of the study. All post-training measurements were performed 24-48 h after the last exercise session to avoid the immediate effects of a single bout of exercise. Subjects were instructed to refrain from any physical activity in the 24 hours before any

scheduled testing session. In addition, measurements before and after the training and control periods were obtained at the same time of day for each subject.

Body composition. Lean body mass and body fat percentage were determined noninvasively by dual energy X-ray absorptiometry (DEXA) using Lunar DPX by General Electric Medical Systems.

Heart rate, blood pressure, and pulse wave velocity. Bilateral brachial and ankle blood pressure, carotid and femoral pulse waves, and heart rate were measured by an automated vascular testing device (VP-2000, Omron Healthcare Bannockburn, IL) [30] after the subject had been lying in a supine position for at least 15 minutes. Ankle-brachial pressure index (ABI) was calculated as ankle systolic blood pressure divided by brachial systolic blood pressure and was used to screen for peripheral artery disease. Carotid and femoral artery pulse waves were recorded by arterial applanation tonometry incorporating an array of 15 micro-piezoresistive transducers placed on the carotid and femoral arteries. The time delay was measured automatically with the foot-to-foot method, and pulse wave velocity was subsequently calculated. Augmentation index was obtained using the arterial tonometry placed on the carotid artery as previously described.[6]

Exercise with diagnostic ECG. To screen for the presence of overt coronary heart disease (CHD), all subjects underwent a diagnostic 12-lead ECG at rest and during incremental exercise to exhaustion. The subject performed a modified-Balke treadmill walking protocol. The ECG was monitored continuously, and BP and ratings of perceived

exertion was recorded each minute. Only those subjects demonstrating no signs or symptoms of CHD were allowed to participate in the study.

Maximal aerobic capacity. Maximal oxygen consumption (VO_2max) was conducted during a graded exercise test on a treadmill. After a five-minute warm up, subjects walked continuously on the treadmill while the slope increased 2% every 2 minutes until the subjects stopped the test (modified Bruce protocol). A Physio-Dyne Max-1 metabolic testing system (Physio-Dyne Instrument Corp; Quogue, NY) determined flow and gas composition from expired air collected using a Hans Rudolph mouthpiece. Subject wore a chest strap heart rate throughout the test. Heart rate and ratings of perceived exertion (RPE) were recorded every minute.

Echocardiography. Heart structure and function were measured noninvasively using a sector transducer connected to an ultrasound machine (Philips iE33 Ultrasound System; Bothel, WA). The transducer was placed in the left parasternal region and from the long axis view. Cardiac output and stroke volume were determined by multiplying the velocity time integral (VTI) of flow at the aortic annulus by its cross-sectional area. The diameter ventricular outflow tract (LVOT) was determined from the long axis 2D image. Pulse wave mode was used to determine the E/A ratio and LVOT VTI.

24-hour (ambulatory) blood pressure. Blood pressure recordings over a 24-h period of normal daily activity were measured using a noninvasive ambulatory monitor (Spacelabs, Redlands, WA). The ambulatory system was calibrated against a mercury sphygmomanometer and the cuff was programmed to inflate automatically every 15 min from 6AM to 11PM and every 20 min between 11 PM and 6 AM. For each individual

subject, the nighttime period was defined as the time when the subject went to bed at night until rising in the following morning. Daytime was determined as the remainder of the 24-hour period.

Carotid arterial compliance. Carotid arterial compliance and β-stiffness index were measured noninvasively by a combination of ultrasound imaging on the carotid artery with simultaneous applanation tonometry on the contralateral artery [13]. A longitudinal image of the common carotid artery was acquired 1-2 cm proximal to the bifurcation using an ultrasound machine equipped with a high-resolution linear array transducer (Philips iE33 Ultrasound System; Bothel, WA). All the ultrasound-derived images of carotid artery were analyzed using the image analysis software (Vascular Research Tool Carotid Analyzer, Medical Imaging Applications, Coralville, IA). Time points that corresponded with maximal systolic expansion and basal diastolic relaxation were selected. The pressure waveform and amplitude were obtained from the contralateral artery using arterial applanation tonometry (VP-2000, Omron Healthcare) and analyzed by waveform browsing software (WinDaq 2000, Dataq Instruments, Akron, OH). Because the baseline levels of carotid blood pressure are subjected to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial and diastolic blood pressure to the brachial artery value as previously described [13].

Flow-mediated dilation (FMD). Brachial FMD was measured using standard procedure as described previously [31]. A pneumatic blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa. Brachial diameter and blood

flow velocity was acquired from a Doppler ultrasound machine equipped with a high-resolution linear array transducer (Philips iE33 ultrasound). After baseline images were obtained for 2 minutes, the cuff was inflated to 100 mmHg above individual subject's systolic blood pressure for 5 minutes. Brachial artery blood flow was measured from 10 sec before to 20 sec after the blood flow occlusion to capture peak reactive hyperemia. Then, the transition from blood flow to diameter measurements was made, and brachial artery diameter was subsequently recorded for 2 min. All ultrasound-derived blood flow and diameter data were analyzed by the same investigator using the image analysis software (Vascular Research Tool Brachial Analyzer, Medical Imaging Applications, Coralville, IA). Flow-mediated dilation was calculated as (maximal artery diameter-baseline artery diameter)/baseline artery diameter x 100 [32]. The average of at least 10 end-diastolic brachial artery diameters was used for baseline diameters, and the mean of 3 peak end-diastolic diameters during reperfusion phase was used for maximum artery diameter.

Cardiovagal BRS. Cardiovagal BRS was determined using Valsalva's maneuver as previously described. [5, 33] After 15 min in the seated upright position, subjects performed Valsalva's maneuver by forcibly exhaling against a closed airway. Subjects were asked to maintain an expiratory mouth pressure of 40 mmHg for 10 seconds. The R-R interval of the ECG and beat-by-beat blood pressure were measured continuously. Subjected performed 3 Valsalva's maneuver at 5 min intervals during which heart rate and BP returned to baseline levels. Data for cardiovagal BRS were recorded and analyzed by waveform browsing software (Windaq 2000) during the phase IV overshoot. Systolic

blood pressure values were linearly regressed against corresponding R-R intervals from the point where the R-R intervals began to lengthen to the point of maximal systolic blood pressure elevation. [25]

Statistical Analyses. Descriptive statistics were used for the analysis of subject characteristics. A significance level of $p < 0.05$ was set *a priori* to determine statistical significance. Physiological variables were compared before and after training period using one-way ANOVA. In the case of a significant ANOVA, LSD's post-hoc analysis was used to determine group differences. In order to determine associations between changes in variables of interest after training, Pearson's correlation coefficient were used.

RESULTS

Twenty four middle-aged and older adults completed the 12-week swim training program whereas 19 subjects completed relaxation/stretching exercise (attention control) program. Subject adherence to the supervised exercise session was >99%. Before the intervention period (at baseline), there were no significant differences in any of the physical characteristic variables between the swimming intervention and the attention control groups (Table 3.1).

Subjects in the swimming intervention group were able to gradually and significantly increase their daily swimming distance from the start of the intervention. For the first 4 weeks (20-40 min per session), subjects swam 550±40 to 1,005±70 m/day. During the final week, subjects averaged 1,417±83 m/day. The mean distance swum

during week 12 was significantly greater than that during week 4 (the start of the 45 min per session swimming). Maximal oxygen consumption on treadmill did not change significantly with the swimming training (Table 3.1). Body mass, adiposity, plasma concentrations of cholesterol, glucose or inflammatory cytokines did not change in either group throughout the intervention period.

As shown in Table 2, there were no group differences in casual blood pressures at rest and 24-h, daytime, or nighttime ambulatory blood pressures at the baseline. Casual (Figure 3.1) and daytime systolic blood pressures decreased significantly ($p<0.05$) with swimming training. A reduction in systolic blood pressure after 12 weeks of swimming training was approximately 9 mmHg. Casual diastolic and mean arterial blood pressures were reduced by 4 and 7 mmHg. Daytime diastolic and mean blood pressures decreased to a similar extent. But these changes did not reach statistical significance. Nighttime blood pressure did not change with the swimming intervention. There were no significant changes in blood pressures in the attention control group.

Carotid systolic blood pressure decreased significantly after swimming training (Table 3.3). Pulse wave velocity and augmentation index did not change significantly in either group during the study period. Swimming exercise produced a 21% increase in central arterial compliance compared with baseline (0.17 ± 0.01 vs. 0.14 ± 0.01 $mm^2/mmHg$; $p<0.05$; Figure 3.2) and a ~12% reduction in the β-stiffness index. No such change was observed in the attention control group.

Univariate correlation analyses were performed to determine which physiologic variables were associated most closely with changes in central artery compliance. The

improvement in carotid artery compliance was not related to changes in arterial blood pressure and other physiologic variables (e.g., body mass, plasma lipid and lipoproteins, fasting plasma glucose, or aerobic fitness).

Flow-mediated dilation (FMD), which was used as an index of endothelial function, improved significantly after 3 months of swimming exercise training (Figure 3.3). FMD increased from 3.3±0.9 to 7.2±1.1 %. There was no significant change in FMD in the attention control group. The improvement in FMD was not related to changes in arterial blood pressure and other physiologic variables (e.g., body mass, plasma lipid and lipoproteins, fasting plasma glucose, or aerobic fitness).

Cardiovagal baroreflex sensitivity (BRS) responses to swimming exercise training are presented in Figure 3.4. Regular swimming exercise increased cardiovagal BRS significantly from 4.1±0.5 to 6.1±0.7 ms/mmHg. There was no significant change in cardiovagal BRS in the attention control group. At baseline, several hemodynamic variables at rest were significantly related to cardiovagal BRS in the pooled study population, including heart rate (r=-0.37), systolic blood pressure (r=-0.36), mean blood pressure (r=-0.39) and diastolic blood pressure (r=-0.37). There were no significant physiological correlates of the change in cardiovagal BRS in response to the swimming exercise intervention.

DISCUSSION

Despite the fact that swimming is widely recommended as exercise modality for heath promotion and disease prevention [16-18], little information is available concerning the influence of regular swimming exercise on CHD risk profile. The major new findings from the study are as follows. First, a relatively brief (12-week) period of swimming exercise decreased both central and peripheral systolic blood pressure in middle-aged and older adults. Second, the reductions in systolic blood pressure were associated with the corresponding reductions in arterial stiffness. Third, regular swimming exercise appears to be a sufficient stimulus to improve cardiovagal BRS. To the best of my knowledge, the present study is the first interventional data to demonstrate the effect of swimming training on both CHD traditional risk factors and vascular functions in previously sedentary individuals. Importantly, the exercise program which consisted of moderate intensity swimming is consistent with the recommended by health care organizations of general health maintenance [17] and can be performed by most, if not all, healthy individuals of this age.

Hypertension poses a major public health problem as the most prevalent vascular disease. Exercise training is an intervention that can decrease blood pressure without negative side effects. Since swimming is a non-weight-bearing, rhythmic, dynamic form of endurance exercise with a low musculoskeletal injury incidence, a substantial number of patients may be directed to swimming as their primary form of physical activity. As such, it is important to determine whether this type of exercise exerts antihypertensive effects. Little information, however, exists on the potential hypotensive effects of regular

swimming exercise. A previous intervention study, in which previously sedentary stage1 or 2 hypertensive individuals were randomized into either 10-week swimming training or sedentary control, demonstrated reductions in systolic and diastolic blood pressure averaging 7 and 3 mmHg, respectively. [51] In the present study, swim training produced an approximately 9 mmHg reduction in systolic blood pressure whereas no significant changes in blood pressure were observed in the attention control group. The relative magnitude of the blood pressure reduction observed after swim training was slightly higher than the previous intervention study but slightly lower than that typically showed in land-based physical activity. Land-based exercise training using training programs equivalent (of similar intensity, frequency and duration) to the present study reported 12 and 6 mmHg reductions in systolic and diastolic blood pressure, respectively. [52, 53]

There are a number of potential explanations for the decrease in blood pressure with regular swimming exercise. Changes in blood volume and the volume regulating hormones have been suggested as potential mechanisms responsible for the antihypertensive effects of exercise training. However, significant changes in plasma or blood volumes after the swimming exercise despite the fact that the training program resulted in a reduction both in systolic and in diastolic blood pressure. [51] More likely explanation resides in changes in vascular function.

Among various vascular functions, the reduction in arterial compliance is associated with impaired cardiovascular function and elevated disease risk. [2] Recent findings indicate that regular aerobic-endurance exercise attenuates age-associated reductions in large artery compliance, and partially restores compliance in previously

sedentary middle-aged and older adults. For example, daily brisk walking for ~3 months improved carotid artery compliance in previously sedentary middle-aged and older men[13] and postmenopausal women. [44] The present study is the first to demonstrate that the age-associated reduction in central arterial compliance can be favorable modified by swimming exercise. The cross-sectional study (Study 1) indicated that central arterial compliance was greater in swimmers than in age-matched sedentary controls, and the level of arterial compliance was not different from that of runners. The present follow-up intervention study allowed us to confirm the cross-sectional observations by demonstrating that regular swimming exercise can increase central arterial compliance in previously sedentary middle-aged and older adults. The results showed a 21% increase in arterial compliance and a 12% reduction in the β-stiffness index after 3 months of regular swimming exercise. Interestingly, the absolute value of central arterial compliance after training was not different from that observed in the middle-aged and older endurance swimmers reported in study 1. These results suggest that relatively short-term swimming exercise can restore some of the loss of arterial compliance in healthy middle-aged and older adults. The enhanced carotid arterial compliance associated with habitual swimming exercise was independent of changes in body composition, blood pressure, and other traditional CHD risk factors, suggesting primary effect of swimming exercise on the arterial wall.

There is surprisingly limited direct evidence as to the mechanism mediating the favorable effects of habitual aerobic exercise on arterial stiffness. A major limitation in this regard is the fact that central arteries are inaccessible in humans, both physically and

with respect to experimental manipulation of potential signaling pathways. One possibility is that exercise minimizes or reverses age-related structural changes in the arterial wall. This may contribute in settings of prolonged exercise training; however limited data from experimental animals do not show an association between habitual exercise-related reductions in large elastic artery stiffness and changes in total expression of major structural proteins.[54] Arterial compliance also can be altered over a short time period via modulation of the sympathetic-adrenergic tone of smooth muscle cells in the arterial wall. [55] In this context, it is possible that regular exercise increased arterial compliance by reducing the chronic suppressive influence exerted by sympathetic-adrenergic tone either directly or by enhancing the sympathoinhibitory effect of NO. [56]

Endothelium plays an important role in the local regulation of vascular tone and structure, mainly by nitric oxide (NO) synthesis and action. [9] Endothelial dysfunction in general and impaired endothelial-dependent vasodilation (EDD) in particular have been associated with the pathogenesis of atherosclerotic vascular disease and acute cardiovascular events. [10] Habitual exercise is associated with enhanced EDD during aging. Three months of land-based exercise (primarily walking) improved EDD in previously sedentary middle-aged and older men [14] and in patients with metabolic syndrome but no clinical disease.[57] To the best of my knowledge, the present study demonstrated, for the first time, that regular swimming exercise is an effective lifestyle intervention, similar to land-based exercise, for reversing the loss in EDD in middle aged and older sedentary peers. Improved endothelial function, if sustained should reduce the risk of cardiovascular disease and related thrombotic events in this population. Moreover,

this improvement was not associated with changes in body mass, adiposity, arterial blood pressure, total cholesterol or VO_2max, suggesting a primary effect of swimming exercise on endothelial cell function.

