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Effects of Exercise on Hypertension

From Cells to Physiological Systems

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Foreword

During bouts of acute exercise, blood pressure rises. Paradoxically, high levels of chronic physical activity and aerobic exercise training can prevent some of the age-associated rise in blood pressure seen in many normal humans, and exercise training can also lower blood pressure in those with hypertension. The rise in blood pressure with acute exercise is driven via neural signals known as central command acting in concert with baroreceptor resetting and feedback from skeletal muscle afferents. Together, these signals reduce the activity of the parasympathetic nervous system and increase the activity of the sympathetic nervous system. These adjustments cause the increase in heart rate and ultimately cardiac output, and also vasoconstriction in many vascular beds. The targets of these neural adjustments also offer clues about the long-protective effects of physical activity and exercise training on blood pressure. Likewise the vasodilation in active skeletal muscles and increases in blood flow might offer clues about long-term adaptations that favor vascular health and reductions in peripheral resistance.

With the overview above as a background, the various sites and mechanisms whereby physical activity and exercise training might influence blood pressure range from the molecular to a systems engineering approach that considers blood pressure regulation as a hydraulic system. Is it possible to integrate the mechanisms operating at so many levels into a coherent story that is consistent with the interventional and epidemiological studies in humans on blood pressure, physical activity, and exercise?

As the first primer on the effects of exercise on human hypertension, *Effects of Exercise on Hypertension*: *From Cells to Physiological Systems* does integrate the mechanisms operating at so many levels into a coherent story. This volume describes the state-of-the-art effects of exercise on the many factors underlying essential hypertension in humans. It contains chapters by distinguished experts on the effects of exercise on physiological systems known to be involved in hypertension development and maintenance as well as less well-known aspects of hypertension such as the blood pressure lowering effects of exercise under ambulatory conditions and the influence of oxidative stress. The emerging areas of the effects of resistance exercise

and concurrent (combined) aerobic and resistance exercise on blood pressure are also highlighted. A unique aspect of the book is that it will discuss the effects of exercise mimetics on vascular cell adaptations in order to begin to elucidate some of the cellular mechanisms that may underlie the blood pressure response to exercise training. In this context, the book is ideal for scholars and professionals in cardiovascular research and medicine, and allied health care professionals and students in cardiovascular exercise physiology and related fields.

The book begins with a section on the influence of modality on the blood pressure response to exercise including public health guidelines related to the Frequency, Intensity, Type, and Time (or FITT) principle of exercise prescription as well as clinical implications of research in this area. The second section is unique and covers mechanisms associated with the blood pressure response to exercise including vascular and autonomic function, the effects of exercise mimetics on vascular cell adaptations, arterial stiffness, hemodynamic adaptations, genetic underpinnings, and animal models. The book concludes with Part III discussing the pleiotropic effects of exercise on other cardiovascular risk factors including dyslipidemia, the metabolic syndrome, inflammation, and oxidative stress. Although the focus of the book is on human hypertension, several chapters include sections covering the effects of exercise on relevant animal models of hypertension.

In the series of chapters in this book, the blood pressure responses to short-term, acute exercise and more long-term, exercise training will be considered at multiple levels of integration. Based on the brief outline above, questions to be addressed within this book are as follows: (1) Does habitual physical activity and aerobic exercise training do something to vascular smooth muscle which makes it less prone to vasoconstriction?; (2) Could the balance between vasoconstricting and vasodilating factors in the vascular endothelium be shifted to favor vasodilation?; (3) Are the vasoconstricting actions of catecholamines released from the sympathetic nerves which are active during acute exercise blunted in the long term?; (4) Are there changes in tonic sympathetic vasoconstrictor nerve activity?; (5) Do the baroreceptors become more distensible and do a "better job" of modulating increases in blood pressure; and (6) How are changes in these mechanisms integrated by the central nervous system so that blood pressure remains in the normal range or even falls in patients with mild hypertension who exercise?

In addition to these fundamental questions that will be largely addressed in the chapters in Part II, other questions that will be discussed in Parts I and III include the following: (1) What is the current consensus on the influence of aerobic, resistance, and concurrent exercise on blood pressure?; (2) What are new and emerging areas of research on the influence of exercise modality on blood pressure?; (3) How are current exercise prescription recommendations for hypertension evolving based on the new findings?; (4) What is the influence of the pleiotropic effects of exercise on other cardiovascular disease risk factors?; and (5) In the post-human genome era what new information is available about the genetics of hypertension and the response to exercise training as therapy?

The many questions outlined above highlight the intellectual challenges, or perhaps the intellectual playground, that involve blood pressure regulation in general

and the effects of exercise and physical activity more specifically. In view of the worldwide pandemic of physical activity, obesity, and high blood pressure, along with the vast social cost of this health condition something has to be done! This volume is a welcome addition to our knowledge and will hopefully frame new questions and new areas of investigation and integration as novel insights about the interactions between exercise and blood pressure. In the great scheme of things, the pressure is on to help the population as a whole to maintain a normal blood pressure and ward off the many negative health consequences of rising blood pressure. Physical activity and exercise training are likely to play a key role in this fight.

Rochester, MN, USA Michael J. Joyner

Preface

This book describes the state-of-the-art effects of exercise on blood pressure as well as the mechanisms underlying essential hypertension in humans. The chapters are written by distinguished experts in the field on current and emerging research regarding the effects of exercise on blood pressure and the physiological systems known to be involved in hypertension development and maintenance from the cellular to the organ to the whole organism level. Each chapter is organized to initially define key terminology and basic concepts; discuss and critique the state of the literature on its given topic as well as the clinical implications and translation of this research into practice; and conclude with the take-home messages, new directions for future research, and a list of key resources for use in the clinic, laboratory, or classroom. The intended audience is academic settings and professional clinicians and scientists working in the areas of allied health, cardiovascular science, cardiovascular and preventive medicine, and exercise science as well as medical and graduate students in the allied health, cardiovascular, and exercise sciences.

The book begins with *Part I Exercise and Hypertension* that contains systematic reviews of the influence of various exercise modalities and physical fitness on blood pressure among those with hypertension framed by the recommended ***F***requency, ***I***ntensity, ***T***ype, and ***T***ime (FITT) principle of exercise prescription. *Part II Mechanisms for the Blood Pressure Lowering Effects of Exercise* discusses various mechanisms associated with the blood pressure response to exercise including vascular function and structure, the effects of exercise mimetics on vascular cell adaptations, arterial stiffness, autonomic function and other hemodynamic adaptations, genetic underpinnings, and myocardial remodeling. The book concludes with *Part III The Pleiotropic Effects of Exercise on Other Cardiovascular Risk Factors and their Interactive Effects with Blood Pressure* that includes dyslipidemia, the metabolic syndrome, inflammation, and oxidative stress.

Although the focus of the book is on human hypertension, several chapters include a brief section covering the effects of exercise on animal models of hypertension. In this book, we have invited leading international scientists in exercise and hypertension to provide up-to-date findings and a vision for their translation into clinical practice. As the reader will see, the outstanding caliber of their contributions has made this project a pleasure to be involved with.

Storrs, CT, USA Linda S. Pescatello

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Acknowledgments

Linda S. Pescatello, Ph.D., F.A.C.S.M., F.A.H.A.

My interest in hypertension was sparked by my grandmother. When I was very little, I remember her being worried about her hypertension when at that time anything below 160 over 100 mmHg was generally not treated, diastolic hypertension was of much more concern than systolic hypertension, and there was little emphasis on the importance of lifestyle modifications such as exercise in the prevention, treatment, and control of hypertension. Fortunately, despite her hypertension, she lived well into her 80s.

In 1981, I had the good fortunate to begin working with a Preventive Cardiologist, Dr. Charles N. Leach, Jr., in cardiac rehabilitation at a community hospital who was one of the pioneering physicians in the use of ambulatory blood pressure monitoring to diagnose hypertension in his patients. Under his mentorship and encouragement, I began a series of studies that continue to this day examining the acute or immediate blood pressure lowering effects of exercise, a response termed *postexercise hypotension*, using ambulatory blood pressure monitoring among adults in the early stages of hypertension. It is very rewarding to see that this work and that of others discussed in this book have established postexercise hypotension as an accepted arsenal in the prevention, treatment, and management of hypertension, although there is still much more to learn about this phenomenon.

My work in the field of exercise and hypertension has provided me with the good fortune of working with leading scientists from all over the world. These include my coauthors on the American College of Sports Medicine Position Stand on *Exercise and Hypertension*—Robert Fagard, M.D., Barry Franklin, Ph.D., F.A.C.S.M., William B. Farquhar, Ph.D., F.A.C.S.M., George A. Kelley, D.A., F.A.C.S.M., and Chester A. Ray, Ph.D., F.A.C.S.M. In more recent years, my collaborations with Paul D. Thompson, M.D., F.A.C.C., F.A.C.S.M., and Beth Taylor, Ph.D., from Hartford Hospital, Hartford, CT; Blair T. Johnson, Ph.D., and Tania B. Huedo-Medina, Ph.D., from the University of Connecticut; and my colleagues from Brazil that include Paulo de Tarso Veras Farinatti, Ph.D., from the Universidade do Estado do Rio de Janeiro. Last, I wish to acknowledge my colleagues from the Department

of Kinesiology and Center for Health, Intervention, and Prevention at the University of Connecticut, and my past and current undergraduate and graduate students, who have been and continue to be instrumental in the research we do on exercise and hypertension.

Linda's Dedication

I dedicate this book to my husband David, daughter Shannon, and son Conor, my parents and two sisters and their families, my good friends, and my pets that have provided me with the love, support, and balance that have enabled me to pursue a career that continues to excite me to this day.

Michael Brown, Ph.D., F.A.C.S.M., F.A.H.A.

I became interested in hypertension when I did an internship in cardiac rehabilitation. I was able to sit in the cardiologists' meetings in which they discussed their patients' cases. I noticed a trend, most of the patients had hypertension. A bit later, I learned that African Americans had the highest prevalence of hypertension in the United States and that at the time, there were no studies on the effects of exercise on hypertension in African Americans. My mission crystallized at that point.

Being accepted into the doctoral program at the University of Maryland College Park gave me the opportunity to train under Dr. James Hagberg. The research he was doing in exercise and hypertension was a fertile training environment for me. Under his mentorship, I received a National Institutes of Health predoctoral training grant. The grant was on the effects of short-term daily aerobic exercise on insulin sensitivity in African Americans with hypertension and led to my first author publication in the journal Hypertension. I completed a postdoctoral fellowship at the University of Michigan, Department of Internal Medicine, Division of Geriatric Medicine, under the mentorship of Dr. Mark Supiano and Dr. Don Dengel. The general focus of our research was age-associated Hypertension and specifically mechanisms of hypertension such as insulin resistance, sympathetic nervous system activity, and sodium sensitivity. Under the guidance of Drs. Supiano and Dengel and the tremendous resources at the University of Michigan, I greatly expanded my research techniques and fine-tuned my experience with conducting exercise training studies. My work has continued to evolve and now includes basic science experiments in endothelial cells.

Throughout my career, I have been fortunate to learn and collaborate with scientists that helped to shape my career. Dr. Joon Park, first my doctoral student, is now a leading researcher on the effects of shear stress on mitochondrial function as it relates to endothelial dysfunction. Dr. Park is a superb young scientist who brought me into the area of endothelial cell research. Dr. Robert Ferrell, a noted geneticist, was a mentor on my National Institutes of Health Career Award. I learned a great deal from Dr. Ferrell and valued his support. Dr. Matthew Weir, a nephrologist and leading expert on renal mechanism of hypertension, was also a mentor of my Career Award. Dr. Weir helped me to sharpen my focus, and I always appreciated his support of exercise research. Dr. Steve Houser, an eminent cardiovascular scientist, was

important during the middle stages of my career as he provided invaluable guidance and insight on both research and career development matters. Lastly, I want to thank Dr. Bo Fernhall for giving me the opportunity to continue to evolve my career in the Department of Kinesiology and Nutrition at the University of Illinois at Chicago. To all of these individuals and others I did not mention, I am forever grateful for your support.

Michael's Dedication

I dedicate this book to two people for without them I would not be in a position to contribute to this book. My mother, Ferne Brown, has been there for me through the ups and downs. My first mentor, Dr. James Hagberg, set me on a path of success for which I will always be grateful. We would also like to thank Gregory Tsongalis, Ph.D., from the Dartmouth Hitchcock Medical Center, who facilitated our communications with the publisher, and Patrick Carr at Springer US/Humana in shepherding this book to print, as well as the many dedicated staff who had a part in making this book an important contribution to the field of exercise and hypertension.

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Part I
Exercise and Hypertension

Chapter 1
The Effects of Aerobic Exercise on Hypertension: Current Consensus and Emerging Research

Linda S. Pescatello, Hayley V. MacDonald, and Blair T. Johnson

Abbreviations

1-RM	One repetition maximum
ACSM	American College of Sports Medicine
BP	Blood pressure
DBP	Diastolic blood pressure
Ex R_x	Exercise prescription
FITT	Frequency, Intensity, Time, and Type
JNC 8	The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
HR	Heart rate
HIIT	High intensity interval training
PEH	Postexercise hypotension
RPE	Rating of perceived exertion
SBP	Systolic blood pressure
US	United States

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VO_{2max}	Maximal oxygen consumption
VO_{2peak}	Peak oxygen consumption
$VO_{2reserve}$	Oxygen consumption reserve

Introduction

Hypertension Is a Major Public Health Problem

Hypertension is one of the most important cardiovascular disease risk factors due to its high prevalence and significant medical costs [1, 2]. Approximately, 78 million Americans (33 %) have hypertension [systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg] and another 71 million (30 %) have prehypertension (SBP ≥ 120 to < 140 mmHg and/or DBP ≥ 80 to < 90 mmHg), amounting to over 60 % of Americans with high blood pressure (BP) [1]. The residual lifetime risk for developing hypertension is 90 % [3]. Prehypertension progresses rapidly to hypertension such that one in 5 people with prehypertension will develop hypertension within 4 years [3–5].

Individuals 50 years of age or younger with prehypertension have double the lifetime risk of stroke, heart failure, coronary heart disease, and intermittent claudication compared to individuals of the same age with normal BP [1]. Hypertension is the most common primary diagnosis in the United States (US), and the leading cause for medication prescriptions among adults over 50 years [6]. Yet, only 75 % of the individuals with hypertension receive pharmacological treatment. Of these, half are not adequately controlled [7]. From 2010 to 2030, the total direct costs attributed to hypertension are projected to triple from $130.7 to $389.9 billion; while the indirect costs due to lost productivity will nearly double from $25.4 to $42.8 billion [2]. These alarming trends illustrate the substantial economic burden hypertension places upon the US health care system.

The Eight Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) recommends lifestyle modifications as initial therapy to prevent, treat, and control hypertension [8]. These lifestyle recommendations include smoking cessation, weight management, reduced sodium intake, moderation of alcohol consumption, an overall healthy dietary pattern consistent with the Dietary Approaches to Stop Hypertension diet, and being physically active. In 2004 the American College of Sports Medicine (ACSM) published an evidence-based position stand evaluating the current state of knowledge on exercise and hypertension, focusing specifically on human studies and essential hypertension [9]. Objectives outlined in the ACSM position stand relevant to this chapter include: (1) addressing the role of acute [immediate, short-term, or postexercise hypotension (PEH)] and chronic (long-term or training) aerobic exercise on BP among individuals with hypertension; and (2) presenting exercise prescription ($Ex\ R_x$) recommendations and special considerations for individuals with hypertension.

There were 25 evidence-based statements made in this position stand regarding the antihypertensive effects of exercise. The categories of evidence used were those

from the National Heart, Lung, and Blood Institute and included: *A*, the highest level of evidence with a large number of randomized, controlled clinical trials supporting these statements; *B*, fewer randomized, controlled clinical trials with inconsistent findings; *C*, observational and nonrandomized studies; and *D*, expert opinion [10]. Overall, only two (8 %) evidence-based statements were given a rating of *A*, ten (40 %) *B*, nine (36 %) *C*, three (12 %) *D*, and one (4 %) *none* indicating the state of the knowledge on the antihypertensive effects of exercise was inconclusive at best [11]. The evidence-based statements made in the ACSM position stand relating to the objectives of this chapter are displayed in Table 1.1.

Table 1.1 Evidence statements on the BP response to aerobic exercise adapted from the 2004 ACSM exercise and hypertension position stand [9]

Section heading	Evidence statement	Evidence category[a]
Exercise BP benefits	• Dynamic aerobic training reduces resting BP in individuals with normal BP and in those with hypertension	A
	• The decrease in BP with aerobic training appears to be more pronounced in those with hypertension	B
	• Aerobic training reduces ambulatory BP and BP measured at a fixed submaximal work load	B
	• BP response differences among individual studies are incompletely explained by the characteristics of the training programs, that is, the weekly exercise frequency, time per session, exercise intensity and type of exercise	B
	• Dynamic exercise acutely reduces BP among people with hypertension for a major portion of the daytime hours	B
	• Resistance training performed according to the ACSM guidelines reduces BP in normotensive and hypertensive adults	B
	• Limited evidence suggests static exercise reduces BP in adults with elevated BP	C
	• Limited evidence suggests resistance exercise has little effect on BP for up to 24 h after the exercise session	C
	• There are currently no studies available to provide a recommendation regarding the acute effects of static exercise on BP in adults	None
	• Regular aerobic exercise reduces BP in older adults as it does in younger persons	B
	• Limited evidence suggests PEH occurs in older adults	C
	• Endurance exercise training reduces BP similarly in men and women	B
	• Limited evidence suggests acute endurance exercise reduces BP similarly in white men and women	C
	• Currently no convincing evidence exists to support the notion ethnic differences exist in the BP response to chronic exercise training	B
	• Currently no convincing evidence exists to support the notion ethnic differences exist in the BP response to acute exercise	C

(continued)

Table 1.1 (continued)

Section heading	Evidence statement	Evidence category[a]
Exercise recommendations	• For persons with high BP, an exercise program that is primarily aerobic-based is recommended	A
	• Resistance training should serve as an adjunct to an aerobic-based program	B
	• The evidence is limited regarding frequency, intensity, and duration recommendations; nonetheless, the antihypertensive effects of exercise appear to occur at a relatively low total volume or dosage	C

[a]*A* the highest level of evidence with a large number of randomized, controlled clinical trials supporting these statements, *B* fewer randomized, controlled clinical trials with inconsistent findings, *C* observational and nonrandomized studies, *D* expert opinion [10]

Purposes of this Chapter

The purposes of this chapter are to: (1) overview the current consensus on the effects of acute (immediate, short-term, or PEH) and chronic (long-term or training) aerobic exercise on BP among individuals with hypertension; (2) discuss new and emerging research on the effects of acute and chronic aerobic exercise on BP that has the potential to alter the way in which aerobic exercise is prescribed to prevent, treat, and control hypertension since the publication of the ACSM position stand on exercise and hypertension; and (3) present Ex R_x recommendations and special considerations for individuals with hypertension that consider this new and emerging research.

Key Terminology and Basic Concepts

The Blood Pressure Response to Acute and Chronic Aerobic Exercise

The BP reductions following acute exercise are immediate but short-term persisting for up to 24 h after the exercise bout [12]. This response is termed PEH [9, 13, 14]. The BP reductions following chronic exercise or exercise training are the long-term BP adaptations that accrue over time. The relationship between the BP response to acute and chronic exercise is unclear, however, they do appear to be related as discussed later in this chapter [9, 15–20].

What Is an Exercise Prescription?

An Ex R_x is the process whereby the recommended physical activity program is designed in a systematic and individualized manner in terms of the Frequency (how often?), Intensity (how hard?), Time (how long?), and Type (what kind?) or FITT principle [9, 14].

The Law of Initial Values

The direction of the response of a body function to an agent depends to a large degree on the initial level of that function. Therefore, BP reductions should be the greatest for those with highest resting BP [19].

The Distinction Between a Systematic Review and Meta-Analysis

A systematic review summarizes empirical evidence from the many separate investigations that address a related outcome or hypothesis. A systematic review should disclose pre-established eligibility criteria and search methods to minimize bias and allow for replication [21]. This chapter is an example of a systematic review on exercise and hypertension. A meta-analysis encompasses a systematic review of the literature, however, it also uses quantitative methods to statistically combine and compare the results of independent studies that address a targeted outcome [22]. This chapter will include discussion of meta-analyses on aerobic exercise and hypertension.

Systematic Review Methods

We performed an updated systematic electronic search of the literature on the BP response to the acute and chronic aerobic exercise since the publication of the ACSM position on exercise and hypertension using PubMed including Medline. This search included human studies of adults 19 years and older that were published in English, had a control/comparison group, and were published between January 1, 2004 and March 28, 2014 (see Fig. 1.1 for the complete search and trial selection details). Our search yielded 2,350 potential reports, of which 108 trials were eligible for inclusion. Of those 108 studies, the authors self-selected 47 studies that were most relevant to the purposes of this chapter.

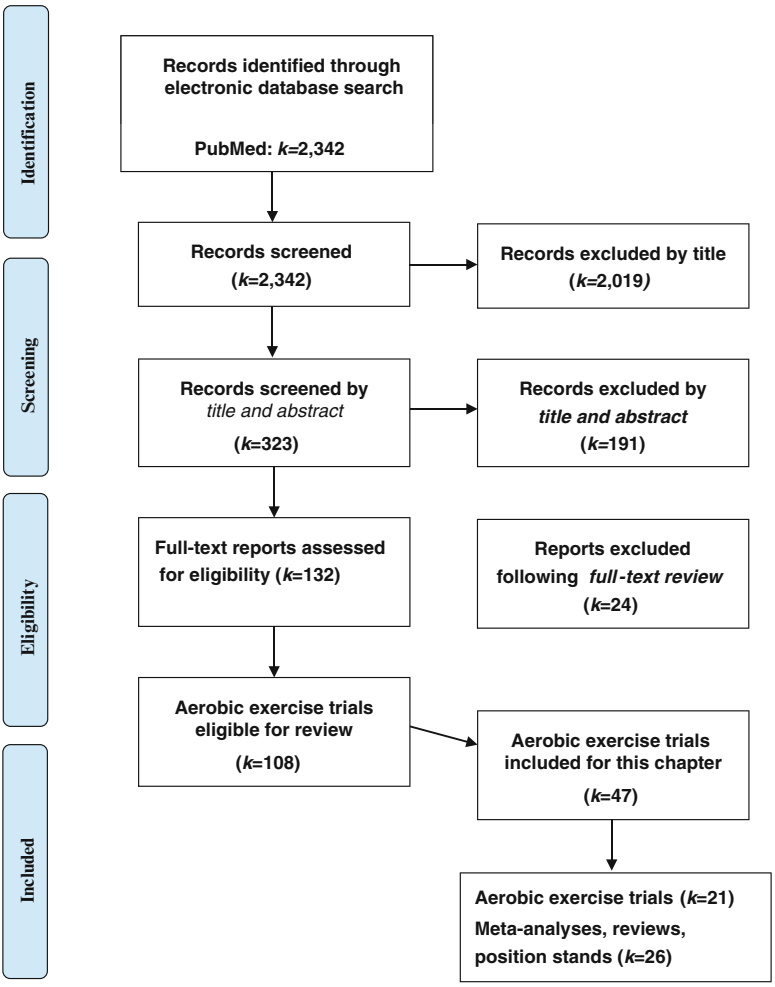

Fig. 1.1 Flow chart detailing the systematic search of potential reports and selection process of included aerobic exercise trials

Relevant Research

Aerobic Exercise and Blood Pressure Effects

Acute, Immediate, or Short-Term Effects or *Postexercise Hypotension*

Current Consensus

In 1981 William Fitzgerald, a non-Hispanic black doctoral student with high BP, took his BP before and after jogging and was one of the first to notice [15]:

> "Jogging depressed my high labile pressure after completing the run. Sometimes my pressure rose to pre-jogging levels within 4 to 10 h and sometimes it did not."

Fitzgerald labeled his serendipitous discovery PEH. More than 10 years later, Kenny and Seals [13] defined PEH as a sustained reduction in SBP and/or DBP below control levels after a single bout of exercise. PEH is now considered an expected physiological response to aerobic exercise. Indeed, a single, isolated session of aerobic exercise of varying durations (10–50 min) and intensities [40–75 % of maximal oxygen consumption (VO_{2max})] or heart rate (HR) reserve immediately reduces BP 5–7 mmHg among individuals with hypertension, and these reductions persist for up to 24 h after the exercise bout [12, 19, 20, 23–35]. More simply, for most people, BP is lower on the days people exercise than on the days they do not exercise. As Table 1.1 summarizes, the ACSM assigned the level of evidence pertaining to the BP response to acute aerobic exercise or PEH a category *B* rating. The ACSM statement had no qualifications about factors that may moderate the BP response to acute aerobic exercise due to a paucity of evidence at that time. Growing research continues to substantiate this category *B* rating suggesting it should be elevated to *A* [36–41].

New and Emerging Research

Ciolac and colleagues [37] evaluated the BP response to an acute bout of moderate intensity aerobic exercise compared to a seated rest control among 50 middle-aged and overweight men and women on antihypertensive medications for an average of 9 years. Ambulatory SBP and DBP were reduced by a mean of 2–4 mmHg for 24 h following aerobic exercise among the total sample; however, statistically significant BP reductions, ranging from 3–7 mmHg, only occurred for subjects with a daytime BP exceeding the control daytime median of 132/84 mmHg. Ciolac et al. [37] concluded their study was one of the first demonstrating PEH is effective antihypertensive therapy among patients on medication for their high BP, and the magnitude of PEH was greatest for those with higher resting BP. Their findings provide additional support to the ACSM evidence-based statement in Table 1.1 that the decrease in BP with aerobic exercise appears to be more pronounced in those with hypertension that was assigned a category *B* rating. Furthermore, their findings are consistent with the conclusions of Pescatello and Kulikowich's systematic review that the BP response to acute aerobic exercise is a function of initial values such that subjects with the highest resting BP experience the largest BP reductions following exercise [19].

In a more recent study, Ciolac and co-investigators [38] randomized 52 men and women on antihypertensive medication to either a continuous, 40 min session of acute aerobic exercise at 60 % HR reserve or an interval aerobic exercise session consisting of alternating 2 min at 50 % HR reserve with 1 min at 80 % HR reserve that totaled 40 min of exercise. Once again, the greatest BP reductions were observed among subjects with a resting BP above the control daytime median of 131/99 mmHg. In addition, BP was significantly reduced 4–8 mmHg for SBP and DBP in the continuous exercise group and 5–6 mmHg for SBP only in the interval exercise group

over 24 h. The new findings of Ciolac et al. [37–39] suggest that moderate to vigorous intensity acute aerobic exercise that is conducted continuously or in intervals elicits PEH.

Consistent with the findings of Ciolac et al. [37, 38], Guidry et al. [40] compared the effects of a short (15 min) and long (30 min) acute aerobic exercise bout performed at light (40 % of VO_{2max}) or moderate (60 % VO_{2max}) intensity on PEH among 45 white, middle-aged overweight men with high normal to Stage 1 hypertension. They found short and long duration acute aerobic exercise reduced SBP an average of 4–6 mmHg compared to control for the remainder of the day, independent of exercise intensity. Average DBP was not different between short and long duration, light intensity acute exercise versus control; but after moderate intensity, DBP was reduced an average of 3 mmHg for the daytime hours after long duration exercise versus control. Guidry et al. [40] concluded an acute bout of aerobic exercise performed for as short as 15 min at light to moderate intensity resulted in PEH for the remainder of the day.

Additional investigation has been done to determine if short, intermittent bouts of aerobic exercise interspersed throughout the day can produce PEH as has been observed with a single bout of continuous aerobic exercise [36, 42–44]. Bhammar and colleagues [36] compared the effects of fractionized aerobic exercise (3, 10 min bouts) spread throughout the day (morning, midday, and afternoon) and one bout of continuous exercise (1, 30 min bout) performed at 60–65 % VO_{2peak} on ambulatory BP among 11 young subjects with prehypertension. They found fractionized exercise was as at least as effective as continuous exercise in eliciting PEH, reducing SBP 3–4 mmHg compared to control throughout the day until the following morning.

Less is known about the antihypertensive effects of very short (<10 min) bouts of aerobic exercise. Miyashita and colleagues [44] investigated the BP response to acute aerobic exercise using multiple, very short bouts (10, 3 min) and a single, continuous (1, 30 min) running bout performed at 70 % VO_{2max} among young men with normal BP ($n=3$) and prehypertension ($n=7$). They found accumulated and continuous aerobic exercise significantly reduced SBP compared to control by 10 mmHg and 8 mmHg, respectively, which persisted up to 24 h following exercise. These findings suggest that brief, 3 min bouts of vigorous intensity running interspersed throughout the day result in PEH, and the antihypertensive effects of very short bouts of vigorous intensity aerobic exercise are similar in magnitude and duration to a bout of continuous vigorous intensity aerobic exercise. The findings of Ciolac et al. [37, 38], Guidry et al. [40], Bhammar et al. [36], and Miyashita et al. [44] are part of a growing literature [42, 45–48] supporting the notion PEH is a low threshold phenomenon in terms of the duration of the exercise bout needed to produce the effect (i.e., durations as short as 3–10 min). More importantly, when these short bouts of exercise are interspersed throughout the day, PEH offers a viable therapeutic lifestyle option for BP control among individuals with high BP as Wilcox and colleagues originally postulated in 1982 [20].

Although evidence was limited, it was the expert opinion of the authors of the ACSM position stand that PEH was also a low threshold phenomenon in terms of

the intensity of the exercise bout needed to induce PEH (i.e., intensities as low as 40 % VO_{2max}) and little additional BP benefit would be achieved with higher intensities [9, 19, 32, 49–51]. It is important to note that when the ACSM position stand was written, there were few published studies involving vigorous intensity acute aerobic exercise among individuals with hypertension due to the potentially adverse cardiovascular and musculoskeletal side effects of vigorous intensity aerobic exercise [52]. Of the few that existed, they may have been subject to Type 2 statistical errors because they lacked sufficient power to detect statistical differences between bouts of varying intensity [19, 31, 32].

There is a growing literature substantiating the cardiovascular health benefits of rigorous intensity exercise [39, 53–55]. Eicher et al. [41] examined the antihypertensive effects of acute bouts of light (40 % VO_{2peak}), moderate (60 % VO_{2peak}), and vigorous (a graded maximal exercise stress test to exhaustion or 100 % VO_{2peak}) intensity aerobic exercise. This study involved 45 middle aged, overweight men ($n = 45$) of European-American descent with pre- to Stage 1 hypertension and borderline dyslipidemia, with 40 % classified as having the metabolic syndrome as defined by the Adult Treatment Panel III [56]. Subjects completed four randomly assigned experiments on different days: a non-exercise control session of seated rest, and 3 cycle exercise bouts, one each at light, moderate, and vigorous intensity, and left the laboratory wearing an ambulatory BP monitor for the remainder of the day.

SBP increased 2.8 ± 1.6 mmHg less after bouts of light, 5.4 ± 1.4 mmHg less after moderate, and 11.7 ± 1.5 mmHg less after vigorous intensity aerobic exercise than control over the daytime hours (Fig. 1.2). Similarly, DBP decreased 1.5 ± 1.2 mmHg more after bouts of light, 2.0 ± 1.0 mmHg more after moderate, and 4.9 ± 1.3 mmHg more after vigorous intensity aerobic exercise versus control over the same time period (Fig. 1.3). Eicher et al. [41] concluded the influence of exercise intensity on PEH occurred in dose response fashion such that for each 10 % increase in relative VO_{2peak}, SBP decreased 1.5 mmHg ($y = -14.9x + 14.0$, $R^2 = 0.998$) and DBP 0.6 mmHg ($y = -5.9x + -0.3$, $R^2 = 0.969$). These findings suggest more vigorous levels of physical exertion acutely lower BP to a greater extent than lower levels of physical exertion for individuals willing and able to tolerate more intense levels of exercise.

Furthermore, Eicher et al. [41] explored resting cardiometabolic biomarkers that may associate with PEH to gain insight into clinical characteristics of people likely and not likely to manifest PEH. Clinical correlates of the metabolic syndrome (i.e., fasting lipids-lipoproteins, and glucose) emerged as correlates of PEH, regardless of exercise intensity; whereas others were intensity-dependent (i.e., C-reactive protein, nitric oxide, fibrinogen, and VO_{2peak}) [57]. These findings suggest that components of the cardiometabolic profile may be eventually used by health care and exercise professionals to identify individuals who are and are not likely to lower BP with exercise so that proper guidance regarding the use of exercise as lifestyle antihypertensive therapy can be given. However, these preliminary findings should be confirmed in a larger, more diverse cohort of men and women.

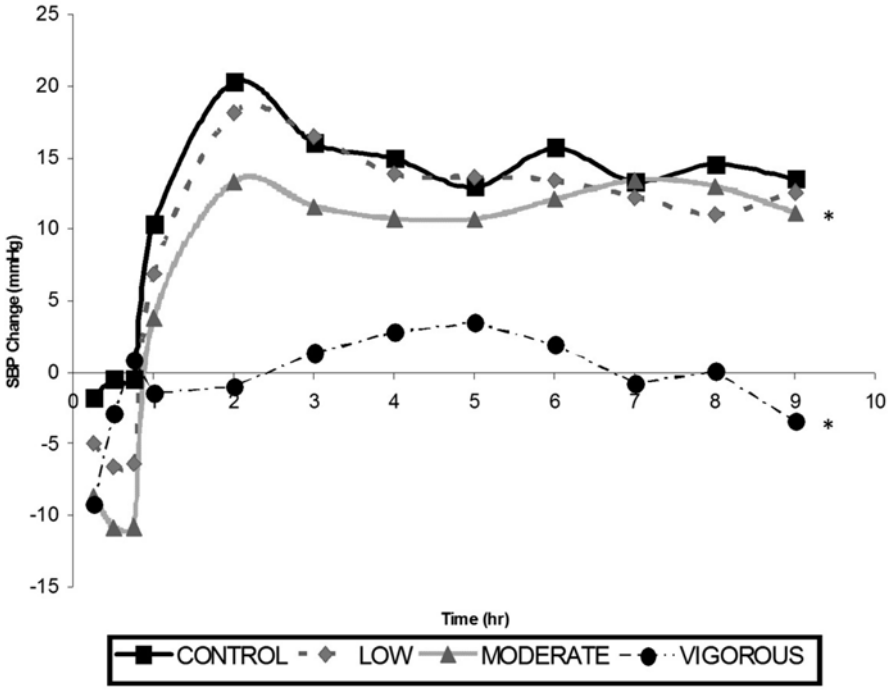

Fig. 1.2 Awake systolic blood pressure change from baseline (Mean ± SEM) at hourly intervals over 9 h after control and exercise compared with baseline values. VO_{2peak} peak oxygen consumption, *CONTROL* non-exercise session of seated rest, *LOW* 40 % VO_{2peak}, *MODERATE* 60 % VO_{2peak}, *VIGOROUS* VO_{2peak}; *$p \leq 0.001$ exercise treatment versus non-exercise control. Reprinted from Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J 2010 Sep; 160(3): 513–520

In summary, new and emerging research suggests that there are important patient/sample characteristics such as resting BP and components of the cardiometabolic profile in addition to aspects of the FITT of the exercise intervention that modulate PEH. PEH is a low threshold event regarding both the time (duration) and intensity of the acute bout of aerobic exercise. Nonetheless, higher levels of physical exertion produce greater BP reductions than lower levels if the individual is willing and able to tolerate them. Despite the plethora of literature on exercise and hypertension, there remains a critical need to identify patient/sample and aerobic exercise intervention characteristics that influence PEH. This information will enable PEH to be prescribed more precisely as antihypertensive therapy for those that manifest PEH, while other therapeutic options can be recommended for those that do not [58]. This new knowledge would not obviate the need for regular aerobic exercise for individuals with hypertension unlikely to respond to PEH as antihypertensive therapy because of its many other health-related benefits, but would hasten the use of alternative therapeutic options for the control of BP in these individuals.

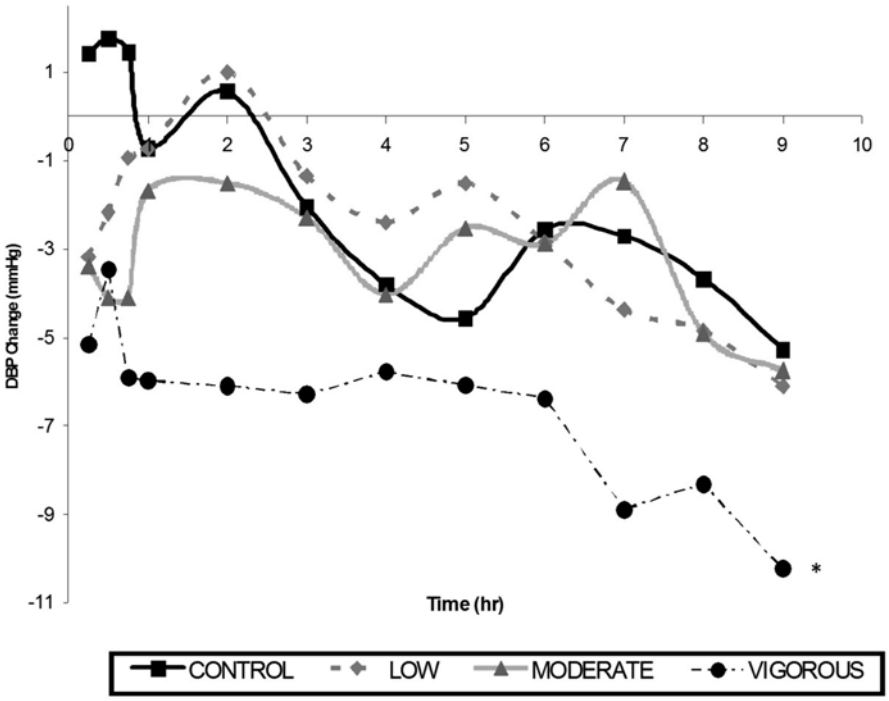

Fig. 1.3 Awake diastolic blood pressure change from baseline (Mean ± SEM) at hourly intervals over 9 h after control and exercise compared with baseline values. VO_{2peak} peak oxygen consumption, *CONTROL* non-exercise session of seated rest, *LOW* 40 % VO_{2peak}, *MODERATE* 60 % VO_{2peak}, *VIGOROUS* VO_{2peak}; *$p \leq 0.001$ exercise treatment versus non-exercise control. Reprinted from Eicher JD, Maresh CM, Tsongalis GJ, Thompson PD, Pescatello LS. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J 2010 Sep; 160(3): 513–520

Chronic, Training, or Long-Term Effects

Current Consensus

The effect of aerobic exercise training on resting BP has been examined extensively with meta-analytic techniques among individuals with normal and high BP [11, 59–63]. The participants in these meta-analyses were generally middle-aged, white men and women, and more often than not, little if any information was provided regarding the use of antihypertensive medications. The training programs averaged 16 weeks and consisted of 3 weekly, 40 min sessions performed at 65 % VO_{2max}. The exercise modalities included walking, jogging, and running in two-thirds of the trials, while cycling was used in the remaining one-third. Cornelissen and Fagard [61] found both resting and ambulatory BP were reduced 2–4 mmHg, and these

reductions were greatest among samples with hypertension (5–7 mmHg) compared to those with prehypertension and normal BP (2 mmHg). For those with hypertension, BP was also reduced at a fixed workload during submaximal exercise. Last, the BP reductions were positively associated with the gains in VO_{2peak}. In a recent meta-analysis, Cornelissen and Smart [63] confirmed these earlier findings that resting BP reductions were greater in adults with hypertension (5–8 mmHg) than those with prehypertension (2 mmHg) and normal BP (1 mmHg). They also found that the BP reductions were directly related to the improvements in VO_{2peak}. In another recent meta-analysis by Cornelissen and colleagues [62], they found ambulatory BP was reduced to lesser levels than previous reports that generally measured BP by auscultation. And in contrast to earlier findings, there were no statistical differences in the magnitude of the reductions in ambulatory BP among samples with hypertension (3–4 mmHg) and normal BP (2–3 mmHg).

Surprisingly, the meta-analyses published to date on the effects of aerobic exercise training and BP have contributed little to our understanding of how population characteristics and the FITT of the exercise intervention moderate the antihypertensive effects of exercise [11]. Two exceptions are the meta-analyses conducted by Whelton et al. [64] and Cornelissen and Smart [63]. Whelton and colleagues [64] examined the effects of exercise training on resting BP among 2,419 individuals that included 1,935 Whites, 391 Asians, and 93 Blacks, and conducted subgroup analyses on BP status, the FITT of the exercise intervention, and race/ethnicity. Similar to most meta-analyses on the effect of aerobic exercise training on BP [59–61, 63], they found the BP reductions were greater among samples with hypertension (4–5 mmHg) than samples with normal BP (2–4 mmHg), and the FITT of the exercise intervention did not influence the BP response to aerobic exercise training. However, subgroup analysis revealed SBP and DBP were reduced by 3/3 mmHg for Whites, 6/7 mmHg for Asians, and 11/3 mmHg for Blacks, respectively. Contrary to the ACSM position stand evidence-based statement in Table 1.1 receiving a category *B* rating that race/ethnicity does not modulate the BP response to aerobic exercise training, the findings of Whelton et al. [64] suggest otherwise.

Cornelissen and Smart's [63] meta-analysis investigated moderators of the BP response to aerobic exercise training. Their sample consisted of 105 aerobic exercise training groups involving men and women with normal BP to Stage 1 hypertension. As previously discussed, the authors confirmed BP reductions were greater among samples with hypertension (5–8 mmHg) than samples with prehypertension and normal BP (1–2 mmHg). In contrast to Whelton et al. [64], Cornelissen and Smart [63] did not find that race/ethnicity influenced the BP response to exercise training. Instead they observed that the men reduced BP to a magnitude that was two times greater than the women, 3–5 versus 1 mmHg, respectively; this result does not support the ACSM evidence-based statement in Table 1.1 that received a category *B* rating that sex/gender does not influence the BP response to exercise training.

Cornelissen and Smart [63] also identified several moderators related to the FITT of the aerobic exercise intervention. They found training programs <24 weeks reduced BP to a greater extent than training programs ≥24 weeks, 3–6 versus 1–2 mmHg, respectively. They also documented that 30–45 min per session

maximized the magnitude of the BP reductions that resulted from aerobic exercise training, and a weekly exercise volume of <210 min resulted in greater BP reductions than a weekly volume ≥210 min. Furthermore, this meta-analysis is the first to report that exercise intensity altered the BP response to aerobic exercise training such that BP reductions were less after low intensity aerobic exercise training (~1 mmHg) compared to moderate to vigorous intensity aerobic exercise training (SBP 4–5 mmHg and DBP 2–3 mmHg).

Collectively, the findings of Whelton et al. [64] and Cornelissen and Smart [63] suggest that race/ethnicity, sex/gender, and aspects of the FITT of the aerobic exercise intervention may play a role in identifying the exercise dose and for whom aerobic exercise training confers the greatest BP benefit. Nonetheless, of the few meta-analyses that have identified factors that appear to alter the BP response to exercise, the results often conflict [11, 58, 65]. One possible explanation for the lack of consistency in reporting moderators of the BP response to aerobic exercise could be due to the large amount of variability among the individual studies with the standard deviation often exceeding the mean BP change [11, 58, 65]. Indeed, 20–25 % of the people with hypertension do not lower their BP after aerobic exercise training and some may even adversely increase BP [9, 19, 50, 51, 58, 65].

Reasons for the variability in the BP response to aerobic exercise training are not clear, but may partially be attributed to study methodological limitations such as small sample sizes with insufficient power to detect differences, nondisclosure of the timing of the BP assessments regarding the proximity to the last exercise bout, the time of day the BP measurements were taken, among others [19, 57, 66]. Without disclosure of these details, it is possible PEH, diurnal variation, and/or detraining effects confounded findings regarding the BP response to aerobic exercise training, thus contributing to this variability. The good news is that despite unknown sources of heterogeneity, almost all of the meta-analyses concluded that resting BP was lowered following aerobic exercise training. Future meta-analyses should be designed that adhere to contemporary high quality standards to improve our understanding of important moderators of the BP response to aerobic exercise training so that aerobic exercise can be more precisely and effectively prescribed as antihypertensive lifestyle therapy [11].

New and Emerging Research

Physiological responses to acute or short-term exercise refer to functional adaptations that occur during and for some time following an isolated exercise session, termed the *last bout effect* [16]. Haskell [16] hypothesized that frequent repetition of these individual exercise sessions produces more permanent functional and structural adaptations, termed the *exercise training response* (chronic or long-term effect). These "more permanent" alterations in structure and function remain for as long as the training regimen is continued and then dissipate quickly returning to pretraining values. We [19, 67] and others [2, 15, 20, 68] have postulated that some,

if not all, of the BP benefit ascribed to aerobic exercise training may be an acute response related to recent exercise or PEH. Several lines of evidence support this hypothesis.

We [19] undertook a systematic review to address this question. The criteria for study inclusion were acute and chronic endurance exercise studies in which BP was measured by ambulatory BP monitoring. A total of 23 investigations met these criteria: eight examined the BP response to acute exercise or PEH and 15 evaluated the BP response to chronic aerobic exercise or training. In all, there were 34 study groups involving middle age, non-Hispanic White men and women who were overweight to obese, mostly sedentary, and they had normal BP (12 groups) or hypertension (22 groups). The reduction in daytime ambulatory SBP was similar after the acute and chronic endurance exercise interventions, 2.0 versus 4.1 mmHg, respectively. The reduction in daytime ambulatory DBP was also not different after the acute and chronic exercise interventions, 1.2 versus 1.9 mmHg. Our findings are consistent with the more recent work of Maeda et al. [69] and Tabara et al. [70] who found the magnitude of the BP reduction following an acute bout of moderate intensity aerobic exercise was of similar magnitude before and after exercise training among older adults with high BP. Thus, it appears BP is reduced to similar levels after acute and chronic exercise suggesting PEH makes a significant contribution to the BP response to aerobic exercise training.

Liu and co-investigators [18] were the first to conduct a study with the primary purpose of determining if PEH could be used to predict the BP response to exercise training among middle-aged men ($n=8$) and women ($n=9$) with prehypertension. Subjects completed a 30 min acute aerobic exercise session at 65 % VO_{2max} before participating in a supervised, 8 week aerobic exercise training program, performed 4 days per week for 30 min per session at 65 % VO_{2max}. The authors were careful to avoid the confounding influence of PEH on the BP response to exercise training by measuring resting BP 48 h after the last exercise bout at the conclusion of exercise training. SBP and DBP were similarly reduced after acute (7/4 mmHg) and chronic (7/5.2 mmHg) exercise, respectively. In addition, the BP response to acute exercise was strongly correlated with the BP response to exercise training, i.e., SBP ($r=0.89$) and DBP ($r=0.75$).

Subsequently, Hecksteden et al. [17] found the BP response to acute and chronic aerobic exercise correlated strongly among a small sample of overweight to obese middle-aged men and women with prehypertension. Their findings and those of Liu et al. [18] support the long held notion that PEH may account for a significant amount of the magnitude of the BP reduction attributed to exercise training. They also suggest that PEH could eventually be used as a tool to identify individuals with hypertension who respond to aerobic exercise as antihypertensive therapy; and when determined not to be responsive, alternative forms of treatment can be more rapidly recommended for the treatment and control of their high BP. Further research is needed to confirm the intriguing findings of Liu et al. [18] and Hecksteden et al. [17] in a larger more diverse sample of adults with hypertension. Nonetheless, they illustrate the need to identify patient/sample and FITT aerobic exercise interventions characteristics that influence the BP response to aerobic exercise training so that exercise can be more precisely and effectively prescribed as antihypertensive therapy [58].

Since the publication of the ACSM position stand on exercise and hypertension [9], there has been a growing body of literature examining the influence of vigorous intensity aerobic exercise training aimed at reducing cardiovascular disease risk among healthy and clinical populations [71–75]. High intensity interval training (HIIT) is characterized by brief periods of very high intensity aerobic exercise (>90 % VO_{2max}) separated by recovery periods of lower intensity exercise or rest [74]. HIIT allows individuals to perform brief periods of vigorous intensity exercise that would not be tolerable for longer periods of time. HIIT can also yield an equal amount of work (i.e., energy expenditure) compared to continuous, moderate intensity exercise in a shorter amount of time [72, 74] making it an attractive alternative to the current ACSM FITT Ex R_x recommendations for hypertension [9, 53]. In addition, several studies have found HIIT to be superior to continuous, moderate intensity aerobic exercise training regarding improvements in cardiovascular disease risk factors when the exercise interventions were matched for exercise volume among a variety of special populations including individuals with coronary artery disease, congestive heart failure, the metabolic syndrome, and overweight and obesity [71–73, 75].

Kessler and colleagues [74] systematically reviewed 24 trials investigating the effect of HIIT on cardiometabolic parameters of which 12 studies examined BP outcomes among subjects taking and not taking antihypertensive medications. Overall, they found BP was not reduced in the aerobic exercise training studies lasting <12 weeks, regardless of antihypertensive medication use. In contrast, there were similar BP reductions for the HIIT and continuous, moderate intensity training groups in the aerobic exercise training studies lasting ≥12 weeks among subjects not taking BP medications. In other recent studies, HIIT reduced BP to a greater extent among samples with higher resting BP, i.e., ~8 mmHg among samples with hypertension [75] and prehypertension [71] compared to ~3 mmHg with normal BP [73]. In summary, these findings suggest that exercise intensity is an important moderator of the BP response to aerobic exercise, and that HIIT could be a viable alternative to the current ACSM FITT Ex R_x recommendations for hypertension as outlined below. However, further investigation is warranted among individuals with hypertension to more definitively determine the benefit-to-risk ratio of exercising at vigorous intensity to lower BP among this population that is predisposed to cardiovascular disease risk.

Clinical Implications and Importance

Exercise Prescription Recommendations

The FITT Exercise Prescription

The FITT Ex R_x recommendations that follow are based upon the current consensus of knowledge regarding the effects of acute and chronic aerobic exercise on hypertension as summarized in this chapter. When appropriate, comment will also be

made on new and emerging research discussed within this chapter that may influence the FITT Ex R_x recommendations for the prevention, treatment, and control of hypertension in the future. Last, although this Chapter only discusses aerobic exercise, the FITT Ex R_x recommendations do include mention of resistance exercise. Chapter 2 provides detailed information on the effects of resistance exercise on hypertension.

For individuals with hypertension, the ACSM recommends the following FITT Ex R_x [9, 53]:

Frequency Aerobic exercise on most, preferably all days of the week supplemented by resistance exercise 2–3 days per week.

This recommendation is made due to the immediate and sustained BP lowering effects of acute aerobic exercise or PEH; or more simply, BP is lower on days when individuals with hypertension exercise than when they do not exercise. Also, individuals with hypertension are often overweight to obese so that large amounts of caloric expenditure should be emphasized [76].

Intensity Moderate intensity aerobic exercise [i.e., 40 % to <60 % oxygen consumption reserve ($VO_{2reserve}$) or HR reserve; 11–13 rating of perceived exertion (RPE) on the 6–20 Borg Scale] [77–79] supplemented by dynamic resistance training at 60–80 % one repetition maximum (1-RM).

Due to emerging evidence that greater BP reductions can be achieved with greater levels of physical exertion [39, 41, 54, 55, 71–75], the aerobic exercise intensity recommendation maybe expanded in the future to include vigorous intensity if the patient or client is willing and able to tolerate higher levels of physical exertion.

Time 30–60 min per day of continuous or intermittent aerobic exercise. If intermittent, bouts should be at least 10 min in duration and be accumulated to total 30–60 min per day of exercise. Resistance exercise should consist of at least 1 set of 8–12 repetitions for each of the major muscle groups.

This recommendation is consistent with the new and emerging evidence that PEH is a low threshold phenomenon regarding the time (duration) of the acute exercise bout; and when several short bouts of exercise of at least 3–10 min are interspersed throughout the day, PEH offers a viable therapeutic lifestyle option for BP control among individuals with high BP [36–38, 40, 42–48].

Type Emphasis should be placed on aerobic activities such as walking, jogging, cycling, and swimming. Resistance training using either machine weights or free weights may supplement aerobic training. Such training programs should consist of 8–10 different exercises targeting the major muscle groups.

This recommendation is made because aerobic exercise training has been consistently shown to lower BP [11], and dynamic resistance training reduces resting BP but to lesser levels than aerobic exercise training (Table 1.1) [9]. See Chapter 2 for additional information on resistance training.

Progression The FITT principle of Ex R_x relating to progression for healthy adults generally applies to those with hypertension [54].

Nonetheless, consideration should be given to the level of BP control, recent changes in antihypertensive drug therapy, medication related adverse effects, and the presence of target organ disease and/or other comorbidities, and adjustments should be made accordingly. Progression should be gradual, avoiding large increases in any of the FITT components of the Ex R_x, especially regarding intensity for most people with hypertension [53].

Conclusion

Hypertension is one of the most important cardiovascular disease risk factors due to its high prevalence and significant medical costs [1]. Indeed, over 60 % of Americans have high BP. Both the JNC8 [8] and ACSM [9] recommend aerobic exercise as initial lifestyle therapy for individuals with hypertension because it lowers BP 5–7 mmHg among those with hypertension. BP reductions of this magnitude can decrease the risk of stroke by 14 %, coronary heart disease by 9 %, and total mortality by 7 % [3, 80]. Furthermore, BP reductions of this magnitude rival those obtained with first line antihypertensive medications [81] as well as with other types of lifestyle therapy [3].

Key Points and Resources

- Hypertension is the most common, modifiable, and costly cardiovascular disease risk factor.
- ACSM recommends 30 min or more of moderate intensity aerobic exercise performed most days of the week supplemented by moderate intensity, dynamic resistance training (see Chapter 2 *Effects of Resistance Exercise on Hypertension*).
- The antihypertensive effects of acute aerobic exercise or PEH are a low threshold event regarding the time (duration) and intensity, and they appear to account for a clinically meaningful proportion of the BP response to aerobic exercise training. Nonetheless, for both acute and chronic exercise, higher levels of physical exertion elicit greater BP reductions than lower levels if the individual is willing and able to tolerate them.
- Despite the volume of literature on exercise and hypertension, there remains a critical need to identify patient/sample and FITT aerobic exercise interventions characteristics that influence the BP response to acute and chronic exercise so that exercise can be more precisely prescribed for those that respond to exercise as antihypertensive therapy, while other therapeutic options can be more rapidly recommended for those that do not.
- American College of Sports Medicine: http://www.acsm.org to access the position stand on exercise and hypertension.

- American Heart Association: http://www.americanheart.org.
- Pescatello LS, Franklin BA, Fagard R, et al. (2004) American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc 36:533–553 [9].
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Chapter 2
Can Resistance Training Play a Role in the Prevention or Treatment of Hypertension?

Ben F. Hurley and Alta Rebekah Gillin

Abbreviations

1-RM	One repetition maximum
ACSM	American College of Sports Medicine
AIT	Aerobic interval training
AT	Aerobic exercise training
BP	Blood pressure
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FITT-VP	Frequency, intensity, time, type, volume, and progression
GXT	Graded exercise testing
IHG	Isometric handgrip training
JNC 7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNC 8	The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
MAP	Mean arterial blood pressure
MVC	Maximum voluntary contraction
PEH	Postexercise hypotension
RCT	Randomized controlled trials
RT	Resistance training
SBP	Systolic blood pressure

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Introduction

The introduction to Chapter 1, *The Effects of Aerobic Exercise on Hypertension*: *Current Consensus and Emerging Research,* described the prevalence and demographics of hypertension in detail. Therefore, the introduction of this chapter will only briefly discuss background information on hypertension and focus more on the relationships among blood pressure (BP), mortality, morbidity, and resistance training (RT).

High BP is the leading preventable cause of disease-specific death in women, the leading preventable cause of death in men due to cardiovascular disease (CVD), and the second leading cause of disease-specific deaths among men and women combined [1]. The Joint National Committee 7 (JNC 7) warned that CVD risk doubles with each increase of 20/10 mmHg starting at a BP of only 115/75 mmHg [2]. Thus, BP should be viewed on a continuum rather than having distinct categories of risk when considering prevention or treatment plans. In addition, BP reductions even in people with normal BP have important health implications because a large proportion of CVD occurs in people with prehypertension [3], and overall cardiovascular morbidity and mortality is reduced in the general population with even modest reductions in resting BP [4]. Although the more recent Joint National Committee 8 (JNC 8) report [5] recommends physical activity as one of the lifestyle modifications for the prevention and treatment of hypertension, it provides no information on the type and amount of physical activity that should be recommended.

The latest American College of Sports Medicine (ACSM) Position Stand on Exercise and Hypertension [4] concluded that small to moderate reductions in BP were reported with some forms of regular resistance exercise, but data from ambulatory measures of BP, acute effects of RT on BP, and randomized controlled trials (RCT) on isometric RT were limited at the time of that report. There have been at least three meta-analyses and dozens of data-based publications on RT and hypertension since the ACSM report. Therefore, this review will provide an update on RT since the publication of the ACSM Position Stand on Exercise and Hypertension [4].

Purposes of this Chapter

The purposes of this chapter are to determine: (1) the effects of acute (immediate, short-term, or postexercise hypotension [PEH]) and chronic (long-term or training) resistance exercise on resting BP and the BP response to exercise; (2) how the BP effects of dynamic RT compare to those of static (isometric) RT and to those of aerobic exercise training (AT), as a reference standard; (3) the effects of RT on common risk factors in those with hypertension; and (4) whether there is sufficient evidence to develop an exercise prescription for optimal reductions in BP using RT as the training modality. Please see Chapter 6 for additional information of the effects of resistance exercise on vascular function and BP.

Key Terminology and Basic Concepts

Acute Exercise Versus Training

Acute exercise is operationally defined in this chapter as acute muscular activity and will be distinguished from "exercise training" (chronic muscular activity) or "training" because "acute exercise" tends to disrupt homeostasis of many physiological systems, whereas "training" raises the threshold at which exercise begins to disrupt homeostasis. Therefore, the physiological change produced during and in some cases following acute exercise may not be the same and is often in the opposite direction as that produced following training.

Endurance Versus Aerobic Exercise Training

There are now at least a dozen studies demonstrating significant increases in time to exhaustion (endurance) in both aerobic and anaerobic activities as a result of RT, despite little to no improvements in aerobic capacity with RT. Therefore the term "aerobic exercise training" (AT) will be used instead of "endurance training" to refer to regular aerobic exercise when comparing physiological differences to RT.

Shortening Versus Concentric and Lengthening Versus Eccentric Phases of Muscle Contractions

The shortening and lengthening phase of muscular activity have commonly been referred to as concentric and eccentric phases, respectively, but these terms are misnomers originating from cardiac nomenclature, and not applicable to skeletal muscle actions. For this reason the terms shortening and lengthening phases will be used instead, as recommended by Faulkner [6].

Isometric Contraction

Some people have suggested that the term "contraction" be avoided when used in reference to "isometric" or the lengthening phase of muscle action because the term "contraction" implies shortening, which does not occur during isometric or in the lengthening phase of muscle action. However, the term "contraction" is appropriate in this context because it refers to the action and not the length of the muscle [6].

Intensity Versus Level of Resistance or Load

The terms "level of resistance" or "load" will be used instead of the ambiguous term "intensity" for describing the work output or force production required in RT because the term "intensity" can also apply to velocity of repetitions, rest intervals, total training volume, etc., used in RT.

Percent (%) of One Repetition Maximum Versus Range of Repetition Maximum

It is common practice to prescribe the level of resistance (load) for RT programs as a percent (%) of one repetitions maximum (1-RM). At least three studies have reported large variations in the number of repetitions that can be completed at any given percent (%) of 1-RM from one exercise to another for the same people and for the same exercise among different people. Therefore, a range of RM, such as 8–12-RM, will be used instead of a given percent (%) of 1-RM for prescribing load.

Methods for Systematic Review

We searched PubMed database between 1985 and 2014, but papers between 1985 and 1995 were excluded if similar information could be obtained from more recent papers. In a few cases, important information relevant to the focus of this review could only be found from published papers prior to 1985. Additional references were identified by reviewing bibliographies from the most current and relevant articles located for this review. Our search included the terms "resistance training," "resistance exercise," "weight training," "isometric exercise," "isometric resistance training," "circuit weight training," "hypertension," "BP," "arterial stiffness" "vascular conductance," "vascular stiffness," "aortic pressure," "central pressure," "cardiometabolic disease risk," "risk factors for metabolic syndrome", and "risk factors for hypertension".

Studies met the following criteria for inclusion and exclusion: (1) published in English; (2) used some form of RT or related outcome of RT, such as strength or muscle mass; (3) some outcome or component of BP or hypertension was assessed; and (4) both RCTs and non-RCTs were included, but only those non-RCT that had other indicators of good internal controls, such as the inclusion of a non-exercise control group were included. Studies were excluded or dismissed with comment if adjustments were not made for potential confounders, or if they had mixed interventions with no attempt to assess the independent effects of RT. Investigations that included hospitalized patients or those whose outcomes were substantially influenced by disease, disability, or medications used by participants were also excluded.

Relevant Research

The following sub-sections will be discussed in this section: (1) Overview of the BP responses to RT from meta-analyses; (2) Effects of acute resistance exercise on resting BP; (3) Effects of dynamic RT on resting BP; (4) Effects of dynamic RT on the BP response to exercise; (5) Effects of isometric RT on resting BP; (6) Dynamic RT vs. AT; (7) Effects of RT on risk factors common in those with hypertension; and (8) Is there sufficient evidence to develop a clinically meaningful exercise prescription for RT? Please see Chapter 6 for additional information of the effects of resistance exercise on vascular function and BP.

Overview of the Blood Pressure Responses to Resistance Training from Meta-Analyses

Cornelissen et al. reported meta-analyses on the effects of RT on BP in 2005 [7], 2011 [8], and 2013 [9]. In their 2005 report, they pooled data from nine RCTs [7] and concluded that RT reduced systolic BP (SBP) by 3.2 mmHg (borderline significant) and diastolic BP (DBP) by 3.5 mmHg when weighted by number of subjects studied. When weighted by the inverse of the variance in the BP change to calculate the overall effect size of training on BP, the magnitude of the reductions was greater (6.0 mmHg for SBP and 4.7 mmHg for DBP).

The updated meta-analysis reported by Cornelissen et al. [8] in 2011 revealed significant reductions in resting BP in 28 study groups with normal BP and prehypertension, but no significant reductions were observed for the five study groups with hypertension. When study groups were compared according to type of RT, it was concluded that isometric handgrip training (IHG) may be more effective for reducing BP than dynamic RT, though the authors cautioned that fewer studies were available for comparison with IHG.

In their second follow-up meta analysis in 2013, Cornelissen and Smart [9] compared the results of dynamic RT studies to those of isometric RT, AT, and concurrent AT and RT studies (Fig. 2.1). There were two rather surprising findings from this comparison. First, AT, dynamic RT, and isometric RT reduced SBP, but concurrent AT and RT did not; and second, isometric RT was a more effective training modality than either dynamic RT or AT for reducing SBP. Similar findings for the effectiveness of isometric RT were reported in another meta-analysis by Kelley and Kelley [10] and is discussed in the section of this chapter on isometric RT. Both study groups [9, 10] acknowledged, however, that more RCTs are needed on isometric RT before a definitive conclusion can be made that isometric RT is the most effective training modality for reducing BP. Cornelissen and Smart [9] concluded that AT appears to be superior than either dynamic RT or concurrent AT and RT for lowering BP, but this conclusion does not appear to be supported by their data showing that the magnitude of reductions in SBP and DBP were similar among the three exercise modality groups overall. Further analysis revealed that AT showed the greatest BP

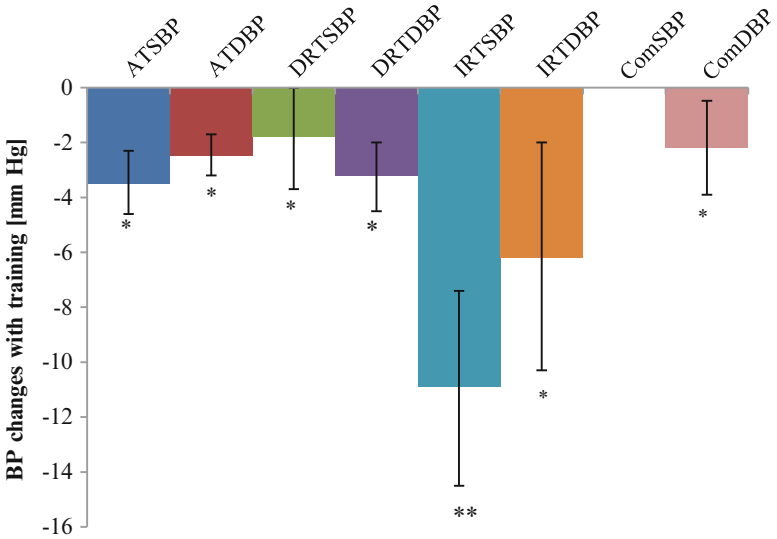

Fig. 2.1 A comparison of the BP responses of AT to DRT, Isometric RT, and concurrent training from a meta-analysis by Cornelissen and Smart [9]. Standard error bars represent 95 % confidence intervals for each training modality. Reductions in SBP for isometric RT (Isometric RTSBP) were significantly greater than those of all other training modalities (**$p < 0.001$). All other training modalities resulted in significantly reduced SBP and DBP (all $p < 0.5$) except ConSBP. *BP* blood pressure, *ATSBP* systolic blood pressure response to aerobic training, *ATDBP* diastolic response to aerobic training, *DRTSBP* systolic blood pressure response to dynamic resistance training, *DRTDBP* diastolic response to dynamic resistance training, *isometric RTSBP* systolic blood pressure response to isometric resistance training, *Isometric RTDBP* diastolic blood pressure response to isometric resistance training, *ConSBP* systolic blood pressure response to concurrent training, *ConDBP* diastolic blood pressure response to concurrent training

improvements in men and those who had hypertension; whereas RT showed the greatest BP improvements in those who had prehypertension. Please see Chapter 3 for more detailed discussions regarding the effects of concurrent exercise on BP.

In conclusion, the results of these meta-analyses suggest that dynamic RT can result in small to moderate reductions in SBP and DBP, particularly among those with prehypertension; whereas reductions in BP with AT appear to occur in those with either prehypertension or hypertension. However, there is a substantially greater number of studies with AT than RT. The limited number of RCTs on the effects of isometric RT show greater reductions in BP than both dynamic RT and AT, but more RCTs are needed before public recommendations are warranted.

Effects of Acute Resistance Exercise on Blood Pressure

Some health care professionals have cautioned against RT for patients with hypertension because it can lead to the Valsalva maneuver, a strenuous and prolonged expiratory effort when the glotus is closed, causing a decrease in venous return to the

heart and an increase in peripheral venous pressures during the initial strain [11]. Venous return increases after the strain has been terminated, leading to increased arterial pressure. A major concern for this effect was highlighted back in 1985 by MacDougall et al. [12] who reported mean values of 320/250 mmHg during a leg press exercise, with one subject exceeding 480/350 mmHg, resulting in up to a four-fold elevation in BP in bodybuilders, lifting weights at or above 80 % of their 1-RM. However, these extremely high BP surges returned to normal within 10 s after the last repetition of each set, which raised the question of how long do high BP surges have to last to produce dangerous effects to the cardiovascular system. To this date, the answer to this question is still unknown to the best of our knowledge [13].

Many studies have reported reductions in post exercise BP with acute resistance exercise [14–20]. For example, Brito et al. [19] observed PEH after one session of RT in patients with mild hypertension. Reductions were observed after resistance exercise was performed at both 50 and 80 % of 1-RM with significantly greater reductions following 80 % (33/15 mmHg for SBP/DBP, respectively) versus 50 % (23/7 mmHg) at 90 min of recovery. In another study, Morais et al. [21] observed significant reductions in mean ambulatory arterial BP (MAP) for up to 8 h after exercise (~8 mmHg below the no exercise control session), and throughout the 24 h monitoring period after circuit resistance exercise performed at a moderate load of 70 % of 1-RM. However, there were no significant reductions over the same time periods after aerobic exercise compared to the control condition in patients with type 2 diabetes mellitus, suggesting that acute resistance exercise has a greater PEH effect in type 2 diabetics than acute aerobic exercise [21]. Likewise, a single bout of resistance exercise lowered BP over a 24 h period, whereas acute aerobic exercise did not lower BP in type 2 diabetics. In this context, Scher et al. [14] also observed significant reductions in SBP and DBP throughout 60 min of recovery after one set of 10 low level resistance exercises (performed at 40 % of 1-RM) compared to resting (8/6 mmHg for SBP/DBP, respectively) and for up to 24 h after two sets of 10 resistance exercises (2 mmHg for SBP only). DBP during sleep was also lower after two sets than after one set of exercises, but neither was significantly lower than the control condition during sleep [14].

Taken together, this section indicates that BP can surge to levels substantially beyond baseline during acute resistance exercise, and is greatly influenced by exercise load, but is reduced below baseline shortly after the exercise ends and can remain below baseline for up to 24 h postexercise. It is unclear if any of the components of the frequency, intensity (load), time, type, volume, and progression (FITT-VP) principle of exercise prescription, have an effect on PEH, because the few studies that have addressed this connection have produced mixed results. For example, Brito et al. [19] showed that high load resistance exercise performed regularly (80 % of 1-RM) was more effective than moderate to low load resistance exercise (50 % of 1-RM) for eliciting PEH, but Scher et al. [14] reported even lower load resistance exercise (40 % of 1-RM) elicited PEH. Although these findings may provide some support for the hypothesis that resistance exercise performed regularly, as is the case with RT, may have a hypotensive effect, they do not provide evidence for BP adaptations resulting from RT.

Effects of Dynamic Resistance Training on Resting Blood Pressure

Mota et al. [22] reported significant reductions in both resting SBP (135 ± 15 to 120 ± 12 mmHg) and DBP (76 ± 9 to 72 ± 9 mmHg) among 64 older women with controlled hypertension as a result of 16 weeks of a RT program that progressed from 60 to 80 % of 1-RM. In a similar study among participants with hypertension who were deprived of their BP medications, Moraes et al. [20] found that SBP fell by 16 mmHg and DBP by 12 mmHg following a 12 week RT program performed three times a week at 60 % of 1-RM. After 4 weeks of detraining, these reductions were still maintained significantly below pre-training values. Similar findings were observed by Nascimento et al. [23], who also compared the effects of a moderate load RT program (8–12 repetitions using a moderate to slightly heavy resistance level derived from a perceived rating scale) to those of detraining effects. Reductions in resting BP with RT were maintained for up to 14 weeks, as evidenced by significantly lower SBP and MAP levels than the BP values before training, even after 14 weeks of detraining [23]. This finding of such a prolonged maintenance of RT-induced BP reductions is quite remarkable and to the best of our knowledge has not been reported to occur for this long with any other training modality.

We studied the effects of a heavy resistance, high volume RT program, i.e., starting each set at a 5-RM load then progressing to a 15-RM within each set of exercise, on resting BP in older men and women in the higher range of prehypertension [3]. Significant reductions in BP were observed in both SBP (131–126 mmHg) and DBP (79–75 mmHg) with RT; and these reductions were maintained for up to 48 h following the last bout of exercise in the RT program (SBP 131–127 mmHg) and were sufficient to shift DBP in men from the prehypertensive or high normal category to the normal range (81–76 mmHg).

The findings of some studies appear to be in conflict with others. For example, Gerage et al. [24] reported a significant reduction in resting SBP (125 ± 8 to 120 ± 7 mmHg), but not in DBP, with 12 weeks of moderate load RT in healthy older women with normal BP. In contrast, Taaffe et al. [25] observed a significant reduction in DBP (77 ± 6 to 74 ± 9 mmHg), but not SBP, with 20 week of heavy RT in a similar age group of women with prehypertension. However, they did observe significant reductions in central SBP (125 ± 10 to 119 ± 12 mmHg) and central DBP (78 ± 6 to 75 ± 9 mmHg), without affecting arterial stiffness with RT. Likewise, Heffernan et al. [26] reported a 5 mmHg reduction in central SBP (134 ± 5 to 129 ± mmHg) and a 7 mmHg reduction in central DBP (84 ± 2 to 77 ± 2 mmHg), as well as reductions in brachial SBP (140 ± 4 mmHg vs. 134 ± 4 mmHg) and brachial DBP (83 ± 2 to 77 ± 2 mmHg) in older men and women with prehypertension and untreated hypertension as a result of moderate load RT (12–15 reps starting at 40 % of 1-RM then progressing to 60 % of 1-RM); whereas no significant changes in any of these BP components were found in a non-exercise control group. Croymans et al. [27] also observed significant decreases in SBP, DBP, and central BP with 12 weeks of a heavy RT program among overweight and obese men. Reductions in central BP

with RT were positively correlated with oxidized low density lipoprotein. The authors suggested that the cardioprotective effects of RT may be at least partially related to its effects on central BP, but offered no potential mechanism to explain this relationship.

There are many studies that show no significant improvements in BP with dynamic RT [28–35]. For example, Conceicao et al. [34] observed no significant change in resting SBP or DBP with 16 weeks of what appears to be moderate load RT in postmenopausal women. Likewise, Heffernan et al. [36] found no changes in brachial SBP, brachial DBP, aortic DBP, and carotid DBP with moderate load RT in African American and in White men.