Exercise-induced increases in shear stress as a result of increased blood flow and pulse pressure to both active and nonactive limbs are thought to be important stimuli for endothelium-mediated vasodilator adaptation to aerobic training because improvements in EDD are observed in arteries outside the exercising limbs. What are the physiological mechanisms underlying the effects of regular swimming exercise on endothelium-dependent vasodilation? Evidence in both humans and experimental animals focused on land-based exercise implicate increased NO bioavailability and reduced degradation of NO by reactive oxygen species (ROS). Inhibitors of endothelial NO synthase (eNOS), the enzyme responsible for NO production in the vascular endothelium, have a much greater effect in suppressing resting blood flow [58] and EDD [43, 59] in exercising older humans and animals than in sedentary controls, indicating augmented basal and stimulated NO bioavailability. Indeed, differences in EDD between sedentary and aerobically exercise-trained older humans and rodents are mediated in part by differences in NO bioavailability. [43, 59, 60] Moreover, in previously sedentary healthy middle-aged and older men, daily brisk walking restores basal NO production to levels observed in young men. [58] Aerobic training-induced improvements in EDD and NO bioavailability are associated with an increase in eNOS gene and protein expression in older rats [60] and an increase in eNOS protein and serine 1177 phosphorylation of eNOS in patients with coronary artery disease [15], but no information is yet available on healthy older humans.

Habitual aerobic exercise may suppress the development of vascular oxidative stress with ageing. This is based on the fact that FMD was not augmented by ascorbic acid (antioxidants) infusion in the older endurance-trained men.[43] Direct evidence that voluntary aerobic exercise reduces vascular oxidative stress with ageing comes from recent work showing that in old mice given access to running wheels, aortic staining for nitrotyrosine, a cellular marker of oxidative modification of proteins, is markedly lower than in old cage controls and similar to young mice. [59] In patients with coronary disease, aerobic exercise training is associated with decreased production of reactive oxygen species and expression of the oxidant-producing enzyme, NADPH oxidase, in the mammary artery. [61] The exact mechanism(s) by which habitual endurance exercise suppresses oxidative stress have not been determined. However, exercise training has been associated with both reduced production of ROS [62] and augmented antioxidant defenses. [63]

Three previous intervention studies [64-66] in middle-aged and older adults based on land-based exercise (primarily walking) found no change in cardiovagal BRS whereas Monahan et al.[25] demonstrated increases in cardiovagal BRS after aerobic exercise training. The use of a less intense exercise stimulus is one explanation for the differences in results between Monahan et al. and the three other studies showing no changes in BRS. Specifically, the total volume of exercise training performed in Monahan's study (5-6 days/week for 45 min/session for 13.5 weeks) was greater than that performed in those three studies (<3 days/week for 20-43 min/session for 6-12 weeks). There were no differences in relative magnitude of cardiovagal BRS improvement after endurance

exercise between the present swimming intervention and Monahan's land-based (walking) intervention study using similar exercise intensity and duration. The previous land-based exercise intervention study showed ~50% increases in cardiovagal BRS in subjects who had higher value after exercise whereas the present study demonstrated ~45% improvements. To the best of our knowledge, this is the first study to demonstrate the beneficial effects of regular swimming on cardiovagal BRS. It is important to emphasize that the increase in cardiovagal BRS was achieved within a 3 month period using a swimming exercise, frequency, and intensity of exercise that most, if not all, healthy middle-aged and older adults are able to perform. The increases in cardiovagal BRS observed with regular swimming exercise were not related to changes in body mass/composition or reductions in resting blood pressure.

In the present intervention study, we found no physiological correlates of increases in cardiovagal BRS. We did not even observe significant correlations between changes in arterial compliance and BRS. One possible explanation is that enhanced carotid artery compliance after swimming exercise may be attributed to stimulus transduction and afferent responsiveness rather than to carotid artery baroreceptor transduction. Another possibility is that an increase in blood volume contributed to the increase in cardiovagal BRS with swimming exercise intervention. Blood volume has been reported to influence absolute blood pressure responses during Valsalva maneuver [67]. Unfortunately, we did not measure blood volume in the present study, but the result of previous swim intervention study [51] indicated that blood volume did not change in response to moderate swimming exercise program.

CONCLUSION

In conclusion, the results of the present study support the idea that swimming exercise elicits hypotensive effects as well as the improvements in vascular function in previously sedentary middle-aged and older adults. This is a clinical important finding because swimming can be a highly suitable exercise mode alternative to land-based exercises for prevention and treatment of risk factors for cardiovascular disease as well as health promotion.

Table 3.1. Selected subject characteristics

Variable	Attention Control		Swimming Training	
	Before	After	Before	After
Men/women (n)	4/15	4/15	7/17	7/17
Age (year)	61 ± 2	-	58 ± 2	-
Height (cm)	165 ± 2	165 ± 2	168 ± 2	167 ± 2
Body mass (kg)	87 ± 4	86 ± 4	81 ± 3	80 ± 3
Body mass index (kg/m^2)	32 ± 1	31 ± 1	29 ± 1	28 ± 1
Body fat (%)	42 ± 2	43 ± 2	39 ± 2	38 ± 2
Lean body mass (kg)	45 ± 2	44 ± 2	45 ± 2	46 ± 2
Physical activity score (unit)	12 ± 2	-	14 ± 2	-
VO_2max (ml/kg/min)	27 ± 1	27 ± 1	28 ± 1	30 ± 1
Total cholesterol (mg/dl)	211 ± 10	196 ± 9	202 ± 8	196 ± 9
LDL-cholesterol (mg/dl)	137 ± 10	132 ± 7	127 ± 8	120 ± 10
HDL-cholesterol(mg/dl)	53 ± 4	52 ± 5	57 ± 4	60 ± 4
Triglyceride (mg/dl)	128 ± 18	125 ± 15	120 ± 12	121 ± 16
Glucose (mg/dl)	102 ± 2	97 ± 2	97 ± 3	94 ± 2
Hemoglobin A1c (%)	4.5 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.5 ± 0.1
IL-6 (pg/mL)	5.2 ± 0.9	4.8 ± 1.1	5.2 ± 2.0	4.8 ± 0.8
IL-7 (pg/mL)	4.2 ± 0.7	2.9 ± 1.0	3.4 ± 0.8	3.5 ± 0.6
IL-10 (pg/mL)	20.4 ± 5.5	19.8 ± 7.1	26.2 ± 10.1	29.1 ± 13.3
TNF-α (pg/mL)	7.5 ± 0.6	7.7 ± 0.9	6.2 ± 0.6	6.4 ± 0.5

Values are mean±SEM. VO_2max=maximal oxygen consumption, IL=interleukin, TNF=tumor necrosis factor,

Table 3.2. Casual blood pressure at rest and 24-hour ambulatory blood pressure

Variable	Attention Control		Swimming Training	
	Before	After	Before	After
Casual Blood Pressure				
Systolic blood pressure (mmHg)	129 ± 4	129 ± 4	131 ± 3	122 ± 4*
Mean blood pressure (mmHg)	96 ± 3	96 ± 3	97 ± 2	90 ± 3
Diastolic blood pressure (mmHg)	76 ± 2	75 ± 2	76 ± 2	72 ± 2
Pulse pressure (mmHg)	53 ± 3	54 ± 1	55 ± 2	51 ± 2
24-hour Ambulatory Blood Pressure				
Daytime systolic blood pressure (mmHg)	132 ± 8	129 ± 5	128 ± 5	119 ± 2*
Daytime mean blood pressure (mmHg)	98 ± 4	95 ± 2	95 ± 3	89 ± 2
Daytime diastolic blood pressure (mmHg)	79 ± 3	80 ± 2	78 ± 3	73 ± 2
Daytime pulse pressure (mmHg)	49 ± 6	49 ± 4	50 ± 3	46 ± 2
Nighttime systolic blood pressure (mmHg)	110 ± 3	108 ± 4	109 ± 4	104 ± 3
Nighttime mean blood pressure (mmHg)	82 ± 2	78 ± 4	81 ± 3	78 ± 2
Nighttime diastolic blood pressure (mmHg)	65 ± 2	63 ± 2	65 ± 2	62 ± 2
Nighttime pulse pressure (mmHg)	45 ± 7	45 ± 4	45 ± 3	43 ± 3

Values are mean±SEM. * $p<0.05$ vs. Before

Table 3.3. Selected hemodynamic measures

Variable	Attention control		Swimming training	
	Before	After	Before	After
Heart rate (beats/min)	63 ± 3	59 ± 2	62 ± 2	58 ± 2
Carotid systolic pressure (mmHg)	112 ± 3	112 ± 3	109 ± 4	102 ± 2*
Carotid pulse pressure (mmHg)	41 ± 2	40 ± 2	41 ± 2	37 ± 1
Carotid artery diameter (mm)	6.8 ± 0.3	6.9 ± 0.2	7.0 ± 0.2	6.9 ± 0.2
Brachial artery diameter (mm)	4.1 ± 0.2	4.2 ± 0.3	3.9 ± 0.1	4.0 ± 0.1
Cardiac output (L/min)	4.2 ± 0.2	4.8 ± 0.4	4.4 ± 0.4	4.9 ± 0.3
cfPWV (cm/sec)	1139 ± 63	1143 ± 65	1190 ± 58	1146 ± 54
baPWV (cm/sec)	1375 ± 46	1378 ± 61	1346 ± 39	1331 ± 35
faPWV (cm/sec)	940 ± 17	945 ± 30	914 ± 20	894 ± 17
Carotid AI (%)	26 ± 3	31 ± 3	30 ± 2	26 ± 2

Values are mean±SEM. * $p<0.05$ vs. Before.

cfPWV=carotid-femoral pulse wave velocity, baPWV=brachial-ankle pulse wave velocity, faPWV=femoral-ankle pulse wave velocity, AI=Augmentation index

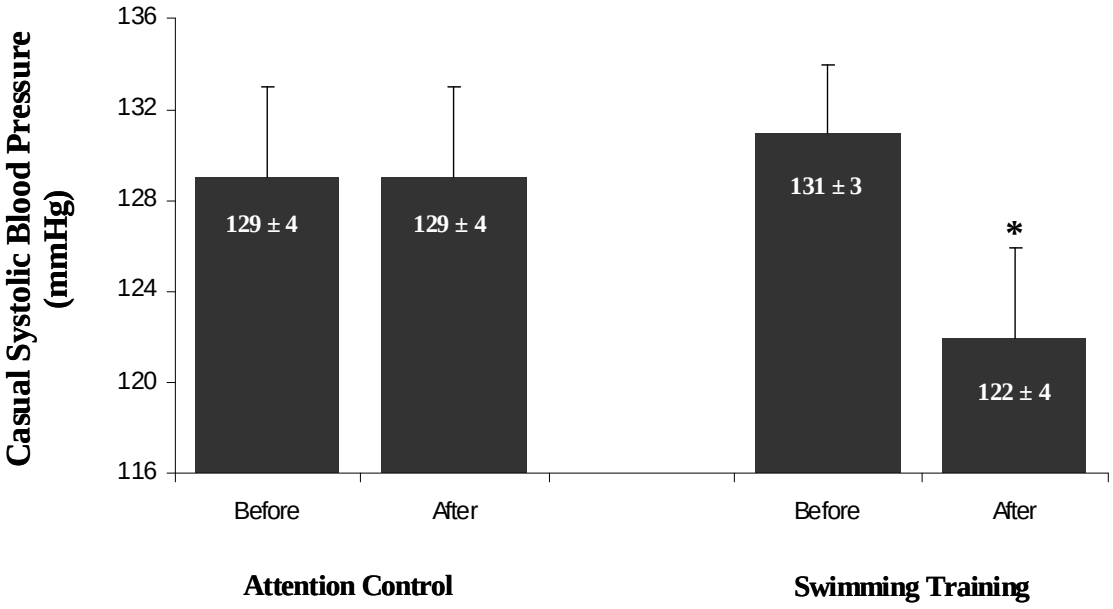

Figure 3.1. Casual systolic blood pressure.
Values are mean±SEM. *p<0.05 vs. Before.

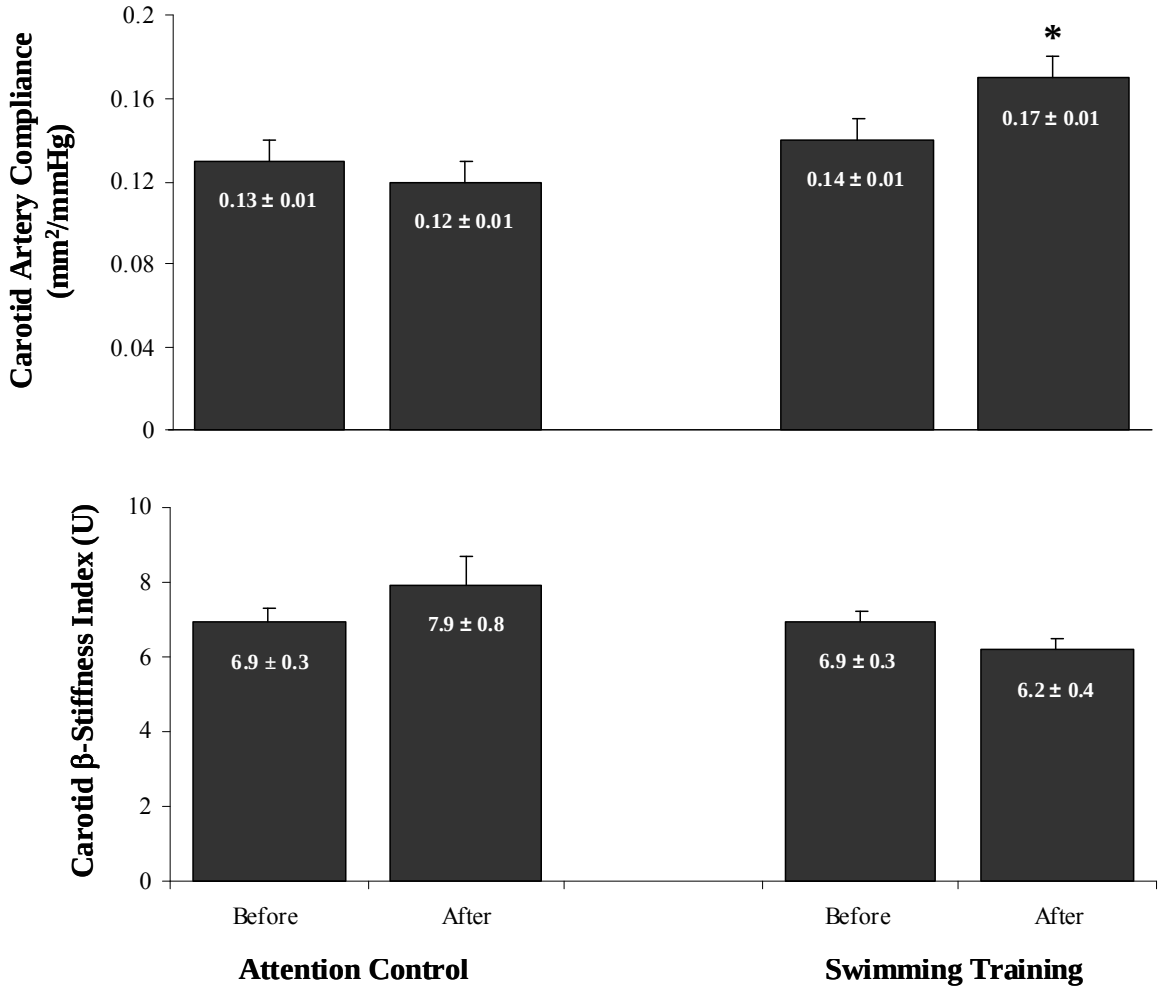

Figure 3.2. Carotid artery compliance and β-stiffness index.

Values are mean±SEM. *p<0.05 vs. Before.

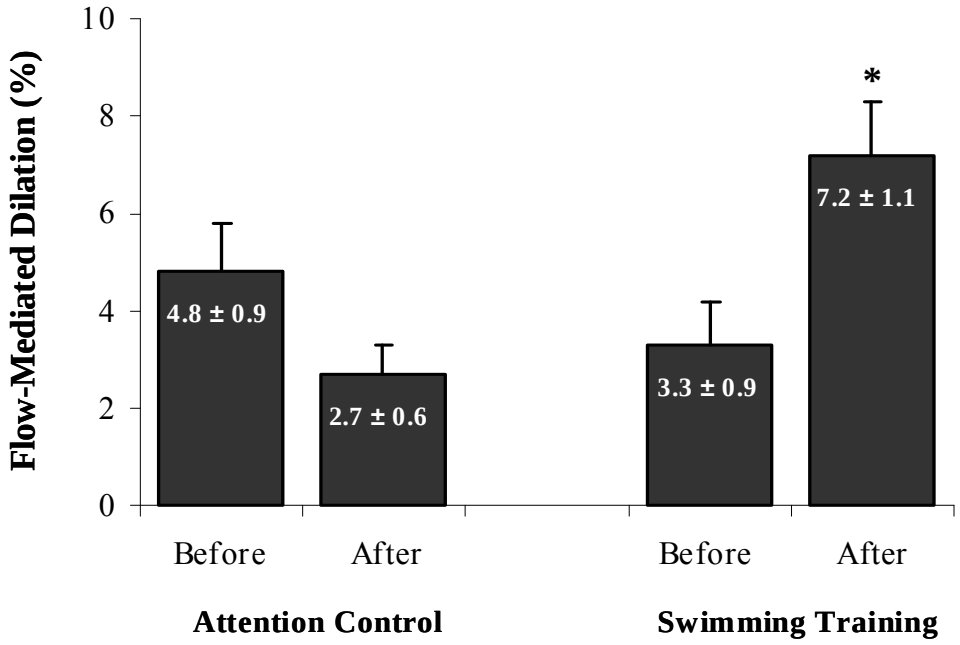

Figure 3.3. Endothelial-dependent vasodilation measured by flow-mediated dilation (FMD).

Values are mean±SEM. *p<0.05 vs. Before.

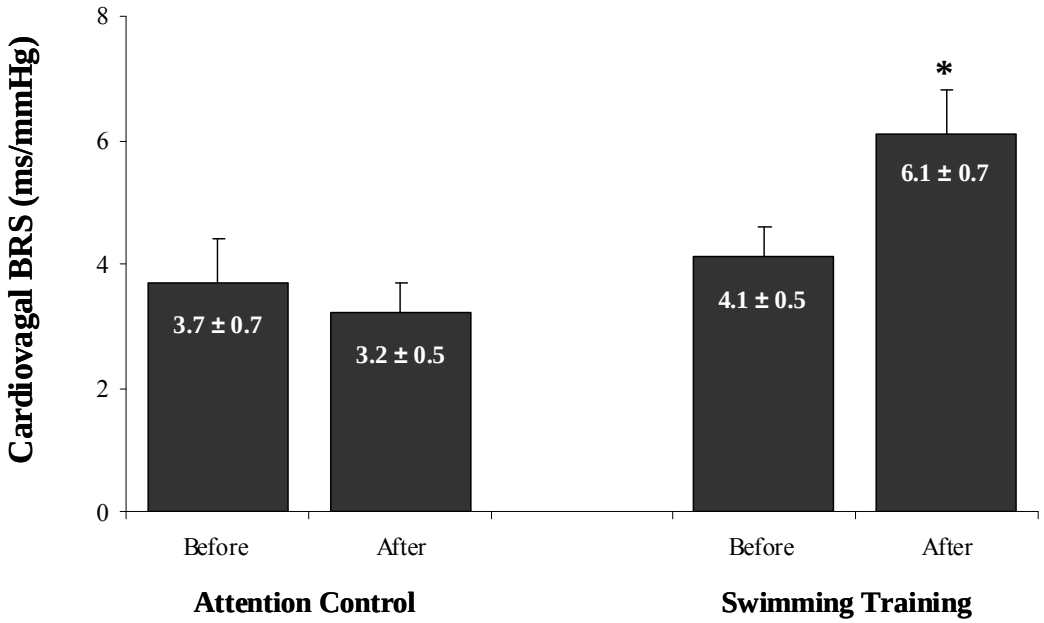

Figure 3.4. Cardiovagal baroreflex sensitivity.

Values are mean±SEM. *p<0.05 vs. Before.

Chapter 4. Review of Literature

Arterial Compliance and Aerobic Exercise

Arterial compliance reflects the ability of an artery to expand and recoil with cardiac pulsation and relaxation. [68] The inverse term of arterial compliance is arterial stiffness. In sedentary humans, the compliance of large sized arteries in cardiothoracic region decreases with advancing age. Tanaka et al. reported 40-50% differences in large elastic arterial compliance between age 25 and 75 yr in healthy adults without clinical disease or major coronary risk factors.[13] These reductions are identified as an independent risk factor for future cardiovascular disease. [55] Arterial stiffness primarily is determined by the intrinsic elastic properties of the artery. The elements of the arterial wall that determine its compliance are the composition of elastin and collagen (structural determinant) and vasoconstrictor tone exerted by its smooth muscle cells (functional determinant). [69] The changes of arterial compliance may be induced by both structural and functional factors. Elastic fibers are the primary determinant of the vascular compliance under physiologic conditions. Calcium deposition in elastic fibers progresses with age, and the degeneration and the decrease of elastic fibers may cause a decrease in arterial wall compliance. When the smooth muscles in the arterial wall are strained, collagen fibers connected in series are stretched and lose distensibility.[70] Functional changes that result in increased vascular smooth muscle tone such as increased sympathetic nervous system activity and bioactivity of locally synthesized

vasoconstrictor molecules (e.g., endothelin-1) and reduced endothelial dilator production, perhaps linked to oxidative stress, also likely contribute.[71]

Habitual physical activity attenuates the increase in arterial stiffness that occurs with aging. The evidence underlining the beneficial role of physical activity has been derived from both cross-sectional studies showing that participants who are more physically active have less arterial stiffness than their sedentary counterparts and intervention studies showing favorable arterial adaptations after the period of aerobic exercise. Tanaka et al [13] compared arterial compliance between 54 sedentary, 45 recreationally active and 53 endurance exercise-trained subjects. They reported that central arterial compliance was about 40% higher in endurance-trained older men than in sedentary peers. In the same study, they also did the intervention study and observed a 25% increase in arterial compliance and a 20% reduction in the β stiffness after 3 months of regular aerobic exercise in sedentary middle-aged and older men. In addition, aerobic exercise can improve arterial stiffness in individuals who have cardiovascular diseases. Sugawara and colleagues [72] demonstrated that both moderate and vigorous intensity exercise training induce parallel reductions in β-stiffness index (indicator for arterial stiffness). Moreau et al. [8] reported that carotid arterial stiffness was decreased by ~25% in healthy postmenopausal women after 3 months of aerobic training. Edwards et al [73] assessed arterial stiffness before and after 12 weeks of either aerobic exercise or standard care in coronary artery disease (CAD) patients and reported decrease in arterial stiffness in endurance exercise group.

The possible mechanisms by which regular aerobic exercise lowers central arterial stiffness are both structural and functional adaptations. In animal studies, exercise for 16 wk retarded the age-associated decrease in aortic compliance by decreasing elastin degeneration and calcium deposition in the aortic media.[74, 75] In humans, it may be difficult to expect that the same training effects could be obtained in a short period of training. This may contribute in settings of prolonged exercise training; however, there are no data available to support this mechanism. Functional adaptations may be involved, especially in response to shorter term exercise training. Regular aerobic exercise results in enhanced endothelium-dependent vasodilation [14] and restraint of endothelium-derived vasoconstrictor hormones.[76] These changes might be associated with a modulation of the sympathetic adrenergic tone of smooth muscle cells in the arterial wall. In this context, it is possible that regular exercise increased arterial compliance by reducing the chronic suppressive influence exerted by sympathetic adrenergic tone either directly or by enhancing the sympathoinhibitory effect of nitric oxide. [55]

In contrast to findings on healthy middle-aged and older adults, regular aerobic exercise may not improve arterial stiffness in certain groups of adults with chronically elevated arterial blood pressure. Hypertensive patients have stiffer aortas than normotensive control subjects. [77] Ferrier et al. [78] demonstrated that moderate aerobic exercise training for 8 weeks did not improve large-artery stiffness in patients with isolated systolic hypertension. Seals and co-workers [79] determined the efficacy of three months of either aerobic exercise or dietary sodium restriction for reducing systolic blood pressure (SBP) and large arterial stiffness in postmenopausal women with elevated initial

levels. They reported that sodium restriction lowers SBP more than does aerobic exercise. In contrast, Collier et al. [80] reported the benefits of aerobic exercise on blood pressure and arterial stiffness in pre- or stage-1 essential hypertension. The results showed decrease in central PWV and peripheral PWV after 4 weeks of aerobic training; however these findings were derived from indirect estimates of arterial stiffness.

Swimming Exercise

Epidemiological studies demonstrate that moderate aerobic exercise reduces overall cardiovascular mortality presumably through actions on a broad range of cardiovascular risk factors. [81] A variety of national and international organizations have published a number of exercise guidelines. [17, 82, 83] According to these guidelines, any activities that involve large muscle groups, rhythmic and dynamic in nature are recommended as the modality of physical activity. Accordingly, swimming is often recommended as a mode of exercise for the prevention and treatment of hypertension and cardiovascular disease. Swimming is an attractive form of exercise for all ages because it is largely isotonic, involves multiple muscle groups. Because it does not involve the bearing of body weight, adverse musculoskeletal effects are rare. Moreover, because of colder temperature as well as increased thermoconductivity of water, incidence of heat-related illness is small.

Although swimming is generally accepted to be an excellent exercise for aerobic conditioning, the recommendations have arisen from extrapolation of data from land-based exercise which is different in environment, body position and muscle work.

Swimming training activates a relatively smaller muscle mass compared with a land-based exercise. In this review, using the limited research studies conducted in swimming and swimmers, the focus was placed on the following 4 topics: 1) environmental factors; 2) physical characteristics of swimmers; 3) respiration; 4) swimming and coronary heart disease (CHD) risk factors.

I. Environmental Factors

1) Buoyancy

Body density is slightly higher than that of water. As a result, the magnitude of the buoyant force is smaller than the body weight, and a person tends to sink. Normally, the body can be maintained afloat by inhalation of more air or by muscular work or a combination of both. Inhalation of 1 L of air increases buoyant force by approximately 10 N. Consequently, the buoyant force fluctuates synchronously with the breathing frequency. The amount of water displaced for a given body weight is affected by body composition. Lean body mass displaces considerably less than adipose tissue of an equivalent weight and so is an important determinant of buoyant force. [84]

2) Passive and Active Drag

The main purpose of the propulsive work in swimming is to overcome the resistance of the water (drag) on the body. Drag has been quantified by towing subjects in

an outstretched body position (passive drag), and has been shown to increase approximately in proportion to the velocity squared.

Due to swimming movements, passive drag values are not representative of the "active" drag experienced by the swimmer during actual swimming. Active drag varies as a function of stroke cycle, body configurations, and relative velocity of the body segments in the surrounding water. Active drag was found to be approximately 1.5 to 2 times greater than passive drag at corresponding velocities. [85]

3) Propulsion

The drag force produced by arm and leg movements and lift forces combine to provide propulsion during the swim stroke. Acceleration of the swimmer's body is synchronous with stroke rhythm. In breaststroke, acceleration is large during the propulsive phases of both arm pull and leg kick, while in front crawl, acceleration within the stroke cycle is small. [85] Measurement of acceleration within the stroke cycle has been suggested as an indicator of swimming efficiency. [86] The observation of Holmer [87] indicated a difference in the energy cost of the 4 strokes, a dichotomy between the 2 symmetric strokes (butterfly and breaststroke) and the asymmetrical strokes (backstroke and front crawl). The latter is more economical. In a calculation of the total energy expenditure of swimming, the energy spent in accelerating the body is probably negligible in the backstroke and front crawl. In breaststroke, however, this energy cost might be significant.

4) Thermal stress

4.1) Body heat loss

Heat dissipation from the body increases during periods of exercise in the water because of the very high convective heat transfer from the skin to the water. Within a few minutes after immersion, a swimmer's skin temperature lowers to the water temperature within 1°C if one stays immobile. With sustained hard work such as swimming, however enough heat is produced to balance the heat loss, even in water at a temperature of 24-25°C. Thus, most swimmers can maintain an unchanged body temperature. [88] Body temperatures were lowest among the lean less-trained swimmers, whereas lean, competitive swimmers had a less extensive body cooling because of their high energy output and short exposure time (high swimming speed). [88]

4.2) Optimal water temperature

For most swimmers the optimal temperature for maximal performance in sprints appears to be around 28-30°C, since little is stored and performance is not be impaired.[88] In longer swimming races and during training, optimal temperature might be somewhat lower. For recreational swimming, where energy expenditure is low or moderate, a water temperature of 28°C or warmer seems advisable for maintaining thermal balance.