It is unclear what factors might explain the differences in findings between those studies that report reductions in resting BP and those reporting no reductions in BP with RT. However, dynamic RT programs that used low to moderate loads tended to be at least as effective and often more effective than those using heavy resistance loads. For example, Tsutsumi et al. [37] compared low load RT (55–65 % of 1-RM) to heavy load RT (75–85 % of 1-RM) in older adults with normal BP. Both training loads significantly decreased SBP, but a greater reduction was reported in the low load (13.4 mmHg) than the heavy load RT program (6.1 mmHg). A significant drop in DBP was also found in the low load training group, but not in the heavy load group. Similarly, Van Hoof et al. [38] reported no significant reductions in BP with heavy load (70–90 % of 1-RM) RT. Other than training load and a few studies that have compared training frequencies, little information is known about various levels of the FITT-VP components to determine the optimal RT protocol for reducing BP.

Thus, in conclusion, some studies show significant BP reductions with dynamic RT, whereas others do not, but we are not aware of any study that has identified a component of the FITT-VP model of exercise prescription that is likely to explain this difference. However, the findings are more consistent on the effects of dynamic RT training on the BP responses to exercise, as described in the next section.

Effects of Dynamic Resistance Training on the Blood Pressure Response to Exercise

There are many studies that have assessed the BP responses during graded exercise tests (GXT) before and after several week of RT. Here are three examples [20, 33, 39]. Lovell et al. [33] observed a reduced SBP response to a GXT after 16 weeks of RT compared to before training. Using the same comparisons, Vincent et al. [39] observed reductions in DBP and MAP during a GXT with 16 weeks of RT, but no significant changes in exercise SBP or resting BP. The greatest reductions in DBP and MAP during a GXT in this study occurred with heavy RT (i.e., 80 % of 1-RM) [39]. Thus, RT may be beneficial to some aspects of cardiovascular function during aerobic exercise, despite not always reducing resting BP or aerobic capacity.

Beck et al. [40] reported reductions in myocardial oxygen demand with RT in participants with prehypertension, suggesting that RT may elicit other more generalized

cardiovascular adaptations. This finding has particular relevance and importance for those at high risk for atherosclerosis or older adults who participate in rigorous activities in which the myocardial oxygen demand could exceed the supply, placing them at risk for a myocardial infarction In this context, Parker and coworkers [41] demonstrated that 16 weeks of RT significantly decreased heart rate, BP, and the rate pressure product, an index of myocardial oxygen demand, during a weight-loaded submaximal treadmill walking test in 60–77 year old women, despite no changes in aerobic capacity. In another study, these same indicators of myocardial oxygen demand were reduced during a RT exercise session after training compared to before training [42]. A result that translates into improved cardiovascular function during physical performance as a result of RT. In addition, Ades et al. [43], observed a 38 % improvement in treadmill walking endurance in 65–79 year old women with RT, despite no significant increase in their aerobic capacity. The specific mechanisms for these submaximal BP and other cardiovascular adaptations with RT are not well understood, but possible explanations include changes in fiber type recruitment (i.e., greater rate of type I and a reduced rate of type II muscle fiber recruitment, less occlusion of blood flow, and increased lactate threshold) [44].

In an unpublished pilot study, we found significant reductions in myocardial oxygen demand in response to activities designed to simulate walking up stairs while carrying heavy objects, such as groceries. These reductions were elicited by reductions in heart rate, BP, and blood catecholamine levels while performing these activities, suggesting that RT can improve the myocardial oxygen supply/demand ratio, while performing common activities of daily living. These findings support the hypothesis that RT may raise the activity threshold for being at risk for a myocardial infarction among high risk older sedentary individuals.

In summary, even when resting BP is unchanged with RT, BP during physical activity may be reduced, resulting in improved functional and health outcomes, particularly among older adults [33, 39, 41, 42]. Please see Chapter 4 for a detailed discussion of the clinical significance of the BP response during submaximal exercise.

Effects of Isometric Resistance Training on Resting Blood Pressure

Overview from Meta-Analyses

The most current ACSM Guidelines for Exercise Testing and Prescription (ninth Edition) [45] did not address the issue of whether isometric RT is effective for reducing BP due to limited evidence, while the 2004 ACSM Position Stand on Exercise and Hypertension [4] concluded that limited data suggests isometric RT reduces BP in adults with elevated BP. However, since the ACSM position stand, there has been at least three RCTs and many more non-RCTs that are otherwise well

controlled studies on the effects of isometric RT on resting BP, supporting the use of this training modality for reducing BP. In addition, a 2010 meta-analysis [10] concludes that significant isometric RT minus no-exercise control group reductions of 13 mmHg and 8 mmHg for SBP and DBP, respectively, were observed. Similar reductions were reported for SBP and even greater effects were observed for DBP with isometric RT. Please see Chapter 6 for additional information of the effects of isometric exercise on vascular function and BP.

In a 2013 meta-analysis by Cornelissen and Smart [9], greater BP reductions were found with isometric RT (11/6 mmHg for SBP/DBP, respectively) than dynamic RT (23 mmHg for SBP/DBP) and those from AT studies (4/3 mmHg for SBP/DBP). However, in this meta-analysis there were only five study groups of isometric RT compared to 29 dynamic RT and 105 AT study groups and only one isometric RT investigation that studied participants with hypertension. Nevertheless, there are many other isometric RT studies not included in this meta-analysis, presumably because of not being RCTs, but otherwise well controlled, also showing greater reductions in BP [46, 47] than is typically reported for either dynamic RT or AT.

In a subgroup analysis of the dynamic RT groups in this meta-analysis [9], men and women were approximately equally represented, with about 45 % under the age of 50, 41 % with normal BP, 45 % with prehypertension, and 14 % with hypertension. The duration of the dynamic RT programs were variable, with ~17 % <12 weeks, 62 % between 12 and 24 weeks, and 21 % >24 weeks. Of these, 7 % used a low load in their training program, 19 % used a moderate load, and 74 % used a heavy RT load. In the subgroup analysis of the AT study groups, 42 % were men, 58 % were women, 54 % were <50 years, 28 % had normal BP, 48 % had prehypertension, and 25 % had hypertension. Surprisingly, the AT programs that lasted <24 weeks appeared to lower SBP and DBP to a greater extent than those that lasted >24 weeks in duration. Likewise, weekly exercise durations of <150 min per week were more effective than those >210 min per week. However, these findings may be related to intensity because moderate and high intensity training resulted in greater BP reductions than low intensity AT programs [9].

Thus, a higher portion of the AT study groups consisted of participants who had hypertension and a low portion had normal BP compared to the dynamic RT study groups. It would be hard to make this comparison to the isometric RT study groups used in this meta-analysis because there were so few study groups and only one that studied participants with hypertension. Comparing other factors, such as intensity, duration, and frequency of training, among the three training modalities would not be very meaningful, even if it were possible to match the same level of each component, because of the major physiological differences in response to these training modalities. Also, Cornelissen and Smart [9] did not provide a subgroup analysis of these characteristics for the isometric RT programs. However, the training protocols used in the isometric RT studies, particularly for IHG training, are also more homogeneous than those of RT or AT. Cornelissen and Smart [9] did not comment on the clinical utility of the training protocols used for each training modality in this meta-analysis.

Effects of Isometric Handgrip and Leg Isometric Training on Blood Pressure

The previous section provided an overview of meta-analyses that compared the findings of isometric RT to those of other studies using dynamic RT and AT. This section will attempt to distinguish the effects of IHG training from those of leg isometric training programs using primary sources, some of which were not included in the meta-analysis of the previous section. Most of the IHG studies used a training protocol of four sets of 2 min of IHG contractions at 30 % of maximal voluntary contraction (MVC) or minor variations of it, and observed significant reductions in resting BP [46–61]. Not all of these studies were reviewed by Cornelissen and Smart [9] in their meta-analysis. Four additional studies followed an isometric leg training protocol [56–59]. At least four studies used participants who were diagnosed with hypertension [48, 50, 51, 54]. It was unclear in some other studies whether individuals with hypertension were included.

Taylor et al. [46] reported one of the largest improvements in SBP in the RT literature, finding a 19 mmHg decline in SBP with IHG in men and women with hypertension using a typical IHG protocol of four, 2 min handgrip contractions at 30 % of MVC in the left arm. They also observed a 7 mmHg decrease in DBP and an 11 mmHg decrease in MAP with 10 weeks of IHG training. Wiley et al. [47] compared two IHG training protocols in young to middle-aged men and women with prehypertension. A moderate load training program of four, 2 min IHG contractions with 3 min rest intervals between contractions at 30 % of MVC, performed three times per week for 8 weeks was compared to four, 45 s contractions at 50 % of MVC with 1 min rest intervals performed 5 days per week for 5 weeks. The moderate load training program resulted in a 13 mmHg reduction in SBP and a 15 mmHg reduction in DBP, whereas the heavy load training resulted in a 10 mmHg reduction in SBP and a 9 mmHg reduction in DBP. These findings suggest that both moderate and high load IHG training are highly effective in reducing BP, but no analysis was presented to determine whether the moderate load training was more effective than the heavy load protocol.

McGowan et al. studied the effects of unilateral IHG training on BP and related mechanisms in and in participants with normal [53] BP and hypertension [54]. The training program consisted of four, 2 min unilateral IHG contractions at 30 % of MVC, 3 days per week for 8 weeks and resulted in a significant reduction in resting SBP (118.1 ± 2.4 to 113.2 ± 1.3 mmHg). In contrast, DBP remained unchanged from baseline. Using the same training protocol, but comparing unilateral to bilateral training in participants who had hypertension, McGowan et al. [54] found greater reductions in SBP in both bilateral (reduced by 15 mmHg) and unilateral IHG training (reduced by 10 mmHg) in their participants with hypertension compared to their previous findings in individuals with normal BP, but DBP did not change significantly in either group. Garg et al. [61] used a similar training protocol, i.e., 30 % of MVC in those with normal BP, but allowed participants who were capable to sustain contractions for up to 3 min since some people will reach muscular fatigue

prior to 3 min at this load. The rest of the protocol consisted of five, 3 min bouts of IHG exercise with 5 min rest periods for 10 weeks. They observed a 10 mmHg decline in SBP and a 6 mmHg decline in DBP with training.

Though fewer isometric RT studies have used lower limb training protocols than IHG protocols, these training programs also elicit reductions in BP. For example, Howden et al. [56] investigated the effects of 5 weeks of isometric leg training and 5 weeks of isometric arm training in 27 men and women with normal BP. The leg training consisted of four, 2 min bouts of isometric contractions at 20 % of MVC with 3 min of rest between contractions. Following 8 weeks of no exercise the same participants engaged in 5 weeks of isometric arm training using the same training duration and frequency used in the leg training. SBP dropped by 10 mmHg with leg isometric training and by 12 mmHg with arm training.

Three other studies have observed a decrease in BP after isometric leg training [57–59]. Baross et al. [57] studied 30 middle-aged men before and after an 8 week training program (four, 2 min bilateral leg isometric contractions, three times per week). Two groups trained at either 14 % or 8 % of MVC and a third group served as a no exercise control group. There was a significant reduction in resting MAP (5 mmHg) and resting SBP (11 mmHg) after training in the 14 % of MVC group, but there were no significant changes in MAP or SBP in the 8 % of MVC group; suggesting a threshold load of >8 % but ≤14 % of MVC is required for reducing BP with leg isometric RT. Likewise, Wiles et al. [59] compared exercise loads of 10 % (low load) and 20 % (high load) of MVC using isometric double leg extension in young men with normal BP and found significant reductions in BP with both low and high load training. SBP was reduced by 4 mmHg and DBP was reduced by 3 mmHg in the low load group, whereas SBP was reduced by 6 mmHg and DBP was reduced by 3 mmHg in the high load group with training. The training protocol of both groups consisted of four sets of 2 min exercise bouts 3 days per week for 8 weeks. Using this same training protocol, the same group reported similar BP reductions with a load of 24 % of MVC (5/3 mmHg for SBP/DBP), but they also found significant reductions in SBP (5 mmHg) and DBP (3 mmHg), with four, 2 min isometric bilateral leg contractions at 24 % of MVC [58]. Taken together, these results suggest that significant reductions in BP can result from leg isometric leg training with a load as little as 10 % of MVC. We were unable to find any studies that investigated isometric leg training using participants with hypertension. In addition, no studies were found that compared isometric RT directly with dynamic RT.

In summary, it appears that isometric RT consistently reduces BP in those with normal BP and prehypertension (see Chapter 6 for additional information of the effects of resistance exercise on vascular function and BP). The few IHG studies that included participants with hypertension also reported a hypotensive response to IHG training. The magnitude of the BP reductions to both IHG training and isometric leg training tended to be greater than that reported from dynamic RT and at least as much as that previously reported from AT, but we were unable to locate studies that compared these training modalities. However, unlike AT and to some extent dynamic RT, there are no data available, to the best of our knowledge, to support a reduction in other risk factors for cardiometabolic disease with isometric RT. For this reason, isometric RT should not be recommended as a substitute for either dynamic RT or AT.

Dynamic Resistance Training Versus Aerobic Training Effects on Resting Blood Pressure

Because AT often serves as a reference standard for training adaptations and has been so well studied, it is surprising how few studies have compared these two training modalities, especially when considering how many studies have been published on each separately and on how easy it is to assess BP. What may be even more surprising to many readers are the results of the studies that have made this comparison (Table 2.1). The majority of studies we could find that compared the effects of RT on resting BP to those of AT, show no significant differences between these two training modalities in their effectiveness for reducing resting BP; and many showed that neither training modality was effective in lowering BP when compared in the same study. Yet there are many studies showing that both are effective when studied separately, though many more for AT than RT.

Stensvold et al. [31] randomized 43 participants with the metabolic syndrome to either aerobic interval training (AIT), dynamic RT, or combined AIT and RT. AIT consisted of four intervals of treadmill walking or running at 90–95 % of peak heart rate with 3 min of active recovery between each exercise bout, three times per week. The RT program consisted of two sets of 15–20 repetitions beginning at 40–50 % of 1RM with progressive increases to ~80 % of 1-RM, corresponding to 8–12-RM. Training was performed three times per week for 12 weeks. The concurrent training group performed AIT twice a week and RT once per week. No significant differences in the BP response were observed for AIT, RT, or concurrent training, and none of the groups significantly reduced resting BP with training. In another recent study, Ho et al. [62] compared 12 weeks of a moderate load (four sets of 8–12 repetitions at 10-RM) RT program for 30 min three times per week (n = 16) to the same duration of AT consisting of treadmill exercise at 60 % of heart rate reserve three per week (n = 15), and to a concurrent training program of 15 min of each exercise modality (n = 17) in men and women with overweight and obesity. Only the

Table 2.1 Comparison of resistance training, aerobic training, and concurrent training on the blood pressure response to training

References	RT	AT	Concurrent	Blood pressure change
Stensvold et al. [31]	↔	↔	↔	ND among groups
Ho et al. [62]	↔	↔	↓	ND among groups
Sillanpaa et al. [63]	↓	↓	↔	ND among groups
Smutok et al. [64]	↔	↔		ND among groups
Coconie et al. [65]	↔	↔		ND among groups
Rosenthal et al. [66]	↓	↓		ND among groups
Yoshizawa et al. [35]	↔	↔		ND among groups
Fett et al. [29]	↓	↔		AT > RT
Morais et al. [21]	↓	↓		RT > AT (acute only)

Symbol legend: ↔ = no change, ↓ = significant decrease
ND no differences

concurrent training group and the no exercise control group reduced resting BP. Neither the RT nor the AT groups reduced BP, and there were no significant differences among the training groups.

Likewise, Sillanpaa et al. [63] reported no differences in the BP responses to RT compared to AT or to concurrent training in 62 middle-aged and older women with normal BP after 21 weeks of training [64]. Both SBP and DBP were reduced with RT and AT, but not with concurrent training. Smutok et al. [64] compared 20 weeks of moderate to heavy RT (8–12-RM) to AT 65–75 % of heart rate reserve and a non-exercise control group in 37 middle-aged and older adults with prehypertension and hypertension and found no significant changes in resting BP in any of the groups. Similar findings were reported by Coconie et al. [65] in 49 men and women 70–79 years and by Blumenthal et al. [66], who studied 99 men and women with untreated hypertension (SBP/DBP 140–180/90–105 mmHg) randomly assigned to 4 months of either AT, RT, flexibility training, or a non-exercise control group. Despite significant within group reductions of 7–9 mmHg in resting SBP and 5–6 mmHg in resting DBP following RT, there were no significant differences between any of the training groups [66]. There were also no significant group differences when comparing ambulatory BP readings before and after the training period in this same study [66]. However, no training modality reduced resting BP significantly. Finally, Fett et al. [29] reported a more favorable BP response to AT training compared to circuit RT, but their attrition rate was about 50 %, which raises the question of whether there was a preferential drop out bias in one group compared to the other, thereby threatening the internal validity of the study.

Thus, the overall findings in this section suggest that both training modalities (dynamic RT and AT) appear to be effective for lowering BP when studied separately, but not when compared in the same study. However, the same comparative studies do show BP reductions when both training modalities are performed concurrently (see Chapter 3 for more detailed discussions of the effects of concurrent exercise on BP). There is evidence from a small portion of studies that both AT and RT can shift BP categories in some individuals from hypertension to prehypertension or from prehypertension to normal BP. However, these findings are a bit misleading because the BP reductions largely depend on how close individual participants are to the cut off value for each category, and they tend to undermine the importance of the concept of BP as a risk continuum throughout all levels starting from ~115/75 mmHg.

Effects of Resistance Training on Other Cardiometabolic Risk Factors Among Those with Hypertension

Some of the studies reporting no effects on BP with RT discussed in the section, “Effects of Dynamic Resistance Training on Resting Blood Pressure”, observed reductions in other risk factors for cardiometabolic disease [34]. The vast majority

of people with hypertension have additional risk factors for cardiometabolic disease [67], resulting in over 47 million (~23 %) that have abdominal obesity, dyslipidemia, and elevated blood glucose levels. For example, essential hypertension is often an insulin-resistant state, which is directly correlated with the severity of hypertension [68] and is independently associated with sarcopenia (the loss of muscle mass with age), particularly sarcopenic obesity [69]. Moreover, insulin resistance is associated with both hypertension [70] and sarcopenia [71]. The exact prevalence of those with these particular combinations of risks is not well established, but it is known that all three increase with advanced age and with physical inactivity [72, 73].

These relationships have important implications for the use of RT in older adults with hypertension because RT is considered the exercise training modality of choice for preventing or delaying the adverse consequences of sarcopenia in older adults [74]. In this context, there is a large volume of literature on the effects of RT on risk for the components of the metabolic syndrome [74], including insulin resistance, abdominal obesity, and dyslipidemia as well as elevated BP, but a discussion of this literature is beyond the scope of this review. Nevertheless, it is important to consider these broader relationships when determining the efficacy of an RT intervention for the prevention or treatment of hypertension, given that a major reason for the importance of reducing BP in patients with hypertension is to lower their risk for cardiometabolic diseases, such as the metabolic syndrome and atherosclerosis. For related information, please see Part III for a discussion of the pleiotropic effects of exercise on other CVD risk factors.

Clinical Implications and Importance

Is There Sufficient Evidence to Develop an Exercise Prescription in a Clinically Meaningful Way for Optimal Reductions in Blood Pressure Using Resistance Training as the Exercise Modality?

There is a growing body of evidence supporting the use of RT as an exercise intervention for reducing the risk of hypertension, particularly for those with prehypertension [9, 20, 22, 23, 27, 46, 47, 54]. This evidence becomes clearer when considering RT in a broader context of reducing the risk of cardiometabolic disease, such as the metabolic syndrome; or reducing overall risk of age-related diseases/disabilities in those with hypertension, such as diabetes, osteoporosis, and sarcopenia. However, there is still a relatively small number of RCTs on the effects of RT on BP in participants with hypertension and the few studies available show inconsistent results. In addition, there are even fewer studies that have compared the various components of the FITT-VP principle used in prescribing exercise for RT to serve as a basis for the most optimal exercise prescription plan for lowering BP. Developing

such an exercise prescription at this stage of the research literature would probably have to rely on mimicking the specific training protocols that have produced favorable effects on BP in previous studies without knowing what frequencies, loads, durations, etc., would produce optimal results among those with high BP. Even this is difficult because of conflicting results from studies using the same level of a component of FITT-VP yielding different results. The only component of FITT-VP that shows some level of consistency in the research literature for explaining results is "type" or exercise modality. In this regard, isometric RT appears to more consistently lower BP than dynamic RT.

Moreover, there is some evidence though with mixed results for concern that RT, particularly heavy load RT, may increase arterial stiffness which could be detrimental for cardiovascular function. There is no such evidence for this concern with AT. Therefore, our conclusion at the present time is that there is not sufficient evidence to support a specific exercise prescription for reducing BP with RT.

Conclusion

The Effects of Acute Versus Chronic Resistance Exercise

- The results of at least four relatively recent meta-analyses and a large number of non-randomized, but otherwise well controlled studies, reveal that AT is more consistently effective for reducing resting BP than RT, particularly in those with hypertension. Studies that assess the effects of each training modality separately support this conclusion.
- Acute dynamic resistance exercise results in PEH, usually on the order of 2–10 mmHg for SBP, starting within 30 min after exercise and lasting up to ~24 h in those with hypertension. However, one study [19] reported a 33 mmHg reduction in SBP 90 min postexercise when training with a high load (80 % of 1-RM) and 23 mmHg reduction at the same time point with low load RT (50 % of 1-RM). Other studies show that training loads as low as 40 % of 1-RM elicit PEH, but on the order of 8 and 6 mmHg for SBP and DBP, respectively, 60 min postexercise and 2 mmHg for SBP when assessed 24 h postexercise. At least one study shows a greater PEH with RT than AT (6 mmHg lower than AT) up to 8 h postexercise [21].
- Not all studies show improved BP responses with dynamic RT, but there are a few that show remarkable improvements with dynamic RT in a relatively short time period with long lasting effects. In one case, RT-induced BP reductions were maintained, i.e., they do not return to baseline for 14 weeks after the end of training.
- Results of studies that compare the effects of RT to AT in the same study, with only a few exceptions, either show that both training modalities are just as effective as the other or that neither is effective in reducing BP.

Isometric Resistance Training Versus Dynamic Resistance Training Versus Aerobic Training

- The results of both IHG training and leg isometric RT studies show more consistent reductions in resting BP and use a more consistent training regime than those of either dynamic RT or AT. However, there are fewer well controlled isometric RT investigations than there are for dynamic dynamic RT or AT, particularly among studies that include participants with hypertension.
- Despite the favorable effect that isometric RT (both IHG and leg isometric training) appears to have on BP, it would be hard to justify it as a replacement for either dynamic RT or AT because of the evidence for broader health benefits from both dynamic RT and AT, particularly in the areas of risk factors for cardiometabolic disease and other age-related diseases and disabilities of which no such evidence appears to exist for isometric RT (neither IHG nor leg isometric training).

Exercise Prescription Recommendations

- Because there are so many studies showing such a broad range of effectiveness for dynamic RT on BP, from no effect to a decline of 19 mmHg in SBP, and because few studies have compared different levels of the FITT-VP components in RT programs for their effectiveness in reducing BP, developing an individualized exercise prescription for RT is premature, based on the current state of the existing literature.
- Given that isometric RT does not require much time and could easily be incorporated into a dynamic RT program, we recommend the use of dynamic RT that incorporates isometric RT exercises, such as IHG, for BP control, along with the recommendations provided in Chapter 1 for AT.

Exercise Exposure Time as a Preventive Strategy for Chronic Disease

- Exposure time may be an important factor that links aging, training, and risk factors to disease. According to Kannel and Vasan [75], aging serves as a risk factor for CVD more because it provides a longer exposure time for risk factors than because of primary aging effects. Likewise, interventions such as exercise training, may reduce the incidence of CVD because they reduce exposure time to risk factors. Applying this model to the content of this chapter and Chapter 1, it is possible that exercise training programs, whether AT or RT, may delay or prevent chronic diseases, such as atherosclerosis, through reducing the exposure time of risk factors, such as high BP.

Key Points and Resources

The information provided in Chapter 1 for this section will also apply to this chapter. Therefore, the below list only includes information not already stated in Chapter 1.

- American Council on Exercise: www.acefitness.org
- Centers for Disease Control and Prevention: www.cdc.gov
- International Council on Active Aging: www.icaa.cc
- National Heart, Lung, and Blood Institute Health Information Center: www.nhlbi.nih.gov
- National Institute on Aging Information Center: www.nia.nih.gov and www.nia.nih.gov/Go4Life
- National Strength and Conditioning Association (NSCA): www.nsca.com

Office of Disease Prevteention and Health Promotion: www.odphp.osophs.dhhs.gov

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Chapter 3
Effects of Concurrent Exercise on Hypertension: Current Consensus and Emerging Research

Hayley V. MacDonald, Paulo V. Farinatti, Lauren Lamberti, and Linda S. Pescatello

Abbreviations

ACSM	American College of Sports Medicine
BMI	Body mass index
BP	Blood pressure
DBP	Diastolic blood pressure
Ex R_x	Exercise prescription
FITT-VP	Frequency Intensity, Time, and Type-Volume and Progression
HIIT	High intensity interval training
HR_{max}	Maximal heart rate
HR	Heart rate
MET	Metabolic equivalent

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MetS	Metabolic syndrome
PEH	Postexercise hypotension
RCT	Randomized controlled trial
RPE	Rating of perceived exertion
RM	Repetition maximum
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
VO_{2max}	Maximal oxygen consumption
VO_{2peak}	Peak oxygen consumption
$VO_{2reserve}$	Oxygen consumption reserve

Introduction

The many health benefits from participating in regular exercise are well documented, including lower resting blood pressure (BP) [1, 2]. The acute [immediate, short-term, or postexercise hypotension (PEH)] and chronic (long-term or training) BP response to dynamic aerobic (or endurance) and resistance exercise have been studied extensively. Based on these findings, formal exercise prescription (Ex R_x) guidelines were established for each modality specific to their role in the prevention, treatment, and management of hypertension [3]. (See Chap. 1 and 2 for an expanded discussion on the antihypertensive effects of aerobic and resistance exercise.)

Briefly, the American College of Sports Medicine (ACSM) [3] and other professional organizations and committees [4–7] recommend that individuals with hypertension perform moderate intensity aerobic exercise ≥3–5 days per week, preferably daily, for 30–60 min per day, supplemented by dynamic resistance exercise 2–3 days per week. However, from a practical perspective, exercise sessions designed to lower BP or promote general health [1], rarely include aerobic or resistance exercises exclusively. Instead, *both* aerobic and resistance exercises are performed in a single session or within a couple hours of one another, which is referred to as *concurrent exercise* [8] or *combined* aerobic and resistance exercise [9, 10]. A benefit of performing concurrent rather than aerobic or dynamic resistance training alone is that cardiorespiratory fitness, muscle strength, and other cardiometabolic health biomarkers can be improved simultaneously [10–15]. (See Chaps. 4, 5, 6, 8 and 13 for further discussion on the health benefits of concurrent exercise). Despite simultaneous improvements in multiple health outcomes, the antihypertensive effects of concurrent exercise have yet to be well defined, and it is currently unclear whether *combined* aerobic and resistance exercise offer similar BP benefit to those resulting from aerobic or resistance exercise alone. Furthermore, a general census regarding the optimal Frequency, Intensity, Time, and Type (or FITT principle) of the concurrent Ex R_x for antihypertensive therapy has yet to be identified.

Purposes of this Chapter

The purposes of this chapter are: (1) to overview the literature about the effects of acute (i.e., PEH) and chronic (long-term or training) concurrent exercise on BP among individuals with hypertension; (2) to evaluate how the existing, new, and emerging research on acute and chronic concurrent exercise may alter the way in which exercise programs are designed to prevent, treat, and control hypertension in the future; and (3) to present formal recommendations and special considerations of the concurrent Ex R_x for individuals with hypertension that considers the current and emergent research for this exercise modality as antihypertensive therapy.

Key Terminology and Basic Concepts

What is Concurrent Exercise?

Concurrent exercise most commonly refers to an Ex R_x that involves *both* aerobic and resistance exercises performed within the same exercise session on the same day or within a few hours of one another [8–10]. In some cases, a concurrent training program can also consist of aerobic and resistance exercises that are performed on *separate days* (i.e., *combined* aerobic and resistance exercise). This type of Ex R_x allows for improvements in multiple health outcomes simultaneously, including cardiorespiratory fitness (i.e., endurance), muscle strength, and cardiometabolic health biomarkers [10–15]. Please see Chaps. 4, 5, 6, 8 and 13 for further discussion on the health benefits of concurrent exercise.

Special Considerations for Concurrent Exercise Dose: Modality Order, Intensity, and Volume

The systematic and individualized process for developing an Ex R_x based on the FITT principle was defined in Chap. 1. In addition to the FITT principle, the concurrent Ex R_x has several unique considerations including: (1) the order of performing aerobic and resistance exercise within a single concurrent session (i.e., exercise modality order); (2) the aerobic, resistance, and *overall* concurrent exercise intensity; and (3) the volume of aerobic, resistance, and concurrent exercise achieved during a single bout (i.e., acute) or over the long-term (i.e., chronic or training). For acute trials, the volume of aerobic exercise is equal to *intensity* (metabolic equivalent [MET] units)×*duration* (min per session) [16]; and for resistance exercise, is equal to the *total workload* achieved, which is a summation of the number of sets and repetitions performed during the workout (number of exercises per session×sets per exercise×repetitions per set) [17, 18]. For the purposes of this Chapter, resistance

exercise volume will also be calculated based on the *load lifted* (i.e., *intensity*, MET units) × *duration* (min per session). Therefore, the *total acute volume* achieved in a single concurrent bout will be equal to the sum of the exercise volume achieved for aerobic and resistance exercise (MET-min per session) [16]. For concurrent exercise training, aerobic and resistance exercise volume will be equal to *intensity* (MET units) × *duration* (min per session) × weekly training *frequency* (days per week) [16]; therefore, the *total concurrent training volume* will be equal to the weekly volume achieved for aerobic *and* resistance exercise (MET-min per week).

The Blood Pressure Response to Acute and Chronic Concurrent Exercise

Aerobic and resistance exercise have been shown to lower BP after a single session (i.e., acute) and long-term training (i.e., chronic), but their combined effects on resting BP are less well known. The magnitude of the reported BP reductions among individuals with hypertension are greater for aerobic (5–7 mmHg) than resistance exercise (2–3 mmHg), but have yet to be definitively quantified for concurrent exercise [3]. Primary level evidence supports that concurrent exercise can acutely (3–8 mmHg) [19, 20] and chronically (4–35 mmHg) [19, 21–26] lower resting BP among adults with hypertension by a magnitude that rivals or exceeds those reported with aerobic and resistance exercise alone. However, a recent meta-analysis found that exercise training reduced resting BP by a similar magnitude following concurrent (1–2 mmHg), aerobic (3–4 mmHg), and dynamic resistance training (2–3 mmHg, $p > 0.05$) among apparently healthy adults with normal BP to established hypertension [27].

Due to these conflicting results it is difficult to determine a general consensus on the acute and chronic antihypertensive benefits of concurrent exercise. To date, it remains speculative as to whether the *combined* effects of aerobic and resistance exercise elicit an *additive* BP response, meaning the magnitude of the BP reduction is greater than those reported with aerobic and resistance exercise alone; or, if the addition of resistance to aerobic exercise *attenuates* the BP response associated with aerobic exercise, meaning the magnitude of the BP reduction is *less* than those reported for aerobic but greater than for resistance exercise alone. See Chaps. 4 and 6 for further discussion on these areas of conflict in the existing literature.

Systematic Review Methods

We systematically searched PubMed (including Medline) from its inception to December 10, 2014 to locate all human trials published in English that examined the BP response to the acute or chronic concurrent exercise compared to a non-exercise, non-diet control/comparison group among adult participants (≥19 years). Our electronic literature search was supplemented by reviewing

reference lists of already included trials and any relevant meta-analyses or reviews (see Appendix 3.A. for the full search strategy). We identified 478 potentially qualifying reports and 70 met our inclusion criteria. Of those studies, the authors self-selected six acute and 22 chronic trials that were most relevant to the purposes of this chapter. Figure 3.1 summarizes the selection process of included concurrent exercise trials.

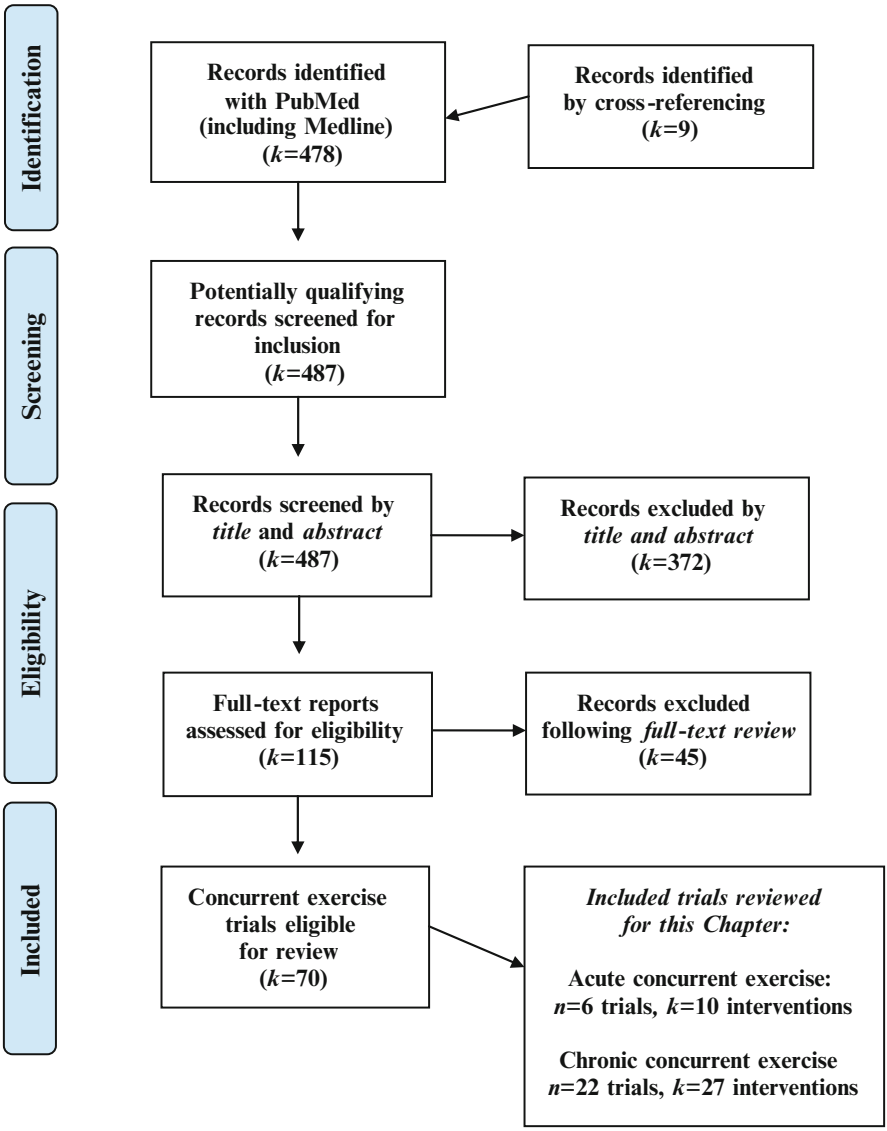

Fig. 3.1 Flow chart detailing the systematic search of potential reports (*k*) and selection process of included aerobic exercise trials (*n*)

Relevant Research

Concurrent Exercise and Blood Pressure Effects

Acute, Immediate, or Short-Term Effects or *Postexercise Hypotension*

Current Consensus

PEH is an expected physiologically response to aerobic exercise (see Chap. 1) even after low intensity exercise (i.e., 40 % of maximal oxygen consumption [VO_{2max}]) and exercise of short duration (i.e., 10 min). Despite the strong and substantial body of research that currently exists, there were few randomized controlled trials (RCTs) at the time of the ACSM position stand; therefore, they assigned a category *B* rating [28] to the level of evidence pertaining to the acute BP lowering effects of aerobic exercise [3]. PEH has also been observed following dynamic resistance exercise (see Chap. 2), but by a smaller magnitude and less consistently than aerobic exercise [3, 29]. For this reason the ACSM assigned a category *C* rating [28] to the level of evidence for dynamic resistance exercise and PEH, which consisted of observational and non-RCTs (see Chap. 1, Table 1.1 for the levels of evidence) [3]. Although the evidence regarding the BP lowering effects of acute aerobic and dynamic resistance exercise had been rated independently, few trials had investigated the BP response to acute concurrent exercise (i.e., *combined* aerobic and resistance exercise). Due to the paucity of available evidence, the position stand did not rate or comment on the level of evidence pertaining to PEH and concurrent exercise.

New and Emerging Research

All of the acute concurrent exercise trials that qualified for this systematic review observed PEH, but there was considerable variability in the reported magnitude (i.e., ~1–11 mmHg) and duration (i.e., 60–120 min) of PEH. These inconsistencies could be attributable to differences in baseline characteristics (i.e., resting BP, age, sex/gender, medication use, etc.) or features of the acute concurrent exercise intervention. Readers are directed to Table 3.1 for a summary of the included acute concurrent exercise trials.

Acute Concurrent Exercise and PEH: The Influence of Baseline Characteristics

Of the six qualifying acute trials, half involved physically active (i.e., trained), healthy, young men [8, 30, 31] with normal resting BP (systolic BP [SBP]/diastolic BP [DBP], ~115/75 mmHg, respectively) and weight (body mass index [BMI] ~24 kg/m^2). On average, these trials found concurrent exercise induced PEH (~6/3 mmHg), an effect that persisted up to 120 min after exercise (see Table 3.1). An even greater magnitude of

Table 3.1 Qualifying acute concurrent exercise trials: a summary of the baseline sample characteristics, experimental design, features of the acute exercise intervention and the reported magnitude and duration of postexercise hypotension ($n = 6$)

	Baseline clinical characteristics			Features of the acute intervention	PEH magnitude[d] and duration[e]	
Author (Yr)	*N*, age, BMI	Health status[a,b]	Resting SBP/DBP (mmHg) and PEH assessment	Experimental design and exercise characteristics[c]	SBP (mmHg)	DBP (mmHg)
Keese (2011) [8]	*N* = 21 M, 20.7 ± 0.7 yr, 24.8 ± 0.5 kg/m^2	Trained, Healthy, NBP	*N* = 111.5 ± 2.6/73.9 ± 3.6	Study design: randomized, counter-balanced cross-over; ≥48–72 h between sessions. Con (60 min): seated rest	Con ↔	Con ↔
			Pre-BP: seated rest, 20 min, laboratory			
			PEH: seated recovery, 120 min, laboratory			
				AE: 60 min, cycling, 65 % VO_{2peak} (7.2 MET)	AE ↓ −6.3 ± 6.0*,# (120 min)**,§	AE ↓ −1.8 ± 4.6*,# (50 min)*,§
				AE volume = 432 MET-min/session		
				RE (60 min): 3 sets × 6–8 reps, 80 % 1-RM (9.0 MET), 8 RT exercises (3 upper/5 lower)	RE ↓ −4.1 ± 9.2*,# (80 min)*	RE ↓ −1.8 ± 5.0*,# (20 min)*
				RE volume (total reps/session) = ~168 *or* 540 MET-min/session		
				CE (60 min), AE was performed *after* RE: AE = 20 min, cycling, 65 % VO_{2peak} + RE = 2 sets × 6–8 reps, 80 % 1-RM, 8 RT exercises	CE ↓ −5.1 ± 10.1*,# (120 min)**,§	CE ↓ −1.6 ± 2.7*,# (40 min)*
				CE volume = AE (144) + RE (360) = 504 MET-min/session		

(continued)

Table 3.1 (continued)

Author (Yr)	Baseline clinical characteristics			Features of the acute intervention	PEH magnitude[d] and duration[e]	
	N, age, BMI	Health status[a,b]	Resting SBP/DBP (mmHg) and PEH assessment	Experimental design and exercise characteristics[c]	SBP (mmHg)	DBP (mmHg)
Ruiz (2011) [31]	*N* = 11 M, 26.8 ± 2.9 yr, 24.3 ± 1.6 kg/m^2	Trained, Healthy, NBP-PreHTN	*N* = ~122/76	Study design: counter-balanced, cross-over; 48 h between sessions. Con: no separate non-exercise or 'sham' session; used resting BP values		
			AE = 121.8 ± 9.0/74.4 ± 9.5			
			RE = 122.0 ± 6.9/78.5 ± 6.5			
			CE = 123.5 ± 8.1/76.7 ± 9.4	**AE**: 40 min, cycling, 60–70 % HRR (7.2 MET)	AE ↓ −5.0 to −7.0*,# (60 min)*,#	AE ↔ #
			Pre-BP: seated rest, 10 min, laboratory	**AE volume** = 144 MET-min/session		
			PEH: seated recovery, 60 min, laboratory	**RE**: 3 sets × 12 reps, 12RM (6.0 MET), 8 RT exercises (4 upper/4 lower)	RE ↓ −5.0 to −7.0*,# (60 min)*,#	RE ↔ #
				RE volume (total reps/session) = 288 *or* 210 MET-min/session		
				CE (~70–80 min), AE was performed *before* RE: AE Ex R_x + RE Ex R_x	CE ↓ −5.0 to −7.0*,# (60 min)*,#	CE ↔ #
				CE volume = AE (144) + RE (210) = 354 MET-min/session		
Teixeira (2011) [32]	*N* = 20 M/10 W, 26.0 ± 4.5 yr, 22.1 ± 1.8 kg/m^2	Untrained, Healthy, NBP	*N* = 111.0 ± 8.9/74.0 ± 4.5	Study design: blinded, randomized cross-over; ≥5 days between sessions. Con (60 min): 30 min seated rest on cycle+30 min seated rest on RE machines	Con ↔	Con ↑ +4.0 ± 4.5 ($p < 0.05$)
			Con = 109.0 ± 8.9/74.0 ± 4.5			
			AE = 111.0 ± 8.9/75.0 ± 4.5			
			RE = 110.0 ± 8.9/75.0 ± 4.5	**AE**: 30 min, cycling, 75 % VO_{2peak} (8.2 MET)	AE ↓ −13.0 ± 4.5*,§ (120 min)*,†	AE ↓ −3.0 ± 4.5*,# (90 min)*,Π
			CE = 110.0 ± 4.5/73.0 ± 4.5	**AE volume** = 246 MET-min/session		
			Pre-BP: seated rest, 20 min, laboratory	**RE**: 3 sets × 20 reps, 50 % 1-RM (4.9 MET), 6 RT exercises (3 upper/3 lower body)	RE ↓ −8.0 ± 4.5* (60 min)*	RE ↓ −2.0 ± 4.5*,# (30 min)*
			PEH: seated recovery, 120 min, laboratory	**RE volume (total reps/session)** = 360 *or* 294 MET-min/session		
				CE (~60 min), AE was performed before **RE**: AE Ex R_x + RE Ex R_x	CE ↓ −11.0 ± 4.5*,§ (120 min)*	CE ↓ −3.0 ± 4.5*,# (60 min)*
				CE volume (AE + RE) = 540 MET-min/session		

Keese (2012) [30]	*N* = 21 M, 20.7 ± 0.7 yr, 24.8 ± 0.5 kg/m^2	Trained, Healthy, NBP	*N* = 111.5 ± 2.6/73.9 ± 3.6	Study design: randomized counterbalanced order; ~48 h between sessions. Con (60 min): seated rest	Con ↔	Con ↔
			Pre-BP: seated rest, 20 min, laboratory			
			PEH: seated recovery, 120 min, laboratory			
				RE: 2 sets × 6–8 reps, 80 % 1-RM (9.0 MET), 6 RT exercises (3 upper/3 lower)		
				RE volume (total reps/session) = 84 *or* 270 MET-min/session		
				CE50 volume (AE + RE) = 420 MET-min/session	CE50 ↓ −4.2 ± 2.5*,# (60–70 min)*	CE50 ↓ −1.2 ± 1.8* (40 min)*
				AE was performed *after* RE (60 min): AE = 30 min, cycling, 50 % VO_{2peak} (5.0 MET) (150 MET-min/session) + RE Ex R_x		
				CE65 volume (AE + RE) = 486 MET-min/session	CE65 ↓ −4.8 ± 2.7*,# (120 min)*,¶	CE65 ↓ −1.5 ± 2.7*,¶ (40 min)*
				AE was performed *after* RE (60 min): AE = 30 min, cycling, 65 % VO_{2peak} (7.2 MET) (216 MET-min/session) + RE Ex R_x		
				CE80 volume (AE + RE) = 546 MET-min/session	CE80 ↓ −6.0 ± 2.0*,# (120 min)*,¶	CE80 ↓ −1.8 ± 5.5*,¶ (60 min)*,Π
				AE was performed *after* RE (60 min): AE = 30 min, cycling, 80 % VO_{2peak} (9.2 MET) (276 MET-min/session) + RE Ex R_x		

(continued)

Table 3.1 (continued)

Author (Yr)	Baseline clinical characteristics			Features of the acute intervention	PEH magnitude[d] and duration[e]	
	N, age, BMI	Health status[a,b]	Resting SBP/DBP (mmHg) and PEH assessment	Experimental design and exercise characteristics[c]	SBP (mmHg)	DBP (mmHg)
dos Santos (2014) [19]	*N* = 60 W, ~60–65 yr, ~28 ± 4.5 kg/m^2	Sedentary, Healthy, HTN[a]	*N* = ~166/91	Study design: parallel; randomized to a non-exercise Con, or CE involving eccentric RE (CE-ERT) or traditional RE (CE-RT)	Con ↑ +0.2 ± 0.6 (60 min)	Con ↑ +0.9 ± 0.9 (60 min)
			Con = 160.7 ± 9.1/89.9 ± 4.8			
			ERT = 162.7 ± 7.8/85.5 ± 4.3[Π]			
			TRT = 163.1 ± 4.4/88.8 ± 3.6	**AE volume** = 100 MET-min/session; Ex R_x: 20 min, treadmill, 65–75 % MHR (5 MET)		
			Pre-BP: seated rest, 10 min, laboratory	**CE-ERT volume (AE + ERT) = 430 MET-min/session**	ERT ↓ −4.0 ± 0.4*,# (60 min)	ERT ↓ −4.9 ± 1.0**,# (60 min)
			PEH: seated recovery, 60 min, laboratory; pre/post-training (16 wk)	AE was performed *after* RE (70–80 min): AE Ex R_x + ERT = 3 sets × 10 reps, 100 % 10RM (6 MET), 7 RT exercises (4 upper/3 lower body)		
				RE volume (total reps/session) = 210 *or* 330 MET-min/session		
				CE-RT volume (AE + RT) = 359 MET-min/session	RT ↓ −2.5 ± 0.4# (60 min)	RT ↓ −4.2 ± 0.6**,# (60 min)
				AE was performed *after* RE (70–80 min): AE Ex R_x + RT = 3 sets × 10 reps, 70 % 10RM (4.0 MET), 7 RT exercises (4 upper/3 lower body)		
				RE volume (total reps/session) = 210 *or* 220 MET-min/session		

Menêses (2014) [20]	*N* = 19 W, 57.0 ± 8.7 yr, 29.9 ± 3.9 kg/m^2	Sedentary, CVD risk factors[b] HTN[a]	*N* = ~130/68	Study design: blinded, randomized cross-over; ≥48 h between sessions. Con (50 min): 30 min standing on treadmill + 20 min seated rest on RE machines	Con ↑ +9.0 ± 8.7† (30 min)	Con ↑ +6.0 ± 8.7† (30 min)
			Con = 131.0 ± 17.4/69.0 ± 8.7			
			AR = 130.0 ± 13.1/68.0 ± 4.4			
			RA = 128.0 ± 13.1/68.0 ± 8.7 Pre-BP: supine rest, 20 min, laboratory	AE Ex R_x: 30 min, treadmill, 50–60 % HRR (5.0 MET)		
			PEH: supine recovery, 30 min, laboratory	RE Ex R_x: 3 sets × 10 reps, 50 % 1-RM (4.8 MET), 7 RT exercises (4 upper/3 lower)		
				CE-AR volume (AE + RE) = 294 MET-min/session	AR ↔ +1.0 ± 13.1* (30 min)	AR ↔ +3.0 ± 4.4* (30 min)
				AE was performed *before* RE (~50 min): AE Ex R_x (150 MET-min/session) + RE Ex R_x (210 reps/session *or* 100 MET-min/session)		
				CE-RA volume (AE + RE) = 294 MET-min/session	RA ↔ +3.0 ± 13.1* (30 min)	RA ↔ +3.0 ± 8.7* (30 min)
				AE was performed *after* RE (~50 min): RE Ex R_x (210 reps/session *or* 100 MET-min/session) + AE Ex R_x (150 MET-min/session)		

Note: Baseline characteristics and PEH values (mmHg) are reported as *M*ean ± *sd*, unless noted otherwise; *M*ean change and range = *M*ean (*M*in–*M*ax); *M*ean change and 95 % *Confidence Interval* (*CI*) = *M*ean (lower, upper 95%*CI*). *AE* Aerobic exercise, *AR* AE followed by RE, *BP* Blood pressure (mmHg), *BMI* Body mass index (kg/m^2), *CE* Concurrent exercise, *Con* Control, *CVD* Cardiovascular disease, *DBP* Diastolic BP, *ERT* Eccentric resistance training, *Ex* R_x Exercise prescription, *MHR* Maximal heart rate, *HRR* Heart rate reserve, *HTN* Hypertension, *M* Men, *MET* Metabolic equivalent, *MET-min/session* MET-minutes per session, *Min* Minutes, *N* Total sample, *NBP* Normal BP, *PreHTN* Prehypertension, *RA* RE followed by AE, *RE* Resistance exercise, *Reps* Repetitions, *Reps/session* Repetitions per session, *RM* Repetition maximum, *SBP* Systolic BP, VO_{2max} Maximal oxygen consumption, VO_{2peak} Peak oxygen consumption, *W* Women, *Yr* Year

[a]Treated = Subjects taking BP medications: dos Santos (*n* = 60 women, 100 %) [19]: angiotensin converting enzyme inhibitor (*n* = 20, 33 %); angiotensin receptor blockers (*n* = 21, 35 %); calcium channel blocker (dihydropyridine) (*n* = 17, 28 %). Menêses (*n* = 19 women, 100 %) [20]: angiotensin converting enzyme inhibitor (*n* = 11, 21 %); diuretics (*n* = 6, 32 %); angiotensin II antagonists (*n* = 4, 21 %); calcium channel blocker (dihydropyridine) (*n* = 3, 16 %); central α2-adrenergic receptor agonist (*n* = 1, 5 %); combined antihypertensive therapy (*n* = 8, 44 %)

[b]Participants have other CVD risk factors in addition to their high BP: Menêses [20] = Hypercholesterolemia (*n* = 8, 44 %); Obesity (*n* = 15, 83 %)

[c]Volume achieved per session: CE (MET-min/session) = AE MET-min/session + RE MET-min/session; AE (MET-min/session) = MET value × duration (min); RE volume reflects the total number of reps performed per session (i.e., the summation of the sets and reps performed during a workout) [17, 18] = exercises/session × sets/exercise × reps/set *or* RE (MET-min/session) = MET value × duration (min). MET values (i.e., absolute exercise intensity) were estimated using Table 7.1 from the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (9th Edition) [16]; MET values are adjusted by age for young (20–39 year), middle-aged (40–64 year) and older (≥65 year) samples

[d]PEH magnitude (SBP/DBP mmHg), i.e., the difference in BP at *post*-exercise minus *pre*-exercise values, *unless stated otherwise*. A *downward arrow* (↓) indicates a significant reduction ($p \leq 0.05$), *double-headed arrow* (↔) indicates a non-significant change. PEH is different from: *Con ($p < 0.05$); **Con ($p < 0.01$); §RE ($p < 0.05$)

[e]PEH duration (min) is expressed relative to the pre-exercise values, *unless stated otherwise*. PEH duration (min) is different from: †Con ($p < 0.05$); ‡AE ($p < 0.05$); ||CE-50 ($p < 0.05$); ¶CE-50, CE-65 ($ps < 0.05$). #No differences between acute sessions ($p > 0.05$)

PEH was reported by Teixeira and colleagues [32], who found that acute concurrent exercise significantly reduced BP by 11/3 mmHg among 20 untrained adults (50 % women) also with normal BP (~111/74 mmHg); an SBP reduction that was nearly double the magnitude reported for trained young men [8, 30, 31].

Only two qualifying acute trials included adults with established hypertension [19, 20], and both examined PEH among sedentary, middle-aged to older women with hypertension and overweight to obesity (28–32 kg/m^2). Menêses and colleagues [20] observed significant increases in resting BP following control (~9/6 mmHg) but not concurrent exercise (~2/3 mmHg, $p>0.05$), a potential acute BP reduction of ~3–8 mmHg for middle-aged women with hypertension (~130/68 mmHg) who were taking at least one antihypertensive medication to control their high BP. Similarly, dos Santos and colleagues [19] found concurrent exercise elicited PEH by a magnitude of ~3–5 mmHg among 60 older women who were currently taking BP medication to manage their uncontrolled hypertension (~166/91 mmHg); a lesser magnitude than reported by Menêses et al. despite higher baseline values.

In summary, a single bout of concurrent exercise elicited PEH among young, healthy adults with normal BP [8, 31, 32] and middle-aged to older adults with established hypertension who were on antihypertensive drug therapy [19, 20]. Furthermore, the reported magnitude of PEH was similar for the groups with normal BP and hypertension (~3–9 mmHg). The BP response to acute concurrent exercise may be modulated by sex/gender, age, BMI, or training status, however, based on this small, homogeneous sample, we were unable to explore the influence of these potential moderators. Therefore, we can conclude that acute concurrent exercise elicits PEH, and based on the available evidence, the magnitude appears to be similar between populations with normal and high BP.

Exercise Modality and PEH: Aerobic Versus *Resistance* Versus *Concurrent Exercise*

Three trials involving adults with normal BP compared PEH after concurrent, aerobic and resistance exercise [8, 31, 32] within the same group of subjects to determine whether the *combined* effects of aerobic and resistance exercise produced an *additive* BP response to either modality alone, or if the addition of resistance to aerobic exercise *attenuated* the BP reductions associated with aerobic exercise alone. Unfortunately, none of the trials involving adults with hypertension offered the same comparison across exercise modalities.

Ruiz and colleagues [31] investigated the BP response to acute aerobic (40 min at ~65 % heart rate [HR] reserve), resistance (8 exercises at 12 repetition maximum [RM]), and concurrent exercise (~60 min of combined aerobic and resistance exercise) among 11 trained, healthy young men with normal BP (see Table 3.1 for additional details). SBP was reduced compared to baseline values following aerobic, resistance, and concurrent exercise ($p<0.05$), with no observable difference in the magnitude (~5–7 mmHg) or duration (60 min) of PEH among modalities ($p>0.05$). In contrast, DBP was not reduced compared to baseline following any exercise modality ($p>0.05$).

Ruiz et al. concluded that concurrent, aerobic, and resistance exercise elicited PEH among young men with normal BP, suggesting that a variety of training modalities can be used to achieve BP control among populations with high BP.

Keese and colleagues [8] also compared the effects of exercise modality on PEH among 21 trained, healthy young men with normal BP. These authors assigned bouts of aerobic (65 % peak oxygen consumption [VO_{2peak}]), resistance (8 exercises at 80 % 1-RM), and concurrent exercise (6 resistance exercises and 20 min of aerobic exercise), but different from Ruiz et al. [31], they matched experimental sessions by duration (~60 min per session). SBP/DBP were significantly reduced after aerobic (~6/2 mmHg), resistance (~4/2 mmHg), and concurrent exercise (~5/2 mmHg) compared to control, and these reductions were similar across modalities ($ps > 0.05$). In contrast to Ruiz et al. [31], they found that PEH persisted longer following aerobic and concurrent (120 min) than resistance exercise (80 min) for SBP ($ps < 0.05$); and longer for DBP following aerobic (50 min) than concurrent and resistance exercise (40 and 20 min) ($p < 0.05$). Keese et al. concluded that PEH was elicited by a similar magnitude following 60 min of concurrent, aerobic, and resistance exercise, but persisted for a longer period of time following the aerobic and concurrent than resistance sessions.

Consistent with prior investigations [8, 31], Teixeira and colleagues [32] observed PEH after aerobic (30 min at 75 % VO_{2peak}), resistance (6 exercises at 50 % 1-RM), and concurrent exercise (~60 min, *combined* aerobic and resistance) compared to control ($ps < 0.05$) among 20 untrained, healthy young adults with normal BP; but for the first time, they reported modality-specific patterns in the magnitude *and* duration of PEH. They found SBP was reduced by the greatest magnitude and longest duration following aerobic and concurrent (13 and 11 mmHg for 120 min) compared to resistance exercise (8 mmHg for 60 min, $ps < 0.05$). Similar reductions were observed for DBP after all exercise modalities (~2 mmHg, $p > 0.05$), but PEH persisted longer following aerobic (90 min) than concurrent and resistance exercise (60 and 30 min, $p < 0.05$). Teixeira et al. concluded that aerobic, resistance, and concurrent exercise elicited PEH, but contrary to their hypothesis, *combined* aerobic and resistance exercise did not produce an *additive* BP response. Instead, PEH was greater after aerobic (13/2 mmHg) than concurrent (11/2 mmHg), which were both greater than resistance exercise (8/2 mmHg). These findings suggested that concurrent exercise may *attenuate* PEH resulting from aerobic exercise, but may *augment* PEH associated with resistance exercise alone.

Concurrent exercise seems to confer similar BP benefit to those achieved with aerobic exercise alone, and exceed those associated with resistance exercise alone (~3–6 mmHg) when compared directly within the same group of young adults with normal BP [8, 31, 32]. But, the magnitude of PEH is larger than previously reported after isolated aerobic (~1–3 mmHg) [3] and resistance exercise (1–3 mmHg, *ns*) [3, 27] for populations with normal BP, and are more similar to those observed among adults with hypertension [3]. Despite a lack of trials with a direct within comparison among the various exercise modalities, the limited literature involving participants with hypertension showed concurrent exercise elicited PEH by ~3–8 mmHg, which is consistent with the magnitude reported after aerobic exercise exclusively (5–8 mmHg) [3, 27], and greater than those reported with resistance exercise only (~1 mmHg, *ns*) [3, 27, 33] for populations with hypertension.

Concurrent Exercise and PEH: The Influence of Exercise Modality Order

Of the six PEH studies that qualified for this review, two acute concurrent exercise trials ordered aerobic *before* resistance exercise [31, 32], three ordered aerobic *after* resistance exercise [8, 19, 30], and one trial directly compared the influence of exercise modality order on PEH [20]. Collectively, these trials reported similar BP reductions following concurrent exercise that ordered aerobic *before* (~8/3 mmHg) versus *after* (~6/3 mmHg) resistance exercise; however, these trials did not directly compare exercise modality order on PEH among the same participants.

To address the specific question of exercise modality order, Menêses and colleagues [20] asked 19 middle-aged women with hypertension, who were currently taking BP medication, to perform a non-exercise session (i.e., control) and two concurrent exercise bouts consisting of moderate intensity aerobic exercise (30 min at 50–60 % HR reserve) performed *before* and *after* low to moderate resistance exercise loads (5 exercises at 50 % 1-RM, ~20 min) (see Table 3.1). They found SBP/DBP increased significantly after control (~9/6 mmHg), an effect that was abolished with concurrent exercise that ordered aerobic *before* (1/3 mmHg) and *after* (3/3 mmHg) resistance exercise. Menêses et al. concluded that concurrent exercise was effective in eliciting PEH (3–8 mmHg) among women on antihypertensive medication, independent of the exercise modality order ($p > 0.05$). Furthermore, the magnitude of PEH elicited by low to moderate intensity concurrent exercise, regardless of order, rivaled those associated with acute aerobic exercise only among the same population (5–7 mmHg).

Although limited, the preliminary findings from our review do not support that exercise modality order influences the occurrence, magnitude, or duration of PEH following concurrent exercise. Nonetheless, additional investigations on the influence of exercise modality order on PEH are warranted, and should be assessed among more diverse samples involving adults with hypertension, and for longer durations following acute exercise, ideally under conditions of daily living using ambulatory BP monitoring.

Concurrent Exercise and PEH: The Influence of Exercise Volume (Intensity and Duration)

Chapter 1 discussed several lines of evidence supporting that higher intensity aerobic exercise resulted in greater BP reductions than lower intensities of exercise, even when performed in very short bouts (<10 min) (i.e., high intensity interval training or HIIT) [34, 35] (see Chap. 1 for an expanded discussion of HIIT). In support of this evidence, it has been reported that higher but not lower intensities of acute dynamic resistance exercise elicited PEH [36–38], although these findings are less consistent compared to aerobic exercise [29, 39] (see Chaps. 2, 5, 6,

and 8 for additional discussion). Still, these observations suggest that the occurrence and magnitude of PEH may be modulated by exercise intensity, duration, and possibly, their interaction (i.e., exercise volume, MET-min per session). Furthermore, because concurrent exercise consists of separate aerobic *and* resistance components, it is important to elucidate how exercise intensity and duration *independently* modulate PEH for aerobic and resistance exercise, in addition to their *combined* or *concurrent* effects.

Overall, trials involving participants with normal BP combined moderate to vigorous intensity aerobic exercise (~60–75 % VO_{2peak}) [8, 31, 32], and low (50 % 1-RM) [32] to moderately heavy resistance exercise loads (6–8 exercises at 65–80 % 1-RM) for 2–3 sets of 6–20 repetitions with 2 min rest intervals between sets [8, 30, 31]. Trials involving adults with hypertension also prescribed moderate intensity aerobic exercise (~55 % HR reserve *or* 60 % maximal HR [HR_{max}]), and moderate resistance exercise loads (7 exercises at ~60–65 % 1-RM) for 3 sets of 10 repetitions with 1–2 min rest intervals between sets [19, 20]. Half of the acute trials "matched" the exercise duration [32], volume (MET-min per session) [20], or both [31] for the aerobic and resistance components in the concurrent exercise bout (see Table 3.1). In contrast, Keese [8] and dos Santos et al. [19] prescribed shorter duration (20 min) and lower aerobic exercise volume (100–144 MET-min per session) with longer resistance exercise duration (40–60 min) and higher volume (~160–270 MET-min per session) (Table 3.1). Overall, differences in exercise duration and concurrent exercise volume did not appear to significantly modulate PEH, with the exception of Teixeira et al. [32] who prescribed a lower resistance exercise load. They found SBP was reduced by the greatest magnitude following combinations of vigorous intensity aerobic exercise (75 % VO_{2peak}) and lower resistance exercise loads (50 % 1-RM) involving 3 sets of 20 repetitions with 45–90s rest intervals between sets (see Table 3.1). The new and emerging evidence from Teixeira and co-investigators suggest that combinations of moderate to vigorous intensity acute aerobic exercise and resistance exercise consisting of low to moderate loads and higher repetitions (3–4 sets of ≥15 repetitions with 1 min rest intervals between sets) may be more efficacious for reducing BP compared to combinations of high intensity acute aerobic *and* resistance exercises [8, 19, 30].

To better elucidate the influence of aerobic exercise intensity on PEH, Keese and co-investigators [30] had 21 trained, healthy young men with normal BP complete three concurrent exercise sessions consisting of heavy resistance exercise loads (6 exercises at 80 % 1-RM) and low repetitions (2 sets of 6–8 repetitions with 2 min rest intervals between sets), immediately followed by 30 min of aerobic exercise performed at low (50 % VO_{2peak}), moderate (65 % VO_{2peak}), and high (80 % VO_{2peak}) intensity. PEH was observed following all concurrent sessions compared to control ($p < 0.05$), and the magnitude of PEH was similar following aerobic exercise performed at low, moderate, and high intensity (2–6 mmHg, $p > 0.05$) (see Table 3.1). SBP reductions persisted for longer periods of time after concurrent sessions involving higher (≥65 % VO_{2peak}) than lower aerobic exercise intensity (120 versus 60 min, $p < 0.01$). The magnitude of PEH for DBP was also similar following aerobic exercise performed at low, moderate, and high intensity

(1–2 mmHg, $p > 0.05$), and DBP reductions persisted significantly longer following concurrent exercise involving the highest intensity aerobic exercise (120 min; 80 % VO_{2peak}) compared to lower intensities (40–60 min; ≤65 % VO_{2peak}). Keese et al. concluded that concurrent exercise involving heavy resistance exercise loads (80 % 1-RM) and low, moderate, or vigorous (i.e., high) intensity aerobic exercise elicited PEH to a similar magnitude (1–6 mmHg) among young men with normal BP. Although the magnitude of PEH was independent of aerobic exercise intensity, they found that PEH persisted longer following higher (≥65 % VO_{2peak}) than lower intensity aerobic exercise (50 % VO_{2peak}).

Overall, acute concurrent exercise consisting of moderate to vigorous intensity aerobic exercise and low to moderately heavy resistance exercise loads elicited PEH among adults with normal BP (3–11 mmHg) and established hypertension (3–8 mmHg), regardless of whether the aerobic and resistance components were matched for exercise duration (min per session) or volume (MET-min per session). However, new and emerging evidence from our review suggests that concurrent exercise may not be a low threshold PEH event as shown with aerobic exercise, in that it may require moderate to vigorous intensity aerobic exercise combined with low to moderately heavy resistance exercise loads [30, 32]; BP reductions were greatest when acute concurrent exercise consisted of vigorous intensity aerobic exercise and lower resistance exercise loads with higher repetitions [32]. Nonetheless, most of the available evidence is based on healthy, young, recreationally active adults with normal BP, and PEH was only measured in the laboratory and not under ambulatory conditions. Additional PEH investigations are warranted to address these limitations and to determine the effectiveness of acute concurrent exercise as potential lifestyle therapy to prevent, treat, and control hypertension.

Chronic, Training, or Long-Term Effects

Current Consensus

The ACSM assigned a category *A* rating [28] to the level of evidence supporting that aerobic exercise training reduces BP 5–7 mmHg among individuals with hypertension, which is the highest level of evidence supported by the results from a large number of RCTs [3]. There was also evidence to support that dynamic resistance training produced reductions in resting BP of 2–3 mm Hg, but there were fewer RCTs involving adults with hypertension and with inconsistent findings. Therefore, the ACSM assigned a category *B* rating [28] to the level of evidence supporting the BP response to dynamic resistance training among individuals with hypertension (see Chap. 1, Table 1.1 for the levels of evidence) [3]. Consistent with the PEH literature, the antihypertensive effects of *concurrent* aerobic and resistance exercise were not reviewed in the position stand, and the level of evidence was not rated. Consequently, a general consensus on the effectiveness of concurrent exercise training to lower BP among adults with hypertension is lacking [3].

In contrast to the PEH literature, where no meta-analytic investigation of the BP response to acute concurrent exercise had been published, four meta-analyses have examined the antihypertensive effects of concurrent training for adults with type 2 diabetes mellitus (T2DM) [40, 41], the metabolic syndrome (MetS) [42], and among "apparently" healthy adults, free from cardiovascular or other known diseases [27]. In general, these meta-analyses included middle-aged, overweight, white men and women with prehypertension who were sedentary at baseline. Concurrent training programs lasted ~34 weeks and consisted of 3 weekly, 50–60 min sessions performed at 65–70 % VO_{2max} and ~70 % 1-RM for the aerobic and resistance exercise components, respectively [40, 41]. Overall, this "dose" of concurrent training reduced resting BP ~2–4 mmHg among adults with prehypertension and T2DM [40, 41], but not among adults with prehypertension and the MetS [42]. For apparently healthy adults with normal BP to established hypertension and no known disease, Cornelissen and Smart [27] found concurrent training significantly reduced DBP (2 mmHg) but not SBP, and these reductions were similar to those following aerobic (3–5 mmHg) and dynamic resistance training (2–3 mmHg, $ps > 0.05$).

Overall, the BP response to concurrent exercise training among adults with normal BP to established hypertension (~2 mmHg) [27] is consistent with those reported by previously published meta-analyses examining the antihypertensive effects of isolated aerobic exercise training (3–4 mmHg) [27, 43, 44] and dynamic resistance training (~2–3 mmHg) [27, 33] for the same populations (see Chaps. 1 and 2 for an expanded discussion). When these meta-analyses focused on samples with hypertension only, the BP benefit was greater following aerobic exercise training (5–8 mmHg) [27, 43, 44] than dynamic resistance training (1–2 mmHg, *ns*) [27, 33]; yet the influence of resting BP (i.e., the law of initial values) [45] as a potential moderator of the BP response to concurrent training has yet to be investigated. The meta-analyses conducted to date have contributed little to our understanding of how baseline sample and concurrent exercise characteristics modulate BP reductions with training. It remains unclear for who concurrent exercise may work best for as antihypertensive lifestyle therapy, and what "dose" of concurrent exercise confers the optimal therapeutic BP benefit.

New and Emerging Research

To highlight new and emerging research, the authors self-selected 22 concurrent exercise training studies (*n*) that yielded 27 interventions (*k*), which are summarized in Table 3.2. For the purposes of this chapter, only concurrent training studies involving apparently healthy adults with normal BP to established hypertension were included; trials involving adults with metabolic-related diseases (i.e., T2DM, the MetS, etc.) were identified from our search but not reviewed here. Readers are directed to Chaps. 2 and 4 and Parts II and III of this Book for a more comprehensive discussion regarding the pleiotropic effects of exercise on other cardiometabolic risk factors, and their interactions with resting BP.