II. Physical characteristics of swimmers

Particular kinds of body size, shape, and proportions may produce important prerequisites for successful participation in many sports. Among athletes, swimmers are

taller and heavier than a reference population. At the 1976 and 1980 Olympics, the finalists were both taller and heavier for their height by 2.8 kg than the non-finalists [89]. In female Olympic swimmers, Khosla [89] reported that 23 medalists in swimming events in Munich and Montreal had heights equal to and exceeding 174 cm. This places them at the upper end of the distribution of heights for women aged 18 to 24 years in the US. In the study of 30 Swedish girl swimmers, the girls were taller than the Swedish standards and had normal weight. [90] A three-year study by Andrew et al. [91] of male club swimmers indicated greater body size after 12 years of age compared with a reference sample of non-athletes. Height is advantageous in swimming for of many reasons. According to hydrodynamics theory, a taller individual requires less power than a smaller person to advance in water at the same speed. Additional advantages of height in swimming are derived from the greater distance covered by the limbs during the stroke and in the ability to flip turn further from the end of the pool. Thus, a taller swimmer covers a lesser distance in a race.

III. Respiration

Respiration is normally synchronized with the rhythm of movement and this is particularly evident in swimming, which involves a forced inspiratory phase against increased pressure from the surrounding water on the thoracic cage. The inspiratory phase is rapid, followed by slower expiration. Breathing during the front crawl is dependent on the speed of arm movement and can occur when the head is turned to the side in coordination with the arm stroke. In other words, swimming causes a restriction

on respiration which may affect ventilation and gas exchange in the lungs. [86] Previous research indicates that maximal pulmonary ventilation (V_E) during maximum work in free swimming was lower than on land. [92-94] The lower V_E is attributed to decreases in both respiratory rate and tidal volume. The decrement in tidal volume during high intensity prone swimming may be due to the effects of hydrostatic pressure, increased airflow resistance, position of the chest cage, and the involvement of respiratory muscles in arm stroke. [95] During maximum work, respiratory rate is higher in treadmill walking. [95] This is probably related to the free breathing pattern in walking whereas in swimming the respiratory rate is limited by the number of strokes per minute. In back stroke in which free breathing is possible, V_E has been reported to be similar to that measured on treadmill. [94]

In addition, the lower respiratory exchange ratio was also reported in the literature.[90, 94, 95] These may result from a lower alveolar ventilation in swimming exercise in comparison with running. This may indicate an accumulation of more CO_2 during swimming than running and probably results in a higher alveolar P_{CO2}.

IV. Swimming and Coronary Heart Disease (CHD) Risk Factors

1. Maximal Aerobic Power

Maximal aerobic power, VO_2max, is a reproducible measure of the capacity of the cardiovascular system to deliver blood to a large muscle mass involved in dynamic work.[96] Longitudinal studies show that higher levels of VO_2max are associated with a

lower mortality rate from heart disease, even after statistical adjustments for other disease-related risk factors. [12] Moreover, VO_2max is viewed as the single best variable to define the overall physiological changes that occur with aging. [97] VO_2max declines with aging (approximately 1% per year for each year after age 25) [98], irrespective of the amount of training that an individual undergoes. However, the degree to which this decline occur is significantly affected by amount and intensity of physical activity[98]. In addition, VO_2max is an important indicator of physiological functional capacity (PFC). [99] PFC is defined as the ability to perform the physical tasks of daily life and the ease with which these tasks can be performed. [100] PFC also declines at some point with advancing age in human. The experimental approach to studying the effects of aging on PFC is to analyze the peak exercise performances of highly trained athletes with increasing age. Cross-sectional [100] and longitudinal [101] studies of swimming performance reported that 1) peak swimming performance decreases linearly until 70-80 yr of age, where the decline becomes exponential; 2) the rate and magnitude of the age-associated declines in both short- and long duration events are greater in women than in men; 3) these sex-related differences in the decline in swimming performance with age are greatest in short-duration events; and 4) peak performance can be maintained to a slightly older age range in the short-duration events, and the rate and overall magnitude of performance declines are smaller than long-duration events.

Experimental methods

The measurement of VO_2max indicates the cardiorespiratory fitness of an individual and is used in development of an exercise prescription. [102] The evaluation of this parameter is submitted to the principle of the specificity of exercise which suggests that maximal aerobic power tests should be conducted in the real exercise conditions. This principle is even more important in swimming.

Determination of swimming VO_2max has been performed with tethered swimming [94, 103], free swimming [94, 95, 104], and in a swimming flume. [105, 106] The most appropriate way by which swimming VO_2max can be obtained is by the use of a swimming flume. With this apparatus, the water circulates in a specially arranged pool so that the swimmer can swim on the spot at various speeds. [107] Work loads are increased by progressively increasing the water speed until the swimmer is unable to maintain the swimming speed for at least 2 min. Although the swimming flume has been proved to be very useful to study hemodynamic and metabolic responses in swimming [104], its utilization as an evaluation tool is considerably limited by its accessibility.

Free swimming has also been used by many investigators to evaluate energy cost and the maximal oxygen uptake in swimming. [94, 95] In these tests, the gas collection bag was carried by a technician or attached to a cart which followed the swimmer along the side of the pool. The main disadvantage of a free swimming is that the conventional mouthpiece and valve equipment along with the tubing and supporting paraphernalia might become awkward for the swimmer and might refrain him/her from performing adequately. [85]

In the tethered swimming test, the swimmer is attached to a pulley-weight system. The pull on the swimmer was directly backward as the first pulley was immersed and aligned behind the subject. The test consists of 3-minute swims with a 3- to 5-minute rest period. Work loads are increased progressively by adding weights to the apparatus. This is continued until the swimmer is no longer able to support the weight for 3 min. [94, 108] In tethered swimming, the body tends to take an oblique position with the heavy loads and the swimmer has difficulty finding support in a turbulent flow. Tethered swimming has also been shown to produce drag force which are at least double those of free swimming, drag forces for the upper arm being much smaller in free swimming. [85]

Despite these considerations, VO_2max values measured in tethered swimming have been found comparable with values measured in free swimming and flume swimming. Bonen et al.[108] compared the VO_2max between tethered swimming, free swimming and flume swimming obtained in swimmers. The results indicate that the VO_2max obtained from 3 different methods were highly correlated with each other ($r > 0.99$). These findings concur with those of Magel and Faulkner [94] who found a correlation coefficient of 0.90 between free and tethered swimming in 26 highly trained swimmers. Holmer et al.[104] have reported that the VO_2max during free and flume swimming are highly correlated ($r = 0.99$) and do not differ from each other.

Endurance training programs that increase VO_2max involve a large muscle mass in dynamic exercise, and include running, cycling, swimming or cross-country skiing. The VO_2max value during swimming may be expected to be different from that of other types of exercise because swimming is to a high degree an arm work, especially in front

crawl, and take place in horizontal position. Work with the legs can bring the metabolism to a higher level than exercise performed by the arms. The highest value for VO_2max is usually measured with an uphill running test, followed by a walking test up a grade on a treadmill, and then on a cycle ergometer. An arm ergometer test was about 70% of the VO_2max measured with the legs. [109] Assuming VO_2max running uphill as maximal value for a trained individual, the intensity and specificity of swimming training are determined how close to this value the swimmer can come during swimming. Several cross-sectional studies have compared the VO_2max obtained during running [94, 103, 104, 106], walking [95], cycling [93], and swimming. The recreational swimmers achieve 11-25% lower VO_2max during swimming compared with running values [92, 103, 106, 110, 111], and 11% [95] and 15% [93] lower VO_2max than cycling and walking VO_2max. The state of training and the specificity of exercise appear to influence VO_2max attained for work in a particular environment. Holmer et al. [104, 106] reported that elite swimmers attain a slightly lower VO_2max (6%) during swimming compared with running whereas others [94, 103] found the lack of a significant difference between tethered swimming and treadmill running VO_2max.

The differences between land-based exercise and swimming VO_2max have been associated with several factors that determine maximal aerobic power. The major determinants of oxygen uptake are systemic blood flow (cardiac output) and systemic oxygen extraction (arteriovenous oxygen difference). The lower VO_2max during swimming than that during running would have to be due to the differences in one or more of the following physiological variables.

1) Heart rate (HR)

The lower HR during swimming compared with running is one of the important factors contributing to a lower VO_2max during swimming. The studies of HR during swimming, running and cycling exercise showed a linear increase in HR in relation to increasing oxygen uptake. [92] Although the pattern of heart rate response during swimming was similar to that reported for land-based exercise, the maximal HR during swimming is significantly lower than those obtained during running for a similar time period. [112] Holmer [92] reported that maximal HR in swimming was 8 beats/min lower on the average than in cycling and 10 beats/min lower than in running. Lower maximal HR for swimming in comparison to land-based exercise has been noted by other investigators. In 1975, Magel et al. [110] reported maximal HR in tethered swimming13 beats/min lower than in treadmill running in 30 highly trained males. In a follow-up study, McArdle, Magel and colleagues [111] observed maximal HR in swimming 22 beats/min lower than in running in a similar age group of 19 male recreational swimmers.

Several factors are associated with the lowered HR during swimming compared with running, including the smaller size of the exercising muscles during swimming compared with running. The arms and chest muscle provide a greater contribution to propulsion in swimming, particularly in front crawl. In addition, minimal muscle work is needed to support the body in water because of the buoyancy effects, this may minimize loading of muscle mass in swimming compared with running.

Another possible explanation for lower heart rate in swimming compared with running might be the effect of water immersion. Schmid et al. [113] reported that in healthy

subjects, heart rate response to exercise on land and in water are similar up to a work load of 40% VO_2max, but become lower at higher work in water. In agreement with this, Christie et al. [114] showed that heart rate at the heavy exercise is significantly lower in water than on land, averaging 12 beats/min. They hypothesized that the lower HR associated with water immersion may be related to reductions in sympathetic neural outflow in water.

Other factors that may account for the significantly lower heart rate response to swimming compared with running are temperature regulation and heat dissipation in water. Water of swimming pool temperature is a more favorable medium than air for the dissipation of heat produced during intense work resulting in peripheral vasoconstriction, an increase in central blood volume, and slower heart rate.

2) Stroke volume

The second factor determining the lower VO_2max in swimming compared with running is stroke volume (SV). Stroke volume is equal to the difference between end diastolic volume (EDV) and end systolic volume (ESV). Factors that increase stroke volume include (a) an increase in EDV due to an increase in ventricular size or an increase in venous return (preload) (b) an increase in myocardial contractility and (c) a decrease in total peripheral resistance.

Heavy work can elicit a greater stroke volume and a slower heart rate in the supine compared with the upright position. [115, 116] Either supine or prone body position in swimming exercise facilitates venous return and greater cardiac filling which would result in a larger stroke volume and a lower heart rate during submaximal work. Dixon

and Faulkner [103] demonstrated that trained swimmers attain the similar cardiac output at VO_2max during swimming and running. This was achieved through the lower HR (184 beats/min during running and 172 beats/min during swimming) and a higher stroke volume.

In contrast to well-trained swimmers, recreational swimmers can only achieve ~75% of maximal cardiac output during swimming resulting from both lower HR (177 and 157 beats/min) and lower SV (125 ml and 108 ml). This result differs from the studies that compare physiological responses during running and cycling. The lower cardiac output during cycling compared with running is entirely due to smaller SV whereas HR is the same between running and cycling exercise. [117, 118] The lower SV in recreational swimmers indicates the inability of recreational swimmers to maintain a high venous return during swimming, which is probably due to limited blood flow through the muscles of arms, shoulders, and chest. In conclusion, during swimming, recreational swimmers are unable to attain a high maximal HR or SV that they could achieve during either running or cycling.

The other factors that regulate SV are total blood volume (TBV) and plasma volume (PV). Davy and Seals [119] reported that TBV and PV decrease with age. However, among postmenopausal women, TBV is higher in endurance-trained compared with sedentary individuals. [120] Jones et al. [121] reported that among endurance-trained postmenopausal females match for exercise volume and aged adjusted performance, TBV and it components are lower in swimmers compared with runners and the lower TBV and PV of the swimmers are associated with a lower maximal aerobic capacity. Increased

TBV is related with elevated maximal SV thus, the lower VO_2max in swimmers compared with runners is probably due, at least in part, to their lower TBV.

3) Arteriovenous O_2 difference

The last factor to consider when discussing VO_2max is maximal arteriovenous O_2 difference (a-v O_2 difference). Previous literature showed that maximal a-v O_2 difference was lower during swimming compared with running. [103, 106] The low maximal a-v O_2 difference may be due to either a low arterial O_2 content because of hypoventilation, a high mixed venous O_2 content because of a reduced O_2 extraction or combination of both.

2. Arterial Blood Pressure

High blood pressure, which affects nearly 50 million Americans, is a major risk factor for stroke, coronary heart disease, congestive heart failure, and end-stage renal disease. [122] While antihypertensive drugs reduce the risk for cardiovascular and renal disease, concerns have been raised about the potential for deleterious side effects. [82] As a result, interest in lifestyle modification, including aerobic exercise for the treatment and prevention of hypertension, has increased. Epidemiological evidence suggesting that physical training lowers blood pressure (BP) has recently been confirmed by well controlled exercise intervention studies. [123] Meta-analysis is a quantitative approach in which individual study findings are combined to arrive at a more objective conclusion about a body of research. All meta-analyses concluded that BP decreases significantly in response to exercise training. For example, the meta-analysis which included 29 [124], 44 [125], 54 [126] randomized control trials irrespective of the baseline BP, the physical training

was associated with reduction in systolic blood pressure (SBP) / diastolic blood pressure (DBP) averaged 4.7/3.1 mmHg, 3.4/2.4 mmHg and 3.8/2.8 mmHg, respectively. The blood pressure lowering effect is smaller but significant in normotensive subjects, averaging approximately 3/2 mmHg and that the net effect is more pronounced in hypertensive patients who benefit from an average blood pressure reduction of 7/6 mmHg. [125]

In order to determine an optimal exercise program to maximize the decrease in blood pressure, the effectiveness of different training programs is evaluated, but the results from these previous studies remain controversial. Marceau et al.[127] found similar reductions in 24-h ambulatory blood pressure after moderate and hard exercise training. In contrast, Rogers et al. [128] found a lesser reduction in SBP after training at exercise intensities corresponding to 65% - 75% of maximal oxygen uptake than that at 40% of VO_2max. Braiith et al.[129] supported the study of Marceau et al. by demonstrating similar net blood pressure reductions (8 mmHg) when training at 70% and 80-85% of heart rate reserve. The meta-analyses reported that the exercise intensity, frequency and duration did not have any additional impact on reducing blood pressure[124, 125]. When frequency, exercise duration, and exercise intensity were combined in multivariable regression analysis, they explained less than 5% of the variance in the blood pressure responses.[124, 125]

Acute effects of endurance training on BP (postexercise hypotension)

Postexercise hypotension (PEH) is defined as a reduction in blood pressure below baseline levels after a single bout of exercise. [130] PEH occurs in normotensive and hypertensive young, middle-aged, and older men and women, with the greatest BP reductions seen in those with hypertension. [45] In studies to date, peak exercise-induced reductions in SBP and DBP have been on average 18 to 20 and 7 to 9 mmHg, respectively, in hypertensive humans and 8 to 10 and 3 to 5 mmHg, in normotensive humans. [131, 132] Subsequently, PEH may persist for up to 16 h after exercise. [130] The acute depressor effects of endurance exercise are a low-threshold phenomenon with hypotensive response noted after exercise at an intensity of 40% VO_2max. [46, 130]

The potential mechanisms underlying PEH include inhibition of basal sympathetic nerve discharge. [133] Humoral and local factors may also play a role in PEH. Acute exercise increases plasma levels of immunoreactive atrial natriuretic peptide which has potent local vasodilator effects and can induce decreases in arterial blood pressure. [130] Nitric oxide, an endothelium-derived relaxing factor, is released in response to hyperemia associated with physical exercise and contributes to the vasodilation and increased vascular sensitivity. [134] Moreover, the endogenous opioid pathways could induce the hypotension by inhibition of norepinephrine release. [135] Thermoreflexes also thought to play an impotant role in PEH. [136] Exercise increases metabolic heat production and internal body temperature. In humans, sweating and active vasodilation of cutaneous blood vessels are the two primary mechanisms for heat dissipation. Because activation of

these mechanisms increases cutaneous vascular conductance, decreases systemic vascular resistance, and thus can reduce arterial blood pressure.

Acute bouts of swimming have been reported to produce unfavorable increases in BP and HR in elderly swimmers. Itoh et al. [137] showed that after swimming 25 m twice at moderate intensity, SBP increased significantly but the degree of the increase was variable among subjects and independent from rate of perceived exertion. More than half the subjects experienced SBP of 170 mm Hg or higher. Moreover, the investigators demonstrated a high incidence of arrhythmias in this group of subjects. Elite young male swimmers also showed increases in BP after strenuous 25-km open-sea swimming. [138] Exhaustive swimming was associated with depressed left ventricular function as suggested by reduced stroke volume, ejection fraction, and left ventricular fractional shortening. In contrast, cardiac index was increased by 31% and total peripheral resistance was increased by 7%. Immediately after the race, HR, SBP and MAP increased 72%, 100% and 15% relative to the resting value, respectively, whereas DBP decreased 49%. The authors suggested that stimulation of rennin, vasopressin and aldosterone may have been related to the significant increase in SBP. [138] In addition, Marconnet et al. [35] measured arterial blood pressure noninvasively on 243 highly trained athletes including swimmers, runners, skiers and soccer players before and after standard exercise on cycle ergometer. Swimmer's data were compared with non-swimmers. In both sexes in spite of lower ages, swimmers demonstrated higher MAP and SBP than non-swimmers.

Swimming and Arterial Blood Pressure

Most studies to date examining the effect of exercise on lowering BP have employed running, walking or cycling as activity modes. Meta-analysis from 44 randomized control trials reported that the exercise involved walking, jogging, running in 69% of the studies, cycling in 50%, swimming in 3%, and other exercises in 23% of the training regimens. [125] Walking and running is the most popular activity investigated by the researcher. However, swimming is recommended as a mode of exercise for the prevention and treatment of hypertension and cardiovascular disease by various authoritative groups, for example, the American Heart Association [16], World Hypertension League [17] and World Health Organization [18]. This approach assumes that all of the benefits conferred from walking, running and cycling studies may also be applied to swimming. There is some evidence to suggest that swimming may not benefit in lowering blood pressure. Cross-sectional comparisons indicate that swimmers tend to have higher blood pressure at rest than other endurance athletes. [34, 139] The investigators suggested a reduced baroreceptor sensitivity, which suppresses blood pressure, in swimmers as a possible mechanism. In addition, mean arterial blood pressure during maximal swimming is significantly higher than that during maximal running despite the maximal cardiac output during swimming being lower. [34] The greater increase in blood pressure during swimming can be explained by an increased total peripheral resistance due to the lower skin temperature or recruitment of the small exercising musculature, or both. [106]

A recent interventional study suggested that swimming may bring unfavorable, rather than beneficial, effects. Cox et al. [140] studied 116 healthy sedentary women, aged 50-70 years by assigning them to supervised 6-month program of either swimming or walking exercise of similar intensity. The key finding is that both supine and standing systolic blood pressure, were higher, relative to the walking exercise group, in those women who were randomized to the swimming program. A similar trend was noted for diastolic blood pressure. The average difference between the effect of the two training regimens was +4/1 mmHg for supine blood pressure, and +6/2 mmHg for standing blood pressure. There were some limitations in this study that should be noted. Because there was no control group, the primary comparison was between walking and swimming, and thus the study cannot provide precise information as to whether swimming would have led to higher blood pressure compared with the untrained state. Although the authors described their population as normotensive, it should be noted that women with blood pressures of up to 160/100 mmHg were accepted and, of the 116 subjects enrolled, 14 were receiving anti-hypertensive medication at entry.

In contrast to Cox's results, Tanaka et al. [51] reported a reduction in seated and supine systolic BP after 10 weeks of swimming training in middle-aged hypertensive men and women. The reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) averaged 7 and 3 mmHg. The relative magnitude of the blood pressure reduction observed in this swimming study was smaller than that typically reported for land-based physical activity. [53] The investigators compared the results of this study with the previous studies using equivalent training program (of similar intensity, frequency, and duration)

employing walking/jogging [52] and cycling [53] which average 12 mmHg and 6 mmHg reductions in SBP and DBP. They also investigated the potential mechanisms for the antihypertensive effect of swimming exercise. The results found no change in plasma volume and no reduction in forearm resistance after swimming training. The investigators concluded that although forearm vascular resistance did not changed, the possibility of decreased total peripheral resistance as a potential mechanism cannot be excluded.

More recent interventional study supported the results of Tanaka et al. Perini et al. [141] evaluated HR and BP in nine swimmers before and after 5 months of training and competition. The resulted showed that at the end of the season the resting HR decreased 9 beats/min in both supine and sitting position whereas BP decreased 17% only in supine position. Furthermore, they found augmented indices of baroreflex sensibility and concluded that HR vagal control could have been enhanced by swimming training.

Potential Mechanisms for Reduction in BP after Endurance Exercise Training

Because mean arterial pressure is determined by cardiac output and total peripheral resistance (TPR), reduction in blood pressure after endurance exercise must be mediated by decreases in one or both of these variables. Reductions in resting cardiac output do not typically occur after chronic exercise. [83] Thus decreased TPR appears to be the primary mechanism by which resting BP is reduced after exercise training. [83] Reductions in vascular resistance after training are mediated by neurohumoral and structural adaptations, altered vascular responsiveness to vasoactive stimuli, or both.

Neurohumoral adaptation

- *Sympathetic nervous system*

Elevated sympathetic nerve activity is a hallmark observation in essential hypertension. [142] Reductions in central sympathetic nerve outflow or circulating norepinephrine (NE) attenuate vasoconstriction and lead to reductions in BP. [142] Recently, Brown et al. [143] reported that training-induced decreases in BP in older hypertensive subjects were associated with reduced NE release rate. Furthermore, studies indicate baroreflex control of sympathetic nerve activity (SNA) is enhanced by exercise training [132, 144], therefore, providing one potential mechanism of lowering SNA. In addition, hyperinsulinemia and insulin resistance are associated with hypertension and activation of the sympathetic nervous system [145, 146]. Because exercise training improves insulin sensitivity [147], this may be an important mechanism in mediating reductions in sympathetic outflow and BP.

- *Renin-angiotensin system*

Because angiotensin II is a powerful vasoconstrictor and regulator of blood volume, reductions in renin and angiotensin II with training would likely be a contributor to reduced BP. [148]

- *Vascular responsiveness*

Changes in vascular responsiveness are likely to contribute to reduced BP after training. Vascular responsiveness to α-adrenergic receptor stimulation by NE is attenuated after training. [149] In addition, hypertension impairs endothelial function [150], which are associated with greater vascular tone and less vasodilator function.

Endothelial-dependent vasodilation is critically dependent upon the production of nitric oxide. Exercise training has been shown to improve vasodilatory function in healthy subjects. [151]

Structural adaptation

Considerable evidence suggests changes in vascular structure occur in skeletal muscle in response to exercise training. These include vascular remodeling and angiogenesis. However, few data in humans are available concerning the effects of exercise training on the size or number of small arteries and arterioles. The training-induced alterations in vascular structure can elevate the total cross-sectional area of resistance vessel lumina, lower peripheral resistance, and reduce resting blood pressure. [83]

Cross-sectional data indicate endurance-trained subjects have larger arterial lumen diameter in conduit arteries than untrained controls. Moreover, intima-media thickness and the intima-media thickness/lumen ratio were reduced. [152, 153] Similarly, both cross-sectional and longitudinal studies have demonstrated greater arterial compliance after training. [6, 13] In summary, training-induced vascular remodeling may contribute to the antihypertensive effect of exercise.

3. Body Mass and Body Composition

In the United States, obesity has become a serious public health problem. According to the third National Health and Nutrition Examination Survey, 32% of adults

in the United States are overweight and an additional 23% are obese. Moreover, the prevalence of obesity has been increasing sharply among children and adults during the past 3 decades, and the trend is expected to continue. [154]

Overweight and obesity are risk factors for cardiovascular disease, certain cancers, diabetes, and mortality. In addition, overweight also exacerbates many other chronic diseases, such as hypertension, osteoarthritis, gallstones, dyslipidemia, and musculoskeletal problems. [155]

Obesity results from an imbalance between energy intake and expenditure. Although energy expenditure at rest accounts for the majority of daily energy expenditure, resting energy expenditure does not vary among individuals of similar age and sex. [156] Thus, physical activity is an important component of daily energy expenditure [157], and is though to contribute to the observed weight gain.

Regularly-performed aerobic exercise has been reported to have a beneficial effect on obesity. Van Pelt et al. [158] measured body composition in premenopausal and postmenopausal endurance-trained runners and premenopausal and postmenopausal sedentary controls. The results showed that the age-related elevation in total body fat in active women is much smaller than that observed in healthy sedentary adult women. In addition, central adiposity does not differ significantly across age in women who perform endurance exercise, and this contributes to their smaller age-associated elevation in total body fatness. The same investigators also measured the resting metabolic rate (RMR) and adjusted for fat mass and fat free mass (RMR_{adj}). They reported that RMR_{adj} did not

decline in women who perform endurance exercise. Moreover, they found that postmenopausal runners and swimmers had the same level of $RMR_{adj.}$ [159]

Swimming exercise is an exercise modality that is highly recommended for obesity because of minimal weight bearing stress. Recent data related to body weight and body composition have shown that swimming may not be a favorable form of exercise for maintenance or reduction of body weight. Littman et al. [160] examined how different types of physical activity, including swimming, are associated with weight gain attenuation over a 10y period. They used a self-reported questionnaire in the large cohort of middle-aged women and men. They reported that physical activity over 10y was inversely related to weight gain after age 45y. Regarding the type of physical activity, jogging, aerobics and fast cycling were associated with weight gain attenuation in most sex and ages, while walking, swimming, and weight lifting were not.

Although young swimmers have lower body fat and increased lean body mass compared with untrained control [161, 162], swimmers tend to have higher body fat than other endurance athletes. [163] The differences in body mass and body fatness between sedentary, runners and swimmers are pronounced in postmenopausal women group. [19] Body weight and fatness increase with age in women, especially during the postmenopausal years and this is associated with an increased risk of morbidity and premature mortality. [164] Cross-sectional studies in postmenopausal women showed that body mass, percent body fat, waist circumference and waist-to-hip ratio of swimmers were significantly higher than those of runners. [19, 121, 165] The body fat mass of the swimmers was about 40% higher than that of the runners. [19] Mean skinfold thickness has

been reported to be greater in female swimmers than those reported in elite runners. Tuuri et al. [165] showed average subscapular skinfold of 13 mm in swimmers whereas Van Pelt et al. [158] reported the value of 8 mm and 10 mm for premenopausal and postmenopausal runners, respectively. Tanaka et al. [19] determined the relation of body fatness to the coronary risk profile and reported that measures of body fatness were the primary independent determinants of most of the metabolic CHD risk factors. They concluded that the CHD risk factor profile was similar between non-exercisers and swimmers despite the highly active life-style of swimmers. Higher body fat in swimmers may be a requisite phenotype to be successful in swimming. Adipose tissue decreases the body density and hence improves the buoyancy of the body. Partly due to their higher percentage of fatty tissue, women tend to be less dense and displace relative more water than men. [84]

At present, few studies have addressed the effects of swimming exercise intervention on body mass and body fat. Tanaka et al. [166] examined effect of swim training in sedentary obese subjects. The training group swam at 60% of maximal heart rate reserve for 45 min per day for 3 days per week for 10 weeks. The results showed no significant changes in body mass, body fat percentage, body mass index and regional adiposity. Gwinup [167] randomly assigned obese subjects to three types of exercises including brisk walking, riding a stationary bike, or swimming. After 6 months, the women assigned to walking lost 10% of initial weight, the women who cycled lost 12%, but the women who swam lost no weight. Skinfold thickness showed a comparable reduction in the walkers and the cyclists, while the swimmers had no change in skinfold

thickness in this study. The longer period of training has been done by Kasch. [168] He trained sedentary men with running and swimming for 2 years. The VO_2max increased 19% in running group and 20% in swimming group. The mean body weight dropped 1.2 and 3.2 kg in swimming and running group, respectively. However running and swimming over 2-year period result in about equal improvement in aerobic capacity, the runners lost more weight than the swimmers.

One of the possible explanations for the ineffectiveness of swimming exercise in weight loss and reduction of body fat is that swimming may result in increasing energy intake. White et al. [169] determined energy intake immediately after moderate cycling exercise in cold (20°C) and neutral (33°C) water. The results indicated that subjects consumed 44% more calories during the hour following exercise in cold water. More fat calories were consumed after exercise in cold water. Furthermore, caloric intake after the cold-water trial was twofold greater than exercise energy expenditure. The underlying mechanism for the increasing energy intake after swimming remains to be elucidated.