Most concurrent training interventions involved adults with prehypertension (50 %, $k = 14$) or established hypertension (41 %, $k = 10$) at baseline; four interventions (15 %) reported normal BP values at baseline [25, 46, 47], despite involving

Table 3.2 Qualifying concurrent exercise training trials: a summary of the baseline sample characteristics, the Frequency, Intensity, Time, and Type of the concurrent exercise intervention, and resultant blood pressure change for adults with normal to established hypertension blood pressure ($n = 22$, $k = 27$)

	Baseline characteristics			Features of the exercise training intervention:	BP response to training[d]	
Author (Yr)	*N* (W)	BMI Age (yr)	Health status[a,b] resting BP (mmHg)	Experimental design and exercise characteristics including the Frequency, Intensity, Time and Type or FITT[c]	SBP change (mmHg)	DBP change (mmHg)
CET performed in a single exercise session: **AET *first, followed by* RT ($n = 11$, $k = 15$)**						
Okamoto (2007) [47]	*N* = 33 (22)	~22 kg/m²	Healthy, NBP	Length = 8 weeks, supervised		
	Con = 11 (8)	18.8 ± 0.7	113.9 ± 10.3/63.3 ± 7.0	**CET × 2 d/wk (~60 min/session)**: AET = continuous running (treadmill), 60 % MHR (~6.0 MET), 20 min/session + RT (~30–40 min/session) = machines, 7 RT exercises (4 upper/3 lower body), 5 sets × 8–10 reps, 80 % 1-RM (9.2), 2 min rest intervals rest between sets	Con ↔ −1.4	Con ↔ −1.8
	BRT = 11 (7)	18.5 ± 0.7	113.6 ± 11.3/62.5 ± 7.3		BRT ↔ −2.4	BRT ↔ −2.0
	ART = 11 (7)	18.5 ± 0.7	113.5 ± 14.3/64.5 ± 6.3	**CET volume = AET (240) + RT (~644) = ~884 MET-min/wk**	ART ↔ −3.4	ART ↔ −5.2
Laterza (2007) [25]	*N* = 64 (20)	~25 kg/m²	Healthy, NBP-HTN	Length = 16 weeks, supervised		
	Con = 20 (7)	44 ± 4.5	145.0 ± 12.0/94.0 ± 6.0	**CET × 3 d/wk (50 min/session)**: AET = cycle, anaerobic threshold, ~70 % VO_{2peak} (7.2 MET), 40 min/session + RT (10 min/session) = "strength exercises" (sit-up, push-up, pull-up) (~7.2 MET)	Con ↔ +1.0	Con ↔ −1.0
	HTN = 32 (10)	44 ± 4.5	145.0 ± 6.6/94.0 ± 6.6		HTN ↓ −15.0*	HTN ↓ −10.0*
	NBP = 12 (3)	42.0 ± 6.9	117.0 ± 6.9/91.0 ± 6.9	**CET volume = AET (864) + RT (216) = 1,080 MET-min/wk**	NBP ↔ −1.0	NBP ↔ 0.0
Wood (2001) [58]	*N* = 36 (8)	~27 kg/m²	Healthy, PreHTN	Length = 12 weeks, supervised		
	Con = 6 (3)	68.0 ± 5.4	133.5 ± 22.4/78.3 ± 6.9	**Progressive AET (~50–60 min/session)** = cycle/treadmill × 3 d/wk, 60–70 % MHR (~11–13 on Borg RPE scale) (~4.0 MET), progressing from 21 to 45 min/session	Con ↔ −3.8	Con ↔ −2.0
	AET = 10 (6)	69.1 ± 5.3	133.7 ± 16.4/76.8 ± 7.0	**AET volume = 540 MET-min/wk**	AET ↓ −10.3*	AET ↔ −3.6
	RT = 11 (5)	69.8 ± 6.0	129.1 ± 22.5/75.1 ± 10.3	**Progressive RT (~50–60 min/session)** = machines, 8 RT exercises (5upper/3 lower body) × 3 d/wk, 1 set × 12–15 reps, 75 % 5RM (~3.2 MET); 2 sets × 8–12 reps, 8–12RM (~4.7 MET)	RT ↔ −5.0	RT ↔ −2.5
				RT volume = 180 MET-min/wk		
	CET = 9 (5)	66.1 ± 5.5	128.7 ± 13.8/76.6 ± 8.3	**Progressive CET × 3 d/wk (50–60 min/session)**: AET Ex R_x × 30 min/session + RT Ex R_x (20–30 min/session): 1 set × 12–15 reps, 75 % 5RM; 8–12 reps, 8–12RM	CET ↔ +1.2	CET ↔ +1.2
				CET volume = AET (360) + RT (120) = 480 MET-min/wk	*Group* > 0.05	*Group* = 0.06

Ohkubo (2001) [24]	*N* = 39 (20)	67 (60–81)	Healthy, HTN	Length = 25 weeks, supervised		
	Con = 17 (9)	~24 kg/m^2	144.1 ± 10.3/81.7 ± 8.7	**CET × 2 d/wk (120 min/session)**: AET = cycle, 25–60 % HRR (~4.0 MET), 20–30 min/session + progressive RT (30–40 min/session) = therabands, 5 RT exercises (2 upper/3 lower body), 1 set × 20 reps, 20 RM (~3.0 MET)	Con ↔	Con ↔
					CET ↓ −8.0**	CET ↓ −4.0**
	CET = 22 (11)		143.0 ± 11.9/78.7 ± 11.3	**CET volume = AET (200) + RT (210) + stretching (220) = ~630 MET-min/wk**. **Note*. each session began with low intensity (~2.0 MET) warm up (~30–40 min) and cool down (~20 min) consisting of stretching and stepping exercises		
Shaw (2010) [49]	*N* = 37 M	~25 kg/m^2	Healthy, PreHTN	Length = 16 weeks, supervised		
	Con = 12 M	25.0 ± 2.4	122.0 ± 5.7	AET: cycle, walking; rowing, stepping × 3 d/wk, 60 % MHR (4.5 MET), 45–60 min/session	Con ↑ +3.0*	–
	AET = 12 M	25.0 ± 5.6	126.2 ± 7.0	**AET volume = 810 MET-min/wk**	AET ↓ −3.8*	–
	CET = 13 M	26.0 ± 3.1	131.5 ± 9.3	**CET × 3 d/wk (60 min/session)**: AET Ex R_x × 22 min/session + RT (~22 min/session): machines, 8 RT exercises (4 upper/4 lower body), 2 sets × 15 reps, 60 % 1-RM (~6.0 MET)	CET ↓ −10.0**	–
				CET volume = AET (297) + RT (540) = 837 MET-min/wk	*Group* = *0*.097	
Opperman (2012) [52]	*N* = 28 M	39 (28, 49) BMI —	Healthy, PreHTN	Length = 12 weeks, supervised		
	Con = 9 M		135.8 ± 15.5/87.2 ± 8.3	**CET × 2 d/wk (60 min/session)**: AET = cycle, 60–85 % MHR (~6.0 MET), 30 min/session + RT (20–30 min/session) = machines, upper body and abdominal exercises, flexibility (shoulders, low back, legs), 60–85 % MHR (~6.0 MET)	Con ↔ +5.6 %	Con ↔ +4.5 %
					2day ↔ −3.4 %	2day ↓ −6.0 %**
	2day = 13 M		130.1 ± 9.8/87.2 ± 5.5	**CET volume = AET (360) + RT (360) = 720 MET-min/wk**		
	4day = 16 M		130.1 ± 11.6/86.1 ± 7.5	**CET × 4 d/wk (60 min/session)**: AET = cycle, 60–85 % MHR (~6.0 MET), 30 min/session + RT (20–30 min/session) = machines, upper body and abdominal exercises, flexibility (shoulders, low back, legs), 60–85 % MHR (~6.0 MET)	4day ↔ −0.7 %	4day ↔ +0.8 %
				CET volume = AET (720) + RT (720) = 1,440 MET-min/wk	*Group* > 0.05	*Group* > 0.05

(continued)

Table 3.2 (continued)

Author (Yr)	Baseline characteristics			Features of the exercise training intervention:	BP response to trainingd	
	N (W)	BMI Age (yr)	Health statusa,b resting BP (mmHg)	Experimental design and exercise characteristics including the Frequency, Intensity, Time and Type or FITTc	SBP change (mmHg)	DBP change (mmHg)
Guimaraes (2010) [54]	*N* = 43 (30)	BMI —	Healthy, PreHTN-HTN (*100 % treated*)	Length = 12 weeks, supervised and unsupervised sessions (*24-h ambulatory BP)		
	Con = 11 (9)	47.0 ± 6.0	128.0 ± 9.0/83.0 ± 9.0	**CET-CNT × 3 d/wk (60 min/session)**: AET = continuous (treadmill), 60 % HRR (6.0 MET), 40 min/session + RT (20 min/session) = 'sub-maximal' RT (5.0 MET)	Con ↔ (0, −3)	Con ↔ (0, −1)
	CNT = 16 (9)	50.0 ± 8.0	124.0 ± 9.0/81.0 ± 9.0	**CET-CNT volume = AET (720) + RT (300) = 1,020 MET-min/wk**	CNT ↔ (0, −1)	CNT ↔ (−1, −2)
	AIT = 16 (12)	45.0 ± 9.0	125.0 ± 9.0/81.0 ± 5.0	**CET-AIT × 3 d/wk (60 min/session)**: AET = interval (treadmill), 2 min at 50 % HRR (5.0 MET) alternating with 1 min at 80 % HRR (7.7 MET), 40 min/session (~60 % HRR; 6.4 MET) + RT (20 min/session) = 'sub-maximal' RT (5.0 MET)	AIT ↔ (−1, −2)	AIT ↔ (−1, −3)
	CNT + AIT			**CET-AIT volume = AET (768) + RT (300) = 1,068 MET-min/wk**	CNT + AIT ↔	CNT + AIT ↓ −2.0**
Ho (2012) [46]	*N* = 64 (54)	~33 kg/m^2	Healthy, NBP-HTN	Length = 12 weeks, supervised		
	Con = 16 (15)	52 (40, 66)	120.0 (108–134)/65.4 (48–79)	Non-exercise control received 'placebo' dietary supplement (~2 g of breadcrumbs and 0.1 g of Equal artificial sweetener), participants took supplement once daily.	Con ↓ −4.0* (−3.3 %)	Con ↓ −2.2* (−3.3 %)
	AET = 15 (12)	55 (44–62)	119.9 (96–159)/67.4 (55–86) (*7% treated*)	AET: walking (treadmill) × 5 d/wk, 60 % HRR (~6.0 MET), 30 min/session	AET ↔ +0.6	AET ↔ +0.2
				AET volume = 1,500 MET-min/week		
	RT = 16 (13)	52 (43–59)	125.9 (96–160)/70.9 (60–92) (*13% treated*)	RT (~30 min/session): machines, 5 RT exercises (3 upper/2 lower body) × 5 d/wk, 4 sets × 8–12 reps, 10RM (~75 % 1-RM) (5.0 MET)	RT ↔ −1.7	RT ↔ −1.0
				RT volume = 1,000 MET-min/wk		
	CET = 17 (14)	53 (43–64)	117.7 (102–150)/66.4 (58–79) (*6% treated*)	**CET × 5 d/wk (30 min/session)**: AET Ex R_x × 15 min/session + RT Ex R_x (15 min/session): 2 sets × 8–12 reps	CET ↓ −5.0* (−4.3 %)	CET ↔ −2.9 (−4.2 %)
				CET volume = AET (450) + RT (500) = 950 MET-min/wk	*Group* > 0.05	

Seo (2011) [53]	*N* = 20 W	~25 kg/m^2	Healthy, obese, NBP- PreHTN	Length = 12 weeks, supervised		
	Con = 10 W	40.1 ± 4.0	119.9 ± 9.8/72.8 ± 10.7		Con ↔	Con ↔
	CET = 10 W	39.8 ± 5.3	121.2 ± 8.0/78.6 ± 6.0	**CET × 3 d/wk (60 min/session)**: AET = continuous running (treadmill), 60–70 % HRR (7.2 MET), 30 min/session + RT (30 min/session) = machines, 6 RT exercises (3 upper/3 lower body), 3 sets × 10 reps, 10RM (~75 % 1-RM) (5.0 MET)	CET ↔	CET ↓ −3.4**
				CET volume = AET (648) + RT (450) = 1,098 MET-min/wk		
Seo (2010) [55]	*N* = 22 W	~26 kg/m^2	Healthy, PreHTN-HTN	Length = 12 weeks, supervised		
	Con = 7 W	54.0 ± 3.6	132.0 ± 13.8/87.3 ± 10.0	Progressive AET: walking and aerobics × 3 d/wk, 60–80 % HRR (~5.0 MET), 60 min/session	Con ↔ −2.1	Con ↔ −2.6
	AET = 7 W	55.0 ± 4.8	136.4 ± 19.6/94.1 ± 17.8	**AET volume = 900 MET-min/wk**	AET ↔ +2.0	AET ↔ −0.6
	CET = 8 W	58.0 ± 4.2	126.5 ± 14.4/86.5 ± 11.7	**CET × 3 d/wk (60 min/session)**: AET Ex R_x × 20 min/session + RT (30–40 min/session): machines, 8 RT exercises (5 upper/3 lower body), 3 sets × 10–12 reps, 50–70 % 1-RM (~4.9MET)	CET ↔ −7.7	CET ↔ −3.5
				CET volume = AET (300) + RT (485) = 785 MET-min/wk	*Group* > 0.05	*Group* > 0.05
Nishijima (2007) [48]	*N* = 501 (292)	~27 kg/m^2	Healthy, PreHTN-HTN	Length = 24 weeks, supervised		
	Con = 252 (145)	66.9 ± 6.9	141.3 ± 17.6/83.3 ± 10.6 (*41 % treated*)	**CET × 2.6 d/wk (60–90 min/session)**: AET = cycle, 40–70 % VO_{2peak} (~4.0 MET), 20–40 min/session + RT (20 min/session) = "4 light RT exercises" (3 upper/1 lower body), 2 sets × 20 reps, 20RM (~3.2 MET); light stretching pre-and-post training (20 min total, ~1.6 MET)	Con ↔	Con ↔
					CET ↓ −8.3* (−10.0, −6.6)	CET ↓ −4.8* (−5.7, −3.8)
	CET = 249 (147)	67.0 ± 6.7	139.3 ± 16.4/82.3 ± 9.7 (*46 % treated*)	**CET volume = AET (312) + RT (~166) + stretching (83) = ~562 MET-min/wk**		
CET performed in a single exercise session: **RT *first, followed by* AET** (***n*** = **4**, ***k*** = **5**)						

(continued)

Table 3.2 (continued)

Author (Yr)	Baseline characteristics			Features of the exercise training intervention:	BP response to trainingd	
	N (W)	BMI Age (yr)	Health statusa,b resting BP (mmHg)	Experimental design and exercise characteristics including the Frequency, Intensity, Time and Type or FITTc	SBP change (mmHg)	DBP change (mmHg)
Figueroa (2011) [51]	*N* = 24 W	~24 kg/m^2	Post-Menopausal, Healthy, NBP-PreHTN	Length = 12 weeks, supervised		
	Con = 12 W	54.0 ± 3.5	120.0 ± 6.9/73.0 ± 3.5	**CET × 3 d/wk (40 min/session)**: AET = treadmill walking, 60 % MHR (~4.0 MET), 20 min/session + RT (20 min/session) = machine circuit, 9 RT exercises (4 upper/5 lower body), 1 set × 12 reps, 60 % 1-RM (~4.0 MET)	Con ↔	Con ↔
	CET = 12 W	54.0 ± 6.9	124.0 ± 6.9/73.0 ± 6.9		CET ↓ −6.0 ± 1.9	CET ↓ −4.8 ± 1.7
				CET volume = AET (210) + RT (270) = 480 MET-min/wk		
Stewart (2005) [21]	*N* = 104 (53)	~30 kg/m^2	Healthy, HTN	Length = 24 weeks, supervised		
	Con = 53 (27)	64.1 (62.4, 65.8)	141.7 (139.7,143.8)/76.4 (73.9, 78.9)	**CET × 3 d/wk (75–85 min/session)**: AET = treadmill, cycle, stair stepper, 60–90 % MHR (~4.6 MET), 45 min/session + RT (~30–40 min/session) = machines, 7 RT exercises (4 upper/3 lower body), 2 sets × 10–15 reps, 50 % 1-RM (4.0 MET)	Con ↔	Con ↔
	CET = 51 (26)	63 (62, 65)	140.3 (138.2,142.4)/76.8 (74.8, 78.9)	**CET volume = AET (621) + RT (360–480) = ~1,041 (981–1,101) MET-min/wk**	CET ↓ −5.3* (−8.1, −2.5)	CET ↓ −3.7* (−5.1, −2.4)
Filho (2013) [26]	*N* = 54 W	~29 kg/m^2	Healthy, HTN	Length = 16 weeks, supervised		
	Con = 27 W	66.6 ± 6.0	147.8 ± 12.2/92.1 ± 7.5	**CET × 3 d/wk (60–70 min/session)**: AET = walking, "moderate" (3.5 MET), 25 min/session + RT (15 min/session) = RT bands and dumbbells, 2 sets × 12 reps, "moderate" (4.5 MET); light stretching pre-and-post RT (20 min total, ~1.6 MET)	Con ↔	Con ↔
	CET = 27 W	68.9 ± 6.8	145.3 ± 14.3/95.8 ± 8.6	**CET volume = AET (300) + RT (180) + stretching (~83) = ~563 MET-min/wk**	CET ↓ −9.9**	CET ↓ −9.1**

dos Santos (2014) [19]	*N* = 60 W	~28 kg/m²	Healthy, PreHTN (*100% treated*)	Length = 16 weeks, supervised		
	Con = 20 W	63.1 ± 2.3	160.7 ± 9.1/89.9 ± 4.8	**CET × 3 d/wk (70–80 min/session)**: AET = treadmill walking, 65–75 % THR (5.0 MET), 20 min/session + ERT (50–60 min/session) = dumbbells and machines, 7 RT exercises (3 upper/4 lower body), 3 sets × 10 reps, 100 % 10RM (6.0 MET); 110 % 10RM (~6.7 MET); 120 % 10RM (~7.5 MET)	Con ↔	Con ↔
	ERT = 20 W	64.2 ± 3.1	162.7 ± 7.8/85.5 ± 4.3	**CET volume = AET (300) + RT (1,111) = ~1,411 MET-min/wk**	ERT ↓ −30.9**	ERT ↓ −11.9**
	RT = 20 W	62.6 ± 2.5	163.1 ± 4.4/88.8 ± 3.6	**CET × 3 d/wk (70–80 min/session)**: AET = treadmill walking, 65–75 % THR (5.0 MET), 20 min/session + RT (50–60 min/session): dumbbells and machines, 7 RT exercises (3 upper/4 lower body), 3 sets × 10 reps, 70 % 10RM (4.0 MET); 80 % 10RM (4.5 MET); 90 % 10RM (5.0 MET)	RT ↓ −35.1**	RT ↓ −12.0**
				CET volume = AET (300) + RT (~743) = ~1,043 MET-min/wk		
CET performed in a single exercise session: **AET** and **RT are performed *simultaneously using a circuit training*** (**i.e.**, ***alternating bouts***) (n = **2**, k = **3**)						
Miura (2008) [59]	*N* = 77 W	~24 kg/m²	Healthy, PreHTN	Length = 12 weeks, supervised		
	Con = 23 W	68.9 ± 7.5	122.9 ± 13.7/71.7 ± 9.1	**CET × 1 d/wk (60 min/session)**: AET = cycle, 54 % HRR (~4.5 MET), 20 min/session + RT and 4 chair exercises (~40 min/session) = circuit RT (rubber tubes, light dumbbells), 6–8 stations (6 upper/2 lower body), 3–5 sets × 15–20 reps, ~44 % HRR (~3.7 MET)	Con ↔	Con ↔
	1day = 29 W	68.8 ± 6.5	126.2 ± 14.0/73.8 ± 7.8	**CET volume = 160 MET-min/wk**	1day ↔	1day ↔
	2day = 25 W	69.5 ± 7.0	123.3 ± 13.7/73.0 ± 9.2	**CET × 2 d/wk (60 min/session)**: AET = cycle, 54 % HRR (~4.5 MET), 20 min/session + RT and 4 chair exercises (~40 min/session) = circuit RT (rubber tubes, light dumbbells), 6–8 stations (6 upper/2 lower body), 3–5 sets × 15–20 reps, ~44 % HRR (~3.7 MET)	2day ↔	2day ↔
				CET volume = 320 MET-min/wk		

(continued)

Table 3.2 (continued)

Author (Yr)	Baseline characteristics			Features of the exercise training intervention:	BP response to trainingd	
	N (W)	BMI Age (yr)	Health statusa,b resting BP (mmHg)	Experimental design and exercise characteristics including the Frequency, Intensity, Time and Type or FITTc	SBP change (mmHg)	DBP change (mmHg)
Shin (2009) [22]	*N* = 48 W	~25 kg/m^2	Disease (98 %), HTN	Length = 8 weeks, supervised		
	Con = 22 W	75.1 ± 8.2	139.8 ± 19.4/78.0 ± 9.8	**CET × 2 d/wk (30–50 min/session)**: AET = rhythmic movements "to improve fitness" + RT = "muscle strengthening exercises," 40–50 % to 60–65 % MHR (2.0–4.0 MET)	Con ↔	Con ↔
	CET = 26 W	76.6 ± 6.8	140.0 ± 16.5/88.2 ± 13.5	**CET volume = 240–300 MET-min/wk**	CET ↔	CET ↓ −9.7**
CET performed as *combined training*: AET and RT are performed on *separate days* (*n* = 5, *k* = 5)						
Tseng (2013) [50]	*N* = 40 M	~31 kg/m^2	Healthy, NBP-PreHTN	Length = 12 weeks, supervised		
	Con = 10 M	22.3 ± 3.2	126.0 ± 4.1/81.7 ± 5.1	Progressive AET (45–60 min/session): walk/run (treadmill) × 5 d/wk, 50–60 % to 60–70 % MHR (~5.0 MET), 15–45 min/session	Con ↔ +0.4 ± 1.3	Con ↔ −0.2 ± 0.9
	AET = 10 M	22.1 ± 3.5	126.7 ± 6.6/86.0 ± 2.8	**AET volume = 1,125 MET-min/wk**	AET ↓ −7.5 ± 0.9**	AET ↓ −5.8 ± 0.9**
	RT = 10 M	21.3 ± 1.9	124.0 ± 6.0/77.7 ± 5.4	Progressive RT (45–60 min/session): machines, 11 RT exercises (5 upper/6 lower body) × 5 d/wk, 3 sets × 10–15 reps, 50–60 % 1-RM (~4.8 MET); 10–12 reps, 60–70 % 1-RM (~6.0 MET); 8–10 reps, 70–80 % 1-RM (~7.1 MET)	RT ↓ −5.4 ± 0.9**	RT ↓ −4.3 ± 0.6**
				RT volume = 1,125 MET-min/wk		
	CET = 10 M	22.2 ± 2.2	130.2 ± 7.9/82.8 ± 5.4	**Progressive, periodized CET × 5 d/wk (~45–60 min/session)**: AET Ex R_x × 3 *or* 2 d/wk + RT Ex R_x × 2 *or* 3 d/wk on *even* versus *odd* weeks	CET ↓ −7.2 ± 1.3**	CET ↓ −5.6 ± 0.9**
				CET volume = AET (675/450) + RT (540/810) = 1,215 or **1,260 MET-min/wk**	*Group* > 0.05	*Group* > 0.05

Sillanpää (2009) [56]	*N* = 61 M	~24 kg/m^2	Healthy, PreHTN	Length = 21 weeks, supervised		
	Con = 14 M	53.8 ± 7.7	135.0 ± 10.0/86.0 ± 8.0	Progressive AET: cycling × 2 d/wk, anaerobic threshold (~70 % VO_{2peak}) (~7.0 MET), 30 min/session; 60–70 % VO_{2peak} (~5.5 MET), 45–60 min/session; 60–70 % VO_{2peak} (~5.5 MET), 60–90 min/session	Con ↔ −4.0 ± 6.0	Con ↔ −1.0 ± 6.0
	AET = 17 M	52.6 ± 7.9	127.0 ± 15.0/82.0 ± 8.0	**AET volume = ~660 (420–915) MET-min/wk**	AET ↓ −6.0 ± 8.0**	AET ↓ −4.0 ± 6.0**
	RT = 15 M	54.1 ± 6.0	127.0 ± 17.0/83.0 ± 11.0	Progressive, periodized RT (~60–90 min/session): machines, 7–8 RT exercises (4–5 upper/3 lower body) × 2 d/wk, 3–4 sets × 15–20 reps, 40–60 % 1-RM (4.0 MET); 10–15 reps, 60–80 % 1-RM (6.0 MET); 6–8 reps, 70–90 % 1-RM (9.0 MET)	RT ↓ −9.0 ± 8.0**	RT ↓ −5.0 ± 7.0**
				RT volume = ~464 (441–490) MET-min/wk		
	CET = 15 M	56.3 ± 6.8	132.0 ± 10.0/85.0 ± 11.0	**Progressive, periodized CET × 4 d/wk (~60–90 min/session)**: AET Ex R_x × 2 d/wk + RT Ex R_x × 2 d/wk	CET ↔ +1.0 ± 8.0	CET ↔ −1.0 ± 7.0
				CET volume = AET (~660) + RT (~464) = ~1,125 (910–1,356) MET-min/wk	*Group* < 0.01	*Group* = 0.08
Sillanpää (2009) [57]	*N* = 30 W	~23 kg/m^2	Post-Menopausal, Healthy, PreHTN	Length = 21 weeks, supervised		
	Con = 12 W	51.4 ± 7.8	130.0 ± 18.0/76.0 ± 9.0	Progressive AET: cycling × 2 d/wk, anaerobic threshold (~70 % VO_{2peak}) (~7.0 MET), 30 min/session; 60–70 % VO_{2peak} (~5.5 MET), 45–60 min/session; 60–70 % VO_{2peak} (~5.5 MET), 60–90 min/session	Con ↔ −9.0 ± 7.0	Con ↔ −3.0 ± 5.0
	AET = 15 W	51.7 ± 6.9	128.0 ± 16.0/79.0 ± 11.0	**AET volume = ~660 (420–915) MET-min/wk**	AET ↔ −2.0 ± 11.0	AET ↔ −1.0 ± 7.0
	RT = 17 W	50.8 ± 7.9	126.0 ± 17.0/74.0 ± 10.0	Progressive, periodized RT (~60–90 min/session): machines, 7–8 RT exercises (4–5 upper/3 lower body) × 2 d/wk, 3–4 sets × 15–20 reps, 40–60 % 1-RM (4.0 MET); 10–15 reps, 60–80 % 1-RM (6.0 MET); 6–8 reps, 70–90 % 1-RM (9.0 MET)	RT ↔ 0.0 ± 10.0	RT ↔ −1.0 ± 7.0
				RT volume = ~464 (441–490) MET-min/wk		
	CET = 18 W	49.8 ± 6.8	125.0 ± 17.0/75.0 ± 8.0	**Progressive, periodized CET × 4 d/wk (~60–90 min/session)**: AET Ex R_x × 2 d/wk + RT Ex R_x × 2 d/wk	CET ↔ +1.0 ± 9.0	CET ↔ +3.0 ± 5.0
				CET volume = AET (~660) + RT (~464) = ~1,125 (910–1,356) MET-min/wk	*Group* = 0.06	*Group* = 0.05

(continued)

Table 3.2 (continued)

Author (Yr)	Baseline characteristics			Features of the exercise training intervention:	BP response to trainingd	
	N (W)	BMI Age (yr)	Health statusa,b resting BP (mmHg)	Experimental design and exercise characteristics including the Frequency, Intensity, Time and Type or FITTc	SBP change (mmHg)	DBP change (mmHg)
Vianna (2012) [60]	*N* = 70 (46)	~27 kg/m^2	Healthy, HTN	Length = 16 weeks, supervised		
	Con = 35 (20)	69.8 ± 8.1		**CET × 3 d/wk (60 min/session)**: AET = walking (1 d/wk), "hydro-gymnastics" (1 d/wk), 55–65 % MHR or RPE 12–13 (~4.0 MET), 45–50 min/session + RT (45–50 min/session) = "muscle strengthening exercises" × 1 d/wk, RPE 12–13 (~4.0 MET)	Con ↔	Con ↔
	CET = 35 (26)	68.7 ± 5.9		**CET volume = AET (360) + RT (180) = 540 MET-min/wk**	CET ↔	CET ↔
Sousa (2013) [23]	*N* = 33 M	69.1 ± 5.0 ~ 27 kg/m^2	Healthy, HTN	Length = 32 weeks, supervised		
	Con = 17 M		138.8 ± 15.9/81.4 ± 11.0	Progressive AET: walking, jogging, dancing (land × 2 d/wk) and water-based (1 d/wk) × 3 d/wk, RPE = 12–17 (Borg RPE scale; moderate-vigorous) (~5.8 MET), 60 min/session	Con ↔ −0.3	Con ↔ −3.6
	AET = 15 M		149.4 ± 25.1/80.4 ± 7.6	**AET volume = 1,044 MET-min/wk**	AET ↓ −14.8*	AET ↓ −5.8*
	CET = 16 M		148.5 ± 15.1/82.8 ± 9.6	**Progressive, periodized CET × 3 d/wk (60 min/session)**: AET Ex R_x × 2 d/wk (AET × 1 d/wk land and water) + progressive RT (60 min/session): machine circuit, 7 RT exercises (4 upper/3 lower body) × 1 d/wk, 3 sets × 10–12 reps, 65 % 1-RM (5.0 MET); 8–10 reps, 75 % 1-RM (6.0 MET); 10–12 reps, 65 % 1-RM (5.0 MET)	CET ↓ −24.0**	CET ↓ −12.0*
				CET volume = AET (696) + RT (~330) = 1,026 MET-min/wk	*Group* > 0.05	*Group* > 0.05

Note: Baseline characteristics and SBP/DBP change values (mmHg) are reported as *M*ean ± *sd*, unless noted otherwise; *M*ean change and range = *M*ean (*M*in–*M*ax); *M*ean change and 95%CI interval = *M*ean (lower, upper 95%*CI*). *AET* Aerobic exercise training, *AIT* Aerobic interval training, *ART* After RT, *BRT* Before RT, *BP* Blood pressure (mmHg), *BMI* Body mass index (kg/m^2), *CE* Concurrent exercise group, *Con* Control group, *d/wk* days per week, *DBP* Diastolic BP, *ERT* Eccentric resistance training, *HR* Heart rate (beats per minute), *MHR* Maximal heart rate, *HRR* Heart rate reserve, *HTN* Hypertension, *M* Men, *MVC* Maximum voluntary contraction, *MET* Metabolic equivalent, *MET-min/wk* MET minutes per week, *Min/session* Minutes per session, *N* = Total number of exercise and control participants, *NBP* Normal BP, *PreHTN* Prehypertension, *PR-AET* Progressive AET, *PRT* Progressive RT, *SBP* Systolic BP, *THR* Target heart rate, *RPE* Rating of perceived exertion (6–20 Borg Scale), *Reps* Repetitions, *RT* Resistance training, VO_{2max} Maximal oxygen uptake, VO_{2peak} Peak oxygen uptake, *Wk* Weeks, *W* Women, *RM* Repetition maximum, *Yr* Year

[a]Health Status describes BP classification based on mean resting values and the general health of the study participants. "Healthy" indicates that participants were free from disease and/or other health conditions (other than high BP) during the intervention

[b]Treated = Indicates the percentage of subjects taking BP medications

[c]Training volume (MET-min/wk): CE = AE + RE; AE and RT = MET value × duration (min) × frequency (d/wk). MET values (i.e., absolute exercise intensity) were estimated using Table 7.1 from the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (9th Edition) [16]; MET values are adjusted by age for young (20–39 year), middle-aged (40–64 year) and older (≥65 year) samples

[d]The BP response to training (BP Change, mmHg), i.e., the difference in BP at *post*-training minus *pre*-training. A *downward arrow* (↓) indicates a significant reduction ($p \leq 0.05$), *double-headed arrow* (↔) indicates a non-significant change; the direction and magnitude of the reported change (mmHg) are provided where possible. *$p < 0.05$; **$p < 0.01$ difference from pre-training BP. The reported difference in BP change between intervention groups (including control) is indicated by *group* and associated *p*-value

adults with BP ranging from normal to established hypertension [46]. On average, concurrent training programs lasted 16 weeks (8–32 weeks) and consisted of 3 weekly, 60–70 min sessions (~30 min per exercise) performed at moderate to vigorous intensity aerobic exercise (~60–80 % VO_{2peak}) and moderate resistance exercise loads (60 to ~75 % 1-RM) (see Table 3.2). This "dose" of concurrent exercise significantly reduced resting BP ~6/4 mmHg among trials involving participants with normal BP to established hypertension, although these reductions varied widely for SBP (i.e., 5–35 mmHg) and DBP (i.e., 2–12 mmHg) (see Table 3.2).

Concurrent Exercise Training and Blood Pressure: The Influence of Baseline Characteristics

Concurrent training conferred the greatest antihypertensive benefit for participants with hypertension (~15/9 mmHg) [19, 21–26, 48] compared to prehypertension (~7/4 mmHg) [46, 49–51] and normal BP [25, 47], independent of concurrent training intervention characteristics. BP reductions were greater among older (≥60 years) (11/6 mmHg) compared to middle-aged and younger (18 to <60 years) samples (3/2 mmHg); trials involving older samples also reported the highest resting BP values (~144/83 mmHg). In addition, it seems that sex/gender may independently *or* interactively (with resting BP) modulate the magnitude of BP reductions that result from concurrent exercise training, although the results are mixed. For samples with prehypertension, BP was reduced to a greater extent among interventions involving all men (~6–10 mmHg) [49, 50, 52] than all women (~3–6 mmHg) [51, 53] and samples involving both men and women (~2–5 mmHg) [46, 54]. In contrast, samples with hypertension reduced resting BP by a similar magnitude for interventions involving all women (~10–35 mmHg) [19, 26] and all men (~12–24 mmHg) [23], and interestingly, trials involving men and women exclusively achieved greater BP benefit than interventions involved mixed samples (~4–8 mmHg) [21, 24, 48]. Finally, our review found concurrent training conferred greater BP benefit than previously reported by meta-analyses (~4–15 versus ~2 mmHg), and for the first time, showed that baseline characteristics, such as resting BP and sex/gender, may modulate BP reductions with concurrent training; patterns that were not observed for the PEH investigations (see Table 3.1).

In summary, concurrent exercise training has the potential to be a viable lifestyle therapy to lower BP, especially among those who need it the most (i.e., adults with the highest baseline values). Participants with normal BP received little or no antihypertensive benefit from concurrent training, while participants with pre-to-established hypertension achieved the greatest BP benefit. Furthermore, our review suggests that BP reductions following concurrent exercise training may be sex/gender dependent, an observation that has been reported for BP reductions following aerobic exercise training [27]. Future research should focus on identifying how patient characteristics, the FITT of the concurrent exercise intervention, and their interactions, modulate the BP response to training so that concurrent exercise can be more effectively used as antihypertensive therapy among adults with hypertension.

Exercise Modality and Blood Pressure: Aerobic Versus *Resistance* Versus *Concurrent Training*

Several trials involving healthy adults with normal BP to established hypertension [23, 49, 55–58] compared the antihypertensive effects of concurrent, aerobic, and dynamic resistance training to determine whether the *combined* effects of aerobic and resistance training yielded BP reductions that were equivalent to or greater than the magnitude reported with aerobic or dynamic resistance training alone (i.e., *additive* BP response). Specifically, five studies compared all three training modalities [46, 50, 56–58] and three trials compared concurrent to aerobic training [23, 49, 55] with mixed results. Of these eight studies, half observed similar reductions in BP following concurrent training (~4–8 mmHg) [23, 46, 49, 50] compared to aerobic or dynamic resistance training alone, while the other half found no effect of concurrent exercise training on resting BP [55–58] (see Table 3.2). A closer examination of the baseline sample characteristics and the components of the concurrent Ex R_x may provide additional insight into these inconsistent findings.

Tseng and co-investigators [50] had 40 young men with normal BP to prehypertension and obesity (~30 kg/m^2) perform ~45 min of moderate to vigorous intensity aerobic, resistance, or *combined* exercise training (aerobic and resistance exercise performed on *separate days*), 5 days weekly for 12 weeks (see Table 3.2). Tseng et al. found that resting BP was reduced by ~4–8 mmHg compared to baseline ($p<0.001$), and these reductions were similar following aerobic (6–8 mmHg), resistance (4–5 mmHg), and concurrent exercise training (6–7 mmHg, $p>0.05$). Sousa and co-investigators [23] also found that 60 min of moderate to vigorous intensity *combined* aerobic (2 days per week) and resistance (1 days per week) exercise training performed 3 days weekly for 32 weeks reduced BP compared to pre-training among older men with hypertension (24/12 mmHg, $p<0.01$), reductions that were similar to those achieved with aerobic training exclusively (15/6 mmHg, $p>0.05$).

Both Tseng and Sousa et al. prescribed aerobic and resistance exercise on *separate days*, but in contrast, Shaw and colleagues [49] evaluated the BP response to 45 min of moderate intensity aerobic or concurrent exercise (~22 min per session of aerobic *and* resistance exercise in the *same session*), 3 days weekly for 16 weeks among 37 sedentary young, African American men with prehypertension. Shaw et al. found SBP was reduced following aerobic and concurrent exercise training (4 versus 10 mmHg, $ps<0.05$), an effect that tended to be greater following concurrent than aerobic exercise ($p=0.097$).

Finally, Ho and colleagues [46] compared the antihypertensive effects of moderate to vigorous intensity aerobic, dynamic resistance, and concurrent exercise training (15 min per session of aerobic *and* resistance exercise) performed for 30 min, 5 days per week among 64 middle-aged adults (84 % women) with normal BP to prehypertension and obesity (~33 kg/m^2), and 8 % ($n=5$) of their sample were taking BP medications to control their high BP. Consistent with Shaw et al., they found SBP was reduced ~5 mmHg ($p=0.034$) after 12 weeks of concurrent training, but different from previous studies, resting BP was not reduced with isolated aerobic or

dynamic resistance training. Ho and colleagues reported a similar, non-significant trend for DBP (~2.9 mmHg, $p = 0.055$) (see Table 3.2).

Our review of the new and emerging research regarding the influence of exercise modality on the BP response to concurrent training shows mixed results. Four of the eight trials found concurrent exercise training conferred similar BP benefits to those achieved with aerobic and dynamic resistance training alone among young men with prehypertension [49] and obesity (6–10 mmHg) [50], older men with hypertension (12–24 mmHg) [23], and middle-aged adults with prehypertension and obesity (3–5 mmHg) [46], despite widely varying concurrent exercise training programs. In contrast, *combined* aerobic and resistance exercise performed on *separate days* did not reduce BP among middle-aged men [56] and women [57] with prehypertension; similar findings were reported following *concurrent* exercise training (i.e., on the *same day*) among middle-aged women [55] and older adults with pre-to-established hypertension [58] (see Table 3.2). Differences in baseline characteristics, the concurrent Ex R_x, and other unidentified intervention features may have contributed to the mixed findings we observed. Our review highlights the critical need to better understanding how baseline characteristics, concurrent exercise intervention features, and their interactions moderate the BP response to concurrent training before it can be used as antihypertensive lifestyle therapy.

Concurrent Training and Blood Pressure: The Influence of Exercise Modality Order

Of the 22 concurrent exercise training trials that qualified for this review, 11 ordered aerobic *before* resistance exercise [24, 25, 46–49, 52–55, 58], four ordered aerobic *after* resistance exercise [19, 21, 26, 51], two prescribed concurrent exercise using circuit-style training (i.e., alternating bouts of aerobic and resistance exercises) [22, 59], and five prescribed aerobic and resistance exercises on *separate days* (i.e., *combined* exercise training) [23, 50, 56, 57, 60] (see Table 3.2). On average, BP was reduced by a larger magnitude among trials that ordered aerobic *after* (4–35 mmHg) than *before* (2–15 mmHg) or *during* (i.e., circuit) (DBP ~10 mmHg) resistance exercise, and when compared to *combined* aerobic and resistance exercise training (4–6 mmHg). However, only one concurrent training intervention directly compared the influence of exercise modality order on resting BP within the same group of participants. Okamoto and colleagues [47] asked 33 young, healthy adults (67 % women) with normal BP to perform no exercise (i.e., control) or 8 weeks of moderate intensity aerobic exercise (60 % HR_{max}) *before* versus *after* heavy dynamic resistance exercise (80 % 1-RM) twice weekly (see Table 3.2). There were no significant changes in resting BP with concurrent training, regardless of exercise modality order.

Given that BP reductions appear to occur as a function of baseline values (i.e., the law of initial values as described in Chap. 1), the absence of BP benefits reported by Okamoto and colleagues are not unexpected as study participants had normal BP,

but most importantly, their results cannot be generalized to middle-aged and older adults with hypertension. Unfortunately, no concurrent training interventions directly compared the influence of exercise modality order among adults with pre-to-established hypertension. Nonetheless, when we compared the magnitude of the BP reductions achieved with concurrent training by exercise modality order among adults with hypertension, there appeared to be similar DBP benefit when aerobic was performed *after* (4–12 mmHg) [19, 21, 26], *before* (2–10 mmHg) [24, 25, 54], and *during* (~10 mmHg) dynamic resistance exercise [22]. A wider range was reported for SBP reductions among trials ordering aerobic *after* (5–35 mmHg) compared to *before* (8–15 mmHg) dynamic resistance exercise. Only two trials involving adults with hypertension prescribed *combined* aerobic and resistance training on *separate days*, and with mixed results. As discussed earlier, Sousa et al. [23] reported large BP reductions following 32 weeks of *combined* aerobic and resistance training (24/12 mmHg). In contrast, Vianna and co-investigators [60] found 16 weeks of *combined* aerobic (2 days per week) and dynamic RT (1 day per week) did not reduce resting BP among older adults (66 % women) with hypertension, despite using an Ex R_x similar to Sousa and colleagues (see Table 3.2).

In summary, the BP reductions associated with concurrent exercise training seem to be independent of exercise modality order, which is consistent with earlier observations regarding PEH and acute concurrent exercise. On the other hand, greater antihypertensive benefits may be achieved when aerobic and resistance exercises are executed *in a single exercise session* (*i.e.*, *concurrently*) than on *separate days* (*i.e.*, *combined*). Due to the paucity of trials directly comparing the influence of exercise modality order (i.e., aerobic is performed *before* versus *after* versus *during* resistance exercise) and training program type (i.e., *concurrent* versus *combined*) among adults with hypertension, it has yet to be determined if greater BP benefits can be achieved or optimized with a specific exercise order or training program, or if the antihypertensive effects of concurrent exercise training occur independently of these special FITT considerations.

Concurrent Training and Blood Pressure: The Influence of Exercise Intensity and Volume

New and emerging evidence discussed earlier in the chapter suggests that PEH following acute concurrent exercise may not be a low threshold event that is potentiated by combinations of higher intensity aerobic exercise [30] and lower dynamic resistance exercise loads with higher repetitions [32]. On the other hand, these observations involved predominantly young samples with normal BP; therefore it is unclear whether these same BP lowering patterns will emerge for middle-aged and older adults with high BP following concurrent exercise training.

On average, trials involving participants with normal BP to prehypertension combined moderate (~58 % HR reserve; 63 % HR_{max}) [46, 47, 49–55, 58, 59] to vigorous (~70 % VO_{2peak}) intensity aerobic exercise [25, 56, 57] and moderately heavy resistance

training loads (8 exercises at 60–80 % 1-RM) for 3–4 sets of 6–12 repetitions with 1–2 min rest intervals between sets. Trials involving adults with hypertension also prescribed moderate (43 % HR reserve; 66 % HR_{max}) to vigorous intensity aerobic exercise (~64 % VO_{2peak}), but in combination with low (40–50 % 1-RM) [21, 22, 24, 48] to moderately heavy resistance training loads (6 exercises at 60 to ~80 % 1-RM) [19, 23, 25, 26, 60] for 2 sets of ~15 repetitions with ≤1 min rest intervals between sets. Similar BP reductions were observed among adults with pre-to-established hypertension following concurrent exercise training that consisted of aerobic and resistance exercise performed at low to moderate (~7/7 mmHg) [22, 24, 26, 48] and moderate intensity (~8/3 mmHg) [19, 21, 49, 51]; while combinations of moderate to vigorous intensity aerobic exercise and moderate to heavy resistance training loads yielded the largest BP reductions (~10/7 mmHg) [19, 23, 25, 46, 50]. For trials involving adults with established hypertension, BP reductions occurred in a dose–response pattern as a function of concurrent exercise intensity, where moderate to vigorous intensity concurrent training provided the greatest BP reductions (~23/11 mmHg) [19, 23, 25] compared to concurrent training performed at moderate (~14/5 mmHg) [19, 21] and low to moderate intensity (~7/7 mmHg) [22, 24, 26, 48].

All but one trial involving participants with hypertension found that concurrent exercise training reduced resting BP. As previously discussed, Vianna and colleagues [60] found resting BP was not lower among 70 older adults (66 % women) with hypertension after 16 weeks of *combined*, moderate intensity aerobic (2 days per week) and resistance (1 day per week) exercise training, performed for 60 min per session, 3 days per week. Despite a similar experimental design as Sousa et al. [23], the study participants trained for a shorter duration (16 versus 32 weeks), at lower exercise intensity (rating of perceived exertion [RPE] rating 12 versus 15), and achieved a lower volume of weekly exercise (540 versus 1,026 MET-min per week), comparatively. Several trials achieved similar weekly volume as Vianna et al., but they prescribed *concurrent* aerobic and resistance exercise (i.e., executed in the *same session*) [26] and implemented a longer training period (24–25 weeks) [24, 48], despite being performed at lower or equivalent exercise intensities (see Table 3.2). These examples not only highlight the important and influential role of concurrent exercise intensity independently, but also interactively with other FITT variables of the concurrent training intervention (i.e., *frequency* × *duration* = *concurrent exercise volume*, MET-min per week).

Consistent with the ACSM Ex R_x recommendations for apparently healthy adults [1], several trials have showed greater BP lowering effects with greater "doses" *or* higher volumes of concurrent exercise (i.e., 500 to ≥1,000 MET-min per week), which is equal to the summation of weekly volume for the aerobic and resistance exercise components (defined earlier in Key Terminology and Basic Concepts). Adults with pre-to-established hypertension that exercised 3–4 days per week and achieved >800 MET-min per week (~1,140 MET-min per week) lowered resting BP by ~10/5 mmHg [19, 21, 23, 25, 46, 49, 50, 52–54, 56, 57], a greater magnitude than those (~3 mmHg) achieved with a lower training frequency (2–3 days per week) and exercise volume (~521 MET-min per week) [22, 24, 48, 51, 52, 55, 58–60]. These effects were more pronounced among participants with hypertension (~22/10 mmHg),

who achieved the greatest BP reductions with high volumes of concurrent exercise (~1,120 MET-min per week), performed 3 days weekly for ~80 min per session (aerobic and resistance exercises lasted ~37 and ~43 min per session) [19, 21, 25].

Overall, concurrent exercise training performed at low to moderate intensity was effective at lowering resting BP by ~3–14 mmHg among adults with pre-to-established hypertension. However, the greatest antihypertensive benefits were conferred with moderate to vigorous intensity aerobic exercise and moderate to heavy resistance training loads for adults with high BP (7–10 mmHg) and established hypertension (11–23 mmHg). Finally, high volumes of concurrent exercise (>800 MET-min per week) performed 3 days weekly elicited greater BP reductions (~5–10 mmHg) than lower concurrent exercise training volumes (>800 MET-min per week) achieved with twice weekly training (~3 mmHg) among adults with high BP.

Clinical Implications and Importance

Exercise Prescription Recommendations

The FITT-VP Exercise Prescription

In the absence of consensus regarding the acute and chronic effects of concurrent exercise on hypertension, the following FITT Ex R_x recommendations including Volume and Progression (i.e., FITT-VP) will be based upon the information obtained and synthesized for this systematic review of the literature that is summarized in Tables 3.1 and 3.2, along with new and emerging research that has been discussed within this Chapter. Although this Chapter discusses the *concurrent* or *combined* effects of aerobic and resistance exercise, Chaps. 1 and 2 provide detailed information on the FITT Ex R_x recommendations for aerobic and resistance exercise performed alone among adults with hypertension.

Frequency. *Concurrent* and *combined* exercise training reduced BP among adults with high BP, but resting BP was reduced to greater levels when aerobic and resistance exercises were performed *concurrently*, in the *same session*, on 3 or more days per week (5–10 mmHg) [19, 21, 25, 26, 49, 51–55, 58] compared to twice weekly concurrent training (3–5 mmHg) [22, 24, 48, 52, 59] and *combined* exercise training (3–6 mmHg) [23, 46, 50, 56, 57, 60]. Adults with hypertension achieved the greatest antihypertensive benefit from concurrent training when it was performed 3 days weekly (~8–17 mmHg).

Accordingly, *concurrent* exercise should be performed at least 3 days per week, and these recommendations are consistent with the ACSM Ex R_x recommendations for exercise and hypertension [3].

Intensity. Combinations of low to moderate intensity aerobic exercise (i.e., 40–<60 % oxygen consumption reserve [VO_2R] or HR reserve; RPE of 11–13 on the 6–20

Borg Scale) and low to moderately heavy dynamic resistance exercise loads (~50–80 % 1-RM) were effective in lowering resting BP among adults with pre-to-established hypertension (~3–14 mmHg), and again are consistent with the ACSM Ex R_x recommendations for exercise and hypertension [3].

New and emerging research involving adults with hypertension indicates that the BP reductions resulting from concurrent exercise occur in a dose–response pattern as a function of intensity; BP reductions were greatest following combinations of moderate to vigorous intensity aerobic exercise and moderate to heavy dynamic resistance exercise loads among adults with high BP (7–10 mmHg) and established hypertension (11–23 mmHg) [19, 23, 25].

Time. *Concurrent exercise* training performed for ~45–80 min per session involving 20–40 min of aerobic and 15–40 min of resistance exercise reduced resting BP ~6–18 mmHg among adults with pre-to-established hypertension. Trials involving adults with hypertension prescribed 5–7 resistance exercises that targeted the major muscle groups of the upper and lower body using low (40–50 % 1-RM) to moderately heavy resistance training loads (60–80 % 1-RM) for 2–3 sets of 10–20 repetitions with ~1 min rest intervals between sets.

Accordingly, adults with hypertension should performed *concurrent* exercise for 45–80 min per session, consisting of ~30 min of aerobic exercise and 15–40 min of dynamic resistance exercise. This "dose" of concurrent exercise aligns with the ACSM Ex R_x recommendations for exercise and hypertension [3] and incorporates the guidelines put forth by the ACSM for resistance training for healthy adults [18].

Type. Concurrent exercise training conferred similar antihypertensive benefit for adults with hypertension when aerobic exercise was performed *after* (~5–35 mmHg) [19, 21, 26], *before* (2–15 mmHg) [24, 25, 54], and *during* (~10 mmHg) [22] dynamic resistance training.

Therefore, emphasis should be placed on aerobic activities such as walking, jogging or cycling, and dynamic resistance exercise should involve machine weights, free weights, or circuit-style resistance training, regardless of exercise modality order.

Volume. Adults with high BP that exercised 3–4 days per week and achieved >800 MET-min per week lowered resting BP by ~10/5 mmHg [19, 21, 23, 25, 46, 49, 50, 52–54, 56, 57], a greater magnitude than those (~3 mmHg) achieved with a lower training frequency (2–3 days per week) and exercise volume (~521 MET-min per week) [22, 24, 48, 51, 52, 55, 58–60]. These effects were more pronounced among participants with hypertension (~22/10 mmHg), who achieved the greatest BP reductions with high volumes of concurrent exercise (~1,120 MET-min per week).

Therefore, concurrent exercise training programs designed to lower high BP should achieve a weekly volume of ~800–1,200 MET-min per week through combinations of low to moderate intensity aerobic exercise and moderate dynamic resistance exercise loads. These recommendations are consistent with those put forth by the ACSM for

developing and maintaining health and fitness in apparently healthy adults (500–≥1,000 MET-min per week) [1], and this "dose" conferred the greatest antihypertensive benefits among adults with pre-to-established hypertension.

Progression. The FITT-VP principle of Ex R_x relating to progression for healthy adults generally applies to those with hypertension [1]. Modifications to the concurrent Ex R_x and training progression should be considered if there are changes in BP control, antihypertensive medications, and/or in the presence of target organ disease and/or other comorbidities [16].

The progression of concurrent exercise should be gradual for most people with hypertension, especially regarding increases in concurrent exercise intensity and volume [16]. The readers are directed to Chaps. 1 and 2 for additional information regarding special considerations for aerobic and resistance exercise alone.

Conclusion

Concurrent exercise training allows for improvements in cardiorespiratory fitness, muscle strength, and other cardiometabolic health biomarkers to be achieved simultaneously [10–15]. In this Chapter we show that the BP reductions resulting from acute (3–8 mmHg) [19, 20] and chronic (9–15 mmHg) [19, 21–26, 48] concurrent exercise are similar to those achieved with isolated aerobic exercise (5–8 mmHg) [27, 43, 44] and exceed those reported with isolated dynamic resistance exercise (1–2 mmHg, *ns*) [27, 33] for populations with hypertension. BP reductions following concurrent exercise seem to be independent of exercise modality order (i.e., aerobic is performed *before* versus *after* versus *during* resistance exercise), but greater antihypertensive benefits may be achieved when aerobic and resistance exercises are executed *in a single exercise session* (*i.e.*, *concurrently*) than on *separate days* (*i.e.*, *combined*). Furthermore, our review showed that BP was reduced in a dose–response pattern as a function of concurrent training intensity among adults with hypertension, where combinations of moderate to vigorous intensity aerobic exercise and moderate dynamic resistance training loads conferred the greatest BP benefit. Nonetheless, the literature upon which these conclusions were drawn is limited. Additional research is needed to establish the efficacy of concurrent exercise as antihypertensive therapy so that it can be prescribed optimally to those populations that stand to benefit most from its BP lowering effects. Furthermore, the examination of the antihypertensive benefits of concurrent exercise should expand beyond the confines of the laboratory into conditions of everyday living by integrating ambulatory BP monitoring.

Key Points and Resources

- Limited available evidence shows that acute concurrent exercise elicits PEH by a similar magnitude (3–9 mmHg) among young, healthy adults with normal BP [8, 31, 32] and middle-aged to older adults with established hypertension [19,

20]. In contrast, concurrent exercise training conferred the greatest antihypertensive benefit for participants with hypertension (~15/9 mmHg) [14, 16–21, 43] compared to prehypertension (~7/4 mmHg) [41, 44–46] and normal BP [20, 42], independent of concurrent training intervention characteristics. New and emerging research from our review suggests that baseline characteristics (i.e., resting BP, sex/gender, age) may modulate BP reductions with training; patterns that were not observed for the PEH investigations.

- Acute concurrent exercise elicits PEH to a similar magnitude as reported after aerobic and resistance exercise alone when compared directly within the same group of young adults with normal BP (~3–6 mmHg) [8, 31, 32]; a larger magnitude than previously reported after isolated aerobic and resistance exercise for populations with normal BP. For adults with hypertension, the magnitude of PEH was consistent with those associated with aerobic exercise exclusively but greater than those reported with resistance exercise alone. New and emerging research regarding the influence of exercise modality on the BP response to concurrent training is mixed, but several trials reported similar antihypertensive effects to those achieved with aerobic and dynamic resistance training alone among adults with high BP [23, 46, 49, 50]. These inconsistencies highlight the need to better understand how baseline characteristics and features of the exercise intervention moderate the BP response to concurrent training before it can be used as antihypertensive lifestyle therapy.
- Acute concurrent exercise consisting of moderate to vigorous intensity aerobic exercise and low to moderately heavy resistance exercise loads elicited PEH among adults with normal BP (3–11 mmHg) and established hypertension (3–8 mmHg), independent of exercise modality order. Concurrent exercise training performed at low to moderate intensity reduced BP among adults with pre-to-established hypertension (3–14 mmHg), however, moderate to vigorous intensity aerobic exercise and moderate dynamic resistance training loads performed *concurrently* (i.e., on the *same day*) conferred the greatest antihypertensive benefit among adults with established hypertension (11–23 mmHg).
- Finally, adults with hypertension reduced BP to the greatest extent with higher volumes of concurrent exercise (>800 MET-min per week) performed 3 days weekly (~5–10 mmHg) than lower concurrent training volumes (<800 MET-min per week) achieved with twice weekly training (~3 mmHg).
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Appendix 3.A. Full Search Strategy for PubMed (Including Medline)

Search Dates for Randomized Controlled Trials: **From inception—December 10**, **2014**.

Hits: **478**

("mean arterial" OR "blood pressure"[mesh] OR "blood pressure" OR "blood pressures" OR "arterial pressure" OR "arterial pressures" OR hypertension OR hypotension OR normotension OR hypertensive OR hypotensive OR normotensive OR "systolic pressure" OR "diastolic pressure" OR "pulse pressure" OR "venous pressure" OR "pressure monitor" OR hypotension OR PEH OR "postexercise hypotension" OR "pre hypertension" OR "bp response" OR "bp decrease" OR "bp reduction" OR "bp monitor" OR "bp monitors" OR "bp measurement")

AND ("exercise"[mesh] OR exercise OR exercises OR "combination training" OR "combined exercise" OR "concurrent exercise" OR running OR bicycl* OR treadmill* OR "endurance training" OR "speed training" OR "interval training" OR plyometric* OR "HIIT" OR "training duration" OR "training frequency" OR "training intensity" OR "aerobic endurance")

AND ("weight lifting" OR "weight training" OR "resistance training" OR "strength training" OR "circuit training" OR "training duration" OR "training frequency" OR "training intensity" OR "combined training")

AND ("randomized controlled trial"[pt] OR controlled clinical trial[pt] OR "randomized controlled trial"[publication type] OR random allocation[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR "latin square"[tw] OR random*[tw] OR research design[mh:noexp] OR "comparative study"[publication type] OR "evaluation studies"[publication type] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controlled[tw])

NOT ("DASH"[tiab] OR cancer OR neoplasms OR review[pt] OR fibromyalgia OR alzheimers OR alzheimer OR pregnant OR pregnancy OR "obesity/drug therapy"[mesh] OR "diet therapy"[mesh] OR "diet therapy"[subheading] OR caffeine OR "eating change" OR "activities of daily living" "dehydration" OR "dehydrate" OR "dehydrated" OR "dietary salt" OR sodium OR epilepsy OR influenza OR flu OR pneumonia OR septicemia OR arthritis OR hiv OR "Acquired Immunodeficiency Syndrome" OR meningitis OR "substance abuse" OR alcoholism OR "drug abuse" OR "Cross-Sectional Studies"[MeSH Terms] OR "Prospective Studies"[MeSH Terms] OR "epidemiology"[Subheading]). **Filters activated**: **Humans**, **Adult**: **19+ years**

Filters activated: Humans, Adult: 19+ years

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Chapter 4
The Impact of Exercise and Physical Fitness on Blood Pressure, Left Ventricular Hypertrophy, and Mortality Among Individuals with Prehypertension and Hypertension

Peter Kokkinos

Abbreviations

ACSM	American College of Sports Medicine
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
JNC 7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNC 8	The Eighth Joint National Committee on the Management of High Blood Pressure
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
METs	Metabolic energy equivalents
SBP	Systolic blood pressure
United States	US

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Introduction

Clinical Significance of Elevated Blood Pressure

Chronic hypertension, defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, is a major and the most common risk factor for mortality and development of cardiovascular disease (CVD) [1, 2]. Approximately one third of the adult population in the United States (US) (78 million) has hypertension [3] and about 1 billion worldwide with an estimated 60 % increase by the year 2025 [4].

Recent evidence supports that a progressive increase in CVD risk extends below a blood pressure (BP) of 140/90 mmHg, traditionally defined as the threshold level for hypertension. Increased risk is evident beyond BP levels of 115/75 mmHg, and doubles for every 20 mmHg incremental increase in SBP or 10 mmHg in DBP [5]. Consequently, in 2003 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) classified BP levels of 120–139 mmHg for SBP and /or 80–89 mmHg for DBP as prehypertension [1].

Prehypertension is associated with traditional CVD risk factors, increased CV events, and target organ damage [6–8]. Approximately 42 million men and 28 million women (37 % of the adult US population) have prehypertension, a frequent precursor of hypertension [2, 9]. The rate of progression from prehypertension to hypertension is positively associated with age, baseline BP, and co-morbidities [10–12]. For individuals ≥65 years of age, the 4 year incidence rate of progression to hypertension is estimated to be 26 % for those with BP between 120 and 129 or 80–84 mmHg and 50 % for those with BP 130–139 or 85–89 mmHg [10]. In one's lifetime, the risk for developing hypertension among middle-aged and older individuals is 90 % [10]. Recent evidence also suggests that hypertension is an outcome of lifestyle factors, including physical inactivity [11–14].

Chronically elevated BP leads to structural changes of the left ventricle, consisting of increased cardiac wall thickness and left ventricular mass (LVM) and reduced left ventricular chamber size, a condition known as concentric left ventricular hypertrophy (LVH) [15, 16]. Increased LVM, especially when characterized by concentric geometry, is considered an independent predictor of CV events and a risk factor for mortality [17, 18].

Reductions in BP with most antihypertensive agents are associated with LVH regression and improvement in CV prognosis. The degree of LVH regression is directly related to the degree of BP reduction, suggesting at least in part, that the stimulus for LVH is pressure overload [19–22]. Exercise-related BP reductions in individuals with mild to moderate hypertension have been documented by a plethora of studies and findings have been summarized by several reviews and meta-analysis [23–27]. In general, these studies support that structured aerobic exercise training programs of moderate intensity or increased physical activity of adequate volume and intensity result in an independent reduction of approximately 4–10 mmHg in SBP and 3–8 mmHg in DBP for individuals with Stage 1

hypertension, regardless of age or gender. Relatively small reductions in BP achieved by antihypertensive therapy lead to substantial health benefits and mortality risk reduction [3]. It is reasonable to assume that similar exercise-induced reductions in BP should lead to similar health benefits. See Chapter 1 for additional information on aerobic exercise training.

Purposes of this Chapter

The main objectives of this chapter are to present the current consensus on: (1) the preventive aspects of exercise and physical fitness on the age-related progressive increase in BP and development of hypertension; (2) the interactions among exercise, BP, and LVH; and (3) the association between exercise capacity and mortality risk in individuals with prehypertension and hypertension.

Key Terminology and Basic Concepts

Ambulatory Blood Pressure Monitoring

Ambulatory BP monitoring measures BP at regular intervals over a 24 h period under conditions of daily living. Ambulatory BP monitoring minimizes the "white coat effect" which can overestimate BP, especially in susceptible people.

Exaggerated Blood Pressure

An increase in SBP >200 mmHg or DBP >110 mmHg during sub-maximal and maximal exercise is considered an exaggerated BP response [28–31].

Prehypertension

SBP of 120–139 mmHg and/or DBP 70–89 mmHg is classified as prehypertension.

Cardiac Hypertrophy and Left Ventricular Hypertrophy

Structural changes of the left ventricle, consisting of increased cardiac wall thickness and LVM and reduced left ventricular chamber size are referred to as concentric hypertrophy.

Left Ventricular Mass and Left Ventricular Mass Index

The estimated weight of the heart in grams is referred to as LVM. The LVM is generally adjusted for body size (body surface area) or height ($m^{2.7}$) and referred to as LVM Index.

Systematic Review Methods

A systematic electronic search of the literature was performed using PubMed on aerobic exercise and its impact on BP and cardiac hypertrophy. The search was an update of a previous review published in 2010 regarding exercise and clinical outcomes [23]. The search included human studies of adults 19 years and older that were published in English, had a control/comparison group, and were published between January 1, 2000 and August 28, 2014. This search identified a total of 1,685 reports. Further review by title yielded 210 potentially qualifying studies. These 210 studies were then reviewed by title and abstract of which 121 potential studies remained. These 121 studies were reviewed by full-text, yielding 102 qualifying studies. Of these 92 studies, the author self-selected those most relevant to the purposes of this chapter.

Relevant Research

Preventive Aspects of Exercise and Physical Fitness

The progressive increase in BP and consequent development of hypertension do not appear to be a fundamental feature of human aging, but the outcome of lifestyle factors such as diets high in salt and fat, excess body weight, and physical inactivity [11–14]. Conversely, low salt and/or low fat diets, weight loss, and increased physical activity contribute significantly to BP control [11–14, 32–35]. The preventive aspects of physical activity in particular have been summarized recently [36]. Recent evidence from a large epidemiologic study supports that the physical fitness status of the individual is inversely related to the rate of progression from prehypertension to hypertension. Increased exercise capacity, as reflected by peak metabolic energy equivalents (METs) achieved during a standardized exercise test, was inversely associated with the rate of progression to hypertension in 2,303 middle-aged, male veterans with prehypertension followed for over 9.2 years. Compared to the individuals with the highest exercise capacity (>10 METs), the multivariate-adjusted risk for developing hypertension was 36 % higher for those with an exercise capacity of 8.6–10 METs; 66 % for those between 6.6–8.5 METs, and 72 % higher for individuals who achieved ≤6.5 METs [33]. An inverse, dose

response association between the risk for developing hypertension and recreational physical activity levels was also reported by a recent meta-analysis of 13 prospective cohort studies [27]. This is particularly important for individuals with prehypertension, since antihypertensive medications are generally not prescribed to lower BP or prevent the progression to hypertension. Thus, the American College of Sports Medicine (ACSM) and the Eighth Joint National Committee on the management of high BP (JNC 8) recommend lifestyle modifications as initial lifestyle therapy to prevent, treat, and control hypertension [25, 37].

Exercise Effects on Blood Pressure and Cardiac Hypertrophy

Structural changes of the left ventricle, consisting of increased cardiac wall thickness and LVM and reduced left ventricular chamber size (concentric hypertrophy) are often manifestations of cardiac injury or hypertension [15, 16]. Increased LVM especially when characterized by concentric geometry is considered an independent predictor of CV events for mortality [17, 18]. Conversely, a reduction in BP by different antihypertensive agents is associated with LVH regression and improvement in prognosis. The degree of LVH regression is directly related to the degree of BP reduction, suggesting, at least in part, that the stimulus for LVH is pressure overload [19–22].

In this regard, it is reasonable to assume that exercise-related reductions in BP may have similar impact on LVH regression. Support for this premise is provided by several interventional studies [38–43]. In our study of individuals with Stage 2 hypertension [38], there was a significant reduction in cardiac wall thickness and LVM index (LVM adjusted for body surface area or height) after 16 weeks of aerobic training; reductions similar in magnitude to that observed with most antihypertensive medications. Similar findings were noted in a cohort of overweight women (n = 45) and men (n = 37) undergoing 6 months of exercise training or behavioral modification for weight loss versus a control. Participants in both interventions (exercise and weight loss groups) exhibited significant reductions in BP and cardiac wall thickness when compared to the control group [39]. Significant reductions in cardiac wall thickness and LVM index with no significant changes in chamber size were also reported in 16 patients with hypertension after 24 weeks of aerobic exercise training [41]. Similar findings were also observed in 11 middle aged subjects with hypertension who exercised with no changes in the control group [40]. A trend towards lower LVM was also noted in middle-aged men and women with hypertension after aerobic exercise training [43]. Finally, in the Ambulatory Recording Venetia Study (HARVEST) [42], BP decreased in physically active individuals (n = 173) and increased slightly in the sedentary group (n = 281), during a median follow-up of 8.3 years. In addition, physically active individuals were less likely to develop LVH compared to their sedentary counterparts.

In contrast, no exercise-related changes in left ventricular mass were observed in 23 individuals with obesity and a mean baseline BP 131/84 mmHg, despite

significant reductions in BP [44]. Similarly, no structural or functional cardiac changes were noted after 24 weeks of aerobic exercise and resistance training in 51 individuals with overweight and obesity and an untreated baseline SBP of 130–150 mmHg or DBP 85–99 mmHg [45]. However, the findings of these two studies should be interpreted with caution. In the one study [45], it is not clear as to how many of the participants were truly hypertensive, since the baseline BP range was 130–150 mmHg for SBP or 85–99 mmHg for DBP. The exercise intervention was also a mixture of both aerobic and resistance training. Moreover, based on baseline LVM index normal values (63.6 g m^{-2}), cardiac remodeling was absent. Thus, exercise or any other intervention cannot "fix" what is not broken. In the other study [44], a closer scrutiny of the findings revealed that the LVM index decreased by approximately 8 % (baseline of 153 g m^{-2} at baseline versus 141 g m^{-2} after exercise) in the exercise group, and increased by approximately 10 % (baseline of 141g m^{-2} at baseline versus155 g m^{-2} after exercise) in the control group. Cardiac wall thickness also decreased after exercise, although statistical significance was not achieved, perhaps due to relatively small number of patients studied (n = 7). These authors also reported that the exercise group had significantly greater wall thickness at baseline, and this was the only group to show a reduction in wall thickness after 12 weeks of exercise training. Collectively, the limited evidence regarding the effects of aerobic exercise on cardiac remodeling supports that LVH regression is likely to occur, if the proper exercise modality is used, in populations with LVH. However, more interventional studies are needed to confirm these findings.

Clinical Significance of the Blood Pressure Response to Peak Exercise

Normally, during exercise, SBP rises progressively with increased workload (a dose–response association) and plateaus at approximately 180–200 mmHg, while DBP remains close to or even lower than resting levels [23]. However, in some individuals with prehypertension and established hypertension, SBP rises disproportionately to the workload, achieving levels beyond 200 mmHg during submaximal and maximal exercise. Although a definitive threshold for an abnormal BP response to exercise has not been established, it is generally accepted that an increase in SBP >200 mmHg or DBP >110 mmHg at sub-maximal or peak exercise is considered an exaggerated BP response to exercise [28–31].

The exaggerated rise in the SBP response at peak exercise has been associated with LVH [28, 29, 46], future hypertension [47, 48], and CVD morbidity and mortality [30, 31]. However, others have found no relationship [49, 50], and in one study involving adults evaluated for coronary artery disease (CAD), an exaggerated SBP response at peak exercise (≥210 mmHg) was associated with lower likelihood of angiographically determined severity of CAD and lower mortality rates [51].

In some aspects, this finding may be misleading and further clarification is necessary. In individuals with relatively severe CAD, myocardial ischemia is likely to ensue, especially at maximal or near maximal workloads. This in turn will lead to an attenuated inotropic response or a lower SBP than expected, and often termination of exercise. Thus, under these conditions, a lower SBP achieved during peak exercise could be indicative of more severe CAD. However, under similar conditions and similar populations without significant CAD, myocardial perfusion is preserved even at peak exercise workload, myocardial contractility is sustained, and relatively higher workloads are achieved. Higher workloads are likely to yield a higher SBP response at peak exercise as shown when comparisons were made between endurance athletes and sedentary individuals [52]. Thus, in relatively healthy populations, the SBP response to peak exercise may not be an indicator of severity of CAD and related future events.

Clinical Significance of the Blood Pressure Response to Submaximal Exercise

Myocardial ischemia among individuals without significant CAD is not likely to occur at substantially lower workloads. Therefore, myocardial contractility and consequently the SBP response at a relatively low submaximal workload of approximately 4–5 METs are preserved. Thus, an exaggerated BP response at this workload is likely to reflect a compromised cardiovascular system, and therefore may have a greater potential to predict the presence of LVH or the risk for developing LVH. This hypothesis was tested in 790 middle aged, individuals with prehypertension [53]. Participants underwent echocardiographic studies to assess cardiac structure and function, 24 h ambulatory BP monitoring, and a standard exercise stress test (Bruce protocol) to assess peak exercise capacity and exercise BP. The investigators reported a strong association between the BP response at the submaximal workload of approximately 4–5 METs and LVH. More specifically, individuals who achieved a SBP $\geq$150 mmHg at an exercise intensity of 4–5 METs had a significantly higher LVM index (49.8 ± 10.2 g $m^{-2.7}$ vs. 36.6 ± 6.3 g $m^{-2.7}$; $p < 0.001$) and lower exercise capacity (7.7 ± 1.6 vs. 9.0 ± 1.1 METs; $p < 0.001$) compared to those with a SBP below this level. Furthermore, the risk of having LVH increased fourfold for every 10 mmHg rise in SBP beyond the threshold of 150 mmHg at approximately 5 METs. It is important to emphasize that resting BP in these two groups (i.e., SBP <150 mmHg and $\geq$150 mmHg) was similar. Lin et al. reported similar findings among 49 individuals with hypertension at the exercise workload of approximately 7 METs. SBP at this workload was directly and independently associated with cardiac wall thickness and LVM index. This association was stronger than with office BP and 24 h ambulatory BP [54].

The clinical significance of the BP response to submaximal workloads of approximately 4–5 METs is that it reflects BP during most daily activities. This is

supported by the similarity between the BP of individuals with prehypertension (n = 790) at the workload of 4–5 METs (148 ± 12 mmHg) and daytime ambulatory BP (144 ± 11 mmHg) [55]. Thus, the association between SBP during physical exertion and LVM [53, 55] suggests that the daily exposure to relatively high BP (SBP ≥ 150 mmHg) provides the impetus for an increase in LVM even among those with prehypertension [36].

Physical Fitness and the Blood Pressure Response to Exercise

A noteworthy finding of the above studies [53, 55] was that the peak exercise capacity of individuals with a SBP response ≥150 mmHg at the workload of approximately 4–5 METs was significantly lower when compared to those with an exercise BP <150 mmHg (i.e., 7.7 ± 1.6 METs vs. 9.0 ± 1.1 METs, respectively). This finding suggests that the BP response to exercise may be modulated by the physical fitness level of the individual. In this regard, the investigators reported an inverse association between exercise capacity, the BP response to exercise, and LVM [53, 55]. Furthermore, the SBP of physically fit individuals at an exercise intensity of approximately 5 METs was significantly higher for the High-Fit (155 ± 14 mmHg) compared to Moderate-Fit (146 ± 10 mmHg) and Low-Fit (144 ± 10 mmHg) individuals. Similarly, Low-Fit individuals had significantly higher LVM index (48 ± 12 g $m^{-2.7}$) compared to Moderate-Fit (41 ± 10 g $m^{-2.7}$) and High-Fit (41 ± 9 g $m^{-2.7}$). In addition, for every 1-MET increase in the workload achieved, there was a 42 % reduction in the risk for LVH [53]. Finally, in a randomized controlled study, 16 weeks of aerobic training resulted in significantly lower BP at approximately 3 and 5 METs [56] (Fig. 4.1) and a significant regression in LVM index [38] (Fig. 4.2).

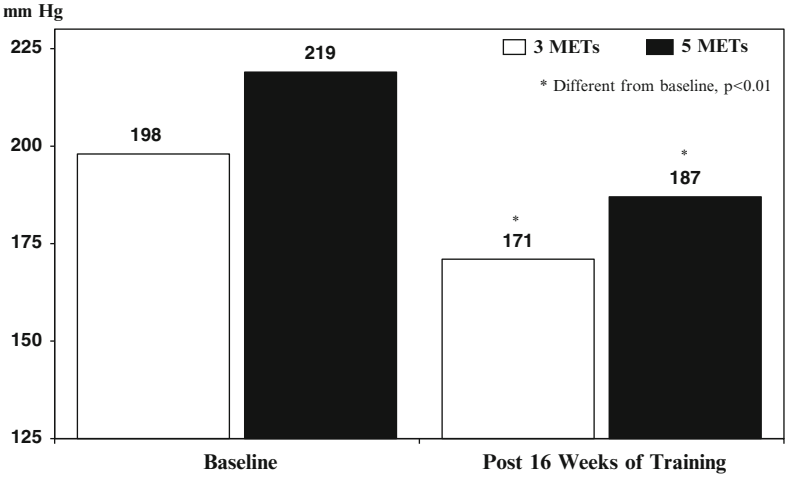

Fig. 4.1 Systolic blood pressure (SBP) at approximately 3 and 5 metabolic energy equivalents (METs) at baseline and after 16 weeks of aerobic exercise (Adapted from ref. [56])

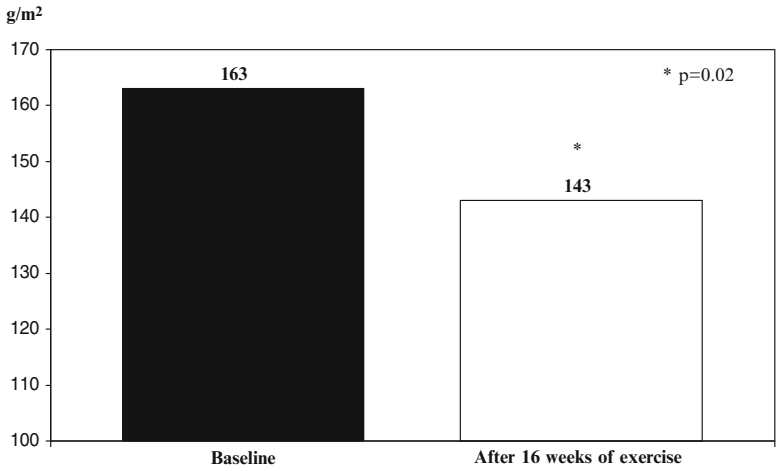

Fig. 4.2 Left ventricular mass (LVM) index at baseline and after 16 weeks of aerobic exercise (Adapted from ref. [38])

Collectively, the aforementioned findings suggest the following: (1) the BP response at the workloads of approximately 4–5 METs reflects the BP during daily activities; (2) this daily exposure to an exaggerated BP response at relatively low workloads encountered by daily activities provides the impetus for increases in LVM and progression to LVH; and (3) increased physical fitness achieved by regularly performed exercises of moderate intensity modulates the exaggerated BP response. Consequently, lower daily BP leads to LVM regression [36].

Exercise Capacity and Mortality Risk Among Adults with Prehypertension and Hypertension

Relatively small reductions in BP achieved by antihypertensive therapy lead to substantial health benefits [3]. It is reasonable to assume that similar exercise-induced reductions in BP should lead to similar health benefits. In this regard, findings from large and well-controlled epidemiologic studies support an independent, inverse, and graded association between exercise capacity and mortality risk in individuals with prehypertension and hypertension [57–61]. Specifically, Blair and co-investigators [57] reported significantly lower death rates in physically fit men with hypertension compared to those that were less physically fit, regardless of age, risk factors, and length of follow up.

Kokkinos and co-investigators also assessed the mortality risk associated with physical fitness status in a cohort of 4,631 veterans with hypertension and multiple CVD factors [58]. Physical fitness was assessed with a graded exercise stress using the Bruce protocol and recorded as peak METs. The investigators established four

Table 4.1 Mortality risk (hazard ratios) according to physical fitness status and risk factors (Adapted from ref. [58])

	Least-fit	Low-fit	Moderate-fit	High-fit
Group	≤5 METs	5.1–7 METs	7.1–10 METs	>10 METs
Entire cohort	1.0	0.66 (0.58–0.76)	0.41 (0.35–0.50)	0.29 (0.21–0.40)
No cardiovascular disease risk factors	1.0	0.66 (0.48–0.89)	0.48 (0.32–0.71)	0.33 (0.18–0.62)
≥2 Cardiovascular disease risk factors	1.47 (1.2–1.8)	0.97 (0.78–1.21)	0.56 (0.43–0.72)	0.37 (0.24–0.56)

MET metabolic energy equivalents

fitness categories based on the peak MET level achieved: Least-Fit (≤5 METs); Low-Fit (5.1–7 METs); Moderate-Fit (7.1–10 METs); and High-Fit (>10 METs). Overall, there was a 13 % decrease in mortality for every 1-MET increase in exercise capacity. When compared to the individuals in the Least-Fit category, mortality risk was 34 % lower for those in the next fitness category (Low-Fit) and declined progressively to over 70 % among individuals with the highest fitness category. The risk, based on physical fitness status (least fit to most fit) and the presence or absence of additional CVD risk factors were then compared. Among the least-fit, individuals with additional CVD risk factors had a 47 % higher mortality rate compared to those without CVD risk factors. The increased risk imposed by a low fitness level and additional CVD risk factors was eliminated by relatively small increases in exercise capacity (5.1–7 METs), and declined progressively with higher exercise capacity (Table 4.1).

Similarly, in a relatively smaller cohort of middle aged veterans with hypertension, Myers and co-investigators reported that the relative risk of mortality for those with an exercise capacity of <5 METs was approximately double compared to those with an exercise capacity of >8 METs [59].

Faselis and colleagues also examined the interaction between exercise capacity and mortality risk in veterans with hypertension according to body mass index (BMI). These authors observed progressively lower mortality rates with increased exercise capacity within each BMI category. The mortality risk reduction ranged from approximately 40 % in those with an exercise capacity of 5.1–7.5 METs to 70 % in those with >7.5 METs [60]. A noteworthy finding in this study was that physical fitness tended to have a greater impact in those with BMI <25 kg m^{-2} (normal weight) than those with BMI ≥30 kg m^{-2} (obese). For each 1 MET increase in exercise capacity, the adjusted risk was 20 % for individuals that were normal weight, 12 % for those that were overweight, and 25 % for those that were obese [60]. Similarly, the mortality risk observed in High-Fit individuals (exercise capacity >7.5 METs) within each BMI category increased as BMI increased. Specifically, mortality risk was 66 %, 55 %, and 72 % for those with BMI < 25 kg m^{-2}; 25–29.9 kg m^{-2}, and ≥30 kg m^{-2}, respectively.

To explore the fitness-fatness debate and mortality risk relationship further, Faselis et al. examined whether being of normal weight but low fit carries a more favorable risk than being overweight or obese but fit. Compared to the normal weight but unfit individuals, the mortality risk was 47 % and 60 % lower for the overweight-moderate-fit and overweight-high-fit individuals, respectively. Similarly, the risk was 55 % lower for the obese-moderate-fit and 78 % lower for the obese-high-fit individuals. These findings suggest that it is more beneficial to be fit and overweight or obese rather than normal weight and unfit. Furthermore, it appears that individuals with obesity and hypertension may benefit at least as much from being physically fit than their counterparts that are normal weight or overweight with hypertension [60]. The favorable impact of physical fitness status on the BMI-mortality risk association has also been shown recently in a large male cohort [61]. Collectively, these findings suggest that improving physical fitness has a greater impact on health than lowering body weight even in the presence of hypertension.

Finally, similar trends in fitness-mortality risk associations were noted in 4,478 individuals with prehypertension regardless of age [62], and those with BP in the high normal range [63]. Specifically, when assessing the mortality risk according to fitness categories, the most pronounced reduction in risk (40 % lower) was observed when comparing the Low-Fit individuals (Peak MET level 6.1–8.0) to the Least-Fit (peak MET level ≤6.0). Higher fitness levels (Moderate and High-Fit categories) were accompanied by even greater reductions in risk (58 % and 73 %, respectively). The trends were similar but more pronounced among younger than older individuals. For every 1 MET increase in exercise capacity the adjusted risk was 18 % lower for those ≤60 years and 12 % for individuals >60 years.

Clinical Implications

The findings presented in this chapter support that exercise can be implemented to modulate the age related increase in BP [27, 32–35], cardiac remodeling (LVH regression) [36, 38–43], lower BP in individuals with hypertension [23–27], and lower mortality risk [36, 57–60, 62, 63]. It is noteworthy that the aforementioned health benefits are achievable at a physical fitness level represented by an exercise capacity >5 METs. This has a significant clinical and public health impact because this level of physical fitness is achievable by a brisk walk of 20–40 min, most days of the week, a physical activity level attainable by most middle aged and older individuals. Since walking requires virtually no instructions, has a relatively low cost, carries a low risk of injury, and can be easily implemented in large populations, it represents the ideal form of exercise for individuals with hypertension at any age.

Conclusions

Sufficient evidence form interventional and large epidemiologic studies support that aerobic exercise training of moderate intensity favorably influences BP, cardiac remodeling, and mortality risk in individuals with prehypertension and hypertension. The level of exercise necessary for the aforementioned health benefits is relatively low (i.e., brisk walk of 20–40 min, most days of the week), and is achievable by most middle aged and older individuals. Surprisingly, physical activity is currently underutilized for the prevention, treatment, and control of hypertension. For these many reasons, increased physical activity should be an important component of the antihypertensive regimen and should be promoted as such by health care, exercise, and public health professionals alike.

Key Points and Resources

- Hypertension is the most common, costly, and preventable CVD risk factor.
- Increased physical fitness status favorably modulates the age related progressive increase in BP and development of hypertension, reduces elevated BP in individuals with hypertension, and reverses LVH.
- Increased exercise capacity lowers mortality risk in individuals with prehypertension and hypertension.
- The SBP response at a relatively low submaximal workload of approximately 4–5 METs may have a greater potential to predict the presence of LVH or the risk for developing LVH than an exaggerated BP response to peak exercise and better relates to activities of daily living.
- There is overwhelming support that increased physical activity favorably influences BP and CVD risk in individuals with hypertension; yet it is surprisingly underutilized for the prevention, treatment, and control of hypertension.
- American College of Sports Medicine: http://www.acsm.org to access the position stand on exercise and hypertension.
- American Heart Association: http://www.american heart.org.
- National Heart Lung and Blood Institute: http://www.nhlbi.nih.gov/hbp.
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Part II
Mechanisms for the Blood Pressure Lowering Effects of Exercise

Chapter 5
Aerobic Exercise Training: Effects on Vascular Function and Structure

Dick H.J. Thijssen, Andrew Maiorana, and Daniel J. Green

Abbreviations

ACE	Angiotensin converting enzyme
ACh	Acetylcholine
ANG II	Angiotensin II
BP	Blood pressure
eNOS	Endothelial nitric oxide synthase
ET-1	Endothelin-1
FITT	The frequency, intensity, time, and type principle of exercise prescription
FMD	Flow mediated dilation
HITT	High intensity interval training
HR	Heart rate
ICAM-1	Intracellular adhesion molecule 1

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IMT	Intima medial thickness
MAP	Mean arterial pressure
MCP-1	Monocyte chemotactic protein 1
MSNA	Muscle sympathetic nerve activity
NO	Nitric oxide
p22-phox	Neutrophil cytochrome b light chain
p47-phox	47-kDa cytosolic subunit of nicotinamide adenine dinucleotide phosphate
Q	Cardiac output
ROS	Reactive oxygen species
SNS	Sympathetic nervous system
SVR	Systemic vascular resistance
VO_{2max}	Maximum oxygen consumption

Introduction

Contemporary Westerners have reached an historical pinnacle of physical inactivity and further technological change is likely to exacerbate this [1]. Physical inactivity is an independent risk factor for atherosclerosis and cardiovascular diseases [2–4] and low cardiorespiratory fitness is a strong independent predictor of all-cause mortality [5]. Physical inactivity is a key factor in the etiology and progression of cardiovascular diseases, including hypertension. Regular physical exercise is associated with reduction in primary [6–9] and secondary vascular events [10, 11]. Meta-analyses, including those of exercise-based cardiac rehabilitation undertaken in the contemporary era, indicate that ~30 % exercise-related benefit is evident in terms of cardiac events relative to usual care [12]. This magnitude of benefit approximates or exceeds that associated with antihypertensive or lipid lowering medication interventions in large multicenter trials [13, 14], with a recent analysis concluding that exercise and drug interventions are similar in terms of their mortality benefits in secondary prevention [15]. These data indicate that exercise training and maintenance of physical fitness have important impacts on the prevalence and progression of cardiovascular disease, at least partly through changes in cardiovascular risk factors such as hypertension.

Purposes of this Chapter

This chapter discusses the impact of aerobic exercise training on the vasculature that may explain the blood pressure (BP) lowering effects of exercise training [16, 17]. We first provide an overview of the techniques use to assess

vasculature structure and function followed by relevant research regarding the influence of aerobic exercise training on vascular structure and function. The potential mechanisms that contribute to vascular adaptations to aerobic exercise are then discussed. Last, we integrate the available knowledge in this area to provide evidence-based guidelines for the benefits of exercise training on vascular health among individuals with hypertension. Please see related discussions to these topics in Chapters 1, 7–9.

Key Terminology and Basic Concepts

Aerobic Exercise

The term aerobic exercise training is typically used to refer to episodic whole-body exercise, characterised by use of the large muscle groups of the lower limbs (e.g., walking, running, cycling), sometimes combined with the upper extremities (e.g., rowing, swimming). It involves repeated dynamic muscular contractions that impact the cardiac and pulmonary systems, with marked increases in heart rate, ventilation and oxygen consumption. Most scientific literature has defined aerobic exercise as prolonged periods of exercise (>10 min) at moderate-to-high exercise intensity (60–80 % of the maximal heart rate). However, important differences exist between studies regarding the frequency (2–7 days per week), intensity (25–90 % of the maximal heart rate), time (30–60 min) and type (e.g. walking, running, cycling, rowing) of aerobic exercise training.

Vascular Functional and Structural Adaptations to Aerobic Exercise Training

Mean arterial pressure (MAP) is determined by cardiac output (Q) (derived by multiplying stroke volume [SV] and heart rate [HR]) and systemic vascular resistance [SVR] (MAP=Q×[SV×HR]×SVR). Studies in healthy subjects and those with hypertension have reported that aerobic training induces a decrease in heart rate (~10 %), which is counterbalanced by an increase in SV (~15 %), consequently leading to an unchanged or even slightly increased Q at rest. Given this preserved Q, the BP lowering effect of aerobic exercise training must be related to decreases in peripheral vascular resistance [18]. These changes in peripheral vascular resistance are mediated by functional and/or structural adaptations in the vasculature in conduit, resistance, *and* microvessels. In addition to the decrease in BP, improved vascular function and structure may also be related to decreased cardiovascular risk [19].

Techniques Used to Examine Vascular Structure and Function

How Is Artery Structure and Function Studied?

The in vivo assessment of arterial function and structure varies according to their size and functional classification. Conduit arteries have been defined as having a diameter: >1,000 μm, small arteries 300–1,000 μm, resistance arteries and arterioles diameter: 10–300 μm, and capillaries diameter: <6 μm [20]. In these terms, arteries that contribute substantively to vascular resistance and the systemic control of BP include small arteries, and resistance arteries and arterioles; henceforth collectively referred to in this ter as resistance vessels [20]. Below, we have discussed commonly adopted methods that are used to examine conduit and resistance artery vascular function and structure.

How Is Resistance Artery Structure and Function Studied?

Structure of Conduit Arteries (Diameter Assessment)

Echo-Doppler is used to assess the structure of conduit arteries. It allows for valid and reproducible assessment of resting diameters of nearly all superficial (<5 cm) conduit arteries in the upper and lower limbs, as well as the carotid arteries. Although resting diameter provides a surrogate measure of conduit artery structure in vivo, competing vasodilator and constrictor influences impact upon resting arterial tone. It has therefore been proposed that peak artery diameter, which represents a physiological capacity, may serve as a more valid structural index because it diminishes the impact of functional differences between subjects [21].

Structure of Conduit Arteries (Wall Thickness)

High-resolution ultrasound can also be used to assess conduit artery intima medial thickness (IMT) (Fig. 5.1), a surrogate measure of wall thickness. Atherosclerosis initially forms within these layers, and the assessment of IMT is therefore believed to reflect the presence of subclinical atherosclerosis. Nonetheless, it should be taken into consideration that the abundant presence of smooth muscle cells in the media layer of the arterial wall contributes to acute changes in IMT, under direct influence of vasodilator or vasoconstrictor substances [22]. Several studies have established that carotid IMT is associated with increased risk for adverse cerebral events (e.g., stroke) [23–27]. A larger carotid IMT is also associated with increased risk for cardiac (e.g., angina pectoris, myocardial infarction) [23, 25, 28–30] and peripheral vascular events (e.g., peripheral artery disease, hypertension) [31, 32]. A meta-analysis found that a 0.1 mm increase in carotid artery IMT is associated with an increase in age- and sex-adjusted relative risk of 18 % for stroke and 15 % for myocardial infarction [33], highlighting the clinical significance of IMT. Studies

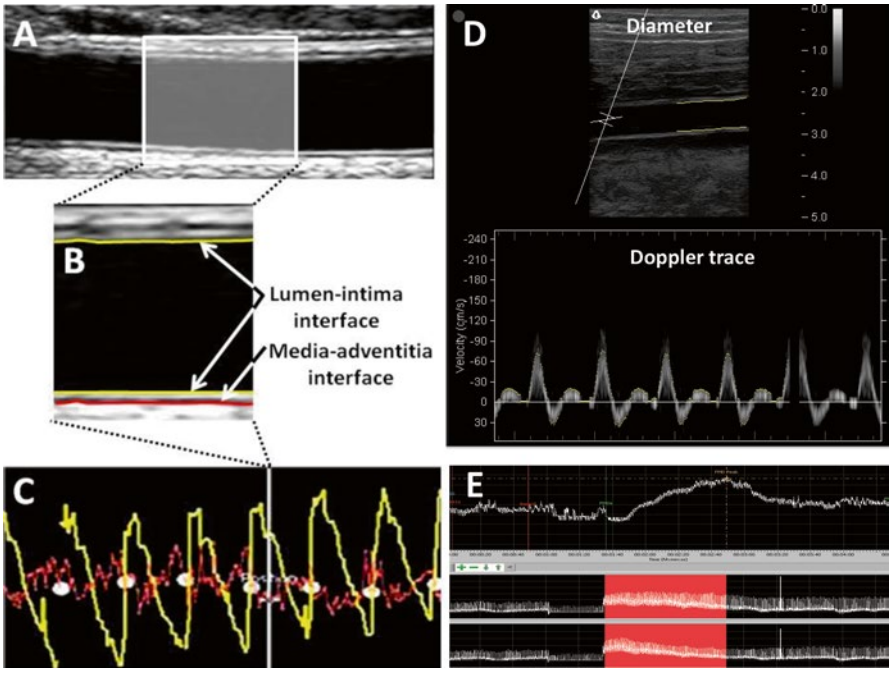

Fig. 5.1 Assessment of conduit artery structure and function. Ultrasound image of a carotid artery (**a**) from a healthy subject. Clearly demarked lines represent the lumen–intima interface (*yellow line*) and media–adventitia interface (*red line*, **b**), that are used to assess the intima-media thickness of a conduit artery. These images are then used to examine the change in diameter (*yellow line* to *yellow line*) and intima-media thickness (*yellow line* far wall to *red line* far wall) across the cardiac cycle. (**c**) Ultrasound image of a brachial artery (**d**) of a healthy subject, combined with a Doppler tracing of the red blood cell velocity in the same vessel. Based on the clearly demarked lines on the artery wall and from the Doppler trace (both *yellow lines*) in figure **d**, changes in diameter and blood velocity is presented across time (**e**). This allows for the identification of the peak diameter after cuff occlusion (i.e. *red area*) as a measure of vascular function

proposed that the annual change in IMT, rather than the carotid IMT itself, could be a stronger predictor for future events. However, a recent meta-analyses found no predictive effect of the *annual change* in carotid artery IMT [34], which also highlights the technical difficulty of measuring small changes in arterial wall thickness with current ultrasound techniques.

Function of Conduit Arteries (Endothelial Function)

In conduit arteries, endothelium-dependent vasodilator function is assessed by high resolution ultrasound following an increase in blood flow, which triggers shear stress-mediated vasodilation [35]. This technique is commonly referred to as the

flow mediated dilation (FMD). The dilation is at least partly mediated by nitric oxide (NO) [36–39], and serves as a valid index of conduit artery endothelium-dependent NO function [40]. FMD is often performed in the brachial artery, where it is demonstrated to be correlated with coronary endothelial function [41, 42]. Moreover, the brachial artery FMD has independent predictive capacity for future cardiovascular events [43–45]. These studies found that a 1 % increase in brachial artery FMD is associated with a 13 % reduction in cardiovascular risk in subjects at increased cardiovascular risk [43], while a 1 % change in FMD is associated with a 4 % change in cardiovascular risk in healthy, asymptomatic subjects [44].

How Are Resistance Artery Structure and Function Studied?

Structure of Resistance Arteries

Peripheral resistance vessel structure in humans has traditionally been assessed from measurement of the hyperemic (blood flow) response to a maximal vasodilator stimulus [46–48]. The conceptual basis for this approach is that assessment of resting blood flow reveals little information regarding the collective cross-sectional area of the resistance vessel bed, because of confounding and competitive influences of vasodilator and constrictor stimuli on basal tone. In contrast, measurement of blood flow in response to a vasodilator stimulus that elicits maximal or peak vasodilation provides insight into the capacity of the resistance vessel bed in question. In this context, peak reactive hyperemia after 10 min of limb ischemia induced by cuff inflation cannot be significantly increased by co-infusion of vasodilator agents [46]. Assessment of peak blood flow responses historically involved plethysmographic blood flow measurement [49], however, Doppler ultrasound methodology has recently been applied [21].

Function of Resistance Arteries

Vascular function of the resistance vessels can be examined by constructing dose–response curves to intra-arterial infusion of vasoactive substances. Blood flow is assessed using plethysmographic approaches to detect changes in limb volume, or direct conduit artery imaging using duplex ultrasound. Evaluating the responses to endothelium-dependent and -independent vasodilators provides information about the impacts, in vivo, of exercise training on specific dilator pathways [50, 51].

Methods

We summarized papers that examined the impact of aerobic exercise training on BP in healthy asymptomatic subjects and subjects with pre- and established hypertension. Using PubMed as our primary search engine, we searched for papers that

involved aerobic exercise training ('exercise training OR aerobic training OR aerobic exercise training OR endurance training OR endurance exercise training'). We excluded papers that used alternative modes of exercise and/or combined aerobic exercise training with (high-intensity) resistance exercise training. To specifically discuss the effects of aerobic training in hypertension, we combined the search strategy as stated above with 'hypert* OR pre-hypert* OR prehypert* OR high blood pressure'. The effects of aerobic training on BP are largely explained through changes in the vasculature. Therefore, to better understand the impact of aerobic exercise training on BP regulation, we expanded our search to studies that explored the impact of aerobic training on conduit and resistance arteries.

Relevant Research

Effect of Aerobic Exercise Training on Vascular Structure

Conduit Artery Diameter

Several cross-sectional and longitudinal studies suggest that aerobic training is associated with enlargement of skeletal muscle conduit arteries in humans. In an early study, it was observed that (predominantly) aerobic-trained athletes have increased resting diameters in large arteries (i.e., aorta, carotid, subclavian arteries) relative to matched sedentary controls [52]. These differences persisted after correction for body surface area between groups. In contrast, wheelchair athletes demonstrated enhanced dimensions in the aortic arch and subclavian artery, but lower values in the abdominal aorta and mesenteric artery [53]. These findings essentially extended previous reports of enlargement in conduit arteries of endurance-type athletes compared to control subjects [54, 55].

Recently, conduit artery diameter was examined in dominant and non-dominant limbs of different types of athletes, including wheelchair athletes [56, 57]. This series of studies revealed the largest brachial artery diameter in athletic groups who were primarily engaged in upper limb dominant exercise (i.e., canoeists and kayakers). More specifically, a within-subject comparison performed between the dominant and non-dominant brachial arteries of elite squash players revealed a localized outward remodeling of the dominant brachial artery. These findings suggest the presence of localized adaptation of diameter in response to exercise training.

In studies of healthy, young men, significant increases in the dimensions of the ascending and abdominal aorta were observed following 8 weeks of cycle ergometer training [58]; and of the femoral artery in the trained, but not untrained limb, after 6 weeks of one-legged cycle exercise [59]. These training effects were reversed following detraining [59]. More recently, Spence et al. performed a 6 month exercise training study to assess the effect of aerobic exercise training in healthy male subjects on brachial, femoral, and carotid artery diameter [60]. While no improvements were observed in brachial and carotid artery diameter, a significant and marked increase was observed in femoral artery resting diameter. These observations

Table 5.1 Summary of the initial (0–4 weeks) and long-term (>8 weeks) changes in conduit artery function (i.e. flow-mediated dilation (FMD)) and structure (i.e. diameter (D) and intima-media thickness (IMT)) and resistance artery function (i.e. intra-brachial infusion of endothelium-dependent and independent vasoactive substances) and structure (i.e. peak blood flow (BF_{peak})) in the active area and non-active area in response to endurance exercise training

		Active area		Non-active area	
		Initial change	Long-term change	Initial change	Long-term change
Conduit artery	Function (FMD)	↑	↑/↔[a]	↑	↑/↔[a]
	Structure (D)	↔	↑	↔	↔
	Structure (IMT)	↔	↓	↔	↓
Resistance artery	Function (invasive)	↑	↑/↔[a]	↑	↑/↔[a]
	Structure (BF_{peak})	↔	↑	↔	↑

[a]The size and direction of the effect size may differ between healthy subjects (↔) and subjects with cardiovascular disease/risk (↑)

strongly support the ability of aerobic training to result in outward remodeling of conduit arteries, leading to larger conduit artery diameters in healthy subjects [60]. Moreover, this process in healthy young subjects is rapid and depends on local, rather than systemic factors (Table 5.1).

Conduit Artery Wall Thickness

Cross-sectional studies on the impact of aerobic exercise training on carotid artery IMT in healthy subjects have reported conflicting results. For example, several studies found no significant difference in carotid IMT between trained subjects and sedentary controls in young, middle aged, or older cohorts [61–63]. These findings are supported by studies involving aerobic training in sedentary subjects that found no effect of 8–12 weeks of aerobic exercise training on carotid IMT [61, 64, 65]. A more recent study, however, found a significantly lower carotid artery IMT in elite squash players compared with less active controls [56]. The difference in training intensity and/or load may explain these disparate results, as elite squash players exercised >22 h per week at high intensity [56], while others studies involved aerobic training (cross-sectional and longitudinal studies) exercising >3 h per week [62] or >5 days per week [61, 63].

A limited number of cross-sectional studies have examined the effect of aerobic exercise training on the wall thickness of the peripheral arteries. In contrast to findings in the carotid artery, lower femoral artery IMT was observed in aerobic trained men and women compared with their sedentary peers [66, 67]. Also, when studying elite athletes (i.e., squash players), a lower peripheral artery IMT was found in the femoral and brachial arteries compared to their sedentary controls [56]. Studies that adopted longitudinal training designs also reported smaller IMT of peripheral conduit arteries after 12–24 weeks of aerobic training [66, 68]. Taken together, aerobic training studies performed in healthy, predominantly Caucasian subjects indicate that aerobic exercise training leads to a smaller IMT in peripheral arteries supplying the active skeletal muscle (Table 5.1).

In subjects with cardiovascular risk factors, such as hypertension, an *a priori* increased IMT is typically found in the carotid and peripheral vessels. This finding potentially allows for marked effects of aerobic exercise training in these subjects [69]. In individuals with hypertension, an inverse relationship was present between cardiorespiratory fitness and carotid artery atherosclerosis (defined as a wall thickness >1.2 mm) [70]. Another study in subjects with hypertension demonstrated that higher self-reported physical activity was associated with a lower 6.5 year increase in carotid IMT [71]. Although these between-subject studies suggest that training is associated with a smaller IMT in subjects with hypertension, no study has directly examined the effect of aerobic training on carotid or peripheral artery IMT.

Resistance Arteries

Sinoway et al. performed two of the earliest studies which specifically addressed the impact of aerobic training on resistance vessel "structure" in healthy subjects. By using a stimulus that induced peak dilation, without inducing reflex changes in vasomotor control, they sought to assess the effect of aerobic exercise training on structural resistance artery adaptation. Sinoway and colleagues demonstrated that the preferred limbs of tennis players exhibit higher peak vasodilator responses than the non-preferred limbs of these athletes or either limb of non-tennis playing control subjects [72]. This finding was later confirmed in elite tennis players [73]. Comparable effects of an enhanced maximal peak blood flow have been reported after different types of aerobic exercise training across a large age range [74–76]. In subjects with hypertension, who demonstrate lower *a priori* peak dilator responses, aerobic exercise training increases forearm peak blood flow [77].

The enhanced intrinsic vasodilator capacity of active muscle beds following training may conceivably result from the well-established increase in capillary density that occurs with training [78]. However, muscle blood flow is not dependent upon capillary density [79]. While capillaries regulate transit time and oxygen extraction, they contribute much less resistance to flow than upstream arterioles [20, 80, 81]. Electrical stimulation studies suggest that the time-course of adaptation in capillary density (~4 days) [82] is dissociated from adaptations in peak blood flows (14–28 days) [83]. Adaptations in peak blood flow with training, therefore reflect changes in the caliber or cross-sectional area of the "resistance arteries", rather than increases in capillarity

Summary of the Impacts of Aerobic Exercise Training on Arterial Structure

In summary, aerobic exercise training represents a potent stimulus for conduit and resistance arteries to adapt. More specifically, aerobic exercise training in healthy, predominantly Caucasian subjects leads to larger conduit artery diameters and smaller conduit artery IMT. Conduit artery remodeling represents a

process that depends on a localized process in the active limbs; while the decrease in IMT is observed in the active and non-active limbs, suggesting the presence of a systemic effect of aerobic exercise training on IMT. Finally, aerobic exercise training also leads to enlargement of the resistance arterial vascular bed, a localized process that occurs in active limbs. These structural adaptations may contribute to the benefits of exercise training on BP. While a larger resistance arterial bed can lower peripheral resistance, and therefore BP, it should be acknowledged that remodeling of conduit arteries unlikely play an important role in peripheral vascular tone.

Effect of Aerobic Training on Vascular Function

The function of conduit and resistance vessels reflects the balance between competing effects of vasodilator and vasoconstrictor influences. Discussion of vascular function will primarily focus on the impact on NO bioavailability, given its important role as a vasodilator as well as its anti-atherosclerotic and anti-thrombotic effects. Studies examining vasoconstrictor pathways have focussed on endothelin-1 (ET-1) and angiotensin II (ANG II), arguably the most important vasoconstrictors, and the sympathetic nervous system (SNS).

Vasodilator Function

Conduit Arteries

A number of studies have examined the effects of aerobic training on conduit artery vascular function using FMD. In healthy subjects, improvement in conduit artery FMD is not a generalised finding [64, 84]. In contrast, aerobic training undertaken in subjects with *a priori* impairment in conduit artery endothelial function typically demonstrate enhanced FMD responses after aerobic exercise training [85, 86]. Indeed, studies undertaken in subjects with hypertension [87, 88], who exhibit endothelial dysfunction, demonstrate enhanced FMD responses following different aerobic training programs. Given the conflicting results of aerobic exercise training on conduit artery FMD in subjects with normal BP, one may question whether individuals with prehypertension benefit from aerobic training. Interestingly, significant improvement in brachial artery FMD after prolonged (12 weeks) aerobic exercise training was found in subjects diagnosed with Stage I hypertension (or prehypertension), but not in subjects with normal BP [87]. Therefore, conduit artery function appears more amenable to enhancement in subjects with pre to established hypertension, who exhibit impaired vasomotor and endothelial function *a priori*, than in healthy subjects with less impaired vascular function prior to training.

Resistance Arteries

The impact of aerobic exercise training in healthy control subjects has frequently been studied in resistance arteries using plethysmography. In young subjects who undertook aerobic cycle exercise training, improvement in basal NO function was observed, but no changes in endothelial function were apparent [89]. Despite the improvement in NO bioavailability in this study, no changes in basal limb blood flow were found after training, possibly because of a compensatory increase in sympathetic vasoconstrictor tone [90].

Consistent with the case for conduit artery function (above), there is no apparent consensus regarding the impact of aerobic training on resistance vessel function in healthy (young) subjects; whereas the majority of studies performed in subjects with impaired endothelial function have documented improvement. For example, aerobic exercise training in middle aged subjects enhanced endothelial function [91, 92] and improved NO bioavailability [90]. Furthermore, 12 weeks of aerobic exercise training in subjects with hypertension improved peripheral resistance artery endothelial function [77, 92].

Several important studies have indicated a beneficial impact of aerobic training on coronary vasodilator function among patients with coronary artery disease [93–95] and heart failure [96]. For example, Hambrecht and colleagues studied 19 patients with stable coronary artery disease that were randomised to aerobic training or control groups for a 4 week period [95]. Intra-coronary infusion of acetylcholine (ACh) and adenosine were used to assess epicardial coronary artery vasodilator function and resistance vessel function, respectively. Training improved coronary conduit and resistance artery vasodilator function. In a subsequent study, the authors found that home-based aerobic training sustained some of these effects [97]. These authors also completed a comprehensive study which concluded that aerobic training improves vasodilator function in vivo by upregulating NO synthase protein expression and by increasing phosphorylation of NO synthase, effects consistent with a shear-stress mechanism for enhanced NO bioactivity with training [94]. Taken together, these findings strongly support the presence of an improvement of resistance artery vascular function after aerobic exercise training in subjects with cardiovascular disease or risk (Table 5.1).

Vasoconstrictor Function

When studying the contribution of ET-1 and Ang II to the regulation of baseline vascular tone, studies have found that these constrictors do not importantly contribute to the regulation of baseline resting tone in healthy, young subjects [98–100]. It is therefore unlikely that aerobic exercise training in healthy subjects importantly alters vasoconstrictor function. In contrast, older humans exhibit increased ET-1-mediated vascular tone in the leg [101] and forearm [102]. More importantly, aerobic training is able to reverse the contribution of ET-1 to baseline

vascular tone in older humans [101, 102]. Regarding Ang II, aerobic exercise training in patients with stable coronary artery disease induced a 49 % reduction in Ang II-induced vasoconstriction [103]. While the evidence relating to aerobic training effects on vasoconstrictor pathways is far less comprehensive than that for vasodilator mechanisms, aerobic exercise training seems to have a beneficial effect on vasoconstrictor pathways in those with an *a priori* increased contribution of vasoconstrictors to vascular tone.

The question of whether neurally-mediated vasoconstriction is modified by aerobic training is complex and various approaches to this question have produced contradictory results. On the one hand, there is strong evidence that heart rate variability, a measure of autonomic balance, is improved by aerobic training [104–106] and is related to physical activity levels [107] (see Chapter 9 for a more detailed discussion of the effects of exercise on autonomic function). Other studies suggest that noradrenaline levels diminish following training [108]. In keeping with these findings, training ameliorates the effect of aging on baroreflex function [109], an effect which may be related to enhanced arterial vasodilator function, arterial distensibility, and signal transduction in barosensitive zones [110]. In addition, muscle sympathetic nerve activity (MSNA) may decrease as a result of aerobic training [111] including subjects with elevated SNS activity *a priori* [112]. Finally, repeated bouts of exercise are associated cyclic activation of brainstem centres, such as the rostral ventrolateral medulla, may modulate central sympathetic output and SNS mediated vasoconstriction [113]. These studies suggest that sympathetic nerve mediated vasoconstrictor tone may decrease as a result of aerobic training in humans.

However, there is also evidence to the contrary. Studies performed in healthy subjects suggest that MSNA does not change with training [112] and noradrenaline spill-over may also be similar following training when expressed in relative terms [114]. In addition, α-adrenoceptor blockade (i.e., a direct measure to examine the role of the SNS), revealed an increased level of basal sympathetic vasoconstrictor tone following aerobic training in healthy volunteers [90], consistent with other evidence of elevated basal sympathetic tone following training [115]. Despite this apparent increase in resting sympathetic tone, basal blood flows are not decreased by training, a finding likely due to a compensatory increased vasodilator function or remodelling. Hence, increased vasodilator function or arterial remodelling following training may be offset by elevated sympathetic tone, with the result that resting blood flows and arterial diameters remain unchanged. In keeping with this, there is evidence in coronary arteries consistent with elevated basal vasoconstriction tone in trained subjects who also possessed enlarged arteries [116].

Specifically for individuals with hypertension, relatively few studies have focused on the impact of aerobic training on the SNS. A previous report examined the impact of a 4 month, pre-dominant lower limb aerobic exercise training on baroreflex control of MSNA in (never-medicated) patients with hypertension [117]. The drop in BP after training was accompanied by a drop in MSNA level as well as a significant improvement in baroreflex control during BP manipulations in these subjects. Interestingly, the authors even reported a significant positive relation between the decrease in resting MSNA and the drop in MAP.

In summary, evidence in humans suggests that aerobic training can improve the contribution of ET-1 and ANG II in the regulation of vascular tone in those with *a priori* elevated contribution of vasoconstrictors to regulate vascular tone. In addition, some evidence suggests that aerobic training has a direct effect on the SNS, most likely resulting in improvement in baroreflex sensitivity and attenuation of the contribution of the SNS to the regulation of vascular tone in those with an *a priori* elevation in SNS tone. A smaller contribution of vasoconstrictor pathways to regulate tone after periods of training may represent a key mechanism contributing to the BP lowering effect of exercise training.

Time Course of Vascular Functional–Structural Adaptation

Although aerobic exercise training alters both conduit and resistance vessel function and structure, the time-course of these changes likely differs. In animals, short duration aerobic exercise training (2–4 weeks) improved vasodilator function in muscle arterioles [118, 119] and the aorta [120, 121]. Also in conduit vessels, improved vasodilator function has been observed after short duration aerobic exercise training (i.e., 7 days) [122]. These findings suggest that improved vascular *function*, demonstrated by an increased production of endothelial NO, occurs rapidly in response to aerobic training, particularly in arteries supplying the exercising muscle beds [123].

Animal studies performed over a longer duration have not consistently shown augmented endothelial function in healthy animals. Endothelium-dependent vasodilation was unaltered after 16–20 weeks of training in pigs [124] and 16 weeks in rats [125]. There is also evidence that endothelial nitric oxide synthase (eNOS) expression is time-dependent. Expression of eNOS protein and enhanced vasodilator function [126] were evident after 1 week of training in pigs, whereas these changes were not present after 16 weeks [127]. Although these data suggest that long-term training is not consistently associated with enhanced vasodilator function, prolonged aerobic training enlarges arterial diameters in animals [128–131]. Laughlin proposed, on the basis of these animal data, that a distinct time-course for change in arterial function and structure may exist in response to exercise training [123]. These data in animals resulted in the hypothesis [86] that, in humans, vascular remodelling, an endothelium and NO-dependent phenomenon [132–137], may partly supplant the need for acutely responsive vasodilator mechanisms to normalise shear stress during exercise bouts [86].

Recently, Tinken et al. completed a study in which measures of brachial and popliteal artery function and structure were collected every 2 weeks across an 8 week aerobic training program in healthy, young male subjects [138]. The results indicated that functional adaptation preceded changes in artery peak vasodilator capacity. These findings support the notion that functional adaptations may be superseded by structural changes including artery remodelling that may normalise shear stress. They confirm previous reports that endothelial function rapidly adapts

to training and detraining [139, 140]. Moreover, others have now confirmed the time-dependent changes in conduit artery function in healthy subjects during aerobic exercise training [141].

In summary, animal studies suggest that short-term aerobic training enhances eNOS and NO production and bioactivity, producing a short-term buffer to the increased shear associated with exercise. With continued training, at least in the peripheral circulation, structural changes in the vessels occur, resulting in an increase in lumen diameter [20, 135]. Whether a similar time-course in vascular adaptations is present in subjects with pre and established hypertension is currently unknown. Furthermore, little is known whether the distinct time-course in functional and structural vascular adaptations lead to a time-course in adaptation of BP or BP control.

Local Versus Systemic Adaptations

An important question for prescribing aerobic exercise training is whether such exercise leads to local or systemic adaptations in the vasculature. This question is of particular importance when exercise is prescribed with the aim of modulating BP, which requires systemic adaptation in vascular resistance. Studies that have investigated the impact of lower limb aerobic exercise training on vascular function in humans typically found improvement in upper limb vascular function [89, 91, 92, 142–144]. Hence, the vast majority of studies that examined the impact of aerobic exercise training reveal systemic improvements in vascular function in conduit and resistance vessels (Table 5.1).

In terms of generalized effects of training on vascular *structure*, results depend upon the vascular territory examined. It is well established that aerobic training leads to an outward remodeling of conduit artery diameter which supply the active muscle beds. For example, brachial diameters are significantly larger in elite canoe paddlers and wheelchair athletes, compared to control subjects, while superficial femoral artery diameters are significantly larger in runners and cyclists than controls and paraplegic subjects [57]. In addition, the dominant and non-dominant arms of elite tennis players differ in terms of conduit and resistance artery remodelling [53, 73], a finding reinforced by observation of larger racquet arm brachial diameters in elite squash players [56]. Aerobic exercise training, despite its strong and systemic stimulus, therefore seems to result in a local impact on conduit artery diameter remodelling. There is little extant evidence for remodelling of artery size in vessel beds outside those involved directly in the exercise stimulus.

Information regarding the impact of aerobic exercise training on local or systemic adaptations in wall thickness is scarce. Most studies that examined the impact of aerobic exercise training have adopted cross-sectional comparisons. Rowley et al. assessed carotid, brachial, and superficial femoral artery wall thickness in elite athletes engaged in predominantly lower limb (i.e., runners/cyclists) or upper limb (i.e., canoe paddlers) exercise and matched able bodied, recreationally active, controls. In this study, wheelchair controls and athletes were also studied to further

examine the impact of aerobic training on arterial wall thickness. Diminished wall thickness was observed in all arteries of able bodied athletes compared to controls, including wheelchair athletes compared to wheelchair controls [57]. A further study of elite squash players also confirmed decreased brachial artery wall thickness, which in contrast to the effects on lumen diameter, was apparent in *both* limbs [56]. This finding suggests that aerobic exercise training results in changes in wall thickness in athletes, which may be a systemic phenomenon. In support of this notion, longitudinal training studies suggest that peripheral arterial wall thickness decreases after lower limb aerobic exercise training in femoral [66], popliteal, and brachial [68, 145] arteries. Although limited in scope, these data support the presence of systemic changes in conduit artery wall thickness after aerobic exercise training.

In summary, aerobic exercise training represents a potent stimulus for systemic adaptations in conduit and resistance artery function, but also for systemic improvements in conduit artery wall thickness (but not diameter) and resistance artery structure (Table 5.1). These findings suggest that aerobic exercise training leads to beneficial changes in vascular function and structure beyond the active vascular bed, assuming a sufficiently large active muscle mass is activated. The presence of systemic vascular adaptation after large muscle activity is of special importance for BP lowering, as lowering of total peripheral vascular tone is an important pathway to explain the benefits of exercise training on BP.

Mechanisms Responsible for Arterial Adaptation to Aerobic Exercise Training

Shear Stress

Exercise produces large increases in blood flow to the heart and active skeletal muscle [146]. These increases in blood flow during exercise generate shear forces that act on the endothelium that alter gene expression in endothelial and vascular smooth muscle cells [147–149]. The beneficial effects of exercise on vascular health have often been attributed to exercise-induced increases in mean shear stress [150–153]. This hypothesis is supported by data obtained from cell culture and isolated vessel preparations which demonstrate that increased shear stress positively modifies the expression of genes involved in the atherosclerotic process [154–159]. The impact that shear stress has on gene expression is highlighted by reports that increases in shear stress change the expression of approximately 3,000 cultured endothelial cell genes as assessed by microarray analysis [160].

The limited data obtained from in vivo models also support the notion that increases in mean shear stress provide a stimulus that is anti-atherogenic. Specifically, increases in shear stress, produced by arteriovenous fistulas in rats and dogs, have been reported to increase messenger ribonucleic acid (mRNA), protein, and activity of eNOS and decrease bioavailability of ET-1 [151, 152]. In humans, unopposed increases in retrograde shear stress acutely impair endothelial function

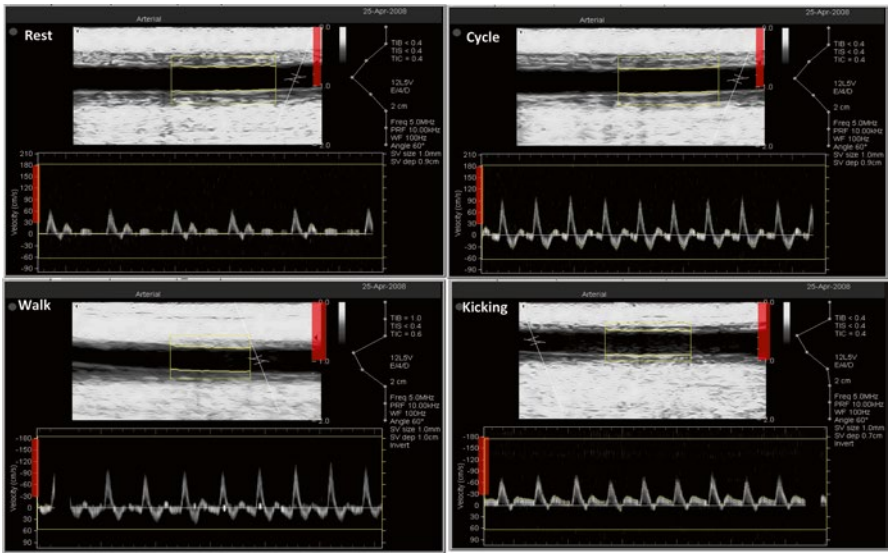

Fig. 5.2 Blood flow patterns during exercise. Echo-Doppler images from the brachial artery diameter and blood flow pattern under resting conditions (**a**), leg cycling exercise (**b**), walking exercise (**c**), and leg kicking exercise (**d**). Note the marked differences in blood flow patterns between the four different conditions

[161, 162], while some evidence suggests that increases in antegrade shear are associated with enhanced FMD [141, 163, 164]. See Chapter 7 for more detailed information about the effects of the application of in vitro shear stress on endothelial cell gene expression.

Data linking increases in mean shear stress to atheroprotective changes in gene expression has focused attention on mean shear as a modulating stimulus. However, it is important to acknowledge that the pattern of the hemodynamic profile seems to play an import role. This notion is supported by observations regarding significant changes in the pattern of shear when transitioning from rest to exercise [165] (Fig. 5.2). During the initial phase of lower limb aerobic exercise (such as cycling), the pattern of brachial artery blood flow through the conduit arteries becomes more oscillatory in nature, resulting in both the antegrade (i.e., forward) and retrograde (i.e., backward) components of blood flow. It is believed that the increase in retrograde component of the blood flow pattern during the initial phase of exercise is mediated through an increase in peripheral artery resistance [166], perhaps as a consequence of the activation of the SNS.

The initial increase in retrograde flow and shear stress, and therefore, oscillatory shear does not necessarily indicate that exercise leads to potentially harmful effects on the endothelium. Recent data demonstrate that changes in the pattern of blood flow through conduit arteries are subject to change as exercise continues [167]. The favorable shear pattern of largely antegrade shear during prolonged exercise is associated with beneficial adaptation in the vessels. Hambrecht and colleagues provided

an insight into the mechanisms responsible for exercise-mediated improvements in endothelial function [94]. They studied the impact of 4 weeks of cycle exercise on the internal mammary artery of subjects with coronary artery disease awaiting coronary artery bypass surgery. Training increased peak endothelium-dependent flow and FMD responses in the arteries of trained subjects, but not sedentary controls. After the final training session and the repeat in vivo vascular function assessments, a section of the internal mammary artery was harvested for in vitro vascular function assessment, immunohistochemistry, NO synthase mRNA isolation, and protein quantification. Aerobic training was associated with significantly higher NO synthase mRNA and protein expression and higher shear stress related eNOS phosphorylation, which correlated with in vivo ACh mediated vasodilator capacity. Aerobic training therefore improves endothelial function in vivo by upregulating NO synthase protein expression and by increasing phosphorylation of this enzyme, effects consistent with a shear stress mechanism for enhanced NO bioactivity with training.

More recently, to examine the suggestion that shear is a key mechanism responsible for changes in endothelium-mediated vasodilator function following aerobic training, subjects performed a single bout of cycle exercise [163]. During the exercise session, a cuff was placed around one arm to unilaterally decrease the exercise-induced elevation in blood flow and shear stress [163]. While vasodilator function improved immediately after exercise in the limb exposed to increases in shear stress, no changes were observed in the cuffed arm. To follow-up on this observation, we adopted the same model (i.e., unilateral cuff inflation to attenuate the exercise-induced blood flow and shear stress response) and performed 8 weeks of cycle exercise training [141]. We found significant, time-dependent changes in vasodilator function and structure of the brachial artery in the non-cuffed arm, while such adaptations were non-existing in the cuffed arm. Taken together, these data resulted in the conclusion that shear stress is a principal physiological stimulus to the vascular adaptation associated with aerobic training in vivo.

In order to confirm the importance of shear stress, independent of the complex stimulus of exercise, subsequent studies induced repeated episodic increases in shear stress at rest, using heating. As above, the experimental approach involved cuffing one arm during the heating bouts to provide a within subjects experimental manipulation of shear. Only the limb exposed to the greater change in blood flow and shear during heating bouts, that is, the forearm that was not exposed to cuffing, demonstrated improvement in NO-mediated vasodilator responses [168, 169]. We found that these adaptations occur in response to repeated exposure to *direct* (local) application of heat to the arm by submerging arms in a warm water [169], but also by repeated exposure to systemic heating by submerging the lower limbs in warm water which elevates upper limb shear rate through systemic thermoregulatory adjustments [170]. These findings suggest that increases in shear, independent on the method of inducing elevation in shear, can induce adaptation of vessels.

The majority of studies demonstrate an important role for the increase in shear stress in inducing structural vascular adaptation in response to aerobic exercise training. The classic study of Langille and O'Donnell established a link between changes in flow (or shear) and the endothelium to induce arterial remodelling [134].

They examined rabbit carotid arteries after unilateral ligation-mediated chronic decreases in flow (70 % reduction for 2 weeks). The diameter of the ligated vessel was significantly smaller than the contralateral control vessel; and this change was dependent upon the endothelium, inferring that flow-mediated changes in vessel structure are dependent upon the release of a substance from endothelial cells.

Taken together, the above data are consistent with the evolving hypothesis that arterial shear stress is a homeostatically regulated variable and plays a pivotal role in adaptations of the vascular bed in response to aerobic exercise training [86, 171]. In this conceptual framework, shear stress mediated arterial enlargement, which acts to mitigate the increases in transmural pressure and wall stress brought about by repeated exercise bouts [135, 172–177], and is dependent on an intact endothelium [134]. The consequent "structural" normalization of shear may obviate the need for ongoing and acute functional adaptations [85, 86]. This hypothesis [86] clearly fits with the time-course of changes in vascular function and structure, as described in an earlier paragraph in this chapter.

Cyclic Pressure

Increases in blood flow during aerobic exercise are also accompanied by significant increases in pulse pressure. This elevation in pressure across the cardiac cycle produces an increase in the rhythmic stretching (i.e., cyclic strain) of endothelial and vascular smooth muscle cells across the vasculature. The systemic nature of cyclic strain makes it an attractive mechanism for describing how aerobic exercise training positively impacts vascular adaptation, especially given the systemic nature of vascular adaptations to this type of exercise.

Data initially obtained from in vitro cell culture preparations suggested that cyclic strain produced an anti-atherogenic endothelial cell phenotype through the upregulation of eNOS mRNA, protein, and enzyme activity [178, 179]. In contrast, other experiments reported that cyclic strain did not change eNOS mRNA expression in cultured endothelial cells [159, 180]. The lack of changes in eNOS expression in addition to reported increases in monocyte chemotactic protein 1 (MCP-1) [181], intracellular adhesion molecule 1 (ICAM-1) [182–184], ET-1 [159], E-selectin [182], and reactive oxygen species (ROS) production [181, 184] suggests that cyclic strain likely produces a pro-atherogenic phenotype in cultured endothelial cells. More recent data obtained from isolated vessel preparations suggest that reducing the cyclic strain stimulus decreases the phosphorylation of serine 1177 on eNOS and increases ROS production through the upregulation of neutrophil cytochrome b light chain (p22-phox) and 47-kDa cytosolic subunit (p47-phox) of nicotinamide adenine dinucleotide phosphate [185].

The discrepancy in results obtained from endothelial cell culture and isolated whole vessel preparations cannot be accounted for by the presence of vascular smooth muscle in the later experimental paradigm, given that cyclic strain increases ROS production and MCP-1 in smooth muscle cell culture [186, 187]. One might speculate that reported differences between data obtained in endothelial and smooth

muscle cell culture versus whole vessel preparations may reflect the necessary cross talk between endothelial and vascular smooth muscle cells in producing an anti-atherogenic phenotype when exposed to a cyclic strain stimulus. Future research using cocultured endothelial and vascular smooth muscle cells will be required to determine if cross talk between endothelial and smooth muscle cells produces an anti-atherogenic cell phenotype in response to cyclic strain.

In humans, it is extremely difficult to selectively examine the impact of cyclic strain and repetitive increases in BP on the vasculature as each change in pressure will be associated with a change in blood flow and shear rate. This is probably an important reason why studies in humans have not attempted to specifically address the role of cyclic strain on the exercise-induced vascular adaptations. Although further studies are required, cyclic strain may be a potentially important stimulus for the arteries to adapt in response to aerobic exercise training.

Clinical Implications and Importance

Exercise Prescription Recommendations for Vascular Health Among Individuals with Hypertension

Prescribing exercise training to subjects with hypertension cannot be performed without specific suggestions regarding the frequency, intensity, time and type (FITT) of exercise; i.e., the 'dose' of the 'medication' of the FITT principle of exercise prescription. Unfortunately, most of this area is currently unexplored and no well-designed studies have been performed for an evidence-based prescription of aerobic exercise training for vascular health among individuals with hypertension. The (limited) evidence currently available around these FITT of exercise prescription for vascular health among individuals with hypertension that determine the 'dose of exercise' is summarised below.

Frequency Studies that have examined the effects of aerobic exercise training on the vasculature have used training regimes that varied between 2 and 6 times per week [77, 87, 88, 92, 117, 188–191]. However, no direct comparisons have been made between exercise training strategies that differ in the frequency of exercise training.

Intensity Although not specifically examined in subjects with hypertension, some studies have studies the impact of different intensities of exercise upon the magnitude of vascular adaptation. A well-designed and controlled study by Goto et al. [192] examined the effects of low (25 % of maximum oxygen consumption [$\dot{V}O_{2max}$]), moderate (50 % $\dot{V}O_{2max}$), and high (75 % $\dot{V}O_{2max}$) intensity aerobic training in young men. Endothelium-dependent forearm vasodilation improved in the moderate intensity group, but not in other groups. The reason for the lack of vascular adaptation in the low intensity aerobic training group may relate to the stimulus falling below a given threshold to induce vascular remodelling. In contrast, the reason for the lack of changes in the high intensity aerobic training group is not

likely to relate to an insufficient stimulus. The authors provided evidence that increased oxidative stress may have counteracted the beneficial effects of shear stress and exercise on the vasculature among the high intensity group.

A previous study from Bergholm *et al*. provided further evidence for this hypothesis. They reported that 3 months of high intensity running in physically fit male subjects reduced endothelium-dependent function [193]. The degree of endothelial dysfunction following training was greatest in subjects with the largest improvements in $\dot{V}O_{2max}$. The authors postulated that the training-induced decrease in circulating antioxidant levels may have adversely affected endothelial function in the highly trained or overtrained state. Alternatively, one should also consider the possibility of a distinct time-course in adaptations in vascular function and structure to different intensities of exercise.

Time Although very little is known about this topic, a recent pooled analysis revealed that a larger effect of aerobic exercise training on conduit artery endothelial function can be expected after a longer training intervention [194]. Whether a comparable relation is present for resistance artery adaptations is currently unknown.

Type A more detailed comparison between aerobic and resistance exercise training will follow in Chapter 6. When comparing different types of aerobic exercise, it should be notes that more recent studies have introduced high intensity interval training (HIIT). HIIT involves repeated exposure to short periods (1–4 min) of high intensity exercise (>90 % maximal workload) interspersed with similarly long periods of low intensity exercise (<40 % maximal workload). Studies that have directly examined the impact of HIIT found improved conduit artery vasodilator function in patients with heart failure [195], the metabolic syndrome [196], and patients with coronary artery disease [197, 198]. Some studies have even directly compared HIIT with aerobic exercise training have suggested the presence of a superior effect of HIIT to improve vasodilator function [195, 196, 199], although results are conflicting [198]. While these studies highlight the presence of (potentially more) successful training interventions to alter vascular function, future studies are necessary to identify the most appropriate type of training to improve the vasculature. Please see Chapter 1 for a detailed discussion of the FITT principle of exercise prescription targeting BP among individuals with hypertension, including comment on HITT.

Conclusion

Aerobic exercise training has well-established BP lowering effects (see Chapter 1). The drop in BP is largely explained by the decline in peripheral vascular resistance, as Q does not change or even increases after training due to enlargement of the cardiac dimensions and subsequent increases in SV among healthy individuals other than their high BP. Exploring the mechanisms of the drop in BP, studies have revealed systemic improvement in vascular function as well as structural enlargement in conduit and resistance vessels. These beneficial adaptations in vascular function and structure should contribute, at least partly, to the drop in resting BP that result from aerobic exercise training among individuals with pre to established

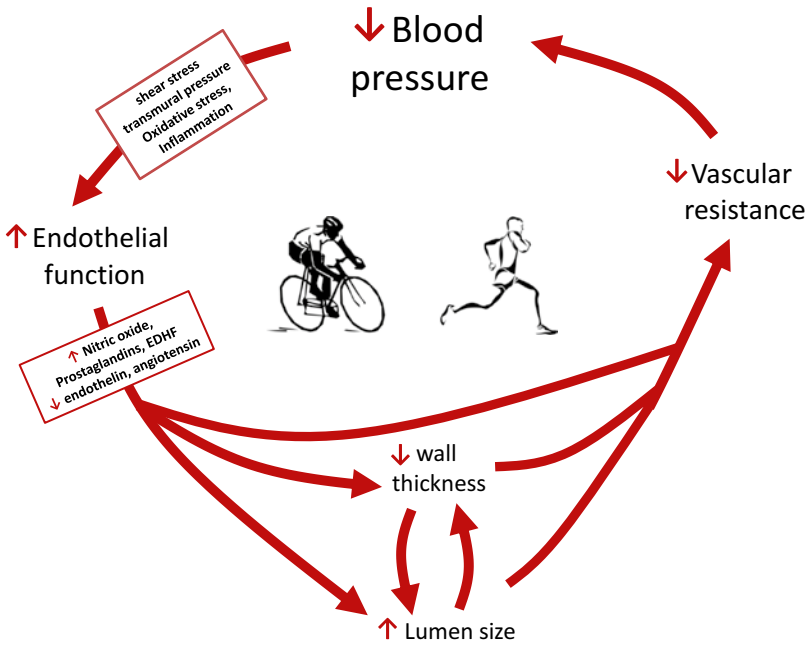

Fig. 5.3 Conceptual framework how exercise training influences blood pressure. This figure represents a conceptual framework how exercise training influences vascular function and structure, including the various hemodynamic stimuli which are presented in the boxes, ultimately leading to a decrease in peripheral vascular resistance and mean arterial blood pressure (*EDHF* endothelium-derived hyperpolarizing factor)

hypertension; while this process may also occur during the development of prehypertension and its progression to established hypertension.

Accordingly, BP appears to have a strong interplay with vascular function and structural characteristics, that both can be influenced in opposite directions (Fig. 5.3). While various stimuli such as cyclic pressure, endothelial progenitor cells and circulating hormones may contribute to the benefits of exercise, repeated increases in shear stress (or blood flow) represents a key stimulus to mediate the vascular adaptations to aerobic training. Shear stress directly acts upon the endothelium, leading to improvement in vascular function and enlargement of conduit and resistance arteries in the active and non-active regions. Such adaptations seem to bi-directionally influence BP regulation, however, the interplay among vascular adaptations as they relate to the BP reductions that occur following aerobic exercise training should be explored further to better elucidate the relationships among the two.

Key Points and Resources

- Prolonged aerobic exercise training lowers BP, especially in those with elevated levels of BP, which is likely mediated through a decrease in peripheral vascular resistance.

- Aerobic exercise training leads to (rapid) systemic improvements in vascular function, which are both evident in conduit and resistance arteries. Adaptations in vascular structure, i.e., dimension and wall thickness, occur more slowly and are predominantly present locally in physically active areas.
- In healthy subjects, the initial improvements in vascular function return towards baseline once structural enlargement of the blood vessels occur, which highlight the strong and complex interplay between functional and structural adaptations to exercise training. Whether a similar interplay is present in subjects with (pre) hypertension is currently under debate.
- Repeated elevation in shear stress, or the dragging force of blood upon the vascular wall, represents a key stimulus that mediates functional and structural vascular adaptation. Cyclic pressure and the release of circulating factors may also contribute to the benefits of aerobic exercise training on the vasculature.
- Despite the volume of literature on aerobic exercise training and vascular adaptation, there remains a critical need for randomized controlled trials in patients with hypertension to identify the FITT aerobic exercise training interventions characteristics that optimally alter vascular function and structure. This new information will eventually contribute to evidence-based prescription of optimal (and personalized) guidelines for aerobic exercise training.
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Chapter 6
Resistance Exercise and Adaptation in Vascular Structure and Function

Andrew Maiorana, Dick H.J. Thijssen, and Daniel J. Green

Abbreviations

1-RM	One repetition maximum
ACh	Acetylcholine
BP	Blood pressure
CHF	Chronic heart failure
DBP	Diastolic blood pressure
FITT	Frequency, intensity, time, and type principle of exercise prescription
FMD	Flow mediated dilation
HR	Heart rate
IMT	Intimal medial thickness
MVC	Maximum voluntary contraction
NO	Nitric oxide
SBP	Systolic blood pressure

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Introduction

Regular physical activity and exercise are important lifestyle factors for maintaining good health and reducing the risk of development of a range of chronic diseases. Aerobic activities, such as walking, cycling and swimming, have traditionally been recommended in population health messages [1]. However, recent position statements have highlighted the importance of including resistance exercise training to comprehensively address health and fitness [2–5]. These statements acknowledge the role of resistance training in maintaining and improving skeletal muscle strength, an outcome which is not fully achieved through aerobic training. Indeed, muscle strength is essential to maintaining normal functioning and quality of life across the lifespan because it is fundamental to many routine tasks of daily life, from elevating the body from a seated position to carrying bags and performing essential activities of daily living. Reduction in muscle strength occurs with physical inactivity, ageing, and many chronic diseases, highlighting the potential benefits of resistance training. Compared to the well-established, beneficial effects of resistance training on skeletal muscles, effects on the vasculature are less well defined.

Purposes of this Chapter

The primary purpose of this Chapter is to summarize the effects of resistance training on vascular structure and function to offer insight into its effects on vascular health; however, commentary on how these effects may translate to lower blood pressure (BP) is also included. Please see Chap. 2 for an in-depth discussion of the effects of resistance exercise on BP.

Key Terminology and Basic Concepts

Resistance Exercise

Physical activity spans a broad range of physical stimuli, ranging from low intensity muscle contractions which only engage small body segments to actions that work against external loads and impart a significant opposing force to muscular work. The latter type of exercise is commonly known as *resistance exercise*, by virtue of the external force 'resisting' muscular contraction. The most common method of applying resistance to muscles is through the lifting of weights (e.g., using free weights or pin loaded machines). Other approaches can include elastic bands (e.g., therabands), the raising of limbs, and body segments against gravity and hydraulic resistance.

Types of External Force Opposing Muscular Action and Their Distinctions

The mechanical properties of resistance exercise are largely characterised by the external force opposing muscular action [3]. If the opposing resistance is greater than the force generated by the muscular action, the muscle develops tension but does not shorten. This is described as an *isometric* contraction. When the muscular length changes in the setting of a constant external resistance, this is commonly called an *isotonic* contraction. While the term suggests equal muscular *tension* throughout the action, this is not purely correct, because muscle tension may vary even though the external resistance remains constant. When the muscular force overcomes the resistive force to produce a dynamic movement, a *concentric* contraction has occurred. An *eccentric* contraction occurs when the muscle force generated is less than the force of the load (voluntarily or otherwise).

In the past, resistance exercise has sometimes been described synonymously with isometric exercise. This fails to acknowledge the complex nature of resistance exercise. Indeed, many muscular actions involve a combination of isometric and isotonic contractions. During a simple biceps curl for example, the muscles of the hand and forearm contract isometrically, while gripping the dumbbell and isotonic contraction occurs in the biceps brachii to vary the joint angle at the elbow as the weight is lifted and lowered. Furthermore, it should be recognised that contractions underpinning classic forms of "aerobic" and "resistance" exercise exist on a continuum which is modulated by the nature or magnitude of the external load. For example, cycling is typically considered an 'aerobic' exercise, however, cycling against a high resistance can achieve a strength training effect [6].

Rationale for Resistance Training for Health Management

Aerobic exercise has historically been the primary focus of physical activity for health benefit. However, the intensity of muscular contraction typically employed during aerobic exercise induces relatively modest effects on muscular mass and strength. Skeletal muscle mass and function typically peak in the fourth decade of life and then start to decline at a rate of approximately 10 % per decade [7]. For many elderly people, sarcopenia (i.e., muscle wasting) and poor muscular strength significantly impair the ability to undertake everyday tasks, increasing the risk of falls and adversely affecting quality of life. To maintain and improve muscular strength, even in the elderly, muscles require frequent exposure to stimuli that activate sufficient force production to induce skeletal muscle fibre hypertrophy and optimize the firing pattern of motor units. This exposure can be achieved effectively through well designed resistance exercise training programs, individualized according to the age and clinical history of the patient [8].

There has traditionally been some reticence expressed about applying resistance exercise training in individuals with or at risk for cardiovascular disease due to concerns about an adverse effect on the vasculature or an inappropriate hemodynamic response [9, 10]. However, more recently, there has been a growing appreciation of the broad benefits of resistance exercise training for optimizing health and fitness and the prevention and management of cardiovascular disease [3]. A recent meta-analysis by Cornelissen et al. identified that resistance exercise training may have cardiovascular benefits, including reduced BP, and improved body composition and triglyceride levels [11]. The authors pooled interventions according to whether they involved dynamic resistance training ($k = 25$ trials) or isometric handgrip training ($k = 3$ trials). Handgrip training was the only mode of exercise employed in the isometric training trials. Both forms of exercise reduced BP, but a more pronounced reduction was observed with isometric handgrip training (11.8/5.8 mmHg) compared with dynamic resistance training (2.6/-3.1 mmHg). Due to the small number of trials involving isometric handgrip exercise, these results warrant confirmation from randomized controlled trials directly comparing dynamic and isometric exercise, and evaluating other forms of isometric exercise. Nonetheless, the main message remains that resistance exercise training, even when performed with a relatively small muscle mass, seems to have a BP lowering effect, however, the mechanisms remain undefined. See Chap. 2 for a detailed discussion on the role of resistance exercise in the prevention and treatment of hypertension.

The Influence of the Hemodynamic Response to Resistance Exercise on the Blood Vessels

In the context of the vasculature, it is pertinent to recognize that an important stimulus to adaptation involves changes in blood flow through the arterial lumen and pressure differences across the vessel wall. The forces can be collectively referred to as *hemodynamic stimuli*. For example, systemic changes in pulse pressure and heart rate (HR) and local release of vasoactive substances, which have been well documented during aerobic exercise, generate a recurrent hemodynamic (shear) stress that is associated with vascular function and structure adaptation following training [12, 13]. Less is known about how resistance exercise protocols influence vascular hemodynamics, although consistent with aerobic exercise, differences in upstream arterial driving pressure relative to downstream pressure in the resistance vessels is likely to be an important determinant.

Pure isometric exercise involves a modest increase in cardiac output in the setting of restricted muscular blood flow as a result of the increased intramuscular tissue pressure and direct occlusive transmural pressure on the artery caused by the contraction. The intensity of contraction required to restrict and occlude muscle blood flow remains controversial. In an early study, Humphreys and Lind [14] noted progressively increased forearm blood flow during hand grip isometric exercise at intensities up to 50 % of the maximum voluntary contraction (MVC).

However, others have found that forearm blood flow decreased from 20 to 25 % MVC [15, 16] and as low as 10 % MVC [17]. These findings indicate that at some point in the intensity continuum, blood flow will be restricted as a direct result of the isometric contraction, which is in contrast to aerobic exercise which facilitates larger blood flow to the muscles at higher intensities. Vasoconstriction also occurs in vascular beds supplying inactive muscles during isometric exercise. The consequent increase in vascular tone (from the inactive *and* active regions) in the setting of an increased cardiac output results in a disproportionate rise in systolic (SBP) and diastolic (DBP) BP compared with that during dynamic, aerobic exercise that imposes a 'pressure load' on the cardiovascular system.

Since the seminal work of Barcroft and Millen, it has been recognized that the periods of vascular occlusion during isometric contractions are followed by a period of reactive hyperaemia [15], creating rhythmic fluctuations in blood flow depending on whether the muscle is contracted or relaxed. Resistance exercise, in practice, is rarely purely isometric. For example lifting weights, a common method of providing resistance exercise, typically has an isometric and dynamic component and is characterized by frequent periods of rest. Accordingly, the hemodynamic response during resistance exercise represents a hybrid of that observed during pure isometric or dynamic exercise, with sets of exercise punctuated by bouts of localized hyperemia during periods of recovery. Therefore, resistance exercise as applied in practice is likely to result in periods of (muscle contraction-induced) restrictions in blood flow, post-contraction hyperemia, and dynamic exercise-mediated increases in blood flow. However, definitive studies using contemporary technology to describe blood flow to different regions during resistance exercise are currently lacking.

We have previously noted distinct patterns of blood flow in the brachial artery between aerobic (cycling) and resistance exercise (handgrip) [12]. During aerobic cycling exercise at low intensities, sympathetic vasoconstriction of the inactive forearm vessels results in a resistance to forward flow leading to an oscillatory pattern of systolic antegrade movement, followed by retrograde flow during diastole. When the systolic driving force increases at higher exercise intensities, the resistance to flow is overcome [18]. In contrast, resistance (handgrip) exercise results in a largely antegrade brachial artery flow, possibly initiated by local metabolic by products [19] that leads to a decreased downstream resistance in the forearm, in combination with a small increase in the upstream driving force for flow, despite only modest increases in HR and SBP. The handgrip exercise model might also reflect blood flow changes that occur locally with resistance exercise in other small muscle groups.

In contrast, dynamic resistance exercise involving large or multiple muscle groups may produce a systemic hemodynamic response, more characteristic of that occurring during cycle ergometry. Indeed, systemic hemodynamic changes in HR and BP are well documented during resistance exercise of this nature [20]. The resulting hemodynamic stimulus may potentiate the upregulation of anti-atherogenic genes, contribute to improvements in endothelial function, and create an environment for better BP control, similar to that which occurs in response to aerobic exercise [21, 22]. Resistance exercise can be modulated in a variety of ways [23] (Table 6.1),

Table 6.1 Determinants of resistance exercise stimuli that influence the acute hemodynamic response

Resistance exercise determinants	Impact on hemodynamic response
1. Magnitude of the load	↑ BP *response*, proportional to the %1-RM
	↑Vessel compression with ↑increased %1-RM
2. Number of repetitions	↑HR and BP *response* with ↑ repetitions
3. Number of sets	↑HR and BP *response* with subsequent sets (if recovery is incomplete between sets)
4. Rest in-between sets	↑HR and BP *recovery* with prolonged rest between sets
5. Fractional and temporal distribution of the contraction modes per repetition and duration of one repetition	↑ BP *response* with prolonged duration of contractions
	↑ HR *response* with more rapid contractions
6. Rest in between repetitions	↑ Muscle hyperaemia between contraction with prolonged rests between reps
7. Time under tension	HR and BP *responses* ↑proportionally to the time under tension
8. Volitional muscular failure	↑HR and BP *response* when volitional muscle fatigue is achieved, than not
9. Range of motion	↑HR *response* with greater range of motion. Effects on BP unknown
10. Anatomical definition of the exercise (exercise form)	Variable effects on HR and BP dependent on body position (i.e., upright vs. supine)

Adapted from Toigo and Boutellier [23]
BP blood pressure, *1-RM* one repetition maximum, *HR* heart rate

all of which are likely to influence the acute hemodynamic response elicited as a result of the exercise. As such, the stimulus on the vasculature might be expected to vary. However, while determinants # 1–3 (and to a lesser extent 4 and 5) are often described, determinants # 6–10 have rarely been considered in the literature pertaining to resistance training and vascular adaptation.

Methods

Papers sourced for this review examined the impact of resistance exercise training on vascular structure and function, specifically endothelium dependent and independent effects. Using PubMed as the primary search engine, we searched for papers that involved resistance exercise training ('resistance training OR resistance exercise training OR strength training OR weightlifting OR handgrip training OR isometric handgrip training OR isometric exercise training'). We included papers that used combined aerobic and 'resistance' exercise (i.e., concurrent) training, but excluded modes of 'resistance training' in which training intensity was not accurately quantified, such as *therabands*. To specifically discuss the effects of resistance training on vascular function and structure, we combined the search strategy

as stated above with 'vascular OR blood flow OR dilat* OR endothel*'. Papers included in the review were limited to human studies published in English. There were no restrictions on the year of publication. The reference lists of articles identified were reviewed and articles that met the above criteria were included. A detailed description of the methods involved in the assessment of vascular function and structure is outlined in Chapter 5 **Aerobic Exercise Training: Effects on Vascular Function and Structure**.

Effects on Whole Body Resistance Exercise Training

Whole body resistance exercise training in the context of this section relates to training protocols that involve dynamic resistance exercise of multiple muscle groups across the upper and lower body, consistent with the approach recommended in current guidelines to achieve health benefits.

Effects of Whole Body Resistance Training on Vascular Structure

Conduit Artery Diameter

Arterial diameter has the capacity to adapt in response to changes in body size and composition [24–26]. These observations suggest that artery size may be influenced by resistance training-induced changes in muscle bulk or associated blood flows. One potential mechanism for structural remodelling of the conduit arteries in response to resistance training is the hemodynamic effect of resistance exercise which may mediate changes in vascular structure to maintain peak shear rate. In support of this hypothesis, 6 months of high intensity resistance exercise training involving predominantly upper limb exercises increased the lumen diameter of the brachial artery in healthy young males [27]. These findings suggest that resistance training increases arterial lumen size in conduit arteries feeding active muscle beds.

Conduit Artery Wall Thickness

Cross-sectional studies suggest that prolonged, high intensity resistance exercise training may lead to arterial "thickening" as expressed by increased arterial intimal medial thickness (IMT); resistance trained masters athletes had significantly larger femoral IMT than age-matched sedentary controls [28]. However, the clinical relevance of modest changes in IMT with long-term exposure to resistance exercise training is unclear and prospective trials of resistance training have not supported this assertion. For example, 12 months of whole body moderate intensity resistance

training (3 sets of 8–10 repetitions, twice weekly) had no effect on carotid IMT in healthy, but overweight women [29]. Similarly, carotid artery IMT was unchanged after either 3 months of whole body resistance training in young men [30], or 4 months of whole body resistance training in young and middle aged men [9]. In contrast, 6 months of high intensity resistance exercise training in healthy young males significantly decreased carotid artery IMT, with non-significant reductions in brachial and femoral artery IMT [31]. The change in carotid IMT in this study, compared to interventions of a shorter duration, suggest that intensive longer term training may be required to reduce carotid arterial wall thickness, consistent with observations following aerobic exercise training [32].

Decreased brachial artery IMT was recently observed following 12 weeks of aerobic or resistance exercise in patients with congestive heart failure (CHF) [33]. While structural adaptations occurred with both modes of exercise, the effect of whole body resistance exercise was more pronounced. In contrast to the study by Spence et al [27], these adaptations to the brachial artery occurred despite minimal involvement of the upper limbs in either mode of training, suggesting a systemic effect, possibly through endothelium dependent upregulation of nitric oxide (NO) production due to increased shear stress in vessels remote to the exercising limb.