4. Blood Lipids and Lipoproteins

The major function of plasma lipoproteins is to transport lipids for cellular metabolism. Circulatory lipoproteins are subdivided according to their hydrated density into 4 main species: chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). Lipoproteins are made up of lipids (triglycerides, phospholipids, unesterified cholesterol and cholesterol esters) and proteins (apolipoproteins or apoproteins). [170]

The interrelationship between lipoprotein cholesterol levels, exercise, and coronary heart disease has received considerable attention. An elevated HDL is strongly associated with a decreased risk of coronary heart disease. [171] Cross-sectional studies found that, compared with non-athletes, athletes generally have 40–50% higher levels of HDL cholesterol, while triglyceride (TG) levels are 20% lower and LDL cholesterol levels are 5-10% lower. [172]

Few studies on this topic have been directly concerned with swimmers. Smith et al. [173], after controlling for alcohol consumption, adiposity, oral contraceptive use, and dietary intake, reported an increased level of HDL and HDL/ total cholesterol in young female competitive swimmers compared with sedentary controls. In contrast, Zonderland et al. [174] and Schnabel et al [175] reported no differences in the HDL level between young swimmers and control group. The same level of HDL between swimmers and sedentary counterparts also demonstrated in postmenopausal women population. [19] Morover, the total and LDL cholesterol levels of the swimmers tend to be lower than those of young sedentary controls. [175, 176] The lower total cholesterol and LDL cholesterol are not typically observed in land-based exercise-trained athletes and appear to be unique to swimmers. In addition, a cross-sectional study has reported positive correlations between HDL or HDL/total cholesterol and maximal oxygen uptake in runners and soccer players but not in swimmers. [175]

Longitudinal or interventional studies are consistent with those cross-sectional findings. Barr et al [176] demonstrated that HDL cholesterol levels did not change in male collegiate swimmers throughout a season, although exercise volume increased

substantially and body fat decreased. They also reported that total and LDL cholesterol levels were lower at the 20-wk time point compared with the start of the study. Water-based exercise has been shown to reduce total cholesterol and LDL cholesterol; no effect was found with regard to HDL cholesterol [177]. Tanaka et al. [166] also reported that a short term supervised swim training did not result in significant increases in HDL-cholesterol concentration in sedentary obese middle-aged adults.

Based on the research studies conducted in swimming exercise interventions, the possibility exists that acute bout of swimming may affect lipid metabolism differently from other endurances activities. However, there is little or no support for this. Ohkuwa and Itoh [178] reported that HDL cholesterol and glycerol concentrations were significantly elevated following an anaerobic swim test. They suggested that the elevation in HDL cholesterol may be induced by an increase in lipoprotein lipase activity. In addition, the increment in glycerol level suggested that anaerobic swimming exercise induced the lypolysis. In contrast, Bermingham et al. [179] studied the HDL cholesterol level after acute exercise on land compared with in water in cardiac patients. They found the increase in HDL cholesterol only in patients who exercised on land.

5. Glucose Metabolism and Insulin Sensitivity

The widespread prevalence of type 2 diabetes in the United States of America (US) has been consistently increasing over the past three decades, now accounting for annual health care costs of ~$132 billion dollars. The disease has also reached epidemic proportions around the world, and with a predicted global prevalence of over 300 million

by 2025. [180] Type 2 diabetes is strongly associated with significant increases in morbidity and mortality, and directly linked to pathogenic consequences in the eyes, kidney and nerves as well as microvascular and macrovascular complications that promote cardiovascular disease.

Obesity and/or lack of physical activity are two of the main determining factors in the development of insulin resistance that precedes the diagnosis of type 2 diabetes. In epidemiological studies, even a single session of exercise can improve glucose control in type 2 diabetes and ameliorate insulin resistance. [181] Roger et al [182] noted that one week of daily exercise at 70% of VO_2max reduced insulin resistance in patients with type 2 diabetes and improved glucose tolerance. As many of the diabetic patients are obese, swimming would be an ideal form of exercise for these patients.

In cross-sectional study, Tanaka et al.[19] demonstrated that the fasting plasma concentration of insulin was lower and insulin sensitivity was greater in postmenopausal swimmers compared with sedentary control. The level of insulin sensitivity of swimmers was not different from the runners who were matched for age, training volume, and exercise performance levels. Sideraviciute et al.[183] examined the effects of 14-week swimming training in young girls with type 1 diabetes and reported a significant reduction in the concentration of hemoglobin A1c, an indicator of average glucose load over the past several months. This interventional study showed that regular swimming is associated with the better glycemic control. However a time control group was not included.

V. Summary

Swimming exercise has been recommended by various authorities as a form of exercise to improve aerobic fitness and cardiovascular health and is a potential useful alternative to land-based exercises. Physiological responses to swimming are different from land-based exercise in many aspects due to hydrostatic pressure, facial immersion and the prone body position. As a result, research finding obtained from land-based exercise training cannot be extrapolated to swimming. The impacts of swimming on relative risk of developing CHD seem to be small or none. Because the available evidences using swimming exercise intervention are limited, further studies are needed to establish the effect of regular swimming on CHD risks in humans.

Chapter 5: Summary and Future Directions

SUMMARY

Adults who regularly perform aerobic exercise have less large elastic artery stiffness and largely preserved vascular endothelial function with aging. A moderate-intensity aerobic exercise intervention can improve/restore large elastic artery stiffness and EDD in middle-aged and older adults. Each of aforementioned studies is based on land-based exercise (e.g. walking, running, and cycling). Currently, there is no scientific evidence to date indicating that swimming is equally efficacious to land-based exercise modes in improving large elastic artery compliance and vascular function.

The purpose of this dissertation study was to determine the role of swimming exercise on age-related reduction in vascular function. The primary hypothesis is that regular swimming exercise will either prevent or attenuate the age-associated reduction in dynamic central arterial compliance and EDD and at least partially restore levels in healthy middle-aged and older sedentary adults. In order to address this, we used both cross-sectional and intervention experimental approaches. Collectively, the projects outlined in this discussion support the role of swimming exercise in improving vascular function in previously sedentary middle-aged and older adults. The main new findings of this dissertation projects are: 1) the magnitude of the age-related reduction in central arterial compliance is attenuated in adults who regularly perform swimming exercise; 2) a relatively brief (12-week) period of regular swimming exercise can restore some of the loss of central arterial compliance and EDD in previously sedentary middle-aged and

older adults; 3) the ability of regular swimming exercise to increase central arterial compliance and EDD in this population does not depend on changes in body weight/composition, arterial blood pressure, metabolic risk factors for atherosclerosis, or maximal aerobic capacity; 4) 12-week swimming training decreased both central and peripheral systolic blood pressure in middle-aged and older adults; and 5) regular swimming exercise appears to be a sufficient stimulus to improve cardiovagal baroreflex sensitivity.

Taken together, regular swimming exercise, similar to land-based exercise, can play a major role in the prevention of premature CVD-related morbidity and mortality and the promotion of healthy aging.

FUTURE DIRECTIONS

Swimming is an attractive form of exercise because it does not involve bearing of body weight. In addition, because of colder temperature as well as increased thermoconductivity of water, the incidence of heat-related illness is small.[184] As such, it is an ideal form of exercise for obese patients, the elderly and patients with arthritis. Moreover, swimming training is established as an integrated part of treatment regimes in both patients with myocardial infarction (MI) and chronic congestive heart failure (CHF).[185] However, no data are available on the efficacy of habitual swimming exercise for treating vascular dysfunction in adults with clinical CVD or risk factors for CVD. A practical, but important issue, in clinical practice exercise is the volume and intensity of swimming exercise that are safe for patients. Investigation aimed at determining the

efficacy of regular swimming exercise in treating large elastic artery stiffness and vascular endothelial dysfunction in middle-aged and older adults with CVD risk factors and/or clinical CVD are warranted.

Very little is known about the mechanisms by which habitual exercise influences vascular function. The main limitation with human investigations is a lack of access to internal (nonperipheral) arteries for tissue sampling and manipulation of signaling pathways, particularly in healthy adults. In vivo and in vitro animal and vascular cell models, as well as innovative methods in humans, will be needed to pursue these issues. One potential mechanism previously implicated in land-based exercise studies is reduced oxidative stress.[186] Studies aimed at identifying the anti-vascular aging effects of swimming exercise mediated in part by suppressing the development of oxidative stress are needed because it can be investigated in human.

Appendix A: Definition of Terms

Arterial compliance: the artery's ability to expand and contract with cardiac pulsation and relaxation. In this study, arterial compliance is measured as Doppler Ultrasound technique.

Arterial stiffness: progressive hardening of arterial wall and change in ability to cushion the pulsatile flow from the heart to steady flow through the arterial tree. In this study, arterial stiffness is measured as pulse wave velocity.

Pulse wave velocity: speed of travel of the pulse along an arterial segment
PWV (cm/s) = arterial path length / Δpulse transit time

Endothelial function: the ability of the thin cells lining the inside of a blood vessel to respond to changes in blood flow, stretch, circulating substances, and inflammatory mediators

Endothelial-dependent vasodilation: increase in arterial diameter in response to increased shear stress or acetylcholine infusion. Shear stress increases production of nitric oxide in endothelial cells. Nitric oxide diffuses to adjacent vascular smooth muscle cells and causes them to relax (vasodilation).

Flow mediated dilatation: a change in blood flow through a vessel causes a change in the arterial diameter. An increase in blood flow increases shear stress acting on the vessel wall and causes dilation to maintain perfusion. See endothelial-dependent vasodilation.

Nitric Oxide (NO): one of endothelium-derived relaxing factor (EDRF). Nitric oxide is synthesized from arginine by nitric oxide synthase (NOS). NO formed by the endothelial

isoform of NOS is a vasodilator and inhibits platelet activity, vascular smooth muscle cell growth, and leukocyte adhesion.

Oxidative stress: an imbalance between production of free radicals (reactive oxygen species) and removal by antioxidants (enzymes, vitamins).

Vascular function: general term to describe changes in the arterial tree including arterial stiffness and endothelial-dependent vasodilation.

Middle-aged and older adults: age between 35-75 years

Sedentary: description of an individual who has participated in less than 1 hour a week of physical activity for one year prior to this study.

Swimmer: description of an individual who has swum at least three times per week at least for two years

Runner: description of an individual who has run at least three times per week for at least two years

Appendix B: Questionnaires

Research Health Questionnaire

Cardiovascular Aging Research Laboratory
University of Texas at Austin

Personal Information

Phone Number _____ Email _____
Date of Birth _____ Age _____ Sex _ Male _ Female
Who is your physician? _____ Phone _____
In case of emergency, contact _____ Phone _____

Please circle the highest grade in school you have completed:

Elementary school	1	2	3	4	5	6	7	8
High school	9	10	11	12				
College/Post Grad	13	14	15	16	17	18	19	20+

What is your marital status? _ Single _ Married; _ Widowed _ Divorced; Separated

Ethnic Background: _ Hispanic or Latino _ Not Hispanic or Latino

Race:
_ White _ American Indian/Alaskan Native _ Pacific Islander
_ Black or African American _ Asian

Symptoms or Signs Suggestive of Disease

Check appropriate box:

Yes	No		
_	_	1.	Have you experienced unusual pain or discomfort in your check, neck, jaw, arms or other areas that may be due to heart problems?
_	_	2.	Have you experienced unusual fatigue or shortness of breath at rest, during usual activities, or during mild-to-moderate exercise (e.g., climbing stairs, carrying groceries, brisk walking, cycling)?
_	_	3.	When you stand up, or sometimes during the night while you are sleeping, do you have difficulty breathing?
_	_	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
_	_	5.	Do you suffer from swelling of the ankles (ankle edema)?
_	_	6.	Have you experienced an unusual and rapid throbbing or fluttering of the heart?
_	_	7.	Have you experienced severe pain in your leg muscles during walking?
_	_	8.	Has a doctor told you that you have a heart murmur?

Chronic Disease Risk Factors

Check appropriate box:

Yes	No		
_	_	9a.	Are you a male over age 45 years or a female over age 55 years?
_	_		b. Are you a female who has experienced premature menopause?
_	_		c. If you answered "yes" to 9b, are you on estrogen replacement therapy?
_	_	10.	Has your father or brother had a heart attack or died suddenly of heart disease before the age of 55; has your mother or sister experienced these heart problems before the age of 65?

Yes No

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_	_	11.	Are you a current cigarette smoker?
_	_	12.	Has a doctor told you that you have high blood pressure (more than 140/90 mm Hg) or a heart condition?
_	_	13.	Is your total serum cholesterol greater than 200 mg/dl, or has a doctor told you that your cholesterol is at a high risk-level?
_	_	14.	Do you have diabetes mellitus?
_	_	15.	Are you physically inactive and sedentary (little physical activity on the job or during leisure time)?
_	_	16.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
_	_	17.	During the past year, would you say that you have experienced enough stress, strain, and pressure to have a significant effect on your health?
_	_	18.	Do you eat foods nearly every day that are high in fat and cholesterol such as fatty meats, cheese, fried foods, butter, whole milk, or eggs?
_	_	19.	Do you weigh 30 or more pounds than you should?
_	_	20.	Do you know of any other reason you should not do physical activity?

Medical History

21. *Please check which of the following conditions you have had or now have. Also check medical conditions in your family (father, mother, brother(s), or sister(s)). Check as many as apply.*

Self	Family	Medical Condition	Self	Family	Medical Condition
_	_	Coronary heart disease, heart attack; by-pass surgery	_	_	Major injury/fracture to foot, leg, knee
_	_	Arrhythmias	_	_	Major injury to back or neck
_	_	Angina	_	_	Major injury/fracture to hip or shoulder
_	_	High blood pressure	_	_	Rheumatoid Arthritis
_	_	Peripheral vascular disease	_	_	Osteoarthritis
_	_	Phlebitis or emboli	_	_	Gout
_	_	Other heart problems	_	_	Osteoporosis
_	_	Stroke	_	_	Fibromyalgia
_	_	Asthma	_	_	Diabetes mellitus
_	_	Bronchitis	_	_	Kidney disease
_	_	COPD (emphysema)	_	_	Cataracts
_	_	Lung cancer	_	_	Glaucoma
_	_	Breast cancer	_	_	Hearing loss
_	_	Prostate cancer	_	_	Depression
_	_	Skin cancer	_	_	Anxiety, phobias
_	_	Colorectal cancer	_	_	Eating disorders
_	_	Other cancer. Specify:	_	_	Sleeping problems
_	_	Gallstones/gallbladder disease	_	_	Substance abuse problems (alcohol, other drugs, etc.)
_	_	Liver disease (cirrhosis)	_	_	Chronic Fatigue Syndrome
_	_	Hepatitis	_	_	Thyroid problems

Self	Family	Medical Condition	Self	Family	Medical Condition
_	_	Anemia (low iron)	_	_	Hysterectomy
_	_	Stomach/duodenal ulcer	_	_	Problems with menstruation
_	_	Rectal growth or bleeding	_	_	Pregnant (now? Yes ___ No___)
_	_	Crohne's disease	_	_	Post-menopausal (date:)
_	_	Irritable bowel syndrome	_	_	Allergies
_	_	Marfan's syndrome	_	_	Raynaud's disease

Any other health problems. Please specify and include information on any recent illnesses, hospitalizations, or surgical procedures.