In combination, these studies suggest that prolonged resistance exercise training may decrease, rather than increase carotid artery IMT in healthy individuals. While the effect of resistance training on artery wall thickness is less clear in patients with established cardiovascular disease, a preliminary study in patients with CHF found that peripheral conduit vessel function was decreased. In summary, there is little evidence to support that vascular structure is adversely affected by recreational resistance training, nor that the increased IMT observed in resistance trained athletes in a cross sectional study [28] has clinical significance. Instead, it may just be an innocuous adaptation, similar to the benign cardiac hypertrophy often observed with prolonged resistance training [34].

Effects on Whole Body Resistance Exercise on Vascular Function

Vascular Compliance

Historical concerns that prolonged resistance exercise training may be detrimental to vascular health largely stem from studies linking resistance training to increased arterial stiffness in otherwise healthy men [9, 35], although this has not been a universal finding [30, 36]. A recent meta-analysis may help clarify this issue. This meta-analysis revealed that increased arterial stiffness was only evident in young subjects who undertook high intensity exercise, with no effect observed in middle aged subjects who trained at moderate intensities [37]. While the clinical significance of slightly elevated arterial stiffness in healthy, young individuals remains unclear, these findings raise the intriguing hypothesis that the impact of resistance

exercise training on the vasculature may be dependent on age, training intensity, or both. It is feasible that reduced arterial compliance following resistance training is countered by positive endothelial adaptations. Kawano and colleagues found that men with at least a 10 year history of regular, vigorous intensity resistance training demonstrated lower carotid arterial compliance compared with age-matched control subjects [38]. However, this adaptation did not translate to impaired endothelial function of the carotid artery in response to the cold pressor test, an assessment of the balance between adrenergic vasoconstriction and vasodilation [39].

Conduit Artery Vasodilator Function

Several studies have examined the impact of whole body resistance exercise training on conduit artery flow mediated dilatation (FMD), an ultrasound technique used extensively to measure conduit artery endothelium dependent NO function (see Chap. 5 for a more detailed description of this technique). In adults with obesity, 12 weeks of leg press exercise performed at 90 % one repetition maximum (1-RM), plus abdominal and back exercises, resulted in significant improvement in brachial artery FMD; an outcome also observed in a parallel group performing moderate intensity (60–70 % maximum HR) continuous aerobic exercise [40]. The training-induced improvement in endothelial function occurred in association with reduced levels of antioxidants, suggesting that reductions in oxidative stress may contribute to the upregulation of endothelial function. Long term (1 year) whole body resistance exercise training has also been shown to improve FMD, independent of any change in cardiovascular risk factors in overweight but healthy eumenorrheic women [29]. In patients with a history of myocardial infarction, only 4 weeks of whole body resistance training (at 60 % 1-RM) was sufficient to improve FMD [41]; but the improvements in FMD disappeared after 1 month of detraining, highlighting the transient nature of training-induced vascular adaptations.

It must be emphasised that a positive effect of resistance training on vascular function is not a universal finding. Twelve weeks of progressive resistance training at up to 90 % 1-RM performed 5 times a week in healthy young males failed to improve FMD [42]. An important difference with other studies, which found improvement in vascular function is that this study included young healthy subjects, who likely had normal (or "optimized") endothelial function *a priori*.

Resistance exercise training is often prescribed in combination with aerobic exercise termed *concurrent exercise training*. An early study by Clarkson et al. in young army recruits found that daily 3 mile runs and upper body strength and endurance exercises significantly increased brachial artery FMD [43]. Several subsequent studies examining conduit artery endothelial function adopted a circuit of combined aerobic and resistance exercise performed in alternating bouts. In subjects with medical histories associated with impaired vascular function *a priori* (i.e., in the presence of cardiovascular conditions or risk factors known to adversely affect vascular function), 8 weeks of concurrent exercise training improved FMD in subjects

with type 2 diabetes mellitus [44], coronary artery disease [45], and individuals on medication for hypercholesterolemia [46].

These findings confirm that in chronic conditions associated with vasculopathy (i.e., disorders of the blood vessels), resistance training appears to complement the well documented benefits of aerobic training. In fact, combining resistance and aerobic training may have an additive benefit on vascular function; for, 12 weeks of concurrent exercise training in patients with CHF produced greater improvement in vascular function than aerobic interval training alone [47]. It was speculated that the increased peripheral blood flow associated with a larger exercising muscle mass during resistance training mediated the more dramatic improvements in vascular function. It may also be the case that including a resistance training component in an exercise regimen may complement the BP lowering effects of aerobic exercise [11].

In summary, consistent with the effects of aerobic exercise training, whole body resistance exercise induces positive adaptations in conduit artery vascular function, which are more readily expressed in subjects with an *a priori* lower conduit artery endothelial function (i.e., in the presence of cardiovascular conditions or risk factors known to adversely affect vascular function) than "normal" endothelial function. This concept has been termed the *law of initial values*, and is discussed further in Chap. 1. In cohorts with established cardiovascular disease or risk factors, improvements appear to occur across a range of varying intensities and durations of resistance training. In healthy individuals, resistance training performed in isolation has not been shown to improve vascular function. However, concurrent exercise training at high intensity may demonstrate beneficial effects on vascular function in healthy volunteers. See Chap. 4 for more detailed discussions of the effects of concurrent exercise on BP.

Effects of Whole Body Resistance Exercise on Resistance Artery Vasodilator Function

An early, small ($n=9$) and uncontrolled study of resistance training in patients with CHF increased basal forearm blood flow, but not vasodilator responses to exercise or limb ischemia [48]. However, in a follow up study by the same researchers involving a randomized controlled protocol, the forearm vasodilator response to exercise and limb ischemia was increased after whole body resistance training, highlighting the potential for positive adaptations to resistance vessels in response to predominantly resistance exercise in patients with CHF [49]. The effects of resistance *versus* aerobic training on reactive hyperemic forearm blood flow was evaluated in individuals with pre- or Stage 1 essential hypertension not taking medications for their high BP randomly assigned to 4 weeks of training [50]. The two modes of training were well matched for frequency and intensity. Peak forearm blood flow following a 5 minute occlusion increased in response to both training modes, but the magnitude of change was greater following resistance training.

This finding raises the intriguing possibility that resistance training may upregulate vascular function to a greater extent than aerobic exercise in resistance vessels of individuals with hypertension, an adaptation that occurs rapidly and may contribute to the effects of resistance exercise in improving BP [11]. In support of this premise among young, healthy individuals, moderate to high intensity resistance training (8–12-RM) improved resistance vessel endothelial function, a finding which was similarly present in both young African American and Caucasian men [51]. This result may have specific clinical relevance to African American men, a group who experience a disproportionately high burden on hypertension and related disorders [52, 53].

In a unique study of different training volumes on forearm vascular function [54], healthy young subjects were randomized to either a high volume group (3 sets per station) or a low volume group (1 set per station) of whole body resistance exercise. For each station, participants performed 2 or 3 exercises at 8–12-RM. Training was conducted 3 days per week for 5 weeks. Vascular function did not change for either group following training. However, when the poorest pretraining vascular measures were pooled into one group, regardless of training volume, there was a significant increase in forearm reactive hyperemic blood flow observed following training. This finding supports the hypothesis that subjects with poorer *a priori* vascular function are more amenable to training-induced adaptation and this may be a more important determinant of training-induced adaptations than training load.

Combined or concurrent aerobic (70–85 % maximum HR) and resistance exercise (50–65 % 1-RM) circuit training also improved forearm resistance vessel response to intrabrachial infusions of the endothelium dependent vasodilator acetylcholine (ACh) in patients with CHF [55], hypercholesterolemia [46] and type 2 diabetes mellitus [44]; all groups with impaired vascular function *a priori*. These studies deliberately avoided engagement of the forearm muscles during training, suggesting that the vascular adaptations observed were systemic in nature. However, a similar training protocol failed to enhance resistance vessel function in healthy, middle aged subjects [56]. In combination, these observations suggest that moderate intensity training involving a resistance component provides a stimulus to upregulate endothelial function when it is suboptimal at baseline, but may be insufficient to improve endothelial function in subjects without impairment. Notably, the effects of concurrent exercise training improved endothelial function to near normal levels in participants with CHF and in just 8 weeks (Fig. 6.1).

In summary, adaptations to resistance vessel function in response to resistance training appear to occur rapidly (within 5 weeks) when vascular function is suboptimal at baseline. However, when pretraining vascular function is better (i.e., at a level observed in young, healthy individuals) the effect of resistance training is equivocal, although there is there is some evidence for a beneficial effect of resistance training at higher intensities The presence of systemic vascular adaptations and associated reductions in total peripheral vascular tone in response to whole body resistance training may be a mechanism by which resistance training lowers BP [11]. This highlights the potential of resistance training in preventing age-related increases in BP and as a therapeutic modality for reducing BP in individuals with pre- and established hypertension, although there is a scarcity of data from this latter group.

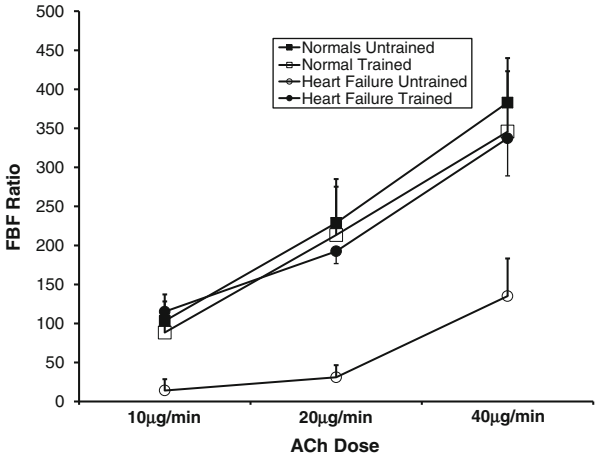

Fig. 6.1 Forearm blood flow (FBF) response to three incremental doses of acetylcholine (ACh) in healthy individuals and subjects with heart failure following usual activity (untrained) and 8 weeks of concurrent circuit training (trained). This figure was adapted from Figure 3, Maiorana et al. 2000 [55] and Figure 3, Maiorana et al. 2001 [56]. *FBF* forearm blood flow, *ACH* acetycholine

Effects of Isolated, Small Muscle Group Resistance Training

Handgrip training has been a commonly employed model of exercise for evaluating vasomotor control of vessels supplying a small muscle group and represents resistance training of the forearm musculature. Often termed *isometric handgrip training*, the "isometric" description is somewhat misleading in that the action involved is rarely purely isometric because there is a period of dynamic contraction at the commencement of the gripping process. The relative contribution of isometric *versus* dynamic muscle contraction is dependent on the intensity of exercise and the duration that the 'handgrip' is maintained (i.e., the temporal distribution of the dynamic versus isometric contractions). This type of exercise which involves localized contractions of the forearms without the involvement of other muscle groups provides insight into the impact of a localized stimulus in the absence of systemic changes in cardiovascular hemodynamics.

Effects on Isometric Handgrip Exercise on Vascular Structure

An early handgrip training study by Sinoway et al. in healthy individuals identified localized resistance vessel remodeling, independent of skeletal muscle hypertrophy and sympathetic or circulatory influences [57]. These findings which were later confirmed [58] indicated that resistance artery remodeling occurs in response to

resistance exercise as a result of localized and intrinsic vascular stimuli. More recently, Hunt et al. reported popliteal artery remodeling following 6 weeks of low load (30 % MVC) unilateral plantar flexion resistance exercise with blood flow restriction [59]. This supplanted an early increase in FMD which returned to baseline levels after 6 weeks. Training also resulted in increased post occlusion blood flow, a reflection on resistance vessel structural adaptation (i.e., cross-sectional area). In combination, these findings propose that resistance vessel structural adaptations and conduit vessel function precede changes in conduit artery structure. Changes were only evident in the trained limb indicating a localized effect. The rapid vascular adaptations observed may reflect the ischemic stimulus during training or the effects of postocclusion reactive hyperemia.

Effects of Isometric Handgrip Exercise on Vascular Function

Conduit Vessel Vasodilator Function

The impact of isometric handgrip exercise on conduit artery function has been examined in subjects with CHF [60, 61] and hypertension [62]. Hornig and colleagues [60] performed an early study in which radial artery FMD was enhanced after 4 weeks of handgrip training, an improvement that was abolished using NO blockade. Hambrecht et al. [61] also demonstrated that handgrip exercise training, particularly with L-arginine supplementation (a biological precursor of endogenous NO in situ), enhanced radial artery diameter change in response to ACh infusion. These findings have important clinical relevance to patients with CHF because they indicate that vascular adaptations can occur with exercise involving isolated muscle groups such as with isometric handgrip exercise, a training approach that can be used in patients with advanced disease in whom exercise tolerance is severely impaired. Accordingly, targeted muscle training may reverse the peripheral abnormalities which limit functional capacity in individuals with CHF by decreasing peripheral resistance and enhancing oxygen delivery, without the hemodynamic burden associated with more systemic forms of training. Finally, McGowan observed enhanced brachial FMD responses after isometric handgrip exercise training in patients with primary hypertension [62, 63], highlighting the potential role of resistance exercise training in the management of elevated BP [11].

Effects of Isometric Handgrip Exercise on Resistance Vessel Vasodilator Function

In healthy young men, 4 weeks of low (approximately 30 % MVC) [58] or high (approximately 70 % of MVC) intensity [64] handgrip training failed to improve forearm blood flow responses to ACh. In contrast, low intensity handgrip training in

middle aged subjects significantly improved endothelial function [65], suggesting that the decrease in endothelial function that occurs with ageing may be more responsive to training than in 'younger' vessels. In combination, these findings provide further support for the hypothesis that vessels with suboptimal endothelial function *a priori* may be more responsive to the effects of resistance exercise training, and that this may be the case in response to both a localized as well as systemic training stimuli.

Local versus Systemic Adaptations to Resistance Exercise Training

There is convincing evidence across a range of clinical cohorts that resistance exercise training can lead to adaptations in vascular structure and function. These adaptations appear to occur as both localized and systemic training effects. There are several possible mechanisms that may underlie these changes. Exercise-induced shear stress, a well-established mediator of vascular function and structure [32] may act on vessels locally [66], as well as vascular beds remote to the exercising muscle when multiple, large muscle groups are employed in the training intervention. These changes in blood flow in remote areas are likely due to systemic changes in vascular hemodynamics, including exercise-related arterial or transmural pressure changes [21]. Other potential mediators include circulating factors and reduced oxidative stress resulting from the exercise intervention. Further research is required to determine the relative contribution of these mechanisms in response to varying resistance exercise training regimens.

Clinical Implications and Importance

The body of literature describing the effects of resistance exercise training on vascular function and structure is less extensive than that related to aerobic exercise training. Moreover, there is a lack of trials directly comparing different resistance training interventions so guidelines on the *F*requency, *I*ntensity, *T*ime, and *T*ype (or FITT) principle of exercise prescription need to be informed by the consensus from findings across different studies that we have consolidated below for the effects of whole body resistance training on vascular function and structure.

Frequency Studies that have examined the effects of whole body resistance training on vascular function and structure have most commonly employed 2–3 days per week of training, consistent with resistance training guidelines. This frequency of training has been associated with significant improvements in muscular strength [3], as well as improvements in vascular function. Given the importance of

regular aerobic exercise for optimal health, and the challenge many people have in fitting exercise into the competing demands of their life, the broadly recommended frequency of resistance exercise at least 2–3 times weekly would also appear appropriate to achieve good vascular health. However, it should be acknowledged that no previous study has directly compared the impact of different resistance training frequencies on BP. Concurrent exercise training performed 3 times a week offers a way of achieving the combined benefits of both modes of exercise in a time efficient manner and has proven effective in improving vascular function in a variety of different cohorts [44–46, 55].

Intensity A wide range of intensities have been applied to studies investigating the effects of resistance training on vascular function. While high intensity resistance training has been associated with increased arterial stiffness, there is no evidence that it adversely affects conduit or resistance vascular function. The majority of studies in cohorts with established pathology (including hypertension) that have reported positive adaptations prescribed exercise in the range of 40–70 % 1-RM commonly considered moderate intensity. Higher intensities (>80 % 1-RM) have been prescribed in healthy individuals. While these protocols have produced equivocal results in terms of vascular function, positive changes to arterial structure as reflected by decreased IMT have been reported [31]. No evidence currently exists that these adaptations have adverse pathological implications.

Time Exercise time in the context of resistance exercise can be expressed in a variety of ways. For the purpose of the recommendations being made, and consistent with the concept applied to aerobic exercise training, "time" is expressed as the total time of an individual exercise session. Most studies involving whole body resistance exercise that have been effective in improving vascular function and structure outcomes have prescribed exercise for approximately 45–60 min each training session. This allows 2–3 sets of 6–8 exercises to be performed addressing major functional muscle groups. Assuming 30–60 s per exercise and 30–90 s of rest between exercises, protocols are typically completed within an hour.

Type Two types of resistance exercise have been considered in the literature and discussed in this Chapter pertaining to vascular function and structure; dynamic (*isotonic*) exercise (i.e., whole body) and isometric handgrip training. Both have resulted in beneficial vascular adaptations including lower BP. However, the broader range of benefits associated with dynamic exercise training that incorporates major muscle groups, and the potential for this modality to have systemic vascular effects, supports the widespread adoption of whole body dynamic exercise training for both healthy and clinical populations. Nonetheless, a meta-analysis by Cornelissen et al. that contains data from three isometric handgrip training studies suggests that this mode of exercise can produce a dramatic BP lowering effect, although the literature is small and the mechanisms are not clear [11]. Randomized controlled trials directly comparing the effects of dynamic and isometric exercise are required to gain insight into their BP lowering potential in healthy and clinical cohorts.

Conclusion

While studies examining the effects of resistance exercise on vascular function have produced some conflicting results, the weight of evidence supports a beneficial effect of resistance exercise training on the function and structure of the vasculature. Positive adaptations appear to occur in both conduit and resistance vessels, suggesting they may contribute to the observed BP lowering effect of resistance exercise training (see Chap. 2 for an in-depth discussion on the effects of resistance exercise on BP). It is noteworthy that patient groups and older populations with impaired vascular function *a priori* appear to be most responsive to resistance training, and these positive adaptations are observed at a lower threshold of training in these individuals than those with normal vascular function. When equivocal findings exist, this is likely influenced by factors including different resistance training interventions, variability in assessment techniques, and subject characteristics (e.g., younger age and optimal vascular health at baseline). Despite these potential confounders, there is very little evidence from the literature that resistance training impairs vascular function, and less still that it contributes to clinically significant vascular pathology. While traditional training parameters that include the FITT principle of exercise prescription are typically well described, other factors that have potential to influence the response of the vasculature to resistance training are very rarely reported (i.e., fractional and temporal distribution contractions, duration of repetitions, rest between repetitions, time under tension, etc). The *FITT* principle of exercise prescription as applied to aerobic exercise training is limited for describing the array of training variables that are likely to influence the acute hemodynamic response to resistance exercise as well as the training-induced adaptations to vascular structure and function. Examining a broader array of resistance exercise variables (see Table 6.1) by directly comparing training interventions with these variables manipulated is required to unravel the optimal resistance training prescription for vascular outcomes and is an important area for future research. In practice, resistance training should be encouraged across a broad spectrum of age groups and clinical conditions, including patients with hypertension and established cardiovascular disease, for its well established effects on muscular strength and function and BP, but also for its potential to improve vascular health.

Key Points and Resources

- Resistance training results in positive adaptations to vascular structure and function.
- Beneficial changes in vascular function can occur as a localized adaptation as with isometric handgrip exercise, or systemically with whole body resistance training that involves a large muscle mass.
- Adaptations are most commonly observed when vascular function is impaired *a priori* (i.e., in the presence of cardiovascular conditions or risk factors known to adversely affect vascular function).

- Comprehensive exercise programs should include a resistance exercise training component, not only for improving muscular strength but also its many other benefits that include BP management and vascular health.
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Chapter 7
Effects of In Vitro Laminar Shear Stress as an Exercise Mimetic on Endothelial Cell Health

Michael D. Brown and Joon-Young Park

Abbreviations

BAEC	Bovine aortic endothelial cell
BH_4	Tetrahydrobiopterin
cGMP	Cyclic guanosine monophosphate
COX	Cyclooxygenase
CVD	Cardiovascular disease
EC	Endothelial cell
ECE	Endothelin converting enzyme
eNOS	Endothelial nitric oxide synthase
ET-1	Endothelin-1
GPX	Glutathione peroxidase
HAEC	Human aortic endothelial cell
HCAEC	Human coronary artery endothelial cell
HMVEC	Human microvessel endothelial cell
HUAEC	Human umbilical artery endothelial cell
HUVEC	Human umbilical vein endothelial cell
ICAM-1	Intracellular adhesion molecule-1
IL-6	Interlukin-6
JAK-STAT	Janus kinase-signal transducer and activator of transcription

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KLF2	Krüppel-like factor 2
LSS	Laminar shear stress
MCP	Monocyte chemotactic protein 1
miRNA	Micro ribonucleic acid
mRNA	Messenger ribonucleic acid
mtDNA	Mitochondrial deoxribonucleic acid
NADPH	Nicotanimide adenine dinucleotide phosphate oxidase
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
NOS	Nitric oxide synthase
Nox	Nicotanimide adenine dinucleotide phosphate oxidase
Nrf2	Nuclear factor erythroid 2-like-2
P13k/Akt	Phosphoinositide 3-kinase inhibitor/protein kinase B
PG	Prostaglandin
PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
PGHS	Prostaglandin G/H synthase
PGI_2	Prostaglandin-2
PKA	Protein Kinase A
PTEN	Phosphatase and tensin homolog
ROS	Reactive oxygen species
Ser	Serine
SIRT1	Sirtuin 1
SOD	Superoxide dismutase
TNF-α	Tumor necrosis factor-alpha
Trx	Thioredoxin
VCAM-1	Vascular cell adhesion molecule-1

Introduction

The vascular endothelium originates from the embryonic mesoderm and forms a monolayer of endothelial cells (EC) that line the intimal surface of all blood vessels. It was originally thought that the endothelium was only a passive barrier between the blood and tissues. We now know that the endothelium is a highly dynamic organ because it senses both chemical and mechanical stimuli, integrates the signals, and transduces the signals across the membrane and into the EC. The endothelium is the major regulator of vascular homeostasis as it regulates the balance between vasodilation and vasoconstriction, smooth muscle proliferation and migration, thrombogenesis, and fibrinolysis. As with most organs, when the balance in the regulation point is disrupted, organ dysfunction ensues.

It is well known that the endothelium is an important determinant of resting vascular tone, and therefore, it is not surprising that endothelial dysfunction has been associated with hypertension. The term *"endothelial dysfunction*" was created in the mid-1980s after the seminal experiments by Furchgott and Zawadzki [1] showing that

blood vessel relaxation in response to acetylcholine required the presence of ECs. Endothelial dysfunction was first shown in human hypertension in 1990 [2]. Damage to the endothelium creates an arterial environment (i.e., pro-inflammatory, pro-oxidant) that supports the initiation and development of high blood pressure. This "activated" endothelium leads to the production of messenger molecules and the expression of pro-inflammatory cytokines and adhesion molecules. Studies have implicated a dysfunctional endothelium as a risk factor for future cardiovascular events [3].

The blood pressure-lowering effect of aerobic exercise training in people with hypertension has been well documented and ascribed, in part, to direct adaptations of ECs. It is now well accepted that aerobic exercise training is a nonpharmacologic therapy to improve endothelial function. It is generally agreed that the stimulus for exercise-induced adaptations of ECs is the intravascular shear stress associated with blood flowing along the ECs. The studies of Jean Poiseuille resulted in theories describing the flow inside a cylindrical conduit, widely known as Poiseuille's law (i.e., the rate of flow through a tube is directly proportional to the driving pressure and the fourth power of the radius) [4]. It is the nature and magnitude of the blood flow during exercise that leads to the beneficial adaptations of ECs.

Purposes of this Chapter

There are several purposes of this chapter: (1) to review endothelial dysfunction at the cellular level, (2) to describe the different types of experimental shear stress to which endothelial cells are exposed and the methodology used to examine them; and (3) to specifically describe the effects of high physiological levels of laminar shear stress (LSS) on the expression of genes and proteins directly related to endothelial health. The criteria by which we selected genes and/or proteins were that: (1) the effects of LSS had to be well documented and consistent, and (2) the genes and/or proteins are candidates for hypertension. Please see Table 7.1 for a list of

Table 7.1 Biological systems in which genes that influence endothelial cell function are modulated by laminar shear stress

Biological system	Example
Adhesion	PGI_2
Coagulation and anti-coagulation	PGI_2, NO
Inflammation	TNF-α, IL-6
Metabolism	PGC-1α and SIRT1
Oxidants and anti-oxidants	NOx and SOD
Vasoregulation	NO and ET systems and PGI_2

In the left column are examples of genes/proteins that were discussed in the current chapter
PGI2 Prostaglandin-2, *NO* nitric oxide, *TNF-α* tumor necrosis factor-alpha, *IL-6* Interlukin-6, *PGC-1α* peroxisome proliferator-activated receptor-gamma coactivator 1, *SIRT1* sirtuin 1, *NOx* nicotinamide adenine dinucleotide phosphate, *SOD* superoxide dismutase, *ET* endothelin. Adapted from Chen et al. [163], Ohura et al. [17], and Wei et al. [164]

biological systems in which there is compelling evidence for EC genes that are modulated by LSS. For example, genes coding for proteins in nitric oxide (NO) and endothelin systems would fall under the "vasoregulation" category, and genes coding for superoxide dismutase (SOD) would fall into the "oxidants and antioxidants" category. Also please see Chap. 10 for detailed discussions on the genetics of the blood pressure response to exercise training.

Key Terminology and Basic Concepts

What is Laminar Shear Stress (LSS)?

There are basically two types of shear stresses on ECs: (1) unidirectional/laminar, and (2) disturbed/oscillatory. Laminar blood flow is characteristic of steady, undisturbed blood flow that creates a constant shear stress along the EC surface. EC exposed to laminar flow typically exhibit an anti-atherogenic and vasoprotective phenotype. Bifurcations points in the arterial tree change the flow patterns such that there is a low and oscillatory shear stress flow pattern beyond the bifurcation [5]. This type of flow pattern co-localizes with atherosclerotic lesions [5].

It is important to note that regions of low flow and high oscillatory shear stress observed during resting conditions are dramatically reduced during a session of aerobic exercise. These regions experience higher flow and the hemodynamics profile is converted to one that is laminar [6].

What is Chronic Shear Stress Exposure In Vitro*?*

Any duration of the applied LSS >6 h is considered by most to be a chronic exposure. The reason for this is that after 6 h is when protein expression (adaptive) changes can be detected. These changes in the protein expression profile are consistent with the known beneficial endothelial adaptations that result from chronic aerobic exercise training. Most studies that chronically sheared ECs reported herein used durations between 12 and 48 h, with 24 h being the most common duration.

What are Low and High Levels of Shear Stress?

Malek et al. described the normal magnitudes of shear stress in veins and arteries, and in low-shear and high-shear pathologic states [5]. Normal arterial shear stress levels range from 10 to 70 dyn cm^{-2}. Lower levels (<4 dyn cm^{-2}) stimulate an atherogenic phenotype, while levels ≥10 dyn cm^{-2} induce an atheroprotective

phenotype. Studies have shown that a prolonged (24 h) high physiological level of LSS profoundly alters the EC phenotype by modifying the gene expression profile creating an environment that is anti-inflammatory, anti-oxidant, and anti-apoptotic [7].

The Endothelium, Shear Stress, and Mechanotransduction

Due to the viscosity of the blood, the flow of blood exposes ECs to a tangential friction force called *hemodynamic shear stress*. Hemodynamic shear stress is a major determinant of vessel diameter and vascular remodeling [8, 9]. Structurally, ECs alter their morphology depending on the nature of the shear stress. Unidirectional high levels of shear stress, or LSS, causes ECs to align in the direction of the shear stress and take on a longitudinal or fusiform shape compared to the typical cobblestone shape (Fig. 7.1). This reorientation streamlines the EC, decreasing the effective resistance and lowering shear stress [10].

Mechanotransduction describes the interaction between biomechanical forces and EC function. Therefore, the mechanical forces acting on the luminal side of ECs cause deformation of the EC which is transmitted through the cytoskeleton to the nucleus [11]. There are various types of mechanosensors such as ion channels, and G-protein-coupled and tyrosine kinase receptors to name a few [12]. The endothelium responds to a sudden increase in shear stress within milliseconds [13]. This immediate response is followed within a few hours by changes in the regulation of many genes (Fig. 7.2).

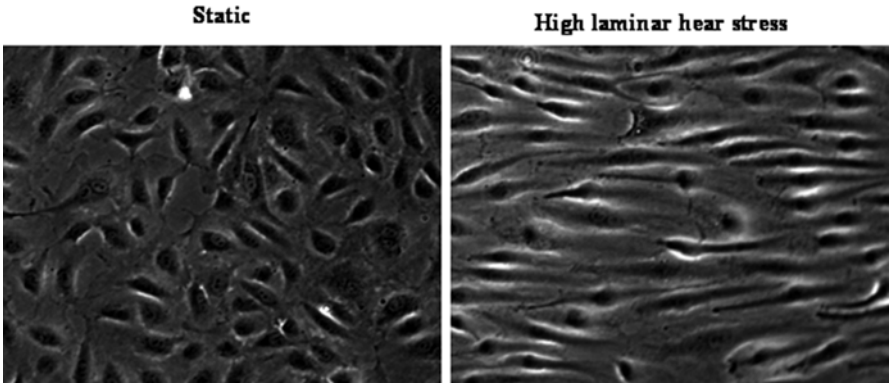

Fig. 7.1 The morphological change in endothelial cells after 24 h of laminar shear stress compared to a static (no flow) condition

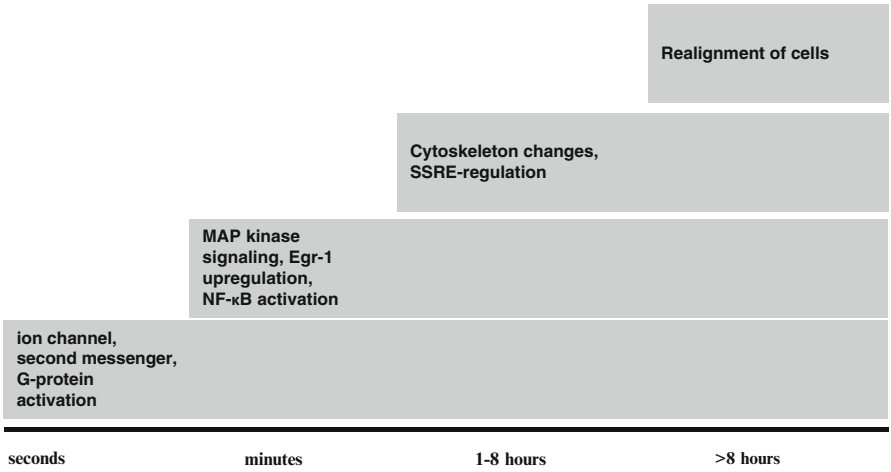

Fig. 7.2 Key events in the endothelial cell response to fluid shear stress. Adapted from Braddock et al. [13]

Shear Stress-Induced Gene Expression

Shear stress dramatically alters the phenotype of the endothelium by regulating certain flow-responsive genes. Transcription factors provide the link between early membrane-proximal signaling events and changes in the expression of many genes. Two of the most important shear stress-induced transcription factors are Krüppel-like factor 2 (KLF2) and nuclear factor erythroid 2-like 2 (Nrf2). Together, these two transcription factors control approximately 70 % of shear stress-induced EC gene expression [14].

Many genes known to be regulated by shear stress contain a shear stress responsive element [15] in their promoter regions as well as other sequences that are sensitive to shear stress [16]. DNA microarray technology has identified EC shear stress responsive genes and their functional gene groups [17]. It appears that there are about 3,000 EC genes that are modified by shear stress. Please see Chap. 10 for detailed discussions on the genetics of the blood pressure response to exercise training.

Systematic Review Methods

We performed a systematic comprehensive electronic PubMed search on key genes and/or proteins that are known to be responsive the LSS. Our goal was to focus on those genes that are well established in the hypertension literature, so called “hypertension candidate genes.” For example, when searching for endothelial nitric oxide

synthase (eNOS), we used the search terms "endothelial nitric oxide synthase AND endothelial cell OR endothelium AND laminar shear stress OR shear stress." Since EC shear stress studies were not performed until the 1980s, we did not limit the search to a defined time of publication.

The criteria by which we selected genes and/or proteins were that: (1) the effects of LSS had to be consistently well documented, and (2) the genes and/or proteins are candidate genes for hypertension. Because the level of LSS (dyne cm^{-2}) can be accurately adjusted, we considered any magnitude of LSS >10 dyn cm^{-2} to be a high physiological levels of LSS.

Activation of an EC is typically caused by direct injury, oxidative stress, and/or inflammation. Oxidative stress is often a common denominator of many chronic diseases including hypertension [18, 19]. Ultimately, the net effect is a reduction in vasodilating capacity of the endothelium. Therefore, we also focused on genes and/or proteins related to oxidative stress and inflammation. The genes/proteins are divided into categories: vasoactive mediators (eNOS, endothelin-1 [ET-1], and prostaglandin [PG]); oxidative stress (nicotanimide adenine dinucleotide phosphate [NADPH] oxidase [Nox]), catalase, glutathione peroxidase (GPX), and mitochondrial reactive oxygen species (ROS); and inflammatory mediators (tumor necrosis factor-alpha [TNF-α], interlukin-6 [IL-6], and monocyte chemotactic protein 1 (MCP 1).

Types of Endothelial Cells Included in this Review

There are many different types of EC used in cell culture research. They can generally be divided between artery-derived and vein-derived and between human-derived and animal-derived. In addition, it should be taken into consideration what environment is being modeled in a particular experiment. For example, human aortic EC (HAECs) may be best suited for atherosclerosis studies. The most commonly used EC type is human umbilical vein EC (HUVECs). HUVECs are easier to obtain and are highly proliferative. Also, obtained from umbilical cords are human umbilical artery ECs (HUAECs). Another very common EC type used in research is bovine aortic EC (BAECs). In general, any tissue or organ in which ECs can be obtained and cultured could be used in cell culture studies. The use of microvessel ECs (human microvessel ECs, HMVECs) is becoming popular because they can be obtained and isolated via muscle or fat biopsy. In some cases, ECs can be obtained directly from donors (e.g., umbilical cords), but nearly all EC types can be purchased in cryopreserved vials.

It has long been thought that functional differences between arterial and venous ECs were due only to the hemodynamic environmental cues. We now also know that differences between arterial and venous ECs are also caused by developmental expression of genes [20]. There are approximately 18 genes that are expressed in artery and not in vein endothelium [20]. There are approximately eight genes that are expressed in vein but not artery endothelium [20]. The roles of many of these 18 genes remain unknown.

In terms of EC type responsiveness to LSS, Ohura et al. compared the gene expression profile of 5,600 human genes in HUVECs and human coronary artery endothelial cells (HCAECs) [17]. In response to 15 dyn cm^{-2}, 3.2 % of the HUVECs and 3.0 % of the HCAECs changed their gene expression. In the HUVECs, 50 genes had a greater than twofold increase in expression and 131 genes showed reduced expression of more than 50 %. For the HCAECs, 50 genes also had a greater than twofold increase in expression and 120 genes showed reduced expression of more than 50 %.

Methods of Applying In Vitro Laminar Shear Stress

Cone and Plate

This system uses a rotating cone typically made of Teflon positioned in the center of a cell culture dish. ECs are gown on the bottom of a culture dish and are adherent. The angle of the cone is typically 0.5°, and the tip of the cone is placed in the culture medium and rotated at a given velocity. This produces a steady laminar flow pattern across the EC. By knowing the cone rotation velocity (ω), the angle of the cone (Θ), and the viscosity (μ), shear stress (τ_w) can be calculated as $\tau_w = \omega\mu/\Theta$ [21].

Parallel Flow Chamber

The parallel flow system is quite different from the cone and plate system. It is a closed loop system configuration. It is commercially available. A typical parallel-plate flow chamber consists of a flow control unit similar to a pump, a chamber which holds a coverslip, and a coverslip. The ECs are grown on the coverslip and then placed into the chamber. The chamber includes inlet and outlet ports, and a vacuum slot [22]. Cell culture media is circulated through the flow chamber creating a fluid shear stress to the adherent cells. This produces a steady unidirectional flow pattern across the EC. In order to calculate shear stress, flow, viscosity, and the thickness and the width of the flow chamber must be known.

Relevant Research

Effects of High Physiological Levels of Laminar Shear Stress on Vasoactive Mediators

The Nitric Oxide System

An imbalance between vasodilators and vasoconstrictors could lead to an increase in vascular tone and elevated blood pressure. Furchgott and Zawadzki first discovered an endothelium-derived relaxing factor [1] which was later identified as NO

[23, 24]. NO is known to be the most potent endogenous vasodilator which is generated from an amino acid, L-arginine [25], through a series of electron transfer reactions that is catalyzed by NO synthase (NOS) [26]. In response to shear stress, eNOS produces NO which rapidly diffuses into the underlying vascular smooth muscle where it activates soluble guanylate cyclase to increase the intracellular level 3′, 5′-cyclic guanosine monophosphate (cGMP). This second messenger induces vascular smooth muscle relaxation by reducing intracellular free calcium concentration, activating potassium channels leading to hyperpolarization, and impeding smooth muscle myosin-actin cross-bridge formation.

Early evidence showing impaired endothelium-dependent vasorelaxation in various small and large peripheral vessels was collected from different experimental animal models of hypertension [27–29]. Subsequently, Panza et al. and other groups independently showed that subjects with hypertension had reduced NO-mediated vascular relaxation compared to control subjects with normal blood pressure [30–32].

The seminal experiments published by William Sessa in 1994 showed that chronic exercise (e.g., sustained bouts of high laminar blood flow) increased NO production and eNOS gene expression in coronary arteries and aortas of canines [33]. Since then, numerous studies have confirmed these findings [34, 35]. An increase in eNOS expression and NO production means a healthier endothelium and is conducive to an arterial wall environment favoring lower blood pressure. Shear stress increases eNOS expression and activity through transcriptional, post-transcriptional, and post-translational mechanisms. Since the early 1990s, shear stress-induced increase in eNOS messenger ribonucleic acid (mRNA) and eNOS protein expressions has been universally observed in cultured ECs [36–38] and in intact arteries [39, 40]. Nishida et al. demonstrated for the first time that 24 h of LSS at 15 dyn cm^{-2} increased eNOS mRNA expression in BAECs [37].

Transcriptional regulatory mechanisms of shear-induced eNOS gene expression involve nuclear factor kappa B (NF-kB). The eNOS gene promoter contains a shear stress response element with the core sequence GAGACC allowing the binding of NF-kB p50/p65 [41]. The exposure of ECs to shear results in nuclear translocalization of p50/p65 suggests NF-kB-dependent eNOS transcription [42, 43]. Another transcriptional regulator of eNOS is KLF2. KLF2 is known as the master regulator of endothelial function inducing numerous genes associated with anti-inflammatory, anti-thrombotic, and anti-oxidative phenotypes [44, 45]. Together, NF-kB and KLF2-mediated transcriptional mechanisms may act to coordinate optimal eNOS gene induction.

In addition, shear stress also modulates eNOS activity by post-translational protein modifications. eNOS protein has multiple serine/threonine phosphorylation residues, and differential phosphorylation of eNOS at various sites plays an important role in the regulation of enzyme activity. It is well documented that the phosphorylation sites where shear-sensitive phosphorylation occurs are Serine (Ser)-1177 and Ser-633 [46, 47]. Shear stress induces Ser-1177 phosphorylation and activation of eNOS through the phosphoinositide 3-kinase inhibitor/protein kinase B (PI3K/Akt) pathway [48]. Boo and co-workers demonstrated that shear stress stimulates eNOS by a Ser-633 phosphorylation protein kinase A (PKA)-dependent mechanism [46].

For normal eNOS activation, tetrahydrobiopterin (BH_4) [49], flavin adenine nucleotide [50, 51], and NADPH [52] are required as cofactors. Under less than optimal concentrations of these co-factors, eNOS generates superoxide and hydrogen peroxide through a process referred to as "*eNOS uncoupling"* instead of NO [53–55]. This reduces NO bioavailability and leads to endothelial dysfunction. It has been documented that BH_4 preserves eNOS dimerization and improves endothelial function [55]. LSS has been found to increase BH_4 generation [56].

In summary, studies consistently show that high physiological levels of LSS increase the levels of components of the NO system. This leads to increased endothelial-dependent vasodilatory capacity and a vessel wall environment that supports low blood pressure. These in vitro changes are consistent with the endothelial adaptive response to aerobic exercise training.

The Endothelin System

Another vasoactive mediator that is regulated by shear stress is ET-1. ET-1 is a 21 amino acid peptide synthesized by ECs and is known as the most potent and long lasting endogenous vasoconstrictor [57, 58]. In ECs, ET-1 synthesis begins with preproET gene transcription that produces a long 203 amino acid (preproET-1). This peptide is cleaved to become Big ET1. Finally, Big ET1 is cleaved by endothelin converting enzyme (ECE) to form the active ET-1 peptide. ET-1 acts in a paracrine (i.e., stimulating nearby cells) and autocrine (i.e., self-stimulating) fashion on ET_A and ET_B receptors on adjacent ECs or vascular smooth muscle cells. ET-1 binding to ET_A receptors on vascular smooth muscle causes constriction, proliferation, and hypertrophy [59]. ET-1 binding to endothelial ET_B receptors on ECs produces NO and prostaglandin (PGI_2) production which cause vasorelaxation [60].

Due to its long lasting vasoconstrictive effects, it has been thought that ET-1 and its receptors may play a role in hypertension. In addition, ET-1 stimulates vascular oxidative stress which may be an alternative pathway for ET-1 to contribute to hypertension. Most patients with hypertension exhibit normal to slightly elevated plasma levels of ET-1 [60]. However, African Americans with hypertension demonstrate increased plasma ET-1 levels compared to African American controls with normal blood pressure [25, 61]. When individuals with similar levels of blood pressure are compared, plasma ET-1 levels are not different between African American and Caucasians [62]. It has been observed that the endothelin system is upregulated in individuals with severe hypertension when associated with cardiovascular disease (CVD) [63]. It should be noted that plasma levels do not necessarily reflect tissue levels, and differences in plasma concentrations could also be due to the rapid ET-1 clearance from the blood. In rat models of hypertension, nonselective $ET_{A/B}$ receptor antagonism (i.e., with bosentan) reduced vascular hypertrophy and remodeling more than could be explained by the modest blood pressure lowering effect [60]. Clinical trials in humans have shown that non-selective ET receptor antagonists combined with $ET_{A/B}$ receptor antagonists significantly reduce blood pressure [64].

High physiological levels of LSS in ECs downregulate preproET-1 mRNA and ECE mRNA levels and reduce ET-1 synthesis. Sharefkin et al. [65] was the first to show some of these effects. They determined the effects of LSS at a magnitude of 25 dyn cm^{-2} for 24 h on preproET-1 mRNA expression and the rate of ET-1 secretion into the cell culture media in HUVECs using a parallel flow system. After 24 h, preproET-1 mRNA expression was decreased to the point that it was nearly nondetectable. ET-1 release into the cell culture media was decreased by 60–70 % which began at hour 4 of LSS and was sustained throughout the 24 h period. Masatsugu et al. examined the effects of 24 h of LSS (15 dyn cm^{-2}) on ECE-1 and ET-1 mRNA levels in HUVECs and BAECs [66]. The investigators used a parallel flow system to induce LSS. ECE-1 mRNA expression was significantly downregulated in both EC types. ET-1 mRNA expression was significantly decreased in the BAECs. Malek et al. used a cone and plate system to apply LSS at 20 dyn cm^{-2} for 6 h in BAECs [67]. They showed a steady downregulation in ET-1 mRNA levels but also found that ET-1 mRNA downregulation was a least partly dependent on intracellular calcium signaling and tyrosine kinase activity. A later study did not find a role for tyrosine kinase in LSS-induced downregulation of ET-1 secretion [68].

Lastly, Morawietz and colleagues investigated the effects of low (1 dyn cm^{-2}), medium (15 dyn cm^{-2}), and high (30 dyn cm^{-2}) levels of LSS for 24 h on preproET-1 and ECE mRNA levels as well as on ET-1 secretion [68]. They studied HUVECs and used a cone and plate system to apply the LSS. A dose-dependent downregulation of preproET-1 and ECE mRNA expression was observed. This study was the first to also measure ET_B receptor gene expression and found that ET_B receptor mRNA levels increased in a LSS dose-dependent manner. This is especially important relative to blood pressure regulation because activation of ET_B receptors leads to an increase in NO production.

Taken together, these previous studies show exceptional consistency with respect to the effects of the application of chronic LSS at high physiological magnitudes on the endothelin system. It appears that there is a dose-dependency of the responses of components of the endothelin system to physiological levels of LSS. It could be argued that 15 and 30 dyn cm^{-2} of LSS are achieved during aerobic exercise. Interestingly, the effects of LSS decrease the release of ET-1 but enhance the release of NO from ECs. These observed changes are consistent with a healthy endothelium and an arterial wall environment that supports low blood pressure.

The Prostaglandin System

This pathway is commonly thought of as pro-inflammatory in most cell types, but in ECs, the major product is PGI_2, a vasodilator and potent inhibitor of platelet aggregation and leukocyte activation and adhesion. Prostanoids are a family of bioactive lipids that are synthesized by cyclooxygenase (COX) from arachidonic acid. PGI_2 is produced in ECs by COX-2. COX-2 produces PGI_2 in response to stimulation, whereas COX-1 is responsible for basal levels of PGI_2. PGI_2 performs its function through a paracrine signaling cascade that involves G protein-coupled receptors.

PGI_2 is considered to be one of the most important prostanoids in regulating the homeostasis of the cardiovascular system because of its potent vasodilatory and anti-platelet aggregation effects, but also because of its ability to inhibit leukocyte adhesion and vascular smooth muscle proliferation [69]. PGI_2 has been used successfully to treat clinical complications of peripheral vascular disease [70]. Because of these known effects, PGI_2 is known to be atheroprotective and vasoprotective.

The PGI_2 response to LSS was the first documented response of ECs to shear stress [71]. Herschman investigated HUVECs and used a version of the cone and plate system to apply LSS at 10 dyn cm^{-2} for 1, 6, and 24 h and measured COX-1 and COX-2 mRNA expression [72]. COX-2 was nearly undetectable in unstimulated HUVECS. There was a significant increase in COX-2 gene expression which was sustained for 24 h. COX-1 mRNA expression was unchanged. Grabowski et al. determined the effects of step increases in shear stress on the production of PGI_2 in BAECs [73]. Step increases in shear stress from 0 to 14 dyn cm^{-2} elicited a rapid rise in PGI_2 production from baseline to peak values within 2 min, after which levels decreased over several minutes. When LSS was increased again there was another burst of PGI_2 production. The authors concluded that ECs produce bursts of PGI_2 in response to suddenly imposed arterial-like shear stress, and the peak rate of production increases with shear stress.

McCormick et al. assessed the response of prostaglandin H synthase isoforms 1 and 2 (PGHS-1 and PGHS-2), key rate limiting enzymes in the synthesis of PGI_2, to 4, 15, and 25 dyn cm^{-2} using a parallel flow chamber [74]. In response to all three magnitudes of LSS, there was an initial decrease in both PGHS-1 and PGHS-2 protein expression followed by a sustained increase for PGHS-1, but only a transient increase for PGHS-2. In addition, changing LSS magnitude affected PGHS-2 but not PGHS-1. Increases in shear stress levels from 4 to 15 or 25 dyn cm^{-2} caused a decrease in PGHS-2. The authors concluded that the regulation of PGHS-2, but not PGHS-1, by LSS is dependent upon the magnitude of the LSS. Given the differential regulation of these two PGI_2 synthesizing enzymes by LSS in ECs suggests that they play important roles in vascular homeostasis.

In summary, key components of the prostaglandin system are clearly responsive to high physiological levels of LSS. In nearly all cases, the patterns of gene and protein expression in response to LSS are conducive to creating a healthier EC. Specifically, PGI_2 is a potent vasodilator with anticoagulant properties, and therefore, it is reasonable to assume that enhancements in this system are consistent with vasoprotection and lower blood pressure

Effects of High Physiological Levels of Laminar Shear Stress on the Oxidant/Antioxidant System

The redox state in the vascular wall contributes to impaired endothelium-dependent control of vasomotor tone. A major cause of endothelial dysfunction in essential hypertension is decreased availability of NO. Reduced NO bioavailability occurs

due to multiple mechanisms affecting NO synthesis and degradation. Superoxide anions (O_2^-) produced by NADPH oxidase can scavenge NO to form peroxynitrite ($ONOO^-$), which can nitrosylate (i.e., the covalent incorporation of NO into another molecule) membrane proteins, oxidize lipids [75], and reduce NO bioavailability leading to endothelial dysfunction [76].

In the vasculature, ROS contribute to controlling endothelial function and vascular tone, but can have pathophysiological effects when pro-oxidant activity exceeds antioxidant capacity. In this case, conditions such as hypertension are more likely [77]. The problem occurs when ROS generation becomes uncontrolled because it damages proteins, lipids, and DNA which leads to cell injury and dysfunction. Experimental models of hypertension show some degree of oxidative stress [78–82]. When considering the totality of experimental data, it has been suggested that oxidative stress is causally associated with hypertension, at least in animal models [83].

Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase (Nox)

Nox is a transmembrane protein that has a core catalytic subunit and several regulatory subunits. When activated, Nox transfers electrons across membranes in which the final electron acceptor is O_2 and O_2^- is produced [84]. There are seven Nox isoforms many of which are present in vascular tissue [83]. Nox4 has been identified as the major isoform in ECs [85, 86]. The classical Nox isoforms consists of five subunits: p47phox, p67phox, and p40phox, which are cytosolic regulatory proteins; p22phox is a membrane regulatory protein; and gp91phox is the catalytic subunit [87]. The responses of several of these Nox subunits to LSS have been studied.

Many, but not all studies show a direct link between Nox O_2^- generation and blood pressure. Studies that used pharmacological inhibitors of Nox show reduced vascular O_2^- production, and attenuated development of hypertension in Angiotensin II-dependent hypertension [88, 89]. Nox1-deficient mice have reduced vascular O_2^- production, and the blood pressure elevation in response to Angiotensin II is blunted [90]. The overexpression of Nox1 in vascular smooth muscle cells of mice increases blood pressure [91]. Thus, at best, in animal models there appears to be direct effect of Nox generated O_2^- on blood pressure.

In general, LSS applied at high physiological levels to ECs decreases Nox activity and reduces ROS generation which increases NO bioavailability, thus improving EC health [92–95]. White et al. compared LSS at 15 and 75 dyn cm^{-2} for 24 h in HUVECs using a parallel flow chamber [96]. Compared to 15 dyn cm^{-2}, LSS at 75 dyn cm^{-2} decreased Nox subunits Nox2 and Nox4 mRNA expression which was accompanied by suppression of ROS. However, the mRNA expression of p67phox was increased after 75 dyn cm^{-2}. Goettsch et al. investigated Nox4 because it is highly expressed in ECs [97]. The investigators used a cone and plate system to

apply LSS to HUVECs from 1 to 30 dyn cm^{-2}. The authors found that LSS caused a time- and dose-dependent downregulation of Nox4 mRNA expression which was confirmed by a concomitant downregulation in Nox4 protein expression,

De Keulenaer et al. determined the effects of 24 h of LSS on Nox activity and O_2^- production in HUVECs [98]. The magnitude of LSS was 5 dyn cm^{-2} which is considered a low physiological level. They found that at the start of LSS, there was a transient increase in Nox activity that was time-dependent for up to 1 h followed by a decrease back down to basal (static) levels. This finding is consistent with other studies that show an initial acute negative response to shear stress followed by a lowering effect on Nox and ROS over the ensuing 24 h. In addition, most studies of LSS effects on ECs use a low magnitude of LSS of approximately 5 dyn cm^{-2} and compare it to high physiological levels typically greater than 10 dyn cm^{-2}. In nearly all cases, low levels of LSS induce a genetic program of protein expression that is atherogenic and high levels induce an EC phenotype that is atheroprotective and vasoprotective. Therefore, the fact that Nox activity was unchanged after 24 h of LSS at 5 dyn cm^{-2} is not surprising.

Duerrschmidt et al. determined O_2^- production and Nox subunit expression in response to short-term (2 h) and long-term (24 h) LSS in HUVECs using a cone and plate system [95]. HUVECs were sheared at arterial levels of 15, 30, and 50 dyn cm^{-2}. At 2 h at 30 dyn cm^{-2}, there was an initial increase in O_2^- production, but after 24 h at 30 dyn cm^{-2}, O_2^- production was significantly decreased. Short-term LSS (30 dyn cm^{-2}) did not change Nox subunits (i.e., gp91phox, p67phox, p22phox, and p47phox) mRNA expression. However, after 24 h at 30 dyn cm^{-2}, mRNA expression of the subunits gp91phox and p47phox decreased in a time-dependent manner. In a separate experiment, HUVECs were exposed to LSS at 1, 5, 10, 15, 30, or 50 dyn cm^{-2} for 24 h. Nox gp91phox and p47phox mRNA expression decreased in a dose-dependent manner.

The downregulation of gp91phox mRNA expression and protein levels is important because it is the rate-limiting subunit of the Nox complex in human ECs [99, 100]. The downregulation of p47phox is also noteworthy because it is the protein that carries the cytosolic proteins to the membrane proteins to assemble the active oxidase [87, 101]. Together, these changes caused by high physiological levels of LSS are consistent with lower EC oxidative stress which could potentially lead to greater NO bioavailability and potentially lower blood pressure.

We showed using HUVECs obtained for African American and Caucasian donors that 24 h of LSS at 20 dyn cm^{-2} decreased Nox4 protein expression in HUVECs from African Americans and Caucasians [101]. P47phox protein expression significantly decreased only in the HUVECs from African Americans, while Nox 2 expression did not change in either group. It should be noted that under basal conditions, the HUVECs from African Americans exhibited significantly greater levels of protein expression for p47phox, Nox2, and Nox4 than HUVECs from Caucasians which suggests that like most biologic and physiologic variables, the initial level often influences the magnitude of the change (see Chap. 1 for elaboration on the law of initial values). These results also suggest a potential for greater oxidative stress in ECs of African Americans which may contribute to a propensity for greater endothelial dysfunction and hypertension among African Americans.

Mitochondrial Reactive Oxygen Species

The major sites of O_2^- generation under physiological conditions are mitochondrial respiratory complexes I, II, and III. It is a nonenzymatic reaction when oxygen interacts with semiquinone radical (QH^-) or flavins that participate in a one electron reduction of oxygen. Superoxide is rapidly dismutated to H_2O_2 by SOD (Cu-Zn-SOD and Mn-SOD). H_2O_2 undergoes further reduction to water by the glutathione or thioredoxin (Trx) systems. The *complete mitochondrial detoxification system* is composed of Mn- and Cu-Zn-SOD [102, 103], glutathion reductase [104] and glutaredoxin [105, 106], mitochondrial Trx [107, 108], mitochondrial Trx reductase [109–112] and mitochondrial peroxiredoxins [113, 114]. Importantly, these mitochondrial antioxidant systems are upregulated by peroxisomal proliferator activated receptor γ co-activator 1α (PGC-1α), a master regulator of mitochondrial biogenesis. This positive regulation increases the cellular capacity to detoxify mitochondrial ROS, preventing endothelial dysfunction in response to oxidative stress conditions [115]. Enhancing structural and functional integrity of mitochondria is an emerging therapeutic option against endothelial dysfunction.

Mitochondrial biogenesis is a complex process involving the replication of mitochondrial DNA (mtDNA), and the expression of mitochondrial proteins encoded by both nuclear and mitochondrial genomes. Mitochondria are considered to be a causative factor in the pathophysiology of most CVD, and thus, they represent a promising target for therapeutic interventions [116]. Recently, potential link between shear stress and mitochondrial biogenesis in ECs has been suggested [117–119]. During the past few years, several studies have highlighted the importance of mitochondria in cell signaling [120], suggesting that mitochondrial biogenesis is essential for endothelial homeostasis [121, 122], and that mitochondria play key roles in critical processes such as maintenance of vasomotor tone [123]. Chen et al. reported that LSS upregulates the key mitochondrial biogenesis regulators including PGC-1α and sirtuin 1 (SIRT1) [117]. Bretón-Romero exposed BAECs and HUVECs to 12 dyn cm^{-2} and found that LSS decreased respiration rate, increased mitochondrial membrane potential, and promoted the mitochondrial generation of ROS with the subsequent oxidation and activation of the antioxidant enzyme, peroxiredoxin 3 [124].

We recently reported that exposure of HUVECs to 20 dyn cm^{-2} of LSS for 48 h enhanced mitochondrial biogenesis, mitochondrial dynamics, and increased mtDNA copy number [125]. We also found that a long-term shear-exposure is sufficient to improve mitochondrial respiration and alter substrates metabolism from anaerobic glycolysis to oxidative phosphorylation-dependent mechanisms in ECs [125].

Given the emerging role for ECs in vascular homeostasis, these recent studies suggest that in addition to the well-known effects of aerobic exercise on skeletal muscle mitochondria, aerobic exercise may also improve EC mitochondrial function. The enhanced function of EC mitochondria may therefore be viewed as beneficial in hypertension because of their role in the regulation of vasomotor tone.

Superoxide Dismutase

Both enzymatic and nonenzymatic defense mechanisms against ROS reside in vascular tissue. There are three isoforms of SOD in mammals (i.e., CuZnSOD, MnSOD, ecSOD), and each has a different subcellular localization, but catalyzes the same reaction. CuZnSOD is the major intracellular SOD. MnSOD is a mitochondrial manganese containing enzyme (MnSOD), and ecSOD is a secretory extracellular Cu/Zn-containing SOD. Extracellular SOD is primarily located in the extracellular matrix and on cell surfaces with a smaller fraction in the plasma and extracellular fluids.

SOD is an oxidoreductase that catalyzes the dismutation of O_2^- to H_2O_2 and O_2. Low antioxidant capacity leading to cellular oxidative stress has been implicated in cardiovascular and renal oxidative damage that is associated with hypertension [83]. In mice deficient in ecSOD, blood pressure is elevated indicating that reduced antioxidant capacity is associated with elevated blood pressure [126].

Most studies show that the expression of each of the three SOD isoforms is upregulated when ECs are exposed to LSS [39, 127, 128]. In fact, Dimmler et al. showed that the upregulation of CuZnSOD by 15 dyn cm^{-2} of LSS played an important role in improving cell survival [129]. However, Duerrschmidt et al. found that LSS application for 20 h at 30 dyn cm^{-2} did not change CuZnSOD protein expression in HUVECs [95]. Topper et al. applied LSS to HUVECs for 24 h at 10 dyn cm^{-2} and found that MnSOD mRNA expression was upregulated at 1, 6 and 24 h. Supportive of the finding by Topper and colleagues, De Keulenaer et al. found that even a LSS magnitude of 5 dyn cm^{-2} as compared to a static no flow condition significantly increased CuZnSOD mRNA expression after 24 h [98]. Inoue et al. examined the effect of LSS of 0.6–15 dyn cm^{-2} on the mRNA and protein expression of CuZnSOD in cultured human aortic ECs [130]. LSS increased CuZnSOD mRNA expression in a time- and dose-dependent manner and also increased CuZnSOD protein content and enzyme activity

Lastly, our group measured MnSOD protein expression and total SOD activity in the culture media of HUVECs obtained from African American and Caucasians before and after 24 h of LSS applied at 5 and 20 dyn cm^{-2} using a cone and plate system [101]. We found that both MnSOD protein expression and total SOD activity were significantly greater after 5 and 20 dyn cm^{-2} only in the HUVECs from African American. Under basal conditions, the HUVECs from Caucasian had significantly greater levels of MnSOD protein expression and total SOD activity. These results suggest that there may be race-dependency responses of ECs to high physiological levels of LSS. However, the underlying mechanisms for the race-dependent differences in EC responses to LSS are unknown.

Glutathione Peroxidase

There are 8 glutathione peroxidase (GPX) isoenzymes identified in different tissues. GPX-1 is ubiquitously expressed and plays a central role in cellular defense against H_2O_2 and organic hydroperoxides. Glutathione peroxidase is essential for removing

H_2O_2, and subsequent products, hydroxyl radicals [131]. Indeed, GPX has been demonstrated to be much more effective than SOD in protecting human cells to oxidative stress [132]. Reduced GPX activity has been associated with development of vascular dysfunction. Chrissobolis et al. demonstrated, using arteries from Gpx1-deficient and Gpx1 transgenic mice, that GPX 1 protects against angiotensin II-induced endothelial dysfunction [133]. LSS (5–20 dyn cm^{-2} for 4–24 h) upregulates GPX mRNA expression in a time- and magnitude-dependent manner. Furthermore, shear stress increases GPX activity [134].

Effects of High Physiological Levels of Laminar Shear Stress on Inflammation

Data from Epidemiologic studies support an association between different inflammatory markers and blood pressure [135]. Studies also suggest that chronic low-grade systemic inflammation may contribute to the development of hypertension through endothelial dysfunction because many of the inflammatory cytokines directly affect vasodilating factors [136–139]. Please see Chap. 14 for detailed discussions of the influence of inflammation on EC function and hypertension.

Most inflammatory cytokines activate the p38/NFκB transcription factor pathway which regulates the expression of many genes involved in the inflammation process. These genes initiate the transcription of proteins such as adhesion molecules (e.g., Vascular cell adhesion molecule-1 [VCAM-1], Intracellular adhesion molecule-1 [ICAM-1]), chemokines (e.g., IL-8) and other pro-inflammatory molecules in EC [140].

Endothelial cells are among the primary physiological targets of the pro-inflammatory TNF-α. TNF-α causes a variety of biological effects including proliferation, differentiation, and apoptosis [141–144]. In addition, TNF-α has been shown to directly downregulate eNOS and NO production in ECs by decreasing eNOS mRNA levels by increasing the rate of mRNA degradation [145]. TNF-α also increases ROS production [146]. These and other untoward effects can lead to endothelial dysfunction.

High physiological levels of LSS are known to cause an anti-inflammatory pattern of gene expression in ECs, and LSS inhibits TNF-α-mediated downstream inflammatory events through a reduction in the expression of inflammatory proteins. As mentioned above, NFκB transcription factor activation initiates the transcription of numerous inflammatory genes. Partridge et al. showed that LSS at 12 dyn cm^{-2} for 16 h suppressed regulators of inflammation by TNF-α through modulating NFκB transcriptional activity in HUVECs [147]. Compared to a low level (0.4 dyn cm^{-2}) of LSS, a high physiological level (12 dyn cm^{-2}) significantly inhibited TNF-α-stimulated VCAM expression. Evidence for this effect was that there was reduced activation of key signaling proteins in the p38 pathway, including NFκB, and reduced association of TNF receptor-1 with TNF receptor-associated factor-2, a protein required for TNF-α-mediated activation of p38 pathway [148].

Surapisitchat et al. determined the effects of 12 dyn cm^{-2} on TNF-α and IL-1-stimulated signaling in HUVECs [149]. IL-1 is a cytokine that induces a complex network of pro-inflammatory cytokines. IL-1α and IL-1β are the most studied members because they were discovered first, and they possess a robust pro-inflammatory response. One study pre-sheared HUVECs and then stimulated them with TNF-α or IL-1 [150]. This would be a model of an exercise trained individual having their endothelium exposed to an inflammatory insult. The authors found that pre-shearing the HUVECs at a high level of physiological LSS reduced activation of the c-Jun N-terminal kinases signaling pathway which is very responsive to cytokines and regulates apoptosis among other cellular functions.

IL-6 is a pro-inflammatory cytokine that has been linked to many chronic diseases and is a primary factor in inducing C-reactive protein, an acute phase reactant released from the liver. ECs can secrete IL-6 when stimulated by other cytokines. IL-6 can also stimulate ECs via the janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways. When this pathway is activated, it can lead to apoptosis and inflammation, both of which further degrade endothelial function. Ni et al. showed that LSS at 16 dyn cm^{-2} reduced IL-6 activation of JAK2-STAT2 pathway, and that the suppression of this pathway was LSS magnitude-dependent, meaning that the ECs became more resistant to inflammation with increasing magnitudes of LSS [150]. Zeng et al. used lipopolysaccharide to induce an inflammatory response and apoptosis in HUVECS [151]. They applied low (4 dyn cm^{-2}) and high (15 dyn cm^{-2}) magnitudes of LSS for 24 h. As expected, they found significant apoptosis when stimulated with lipopolysaccharide. They also found that the high magnitude of LSS was more effective at attenuating IL-6 generation over the 24 h as compared to the low magnitude of LSS. Together, these studies demonstrate that LSS applied at a high physiological level reduces the deleterious effects of IL-6 on ECs and also reduces IL-6 generation by ECs creating an anti-inflammatory environment within ECs. An endothelium that is anti-inflammatory is healthier which supports a healthy level of blood pressure.

New and Emerging Evidence

A limitation of in vitro experiments with ECs is that they are isolated from contact with vascular smooth muscle cells. Heterocellular interactions between vascular smooth muscle cells and ECs play important roles in the maintenance of normal vascular structure and function [152, 153]. Within the vessel wall, EC and vascular smooth muscle functions are achieved by intercellular signaling, including direct physical contact and paracrine interaction [153]. This has led scientists to develop co-culture systems in which they can induce flow. These systems allow them to assess the responses of ECs to shear stress when they have contact with vascular smooth muscle cells.

MicroRNAs (miRNAs) are a class of small non-coding RNAs (~22 nucleotides) that post-transcriptionally regulate the expression of genes. miRNAs are known to

play an important role in EC biology including proliferation, differentiation, cellular redox state, activation, and apoptosis [154–156]. Studies have identified several miRNAs that are distinctly regulated by LSS and oscillatory shear stress, that play important roles in eNOS expression (i.e., miR-221/222 and miRNA-214) and activity (i.e. miRNA-21, miRNA-33 and miRNA-217) [156–160]. Unidirectional LSS upregulates miRNA-21 expression which activates the PI3K/Akt/eNOS (p-S1177) pathway [160], where phosphatase and tensin homolog (PTEN) antagonizes the PI3K/Akt pathway. Holliday-Ankeny et al. reported that LSS-induced miR-148a indirectly activates eNOS [161]. LSS-induced miRNAs further regulate eNOS activity by targeting modulators of post-translational modification of eNOS.

Clinical Implications and Importance

It should be kept in mind that the data largely described in this chapter were collected from isolated EC culture experiments and may not necessarily reflect the in vivo environment. Nonetheless, the changes in gene and protein expression brought about by high physiological levels of LSS are uniformly consistent with the improvements in in vivo endothelial function measurements with exercise training. Since there is convincing evidence that it is the repeated bouts of elevated intraluminal LSS occurring during exercise training that elicits endothelial adaptations, then in our opinion the in vitro LSS model provides valuable mechanistic insights into these adaptations (Please see Chap. 5 for a detailed discussion of this evidence). Furthermore, it is well documented that individuals with hypertension tend to have impaired endothelial function compared to individuals with normal blood pressure and that endothelial dysfunction predicts future CVD risk [2, 162]. Given these facts, the clinical implications are twofold. First, the pattern of the gene expression in response to high physiological levels of LSS is one that creates an anti-inflammatory, anti-oxidant, and vasodilatory phenotype; effects that are consistent with low blood pressure. Second, by interrogating the underlying mechanistic pathways leading to healthy arteries could open the door for both nonpharmacologic and pharmacologic targets for improving vascular health.

Conclusion

To date, most if not all, studies of the effects of physiological levels of LSS on ECs are consistent with the effects of aerobic exercise training on endothelial function in humans (see Chap. 5 for the effects of aerobic exercise on vascular function). When exposed to high physiological levels of LSS, the gene expression profile of ECs becomes anti-oxidative and anti-inflammatory both of which lead to an increase in NO bioavailability. This LSS also directly increases vasodilatory factors and decreases vasoconstrictor factors. All of these changes create a vessel wall that is

more healthy and protective against hypertension. It must be kept in mind that the application of in vitro shear stress is experimental and cannot fully simulate in vivo blood flow. However, it can approximate physiological levels of shear stress experienced by ECs.

Key Points and Resources

- The application of in vitro LSS has been used to better understand the effects of exercise on ECs.
- LSS profoundly alters the EC phenotype by modifying the gene expression profile creating an environment that is anti-inflammatory, anti-oxidant, anti-apoptotic, and vasoprotective.
- The EC adaptive response to LSS is consistent with the in vivo adaptive response of the endothelium to aerobic exercise training
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Chapter 8
Effects of Regular Exercise on Arterial Stiffness

Hirofumi Tanaka

Abbreviations

AHA	American Heart Association
AI	Augmentation index
CVD	Cardiovascular disease
NOS	Nitric oxide synthase
PWV	Pulse wave velocity

Introduction

It is well established that cardiovascular disease (CVD) is the number one cause of mortality in both men and women in most industrialized countries including the United States [1]. Over 80 % of CVD prevalence can be attributed to the disease of blood vessels as coronary artery disease, stroke, and hypertension are all arterial diseases. The most prominent change in the blood vessels that can contribute to the prevalence of CVD is the stiffening or hardening of arteries. Arterial stiffness is an independent predictor of adverse CVD mortality and morbidity [2, 3] and can induce a number of subsequent cardiovascular sequela including hypertension, left ventricular hypertrophy, coronary ischemia, and stroke [4–6].

The exact cause of arterial stiffening is not well understood, but a number of structural and functional elements would likely contribute to this process (Fig. 8.1) [7–9].

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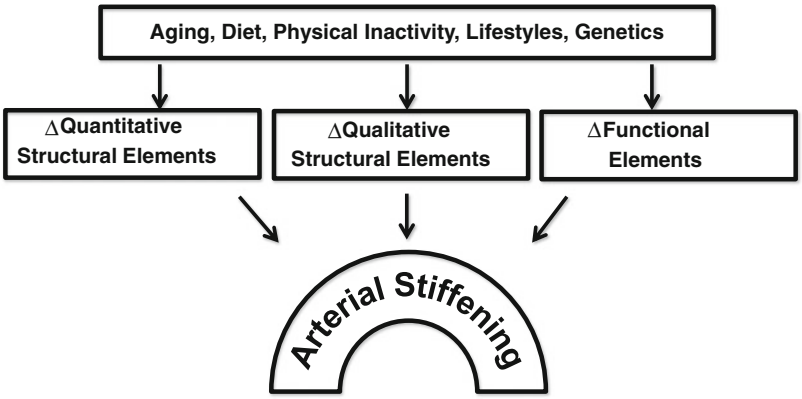

Fig. 8.1 Causes of arterial stiffening

Although epidemiological studies demonstrated relations between arterial stiffening (i.e., arteriosclerosis) and arterial wall thickening (i.e., atherosclerosis) [10], arteries undergo stiffening or hardening independent of atherosclerosis. Marked arterial stiffening with advancing age has been observed in rural Chinese populations where the incidence and prevalence of atherosclerosis are very low [11], in a rigorously screened population in the United States [12–14], and in beagle dogs that do not develop atherosclerosis [15]. Arterial stiffening is not a universal change affecting the entire arterial tree and manifests much more clearly in central elastic or cardiothoracic arteries where the pulsation of pressure pulses must be effectively buffered before it reaches the capillary circulation that lacks defense mechanisms for arterial pulsations [12, 16]. It is thus likely that the mechanisms inducing arterial stiffening would include the interaction between mechanical distension and vasoactive factors.

Purposes of This Chapter

Since CVD has a very long asymptomatic or latent phase of development, primary and secondary prevention is the most effective means to contain the progression and manifestation of CVD [17]. The universal first-line approach for the prevention of CVD is lifestyle modifications including regular exercise [17, 18]. For this reason, there has been increasing interest in evaluating the effects of regular exercise on arterial stiffening [19, 20]. Is habitual aerobic exercise capable of reducing arterial stiffness that is greatly influenced by structural elements in the arterial wall? If so, what physiological factors are responsible for such destiffening effects? What about the influence of resistance training on arterial stiffening? Accordingly, the primary objective of this Chapter is to review and synthesize previous research studies to address the impact of regular exercise on arterial stiffening as an early marker of subclinical CVD.

Key Terminology and Basic Concepts

In this Chapter, aerobic (endurance) exercise and resistance (strength) exercise training studies are discussed separately as these exercise training modalities appear to exert distinct effects on the arterial elasticity. In each section below, cross-sectional findings are discussed first followed by interventional findings.

Much of the confusion in the area of arterial stiffness arises from the different terminologies used to express the elastic properties of arteries. They include arterial stiffness, compliance, distensibility, elasticity, and elastic modulus. The terms "compliance" and "distensibility" are the inverse of "stiffness" in terms of the directions for rigidity. Even though there has been an attempt to standardize the terminologies for arterial stiffness [21], these terms cannot be used interchangeably because each term has different meanings derived from different methodologies as shown below.

Arterial Compliance

The absolute vessel diameter change for a given pressure change.

Arterial Distensibility

The relative diameter vessel change for a given pressure change.

Elastic Modulus

The pressure change required for 100 % stretch from resting vessel diameter.

Methods

There are a number of techniques that have been used to estimate arterial stiffness. Historically, arterial stiffness has been measured in vitro using excised arteries [22, 23]. However, results derived from in vitro measurements may not be applicable to intact vessels [24] because of the sympathetic vasoconstrictor tone and hormonal milieu that the arteries are exposed to in vivo. One of the most frequently used in vivo noninvasive techniques to estimate arterial stiffness is pulse wave velocity (PWV) [22, 25, 26]. PWV is measured from the "foot" of pressure waves recorded

at two points along the path of the arterial pulse wave. The more rapid the pulse wave, the more rigid the artery. PWV can be measured at a variety of arterial segments but the most popular and most established measure of PWV is aortic or carotid-femoral PWV. Another approach is to determine the augmentation index or AI related to the reflected systolic blood pressure waveform obtained on arterial tonometry [27]. AI was used frequently in the past as an index of arterial stiffness, but more recently it is used as an index of arterial wave reflection that is indirectly related to arterial stiffness. Technological advances in ultrasound imaging have significantly improved the image resolution of arteries. When combined with computer-based image analyses and arterial tonometry on the contralateral artery, ultrasound imaging enables robust measurement of arterial distensibility and compliance [13, 28].

In order to review relevant research in this area, a systematic electronic search of the literature on the association between habitual exercise and arterial stiffness was conducted mainly using PubMed. Additionally, cross-referencing of the identified articles was carefully conducted. Although arterial stiffening is clearly an age-associated disease, age-associated changes are difficult to assess in humans especially in relation to the preventive effects of regular or life-long exercise. Accordingly, both cross-sectional and interventional studies were included.

Relevant Research

Aerobic Exercise Training

A number of investigators have reported that arterial stiffness increases during a acute single bout of aerobic exercise [29, 30]. The acute increase in arterial stiffness seems reasonable given the observation that during graded exercise, systolic blood pressure increases markedly while diastolic blood pressure remains unchanged or slightly decreases resulting in a large increase in pulse pressure [31] that is closely associated with arterial stiffness. Following exercise, however, arterial stiffness appears to fall below the baseline levels [32]. The acute effects of exercise on arterial stiffness seem to disappear within a few hours following exercise [32]. Thus, it is reasonable to assume that the effects of regular exercise on arterial stiffness, if any, are not due to a residual effect of the last bout of exercise but rather due to chronic adaptation of cardiovascular system as the measurements are typically performed >24 h after the last bout of aerobic exercise.

Middle aged and older men who performed endurance exercise on a regular basis demonstrate lower levels of aortic PWV and carotid AI than their sedentary peers [14]. We also reported that significant age-related increases in central arterial stiffness were absent in physically active women and that aerobic fitness was strongly and favorably associated with arterial stiffness [12]. These cross-sectional findings provide support for a role of regular aerobic exercise in the primary prevention of arterial stiffening that occurs with advancing age.

Unknown to most, the first intervention study to determine the influence of exercise training on arterial stiffness was conducted in Japan (This is in part because this paper was published only in Japanese) in 1983. A total of 80 healthy young men, who were new recruits for the Japanese self-defense or military school, were studied before and after 9 months of physical training incorporating a variety of exercise modes, including distance running, calisthenics, soccer, handball, judo, and swimming [33]. At the end of the training period, there was a small but significant reduction in aortic PWV, indicating a small reduction in arterial stiffness. We have also reported that a relatively brief period (3 months) of aerobic exercise can increase central arterial compliance in apparently healthy, middle aged and older adults [13, 28]. This improvement was not associated with changes in body weight, adiposity, blood pressure, or plasma cholesterol, indicating a direct effect of habitual exercise on arterial compliance.

Importantly, this small reduction in arterial stiffness was accomplished with an intensity (moderate) and type (walking) of physical activity that can be performed by most, if not all, healthy older adults [13, 28]. Interestingly, the beneficial effect of aerobic training involves only central elastic arteries whose elastic properties dampen fluctuations in pressure and flow [12, 13]. Additionally, the beneficial effects of regular aerobic exercise on arterial compliance are associated with a favorable influence on arterial blood pressure and arterial baroreflex sensitivity [20, 34, 35], indicating that the beneficial effect of regular exercise would extend to sequelae of arterial stiffening. Thus, the beneficial effects of habitual exercise lead not only to arterial destiffening but also to the attenuation of the adverse outcomes caused by arterial stiffening.

Most of the exercise training studies to date have focused on land-based exercises such as walking [13, 28] and cycling [32, 36]. Swimming is an attractive form of exercise as it is easily accessible, inexpensive, and isotonic [37]. Because of the buoyancy of water, compressive stress on joints is small, and orthopedic injury rate is low [38]. Due to cold temperature and increased thermoconductivity of surrounding water, heat-related illness is extremely low [39]. Thus, swimming can be an ideal form of exercise for those at elevated risks of vascular disease, including the elderly, and people with obesity and/or arthritis [37].

In the first cross-sectional study to address the effect of swim training on arterial elasticity [40], arterial compliance of middle-aged and older swimmers was compared with those of runners and sedentary controls. Central artery compliance was greater in swimmers than in age-matched sedentary controls, and the level of arterial compliance was not different between swimmers and runners, suggesting that high levels of regular swimming exercise may prevent arterial stiffening similar to land-based exercises. Subsequently, a swimming exercise intervention study involving previously sedentary middle aged and older adults was conducted. This follow-up intervention study allowed us to confirm the cross-sectional observations by demonstrating that regular swimming exercise produced a 21 % increase in arterial compliance and a 12 % reduction in the β-stiffness index, a measure of arterial stiffness that adjusts for the effect of alterations in distending pressure on arterial diameter, after 3 months of regular swimming exercise [41]. In summary, evidence from

both cross-sectional and interventional studies collectively indicates that regular swimming is beneficial in improving the elasticity of central arteries in middle-aged and older adults.

As discussed above, habitual aerobic exercise is an effective lifestyle intervention for preventing and reversing arterial stiffening for healthy adults. When prescribed to patients with essential hypertension, however, short-term (2–4 months) aerobic exercise interventions may not be as effective in reducing arterial stiffness as in healthy adults. For example, we reported that 3 months of aerobic exercise training composed of walking and jogging produced very small reductions in arterial stiffness in postmenopausal women with elevated systolic blood pressure [35]. Similarly, short-term aerobic exercise training was unable to reduce arterial stiffness in patients with isolated systolic hypertension [42] or in older patients with Stage I hypertension who had been on antihypertensive medications [43].

Currently, exercise intervention studies targeting patients with other diseases are very limited. In one of these studies, 8 weeks of aerobic exercise training did not change aortic PWV and carotid AI in patients with congestive heart failure [44]. Similarly, no changes in PWV were observed after 2 years of exercise training program in patients with type 2 diabetes mellitus [45]. Interestingly, Ikegami et al. [33] observed a trend for the magnitude of reductions in PWV with exercise training to be reduced in direct proportion to initial body fat levels, suggesting that the degree of destiffening effect of exercise may diminish as the CVD risks of participants increase. Clearly, future studies are warranted to investigate the potential efficacy of long-term (>1 year) aerobic exercise intervention on arterial stiffness in populations with CVD. For related discussions on the effects of aerobic exercise on other metabolic risk factors and vascular function, please see Chap. 5 and the Chapters in Part III.

Mechanisms Underlying Exercise-Induced Reductions in Arterial Stiffness

Considering these findings, the question that emerges is, *If habitual aerobic exercise reduces arterial stiffness*, *then what are the physiological mechanisms underlying its effects*? There are three primary elements of the arterial wall that determine its stiffness (Fig. 8.1). They are: (1) quantitative structural elements (e.g., amount/proportion of elastin and collagen); (2) qualitative structural elements (e.g., fracture/fragmentation of elastic lamellae and the cross-linking of collagen and advanced glycation—sometimes called nonenzymatic glycosylation end-products); and (3) functional elements (vasoconstrictor tone exerted by its smooth muscle cells). Any favorable influences of regular aerobic exercise should involve an attenuation or reversal of one or more of the physiological mechanisms contributing to arterial stiffening.

Structural elements, specifically decreased density of the arterial elastin with corresponding increases in collagen content in the arterial wall, play a major role in increases in arterial stiffness [7]. Because the elastin-collagen composition of the

arterial wall changes over a period of years, it is unlikely that this may be a physiological mechanism underlying reductions in arterial stiffness induced by short-term exercise intervention. In fact, using an animal experiment, we have demonstrated that the influence of regular exercise on arterial stiffness does not appear to be mediated by the quantitative changes in arterial wall elastin and collagen [9]. The results from gene microarray analyses are consistent with this finding since the gene expression of structural proteins (e.g., various types of collagens and procollagens) and enzymes that modulate structural proteins and the extracellular matrix (e.g., collagenase, matrix metalloproteinases) did not change significantly with exercise training in the rat aorta [46]. A recent animal study, however, reported that although total collagen content did not change with exercise training, some isoforms of collagen and calcifications were reduced [47]. Thus, we cannot exclude the possibility that qualitative structural elements, including the shift in collagen subtypes and alterations in collagen cross-linking, may play a role in the reductions in arterial stiffness resulting from regular exercise.

A more likely mechanism contributing to the improvements in the elastic properties of arteries with aerobic exercise is the reduction in vasoconstrictor tone exerted by the vascular smooth muscle cells. Because a number of different and interacting vasoactive molecules and peptides could respond to exercise training to influence the contractile states of the vascular smooth muscle cells, it is difficult to elucidate underlying mechanisms using traditional approaches (e.g., pharmacological blockade). In order to identify and confine relevant functional factors responsible for exercise training-induced decreases in arterial stiffness, we relied on the DNA microarray technique (i.e., multiplex lab-on-a-chip that assays large amounts of biological material suing high-throughput screening methods). Microarray provides a powerful and efficient tool by which to compare the differential expression of a large number of genes in a single reaction and enables a systematic analysis of responses of various gene expressions to exercise training. We found that genes associated with nitric oxide synthase (NOS) (along with prostaglandins and C-type natriuretic peptide) were differentially expressed in the aorta of exercise-trained rats [46]. Because the incidence of false positive findings is very high in the microarray analysis, the results were confirmed subsequently using real-time quantitative polymerase chain reaction and protein expressions [46].

Aside from the NO-mediated vasodilation, another important functional element that has been implicated in the pathogenesis of arterial stiffening is sympathetic adrenergic vasoconstrictor tone [48]. The sympathetic nervous system exerts a tonic restraint on the compliance of the common carotid artery, and removal of that restraint produces an immediate increase in its compliance [49]. We assessed the effects of systemic inhibition of α-adrenergic receptors and NOS on arterial compliance before and after 3 months of aerobic exercise training in middle-aged and older adults. Systemic, rather than local, administration of drugs was used in order to target the compliance of "central" (cardiothoracic) arteries, which makes the dominant contribution to the elastic reservoir function of the arterial system [50]. The effect of α-adrenergic receptor tone on the carotid artery significantly decreased following the aerobic exercise training intervention, as evidenced by a diminished

increase in arterial compliance from baseline to phentolamine (i.e., non-specific α-receptor blocker) administration. The NO-dependent vascular tone, however, did not change significantly after aerobic exercise training, as the magnitude of decrease in arterial compliance from the phentolamine administration to the combined phentolamine and L-NMMA (i.e., NOS blocker) administration was similar before and after exercise training [50].

We have also determined whether endothelin-1, a potent endothelium-derived vasoconstrictor peptide, is involved in the mechanisms underlying the increase in arterial compliance with aerobic exercise training [51]. Systemic endothelin-A/B receptor blockade was administered before and after 3 months of exercise training involving middle-aged and older adults. The increase in arterial compliance induced by regular exercise was associated with a corresponding reduction in plasma endothelin-1 concentration as well as the elimination of endothelin-1-mediated vascular tone [51]. These results suggest that aerobic exercise training-induced increases in arterial compliance are mediated, at least in part, through the removal of chronic restraint provided by vasoconstrictor tone and that multiple mechanisms are likely involved in the destiffening process.

Resistance Exercise Training

Prior to 1990, the resistance training modality was emphasized only as a means to develop muscular strength, power, and muscle mass [52, 53]. In recent years, however, statements on physical activity by various health organizations [54–58] have recommended resistance training as an essential part of physical activity preventive and rehabilitative programs. These recommendations are based primarily on the documented impact of resistance training on the attenuation of osteoporosis and sarcopenia (i.e., the age-related loss of muscle mass and strength) [59, 60] as well as on the evidence indicating associations between resistance training and metabolic risk factors [18]. Information concerning the impact of resistance training on vascular function in general, and arterial stiffness in particular, is limited but is emerging. For related discussions on the effects of resistance exercise on other metabolic risk factors and vascular function, please see Chaps. 2 and 6 and the Chapters in Part III as well.

Plasma norepinephrine levels are elevated after a bout of acute resistance exercise, giving rise to the possibility that sympathetic vasoconstrictor tone may also be elevated after resistance exercise [61]. In an attempt to tease out the chronic effects of resistance exercise from the acute effects, we determined the effect of one bout of acute resistance exercise on central arterial compliance [62]. We found that central arterial compliance was decreased immediately and 30 min after acute resistance exercise. These measures returned to baseline levels within 60 min following the bout of resistance exercise. These results suggest that changes in arterial stiffness, if any, that are observed 24–48 h after an exercise bout (typical waiting period for most exercise intervention studies) can be attributed to the chronic effects of resistance exercise training.

Based on a multitude of benefits that resistance training can elicit, it is reasonable to hypothesize that regular resistance exercise would be associated with reduced arterial stiffness. In the first cross-sectional study to address this hypothesis, Bertovic et al. [63] found that young men who performed resistance training on a regular basis demonstrated *lower* levels of systemic arterial compliance than their sedentary peers. We also found in a cross-sectional study that strength-trained middle aged men exhibited *decreased* levels of arterial compliance and that the age-associated reduction in arterial compliance was *greater* in the resistance-trained groups than in sedentary controls [64]. These findings from resistance training studies are in marked contrast to the beneficial effects of regular aerobic exercise that have been observed in the literature [20, 13, 28]. Given the well-known limitation of cross-sectional study designs and the conflicting results between aerobic and resistance training, interventional studies were needed to draw proper conclusions.

In the first intervention study to address this question, we found that several months of strenuous resistance training in young men induced a 20 % reduction in carotid arterial compliance [65]. Moreover, in order to isolate the effects of resistance training on arterial compliance as much as possible, a detraining program was implemented at the conclusion of the resistance training intervention. If the changes in arterial compliance were mediated by resistance training, such changes should return to the baseline level when the stimuli of daily resistance exercise were removed. Indeed during the detraining period, arterial compliance, which was reduced with resistance training, was reversed to the baseline values [65]. In support of these findings, the arterial stiffening effects of strenuous resistance training have since been observed in young women [66] and have been confirmed by a number of other studies [67–70].

Mechanisms Underlying the Strenuous Resistance Training-Induced Increases in Arterial Stiffness

Considering these findings, the question that emerges is, *What are the physiological mechanisms underlying the increase in arterial stiffness with strenuous resistance exercise training*? During resistance exercise bouts, arterial blood pressure increases to as high as 320/250 mmHg [71] and arterial walls are exposed to substantial amounts of distending pressures. There have been several case reports describing aortic dissection during heavy weight lifting exercises [72, 73]. It is possible that arterial stiffening may be caused by smooth muscle hypertrophy and synthesis of extracellular matrix stimulated by repeated elevations in local distending pressure [74] in order to strengthen the arterial wall against the risk of aortic rupture. Indeed, central arterial compliance was associated with arterial wall thickness in a group of resistance-trained adults [64]. Other potential mechanisms include the formation of collagen cross-linking and advanced glycation end products [75] and the increase in vasoconstrictor tone exerted by vasoactive molecules [8]. Although there are numerous vasoactive molecules that can affect

smooth muscle vasoconstrictor tone, endothelin-1 does not appear to play a role in arterial stiffening with resistance exercise training [76].

The aforementioned studies were conducted using strenuous weight training regimens in relatively young healthy subjects with high baseline arterial compliance. Whether or not moderate intensity strength training would further reduce the already low arterial compliance of middle-aged and older adults is a clinically important question. Older individuals are at greater risk for developing CVD as well as for experiencing functional disability associated with sarcopenia [59, 60], and resistance training is being strongly recommended as a preventive intervention for functional capacity with advancing age [54, 55, 57, 60, 77, 78]. As such, it is important to understand the interaction between age and resistance training for the key cardiovascular function of arterial compliance.

To do so, we recruited previously sedentary middle aged and older adults and prescribed a resistance exercise program that was consistent with the recommended guidelines established by the American Heart Association (AHA) [54]. We found that there was no significant decrease in central arterial compliance with strength training in middle-aged and older adults with low baseline arterial compliance [79]. In another study involving healthy postmenopausal women, 18 weeks of a moderate resistance training program did not change AI [80]. Moreover, 12 weeks of leg resistance training did not change aortic PWV in older men though maximal muscular power was increased by 16 % [76]. Collectively, these results suggest that older adults can gain the benefits of moderate resistance training without experiencing arterial stiffening.

Concurrent Training or Cross-Training

Arguably, one of the most effective way to maximize benefits from both aerobic exercise and resistance exercise appears to be the simultaneous performance of both training (i.e., concurrent training or cross-training) [81, 82]. Theoretically, the opposing effects of aerobic and resistance training exercise on central arterial compliance should negate the adverse effects of resistance training on arterial compliance if aerobic exercise training effects equals or exceeds the resistance training effects. This hybrid approach is consistent with the latest exercise recommendation that more inclusive practices of aerobic, resistance, and flexibility exercise training should be recommended as an approach to enhance both overall fitness and health [58].

As an initial approach to address this, we performed a cross-sectional study involving rowers. Rowing is unique because its training encompasses both endurance and strength training components. Rowers require large muscle strength for the acceleration of the boat at the race start and a high endurance capacity to maintain this speed during the race [83]. Likewise, rowers perform a combination of endurance and strength training during their usual training regimen as demonstrated by their large maximal aerobic capacity and muscle strength [83–85]. In order to minimize the weaknesses of the cross-sectional study design and to isolate the influence of rowing as much as possible, rowing and sedentary control groups were

carefully matched for age, body composition, blood lipids, plasma glucose, blood pressure, and dietary sodium intake [86]. Additionally, to isolate the effect of rowing, we excluded individuals for whom rowing was not their primary form of exercise. We demonstrated that central arterial compliance was higher and ß-stiffness index was lower in habitual rowers than in age-matched sedentary controls [86].

The results of subsequent interventional studies are consistent with this cross-sectional study. Concurrently-performed endurance training minimized arterial stiffening that was accompanied by high-intensity resistance training [67]. Additionally, there was a tendency for arterial compliance to increase with combined endurance and resistance training. Other groups have since confirmed these findings [87]. In a study involving healthy postmenopausal women, 3 months of combined circuit weight training and endurance training reduced PWV [87]. From the standpoint of exercise adherence and compliance, this type of concurrent training is highly beneficial as it is more enjoyable and breaks the boredom that often results from long-term participation in a single exercise mode [81, 82]. Thus, stiffening of the large arteries may be avoided if endurance training is incorporated into an exercise program that has a strenuous strength training component. For related discussions on the benefits of concurrent training, please see Chaps. 3, 4, 6, and 13.

Clinical Implications and Importance

There are a number of ways that arterial stiffening can contribute to the increased incidence of CVD (Fig. 8.2). Hypertension is one of the most prevalent risk factors for CVD, and the majority of patients with hypertension are classified as having

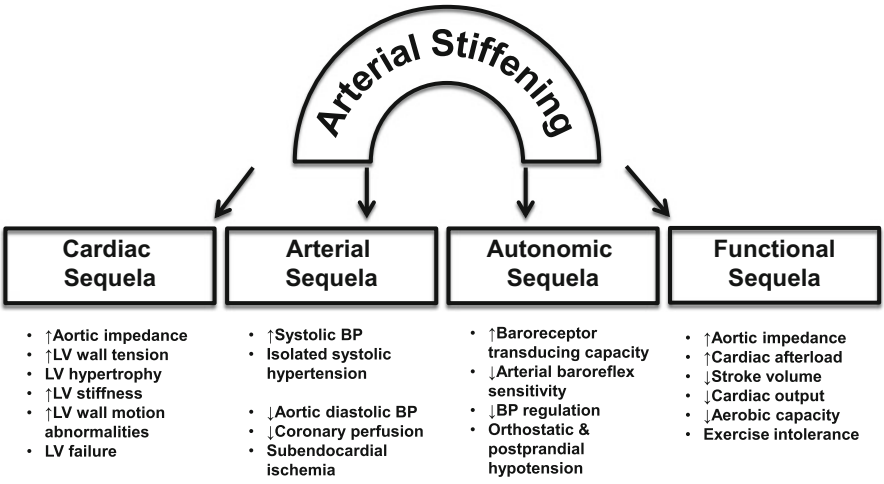

Fig. 8.2 Clinical and functional sequelae of arterial stiffening. *LV* left ventricle, *BP* blood pressure

essential hypertension without known causes of elevated high blood pressure. Most of these patients develop this health condition as they age as blood pressure, more specifically systolic blood pressure, increases progressively with advancing age [88]. Arterial stiffness is now thought to be a primary factor mediating the age-related increases in blood pressure [5]. By absorbing a proportion of the energy in systole and releasing it in diastole, the aorta and large arteries maintain coronary blood flow and avoid an increase in left ventricular afterload. Stiffening of central elastic arteries would reduce the buffering or cushioning effects translating the pulsatile effects of the arteries into arterioles and capillaries where there is very limited ability to cope with the pulsatile stress. Through the impairment of this buffering function, reductions in arterial compliance or increases in arterial stiffness contribute to elevations in systolic blood pressure, left ventricular hypertrophy, and coronary ischemia [4–6, 89]. Indeed, higher arterial stiffness is associated with a greater rate of mortality in patients with end-stage renal failure and essential hypertension [2, 3].

From a functional standpoint, arterial stiffness is significantly and inversely associated with maximal oxygen consumption, one of the most important determinants of exercise capacity as well as a CVD risk factor [12]. Associations between PWV and physical working capacity have also been reported [90]. Stiffening of central elastic arteries could increase aortic impedance and left ventricular afterload, thereby reducing stroke volume and systemic cardiac output, a critical determinant of maximal oxygen consumption [30, 91]. Indeed, the administration of calcium channel blockers that act to reduce arterial stiffness results in an improvement in aerobic exercise performance among older individuals [92]. Through this systemic hemodynamic mechanism, arterial stiffening can contribute to the exercise intolerance typically observed in older populations [93].

Conclusion

Regular aerobic exercise can reduce arterial stiffness in healthy middle aged and older adults and attenuate age-related increases in arterial stiffness. Importantly, this can be accomplished with an intensity (moderate) and type (e.g., walking and swimming) of physical activity that can be performed by most, if not all, adults. The beneficial effects of regular aerobic exercise on arterial stiffness are associated with a favorable influence on arterial blood pressure and arterial baroreflex sensitivity. However, regular aerobic exercise may not be effective in reducing arterial stiffness in patients with existing clinical conditions. In contrast to the effects of aerobic exercise, an intervention incorporating strenuous resistance training increases, rather than decreases, arterial stiffness in young adults. However, the arterial stiffening effect appears to be absent when older adults with already increased arterial stiffness perform moderate intensity resistance exercise programs. Simultaneously performed endurance and resistance training or concurrent training can elicit beneficial adaptations without inducing arterial stiffening effects. Thus, the effects of exercise training on the elastic properties of arteries depend on exercise modes and populations.

Key Points and Resources

- Regularly-performed aerobic exercise is effective in preventing and reversing arterial stiffening that occur with advancing age.
- Arterial stiffness increases after strenuous resistance training in young men but not in older adults with already increased levels of arterial stiffness.
- Concurrently-performed aerobic exercise effectively prevents the arterial stiffening effects of strenuous resistance training.
- Association for Research into Arterial Structure and Physiology http://www.arterysociety.org/
- North America Artery Society http://naartery.org/
- Seals DR, Desouza CA, Donato AJ, Tanaka H (2008) Habitual exercise and arterial aging. J Appl Physiol 105: 1323–1332 [20].

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Chapter 9
Effects of Exercise on Blood Pressure and Autonomic Function and Other Hemodynamic Regulatory Factors

Daniel W. White and Bo Fernhall

Abbreviations

ACh	Acetylcholine
ANGII	Angiotensin II
ANS	Autonomic nervous system
ATP	Adenosine triphosphate
BP	Blood pressure
BRS	Baroreceptor sensitivity
Epi	Epinephrine
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
LBNP	Lower body negative pressure
LF	Low frequency
MAP	Mean arterial pressure
MSNA	Muscle sympathetic nerve activity
NE	Norepinephrine
NO	Nitric oxide
NP/NS	Neck pressure/neck suction
OTT	Orthostatic tolerance test
PSNS	Parasympathetic nervous system
RAAS	Renin-angiotensin-aldosterone system
SNA	Sympathetic nerve activity
SNS	Sympathetic nervous system
SSNA	Skin sympathetic nerve activity

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Introduction

During the course of daily activities, the autonomic nervous system (ANS) maintains hemodynamic homeostasis by actively modulating blood pressure (BP) and cardiac output to match physiologic demands. Most types of hypertension are linked to abnormal ANS activity and altered cardiovascular regulation [1–4]. Beyond the general hypertensive effects, abnormal ANS activity negatively affects multiple physiological systems (vascular, cardiac, renal, metabolic, and immune) thereby amplifying the dysfunction beyond high BP [5]. Exercise training has been shown to be beneficial on ANS function [4, 6, 7]. The exact mechanisms which mediate the beneficial effects of exercise on cardiovascular control are still not entirely understood.

Purpose of This Chapter

The purpose of this chapter is to discuss the effects of exercise on ANS control of the cardiovascular system and the benefits of exercise on maintaining autonomic balance. In this chapter, a brief tutorial of the anatomy and functional properties of the ANS will be presented followed by research that has led to current techniques and philosophies employed in the investigation of cardiovascular control during exercise.

Key Terminology and Basic Concepts

This section of Chap. 9 is a departure in format from previous chapters in that it is a tutorial of the anatomy and physiology of autonomic function defined as, the set of neurological control systems regulating and maintaining cardiovascular homeostasis, that also includes discussion of key terminology and basic concepts. See Table 9.1 for a list and definition of common terms associated with the function of the ANS. The ANS is made up of three branches, the Parasympathetic Nervous System (PSNS), the Sympathetic Nervous System (SNS) and the Enteric Nervous System. This section will discuss the roles of the PSNS and SNS.

Anatomy

The ANS controls involuntary physiologic functions such as heart rate, digestion, fine control of BP, etc. (Fig. 9.1). The cell bodies of the ANS are located in the intermediolateral column (PSNS: stem and sacral cord, SNS: thoracic cord) of the spine and project ventrally to autonomic ganglia (i.e., the point of separation

Table 9.1 List and definition of common terms associated with the function of the autonomic nervous system

ACh	Acetylcholine	One of the primary neurotransmitters in the autonomic nervous system. Released by all pre-ganglionic neurons and post-ganglionic parasympathetic neurons. Causes cardio-deceleration
BRS	Baroreflex sensitivity	The ratio of change in R–R interval to a change in blood pressure. When calculated without perturbation of the system, it is considered spontaneous baroreflex sensitivity which represents sensitivity of the steady-state condition
Epi	Epinephrine	One of the primary neurotransmitters in the autonomic nervous system. Released by the adrenal medulla into the circulation in response to stress. Causes cardio-acceleration and increased vascular tone; "Fight or Flight" response
HF	High frequency	The frequency range from 0.15 to 0.4 Hz in which changes in the length of the cardiac cycle are related to respiration and are mediated by the parasympathetic nervous system
HRV	Heart rate variability	The measurement of changes in length of the cardiac cycle on a beat to beat basis which are representative of modulation by the autonomic nervous system
LBNP	Lower-body negative pressure	A technique used to decrease venous return to the heart and unload the cardiopulmonary baroreceptors by decreasing the ambient pressure within a sealed chamber surrounding a subject below the iliac crest. Decreasing venous return directly decreases stroke volume and cardiac output and activates autonomic reflexes. Unloading the cardiopulmonary baroreceptors increases the sensitivity of the system through feed forward and feedback mechanisms
LF	Low frequency	The frequency range from 0.04 to 0.15 Hz in which changes in the length of the cardiac cycle are related to blood pressure feedback from the baroreflexes and are mediated by both the sympathetic and parasympathetic nervous systems
MSNA	Muscle sympathetic nerve activity	The quantification of the electrical nerve impulses of the sympathetic nervous system which innervate the skeletal muscle blood vessels
NE	Norepinephrine	One of the primary neurotransmitters in the autonomic nervous system. Released by post-ganglionic sympathetic neurons. Causes cardio-acceleration and increased vascular tone; "Fight or Flight" response
NP/NS	Neck pressure/neck suction	A technique used to manipulate the carotid baroreceptors to test baroreflex function non-invasively
OTT	Orthostatic tolerance test	A technique used to passively test the ability of the autonomic nervous system to maintain arterial blood pressure and cerebral perfusion
PSNS	Parasympathetic nervous system	Branch of the autonomic nervous system associated with "Rest and Digest" functions. The cardiovascular actions of this branch are mainly limited to the heart and control the beat to beat modulations in heart rate
SNS	Sympathetic nervous system	Branch of the autonomic nervous system associated with "Fight or Flight" functions. The cardiovascular actions of this branch include increases and decreases in steady-state heart rate and modulation of vascular tone for blood pressure maintenance

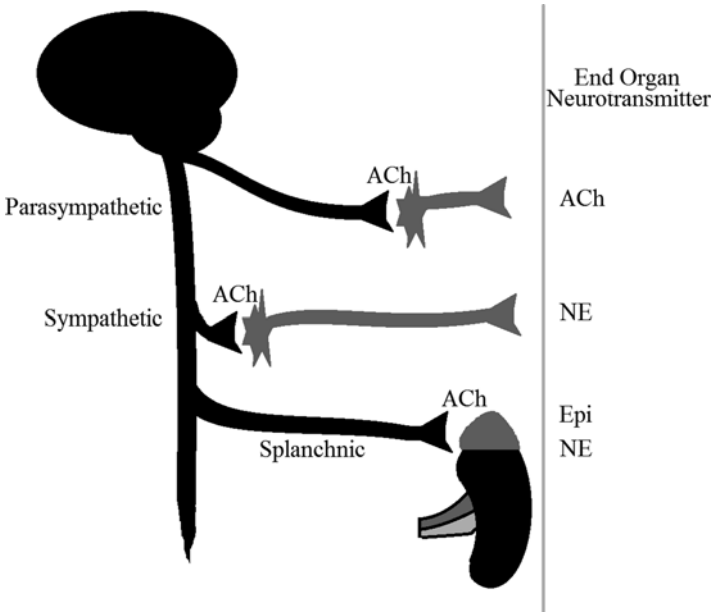

Fig. 9.1 Relative orientations of the pre- and post-ganglionic autonomic neurons. Representation of the autonomic nervous system: Pre-ganglionic, post-ganglionic, and end-organ neurotransmission. Pre-ganglionic parasympathetic neurons are longer with a short post-ganglionic neuron to the end organ. Most pre-ganglionic sympathetic neurons are short and form chain ganglia along both sides of the spine from which the longer post-ganglionic neurons emerge and travel toward their target organs. The adrenal medulla is supplied by the splanchnic nerve and releases neurotransmitter directly into the bloodstream. *ACh* acetylcholine, *NE* norepinephrine, *Epi* epinephrine

between the central and peripheral nervous systems), then to post-ganglionic effector neurons which synapse at target organs: smooth/cardiac muscle and glands. The synapses of the post-ganglionic neurons are diffusely spread in varicosities along the target organs as opposed to the somatic neurons which have discrete nerve endings at the neuromuscular junctions. Higher brain control comes from hypothalamic projections to the medulla, integrating at the nucleus tractus solitarius, ventrolateral medulla (VLM), and the vagal motor nuclei. Peripheral afferent neurons also integrate at the nucleus tractus solitarius providing feedback information from various receptor populations [8].

Efferent neurons of the PSNS originate in both the dorsal motor nucleus of the vagus and in the nucleus ambiguous, previously described as the cardio-inhibitory center of the brain. The efferent PSNS neurons descend via the vagus nerve. Most of the neurons descending from the dorsal motor nucleus of the vagus innervate the gut, controlling digestion, whereas the neurons originating in the nucleus ambiguous innervate the heart allowing for fine control of HR. Parasympathetic ganglia are located near their target organs (Fig. 9.1) [8].

Efferent neurons of the SNS originate in the rostral ventrolateral medulla (rVLM) and descend the intermediolateral column to the thoracic spinal cord where they exit the spine to form paravertebral sympathetic chain ganglia. Cardiac and upper extremity vascular presynaptic sympathetic neurons exit the spinal cord between thoracic vertebra 1 and 5 (T1–T5) and the lower extremity vascular sympathetic between thoracic vertebra T6 and lumbar vertebra 2 (T6–L2). Most SNS neurons controlling cardiovascular function synapse at the paravertebral ganglia with the effector neurons (post ganglionic) projecting to the target organ, whereas the SNS neurons innervating the gut and pelvic organs exit the chain ganglia and synapse within preaortic sympathetic ganglia. Lastly, the adrenal medulla is a specialized cluster of post ganglionic sympathetic effector neurons with no axons or projections. The neurons within the adrenal medulla are activated and release neurotransmitters directly into the circulation (Fig. 9.1) [8].

There are three classic peripheral autonomic neurotransmitters: acetylcholine (ACh), norepinephrine (NE), and epinephrine (Epi). All preganglionic and parasympathetic neurons use ACh as the neurotransmitter, whereas most of the sympathetic nervous system uses NE and Epi with only a few exceptions using ACh [8]. The adrenal medulla releases Epi:NE at a ratio of 4:1. Aiding the classical neurotransmitters, there are a multiple neuromodulators which act by various mechanisms to enhance end organ effects: vasoactive intestinal peptide, neuropeptide Y, nitric oxide (NO), and adenosine triphosphate (ATP) [8].

Physiology

Historically the ANS has been generalized as opposing branches which control distinct reactions to stimuli: PSNS with "Rest and Digest" functions and SNS with "Fight or Flight" functions. However, the activity of the two branches of the ANS are functionally balanced to provide appropriate cardiac output and perfusion to the vital organs which are reflexively modulated to meet various demands including orthostatic changes, temperature regulation, and exercise.

The heart is innervated by both the PSNS and SNS. In general, the PSNS produces a negative chronotropic (i.e., HR) effect while the SNS produces a positive effect. Chronotropic and dromotropic (i.e., conduction speed) effects are associated with direct PSNS and SNS control, whereas inotropic (i.e., ability to produce a forceful contraction) and lusitropic (i.e., myocardial relaxation) effects are mainly due to alterations in SNS activity. The neural pathways of the ANS work in a cooperative antagonistic nature where PSNS release of ACh inhibits the SNS release of NE and vice versa, facilitating the positive actions of each branch of the ANS, thus preventing neurotransmitter competition at dually innervated organs [9].

The different regions of the body are innervated for fine control of blood flow based on demand emanating from the different vascular beds. Most of the visceral organs used for digestion are dually innervated by both the enteric nervous system and the SNS. The peripheral vasculature supplying skeletal muscle is only innervated

by the SNS and relies on the balance of sympathetic nerve activity (SNA) and vasoactive substances to maintain fine control of blood flow especially during exercise [10]. During exercise, this phenomenon is known as functional sympatholysis (i.e., vasoactive molecules released from the active skeletal muscle and/or endothelium that inhibit sympathetic vasoconstriction) [11–14]. The exact mechanisms which control the inhibition of sympathetic influence at the vasculature remain unknown.

Essential Hypertension

There is no single cause of essential hypertension, but it is likely that all essential hypertension involves a neuronal component. Hypertension caused by increased cardiac output or increased systemic vascular resistance are a direct result of ANS dysfunction usually characterized by increased SNS activity and an inhibition of PSNS activity [15], along with increases in angiotensin II (ANGII) [5] termed *neurogenic hypertension*. Neurogenic hypertension is the most common type of hypertension in humans [1] accounting for 40–65 % of cases [4] with a two- to threefold increase in SNS activity [2, 3]. Parallel increases in steady-state SNA and BP have been observed in humans with normal BP and those with pre- and established hypertension [16]. Chronic sympathetic neural activation has been implicated in the etiology and development of neurogenic hypertension [1, 5, 17]. For example in animal models such as the spontaneously hypertensive rat prior to onset of hypertension [18] SNS activity is elevated which can be prevented by neonatal sympathectomy [19, 20].

Commonly associated with hypertension of a neural nature are the renal genetic hypertensions. The inability of the kidneys to effectively regulate blood volume resulting in essential hypertension is the target of many antihypertensive therapies. Renovascular hypertension occurs when blood flow through the renal afferent artery is decreased by some stenotic factor. This decreases glomerular filtration, thereby decreasing sodium delivery to the macula densa which activates the renin angiotensin aldosterone system (RAAS) [21]. The activation of the RAAS increases fluid retention and promotes vasoconstriction which results in hypertension. It is likely that combined with general renal feedback malfunction, and an inability of the kidneys to respond to the neural signals of increased BP, even some types of renal hypertension could be classified as neurogenic in nature (or a result of).

With the realization that pure neurogenic hypertension can be prevented by inhibition of the SNS [20] and knowing that exercise training is implicated in reduced SNS activity and increased PSNS activity [22], it is logical to assume that exercise could be used to prevent the onset of essential hypertension characterized by neurogenic dysfunction and to possibly reduce or reverse early onset neurogenic hypertension. It is within the heart and peripheral vasculature that the role of exercise will now be explored regarding the autonomic adaptations to hypertension and exercise.

Autonomic Nervous System Function and Exercise

In 1841 Volkman showed that HR and BP are modulated by normal respiration and muscle contraction [23]. Marey later reported an inverse relationship between BP and HR which would be come to known as the arterial baroreflex [24]. Hering and Breuer [25] concluded that these responses were vagally modulated.

Krogh and Lindhard [26] observed that HR and BP were immediately elevated at the onset of exercise before any known circulating metabolite could provoke the changes suggesting a parallel activation of the autonomic centers of the brain generated by neural connections from the motor cortex at the onset of exercise. Alam and Smirk [27] later showed maintenance of elevated systemic BP even after cessation of physical work, when the circulation was still captured in the working muscle's vascular bed indicating that there must be some metabolic mechanism from the muscle utilizing a neural pathway.

Studies in Animals to Map the Neural Pathways

Throughout the mid twentieth century, many studies were performed in animals to map the neural pathways of the ANS [28–30]. The techniques used for this work involved the discovery of neuroactive chemical compounds specific to autonomic function [28, 30–41]. It was in the 1960s and 1970s that the central pathways of the ANS were mapped [42, 43] along with peripheral receptor influence on the modulation of the system [44]. Those studies led the way for the development of techniques which are now commonly used in the assessment of autonomic function.

Measurement of Autonomic Function in Humans

Measurement of autonomic function in humans can be characterized into five commonly used techniques: (1) Pharmacologic blockade, where muscarinic and adrenergic antagonists are given separately and/or combined; (2) Direct recordings of sympathetic nerve activity using microneurography; (3) Biochemical measurements of NE across a vascular bed (NE spillover); (4) Measures of HR and BP variability where beat to beat fluctuations in HR and/or BP are used as indices of parasympathetic (HR) and sympathetic (BP) modulation; (5) Measures of beat to beat changes in HR and BP in response to stressors such as orthostasis, lower body negative pressure (LBNP), neck pressure/neck suction (NP/NS) or pharmacological manipulation of the vasculature and BP.

Pharmacological blockade is useful for isolating the influence of one or both branches of the ANS for the analysis of branch/system specific effects on cardiovascular function. Study procedures are often repeated with each experimental condition and differences are attributed to the action of the blocked branch of the ANS (Fig. 9.2). Using this technique in separate studies Bevegard et al. [45] and

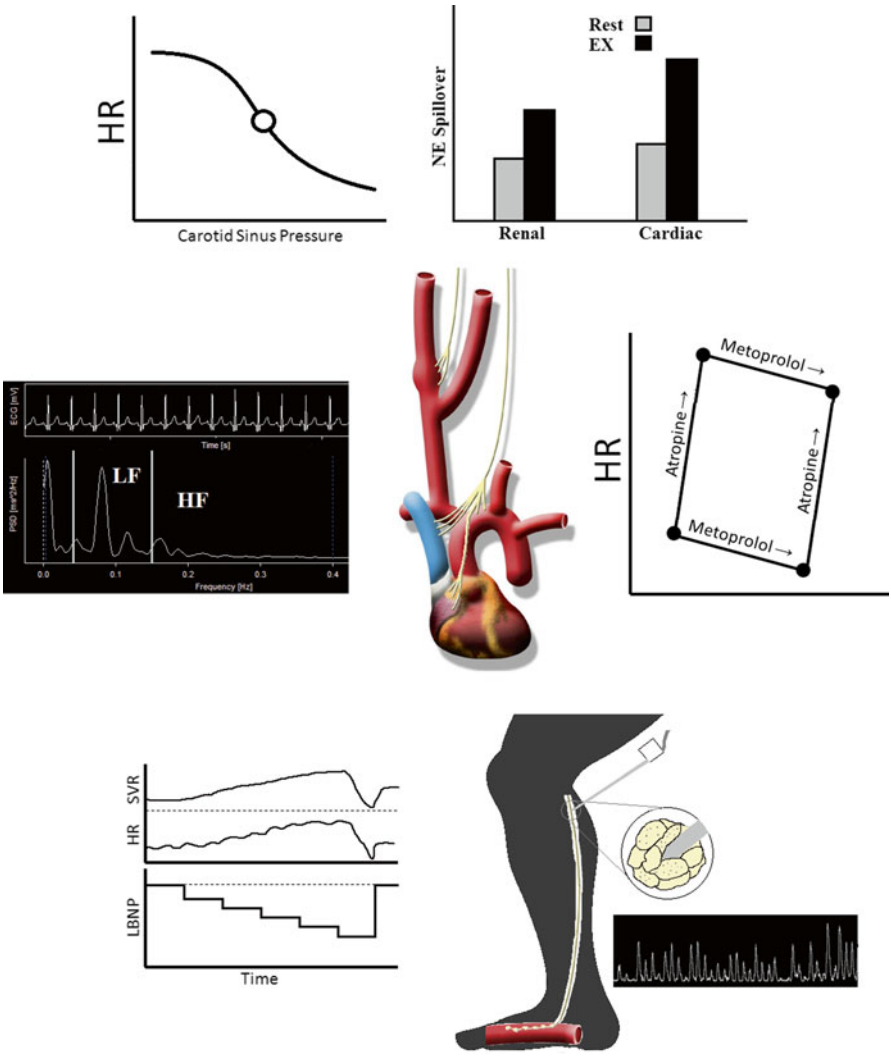

Fig. 9.2 Autonomic testing data examples. Typical data output from various methods of autonomic assessment. (*Clockwise* from *top left*) **Standard baroreflex curve**. The *curve* shows the relationship of HR to an acute change in carotid sinus pressure. The *open circle* in the middle indicates the operating point of the reflex where steady-state HR and carotid sinus pressure exist. During exercise, this operating point moves up the curve toward the plateau. **Measurements of NE spillover**. Typical data showing an increase in NE with exercise. **Double-blockade of the heart with metoprolol and atropine**. The *arrows* show the change in HR with the addition of each drug. The final point is the intrinsic HR. **Microneurography**. This shows the standard positioning of the microelectrode within the peroneal nerve at the fibular head. The *enlarged circle* shows that the tip of the micro electrode must rest within the nerve bundle in close proximity to the desired nerve fiber. **LBNP**. This is a representation of a standard stepped pressure reduction protocol and the corresponding changes in HR and SVR to the point of presyncope. **Heart Rate Variability**. Electrocardiogram tracings and the corresponding frequency analysis of the R–R interval. *HR* heart rate, *NE* norepinephrine, *LBNP* lower body negative pressure, *SVR* systemic vascular resistance

Robinson et al. [46] established the relative influences of the SNS and PSNS during exercise. In both studies it was determined that as the exercise stimulus increases, there is an increase in SNS activity and a decrease in PSNS activity as shown by changes in steady-state HR. Benefits of this technique are the ease of which pharmacological agents can be administered, and there are no equipment or protocol limitations for using the technique. A limitation to the technique is the inability to study organ specific effects when using systemic dosages due to the influence of blockade on the entire system and the disruption of autonomic interactions within the ANS. To overcome this limitation, the use of specific receptor antagonists is recommended, and depending on the study, microdialysis (i.e., a sampling technique used for continuous measurement of extracellular concentrations of substances of virtually any tissue or infusion of very small volumes to a target location) can be implemented to limit systemic exposure to agonists/antagonists (i.e., drugs that work in counteractive directions).

The technique of microneurography is widely used to assess electrical activity in peripheral nerves (Fig. 9.2) [47]. The two common peripheral nerve recordings measure muscle sympathetic nerve activity (MSNA) [48] and skin sympathetic nerve activity (SSNA) [49]. Both measurements detect the firing frequency of efferent sympathetic nerve fibers and quantify the density of the frequency signal over time [50]. MSNA recordings are more prevalent when assessing cardiovascular control because it is a direct recording of the sympathetic nerve fibers innervating the resistance vessels within skeletal muscle which are responsible for fine control of systemic vascular conductance (or resistance) [8]. Muscle sympathetic nerve fibers are also baroresponsive, whereas skin sympathetic nerve fibers are thermo- and startle-responsive and do not appear to significantly influence steady state BP unless extreme thermal environmental factors are present [51]. The benefits of this technique are the direct quantification of sympathetic outflow and the ability to real-time measure responses to multiple sympathoexcitatory stimuli. This technique can also be used during various types of exercise [52–58]. The technique is limited, however, to analysis of postganglionic sympathetic activity as there is no easily accessible parasympathetic neuron in humans. Another limitation to microneurography is the delicate nature of the technique which takes years of training to become efficient in, and requires the subject to remain motionless in the extremity which the measurement is being performed, which limits its success during dynamic exercise. It is also hard to interpret functional outcomes of microneurography recordings as variability between subjects is high; the interpretation of nerve traffic also assumes a direct relation to neurotransmitter release and utilization that may vary between individuals.

The most complex of the invasive techniques is the direct analysis of NE release across an organ (Fig. 9.2). This technique has shown a direct correlation with nerve traffic to the organ in which it is measured [2]. The measurement of catecholamines in the blood can go from very general (systemic venous sampling) to very specific (coronary vein sampling). There is an inverse relationship between the invasiveness of the technique and the functional outcome accuracy of the data [59] (i.e., antecubital venous sampling during leg cycling will not be as accurate as femoral

sampling). Benefits of this technique are a very accurate measure of catecholamine release in a specific vascular bed, and the ability to use it in most experimental conditions (i.e., exercise). A limitation to this technique is that systemic measurements of catecholamines do not account for organ-specific neural activity [59]. The technique is also limited by the cost to collect and analyze samples, the expertise needed for the more invasive procedures, and the specialized equipment for performing the experiments.

Rhythmic oscillatory fluctuations in HR have led to the evaluation of HR variability (HRV) (Fig. 9.2). Both vagal and sympathetic efferent activity affects HRV, but in different frequency bands. Vagal stimulation causes high frequency (HF) modulations, up to 1 Hz; whereas sympathetic stimulation produces low frequency (LF) modulations, typically below 0.15 Hz [60, 61]. Pharmacologic blockade with atropine abolishes most of the HF fluctuations in supporting this measure as an index of vagal modulation on HR. Conversely, propranolol diminishes the LF fluctuations, with relatively little effect on HF HR fluctuations. However, stimulation of both vagal and sympathetic nerves affects LF, suggesting that LF is influenced by both efferent parasympathetic and sympathetic activity [60, 61].

The European Society of Cardiology and the North American Society of Pacing Electrophysiology have produced guidelines for measurement of HRV [62]. Although both time domain and frequency domain analyses can be made, frequency domain analyses using Fourier analysis is common and has been frequently used in exercise studies. LF is defined as the spectral power between 0.04 and 0.14 Hz, with HF defined as spectral power between 0.15 and 0.4 Hz [62]. Although it has been suggested that LF HRV can be used as measure of sympathetic modulation, particularly when expressed as a function total HRV [62], this is probably not appropriate given its dependence on both sympathetic and parasympathetic influences [63]. Similarly, using the ratio of LF/HF has also been suggested as a measure of sympathetic modulation, or as a measure of sympathovagal balance, but neither of these interpretations of HRV appear to be an accurate reflection of the underlying physiology [63]. Consequently, HRV should be considered primarily as a measure of vagal modulation of heart rate. Because many factors influence HRV (e.g., age, body position, hydration status, training status, sleep, exercise and physical activity, medications, etc.) it is important to control for as many of these factors as possible to obtain reliable HRV measurements. Due to the non-invasive nature and relative ease of measurement and analysis, HRV is an attractive tool for evaluation of autonomic function, but it must be carefully applied and interpreted in order to obtain reliable and valid measures.

Other assessments of autonomic function manipulate ANS afferent input and measure the responses using one of the above techniques. Orthostatic tolerance tests (OTT) are a useful way to perturb the system and elicit neurological responses. OTT can be as simple as asking a person to stand after a period of supine acclimatization and measuring HR and BP responses or as controlled as a 70° upright tilt after a 10° head down tilt [64]. NP/NS is used to deform the carotid baroreceptors in order to non-invasively simulate hypo- or hypertension (Fig. 9.2). The immediate HR

responses are a result of parasympathetic activation or withdrawal, whereas the BP changes are a result of changes in systemic vascular resistance [65, 66]. An advantage to this technique is that it is non-invasive and allows for the temporal separation of sympathetic and parasympathetic effects. It can also be used during many different experimental conditions including exercise. LBNP is used to reduce venous return and central blood volume which effectively reduces afferent traffic from the cardiopulmonary baroreceptors to simulate orthostasis, dehydration, or hemorrhage (Fig. 9.2). An advantage to this technique is fine adjustment of central venous pressure without invasive interventions. A disadvantage is the size of the equipment needed for the experiments and the limitations that the equipment puts on mobility. Infusions of vasoactive substances are used to elicit reflex responses due to ANS control. One of the most common is the modified Oxford technique where infusions of a vasodilator (commonly sodium nitroprusside) and then a vasoconstrictor (phenylephrine) are used while HR on BP are measured to yield baroreflex responsiveness [67]. All of these techniques have been used to modulate afferent nerve activity during exercise [52, 68–72] .

Combinations of afferent manipulation and efferent response measurements are useful for teasing out specific pathways and mechanisms. The combination of pharmacologic blockade during exercise along with NP/NS demonstrated that baroreflex changes in HR are parasympathetically mediated even during exercise [66], and that the PSNS continues to be active even up to high intensity exercise [73, 74]. Simultaneous measurements of MSNA or NE spillover during LBNP or tilt table testing have been used to determine the influence of cardiopulmonary baroreceptors on cardiovascular control [75].

Methods

A literature search using PubMed was performed to identify potential scientific articles relating to autonomic function, exercise, and hypertension. An initial search yielded 601 papers of which the full text was obtainable in 434. Of these, 343 papers focused on human research. Although the focus of the this Chapter is on human physiology, some selected papers using animal models were included where no papers using human research were available or if the papers using animal models were considered classic papers. From these 343 papers, fundamental articles were identified by the authors. No limit was set on the date to include in the searches because much of the understanding of ANS and exercise comes from classic papers. The literature cited in this Chapter represents current views in autonomic control and exercise adaptations. Included are references to review articles and original research which have been fundamental in establishing, testing, and confirming these concepts.

Relevant Research

Effects of Acute Exercise on Autonomic Function

During an acute bout of exercise, there is a workload related shift in the influence of each branch of the ANS. This shift appears to move from a system of parasympathetic dominance to a system of sympathetic dominance (Fig. 9.3a) [45, 46, 73]. The reduction in parasympathetic influence with acute exercise is also supported by studies using HRV, showing a gradual reduction in HF with an increase in exercise intensity [76, 77]. The ratio of influence is dependent on mode of exercise, physical fitness level, and loading of the cardiopulmonary baroreceptors. During dynamic leg cycling, the ratio of PSNS: SNS starts at 4:1 during rest and is shifted to 1:1 during about 65 % of maximum effort and then quickly increased to a 1:4 PSNS:SNS at about 75 % maximum effort [73].

Physical fitness level has a large influence on the recovery of the cardiovascular system after an acute bout of exercise. The more physical fit an individual, the more quickly they return to preexercise cardiovascular conditions [78]. HR recovery has been used for many years as a means of assessing cardiovascular fitness [79, 80] and autonomic function [81–85]. Generally, an aerobically fit individual exhibits a faster rate of HR reduction upon cessation of exercise compared to an unfit individual, and is considered to have better autonomic function. Most of this recovery has been associated with an improved vagal reactivation especially with training [85]. This has also been shown using HRV, as Goldberger et al. showed time domain HRV indices of vagal modulation were measurable after the first 60 s of

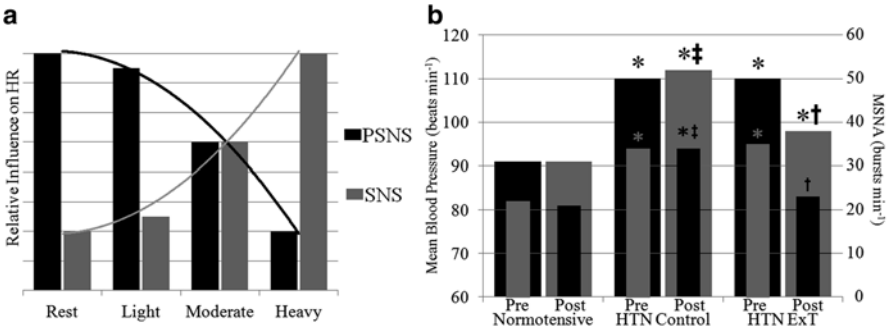

Fig. 9.3 (**a**, **b**). Autonomic balance during exercise and the result of exercise training. (**a**) The relative contributions of the ANS on HR during an acute bout of exercise. As exercise increases the parasympathetic contribution to HR decreases which agrees with HR variability data. (adapted from White & Raven [73]). (**b**) Results of the pre- and post- 4 month exercise intervention in never treated subjects with hypertension. *Large columns* are clinical blood pressure measurements and *inset bars* are MSNA. *Different from normotensive; †different from pre-; ‡different from HTN ExT (adapted from Laterza et al. [102]). *ANS* autonomic nervous system, *HR* heart rate, *MSNA* muscle sympathetic nerve activity, *HTN* hypertension, *ExT* exercise trained, *PSNS* parasympathetic nervous system, *SNS* sympathetic nervous system

recovery and then remained elevated [86]. These increases in vagal modulation during exercise recovery were completely abolished with parasympathetic blockade using atropine. Similar conclusions have been made about the decrease in BP postexercise assuming that there was an immediate decrease in SNA contributing to most of the BP decreases [87]; however, Halliwill and colleagues has recently proposed that the decrease in BP after cessation of exercise and the ensuing postexercise hypotension are due to activation of histamine receptors (H1 and H2) in the vasculature [88]. Current research highlights the importance of sympathetic withdrawal and a reduction in peripheral afferent input regarding autonomic modulation following exercise [89].

Effects of Exercise Training on Autonomic Function

Exercise training is associated with beneficial effects on autonomic function [90]. Cross-sectional studies show that exercise trained individuals have increased HRV, lower resting HR, and lower BP [4, 6, 91, 92]. They also generally have improved baroreflex responsiveness [93, 94]. Deficits in cardiovascular function from lack of exercise have been associated with SNS over activity resulting in decreased cardiovascular reserve [95–98]. Exercise training is associated with decreased baseline SNS activity [4, 94] which may be due to adaptations of the central nervous regions which control sympathetic outflow [6]. Animal models have shown that exercise training favors sympathoinhibition in the medullary nuclei controlling the cardiovascular system [99], and that there is a remodeling of the cardiorespiratory centers in the brain, resulting in lower resting sympathetic outflow and higher resting parasympathetic outflow after exercise training [100, 101].

There has only been one human study that measured SNA in subjects with hypertension before and after an exercise training program [102]. Laterza et al.showed a substantial reduction in MSNA and BP after the training in subjects with hypertension but no changes in MSNA or BP in subjects with normal BP (Fig. 9.3b). They also showed that arterial baroreflex function in individuals with hypertension returned to normal after 4 months of training [102]. While this is the only exercise training study measuring MSNA in individuals with hypertension, multiple studies have shown that exercise training reduces BP in those hypertension [103, 104] which is supported by the American College of Sports Medicine [105] and covered in Chap. 1. However, the decrease in MSNA in individuals with hypertension is supported by findings in subjects with heart failure, who also exhibit elevated baseline SNA. In patients with heart failure, MSNA significantly decreased following 4 months of endurance training, with a concomitant decrease in mean arterial BP (MAP) of 7 mmHg (although this decrease was not statistically significant due to low subject numbers) [106]. Neither MSNA nor BP changed in the control group.

It is commonly accepted that exercise training lowers both HR and BP. The reduction in HR is thought to be a function of increased vagal tone, but data also suggest a possible structural adaptation of the sinoatrial node. Katona et al.[107]

used double blockade and mathematical models to estimate the influence of the SNS and PSNS on HR in athletes and non-athletes at rest and concluded that the lower HR in athletes was due to decreases in the intrinsic firing rate of the pacemaker cells of the heart. Later Smith et al. [22] using similar methods concluded that along with the lower intrinsic HR, there was a greater parasympathetic dominance over control of HR in the exercise trained individuals.

A number of studies have shown increased parasympathetic modulation using HRV analyses following exercise training. Typically, prolonged or intense (>85 % of maximum HR) exercise training increases HRV in generally healthy populations [108–110]. In fact, Okazaki et al. [110] showed a linear relationship between exercise training load and improvements in HRV in older adults with pre- and Stage 1 hypertension, concomitant with significant decreases in BP. Lower intensity training (70–80 % of HR reserve) also improves HF HRV in individuals with hypertension following 15 weeks of exercise training [111], concomitant with a substantial decrease in MAP (~7 mmHg). Other studies have also shown improvements in total HRV and/or HF HRV with moderate intensity exercise in healthy populations, people with disabilities, and patients with obesity and without type 2 diabetes mellitus, heart disease, and pre- and Stage 1 hypertension [112–115]. Furthermore, resistance exercise training can also improve HRV indices of vagal modulation in healthy young subjects [115, 116], but may decrease HF HRV in individuals with pre-and Stage 1 hypertension, even though BP significantly decreased [112, 117]. Interestingly, recent data suggest that higher baseline vagal modulation may be required for attaining appropriate increases in aerobic capacity following exercise training in both healthy well trained and initially sedentary individuals with obesity [118, 119]. These findings suggest that the autonomic nervous system may exhibit a greater influence on exercise training responses than previously recognized.

Due to the fact that PSNS activity is greater after exercise training, logical reasoning would assume that a central inhibition of sympathetic outflow would contribute to lower BP. Recent findings utilizing chronic electrical baroreceptor stimulation support this concept. Chronic electrical stimulation of baroreceptors in dogs decreases BP, circulating and NE spillover, and MSNA, while increasing HRV and decreasing BP variability [120–122]. Heusser et al. studied humans with resistant hypertension and found similar results; where acute electrical baroreceptor stimulation from an implanted device produced a large decrease in BP (~32 mmHg in systolic BP) concomitant with a large reduction in HR and MSNA, and the reduction in BP was significantly correlated with the reduction in MSNA. In addition, plasma NE concentrations were reduced and correlated with reductions in BP [123]. There was also a sustained decrease in 24 h ambulatory BP with continuous baroreceptor stimulation.

Baroreflex resetting is a phenomenon that occurs as a result of acute exercise that allows for HR and BP to concomitantly increase without evoking the inhibitory responses that would be detrimental to the metabolic demand of exercise [70, 124]. Normally an increase in BP would cause a decrease in HR, but during exercise this response would reduce the ability to exercise by not allowing increases in cardiac output. The exact mechanisms of baroreflex resetting are not fully understood, but

there seems to be a combination of peripheral and central components. In hypertension, baroreflex control of the cardiovascular system is diminished [125, 126] such that there is an inability to functionally change HR, BP, and MSNA in response to increasing BP. But with exercise training, baroreflex control is improved, approaching values of individuals with normal BP [102, 127]. These improvements in baroreflex function are not totally understood; but it is hypothesized that increases in arterial compliance resulting from exercise, increase the sensitivity of the arterial baroreceptors, thereby increasing the sensitivity of the mechanical component of the baroreflex (i.e., The ratio of change in R–R interval to a change in BP) [128]. However, more recent work has shown that while exercise training does indeed improve the mechanical component, most of the improvement in the integrated baroreflex is due to improvements in the neural component [129]. Furthermore, the improvement in the neural component was linearly related to the amount of exercise performed over the 6 month study, whereas the improvement in the mechanical component was not associated with the amount of exercise performed. Last, improvements in systemic energy efficiency may reduce metabolic demand signals from the periphery, reducing sympathetic drive, reducing BP, and restoring baroreflex function [130].

Functional sympatholysis refers to the mechanism by which exercising skeletal muscle counteracts the influence of the sympathetic nervous system in order to reduce local vasoconstriction. This mechanism is important for the maintenance of blood flow during exercise when sympathetic activity is elevated [13]. In men with hypertension, there was an attenuation of functional sympatholysis during exercise and an exaggerated sympathetic vasoconstriction [131]. Exercise training has been shown to improve functional sympatholysis in individuals with hypertension by reducing the sensitivity of the adrenergic receptors on the vascular smooth muscle [14]. Molecular adaptations caused by exercise training are implicated in the maintenance of functional sympatholysis throughout life and may help regain lost function [132, 133].

Clinical Implications and Importance

The mechanisms responsible for improved autonomic function as a result of exercise in individuals with hypertension are not fully known; however, recommendations for improving health through aerobic exercise training in hypertension and other disease states where the autonomic nervous system is involved remains at the forefront of prevention and treatment [130]. Reductions in central oxidative stress have been implicated in the benefits of exercise in individuals with hypertension along with increases in NO [134] (see Section III for greater detail about the pleiotropic effects of exercise). Physical changes such as reductions in body weight and body fat percentage from exercise training can translate into beneficial effects of exercise in individuals with hypertension, possibly by reducing inflammatory cascades associated with obesity which are also known to increase SNA and BP [135].

Autonomic dysfunction is apparent in all forms of hypertension, so it is imperative that research continue to be done to determine the best treatment for the particular hypertension subtype, whether that treatment be exercise, pharmaceuticals, or surgery.

Conclusion

It is clear that autonomic dysfunction occurs in a large number of individuals with hypertension. This is further evidenced by the large number of people with hypertension that have neurogenic hypertension. Autonomic dysfunction also contributes to inappropriate cardiovascular responses to stress, including the stress induced by acute exercises. However, long-term exercise training, especially endurance exercise training, can concomitantly improve autonomic function and decrease BP. These responses are likely at least partly a function of reduced sympathetic and increased parasympathetic outflow, leading to lower cardiac output and peripheral resistance, coupled with increased baroreceptor function. Thus, exercise training, mainly endurance training, can be an effective treatment modality to concomitantly improve autonomic function and reduce BP.

Although a great deal of work has been conducted on the effect of exercise on autonomic function, there is still much to learn. Future work is needed to understand the interplay between exercise training and sympathetic overdrive in the prevention of hypertension. Little is known regarding potential sex differences, but there are documented sex differences in autonomic function [136–138]. Also, the impact of autonomic function on vascular function and how this relationship is influenced by exercise training is still relatively unexplored. There is a need to better understand the effect of different types of exercise (aerobic vs. resistance; land vs. water) and what the most effective exercise prescription would be to improve autonomic function and concomitantly prevent or treat hypertension. The interaction between exercise and other lifestyle interventions, such as salt reducing diets, stress reduction, etc., also needs to be explored further. Most importantly, it is still unknown if alterations in autonomic function as a result of exercise training or other lifestyle interventions will result in reduced mortality and morbidity in individuals with hypertension.

Key Points and Resources

- Autonomic function has a direct impact on BP.
- Hypertension is often characterized by autonomic dysfunction.
- Sympathetic overdrive is a key characteristic among the majority of individuals with hypertension.
- Exercise training can improve autonomic function by decreasing sympathetic activity and increasing vagal modulation.
- Improving autonomic function may be an important pathway for prevention and treatment in hypertension.

- American Academy of Neurology https://www.aan.com/
- American Autonomic Society: http://americanautonomicsociety.org/
- International Society for Autonomic Neuroscience http://autonomicneuroscience.info/ISAN/index.html
- Keystone Symposia on Molecular and Cellular Biology http://keystonesymposia.org

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Chapter 10
Genetics and the Blood Pressure Response to Exercise Training

Tuomo Rankinen

Abbreviations

BP	Blood pressure
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
END1	Endothelin-1
HERITAGE	HEalth RIsk Factors, Exercise TRAining and GEnetics Family Study
GWAS	Genome-wide association studies
SBP	Systolic blood pressure
SD	Standard deviation
SNP	Single nucleotide polymorphism

Introduction

Since the classical studies on British civil servants by Morris et al. [1, 2], American railroad workers by Taylor et al. [3], and on San Francisco longshoremen and Harvard college alumni by Paffenbarger et al. [4, 5], the many positive health effects of a physically active lifestyle have been documented. Individuals engaged in regular physical activities and those with a reasonable level of physical fitness have a lower risk for chronic health problems, such as cardiovascular disease, hypertension, stroke, type 2 diabetes mellitus, and obesity. This evidence is such that several

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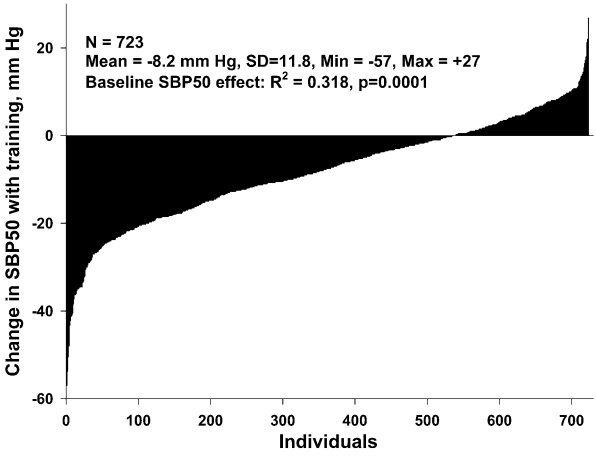

Fig. 10.1 Distribution of the exercise training-induced changes in submaximal exercise (50 W) SBP among participants of the HERITAGE (**HE**alth **RI**sk Factors, Exercise **TRA**ining and **Ge**netics) Family Study. *SBP* systolic blood pressure, *SD* standard deviation

health organizations as well as the U.S. government have recognized the lack of physical activity as a major risk factor for several chronic diseases.

As summarized elsewhere in this Book, regular physical activity is an effective and safe way to prevent the development of hypertension and lower elevated blood pressure (BP) levels (see the chapters in Part I for more detailed information). That said, it is also clear that there are marked inter-individual differences in the adaptation to exercise training. For example, in the **HE**alth **RI**sk Factors, Exercise **TRA**ining and **GE**netics Family Study (HERITAGE), over 700 healthy, sedentary subjects followed an identical, well controlled endurance training program for 20 weeks [6]. As shown in Fig. 10.1, systolic blood pressure (SBP) measured during steady-state submaximal (50 W) exercise decreased on average by 8 mmHg in response to exercise training. However, it is also evident that the responses varied from marked decreases to no changes, or in some cases, even increased. These data underline the notion that the effects of endurance training on cardiovascular traits should be evaluated not only in terms of mean changes but also in terms of response heterogeneity.

Purposes of This Chapter

The purpose of this chapter is to summarize current knowledge on genetics as a determinant of the inter-individual variation in the BP responses to regular exercise, to review progress made in uncovering the molecular genetic basis of genetic architecture of blood pressure responses, and to discuss the future research challenges in exercise BP genetics. Please see Chap. 7 for detailed discussions of the expression of genes and proteins directly related to endothelial health.

Key Terminology and Basic Concepts

Candidate Gene Association Studies

A research strategy where the target gene is selected based on existing knowledge of physiological and molecular pathways that regulate the trait of interest. Only deoxyribonucleic acid (DNA) sequence variants located in the candidate gene locus are examined for the association analyses.

Genome Wide Association Studies

A research strategy where hundreds of thousands (or even millions) of DNA sequence variants (usually single nucleotide polymorphisms [SNPs]) distributed evenly across the entire genome are tested for associations with the trait of interest in a large number of individuals.

Heritability

The proportion of observed phenotypic variance among individuals of a population that is due to genetic differences.

Segregation Analysis

An analytic technique widely used in genetic epidemiology (with pedigree data) to determine if the phenotype of interest is affected by a specific genetic model such as a major gene effect.

Review Methods

Research articles used for this chapter were identified through PubMed literature searches. The majority of the searches were originally done as part of the annual Human Gene Map for Performance and Health-Related Fitness Phenotypes reviews, where all studies dealing with exercise, hemodynamic phenotypes, and DNA sequence variation were identified and reviewed [7–18]. The positive studies (i.e., studies with at least one association with a nominal p-value less than 0.05) were reviewed in the text and incorporated in the summary tables of this chapter, while negative studies were simply listed in the text of this chapter.

Relevant Research

Exercise and Blood Pressure: Evidence from Genetic Epidemiology Studies

Several lines of evidence indicate that there is a genetic component in the regulation of resting BP and the development of hypertension. Estimates of the resting BP heritability have varied from about 20 %, as derived from family studies, up to about 70 % from twin studies [19]. The majority of the studies support a multifactorial model of inheritance with polygenic effects, although major gene effects contributing to BP variability have been reported [20–22]. Only a few studies have investigated the role of genetic factors in the regulation of the BP response to exercise. For the acute (i.e., immediate or short-term) exercise response, a segregation analysis of the diastolic blood pressure (DBP) response to a cycle ergometer exercise test in 864 subjects from 81 pedigrees showed that the phenotypic variance explained by the major gene and polygenic effects were 33.6 % and 16.6 %, respectively [23]. In a large cohort of young monozygotic and dizygotic twins, significant genetic effects were found for the SBP and DBP responses to an incremental cycle ergometer test [24]. These results suggested that the genetic effects found at rest on BP also influenced the exercise phenotypes, although the effects tended to decline with higher exercise intensities.

The only data available at the moment on the heritability of BP responses to aerobic training (i.e., chronic or long-tern exercise) come from HERITAGE. The evidence for familial effects on the resting BP training responses was weak [25], which is not surprising given that hypertension was one of the exclusion criteria of the study and the cohort is composed of individuals with optimal (67 %), normal (22 %), or high normal (8 %) BP. However, when the analyses were repeated in a subsample of families having at least one member with baseline BP above the 95th percentile of the cohort distribution, a putative major locus affecting resting SBP following training was detected [25]. On the other hand, BP measured during steady-state submaximal exercise at 50 W showed a significant decrease with exercise training in HERITAGE subjects (see Fig. 10.1). The strongest predictors of the BP response to training were the baseline BP phenotype level and familial aggregation, i.e., the baseline SBP value explained over 30 % of the variance in the training response, and the maximal heritability of the BP response to training (adjusted for age, sex, body mass index, and baseline trait value) reached 22 %, respectively [26].

Candidate Gene Association Studies and the Blood Pressure Response to Exercise

In addition to evidence from genetic epidemiology studies, successful identification of genes contributing to rare forms of hypertension [27] as well as characterization of several components of well-known BP regulatory pathways (e.g., the renin-angiotensin system [28–30]), fueled early optimism that genes affecting both the BP

responses to acute and chronic exercise could be identified relatively quickly. A host of candidate gene studies followed, targeting genes encoding classic BP and hypertension regulating molecules, such as renin, angiotensinogen, angiotensin converting enzyme, nitric oxide synthases, and endothelins, and their receptors. These studies have been carefully cataloged and reported in a series of review articles entitled, *The Human Gene Map for Performance and Health Related Fitness Phenotypes*, that were published from 2001 [11] to 2009 [7] and in *Advances in Exercise, Fitness and Performance Genomics* reviews that have been published since 2010 [14].

As of 2009, a total of 34 studies had reported positive genetic associations for the hemodynamic responses to acute exercise with seven studies that have reported gene-physical activity or gene-physical fitness interactions on BP and 24 reports for responses to exercise training [7]. The studies were listed as "positive" if the authors reported an association or an interaction with a nominal p value of 0.05 or less; also no attempt was made to evaluate the strengths and weaknesses of the studies in these reviews. As expected, classic hypertension candidate genes were the most popular targets (see Table 10.1 for the list of positive candidate genes associated with hemodynamic training response traits).

Table 10.1 List of "positive" candidate genes for hemodynamic training responses as reported in the latest update of the Human Gene Map for Performance and Health-Related Fitness Phenotypes [7]

Gene	Full name	Training response traits
ACE	Angiotensin I converting enzyme	Left ventricular mass, septal thickness, end-diastolic diameter, DBP, heart rate at 50 W
AGT	Angiotensinogen	DBP at 50 W, resting SBP and DBP
AGTR1	Angiotensin II receptor, type 1	Resting DBP
AMPD1	Adenosine monophosphate deaminase 1	DBPmax
APOE	Apolipoprotein E	Resting SBP
BDKRB2	Bradykinin receptor B2	Left ventricular mass
CHRM2	Cholinergic receptor, muscarinic 2	Heart rate recovery after max exercise
EDN1	Endothelin 1	SBP and PP at 50 W
FABP2	Fatty acid binding protein 2, intestinal	Resting SBP
GNB3	Guanine nucleotide binding protein (G protein), beta polypeptide 3	Resting SBP and DBP, heart rate and stroke volume at 50 W
HBB	Hemoglobin beta	Heart rate at submax exercise
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member	QT interval dispersion on the electrocardiogram at rest
LPL	Lipoprotein lipase	Resting SBP and DBP, left ventricular mass
NFKB1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	Reactive hyperemic blood flow
NOS3	Nitric oxide synthase 3	DBP and heart rate at 50 W
PPARA	Peroxisome proliferator-activated receptor alpha	Left ventricular mass
TTN	Titin	Stroke volume and cardiac output at 50 W

DBP diastolic blood pressure, *SBP* systolic blood pressure

For example, the angiotensin converting enzyme (*ACE*) insertion/deletion (I/D) polymorphism was reported to be associated with the response of left ventricular mass to training in two studies from the same research group [31, 32], such that the DD genotype was associated with a greater increase in left ventricular mass that the II genotype after 10 weeks of basic training in military recruits. Likewise, endothelin-1 (*EDN1*) genetic variants were associated with the SBP response to submaximal exercise after training and interacted with cardiorespiratory fitness level on hypertension risk (i.e., *EDN1* SNPs were associated with greater odds for hypertension only in low-fit individuals) [33]. Other than these findings, there was very little, if any true replication across different laboratories and research groups. Furthermore, the majority of the studies reporting "positive" results were derived from various post-hoc analyses, while the results of the tests addressing the primary hypothesis of the study were negative. However, it should be noted that even if the outcomes of the early candidate gene studies were negative, the scientists were following research strategies that were considered to be more or less state-of-the-art at the time. The limitations of candidate gene approach became obvious later on when empirical data from GWAS efforts started to emerge.