22. *Please check any of the following medications you take regularly and give the name of the medication.*

Medication	**Name of Medication**
_ Heart medicine	_____
_ Blood pressure medicine	_____
_ Blood cholesterol medicine	_____
_ Hormones	_____
_ Birth control medicine	_____
_ Medicine for breathing/lungs	_____
_ Insulin	_____
_ Other medicine for diabetes	_____
_ Arthritis medicine	_____
_ Medicine for depression/anxiety	_____
_ Steroids	_____
_ Thyroid medicine	_____
_ Medicine for ulcers	_____
_ Painkiller medicine	_____
_ Allergy medicine	_____
_ Other (please specify)	_____
	_____
_ Do you have any drug allergies?	_____
_ Dietary supplements (please specify)	_____

Body Weight

23. What is the most you have ever weighed? _____ pounds

24. Are you now trying to:

_ Lose weight _ Gain weight _ Stay about the same _ Not trying to do anything

Stress

25. During the past month, how would you rate your overall level of stress?

_ Very high _ High _ Moderate _ Low

26. In the past year, how much effect has stress had on your health?

_ A lot _ Some _ Hardly any or none

27. On average, how many hours of sleep do you get in a 24-hour period?

_ Less than 5 _ 5-6.9 _ 7-9 _ More than 9

Substance Use

28. How would you describe your cigarette smoking habits?
_ Never smoked
_ Used to smoke. How many years has it been since you smoked? _____ years
_ Still smoke. How many cigarettes a day do you smoke on average? ___cigarettes/day

29. How many alcoholic drinks do you consume? (A "drink" is a glass of wine, a wine cooler, a 16oz bottle/12oz can of beer, a shot glass of liquor, or a mixed drink).
_ Never use alcohol _ Less than 1 per week _ 1-6 per week _ 1 per day
_ 2-3 per day _ More than 3 per day

30. In one sitting, how many drinks do you typically consume? _____
31. How many cups (8 ounces) of coffee do you drink per day? _____
32. How many ounces of sodas containing caffeine do you drink per day? _____

Physical Fitness, Physical Activity/Exercise

33. Considering a 7-**Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your **free time** (write on each line the appropriate number).

a) **STRENUOUS EXERCISE (HEART BEATS RAPIDLY)** **Times Per Week**
(i.e. running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling) _____

b) **MODERATE EXERCISE (NOT EXHAUSTING)**
(i.e. fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing) _____

c) **MILD EXERCISE (MINIMAL EFFORT)**
(i.e. yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking) _____

34. Considering a 7-Day period (a week), during your leisure-time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)

_ OFTEN _ SOMETIMES _ NEVER/RARELY

35. How long have you exercised or played sports regularly?
_ I do not exercise regularly _ Less than 1 year _ 1-2 years
_ 2-5 years _ 5-10 years _ More than 10 years

Occupational Health

36. Please describe your main job title and duties.

_____

37. How much hard physical work is required on your job?
_ A great deal _ A moderate amount _ A little _ None

Appendix C: Vascular Measurements

Pulse Wave Velocity: Carotid-femoral pulse wave velocity (cfPWV) and brachial-ankle pulse wave velocity (baPWV) was measured by the Colin VP-2000 (Colin Medical Instruments; San Antonio, Texas). Subjects rested quietly for 10 minutes in the supine position while laboratory personnel placed blood pressure cuffs, electrodes, and pressure tonometers in the correct anatomical locations. The Colin VP-2000 instrument also records heart rate, heart sound and blood pressure. Applanation tonometry incorporates an array of 12 micropiezoresistive transducers to detect pressure waveforms. The time it takes for the wave to travel between the 2 tonometers, and the distance between the tonometers was used to calculate PWV. Heart rate, bilateral brachial and ankle blood pressures, carotid and femoral pulse waves were measured for 30-seconds at least 3 times per testing period.[30]

Carotid Arterial Compliance: Arterial compliance, a measure of local arterial stiffness at the carotid artery, was measured non-invasively in the supine position. The common carotid artery was first located from a cross-sectional image of the neck, using an ultrasound machine equipped with a high-resolution linear array transducer (L11-3; Phillips iE33 Ultrasound System; Bothel, WA). Once the bifurcation of the common carotid artery is determined, the transducer was rotated to display a longitudinal image of the cephalic portion of the common carotid artery where the bifurcation and a linear segment of the artery are both displayed on the screen (See Image 1C.). Once the

ultrasound image of the carotid artery is optimized for diameter detection, a second investigator located the contralateral carotid artery for assessment of blood pressure using a high-fidelity micromanometer (Millar TCB-500, Millar Instruments; Houston, TX). To correct for investigator hold-down pressure, carotid pressure waveforms were calibrated to mean arterial pressure and diastolic arterial pressure averaged over the previous 15 minutes from a cuff placed on the brachial artery. Simultaneous measurement of carotid diameters and carotid blood pressure were obtained. If the image or the pressure waveforms were not satisfactory, the process was repeated. Images were captured for at least 20 heart cycles and transferred to an offline computer for analysis (Vascular Tools 5-Carotid Analyzer, Medical Imaging Applications, Coralville, IA). Diameter measurements of the carotid artery were taken approximately 1-2 cm proximal to the carotid bulb from the media-adventitia of the far wall to the media-adventitia of the near wall by one investigator. Ten to thirty heart cycles were analyzed. The highest and lowest of both the systolic and diastolic diameter was deleted and the rest were averaged for the calculation. Carotid arterial compliance was calculated as:

$$[(MaxDiam-MinDiam) / MinDiam] / [2*(Pulse\ Pressure)]* \pi * (MinDiam)2$$

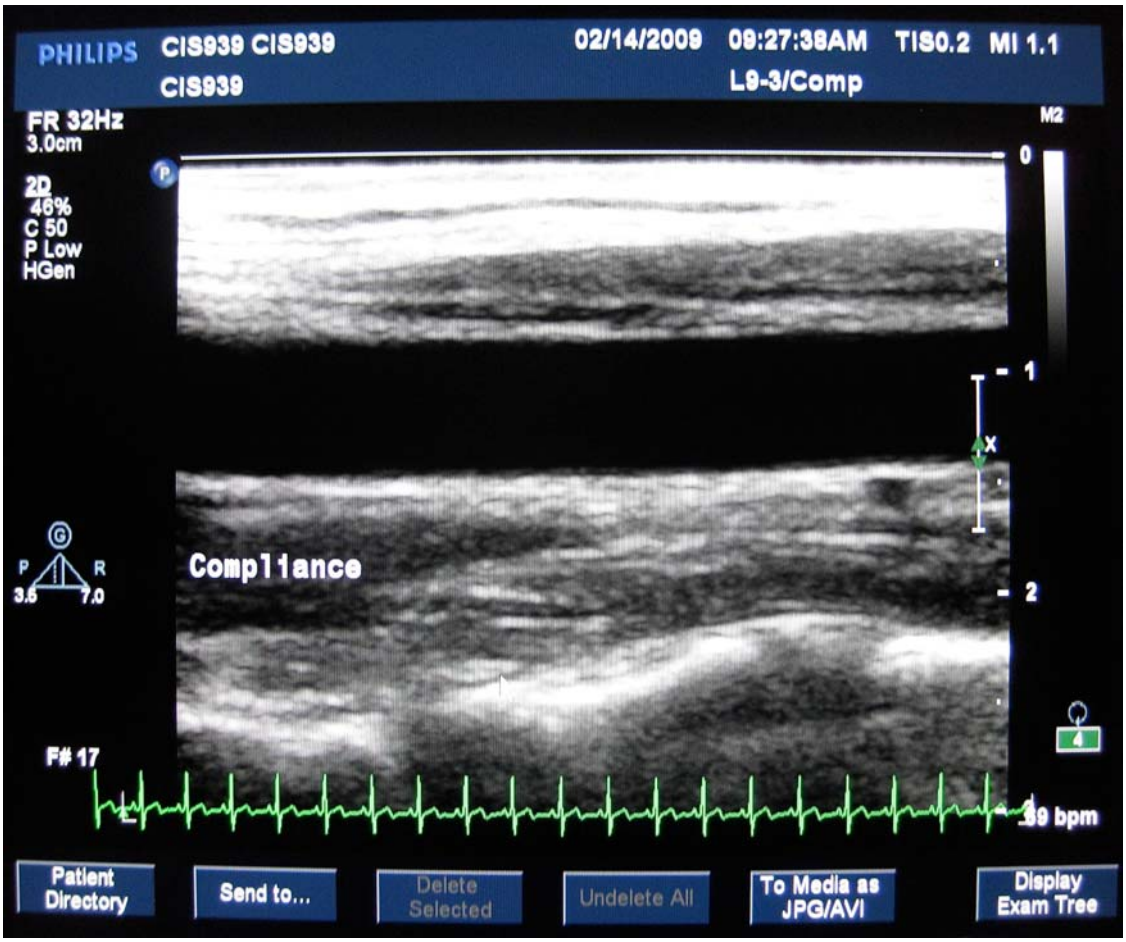

Image 1C. Linear segment of the carotid artery.

Flow-mediated Dilation (FMD): Endothelium-dependent vasodilation was assessed by FMD using noninvasive, standardized procedures.[32] This non-invasive test measures vascular function of the brachial artery by quantifying the amount of arterial vasodilation in response to reactive hyperemia. The subject rested in the supine position for at least 10 minutes before setting up to measure FMD. The right arm was extended and placed in a customized arm support system to prevent movement of the arm and to standardize the position of the ultrasound transducer. (See Image 2C).

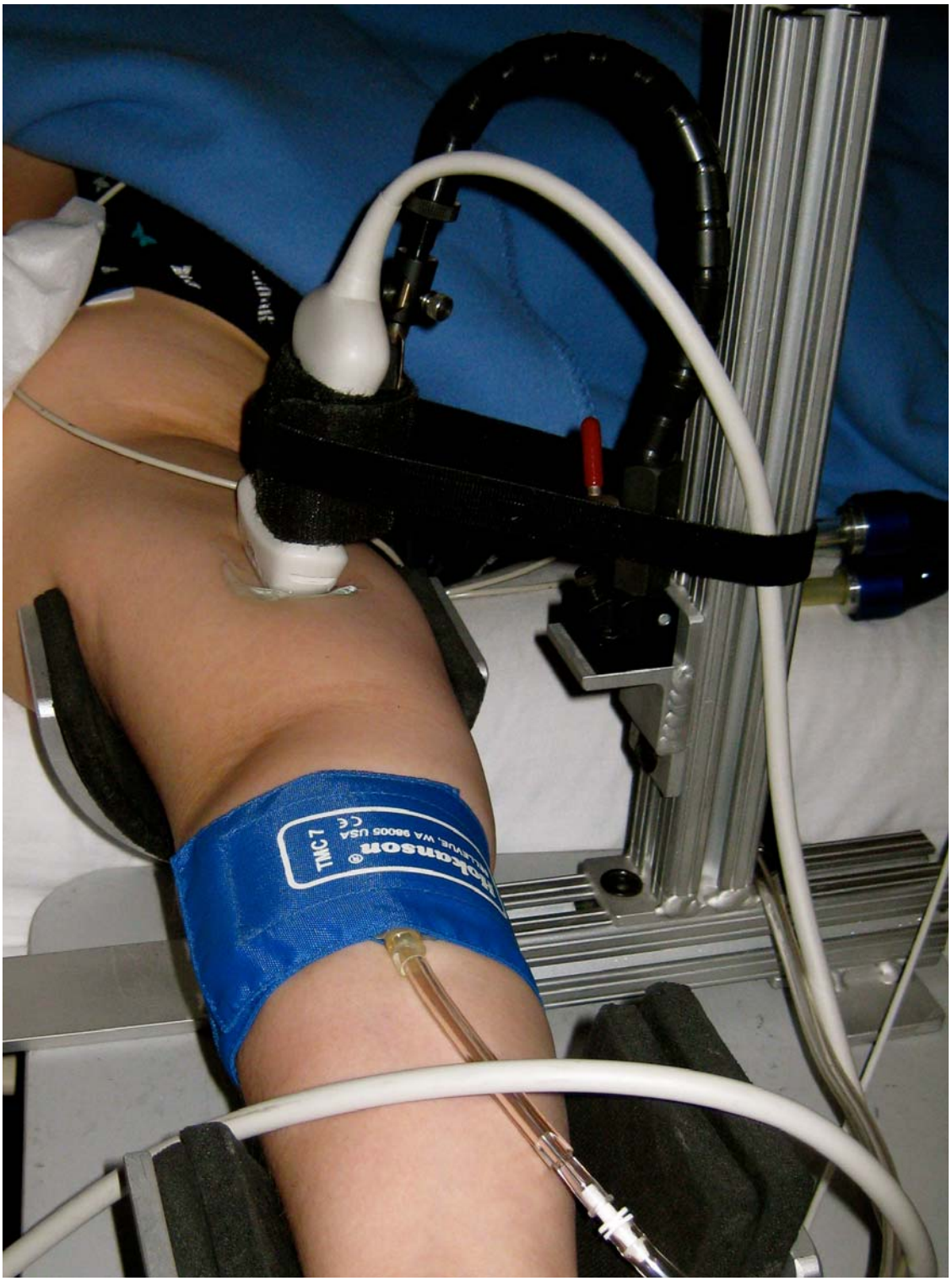

Image 2C. Arm support system used for FMD data collection.

Brachial artery diameters and blood flow velocity were measured from images derived from a Doppler ultrasound machine equipped with a high-resolution linear array transducer (L11-3 transducer, Philips iE33 Ultrasound System; Bothel, WA). Once the subject was resting in a comfortable position, the pneumatic arm cuff was placed on the forearm, 3-5 cm distal to the antecubital fossa and connected to a rapid cuff inflator (E20 Rapid Cuff Inflator, D.E. Hokanson; Bellevue, WA Hokanson). Once a longitudinal image of the brachial artery, 5-10 cm proximal to the antecubital fossa was obtained, the arm stabilizer was secured. One minute of baseline brachial artery diameter and 20 seconds of blood velocity were recorded prior to cuff inflation. The arm cuff was then inflated to 100 mmHg above resting systolic blood pressure (measured prior to baseline image capture) for 5 minutes. Blood velocity was recorded 10 seconds prior to cuff deflation, and 25 seconds after cuff deflation (See Image 3C). At 25 seconds after release of the cuff, the ultrasound was switched to 2D mode to optimize the image for brachial artery diameter measurements for the next 95 seconds. The image files were transferred to an offline computer and stored for later data analysis using commercially available image analysis software (Brachial Analyzer, Medical Imaging Applications; Coralville, IA). Brachial arterial diameter during end-diastole, as determined from the ECG trace, was taken from the media-adventitia interface on the near wall to the media-adventitia far wall boundary. Brachial image analysis was performed by the same investigator. The magnitude of change in end-diastolic diameter was expressed as an absolute percentage of flow-mediated dilation.

$$FMD\% = \frac{\textit{(peak diastolic diameter-baseline diastolic diameter)}}{\textit{baseline diastolic diameter}}$$

To calculate baseline diastolic diameter, at least 20 cardiac cycles with clear media adventitia boundaries were averaged. Peak diastolic diameter was taken from the average of 3 consecutive cardiac cycles demonstrating the largest brachial artery dilation.