The Genetics of the Blood Pressure Response to Exercise in the Genome Wide Association Study Era

It should be noted that lack of replication and over-interpretation of marginal statistical evidence (i.e., false-positive findings) was by no means problems that affected only exercise genetic research. The same phenomenon has been observed with candidate gene studies of all complex multi-factorial traits. By 2006 DNA microarray technology had reached a stage where genotyping hundreds of thousands of DNA sequence variants (mainly single nucleotide polymorphisms, [SNPs]) in a single reaction was possible, making genome wide association studies (GWAS) in large number of subjects a reality. While the first GWAS findings for traits such as type 2 diabetes mellitus, plasma lipid-lipoprotein levels, and body mass index were very promising [34, 35], results for BP and hypertension phenotypes were disappointing.

The first landmark GWAS study based on the Welcome Trust Case-Controls Consortium cohort did not find any DNA markers to be associated with hypertension at genome-wide significance levels (i.e., $p<5\times10^{-8}$) [34]. The first GWAS meta-analysis for resting BP and hypertension published a few years later reported eight genome-wide significant loci, three for SBP and five for DBP [36]. However, even the most significant SNPs explained less than 0.1 % of variance in BP levels. The most recent meta-analysis published in 2011 and based on about 200,000 subjects of Caucasian descent, listed 29 genome-wide significant loci for resting BP traits; 25 for SBP, 26 for DBP, and 11 for hypertension [37]. Of these, 22 were common for both SBP and DBP, and 10 SNPs showed genome-wide significant

associations with all three traits. Although the number of significant SNPs had increased, the effect size of the SNPs remained small. The most significant SNP for SBP and DBP explained about 1 % and 0.7 % of the variance, respectively [37]. Although there are no GWAS reports available for the BP response to exercise phenotypes at the moment, several lessons can be learned from the existing GWAS meta-analyses for other complex traits. First, those analyses have consistently confirmed the suspicion that vast majority of the candidate gene studies published before the GWAS era were indeed false positives. For example, very few, if any of the candidate genes for obesity-related traits [38] were confirmed in the GWAS analyses. Furthermore, the majority of the GWAS-derived and replicated SNPs and genes for complex traits were never even considered as candidate genes.

Second, the effect sizes of individual sequence variants are very small and the genetic architecture of complex traits at the population level consists of hundreds, if not thousands of sequence variants. For example, the latest GWAS meta-analysis estimated that the BP levels in Caucasians are affected by at least 116 SNPs with a 95 % confidence interval ranging from 57 to 174 SNPs [37]. Similarly, the most recent GWAS meta-analysis for adult height reported almost 700 unique autosomal sequence variants affecting human height, a trait that is characterized by very high heritability [39].

Third, the GWAS meta-analyses have clearly demonstrated the need for large sample sizes to have adequate statistical power to detect the variants and conduct appropriate replication studies for those sequence variants that reached sufficient level of statistical significance in the discovery phase. This point is particularly challenging for exercise genetics studies. The average sample size of the candidate gene studies for hemodynamic training response phenotypes in the 2009 Human Fitness Gene map report was 148 (median 102) [7], which is hopelessly underpowered even for candidate gene studies. Furthermore, since exercise intervention studies are considerably more expensive to do than observational cohort studies, it is extremely challenging to find appropriate studies for replication purposes. These are problems that will seriously slow down the progress in exercise genetics and it is unlikely that the situation will improve in the near future.

Clinical Implications and Importance

After more than 20 years of research, the observation that exercise hemodynamic traits are heritable and aggregate in families is still valid. However, during the same time period our views and understanding of molecular genetics of the BP response to exercise have changed drastically. The initial optimism based on “positive” candidate gene studies changed quickly to confusion due to the fact that most of the observations could not be replicated and confirmed. Over the last 5 years, large GWAS meta-analyses for complex multifactorial traits (including resting BP) have shown that at least hundreds, if not thousands of DNA sequence variants contribute

to the overall genetic architecture of these traits, and that it takes very large sample sizes to detect and replicate those associations. While direct empirical GWAS-based evidence is lacking, it is very likely that the same observations regarding the number of SNPs affecting the trait variance and sample size requirements would apply to exercise-related phenotypes as to other complex traits, including resting BP.

Therefore, after more than 20 years of research, we have not really made any meaningful progress in terms of identifying genes and DNA sequence variants affecting the BP responses to regular exercise. Furthermore, it seems that the progress will be minimal in the near future and hope that DNA-based personalized exercise medicine approach could be used to treat BP does not seem realistic at the moment. It is possible that alternative approaches based on other "omics" techniques (e.g., transcriptomics, proteomics, metabolomics, epigenomics, and bioinformatics) will be more informative than traditional genomics alone in terms of understanding inter-individual variation in the BP response to exercise training (see Chap. 7 for information of the expression of genes and proteins directly related to endothelial health). Likewise, the other "omics" may be particularly useful in identifying functional candidate genes for DNA sequence variation studies, and thereby lessening the multiple testing burdens for association studies as compared to standard GWAS approach. However, such data are not available at the moment.

The real question we should address is whether there is a real need to pursue identifying DNA-based predictors of the BP response to exercise training. If it is true that dozens or even hundreds of sequence variants are needed to build a genetic risk score that would predict a few percent of variance in the BP response to exercise training, it is reasonable to argue that an investment on such diagnostic tools does not make much clinical or economic sense. This is particularly true for hemodynamic response to exercise training phenotypes, because unlike several other cardiovascular and metabolic risk factors, hemodynamic responses are strongly affected by baseline trait values. Pre-exercise training BP or heart rate level has been shown to explain 30–45 % variance in the respective training responses, with subjects having higher BP or heart rate at baseline showing greater reductions with training [40–42], i.e., the law of initial values (Please see Chap. 1 for additional information on the law of initial values).

Therefore, it seems that a quick and inexpensive BP measurement in a sedentary patient would provide much more reliable information about expected training responses than a complex and relatively expensive genetic test. Furthermore, the predictive power of baseline BP measurement applies to all races and ethnicities, while a specific genetic testing panel would be needed for each ethnicity. Genomics and other molecular approaches will remain as valuable tools to fine tune our understanding of the mechanisms for BP regulation and its response to exercise. However, the relatively slow progress in molecular research should not prevent us from promoting regular physical activity as an effective and safe way to lower elevated BP and to maintain optimal BP levels, a major premise of this Book.

Conclusion

While regular physical activity provides several cardiometabolic benefits at population level, it should be remembered that within a population there are marked inter-individual differences in responsiveness of these traits to exercise, ranging from marked improvements to no changes to even adverse responses. A fairly convincing body of evidence shows that hemodynamic responses to exercise aggregate in families and are moderately heritable. However, no genes or mutations have been identified yet for exercise BP traits. The inherent requirement of large sample sizes and multiple studies to discover and replicate the genes and DNA sequence variants that affect the BP responses to exercise training in humans makes the progress in exercise genetics research very challenging and slow. The progress may be accelerated if genetic methods are used wisely in combination with other "omics" technology, such as transcriptomics, epigenomics, and metabolomics.

Key Points and Resources

- Physiological responses to exercise show large inter-individual variation within a population, even if the mean population effect is beneficial.
- Non-responsiveness (i.e., lack of expected improvements in outcome variable) to exercise training may take place even if an individual is fully compliant with the exercise program, indicating that non-responsiveness has a biological basis.
- The strongest determinants of the BP response to exercise training are baseline BP level (i.e., a higher baseline BP is associated with a greater BP decrease with training) and familial aggregation.
- Discovery and replication of genes and DNA sequence variants that affect the BP responses to exercise training in humans will require very large study cohorts, which makes the progress in exercise genetics research very slow. The progress may be faster if genetic methods are used together with other "omics" technology such as transcriptomics, epigenomics, and metabolomics.
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Chapter 11
Exercise and Myocardial Remodeling in Animal Models with Hypertension

Joseph R. Libonati

Abbreviations

AHA	American Heart Association
AKT	Protein kinase B
BP	Blood pressure
Ca^{2+}	Calcium
cAMP	Adenosine monophosphate
c-Kit+	Stem cell marker
DNA	Deoxyribonucleic acid
GRK2	G protein receptor kinase 2
HHD	Human hypertensive heart disease
Ki67	Proliferation marker
LV	Left ventricle
Na^{+}	Sodium
NFAT	Nuclear factor of activated T cells
PI3 Kinase	Phosphoinositide 3-kinase
PKA	Protein kinase A activation
SBP	Systolic blood pressure
SERCA2A	Sarcoplasmic reticulum Ca^{2+} ATPase
SHHR	Spontaneously hypertensive heart failure rat
SHR	Spontaneously hypertensive rat
TAC	Transverse aortic constriction

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Introduction

As is the case in humans, exercise has been shown to lower blood pressure (BP), heart rate, and rate-pressure product in animal models of hypertension [1]. However, despite the attenuation of hemodynamic load with exercise, several studies have shown that exercise superimposed on hypertension promotes cardiomyocyte growth [2, 3]. Despite further inducing hypertrophy, some reports have shown that exercise training protects against cardiomyocyte apoptosis [4, 5] and may increase cardiomyocyte proliferation [5], both of which may potentially offset the progressive loss of functional cardiomyocytes associated with pathological hypertrophy. Training has also been long shown to correct contractile protein abnormalities associated with compensatory hypertrophy in rats [6]. Beyond eliciting structural adaptations in the heart, exercise superimposed on hypertension also alters humoral and intracellular signaling [2, 7–9] which are central in the dysfunctional phenotype associated with pathological hypertrophy [10]. In this regard, some of the hallmark putative benefits of exercise in animal models of hypertension are: an improvement in myocardial β adrenergic responsiveness and (calcium) Ca^{2+} signaling [2], a reduction in pacing induced contractile dysfunction [2], a decreased level of oxidative stress [11], and an improvement in endothelial dependent vasorelaxation [12].

Purposes of This Chapter

The general purpose of this chapter is to summarize the literature in how exercise training impacts cardiac remodeling and function in animal models of pressure overload. Specifically, the purposes of this chapter are to: 1) discuss how exercise impacts cardiac remodeling in hypertension with specific reference to key cardiac remodeling signaling pathways; and 2) review myocardial functional adaptations with exercise in animal models of hypertension.

Key Terminology and Basic Concepts

Calcineurin

A Ca^{2+} sensitive, intracellular phosphatase enzyme that is well documented to induce pathological hypertrophy in animal models of pressure overload.

Pathological Hypertrophy

A state of heart growth in which cardiomyocytes increase in cross sectional area primarily by getting thicker (i.e., concentric hypertrophy). Pathological, compensatory hypertrophy is often induced with hypertension.

Physiologic Hypertrophy

A state of heart growth in which cardiomyocytes increase in length (i.e., eccentric hypertrophy). Physiologic hypertrophy is often associated with aerobic exercise training.

Pressure Overload

A physical state in which the heart is exposed to elevated afterload secondary to either genetic, mechanical (transverse aortic banding), or lifestyle factors. Transverse aortic banding is frequently used as an experimental technique to study biological mechanisms associated with pathological cardiac hypertrophy, and increased cell death (i.e., apoptosis) and fibrosis (i.e., collagen deposition) in the heart.

Spontaneously Hypertensive Rat (SHR)

A polygenic animal model of systemic hypertension that well mimics the clinical course in human hypertensive heart disease.

Systolic Elastance

A physiologic slope parameter of the left ventricular pressure volume relationship, i.e., systolic function in relationship to preload.

Methods

An electronic search of the literature using PubMed was performed. In total, four separate searches were generated. In the first, "pressure overload and cardiac hypertrophy in animals" was searched and revealed 2,301 manuscripts published between 1969 to June 2014. A second search for "pathological cardiac hypertrophy and aerobic exercise training in animals" was likewise conducted and revealed 139 papers published between 1966 and June 2014. Third, a search for "hypertension and aerobic exercise training in animals" was conducted and revealed 308 manuscripts published between 1976 and June 2014. Last, a search for the key words "SHR" and "Exercise" and "Heart" was performed and revealed 178 papers published between 1975 and July 2014. Of the recovered papers, the author self-selected those most relevant to the present chapter, with particular attention paid to studies utilizing the SHR model. Results from one meta-analysis [1] on exercise and the SHR were included in the chapter.

Relevant Research

Animal Models

Hypertension induces a pressure overload on the heart. When faced with persistent pressure overload, the heart hypertrophies in order to normalize the left ventricular (LV) wall stress. This adaptation may help regulate cardiac function during conditions of elevated hemodynamic load and is referred to as "compensatory hypertrophy." With compensated myocardial hypertrophy, there is a parallel addition of sarcomeres leading to increases in cardiomyocyte area and width, with an augmentation in LV wall thickness and overall heart mass [13]. Various animal models including; the SHR, transverse aortic banding, nephrectomy, and genetic manipulation have been used to study pressure-induced compensatory hypertrophy. While there are benefits and limitations to each of these models, it is important to recognize differences for each model in recapitulating the complex and multifactorial nature of human hypertensive heart disease (HHD). For example, the persistent and proximal afterload transverse aortic banding induces on the heart greatly differs from the more distal, oscillatory afterload associated with increased total peripheral resistance in the SHR.

A recent American Heart Association (AHA) Scientific Statement on Animal Models of Heart Failure has recommended that; "*Animal models of HHD should have critical characteristics of the disease in humans, including arterial hypertension, an increase in LV mass, and characteristic changes in LV geometry. Cardiac performance should initially be maintained, but eventually diastolic and/or systolic dysfunction should be present. These changes may either be demonstrated by use of echocardiography, magnetic resonance imaging or catheter-based techniques as used in humans. Large-animal models with LV structural and functional impairment may develop a human-like condition of heart failure, including cough, exercise intolerance, and ascites. These features are more difficult to faithfully demonstrate in small animals. Peripheral biomarkers may complement the assessment of animal models of HHD by identifying relevant pathophysiological processes and clarifying the stage and/or severity of disease. Changes in the structure and/or function of myocytes, the interstitium, and the vasculature should also be documented. At the myocyte level, pathological hypertrophy is associated with activation of calcineurin, nuclear factor of activated T-cell (NFAT).*" [13]. The statement goes on to suggest that longitudinal animal models should be utilized with close attention paid to the transition from compensation toward heart failure.

While various animal models have been used to understand the influence of exercise on the hypertensive heart, the greatest abundance of data has been derived from the SHR model [1]. This animal model well mimics the clinical course of untreated essential hypertension in humans and exhibits attributes that are consistent with the AHA Scientific Statement quoted above. It is well documented that concentric hypertrophy occurs in the SHR within 6–12 months of age [10, 14].

The SHR model has been shown to gradually decompensate into heart failure sometime after 15 months of age, but this result is not always reliably observed. The majority of exercise-related effects outlined in this chapter are derived from the SHR model. It must be realized, however, that the mechanisms for hypertension in the SHR are polygenic and may not reflect the genetic underpinnings of human HHD. Thus, other models of pressure-induced hypertrophy are also discussed with respect to exercise training, including work in the spontaneously hypertensive heart failure rat (SHHR) model, the porcine transverse aortic banding (TAC) model, and the Dahl salt sensitive model.

Exercise in Animal Models of Pressure Overload

Blood Pressure and Heart Rate

There are hosts of data showing that exercise training attenuates tail cuff BP in animal models of hypertension [15, 16]. A meta-analysis which surveyed 410 SHR's from 18 reports in the literature showed that mean systolic blood pressure (SBP) increased from 133 mmHg at 1 month of age to 168 mmHg by 4 months of age; illustrating an age dependent effect on BP [1]. With exercise training, a BP lowering effect was found in young SHR relative to sedentary controls. This effect was dramatic in young SHR, as mean SBP declined by nearly 70 mmHg within 5 months of exercise training. However, exercise training did not significantly lower BP in older SHR's, despite those animals performing even greater volumes of exercise relative to younger animals. These data suggest that training can offset hypertension in animals with prehypertension but is less efficacious in animal models of already established hypertension [1]. Interestingly, resting heart rate was also attenuated with exercise training in SHR rats of all ages by 30–50 beats per minute. Shifts in sympathetic and parasympathetic tone may underlie the BP reduction, relative bradycardia, and lower rate pressure product observed with exercise training in SHR [2, 17]; responses that well recapitulates observations in human subjects.

Cardiac Remodeling

The effects of moderate treadmill training and swimming on the heart-to-body weight ratio across the lifespan were also described in a meta-analysis for SHR [1]. In young SHR's, exercise resulted in a very slight reduction in the heart-to-body weight ratio relative to age matched, sedentary controls. However, older SHR's (approximately 4 months of age at the onset of training) did not show different heart-to-body weight ratios relative to sedentary controls. In contrast, the heart-to-body weight ratio increased with training in older rats from the SHHR strain (9–15 months of age) [1]. The overall number of months participating in the exercise program resulted in variable cardiac remodeling, as an increased heart-to-body weight ratio was observed after 2 or 6 months of training, but not after 3 months of training [1].

While forced treadmill exercise training has been the most widely used training model, studies have also been performed in swimming and free wheel running models. While it is difficult to accurately quantify swimming work in rodents, access to free running wheels results in significantly greater distances accrued (35–47 km per week) compared to forced treadmill running (3–8 km per week) [1]. Even though forced treadmill running and free running wheel access were shown to attenuate BP similarly, the heart-to-body weight ratio increased to a greater extent in animals with exposure to free running wheels [1]. These data suggest that other factors beyond mechanical loading, i.e. BP, are important when considering the effects of exercise on myocardial remodeling in hypertension.

In this regard, activation of endocrine (i.e, hormones stimulating target cells via the bloodstream), paracrine (i.e, nearby cells), and autocrine (i.e., self stimulating) growth factors are integral in the development of both pathologic and physiologic hypertrophy. Growth factors largely signal cardiomyocytes through specific G protein coupled mechanisms [18, 19] which increase intracellular Ca^{2+} transients for maintenance of cardiac function during stress conditions. In chronic pressure overload and hypertension, persistent activation of humoral-induced elevations in intracellular Ca^{2+} concentrations stimulates Ca^{2+}-calmodulin-mediated cardiac hypertrophy [18, 19]. Calcineurin, Ca^{2+}-calmodulin-activated protein phosphatase, is a central signaling molecule involved in the development pathological cardiac hypertrophy. It acts by dephosphorylating NFAT transcription factors, promoting NFAT nuclear translocation, and initiating a pro-growth fetal gene program [18, 19]. Genetic activation of calcineurin results in dramatic heart growth and can lead to heart failure; whereas calcineurin inhibition reverses these effects [20, 21]. By contrast, physiologic hypertrophy associated with exercise training is not calcineurin-dependent. Instead physiologic hypertrophy appears to be more reliant on PI3 (phosphoinositide 3)-kinase-AKT (protein kinase B) signaling in the heart [22, 23]. Moreover, AKT is an anti-apoptotic regulator that decreases mitochondrial membrane destabilization and caspase 9 activity which have essential roles in apoptosis [24, 25].

Kolwicz et al., studied cardiac remodeling in SHR undergoing exercise training and reported whole heart enlargement with echocardiography and histomorphometry following exercise training [5]. The pattern of hypertrophy was homogeneously dispersed across several walls of the LV myocardium (i.e., anterior, posterior, and septal walls). Isolated cardiomyocytes from exercise trained SHR's were both longer and wider relative to sedentary controls. This hypertrophic pattern occurred even though training greatly mitigated calcineurin gene and protein expression in the SHR [5]. Interestingly, an increased AKT abundance was not observed in trained SHR hearts [5, 8], suggesting that exercise superimposed on hypertension induces cell growth through different mechanisms than animals with normal BP [22, 23]. Similar findings in swim-trained animals have been reported, such that swim training increased LV weight and LV internal diastolic diameter in SHR [3]. Swimming also increased cardiomyocyte cross-sectional area and normalized calcineurin without any significant changes in AKT signaling. Apoptosis and fibrosis were attenuated in swim-trained animals, and swimming led to improved myocardial vascularization and enhanced fractional shortening on echocardiography [3].

Thus, even though exercise potentiated cardiomyocyte growth, cardiac function was enhanced relative to sedentary controls in both running and swimming models.

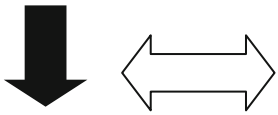
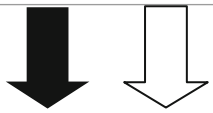
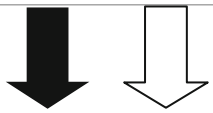
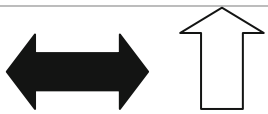
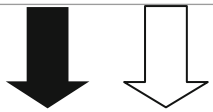
Beyond cardiomyocyte hypertrophy, cardiac remodeling is also influenced by the total number of functional cardiomyocytes, with the progressive loss of cardiomyocytes thought to play an important role in the decompensation toward heart failure. The number of functional cardiomyocytes is established by the balance between dying or apoptotic cardiomyocytes and new cardiomyocyte generation. Cardiomyocyte apoptosis is initiated by both internal and external signaling pathways that lead to cell shrinkage, membrane blebbing, deoxyribonucleic acid (DNA) fragmentation, and chromatin condensation [24]. While apoptotic cell death does not lead to a prolific inflammatory response like necrosis, the loss of functional cardiomyocytes still serves as substrate for replacement fibrosis and is seminal in the transition from compensation to failure [10].

The heart also contains resident cardiac stem cells that are capable of generating new cardiac tissue including cardiomyocytes, albeit at very low rates [26]. It has been shown that hypertension modestly increases Ki67+ cardiomyocytes (i.e., a marker of cardiomyocyte proliferation) as well as the number of endogenous stem cells (i.e., c-Kit+ cells) in the SHR model [5]. The potential for new cell development was, however, outweighed by greater rates of apoptosis in SHR hearts versus Wistar Kyoto, normotensive controls. These data suggest that there are a lesser number of functional cardiomyocytes in the hypertensive heart even early in the time course of the disease, potentially explaining the altered functional phenotype observed in young animals [27]. Of significance, exercise training decreased the rates of cell death with training and tended to augment the Ki67+ cardiomyocytes and c-Kit+ cells in the SHR heart [5]. Other studies have also shown a reduction in apoptosis with training in hypertensive hearts [4, 28, 29] despite some data showing that endurance training accelerates apoptosis in SHR [30]. Collectively, these studies suggest that training may beneficially preserve overall cardiomyocyte number in the presence of hypertension. The hemodynamic and cardiac remodeling responses to exercise training in animal models of pressure overload are summarized in Table 11.1.

Cardiac Function

During compensatory hypertrophy in animals, the heart may exhibit normal cardiac function under resting or unstressed conditions. However, abnormal cardiac function in the hypertensive heart is often manifest with preload stress, sympathetic stress, or ischemia-reperfusion. During these stressful conditions, the heart often shows abnormal systolic and/or diastolic mechanical function. Despite the potential for exercise training to increase overall myocardial mass in hypertension or pressure overload, most studies have reported an improved functional phenotype after training [2–4, 7–9, 27–29, 31–49] (see Fig. 11.1). For example, diminished systolic function in response to increasing preload, i.e. reduced systolic elastance, has been reported very early on in the lifespan of the SHR, far in advance of extensive cardiac remodeling [27]. These findings suggest that functional deterioration can be

Table 11.1 Hemodynamic and cardiac remodeling responses to exercise training in animal models of pressure overload

Attribute	Training effect
Blood pressure	
Heart rate	
Rate pressure product	
Height-to-body weight ratio	
Cardiomyocyte size	
Apoptosis and fibrosis	

Lateral arrow indicates little or no change, *upward arrow* indicates an increase, *downward arrow* indicates a decrease in the selected attribute. *Solid filled arrows* indicate responses in young animals without established hypertension; *open arrows* indicate the responses in older animals with established hypertension

present even in the absence of prominent remodeling. My laboratory group has also shown that exercise training in SHR improved systolic elastance in SHR toward normotensive control values [8]. Increased venous return and augmented preload occurs with acute exercise; hence the improvement of systolic elastance has translational significance as the abnormal cardiac phenotype is often unmasked during acute exercise stress in patients. Exercise training has also been shown to improve cardiac function in the SHR in response to experimental pacing stress [2, 33], an effect that might be related to the putative shifts in Ca^{2+} handling protein activity such as phospholamban [2, 9, 40].

One of the most prolific benefits of exercise training in hypertension is its effects on β adrenergic signaling. The β adrenergic pathway is the main pathway for regulating myocardial inotropy (i.e. strength of contraction), lusitropy (i.e, relaxation), and chronotropy (i.e., heart rate) during stress [50]. The β adrenergic pathway signals through various isoforms of β adrenergic receptors in the heart. Both β1 and β2 adrenergic receptors stimulate adenylyl cyclase and cyclic adenosine monophosphate (cAMP) which lead to increased protein kinase A activation (PKA). PKA phosphorylates key Ca^{2+} cycling proteins including troponin I, L-type Ca^{2+}

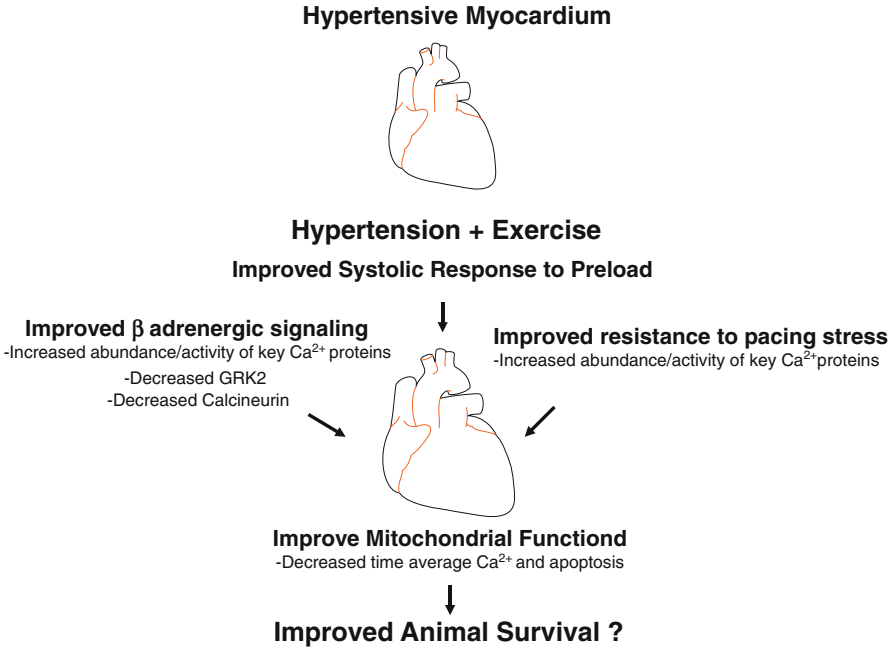


Fig. 11.1 Functional benefits with exercise training in pressure overload. The figure illustrates that chronic training improves the systolic response to preload stress, β adrenergic signaling, the tolerance to pacing stress, and leads to enhanced mitochondrial function. All of these adaptations may lead to improved survival of exercise trained pressure overloaded hearts. *Ca2+* calcium, *GRK2* G protein receptor kinase 2

channels, phospholamban, and ryanodine channels [50], and is regulatory in cardiomyocyte Ca^{2+} balance. Activation of β adrenergic receptors also increases glycogenolysis and cardiac metabolism in cardiomyocytes and can influence ischemia-reperfusion tolerance of the heart.

In situations were sympathetic stress is high, such as hypertension or heart failure, β adrenergic receptors can quickly become desensitized [50–53] leading to a decreased β adrenergic receptor density and signaling in hypertension or heart failure [50–53]. Downregulation of β adrenergic receptors involves the phosphorylation of serine on carboxy-terminal end of the β adrenergic receptors receptor by G protein receptor kinase 2 (GRK2) and/or PKA [53]. This can set the stage for β adrenergic receptors to be internalized by β arrestin, with the internalized β adrenergic receptors being either recycled or degraded, leading to impaired inotropic and lusitropic function [53]. The increased activity of calcineurin in pathological hypertrophy is also involved in blunting β adrenergic receptors since calcineurin opposes protein kinase A (PKA) activity on target Ca^{2+} handling proteins [54, 55].

Studies indicate that exercise training can improve whole heart β adrenergic responsiveness [2, 56, 57] through several possible mechanisms including: 1) increasing the abundance and activity of key Ca^{2+} handling proteins which are targets of PKA [2, 7]; 2) attenuating the increases in GRK2 that occur in hypertension [2]; or 3)

reducing the transcription and protein abundance of calcineurin [5, 8]. We and others have shown that impaired adrenergic responsiveness in hypertensive hearts [54, 55] can be improved with calcineurin antagonism an effect which normalized cardiomyocyte Ca^{2+} handling [54]. Hence when coupled together, exercise training may improve the function of the SHR heart during stressful conditions like acute bouts of exercise by improving systolic elastance, improving the tolerance to pacing challenges, and augmentation normalization of β adrenergic signaling. Together, these mechanisms may normalize time average Ca^{2+} homeostasis and may be seminal in protecting mitochondria from Ca^{2+} mediated apoptosis [25].

There are significant metabolic adaptations that also occur with training in the pressure overloaded heart. In the porcine TAC model, Marshall et al. showed training dependent improvements in coronary blood flow for a given myocardial oxygen consumption and cardiac efficiency [36]. These results built on work by the same group showing that preservation of LV function after exercise training was associated with lower fibrosis and collagen with improved LV mitochondrial function, i.e. a reduced Ca^{2+}-activation of the mitochondrial permeability transition pore [58]. There are, however, only few data on how training mediates ischemia-reperfusion injury in pressure overload. Reger et al., reported no improvement in ischemia-reperfusion tolerance or heat shock protein 72 in trained versus sedentary SHR hearts [59], even though SHR hearts were reported to have a greater Ca^{2+} responsiveness during acidosis [9]. In fact, Reger et al. reported that one bout of moderate intensity acute exercise temporally decreased myocardial tolerance to ischemia-reperfusion in SHR [60].

While the metabolic adaptations to training are seemingly very important, more work is clearly needed to understand how training alters cardiac function during ischemia-reperfusion, particularly in light of two studies showing that exercise training was deleterious to the hypertensive heart [61, 62]. For example, da Costa Rebelo et al. reported that wheel running was deleterious to the SHR by increasing fibrosis. Wheel running was negatively correlated with the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2A)-to-sodium (Na^{+})-Ca^{2+} exchange ratio and many exercising SHR died either spontaneously or had to be killed during the study's 6 month follow-up. These negative effects were, however, improved with captopril treatment [62]. While there are many methodological limitations of this study, the potential for high volumes of exercise to be harmful to the hypertensive heart must be further explored [63].

Conversely, a number of studies in various heart failure models (e.g., SHHR, Dahl Salt, hypertrophic cardiomyopathy) have shown improved survival and/or a slower decompensation toward heart failure with exercise training [32, 34, 35, 41, 49]. For example, in Dahl salt sensitive animals which have a rapid transition toward failure, exercise training decreased mortality without dramatically altering SBP [35]. In the SHHR model, exercise training has repeatedly been shown to delay the onset of heart failure [32, 41]. Moreover, in murine model of hypertrophic cardiomyopathy induced with a mutant myosin heavy chain, exercise prevented myocyte disarray and NFAT activity even in older animals with established disease. Exercise also showed putative effects on glycogen synthase kinase signaling and reduced markers

of apoptosis, leading to improved survival [34]. These studies suggest that exercise training can offset the negative sequelae of already established disease, but more work is warranted to understand the underlying putative mechanisms.

Clinical Implications/Importance

When examining the exercise training responses of animal models of pressure overload, recapitulation of the human phenotype is imperative. Most animal models have used moderate clinically applicable doses of exercise, but there are limited data available across the dose response range for exercise. Clearly identifying putative mechanisms and the required dose of exercise associated with cardioprotection in animal models with pressure overload has direct preclinical significance and can provide a paradigm for isolating protein targets for the development of new pharmacological agents.

Conclusions

In summary, exercise training in animal models with hypertension reduces BP significantly in young animals but has a lesser antihypertensive effect in older animals with established hypertension. Exercise induces a bradycardia independent of age and reduces the rate pressure product. Exercise does not exhibit a clear anti-hypertrophic effect in animals with already established hypertension. Instead more prominent cardiac hypertrophy has been shown in trained, already established hypertensive animal hearts. It remains unclear what the signaling mechanisms are that increase heart hypertrophy in hypertension, as calcineurin is reduced and training has not consistently shown to impact AKT signaling in pressure overloaded hearts. There is limited evidence that exercise increases cardiomyocyte proliferation and increases the abundance of endogenous progenitors. Several studies show that exercise attenuates apoptosis in pressure overload. How these remodeling effects translate into functional benefits remains unclear. Most studies have shown that exercise training improves the cardiac phenotype and animal survival, despite a few studies reporting that extreme levels of exercise can augment the transition toward heart failure. More work is needed in this area. In conclusion, the majority of data in preclinical animal models of pressure overload suggest that exercise training is beneficial to the heart.

Key Points and Resources

- Exercise training lowers heart rate, BP, and the rate pressure product in young animals with hypertension.
- Exercise training lowers heart rate and the rate pressure product in older animals with hypertension, with negligible effects on BP.
- Exercise training potentiates cardiomyocyte growth but reduces apoptosis and fibrosis in animals with hypertension.

- Exercise training causes a reduction in calcineurin signaling; and cardiac growth with exercise training in hypertension may be linked to PI3 (phosphoinositide 3)-kinase-AKT (protein kinase B) signaling.
- Most studies have shown improved cardiac function with exercise training in hypertension including: increased systolic elastance, improved whole heart β adrenergic responsiveness, and greater metabolic efficiency.
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- Houser SR, Margulies KB, Murphy AM, et al. (2012) American Heart Association Council on Basic Cardiovascular Sciences, Council on Clinical Cardiology, and Council on Functional Genomics and Translational Biology. Animal models of heart failure: a scientific statement from the American Heart Association. Circ Res Jun 22;111:131-150 [13].

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Part III
The Pleiotropic Effects of Exercise on Other Cardiovascular Risk Factors and Their Interactive Effects with Blood Pressure

Chapter 12
Exercise and Hypertension in the Framework of the Metabolic Syndrome

Alice S. Ryan

Abbreviations

ACSM	American College of Sports Medicine
AHA	American Heart Association
ATP III	Adult Treatment Panel III
BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
DASH	Dietary approaches to stop hypertension
DBP	Diastolic blood pressure
EGIR	European Group for Study of Insulin Resistance
FITT	Frequency intensity, time, and type
FSIVGTT	Frequently sampled intravenous glucose tolerance test
GS	Glycogen synthase
HDL-C	High density lipoprotein cholesterol
HERITAGE	**HE**alth **RI**sk Factors Exercise **TRA**ining and **GE**netics Family Study
HRmax	Maximal heart rate
HRR	Heart rate reserve
HSL	Hormone sensitive lipase
IDF	International Diabetes Federation
IVGTT	Intravenous glucose tolerance test
LDL-C	Low density lipoprotein cholesterol

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LPL	Lipoprotein lipase
M	Glucose utilization
M/I	Glucose utilization/insulin concentration
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHES	National Health Examination Survey
NHLBI	National Heart Lung, and Blood Institute
RM	Repetition maximum
SBP	Systolic blood pressure
TG	Triglycerides
VLDL	Very low density lipoprotein
VO_{2max}	Maximal oxygen consumption
VO_{2peak}	Peak oxygen consumption
$VO_{2reserve}$	Oxygen uptake reserve
WHO	World Health Organization

Introduction

The metabolic syndrome is a clustering of metabolic diseases and risk factors within an individual (Fig. 12.1) [1]. Reaven [2] was the first to introduce Syndrome X which was characterized by impaired glucose tolerance, dyslipidemia, and hypertension. The clustering of these factors is associated with increased risk of type 2 diabetes mellitus and cardiovascular disease (CVD) [3–6] as well as non-alcoholic fatty liver disease and chronic kidney disease [7, 8]. Diagnosis of metabolic syndrome has approximately a two-fold relative risk for CVD over 5–10 years and at least a five-fold relative risk for type 2 diabetes mellitus [9]. Cardiometabolic risk factors tend to co-exist and as such lifestyle modifications of exercise and diet and pharmacologic therapy are the mainstay of treatment for the metabolic syndrome [1].

Purposes of This Chapter

This chapter will provide a brief history of the metabolic syndrome and detail the current definition(s) of the metabolic syndrome; convey the prevalence of the metabolic syndrome and review the relation of the metabolic syndrome to mortality; discuss the role of exercise and hypertension in the framework of the components of the metabolic syndrome; and review studies of adults with the metabolic syndrome with specific emphasis on the effects of exercise training on the components of the metabolic syndrome. This chapter will conclude by presenting exercise prescription recommendations for individuals with the metabolic syndrome.

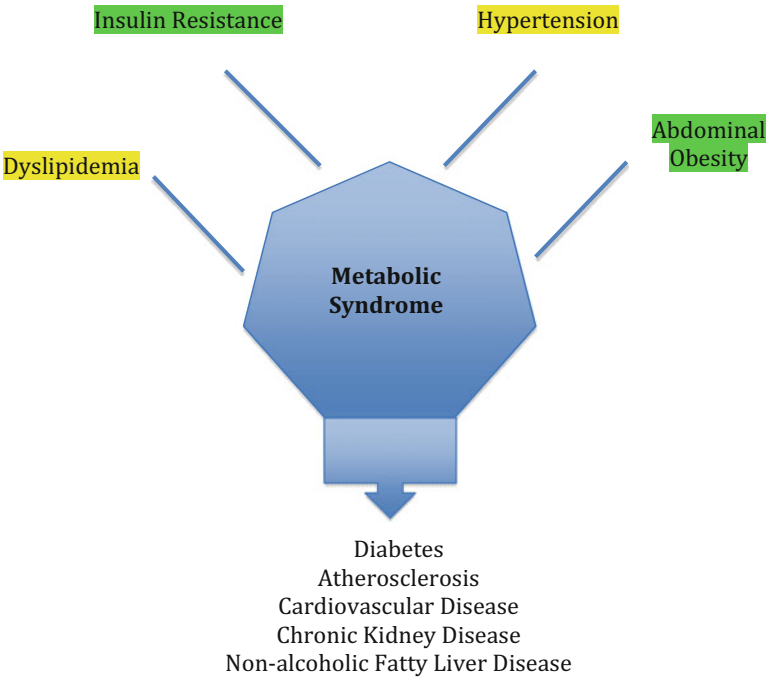

Fig. 12.1 Interactions of the metabolic syndrome

Key Terminology and Basic Concepts

The Metabolic Syndrome: Definition

In 2001, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (ATP III) [10] called attention to the importance of the metabolic syndrome. The World Health Organization (WHO) [11] and the European Group for Study of Insulin Resistance (EGIR) have also selected criteria to define the metabolic syndrome. The International Diabetes Federation (IDF) followed with their definition of the metabolic syndrome [12], which reflected the ATPIII and WHO definitions. Thus, the metabolic syndrome has evolved over the years with various definitions and emphasis on the importance of the various components of the metabolic syndrome.

The criteria and definitions from NCEP, IDF and WHO of the metabolic syndrome are provided in Table 12.1. Clinical measures named in the diagnosis of the metabolic syndrome include insulin resistance, body weight, lipid levels, blood

Table 12.1 Various criteria for the metabolic syndrome

Component	Criteria		
	NCEP/ATP III	IDF	WHO
	Any 3 of 5 constitute diagnosis of metabolic syndrome	Must have central obesity[a] plus two of the other four factors	Insulin resistance plus any two of the other factors
Central obesity/ waist circumference	≥102 cm in men	Europids, Sub-Saharan Africans, Eastern Mediterranean and Middle East: ≥94 cm in men, ≥80 cm in women	>0.90 waist-to-hip ratio in men
	≥88 cm in women	US: ≥102 cm in men, ≥88 cm in women	>0.85 waist-to-hip ratio in women
		South Asians, Chinese, Japanese, Ethnic South and Central Americans: ≥90 cm in men, ≥80 cm in women	And/or BMI > 30 kg/m^{-2}
Triglyceride level	≥150 $mg \cdot dL^{-1}$ or	≥150 $mg \cdot dL^{-1}$ or	≥150 $mg \cdot dL^{-1}$
	On drug treatment for elevated triglycerides	Specific treatment for this lipid abnormality	
HDL-cholesterol	<40 $mg \cdot dL^{-1}$ in men	<40 $mg \cdot dL^{-1}$ in men	<35 $mg \cdot dL^{-1}$ in men
	<50 $mg \cdot dL^{-1}$ in women or	<50 $mg \cdot dL^{-1}$ in women or	<39 $mg \cdot dL^{-1}$ in women
	On drug treatment for reduced HDL-cholesterol	Specific treatment for this lipid abnormality	
Blood pressure	≥130 mmHg systolic blood pressure or	≥130 mmHg systolic blood pressure or	≥140/90 mmHg
	≥85 mmHg diastolic blood pressure or	≥85 mmHg diastolic blood pressure or	
	On antihypertensive drug treatment in a person with a history of hypertension	treatment of previously diagnosed hypertension	
Insulin resistance/ glucose	≥100 $mg \cdot dL^{-1}$ fasting glucose or	≥100 mg/dL fasting glucose or previously diagnosed type 2 diabetes	IGT, IFT, type 2 diabetes or lowered insulin sensitivity measured under hyperinsulinemic-euglycemic conditions (glucose uptake below lowest quartile for population under study)
	On drug treatment for elevated glucose	If fasting glucose above 100 $mg \cdot dL^{-1}$, OGTT is strongly recommended but is not necessary to define presence of the syndrome	
Other			Microalbuminuria

NCEP/ATP National Cholesterol Education Program/ Adult Treatment Panel, *IDF* International Diabetes Foundation, *WHO* World Health Organization

[a]If BMI > 30 $kg \cdot m^{-2}$, obesity can be assumed and waist circumference does not need to be measured

pressure (BP), glucose levels, and other clinical outcomes noted in Table 12.1. A statement from the American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) published in 2005, is a current guide to the diagnosis and management of persons with the metabolic syndrome [1]. In this scientific statement, underlying risk factors for the metabolic syndrome are described as predominately abdominal obesity and insulin resistance and include other factors such as physical inactivity, aging, and hormonal imbalance in the polycystic ovary syndrome [13]. Goals for the lifestyle therapy include the reduction of body weight by 7–10 %, performance of regular moderate intensity physical activity of at least 30 min of continuous or intermittent exercise 5 days per week, and reduced intake of saturated fat, *trans* fat, and cholesterol [1]. Treatments for modifying atherogenic dyslipidemia include drug therapy as well lifestyle modifications. Further recommendations for the clinical management of the metabolic risk factors target lowering elevated blood glucose by weight reduction, increasing physical activity in those with impaired fasting glucose, and instituting both lifestyle therapy and pharmacotherapy in those with type 2 diabetes mellitus.

Management of elevated BP in the metabolic syndrome depends on the presence of diabetes mellitus and chronic kidney disease. Specifically, the AHA and NHLBI [1] recommend that if hypertension is present without these two conditions, then the goal is to target the BP to be <140/90 mmHg. However, in the presence of either diabetes mellitus or chronic kidney disease, then the goal for BP is further reduced to <130/80 mmHg. Table 12.2 includes specific recommendations from this report. Recommendations are made as ways to control the hypertension and in the clinical management of elevated BP including lifestyle therapies [1]. In addition, modifications to the diet include recommendations to follow the Dietary Approaches to Stop Hypertension (DASH) diet which includes a diet rich in fruits and vegetables (8–10 servings per day) providing potassium (~4,700 mg·day^{-1}) and magnesium (~500 mg·day^{-1}) and high amounts of fiber (~31 g·day^{-1}) with reduced amount of saturated fat (~6 % of total kcal), total fat (~27 % of total kcal), and cholesterol (~150 mg·day^{-1}) [14].

Table 12.2 Clinical management recommendations for hypertension in the metabolic syndrome

Risk factor	Level	Recommendation
BP	≥120/80 mmHg	Initiate or maintain lifestyle modification
		• Weight control
		• Increase physical activity
		• Alcohol moderation
		• Increase consumption of fresh fruits, vegetables, low fat dairy products
BP	>140/90 mmHg or	Add BP medication to achieve BP goal
	>130/80 mmHg if presence of chronic kidney disease or diabetes	• Angiotension-converting enzyme inhibitors
		• Angiotensin receptor blockers Diuretics

BP blood pressure

The Metabolic Syndrome: Concordance and Prevalence by Definition in Table 12.1

Marchesini et al. reported that 78 % of patients with type 2 diabetes mellitus fulfill the NCEP ATPIII criteria and 81 % met the WHO criteria indicating good agreement between the two definitions of the metabolic syndrome [15]. The Cardiovascular Health Study found an 80 % concordance in classifying the participants among these same criteria [16]. In a sample of approximately 400 adults with obesity, the prevalence of the metabolic syndrome was higher in those defined by WHO than the NCEP ATP III criteria [17]. Of approximately 2,800 participants in the San Antonio Heart Study, 25 % met both WHO and NCEP ATP III criteria for the metabolic syndrome with an additional 25 % of adults meeting only one of the criteria [18].

The most current to date estimates for the prevalence of the metabolic syndrome by NCEP ATP III criteria in adults older than 20 years from National Health and Nutrition Examination Survey (NHANES) indicated that from 1999 and 2000 to 2009 and 2010, age-adjusted prevalence decreased from 25.5 to 22.9 % with a decrease in the percent of those with elevated BP (32.3–24.0 %) [19]. The reduction in elevated BP, downward trend in elevated triglycerides, and decline in sub-optimal high density lipoprotein cholesterol (HDL-C) from 1999 to 2010 coincide with increases in antihypertensive and lipid modifying therapy. In terms of the prevalence of the individual metabolic syndrome components, black men and women who were non-Mexican-American consistently had a higher prevalence of elevated BP than other ethnic/racial groups, but they had the lowest prevalence of dyslipidemia. The decline in BP in the NHANES data from 2000 to 2009 and 2010 occurred only in white men who were non-Mexican-American and in women who were non-Mexican and Mexican Americans. Despite the slight decline in the prevalence of the metabolic syndrome, about 20 % of adults in the United States are classified as having the metabolic syndrome [19].

Metabolic Syndrome: Associated Risks

The presence of the metabolic syndrome has been used to identify individuals at risk for incident stroke [20], congestive heart failure [21] and death from CVD [3, 15, 18, 22, 23]. The Kuopio Ishcaemic Heart Disease Risk Factor Study of over 1,200 Finnish men showed that men with the metabolic syndrome defined by the NCEP ATP III criteria were almost three-fold more likely to die of coronary heart disease after adjustment for conventional CVD risk factors [23]. Using the WHO criteria, they also reported higher CVD mortality and all-cause mortality in men with the metabolic syndrome. In patients with type 2 diabetes mellitus, the NCEP ATP III criteria were better in identifying the prevalence of previously detected

CVD than the WHO criteria [15]. In the San Antonio Heart Study, the metabolic syndrome as defined by WHO and NCEP ATPIII criteria predicted all-cause and cardiovascular mortality, but the NCEP ATP III criteria were slightly more predictive in lower-risk adults [18].

Mortality risk was assessed in the individuals comprising the third NHANES and utilized the NCEP ATP II 2001 and 2005 criteria (i.e. waist circumference >102 and 88 cm in men and women, respectively; triglycerides (TG) >150 mg·dL^{-1}; HDL-C <40 and 50 in men and women, respectively; systolic blood pressure (SBP) >130 or diastolic blood pressure (DBP) >85 mmHg; and fasting glucose >100 mg·dL^{-1}) [24]. At the time of follow-up in 2000, the prevalence of the metabolic syndrome was similar between men and women over the age of 40 years, specifically 33 and 29 %. The criteria used for the classification of high TG, glucose, and BP was observed in greater proportions of men than women. The criterion of high waist circumference was more often represented in women than men. Furthermore, men and women with the metabolic syndrome were older, had higher body mass index (BMI), larger waist circumference, higher BP, TG levels, and glucose levels and lower HDL-C compared to men and women without the metabolic syndrome. Although there was no significant association between the metabolic syndrome and mortality in men, the metabolic syndrome was an independent risk factor for all-cause, cardiovascular, cardiac, and noncardiovascular mortality in women. These results were more pronounced in postmenopausal women indicating the significance of the metabolic syndrome in older women. In an Italian population of men and women between 25 and 74 years of age, increased risk of cardiovascular and all-cause mortality was greater in those with the metabolic syndrome [25]. The increased risk was related to an elevated BP and impaired fasting blood glucose. In summary, there is strong evidence from long-term prospective studies for an association of the metabolic syndrome with total mortality.

Systematic Review Methods

An electronic search of the literature on metabolic syndrome and exercise was conducted using PubMed. Key words utilized in the initial searches were the metabolic syndrome in combination with exercise, aerobic exercise training, resistance exercise training, and the components of the metabolic syndrome. The search with ‘metabolic syndrome and exercise’ yielded 3,112 citations. This was narrowed to 794 reports for the key words of ‘exercise training and metabolic syndrome’. The author self-selected 89 studies, which included adults (>18 years of age with no upper age limit), were longitudinal investigations or a meta-analysis, included the components of the metabolic syndrome, and were deemed most relevant to this chapter. There were no specific inclusion criteria with regard to the date/year when the article was published up to June 2014. All studies were published in the English language.

Relevant Research

The Components of the Metabolic Syndrome in Relationship to Exercise and Hypertension

Prevalence of Overweight and Obesity

Central adiposity, specifically estimated by waist circumference, is a key component of the metabolic syndrome. Overweight and obesity increase the risk for hypertension. BMI, a measure of an individual's weight in relation to height, is used to define overweight and obesity with a BMI between 25 and 29 kg/m^{-2} defined as overweight and a BMI ≥30 kg/m^{-2} defined as obese. Obesity can be further classified into Class I obesity (30.0–34.9 kg/m^{-2}), Class II obesity (35.0–39.9 kg/m^{-2}), and Class III or morbid obesity (>40 kg/m^{-2}).

In 1960, the National Center for Health Statistics began tracking the prevalence and trends of overweight U.S. adults who then completed the National Health Examination Survey (NHES I), and NHANES I, II, and III continuous to the year 2000 [26]. To illustrate the changing face of obesity in the United States, the prevalence of obesity increased significantly from NHANES II (1976–1980) to NHANES III (1988–1994), specifically from 14.5 to 22.5 % [27]. The prevalence of overweight and obese from 1988 to 1994 was about 55 %. From 1999 to 2004 there was not an increase in prevalence of obesity in women but obesity increased in men.

In NHANES data (2007–2008) [28], there was a 68 % age-adjusted prevalence of overweight and obesity, with a prevalence of 72 % in men and slightly lower prevalence of 64 % among women. The likelihood of being obese was significantly higher if men and women were between 40 and 59 years of age as well as over 60 years compared to younger (20–39 years) men and women. The prevalence of obesity varied by age and racial groups for men and women such that the likelihood of being obese was significantly greater in men and women who were non-Hispanic black compared to non-Hispanic white men and women [28].

Trends in obesity from the 2009–1010 NHANES survey did not differ significantly from the previous data from years 2003 to 2008 with estimates of obesity as 35.5 % in men and a similar 35.8 % in women [29]. Examination of the prevalence of combined overweight and obesity shows an overall prevalence of 68.8 % with slighter higher rates in men (73.9 %) than women (63.7 %) [29]. Approximately 35 % of older (persons aged 65 and over) adults in the NHANES (2007–2010) survey were considered obese [30]. The prevalence of obesity was ~41 % among those 65–74 years old and dropped to ~28 % in those over 75 years of age. Among men, obesity prevalence did not differ by race or ethnicity but among women, a higher percentage of non-Hispanic black women were obese than non-Hispanic white women with no differences between non-Hispanic black and Hispanic women [30]. National survey data can continue to provide a representative sample to assess overall trends and prevalence in overweight and obesity in the United States.

Overweight and Obesity, Blood Pressure, and Exercise Training

Systematic reviews and meta-analyses have tested how efficacious exercise programs are in reducing obesity. In one early meta-analysis of 53 aerobic training studies published between 1950 and 1988, loss of body fat with exercise training averaged 1.5 kg, was greater in men than women, and the energy expended during exercise and initial body fat levels accounted for most of the variance in body weight loss [31]. A meta-analysis of 25 years of published works (1969–1994) including 493 studies of individuals with moderate obesity, diet or diet plus aerobic exercise had an average weight loss of ~11 kg whereas exercise alone had a ~3 kg weight loss [32]. In 14 randomized controlled trials selected from 184 papers published from 1970 to 2010, 6 months of aerobic exercise training had a modest effect on reducing body weight (−1.6 to −2.5 kg) with reductions in both SBP and DBP [33]. In older adults with overweight, exercise was associated with a weight loss of 1.1–6 kg from nine studies systematically reviewed and published between 2000 and 2011 [34]. In summary, these reviews and meta-analysis studies would suggest a ~1.5 to 3 kg loss of body weight with exercise training alone.

Given that exercise training can reduce body weight and the focus of this chapter is exercise training and hypertension within the metabolic syndrome, it should be briefly mentioned that weight loss alone is important in the reduction of risk for hypertension. For example, in adults with overweight in the Framingham study, a weight loss of 6.8 kg or more resulted in a 21–29 % reduction in long-term hypertension risk even after adjustment for multiple factors including age, sex, education, BMI, physical activity, smoking, and alcohol intake [35]. When weight loss was maintained during a 4-year follow-up, there was also a substantial reduction (22–26 %) in hypertension risk. Thus, interventions to reduce overweight and obesity, either through physical activity, diet, or a combination of these lifestyle modifications, are important to consider in obesity-related hypertension.

A meta-analysis of 54 randomized, controlled trials demonstrated that aerobic exercise training reduced BP in persons with normal BP and hypertension [36]; with a mean reduction in SBP of 4 and 2 mmHg in DBP for those with normal BP and ~5 and ~4 mmHg reduction in SBP and DBP, respectively for those with hypertension. The reductions in BP occurred even in participants whose BMI fell into the normal weight range [36]. Furthermore, in this meta-analysis there was no association between the change in body weight and change in BP so that even in trials where the participants did not lose weight, BP was significantly reduced [36]. Furthermore, the reduction in BP was not significantly different among clinical trials even when the frequency, intensity, time, and type (FITT) of the aerobic exercise training varied [36]. Thus, those individuals with hypertension had the greatest BP benefits with aerobic training, independent of body weight change. For a complete review of how various modalities of exercise training influence BP, the reader is referred to section “Introduction”.

The *Obesity Society* and the *American Society of Hypertension* published a position statement in reference to the interaction of obesity and hypertension [37]. This paper also provides clinicians and members of both societies a review of the

cardiovascular risk of obesity-related hypertension and the metabolic syndrome and insight into the lifestyle, pharmacological, and medical management of obesity and hypertension. In summary, a healthy lifestyle facilitates weight loss and is important in the prevention and treatment of obesity-related hypertension.

Insulin Resistance, Blood Pressure, and Exercise Training

An elevated fasting glucose is one component of the metabolic syndrome. When Syndrome X was first established [2], skeletal muscle insulin resistance was credited as the primary underlying mechanism. Insulin resistance is defined as a reduction in glucose disposal rate elicited by a given insulin concentration [38]. Sophisticated methods are available that directly measure insulin sensitivity and are used in studies of insulin resistance include the hyperinsulinemic-euglycemic clamp, the hyperglycemic clamp [39, 40], and the intravenous glucose tolerance test (IVGTT) or frequently sampled intravenous glucose tolerance test (FSIVGTT) with minimal model of analysis of Bergman and colleagues [41].

In the hyperinsulinemic-euglycemic clamp procedure, insulin is infused at physiological rates (10 and 40 mU m^{-2} min^{-1}), intermediate rates (100 mU m^{-2} min^{-1}), and super-physiological rates (>100 mU m^{-2} min^{-1}) to achieve steady-state insulin concentrations. Glucose is infused at a variable rate to maintain euglycemia and the rate of glucose infusion increases progressively until attainment of a steady state over several hours. The glucose infusion rate, equal to the glucose uptake in steady state, is used as an index of whole-body insulin sensitivity. Alternatively, the glucose utilization (M) is divided by the prevailing degree of hyperinsulinemia (or M/I) to obtain an index of insulin sensitivity. In the hyperglycemic clamp technique, plasma glucose is acutely raised and subsequently maintained by adjustment of a variable glucose infusion and the plasma insulin response is measured. The relationship of M to I (i.e., the slope of the curve indicating the amount of glucose infused to maintain hyperglycemia at the desired level and the mean plasma insulin concentration) is used to estimate insulin sensitivity during a hyperglycemic clamp. The IVGTT and FSIVGT approach rely on the pancreatic insulin response to an IV bolus/injection of glucose for the calculation of insulin sensitivity where blood samples are collected at specific time intervals. A computer analysis of the kinetics of glucose and insulin are modeled to derive a measurement of insulin sensitivity.

Of import of this chapter is that insulin resistance is associated with hypertension [42]. Mechanisms that may contribute to the link between insulin resistance and hypertension may include the vasodilatory effects of insulin [43], the effect of insulin on sodium reabsorption in the kidney [44], and the ability of insulin to increase sympathetic nervous system activity [45]. Lifestyle interventions reduce the progression to diabetes mellitus in individuals with impaired glucose tolerance. In the Diabetes Prevention Trial [46], over 3,000 adults who had either high fasting or 2 h postprandial glucose levels but were not diagnostic of diabetes mellitus were randomized to either standard lifestyle recommendations plus placebo, standard lifestyle recommendations plus metformin, or an intensive lifestyle modification program.

The goals of the intensive lifestyle program were to achieve weight reduction of 7 % by a low-calorie, low-fat diet, and perform moderate intensity physical activity such as brisk walking for at least 150 min per week. The program was taught one-to-one for the first 24 weeks of the intervention, and subsequently followed by individual and group sessions (~monthly) for reinforcement. Both the metformin and lifestyle intervention groups experienced prevented or delayed progression to diabetes mellitus during the follow-up period (average of 2.8 years, range 1.8–4.6) compared to the placebo group. The incidence of diabetes mellitus was reduced by 58 % with the lifestyle intervention and by 31 % with metformin, and these reductions were independent of sex/gender and race/ethnicity [47]. At study entry, 30 % of participants had hypertension, which did not change in the intensive lifestyle group [48]. This contrasts the increase in hypertension prevalence in the placebo and metformin groups. The intensive lifestyle modification group reduced SBP (−3.4 mmHg) and DBP (−3.6 mmHg) at 1 year with similar reductions by year 3 (−3.3 and −3.8 mmHg, respectively) [48].

In the Da Qing Diabetes Prevention Study [49], adults with impaired glucose tolerance were followed for 6 years after randomization to control or lifestyle intervention groups (i.e., diet, exercise, or both). Results indicated that the diet plus exercise group reduced the incidence of diabetes mellitus, with the greatest effect in the less insulin resistant groups who had ~50 % decrease in the incidence of diabetes mellitus. In addition, the lifestyle intervention was associated with a 47 % reduction in the incidence of severe, vision-threatening retinopathy over a 20 year interval which was primarily due to the reduced incidence of diabetes in this group [50]. Finally, the 23-year follow-up of the Da Qing study indicated that CVD mortality was ~12 % in the intervention group (diet, exercise, or both) compared to ~20 % in the control group [51], providing additional evidence for benefits of lifestyle modifications.

Aerobic exercise training generally results in an improvement in insulin sensitivity. Sedentary postmenopausal women completed a 5 day per week walking program for 15 weeks at an intensity of 65 % of maximum oxygen consumption (VO_{2max}) and expended a total of 300 kcal·day^{-1} in either one or two daily walking bouts [52]. Fasting glucose, 2 h glucose, and DBP (mean decrease of −3.0 mmHg) were reduced with no difference in the effect of one or two daily bouts of exercise and with little effect on SBP. Women randomized to walk at either 45 or 55 % of VO_2max did not have a significant change in BP; the authors suggest that a higher exercise intensity of 65 % VO_2max is needed to induce minimal changes in CVD risk factors [52]. A relatively short aerobic exercise training program of 12 weeks (60 min 3 times/week at 85 % maximum heart rate [HRmax]) in ~70 year old men and women led to a 11–13 % increase in glucose disposal [53], without changes in body weight or fat mass. In young males, one-legged cycling training 30 min per day, 6 days per week for 10 weeks at 70 % VO_2max increased glucose uptake in the trained leg at three different insulin levels [54]. Both moderate (30 min, 300 kcal·day^{-1}) and high (60 min, 600 kcal·day^{-1}) caloric expenditure aerobic training 5–7 days per week for 11 weeks at an average exercise intensity of 67 % VO_2max increased whole body insulin sensitivity by 28 and 36 % in the moderate and high

energy expenditure groups, respectively, but did not significantly change either SBP or DBP [55]. Moreover, the insulin-stimulated glucose uptake measured by imaging occurred in femoral skeletal muscle but not in femoral subcutaneous or intra- or retroperitoneal visceral adipose tissue [56]. In as little as 6 weeks of aerobic exercise training, glucose utilization increased and hepatic glucose production was more effectively suppressed in young women with obesity [57]. Thus, aerobic training programs from 10 to 15 weeks duration increased skeletal muscle and whole body glucose uptake.

Longer duration of exercise training of 6–9 months also improves insulin sensitivity. Six months of aerobic exercise training (45 min, 5 days per week at 80–85 % of heart rate reserve [HRR]) increased insulin sensitivity measured by the minimal model by 36 % in healthy older men (aged 61–82 years) [58]. In addition, 9 months of aerobic exercise training (45 min, 4 days per week at 80–85 % of HRmax) in 60–70 year old men and women decreased plasma insulin levels by 23 % without changing glucose uptake during a hyperglycemic clamp such that insulin action (M/I) improved after the exercise program [59]. Houmard et al. [60] examined subjects with overweight and obesity in three exercise groups for 6 months that included: 1) low-volume/moderate-intensity (115 min per week, ~12 miles walking/week at 40–55 % VO_{2peak}, 2) low-volume/high-intensity group (~170 min per week, ~20 miles jogging/week at 65–80 % VO_{2peak}), and 3) high-volume/high intensity (~170 min per week, ~20 miles jogging per week at 65–80 % VO_{2peak}). They found that insulin action increased as measured by the IVGTT between 38 and 88 % in these exercise groups compared with a ~4 % decrease observed in the non-exercising control group. Insulin sensitivity index increased more after 6 months of aerobic training that focused on greater exercise duration and frequency than an aerobic training program of lower duration and frequency (i.e., ~170 vs. ~115 min per week) in adults with overweight and obesity. Since these findings occurred regardless of exercise intensity and volume, the authors suggested that training duration be an important consideration if favorable changes in insulin sensitivity is a goal of the exercise prescription [60].

Aerobic exercise has been combined with various forms of weight loss programs or diets to examine their effects on insulin sensitivity. A 16 week aerobic training program (4–6 exercise sessions per week) that progressed from 30 min per session at 60–70 % of HRmax to 40 min per session at 75 % HRmax resulted in a 8 % loss of weight and increased glucose utilization by 49 % in young men and women with obesity [61]. Both a high carbohydrate diet alone or combined with aerobic exercise training (4 days per week, 45 min per day at 80 % VO_2peak) resulted in a loss of body weight and increased insulin stimulated glucose disposal in older participants [62]. A 6 month combined aerobic exercise training (three times per week, 45 min per session at >60 % VO_2max) and weight loss program (6–8 % loss of body weight) effectively improved insulin sensitivity in postmenopausal women with overweight and obesity compared to weight loss alone [63]. The loss of visceral fat was the single independent predictor of the improvement in glucose metabolism.

We have also showed an overall 14 % increase in insulin sensitivity measured by the hyperinsulinemic-euglycemic clamp in postmenopausal women with normal or

impaired glucose tolerance after they completed a 6 month aerobic exercise training program (three times per week, 45 min per session at >85 % HRR) plus caloric restriction or caloric restriction alone [64]. About 40 % of the women were on an antihypertensive medication during the study. SBP significantly decreased in women after either weight loss alone or combined exercise plus weight loss [65]. In testing potential skeletal muscle mechanisms, we reported that the increase in insulin sensitivity was associated with the change in insulin-stimulated skeletal muscle glycogen synthase (GS) fractional activity [64]. In women with impaired glucose tolerance, insulin-stimulated GS independent activity improved, suggesting that the increase in insulin-stimulated GS activity contributed to the improvement in insulin sensitivity after aerobic exercise training plus caloric restriction.

In older, insulin-resistant men with overweight and obesity, a 6 month aerobic exercise training (three times per week, 45–50 min per session at 60–70 % VO_2max) plus weight loss program increased basal citrate synthase activity by 46 % and insulin activation of independent (2.9-fold) and fractional (2.3-fold) activities of GS [66]. Glucose utilization improved 25 %, and the change tended to be related to the increase in insulin activation of GS fractional activity suggesting that aerobic exercise training plus weight loss had a robust effect on insulin activation of skeletal muscle GS activity that likely contributed to improved glucose utilization in these older men with insulin resistance [66]. In summary, aerobic training elicits increases in insulin sensitivity from ~15 to 50 % in a variety of populations including subjects who are healthy and overweight and obese and range in age from young to middle-aged to old.

Several studies [67–69], including some of our own [70–72], have reported an increase in insulin sensitivity using the glucose clamp or the FSIVGT after resistance exercise training. Older men with hypertension who performed resistance training of two sets of 10–12 repetitions that increased the weight lifted by ~5 kg after achieving 12 repetitions at that weight, 3 days per week for 4 months had an approximate 15 % increase in glucose uptake during the glucose clamp [67]. Similar improvements (~24 %) in insulin-stimulated glucose uptake were reported in older men after a 3 times per week, 6 month resistance training program of 11 exercises of one to two sets at 12–15 repetition maximum (RM) [72]. An ~25 % increase in insulin sensitivity by the FSIVGT was reported in older sedentary men newly diagnosed with type 2 diabetes mellitus after a 16 week upper and lower body resistance training program performed twice-weekly for 45–60 min per session [68]. The training program began at 50–70 % of RM for three to four sets of 10–15 repetitions per et for the first 8 weeks and then progressed to five to six repetitions per set at higher loads (70–80 % RM) for the last 8 weeks [68]. Likewise, healthy older men who completed 16 weeks of resistance training at 70–95 % 1-RM 4 days per week had a ~33 % [69] increase in insulin sensitivity by the FSIVGT.

Furthermore, postmenopausal women completed 16 weeks of 14 upper and lower body resistance exercises which began at ~5-RM for the first three to four repetitions with the resistance reduced to complete a total of 15 repetitions for maximal effort on every repetition [71]. Two sets of lower body exercises were performed. Both resistance training with and without weight loss improved insulin

action during a hyperglycemic clamp [71]. A 6 month progressive resistance training program (first 12 weeks one set with 15 repetitions of upper body exercises and two sets of 15 repetitions of lower body exercises, and second 12 weeks one set of 8-RM of upper body exercises and two sets of 10-RM) only tended to improve insulin sensitivity in older (>65 years of age) men and women [70]. In older men with overweight and obesity, there are comparable improvements in insulin-stimulated glucose disposal after either aerobic or resistance exercise training [73], but an increase in insulin activation of skeletal muscle GS occurred only in the aerobic training group. Although little is known regarding the effects of resistance exercise training on insulin sensitivity in disabled populations, we showed a 16 % reduction in insulin area under the curve from an oral glucose tolerance test and a 31 % increase in insulin sensitivity measured during a hyperglycemic clamp in older men and women who were survivors of stroke [74]. In summary, resistance exercise training elicits increases in insulin sensitivity from ~15 to 35 % in a variety of populations including subjects who are healthy and overweight and obese, and range in age from young to middle-aged to old. Thus, both aerobic and resistance training improve insulin sensitivity with a comparable change between exercise modalities.

Lipids and Exercise Training

High fasting TG and low levels of HDL-C are two components of the lipid-lipoprotein profile that also are components of the metabolic syndrome. There is substantial evidence to suggest that physical activity is a preventive for developing CVD by its favorable effect on circulating lipids and lipoproteins (see Chap. 14 for a detailed discussion of lipids and lipoproteins). The lipid triad or "atherogenic lipoprotein phenotype" includes increased plasma TG levels, decreased HDL-C, and the presence of small, dense low density lipoprotein cholesterol (LDL-C) particles [75]. This phenotype is clinically important because of its association with CVD risk [75].

Endurance athletes have higher HDL-C levels and lower TG concentrations than sedentary individuals [76, 77]. Furthermore, endurance athletes who are women have been shown to have a less atherogenic lipoprotein subfraction distribution, as well as a more favorable total lipid profile, than sedentary women of a similar age and BMI [77]. In general, aerobic exercise training increases HDL-C but has marginal effects on total and LDL-C. The increase in HDL-C is usually observed with aerobic exercise training and primarily involves an increase in the HDL_2 fraction and lipoprotein lipase (LPL) activity as well as a reduction in hormone sensitive lipase (HSL) activity [78]. Aerobic exercise training also has been shown to reduce the concentration of small, dense LDL-C particles, increases LDL-C particle diameter, increases HDL_2 mass, and decreases very-low-density lipoprotein (VLDL) mass [76, 79]. Resistance exercise training exercise may have little effect [80–84] or has been shown to improve [4, 85–87] lipid-lipoprotein levels in adults. For a detailed discussion of how exercise training influences the lipids-lipoprotein profile, the reader is referred to Chap. 13.

The Metabolic Syndrome, BP, and Exercise

Regular physical activity and increased physical fitness may decrease the risk of the metabolic syndrome in various populations. In over 1,000 adults, aerobic fitness was inversely associated with metabolic syndrome risk [88]. Moreover, it appears that muscular strength additionally reduces the risk for the metabolic syndrome in women but not in men. The metabolic syndrome in Mexican adults was associated with low levels of physical activity [89]. Specifically, the risk of the metabolic syndrome was reduced among men and women whose leisure time activity was at least 30 min per day. In male firefighters, greater cardiorespiratory fitness was associated with less metabolic abnormalities [90]. In Korean young men, those with moderate to high cardiorespiratory fitness had better metabolic risk profiles than men with low cardiorespiratory fitness [91]. Further, men with low to moderate fitness had odds ratios of ~4.6 and 2.5 for having the metabolic syndrome compared to the high cardiorespiratory fitness group even after adjustment for age, smoking, and percent body fat [91]. In young and middle-aged adults, the benefits of moderate to high cardiorespiratory fitness were only found in those with low waist circumference [92].

Several retrospective analyses convey the importance of physical activity and fitness in metabolic syndrome risk. Changes in metabolic syndrome status and aerobic capacity were studied in men and women participating in a health enhancement program over a 3 year period [93]. Those men and women who increased the time on the treadmill during an exercise test had a decline in the presence of the metabolic syndrome, whereas those who had worse treadmill times, and thus reduced their fitness, acquired the metabolic syndrome [93]. In a prospective ~6 year study of Caucasian middle-aged adults who initially did not have the metabolic syndrome, those individuals who progressed to metabolic syndrome status had lower levels of physical activity energy expenditure even after adjustment for age, smoking, socioeconomic status, and other factors [94]. They further determined that the effect of physical activity on the development of the metabolic syndrome was independent of aerobic fitness and obesity [94].

In a large (over 7,000) group of women who were divided into quintiles by aerobic fitness, the prevalence of the metabolic syndrome was lower across quintiles of increasing fitness after adjustment for age and smoking status [95]. In a 7 year longitudinal follow-up of almost 40,000 individuals who had either low, moderate, or high cardiorespiratory fitness by a treadmill test, greater fitness levels were inversely associated with metabolic syndrome (continuous score based on the average individual component z-scores comprising the metabolic syndrome) in both men and women [96]. In this study, three different statistical models were tested including: model 1 which adjusted for age and examination year; model 2 which adjusted for age, examination year, BMI, smoking, alcohol intake, and family history of CVD; and model 3 which adjusted for age, examination year, BMI, physical activity, smoking, alcohol intake, hypercholesterolemia, hypertension, diabetes, and family history of CVD. Lower metabolic syndrome scores were associated with increased fitness for men in all three models at the same level of significance. In women,

lower metabolic syndrome scores were also observed across fitness groups for models 1 and 2, but model 3 did not show a significant difference between the moderate and high fitness groups. Furthermore, this association was also tested for the individual components so that waist circumference, TG, LDL-C, and DBP were inversely related to fitness in both sexes. HDL-C was significantly and positively related to fitness level in both sexes. Thus, there is a significant inverse relationship between fitness level and the presence of the metabolic syndrome for both men and women.

The efficacy of exercise training in treating the metabolic syndrome was reported in over 600 participants from the **HE**alth **RI**sk Factors, Exercise **TRA**ining and **GE**netics Family Study (HERITAGE) who underwent a 20 week moderate intensity aerobic exercise training program [97]. At baseline, the prevalence of the metabolic syndrome was ~17 %. Notably, ~30 % of the individuals with the metabolic syndrome at baseline were no longer classified as having the metabolic syndrome after completing the training program. These improvements were evident by decreases in TG concentrations (43 % of individuals), BP (38 % of individuals), and waist circumference (28 % of individuals), and improvements in HDL-C (16 % of individuals) and fasting glucose levels (9 % of individuals). Importantly, there were no sex or race differences in the efficacy of the exercise training in treating the metabolic syndrome [97].