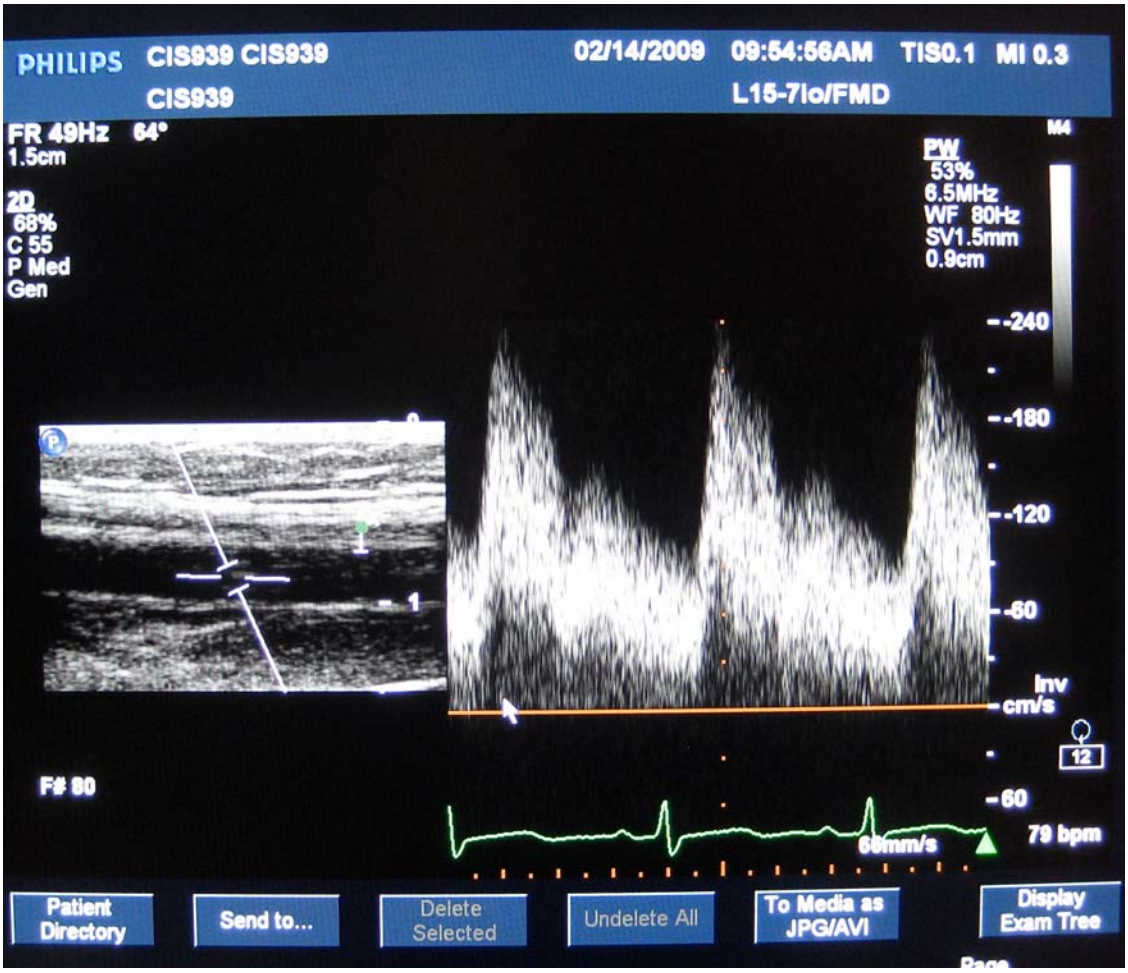

Image 3C. Brachial artery diameter and Doppler velocity upon release of the forearm cuff.

Appendix D: Echocardiography

Procedure:

- Enter subject ID and information on the ultrasound device (Phillips iE33 Ultrasound System; Bothel, WA) by pressing Patient Data.
- Select S5-1 transducer and select preset Adult Echo protocol Parasternal Long Axis View
- . Instruct the subject lay supine in order to attach the 3-lead ECG to measure heart rate. Select Physio if ECG does not appear automatically. Position subject in the left lateral position (lying on left side with the left arm overhead and right arm along the side of the body).
- Place transducer on the left parasternal region usually in the 3rd or 4th intercostal space. The orientation of transducer should point toward the right shoulder of the subject.
- Left ventricular wall motion characteristics and LVOT (left ventricular outflow track) diameter. Position transducer so aortic valve leaflets are visible. Adjust the focus to the appropriate depth around to the aortic valve. Press Freeze to temporarily capture the image and scroll to aortic opening where leaflets areflat (see Image 1D below). Select Analysis and LVOT diameter to quickly measure from anterior leaflet (where root meets the interventricular septum) to posterior leaflet (where it meets the anterior leaflet of the mitral valve). If positioning is

acceptable (LVOT from 2.0-2.2 cm), press Freeze again to show image in real time.

- To record: Select Loop and set to 10-12 heart cycles. When image is clear, press Acquire to record image to the ultrasound hard drive.

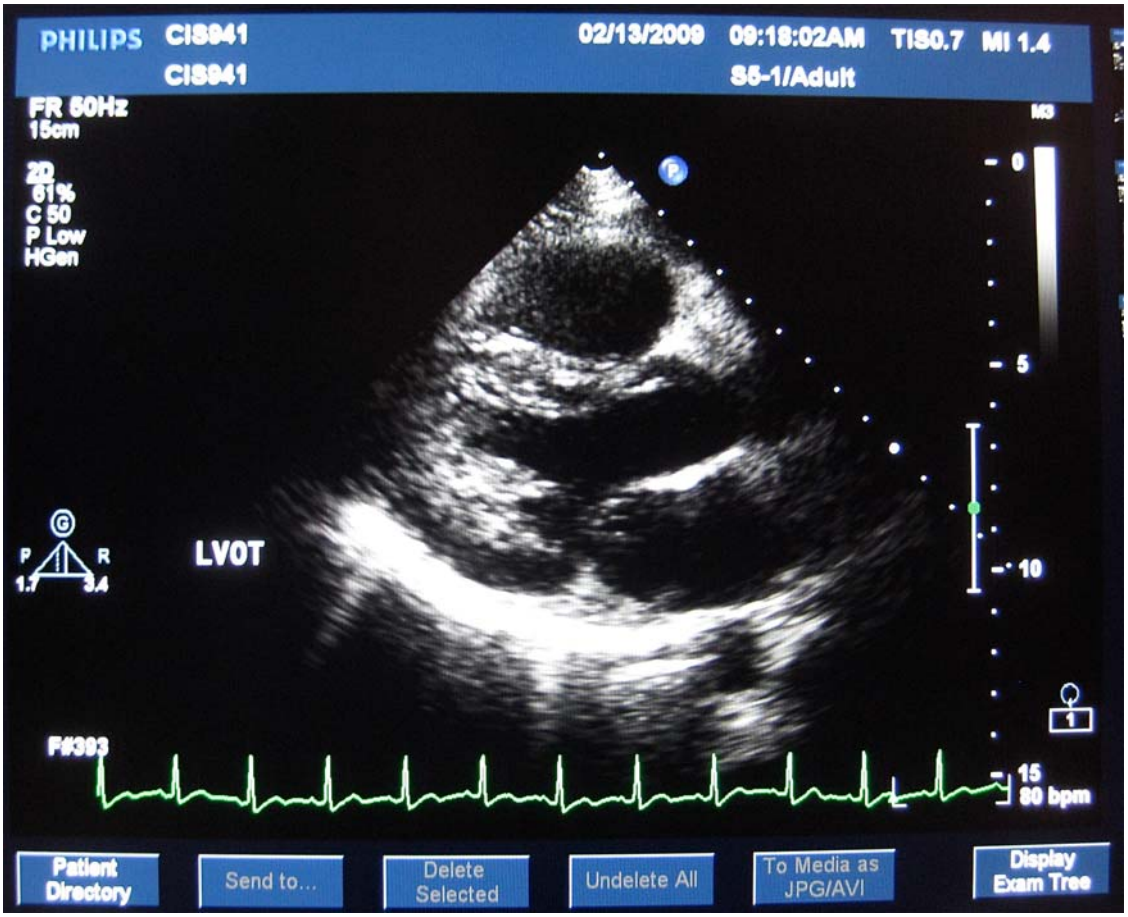

Image 1D. LVOT with open aortic valve leaflets where LVOT area is calculated

Apical 5 Chamber

- Instruct subject to remain in the same position but place the transducer in the vicinity of maximal impulse (approximately 2 cm below the nipple). The transducer should be oriented down towards the bed. Adjust the depth and gain accordingly so that all 5 chambers are visible.
- Pulse Wave (PW): Aortic Velocity Time Integral (VTI) for calculation of stroke volume. In 2D mode, place cursor beam parallel to outflow tract (see Image 2D). Place the cursor ball proximal to valve leaflets. Select PW to detect Doppler blood velocity. If necessary, drop the baseline or adjust the scale. Move the cursor to the largest, cleanest image with downward deflection from baseline. After several cardiac cycles, press Freeze and scroll to a clean signal. Next, select Analysis, select Aortic, select CO LVOT, and select LVOT VTI. To calculate the VTI, trace the entire deceleration time of 1 cardiac cycle and press Enter. Select HR-AV and scroll from the previous R wave to then current R wave to determine the R-R interval. Press Enter to calculate the cardiac output measurement. Cardiac output and stroke volume are determined by multiplying the VTI of flow at the aortic annulus by its cross-sectional area.
- To record: Select Loop and set to 8-12 heart cycles. When waveforms are clear, press Acquire to record image to the ultrasound hard drive.

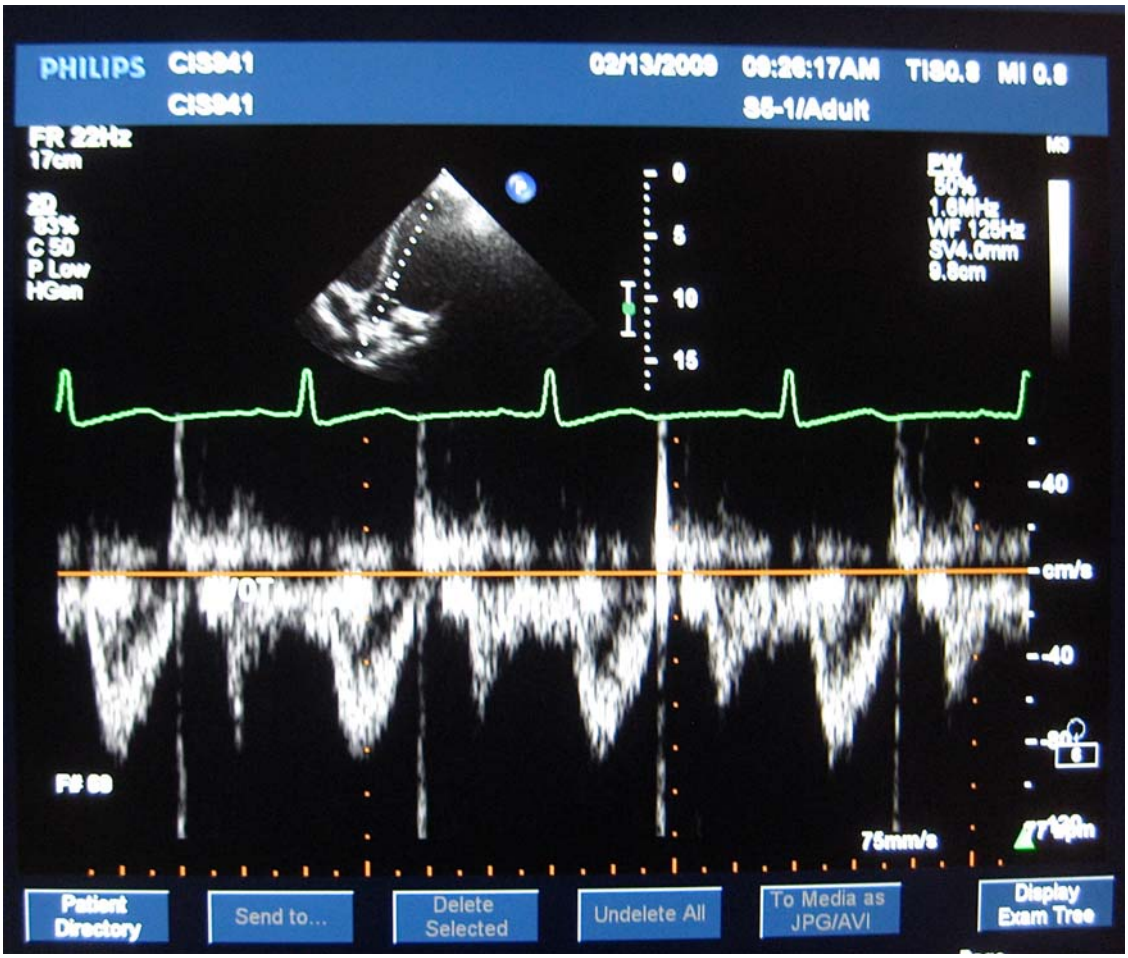

Image 2D. LVOT Doppler velocity for VTI calculation

Appendix E: Analysis of Blood and Plasma

Blood Sample Collection: Blood samples were drawn from the antecubital vein using venapuncture. 10-12 mL of whole blood was obtained from each subject. Whole blood was drawn into EDTA plasma tubes (BD Vacutainer 4mL, Fisher Scientific catalog # 02-689-4).

Whole Blood Analysis and Storage: Immediately after venapuncture, whole blood was drawn into 2 capillary tubes, each filled to 75%, and capped at one end using Crito-seal. Tubes were centrifuged at 10,000 rpm for 10 minutes and read on a Hematocrit reader. EDTA plasma tubes were immediately placed on ice. Whole blood viscosity (500 μL) was analyzed using a Brookfield DV-I+ digital viscometer (Brookfield Engineering Laboratories Inc.; Middleboro, MA). After auto-zeroing the instrument, whole blood was placed in the sample cup. Viscosity, % torque, and temperature were recorded at spindle speeds of 6, 12, 30, 60, and 100 rpm.

Hemoglobin A1c (HbA1c), or glycosylated hemoglobin, is a measurement of long-term (90-120 days) glucose control. HbA1c was measured from 10 μL of whole blood using a Micromat II Hemoglobin A1c Instrument (BioRad Laboratories; Hercules, CA). In all studies, EDTA plasma tubes were centrifuged at 3500 rpm (Eppendorf 5702R; Westbury, NY) for 10 minutes at 4 °C before distributing into microcentrifuge tubes for storage at -80 °C.

Metabolic Risk Factors: Microcentrifuge tubes containing at least 500 μL of EDTA plasma were thawed for analysis of glucose, triglycerides, and cholesterol (LDL, VLDL, and HDL). Samples were measured using a dry-slide Vitros DT60 II Chemical System (Ortho-Clinical Diagnostics; Rochester, NY).

Markers of Inflammation and Disease Activity: Cytokines and inflammatory molecules were analyzed from serum samples using a multiplex assay system (Millipore; Billerica, MA). IL-1β, IL-6, IL-10, IL-12, and TNF-α were analyzed using Milliplex High Sensitivity Human Cytokine Kit.

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