Risk factors associated with the metabolic syndrome were compared in women with and without estrogen replacement therapy in the HERITAGE Family Study [98]. These investigators found no difference in the percentage classified as having the metabolic syndrome between the two groups. However, when the groups were classified with respect to the number of components of the metabolic syndrome, there were a greater percentage of women not taking hormones who had two or more components of the metabolic syndrome [98]. Furthermore, the 20 week exercise training intervention did not improve the overall metabolic syndrome status of either group. It is unclear why these results contrast those from their larger study as described above.

We studied the effects of a 6 month combined weight loss and low intensity walking exercise training program (1 day per week on a treadmill at 50–60 % HRR for 45 min and 2 days per week at the same intensity on their own) in postmenopausal women with and without the metabolic syndrome [99]. There were significant reductions in waist circumference, TG, and glucose levels in women with the metabolic syndrome. When the women with the metabolic syndrome were divided into two groups based on conversion to non-metabolic syndrome status after the weight loss and exercise intervention, those who responded favorably had greater changes in BP and fasting glucose than the non-converters. In women with the metabolic syndrome, the moderate weight loss and low intensity exercise training reduced the prevalence of the metabolic syndrome by 45 %. Furthermore, the results suggested that reductions in TG, glucose, and BP are the metabolic syndrome criteria primarily associated with conversion from metabolic syndrome to non-metabolic syndrome status (Fig. 12.2) [99].

In older (mean age 65 years) men and women with the metabolic syndrome upon enrollment, 12 weeks of aerobic exercise training consisting of treadmill or cycle

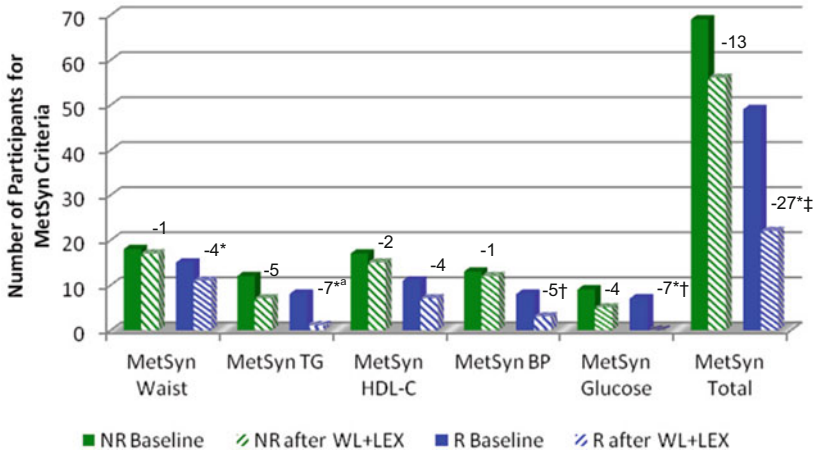

Fig. 12.2 Responses of metabolic syndrome (MetSyn) criteria to weight loss + low intensity exercise (WL+LEX) in Nonresponders (NR) and Responders (R). *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *BP* blood pressure. *Asterisk* Indicates that the difference (pre- and post-WL+LEX) in the number of MetSyn participants with each MetSyn criteria is significant ($P<0.05$). Value of the response in NR versus R, [a]$P=0.07$, †$P<0.05$, ‡$P<0.0001$. Adapted from [99]

exercise 50–60 min per day, 5 days/per week at 80–85 % HRmax or in combination with caloric restriction improved several components of the metabolic syndrome, including reductions in waist circumference, SBP, DBP, fasting glucose, and TG without a change in HDL-Cl [100]. The addition of the weight loss did not appear to have an added benefit to exercise on reductions in these components of the metabolic syndrome [100].

There are a few studies examining the effects of weight regain or exercise detraining in the metabolic syndrome. Thomas et al. [101] studied young and middle-aged men and women with at least two characteristics of the metabolic syndrome who first underwent a combined aerobic (walking or jogging which progressed to 60 % VO_2max for 45 min per day, 5 days per week for 6 months) and diet program followed by randomization to either an exercise group (continued exercise at 60 % VO_2max, 5 days per week, three sessions per week for 4–6 months) or no exercise training group (discontinued exercise training). Energy intake was prescribed to cause regain of lost body weight in the second phase of this study. Changes in body weight were evaluated 4–6 months after the weight loss phase. Waist circumference, TG, and total cholesterol decreased significantly after the weight loss plus exercise program. However, in subjects with a weight regain of over 50 % of lost weight, waist circumference significantly increased and total cholesterol and TG levels generally deteriorated in both groups. Both SBP and DBP decreased after the weight loss plus exercise, but these beneficial effects were maintained only in the exercise group during weight regain [101]. Likewise, the increase in HDL-C was maintained during partial weight regain in the exercise group. The results of this study confirm the benefits of aerobic exercise combined with weight loss on

components of the metabolic syndrome and further suggest that exercise is critical during partial weight regain for maintaining the improvements in some of the components of the metabolic syndrome.

Another study tested the differences in the metabolic syndrome in a large sample of Japanese men who were untrained, those who trained and then detrained, and those who kept training [102]. Those men who detrained over several decades had more metabolic syndrome risk factors compared to those who had continued exercising. Their results suggest that continuance of exercise is important to prevent the loss of the effects of habitual exercise in youth in terms of maintaining favorable improvements in the metabolic syndrome components.

Several studies have examined the effects of exercise training on the metabolic syndrome in middle-aged to older men or women. In subjects (mean age ~53 years) with overweight and obesity, a 9 month high intensity interval aerobic plus resistance training program decreased the prevalence of the metabolic syndrome by 32 % [103]. In the subgroup of individuals with the metabolic syndrome, the intervention resulted in a significant decrease in waist circumference, resting SBP, and TG and increased HDL-C; thus, modifying four components of the metabolic syndrome. Older women with the metabolic syndrome were randomized to either: 1) a 12 month exercise program of two sessions per week that included 20 min of aerobic dance at 70–85 % HRmax, static and dynamic balance exercises, isometric floor exercises, and dynamic strength training of the trunk and legs with elastic belts; and two 20 min home training sessions of isometric exercises, belt and stretching exercises; or 2) a wellness control group that alternated 60 min of low intensity physical activity 1 day per week for 10 weeks with 10 week intervals without training for 12 months [104]. Exercise training decreased TG, SBP, and DBP and increased HDL-C but did not significantly change fasting glucose resulting in a significant decrease in the number of components of the metabolic syndrome criteria. The control group also had significant improvements in BP (decreased SBP and DBP) but did not significantly change TG or HDL-C [104]. Thus, a versatile exercise program is effective in reducing components of the metabolic syndrome in postmenopausal women with the metabolic syndrome.

In older men and women (aged 70–89 years), a 12 month randomized clinical trial of a physical activity intervention (walking 5 or more days per week at least 150 min per week, lower extremity strength exercises performed at a Borg rating of perceived exertion of 15–16 on the 20 point scale of two sets of 10 repetitions, and balance and flexibility exercises) compared to a health education intervention resulted in a decrease in the prevalence of the metabolic syndrome from baseline to 6 months in both groups without a further reduction the last 6 months of the trial in both the physical activity and education groups [105]. Given that the physical activity group did not have a greater effect on the prevalence of the metabolic syndrome compared to the education group, the authors suggested that use of medications may have explained their findings.

A 12 week aerobic exercise training program (5 sessions per week at 60–70 % HRR) compared to control resulted in decreased in waist circumference, BMI, and blood glucose but not BP in premenopausal or postmenopausal women with the

metabolic syndrome [106]. The aerobic training intervention also did not change the BP response to an acute bout of exercise measured at 10 min intervals for 1 h of recovery from exercise in women with the metabolic syndrome regardless of menopausal status [106]. Older (50–70 years) men and women with the metabolic syndrome were randomized to one of three exercise interventions (high-resistance-moderate-aerobic, moderate-resistance-high aerobic, or moderate resistance-moderate aerobic) and compared to a control group who did not have any of the defined criteria of the metabolic syndrome or chronic disease and no routine medications. There was a significant reduction in waist circumference, SBP, DBP, fasting glucose, and TG and an increase in HDL-C in all exercise groups [107]. Although outcomes of the metabolic syndrome improved in all exercise groups, they did not achieve the healthy values reported for the control group (non-metabolic syndrome).

In another study of sedentary patients with the metabolic syndrome that had hypertension and were overweight, weight reduction by diet alone and diet plus exercise (40 min of aerobic training 2 sessions per week at 60–80 % of HRR) resulted in improvements in components of the metabolic syndrome [108]. There were significant reductions in BP, TG levels, hemoglobin A_{1c} levels, and the waist-hip ratio, with significant increases in HDL-C. However, the exercise training program did not confer any added benefit with respect to improvements in the metabolic syndrome components than diet alone. Yet, importantly this study was performed in a rural setting implicating the general applicability of these interventions to sedentary individuals with overweight and the metabolic syndrome.

Exercise training was compared to a control group given guidelines for exercise among older adults (55–75 years) with elevated SBP or DBP not taking medications for their high BP [109]. Those individuals randomized to 6 months of 3 days per week of exercise training performed two sets of 10–15 repetitions at 50 % of 1-RM resistance training as well as 45 min of aerobic exercise at 60–90 % HRmax. Exercise training reduced abdominal fat, SBP, and DBP, and increased HDL-C. Participants had a baseline prevalence of the metabolic syndrome of 42 %, and approximately 18 % of those who participated in a 6 month training program no longer had the metabolic syndrome after exercise training compared to a somewhat similar 15 % of controls. However, a small percentage (~8 %) of controls developed the metabolic syndrome after the control period [109]. Thus, exercise training reduced body fat and improved the number of components of the metabolic syndrome in older adults with mild hypertension.

Finucane et al. conducted a randomized controlled trial of 12 weeks aerobic exercise training (three, 1 h sessions per week of cycling exercise at 50–70 % of maximal watts) versus control (continuance of usual physical activity levels) among older men and women (mean age ~71 years). They found that the exercise group had a reduction in body weight and waist circumference but BP and lipid profiles did not change significantly [110]. Although other metabolic outcomes changed favorably with the exercise training (i.e., insulin levels after glucose load, and intrahepatic lipid), there was only a trend toward a reduced composite metabolic risk score in the intervention group. Thus, not all studies completely agree on which

components of the metabolic syndrome favorably change with exercise training in subjects with the metabolic syndrome, and whether there is a significantly greater response than a non-exercising control group.

Clinical Implications and Importance

The prevalence of the metabolic syndrome is likely to continue to rise given the increase in obesity around the world. Individuals with the metabolic syndrome are at heightened risk for future disease and are more likely to die from CVD. The metabolic syndrome is characterized by abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance. The constellation of phenotypic and metabolic factors place individuals at risk for chronic disease. Hypertension is one component of the metabolic syndrome that is modifiable by medication, weight loss, and exercise training as well as a combination of exercise, diet, and pharmacologic therapy.

Exercise Prescription for the Metabolic Syndrome

Evidence-based exercise prescription recommendations according to the FITT (*F*requency-how often, *I*ntensity-how hard, *T*ime-duration, and *T*ype-mode) principle are provided below according to the American College of Sports Medicine (ACSM) recommendations [111].

Frequency Most adults should accumulate 30–60 min per day (≥150 min per week) of moderate intensity aerobic exercise, 20–60 min per day (≥75 min per week) of vigorous intensity aerobic exercise, or a combination of moderate and vigorous intensity aerobic exercise to attain the recommended targeted volumes of exercise. The recommended amount of exercise may be accumulated in one continuous exercise session or in bouts of ≥10 min over the course of a day.

Intensity Moderate (40 to <60 % HRR or oxygen consumption reserve, $VO_{2reserve}$) to vigorous (60 to <90 % HRR or $VO_{2reserve}$) intensity aerobic exercise is recommended for most adults, and light (30 to <40 % HRR or $VO_{2reserve}$) to moderate intensity aerobic exercise for deconditioned individuals [111].

Time Exercise duration recommendations are an accumulation of 30–60 min per day (≥150 min per week) of moderate intensity aerobic exercise, 20–60 min per day (≥75 min per week) of vigorous intensity aerobic exercise, or a combination of moderate and vigorous intensity aerobic exercise daily to attain the recommended targeted volumes of exercise whether in one continuous exercise session or in bouts of ≥10 min over the course of a day [111].

Type Recommendations for aerobic exercise include rhythmic moderate intensity exercise that involves large muscle groups and requires little skill to perform.

Resistance training should be for each of the major muscle groups performed 2–3 days/week with at least 48 h separating exercises for the same muscle group.

For individuals with the metabolic syndrome, special considerations to the FITT principle should be paid according to the presence of associated CVD risk factors, chronic diseases and health conditions [111]. Additional special considerations for individuals with the metabolic syndrome include the recommendation to begin exercise training at a moderate intensity (i.e. 40 to <60 % $VO_{2reserve}$ or HRR) and if appropriate, progress to a more vigorous intensity (i.e. ≥60 % $VO_{2reserve}$ or HRR) [111]. This totals a minimum of 150 min per week or 30 min per day most days of the week. Further recommendations are to reduce body weight by a gradual increase in physical activity levels to ~300 min per week or 50–60 min on 5 days per week [111]. This can be accomplished through multiple daily bouts of at least 10 min duration or through increases in other forms of moderate intensity physical activities [111]. To promote or maintain weight loss, exercise of longer duration (60–90 min per day) may be needed [111]. Please see detailed discussion in Chaps. 2–4, and 6 of the new and emerging evidence for the cardiometabolic and vascular health improvements that result from resistance and concurrent (aerobic and resistance combined) exercise that would also favorably impact the metabolic syndrome.

Conclusion

Exercise training and increased physical fitness promote positive changes in BP, one of the components of the metabolic syndrome. Different modalities of exercise (i.e., aerobic and resistance exercise training) with and without weight loss have been shown to improve the components of the metabolic syndrome. Adopting a physically active lifestyle should be emphasized in individuals with the metabolic syndrome to reduce cardiovascular events in this population.

Future research could be directed at possible factors that contribute to why some individuals respond better to exercise training in terms of individual components of the metabolic syndrome than others as well as reasons why some individuals can convert from having to not having the metabolic syndrome after exercise training. The optimal exercise prescription for individuals with the metabolic syndrome in terms of the dose response and sustainability of exercise training should be a future research direction. In addition, studies that would help elucidate mechanisms at the whole body and tissue level as well as genetic factors are needed to further translate the benefits of exercise training on the metabolic syndrome. More research also needs to be conducted in well-designed exercise training studies to examine the health implications and long-term effects of exercise training on individuals classified as having the metabolic syndrome. Last, lifestyle strategies to prevent the metabolic syndrome and its components should be another primary area of investigation.

Key Points and Resources

- Hypertension is a critical component of the metabolic syndrome, which includes other criteria, namely central obesity, insulin resistance, and dyslipidemia (high triglycerides and low HDL-C).
- The ACSM recommends exercise training in the management of the metabolic syndrome with special consideration of the presence of associated cardiovascular risk factors [111].
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Chapter 13
Effects of Exercise on Lipid-Lipoproteins

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Abbreviations

ACC	American College of Cardiology
ACSM	American College of Sports Medicine
AHA	American Heart Association
BP	Blood pressure
CAD	Coronary artery disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
ECS	European Society of Cardiology

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HDL-C	High density lipoprotein cholesterol
HMG CoA	Hydroxy-methylglutaryl coenzyme A
LDL-C	Low density lipoprotein cholesterol
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
PCSK9	Proprotein convertase subtilisin/kexin type 9
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglycerides

Introduction

Hypercholesterolemia is defined as abnormally high levels of the atherogenic lipoproteins, of which there are three: very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low density lipoprotein cholesterol (LDL-C).The degree to which lipoproteins cause atherosclerosis depends in part on their size and subsequent ability to enter the arterial wall [1]. LDL-C is the major atherogenic protein and lipid risk marker, as it is strongly associated with atherogenic events such that a 10 % increase in LDL-C leads to an approximate 20 % increase in coronary heart disease (CHD) risk [2, 3]. Triglycerides (TG) are also associated with an increase in CHD events, although their link to CHD is complex and may be related to the other risk factors such as LDL-C and high density lipoprotein cholesterol (HDL-C) subfractions, abdominal obesity, insulin resistance, and hypertension [4]. HDL-C, by contrast, reduces the risk of atherosclerosis and CHD; the lower the level of HDL-C, the higher the risk for CHD [4]. HDL-C is considered one of the most malleable lipoprotein risk markers to lifestyle and behavioral interventions, as it is strongly influenced by obesity, smoking, and physical activity [2].

While the four major blood lipid-lipoprotein measurements (total cholesterol (TC), with components of HDL-C, LDL-C, TG) and their ratios in relationship to each other are the primary targets used to diagnose and treat cardiovascular disease (CVD), there are multiple other lipid-lipoprotein risk markers including VLDL, lipoprotein(a), apolipoproteins subtypes A, B and E, and serum proproteinconvertasesubtilisin/kexin type 9 (PCSK9). For example, lipoprotein(a) is associated with premature coronary disease and atherosclerosis risk [5], while higher levels of PCSK9 decrease the number of hepatic LDL receptors and can produce hypercholesterolemia [6]. However, to date, strong epidemiological and clinical trial evidence regarding the efficacy of treating these other lipid-lipoprotein risk markers has not been established.

Treatment guidelines based primarily on serum LDL-C levels were established by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in May 2001 [4]. These guidelines suggest an LDL-C treatment goal, based on current and estimated CVD and CVD risk factors, ranging from 100 to

160 mg·dl^{-1}. In 2004, the NCEP released an update stating that an LDL-C goal of <70 mg·dl^{-1} is "a reasonable clinical strategy" for patients at very high risk of coronary artery disease (CAD) [3]. Several major clinical trials supported even lower LDL-C goals for many patients (e.g., Heart Protection Study (HPS) [7] and The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT/TIMI-22) [8]). Thus increasing numbers of patients, including older adults and those with low initial LDL-C levels, have been advised to reduce cholesterol through either lifestyle or pharmacological interventions. Recently released guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) dramatically revised the treatment guidelines for hyperlipidemia, focusing on risk of stroke and coronary disease rather than strictly defined target LDL-C levels as a rationale to treat an individual (Table 13.1; [9]). Regardless, abnormal blood lipids remain one of the most common risk factors for cardiovascular and metabolic disease and as such are the emphasis of clinical intervention strategies.

Hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statins are the most effective medications for reducing elevated concentrations of LDL-C and have been documented to reduce cardiac events in both patients with CAD (secondary prevention) and in otherwise healthy subjects (primary prevention). In addition, there are four other classes of cholesterol-lowering drugs (i.e., bile acid sequestrants, fenofibrates, nicotinic acid, and cholesterol absorption inhibitors [10]) which are frequently used in combination with statin therapy. Lifestyle interventions such as diet and exercise are often underutilized in patients with hyperlipidemia, in part because the effectiveness of statin therapy marginalizes these more time-intensive, albeit effective, approaches. Consequently, statins are so effective that they are presently the most commonly prescribed drugs in the United States and the world. According to the Centers for Disease Control (CDC), from 2005 to 2008 approximately 25 % of U.S. adults >45 years reported using a prescription statin drug in the last 30 days, almost 10-fold higher than reported use from 1988 to 1994 [11].

The purpose of the current chapter is to present the relevant research regarding the effectiveness of aerobic and resistance exercise on the lipid-lipoproteins LDL-C, HDL-C, and TG, with reference to the comparable effects evoked by common cholesterol-lowering drugs and interactions between lipid-lowering pharmaceutical therapy and exercise training. This approach is critically important because several recent studies have shown that exercise training may be as, if not more, effective than certain monotherapies for preventing CVD mortality. For example, a recent meta-analysis of major exercise and drug trials (assessing 309 clinical trials with 339,274 participants) found no statistically detectable difference between exercise and drug interventions in mortality outcomes for CHD and prediabetes, and physical activity interventions were actually more effective for secondary prevention of stroke mortality [12]. Consequently, treating exercise as a valuable prescription to prevent and treat CVD requires clinicians and researchers to be well trained in the benefits and effectiveness of exercise training for ameliorating hyperlipidemia. The final section of this chapter will address the impact of cholesterol-lowering drugs and exercise for dyslipidemia on the concurrent treatment of hypertension, as approximately 20 %

Table 13.1 Four major differences between National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [4] and American College of Cardiology (ACC)/American Heart Association (AHA) [9] guidelines

NCEP ATP III guidelines	ACC/AHA guidelines
Treat to target approach	Not enough evidence for targets
• Quantitative guidelines for LDL-C, HDL-C, and TG	• RCTs do not support evidence for numerical targets
• Based on number of CVD risk factors	• Rationale for treating four groups who may benefit from statin therapy
No distinction between cholesterol-lowering drugs	Recommends statin therapy to reduce blood lipid-lipoproteins
• Emphasizes treatment with cholesterol-lowering drugs to achieve targets	• Identifies high and moderate intensity statins (based on percent reduction in LDL-C) for use in secondary and primary prevention
	• Non-statin therapies do not provide substantial risk reduction relative to potential adverse effects
CVD calculated from Framingham Score	Uses a new equation to estimate 10 year CVD risk
• Does not include stroke in calculation, only heart attacks	• Includes stroke and heart attack in calculation of risk
Treatment decisions based on guidelines	Clinician flexibility in treatment decisions
• Clinicians make treatment decisions based on guidelines	• Suggests that treatment decisions in patients who fall outside of the four predefined groups may be influenced by other risk factor assessments at physician discretion

CVD cardiovascular disease, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *RCT* randomized controlled trial, *TG* triglycerides

of adults with high blood pressure commonly have the comorbidity of one or more abnormal lipid-lipoprotein biomarkers, and the prevalence of combined hypertension and hypercholesterolemia increases substantially with age [13].

Key Terminology and Basic Concepts

Coronary Heart Disease and Dyslipidemia

CHD is the single leading cause of death in the United States. For example, according to the most recent data update [14], in 2010, CVD (heart disease and stroke) accounted for 31.9 % of all deaths, or about one of every three deaths in the United States. This equates to >2,150 American adults dying of CVD per day, or one death every 40 s. CHD alone accounted for one in six deaths in 2010, and an estimated 31.9 million adults ≥20 year (or 13.8 % of the population) had hypercholesteremia. Resultantly, treating abnormal blood lipids is vital to reduce deaths related to CVD in the United States.

Guidelines for Cholesterol Management

Current guidelines for the assessment and management of hypercholesterolemia include those provided by the NCEP ATP-III [4], ACC/AHA [9], and the European Society of Cardiology (ESC; [15]). These three sets of guidelines differ substantially in terms of assessment of risk, designation of treatment targets, and resultant prescription of cholesterol-lowering drugs. For example, a recent analysis of application of the guidelines to 4,854 patients from the Rotterdam Study found that statins would be recommended for 97 %, 52 %, and 66 % of men and 67 %, 36 %, and 39 % of women by the ACC/AHA, ATP-III, and ESC guidelines, respectively [16]. Regardless, when the effectiveness of interventions such as diet, weight loss, and pertinent to this chapter, exercise, are evaluated, they are often assessed with respect to treatment targets developed by these guidelines.

Cholesterol-Lowering Medications

There are five major classes of cholesterol-lowering drugs, with effects of monotherapy ranging from a 4–50 % reduction in LDL-C depending on dose and type [10]. These include HMG-CoA reductase inhibitors (statins), niacin, fibric acid derivatives, bile acid binding resins, and cholesterol absorption inhibitors. Statins are the most effective medications for decreasing LDL-C, consequently reducing cardiac events in both patients with CAD [16] and in previously healthy subjects [17]. Statins are extremely well tolerated by most patients, but can produce muscle-related complaints in some individuals. While clinically important rhabdomyolysis with statins is rare with an overall reported incidence of fatal rhabdomyolysis of 1.5 deaths per 10^6 prescriptions [18], statins are more frequently associated with "mild muscle complaints" including myalgia (i.e., pain), cramps, and weakness. The reported incidence of myalgia during therapy with the more powerful statins has varied from 1 % in pharmaceutical company reports [19] to 25 % [20] of patient reports, with several established clinical trials reporting an average of 5–10 % [21, 22]. As there are also reports of cognitive side effects associated with statins [23], and other classes of cholesterol-lowering drugs also evoke side effects ranging from flushing to gastrointestinal discomfort, utilizing lifestyle approaches to improving blood lipid-lipoproteins is the initial recommended treatment among adults at low to moderate CVD risk [4, 9].

Methods

Randomized controlled trials lasting ≥4 weeks investigating the effects of exercise on lipid-lipoproteins in adults (≥18 years), published in English in a peer-reviewed journal indexed in PubMed within the last 10 years and up to July 1, 2014 were included. This search was limited to human studies only and is described in Fig. 13.1.

Relevant Research

Effects of Aerobic and Resistance Exercise on LDL-C

The overall body of work investigating the impact of exercise training on LDL-C finds that aerobic exercise training alone (without concurrent weight loss) does not substantially reduce LDL-C [24]. For example, a recent meta-analysis of the effect of exercise training on lipids in older overweight and obese adults (≥60 years) assessed data from nine randomized controlled trial (RCT)s involving aerobic and/or resistance training. While there was a modest effect of exercise on anthropometric measures such as body mass index and waist circumference, there was no effect on LDL-C [25].Moreover, a meta-analysis of six RCTs comparing diet to aerobic exercise training on blood lipid-lipoproteins reported a statistically insignificant change of only 1.5 % for LDL-C for pooled study data, and the authors concluded that diet was more efficacious at treating high levels of LDL-C than aerobic exercise training [26]. The authors of that study conducted a similar meta-analysis in overweight and obese individuals and reported again no effect of aerobic exercise training on LDL-C beyond reductions achieved with weight loss alone [27]. Similarly, an evaluation of 60 healthy male sedentary controls and 142 professional endurance athletes showed that the professional athletes exhibited an improved TC/LDL-C ratio, but this improvement was largely driven by group differences in HDL-C rather than LDL-C [28].

Cumulatively, these data are in agreement with the finding that aerobic exercise training does not uniformly influence LDL-C, either due to comorbidities, subject population, or differences in exercise prescription. To the latter, for example, a systematic review of aerobic exercise training effects on LDL-C found that only two of 26 studies found a significant decrease in LDL-C of 10–11 % with moderate intensity exercise training, whereas seven of 35 studies reported decreases in LDL-C ranging from 6 to 21 % with high intensity endurance exercise training [29]. While this could indicate that more vigorous intensity aerobic exercise is needed to improve LDL-C, a recent review of 24 studies involving the impact of high intensity interval training on cardiometabolic risk found that no training protocol involving high intensity interval training improved LDL-C [30]. Therefore, it is likely that the relationship between intensity of aerobic exercise and changes in LDL-C is confounded by concurrent changes in other parameters such as body weight and dietary intake, as both dietary restriction alone and the reduction in body weight associated with aerobic exercise do reduce LDL-C [31].

Data from resistance training protocols, while again limited, are somewhat more promising with respect to reductions in LDL-C. In a systematic review of resistance training studies, nine of 23 studies showed significant reductions in LDL-C ranging from 5 to 23 % with at least 12 weeks of resistance training in otherwise healthy adults [29]. Similarly, a meta-analysis of 29 studies with 1,329 men and women found an average and statistically significant reduction of 6.1 $mg \cdot dl^{-1}$ in LDL-C

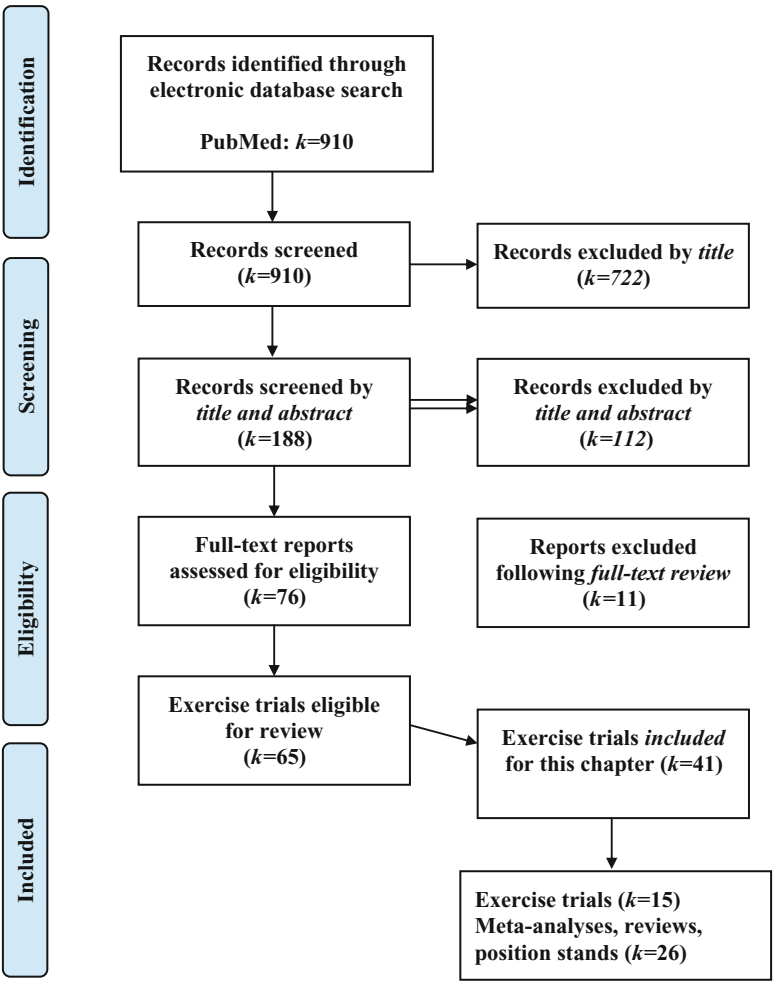

Fig. 13.1 Flow chart detailing the systematic search of potential reports and selection process of included aerobic, resistance and concurrent exercise trials

with at least 4 weeks of progressive resistance training [32]. It has been speculated that changes in body composition (e.g., reduced abdominal subcutaneous fat and visceral fat and increased lean body mass) could underlie the efficacy of resistance training for treating high LDL-C [33]. It should be noted, though, that this magnitude of reduction is less than observed with pharmaceutical monotherapy, contributing to the continued clinical practice of addressing elevated LDL-C with diet and/or cholesterol-lowering drugs.

Effects of Aerobic and Resistance Exercise on HDL-C

Unlike LDL-C, HDL-C is more malleable to aerobic exercise training, with a strong dose-response to exercise training and a seeming volume threshold below which minimal gains are observed. Reviews on the topic suggest that aerobic exercise training volumes of 15–20 miles per week of brisk walking or jogging (that elicit 1,200–2,200 kcal expenditure per week) are associated with an 2–8 $mg \cdot dl^{-1}$ increase in HDL-C, and greater changes in HDL-C levels can be expected with additional increases in exercise training volume [24]. Similarly, a meta-analysis of 25 RCTs investigating the impact of aerobic exercise training on HDL-C reported a statistically significant average 2.5 $mg \cdot dl^{-1}$ increase in HDL-C with training [34]. The minimal exercise volume needed to see these increases was estimated at 120 min or 900 kcal per week, and every 10 min increase in exercise duration was associated with a 1.4 $mg \cdot dl^{-1}$ increase in HDL-C. Unfortunately, though, aerobic exercise training appears to have little effect of on HDL-C in men with low levels of HDL-C (<40 $mg \cdot dl^{-1}$) [35], suggesting that aerobic exercise is least effective for changing HDL-C in adults who stand to benefit the most.

The intensity of exercise may also influence changes in HDL-C. In a systematic review of aerobic exercise training effects on HDL-C, the authors reported that only six of 28 (21 %) of moderate intensity aerobic exercise training studies found a statistically significant increase in HDL-C, but 22 of 37 (59 %) of high intensity endurance trials showed benefits on HDL-C [29]. Moreover, in meta-analyses in which overall pooled data have not shown overall statistically significant increases in HDL-C (in individuals with overweight and obesity, for example), the authors found that changes in HDL-C were directly related to changes in maximal oxygen uptake, again supporting the notion that a sufficient volume and intensity of aerobic exercise is necessary to impact HDL-C [27]. Therefore, cumulative evidence supports a positive relationship between the intensity of aerobic exercise and the magnitude of the observed benefit on raising HDL-C.

In contrast, resistance training seems to evoke minimal effects on HDL-C. The same meta-analysis of RCTs cited above to address the influence of progressive resistance training on LDL-C found no effect of resistance training on HDL-C, with an average change in HDL-C of 0.7 $mg \cdot dl^{-1}$ (1.4 %) that was not significantly different than control [32]. Other meta-analyses have supported this finding [36], and a systematic review of 23 resistance training trials found that only four of 23 improved HDL-C, and of those several involved an aerobic exercise training component that biased results as well [29].

Effects of Aerobic and Resistance Exercise on Triglycerides

Since the link between TG and HDL-C/LDL-C is related and complex, and TG are also influenced by a myriad of physiological and behavioral factors such as insulin resistance, sex, smoking, alcohol use, obesity, and weight loss, it is difficult to

isolate the independent effects of exercise training on TG. As would be expected, then, data regarding aerobic and resistance training on TG are varied. For example, a systematic review of 84 trials found that moderate intensity aerobic exercise reduced TG in three of 27 studies, high intensity aerobic exercise reduced TG in 12 of 35 studies, and resistance training reduced TG in three of 23 studies [29]. Several other meta-analyses have reported more substantial average reductions in TG of 8–9 $mg \cdot dl^{-1}$ with resistance training [31, 36, 37] and 8–20 $mg \cdot dl^{-1}$ with aerobic training [24, 27]. Therefore, while evidence suggests a beneficial role for both aerobic and resistance training in reducing TG, changes with exercise training are neither uniform nor systematic and are likely to be dose and intensity dependent.

Concurrent Aerobic and Resistance Training

Data presented previously in this chapter identify a trend regarding aerobic and resistance training on LDL-C and HDL-C whereby stronger effects of aerobic training are observed on HDL-C, yet stronger effects of resistance training are reported with LDL-C. Of note, emerging evidence suggests that concurrent aerobic and resistance training make evoke the most favorable alterations in lipid-lipoproteins by augmenting HDL-C and lowering LDL-C in the same individuals (Fig. 13.2).

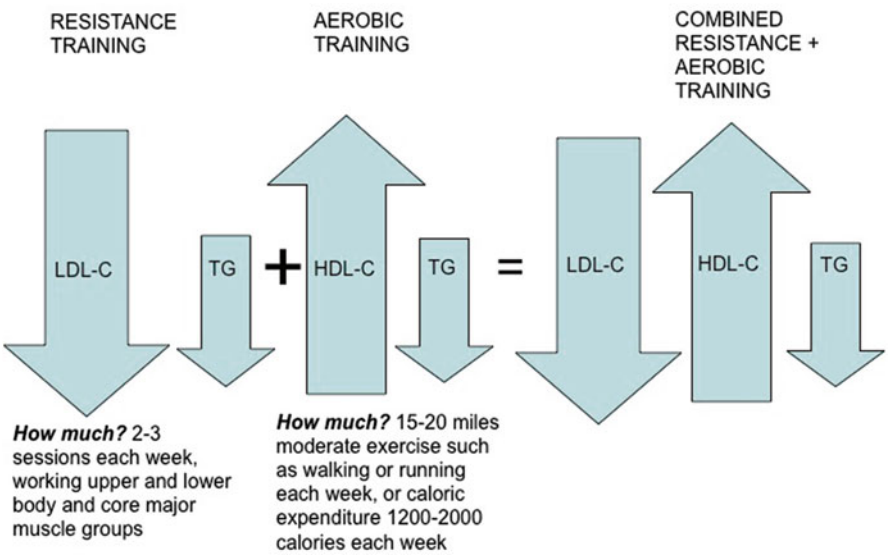

Fig. 13.2 A schematic demonstrating a proposed hypothesis for the effects of resistance training alone, aerobic exercise training alone, and concurrent aerobic and resistance training on LDL-C (low density lipoprotein cholesterol), HDL-C (high density lipoprotein cholesterol), and TG (triglycerides)

For example, a randomized trial comparing 12 weeks of aerobic exercise training to high intensity circuit training (a concurrent resistance and aerobic training protocol), reported almost a 20 $mg \cdot dl^{-1}$ decrease in LDL-C (versus approximately 4 $mg \cdot dl^{-1}$ with aerobic exercise training) with a simultaneous 5 $mg \cdot dl^{-1}$ increase in HDL-C (versus. a non-significant change with aerobic exercise training) [38]. Indeed, in a systematic review of eight studies examining the effects of aerobic, resistance and concurrent exercise training protocols on blood lipids, the authors noted a trend for concurrent aerobic and resistance training to improve both HDL-C (3.5–23 % increase) and LDL-C profiles (4–34 % decrease) [29]. However, given that the systematic review included 84 studies on exercise training (58 RCTs), only eight of which were concurrent training protocols, it is evident that more research is necessary to establish the optimal dose of concurrent aerobic and resistance training for mitigating abnormal lipid-lipoprotein biomarkers.

The Impact of Cholesterol-Lowering Drugs and Their Interaction with Exercise

As has been previously noted, cholesterol-lowering drugs—particularly statins—are extremely efficacious for lowering LDL-C. The average reduction in LDL-C with routine statin monotherapy ranges from 25 to 50 % even at low doses [4]. Therefore, there is a strong clinical bias towards prescribing cholesterol-lowering drugs over exercise for treating hypercholesterolemia. However, data suggest that the combination of exercise training and cholesterol-lowering drugs may be most beneficial for patients with elevated LDL-C. For example, after 12 weeks of resistance training in older adults, LDL-C was reduced on average by 18 $mg \cdot dl^{-1}$, and further lowered by 12 $mg \cdot dl^{-1}$ with the concurrent use of cholesterol-lowering drugs [39].

Similarly, an analysis of over 10,000 veterans in the Veteran's Affairs Medical system [40] found that while both high fitness and statin drug use decreased mortality risk, individuals who were both highly fit and taking a statin had the lowest mortality risk of any study participants (see Chap. 4 for an expanded discussion of this study). The group at highest risk for premature mortality was the group not on statins and with low exercise capacity. Moreover, for the highest fit individuals in this study, the protection against mortality garnered from being very fit was greater than the mortality benefit observed from less fit individuals who were taking statins. Consequently, physicians should regard prescribing and encouraging routine exercise as critically important to health and CVD prevention as a statin prescription.

However, it should also be noted that there are negative associations between statin therapy and physical activity, as the most frequently experienced statin side effect is muscle complaints (cramping, myalgia, soreness and weakness), occurring in approximately 5–10 % of patients [21], and these statin-related muscle complaints

may be exacerbated by exercise. For example, several reports indicate that athletes and/or physically active individuals are less likely to tolerate statin therapy [41], and the muscle damage associated with downhill walking and marathon running is augmented by concurrent statin therapy [42, 43]. Therefore, certain susceptible individuals may experience reduced benefit from the interactions between exercise and statin therapy, and may need to tailor their doses accordingly.

Impact of Cholesterol-Lowering Drugs on Hypertension and Their Interaction with Exercise

A large body of evidence suggests that statin therapy also influences blood pressure (BP). For example, a recent review has shown that statins lower systolic blood pressure (SBP) up to 8.0 mmHg in patients with dyslipidemia and normal BP; 6.0 mmHg in patients without dyslipidemia and with hypertension; and 13.7 mmHg in patients with dyslipidemia and hypertension [44]. However, other reports have found no effect of statins on resting BP, and thus results are inconsistent [45, 46]. Reductions in BP with statins are likely dependent on additional confounding factors such as baseline BP, use of antihypertensive drugs, sex differences, and comorbidities of the population studied. Recent evidence also suggests that statins interact with the renin-angiotensin-aldosterone system (RAAS) through a variety of mechanisms, such as reducing the expression of angiotensin II receptors, altering synthesis and/or signaling of angiotensin II and aldosterone, and blunting systemic oxidative stress [47]. Therefore statins may act alone or in combination with antihypertensive drugs that target the RAAS to lower BP, and consequently the magnitude of reduction in BP observed with statin drugs is also likely dependent on the etiology of each individual's hypertension.

An intriguing question is whether there are interactions between concurrent use of either lipid-lowering and/or BP lowering drugs and exercise training with respect to changes in blood lipids or BP. While there are few comprehensive studies on the topic, limited data suggest there may be overlapping effects. For example, an RCT of a 12 week aerobic dance training protocol on blood lipids in adults with hypertension on BP lowering drugs showed that exercise training had no additional benefit for lipid lowering relative to the control, non-exercise group [48]. In addition, combined statin therapy and exercise training resulted in larger reductions in BP than statin therapy alone in ovariectomized rats [49]. A new RCT comparing time to stroke and other secondary cardiovascular outcomes with antihypertensive treatment to three different SBP targets at two different LDL-C targets will provide important rigorous evidence on the interaction between lipid-lowering and blood pressure-lowering interventions, potentially advancing the field for future study [50]. The reader is also referred to Part 1 for a more detailed discussion of the effects of aerobic (Chap. 1), resistance (Chap. 2), and concurrent (Chap. 3) exercise on BP.

Clinical Implications and Importance

Exercise Prescription Recommendations

According to the 9th edition of the American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription [51], the exercise prescription for individuals with dyslipidemia is similar to that of healthy adults, with an added focus on healthy weight maintenance. Accordingly, aerobic exercise becomes pivotal to the exercise prescription, with resistance and flexibility exercises adjunct to the aerobic training program due to their lesser impact on overall caloric expenditure. This prescription thus entails:

- Frequency: >5 days per week to maximize caloric expenditure
- Intensity: 40–75 % maximal oxygen uptake reserve or heart rate reserve
- Time: 30–60 min per day with 50–60 $min \cdot d^{-1}$ or more of daily exercise recommended for maximum weight loss
- Type: The primary mode should be aerobic physical activities that involve the large muscle groups.

Whether this prescription should be altered based on specific evidence presented in this chapter regarding resistance training and/or concurrent aerobic and resistance training and their effects on LDL-C is not certain, as to date there have not been sufficiently rigorous RCTs investigating the efficacy of various exercise prescriptions on blood lipid profiles. However, it does appear likely that a combined aerobic-resistance training program, entailing sufficient aerobic volume and intensity and a focus on healthy weight maintenance in conjunction with an increased emphasis on weekly resistance training, may optimize changes in both LDL-C and HDL-C. For example, an otherwise healthy patient with hyperlipidemia and mild obesity (body mass index of 32 kg/m^{-2}) could be counseled to follow the ACSM guidelines for aerobic exercise prescription but also add 2 days per week of resistance training, again according to ACSM guidelines, to augment the lipid-lipoprotein lowering effects of aerobic exercise training. In addition, a patient who is taking cholesterol-lowering drugs and/or antihypertensive medication should be assessed periodically for both beneficial (enhanced BP lowering) and negative (statin-associated myalgia) side effects of these drugs when combined with exercise training.

Future Directions

More adults than ever before are using statin therapy to treat hypercholesterolemia because these drugs are generally well tolerated with minimal side effects. Individuals who combine statin therapy with moderate intensity exercise training may potentiate the effects of either therapy alone, with the combined approach thereby proving an effective alternative to multi-drug cholesterol-lowering regimens or monotherapy of a higher dose statin. Whether the latter approach could be effective for treating individuals who cannot tolerate high-dose statin use (due to

various side effects or contraindications to medicine use) has not, to the best of our knowledge, been established clinically. In addition, with newer lipid guidelines removing the emphasis from specific LDL-C targets, the use of exercise training to improve blood lipid profiles may become a more routine approach to treating mild-to-moderate hyperlipidemia should clinicians stray from the standard dose-response hypercholesterolemia treatment protocol of titrating statin therapy to meet numerical LDL-C targets. And finally, given that statin drugs also appear to influence BP, clinicians may ultimately consider both BP and cholesterol targets in physically active individuals taking combined statin-antihypertensive therapy, as the interaction between the two classes of drugs and routine physical activity can augment reductions in blood lipids and BP more than either alone.

Conclusion

Hypercholesterolemia is a major risk factor for CVD and CAD, and treating abnormal blood lipid-lipoproteins (elevated TC, LDL-C and TG as well as low HDL-C) is the focus of both lifestyle and pharmaceutical interventions. Although recent guidelines have questioned the traditional use of quantitative LDL-C, TG, and HDL-C targets, clinicians continue to prescribe diet, physical activity, weight loss, and cholesterol-lowering drugs to improve blood lipid-lipoprotein levels. Although being physically fit appears to augment the influence of statins on mortality risk, most patients with hyperlipidemia will ultimately require medication therapy in addition to diet and exercise lifestyle therapy. Aerobic exercise training, if of moderate intensity with a volume of 15–20 miles per week or caloric expenditure of 1,200–2,200 kcal per week, can be effective for increasing HDL-C and reducing TG, while research suggests that resistance exercise may have a greater impact on reducing LDL-C. To date the effect of statin therapy, particularly on LDL-C, has led to widespread use of these drugs to treat hypercholesterolemia, a trend which is unlikely to change given that these drugs are well-tolerated by the majority of users. However, more research is necessary to better understand the interactions between aerobic and resistance exercise with respect to treating blood lipid-lipoproteins as well as the combined use of exercise training and cholesterol-lowering drugs for improving dyslipidemia in various patient populations. In addition, with increasing numbers of patients treated for both hypertension and hypercholesterolemia, the paucity of data on combined antihypertensive/cholesterol-lowering drugs AND exercise training for patient outcomes represents a large gap in the current knowledge base.

Key Points and Resources

In summary, with respect to the effects of exercise training on blood lipid-lipoproteins:

- CVD accounts for almost 1/3 of deaths in the United States, with dyslipidemia a major risk factor for CVD

- Cholesterol-lowering drugs, particularly statins, are highly efficacious for treating dyslipidemia, particularly elevated LDL-C
- Aerobic exercise generally evokes favorable impacts on raising HDL-C and lowering TG
- Resistance exercise reduces LDL-C more so than aerobic exercise, although the magnitude of effect is smaller than observed with statin therapy
- The combined use of exercise training with statin therapy may be more beneficial than either intervention alone, although further research is needed to support this hypothesis and susceptible individuals on statin therapy may experience new or exacerbated muscle side effects with acute and chronic exercise
- Interactions between aerobic/resistance training, cholesterol-lowering drugs, and/or antihypertensive medications appear to be synergistic; however, future research is needed to confirm these favorable interactions among various patient populations
- Pescatello LS, Riebe D, Arena R. ACSM's guidelines for exercise testing and prescription the 9th Edition. Lippincott Williams & Wilkins, Baltimore, MD, 2013 [51].
- National Heart, Lung, and Blood Institute: www.nhlbi.nih.gov/guidelines/cholesterol/atp4/index.htm
- Overview of the New Cholesterol Treatment Guidelines: http://www.nejm.org/doi/full/10.1056/NEJMms1314569 [52]

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Chapter 14
Endothelial Cell Function and Hypertension: Interactions Among Inflammation, Immune Function, and Exercise

Marc D. Cook

Abbreviations

AMPK	Adenosine monophosphate activated protein kinase
Ang II	Angiotensin II
CAM	Cellular adhesion molecules (intracellular—ICAM vascular—VCAM)
CRP	C-reactive protein
CVD	Cardiovascular disease
EC	Endothelial cells
EnDy	Endothelial dysfunction
eNOS	Endothelial nitric oxide synthase
IL-(1β,ra)	Interleukin-1βeta ra-receptor antagonist
IL-(6 10, 17)	Interleukin-6, 10, 17
Mφ	Macrophage
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor-κB
NOX2	NADPH oxidase 2 subunit
oxLDL	Oxidized low-density lipoprotein
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
ROS	Reactive oxygen species
Th (1,2,17)	T helper (1, 2, 17) cell
TLRs	Toll-like receptors
TNF-α	Tumor necrosis factor-alpha
Treg	Regulatory T cell

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Introduction

When endothelial cells (EC) become dysfunctional, they foster a non-compliant vasculature and accelerate the atherosclerotic process. Davies et al. [1] explains this phenomenon as an, "imbalance of expression in protective pathways and an increased pathological stressed state to which EC must adapt to maintain healthy vascular tissue". If at any point the EC fails to regulate responses appropriately, this constitutes a state of endothelial dysfunction (EnDy) which is the hallmark of hypertension.

Monocytes, lymphocytes, and other differentiated immune cell types are present in the adventitia of large and small blood vessels that affect and protect our organ systems [2–4]. While the EC layer functions as a primary barrier of protection in the vasculature, both innate and adaptive immune cells are important components of the vasculature defense system in moderating tissue damage and pathogen invasion. The EC layer governs the infiltration of immune cell types and controls vascular tissue homeostasis by modulating the expression of, and response to, a number of local and systemic immunologically active peptides, proteins, and receptors that sense signals from neighboring cells and invaders. These signals are important for the activation, migration, and extravasation of effector immune cell types (e.g., monocytes and lymphocytes) into the vasculature to effectively neutralize any foreign or native risk to tissue homeostasis.

There have been multiple studies uncovering the complex involvement of innate and adaptive immune activities in hypertension. Systemic low-grade inflammation is an established mechanism that leads to the progression of vascular wall dysfunction, hypertension, and cardiovascular disease (CVD) [2]. However, both monocyte and lymphocyte cell populations have been probed to expose their potential roles in the pathogenesis and pathology of hypertension. Macrophages (Mφ) and T cells play a significant role in the development and progression of hypertension as they are responsible for peripheral and local inflammation that can modulate the activation of EC and are responsive to peptides specific to the renin-angiotensin system, such as angiotensin II (Ang II).

There are multiple etiologies of the pathogenesis of EnDy and hypertension, including inflammatory, dietary, and genetic components (see Chap. 7 for related discussions of the effects of shear stress on inflammation and gene and protein expression related to endothelial health). As pharmaceutical remedies are prescribed for the management of high blood pressure, their efficacy is not complete in managing or preventing the progression of hypertension [5, 6]. The goal of treatment strategies are to reduce blood pressure and alleviate EnDy through approaches that restore nitric oxide (NO) bioavailability and prevent unwarranted reactive oxygen species (ROS)-related activities [7]. As drug therapeutic strategies are ever increasing, exercise has its own powerful medicinal and anti-inflammatory properties, which are vitally important in regards to rectifying dysregulated vascular function and hypertension.

Purpose of This Chapter

The focus of this chapter will be to highlight the role of immune activities (local to the vasculature, effector organs, and peripherally) in promoting EnDy and hypertension. Additionally, this chapter will provide evidence that habitual exercise beneficially modulates systemic immune function, which will bolster the proposition that exercise should be a primary treatment strategy in the maintenance of healthy immune function and utilized as adjunct therapy in the resolution of inflammation related to EnDy and hypertension.

Key Terminology and Basic Concepts

Pro- and Anti-inflammation

Inflammation is a physiological process that occurs when the body sustains an injury to tissues, recognition of abnormal cells, or infiltration of foreign elements that upset systemic homeostasis. Stimuli that are responsible for this reaction include, but are not limited to, infection (bacteria and viral), damaged tissue and cells, and biological irritants. Inflammation is a protective mechanism by which the body neutralizes and removes harmful material, also initiating healing processes. Pro-inflammatory pathways activate immune (i.e., monocytes and lymphocytes) and neighboring cells (e.g., EC), through autocrine (i.e., self stimulating), paracrine (i.e., stimulating nearby cells), and endocrine (i.e., hormone stimulating target cells via bloodstream) signaling that participate in the local immune response. The anti-inflammatory response is essential in regulating the pro-inflammatory response by moderating immune cell activities. Mainly, this response occurs through the production of anti-inflammatory mediators that quiet aggressive immune activities and aid in the resolution of inflammation and also promotes healing.

Acute and Chronic Inflammation

Acute inflammation is the initial physiological immune response to any threat to homeostasis. This process is normal, necessary, and transient. The acute response is good and indicative of neutralization of foreign prospects and tissue healing. However, chronic inflammation, or the inability of the body to properly regulate the immune response, has been associated with an extensive array of degenerative disorders such as autoimmune diseases, obesity, diabetes mellitus, cancer, and CVD. This chronic phenomenon is responsible for alterations in the activities of immune cell types that become destructive to tissues and their function.

Immune and Endothelial Cell Activation

All cells have the capacity to participate in the immune response by having the ability to produce cytokines and chemokines that act as distress signals when they have been damaged or invaded by pathogens. Immunologically activated cells utilize conserved pathways that ultimately lead to nuclear factor-κB (NF-κB) activation and gene transcription of biological markers of an activated state (i.e., cell surface molecules and cytokine release). NF-κB is a highly regulated transcription factor for multiple cell survival and inflammatory pathway proteins. In this instance, tissues inform immune cells of their distress and activate them to resolve the stimuli. Please see Chap. 7 for related discussions of the effects of shear stress on inflammation and gene and protein expression related to endothelial health.

Methods

Literature Search and Trial Selection Details

A comprehensive search was performed using PubMed in both animal (aerobic) and human (aerobic and resistance) exercise intervention studies that assessed the effect of exercise on systemic and cellular immune function, hypertension effector organ immune activities (i.e., vasculature and kidney), and mechanisms of action by which exercise affects endothelial and immunological health and hypertension. Search terms for systematic review articles in human, animal, and cell models included the combination of terms: acute exercise, exercise training, ROS, adenosine monophosphate activated protein kinase (AMPK), peroxisome proliferator activated receptor-gamma (PPAR-γ), immune function (pro-/anti-inflammatory), chronic inflammation, EnDy, and hypertension. Primary outcomes reported on the interactions among modulation of immune function and endothelial function and hypertension status were included. Topics and articles were excluded if they did not encompass mechanistic perspectives (in vivo and in vitro) of immune activity and inflammation in the endothelium, EnDy and exercise intervention, or outcomes of inflammatory biomarkers in individuals with hypertension (in vitro) after exercise intervention.

Article types searched for human research data encompassed randomized controlled trials, controlled clinical trials, comparative studies, data sets, reviews, and historical articles that focused on exercise and hypertension and inflammation/immune function. Human trials encompassing hypertension and reported on immune biomarkers with some physical activity or exercise intervention were extremely limited and consisted of less than ten primary research articles. Article types searched for animal and endothelial cell model research included journal articles, comparative studies, reviews, and systematic reviews on hypertension animal models (i.e., spontaneous hypertensive rat), exercise, and immune function in endothelial cells. There were approximately 150 primary research articles in hypertension animal models that focused on immune function, and roughly 20 were reviewed for this Chapter, but less than ten included exercise interventions with reported

outcomes on immune function. Primary research papers that provided outcomes of immune function and activation (endothelial and immune) in endothelial cell models consisted of nearly 100 articles, with approximately 60 chosen that were mostly experimental studies and short reviews on the participation of the immune system and its effector molecules (i.e., cytokines and chemokines) in the pathophysiology of endothelial cell dysfunction and hypertension.

Relevant Research

The immune system has significant influence in the vasculature, especially in chronic disease states such as the onset and progression of atherosclerosis and hypertension [8]. Thus, treatments limiting immune activities during the development of vascular dysfunction and hypertension are at the forefront of interventions for clinicians, pharmacologists, and physiologists. Inflammation is directly linked to the development and progression of hypertension [2, 3, 9] (Fig. 14.1). There is evidence that

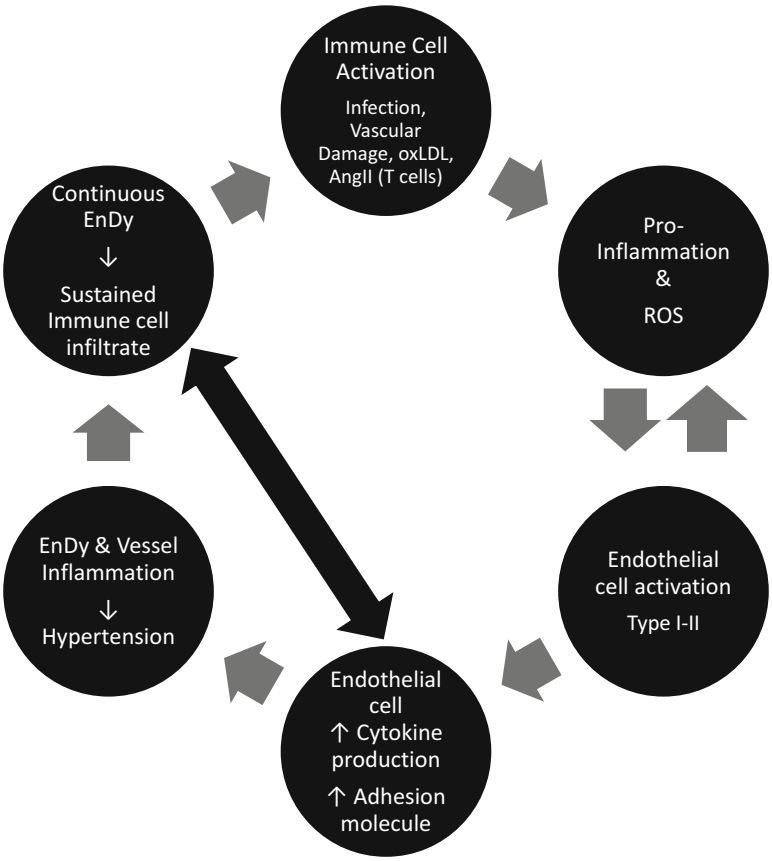

Fig. 14.1 Diagram of the cycle of immune activity and vascular consequences. Angiotensin II (Ang II), oxidized LDL (oxLDL), reactive oxygen species (ROS)

essential hypertension may be, for some, a phenomena of systemic inflammation that drives ROS production and reduces bioavailability of NO promoting the chronic disruption of vascular compliance. Mediators of inflammation, peptides such as cytokines and oxidized lipids (oxLDL) [10], have a profound impact on the vasculature. For example, elevated interleukin-6 (IL-6) is a product of coronary artery disease [11], unstable angina [12], and is strongly associated with increased risk of heart attack [13], and systemic inflammation (pro-inflammatory cytokines) affecting C-reactive protein (CRP) production in the liver [11]. Also, IL-6 is thought to participate in promoting EnDy by enhancing chemokine and adhesion molecule expression [14]. OxLDL is also a profound pro-inflammatory mediator that activates immune cells and EC and plays a substantial role in the inflammatory responses in the vasculature. It initiates the local production of pro-inflammatory cytokines that promote EnDy and aggressive immune cell activities. With this, research begs to answer how immune cells and immune activators interact with the guardians of the vasculature, the EC, and affect their function.

Effects of Inflammation on the Endothelium

Immune cell activation and cytokine release in acute inflammation activates the endothelium, stimulating a normal and transient pro-inflammatory endothelial response that consequently increases ROS. However, chronic inflammation (i.e., low level basal inflammation) ultimately leads to an endothelium that is persistently activated, becoming dysfunctional, and participating in a feed-forward cycle by promoting vascular inflammation and sustained EnDy [2, 3]. In this state, the endothelium is producing cytokines, chemokines, and ROS that chronically reduce NO availability and promote vessel inelasticity. Elevated levels of pro-inflammatory cytokines, such as interleukin-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), are potent activators of EC and are found to be heightened in individuals with essential hypertension [9, 15]. The vasculature is a depot for immune cells where activities that perpetuate systemic inflammation in healthy and disease populations occur. The kidney and the brain are also primary locations of the accumulation of inflammatory cells in individuals with hypertension [16].

The kidney is an essential organ in which immune cells and their mediators play a significant role in the pathogenesis of hypertension [17]. Ang II, the primary effector peptide of the renin-angiotensin system, has been well documented to increase EC activation and promote EnDy, which is characterized by increased pro-inflammatory activities and ROS. Ang II has been shown to activate immune cells and inflammatory processes, via nuclear factor-κB (NF-κB), and the powerful vasoconstrictive mediator endothelin-1 [18]. Further, Ang II infusion elicits an accumulation of effector immune cells in the vasculature [16], and mediates ROS production, vascular hypertrophy, and infiltration of monocytes and Mφ into the tissues that heavily express cellular adhesion molecules [19]. Of note, it is unclear whether inflammation directly stimulates the production and secretion of peptides associated with the renin-angiotensin system, such as angiotensinogen from the liver or renin from kidneys.

Endothelial Participation in Immunity

The vascular endothelium provides a protective barrier for associated organs by separating blood from the tissue compartments. EC perform this important function by acclimating to the needs of the specific tissues in which they reside and regulate the passage of solutes. Activated EC provide inflammatory cues that lead to immune cell activation (i.e., innate and adaptive) and extravasation (i.e., movement of immune cells into tissues from blood vessels), vascular inflammation, and ultimately hypertension [20]. The endothelium participates in many immune-regulated disorders, including but not limited to, sepsis and infection, atherosclerosis, diabetes, vasculitis, and systemic hypertension [21]. Pate et al. [21] has outlined the interactions of the endothelial boundary with infectious, inflammatory, and coagulation pathways. Chronic activation of NF-κB leads to EnDy that is characterized by increased immune cell adhesiveness, a procoagulant state, impairment of vasodilation, and decreased production of NO [22]. These actions are characterized by increased cell adhesion molecule expression, ROS, and pro-inflammatory cytokine production by EC that lead to diminished vascular compliance. NO, itself, has been shown to be a mediator of inflammation through its inhibition of adhesion molecule interactions between EC, circulating leukocytes, and inhibition of platelet aggregation [23]. For example, NO donation in a severe EnDy atherosclerosis mouse model was shown to significantly reduce ROS and vascular inflammation [24].

Endothelial Cell Activation and Immune Cell Interactions

EC activation has been thoroughly described by Pober and Sessa [25]. They elegantly explain the mechanisms of type I and type II activation of EC in acute inflammation, their participation in chronic inflammation, and the endothelial intracellular events that lead to the migration and activation of effector immune cells. Under normal resting circumstances, EC do not interact with peripherally circulating immune cells because they store immune activating proteins within intracellular vesicles and suppress the transcription of adhesion molecules. However, they mediate essential interactions between immune cell types and ligand receptor interactions at the endothelial barrier, as well as participate in and promote the resolution of immune activities. EC activation is mediated through similar pathways as primary immune cells that ultimately activate NF-κB and activating protein-1 transcription factors [22, 26].

To offer a brief characterization of activation status, type 1 activation is facilitated by ligand stimulation of G-protein receptors, such as histamine-1 receptors that are activated in an allergic response, which causes increased Ca^{2+} signaling and leads to recruitment and extravasation of effector immune cells (e.g., neutrophils, T cells, monocytes) to the vascular tissue. This occurrence is transient as G-coupled protein receptors lose their sensitivity and ability to be repeatedly stimulated. However, a more sustained EC activation (type II), is mediated by exogenous pro-inflammatory cytokines (i.e., TNF-α and IL-1β) which activate the powerful pro-inflammatory transcription factors NF-κB and activating protein-1 that initiate

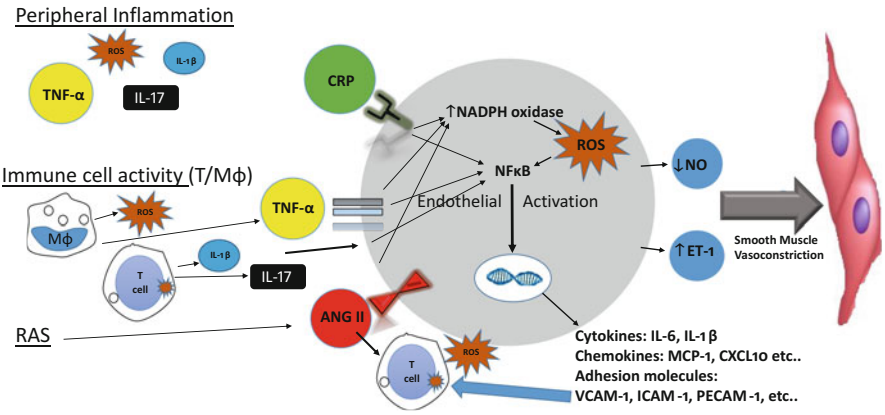

Fig. 14.2 Endothelial immune activation and outcomes. Adapted from Cook-Mills & Deem [20], Pate et al. [21], Frey et al. [29], and Pober and Sessa [25]. Endothelial activation as it is affected by peripheral inflammatory stimuli (cytokines), immune cells and their products of activation (Macrophages—Mφ; T cells) and components of renin-angiotensin system (Ang II). Once the endothelial cell is activated (acutely or chronically) it participates in a cycle that reduces NO bioavailability, through increased ROS production and reduced eNOS expression & activity, and reduced vascular compliance (increased EC endothelin-1 secretion). Angiotensin II (Ang II), cellular adhesion molecules (ICAM-1, VCAM-1, PECAM-1), chemokines (monocyte chemoattractant protein-1; MCP-1, C-X-C motif 10; CXCL10), c-reactive protein (CRP), endothelin-1 (ET-1), interleukins (IL-1β, 6, 10, 17), nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase), nitric oxide (NO), nuclear factor-κB (NF-κB), reactive oxygen species (ROS), tumor necrosis factor (TNF-α)

the synthesis of pro-inflammatory proteins (e.g., chemokines, cytokines, adhesion molecules) (Fig. 14.2). Activation of EC with TNF-α and IL-1β is also responsible for the induction of plasma protein leakage and rearrangement of tight junction proteins leading to gaps between adjacent EC [27].

EC express inflammatory mediators upon stimulation with peripheral cytokines or interaction with immune cell types such as intracellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), platelet endothelial cell adhesion molecule-1, endothelial-leukocyte adhesion molecule (known as E-selectin), platelet adhesion molecule (known as P-selectin), cytokines (i.e., TNF-α, IL-1β, and IL-6), and chemokines [C-X-C Motif Chemokine 10 (L10), Receptor 3 (R3)] [25]. These peptides, proteins, and receptors regulate the EC immune activation state and interaction with peripheral immune cells. They also lead to activation and polarization of the effector immune cell response. Direct interaction between EC and lymphocytes has been thoroughly outlined by Cook-Mills and Deem [20]. EC participate in the migration and extravasation of T cells and this activity further triggers EC inflammatory actions. This process entails receptor/co-receptor interactions between immune cells and activated EC via cell adhesion molecules that facilitates immune cell migration across the endothelial barrier into the tissue. Extravasation of lymphocytes occurs through cytokine stimulation and VCAM-1 activation of endothelial cell nicotinamide adenine dinucleotide phosphate

(NADPH) oxidase. This then activates intracellular signals that modulate tight junction proteins, thereby causing substantial and prolonged gap formation to allow cellular passage [28, 29].

Additionally, EC also express pattern recognition receptors (i.e., toll-like receptors, TLR) that aid in the function of its mechanical barrier properties and immune activities. TLR are important conserved membrane proteins that mediate inflammation by sensing foreign antigens and stimulating downstream pro-inflammatory responses (e.g., cytokine production, expression of co-stimulatory molecules) [30, 31]. The process of chronic inflammation disrupts normal vascular functions, reduces vascular compliance, and ultimately leads to hypertension.

Reactive Oxygen Species and Immune Functions

ROS is important for the activation and facilitation of systemic immune activities, such as proliferation and differentiation of immune cells, activation of pro-inflammatory gene transcripts (e.g., NF-κB, activating protein-1), cytokine production, and neutralization of ingested pathogens by phagocytes (i.e., Mφ) [32–35]. Although necessary for immune functions, inflammation-associated ROS play a significant role in the development of hypertension [34, 36]. ROS production stimulated by cytokines (i.e., TNF-α) is associated with compromised vascular repair, reduced endothelial nitric oxide synthase (eNOS) activity, increased vascular inflammation and inflammatory cell infiltration [37], and increased inflammatory endothelial microparticle production [38]. These detrimental activities of ROS potentiate EnDy and hypertension [39], promote sympathetic outflow, induce vasoconstriction, and cause sodium and volume retention in the kidneys [5]. Blocking NADPH oxidase 2 submit unit (NOX2), a primary superoxide generating enzyme T cell (adaptive immune cell), prevents TNF-α production [16] and translates into an attenuation of hypertension. Further, studies report that scavenging ROS with mitochondrial superoxide dismutase overexpression [40], mitochondrial superoxide dismutase mimetics [36], and blocking TNF-α [34] has been shown to mute elevated pressures in animal models of hypertension. Unfortunately, human clinical trials show mixed results where responses are limited [41, 42], show no effect of broad antioxidant supplementation in lowering blood pressure [43, 44], and/or can not specify a mechanism of action, such as a reduction in immune cell or EC ROS.

Immune Cell Interactions and Hypertension

Macrophages and Hypertension

Innate immunity is a vitally important participant in vascular homeostasis and immune function. Research has establish that Mφ have a substantial role in the pathology of hypertension as these cells have been shown to accumulate in the

kidney and the endothelium during times of vascular distress and damage. This accumulation has been shown to be instigated by modulators of elevated pressures via Ang II and high salt concentrations [16]. Aside from their indispensable protective immune activities, Mφ serve an important function in vascular remodeling and repair. They are integral producers of matrix metalloproteinases (MMP, proteases that are involved in the breakdown of the extracellular matrix), such as MMP-9 also known as gelatinase B, that facilitate the migration of cells which are essential for tissue homeostasis (i.e., EC, smooth muscle cells, immune cells). Dysregulation of Mφ activities is prevalent in atherosclerotic plaques and leads to plaque instability through amplified ROS driven activities, and the extent of vascular Mφ infiltrate directly corresponds to the degree of EnDy [45].

In animal models of hypertension, elegant studies have shown that diminishing Mφ migration to the kidney reduces vascular remodeling, EnDy, and ROS in response to Ang II-induced or salt sensitive hypertension [16]. Further, Wenzel et al. [46] showed that removing neutrophil and Mφ presence using genetic manipulation via Cre-Lox technology (can delete, insert, or translocate targeted genes), lead to a blunted blood pressure response, reduced adhesion molecule expression, EnDy, and ROS in Ang II infused mice. Harrison et al. [16] speculates that activated Mφ may have a substantial impact on neighboring cells and stimulate their activation causing increased production of ROS, chemokine, and cytokine production, and cell adhesion molecule expression which translates into a reduction in endothelium NO availability and vascular smooth muscle cell hypertrophy. Although the activities above may be deemed deleterious, Mφ have also been shown to provide protective actions during high salt diet induced hypertension. In this instance, Mφ accumulate in the subcutaneous space and regulate blood pressure by mediating the proliferation of the lymphatics which leads to a buffering of salt concentrations that augments fluid retention and blood pressure [47].

T Cells and Hypertension

The participation of T cells in the pathogenesis of hypertension has been intensely studied. In regards to vascular health, T cell activation is a significant contributor of inflammatory cues that stimulates ROS production in EC, the kidneys, and other immune cells (innate and adaptive) that drive EC function or dysfunction. Harrison et al. [3] detailed the early studies that support the role of adaptive immunity in hypertension and expose the extent to which T cells participate. As early as the 1960s, investigators found that suppressing the immune system attenuated blood pressure in rats [48]. It was also shown that anti-thymocyte serum [49] and immunosuppressant drugs [50] lower blood pressure in the spontaneously hypertensive rat. Later, investigators revealed that depressed T cell function is apparent in the spontaneously hypertensive rat model and upon restoration of T cell function by engraftment of a normal thymus into the spontaneously hypertensive rat, blood pressure was significantly lowered [51].

Quiroz et al. [52] provides a short review of the studies investigating the role of T cells in the pathogenesis of hypertension using genetically altered mouse models. In rodents with hypertension (i.e., salt sensitive, deoxycorticosterone acetate (DOCA), Dahl rats), studies have shown that suppression and/or deletion of certain populations of adaptive immune cells blunt blood pressure responses and vascular remodeling using Ang II infusion as a hypertensive stimulus. In a mouse model that is unable to generate mature and functional B and T lymphocytes, the rag1−/− knockout mouse, there is a diminished response to Ang II induced hypertension, less small artery remodeling and decreased ROS. In fact, the hypertensive response was restored after the adoptive transfer of T cells from control mice into rag1−/− mice [53], strengthening evidence for the role of T cell involvement in the onset of Ang II induced hypertension.

Crowley et al. [54] found that lymphocyte deficiency also led to significant reduction in kidney injury without affecting the expression of pro-inflammatory cytokines and showing enhanced eNOS and cyclooxygenase-2 expression in the kidney. Ang II-induced hypertension in *scid* mice, a strain which also lacks lymphocyte responses, have blunted blood pressure responses as well [52]. Further, Ang II has been shown to directly activate T cells [55]. Surprisingly, Hoch et al. [56] found that T cells endogenously produce physiological levels of Ang II that stimulate T cell NADPH oxidase and may drive TNF-α production. Meanwhile, both inhibition of angiotensin I-converting enzyme and scavenging ROS lowers TNF-α production from T cells [56].

It is important to note that not all T cells are alike. Meaning, they do not all promote inflammation and cause damage. T helper (Th) 1, 2, and 17 cells are the classic mediators of the pro-inflammatory response and assist adaptive immunity by stimulating B cells to produce stimuli-specific antibodies. Different subsets of T cells produce unique cytokines that regulate their protective roles and some have been implicated in vascular disease progression [2]. For instance, Ang II infused mice that lack IL-17 (i.e., IL-17$^{-/-}$ knock out), develop a blunted blood pressure response, attenuated ROS production, and preserved endothelium-dependent vasodilation [16]. Consequently, a key stimulus of IL-17 production is IL-6, which is chronically elevated in individuals with hypertension and is often shown to be excessively produced by dysfunctional EC in culture [38, 57].

On the other hand, regulatory T cells (Treg) govern immune tolerance to self-antigens and homeostasis of both innate and adaptive immune responses by producing cytokines which regulate the activity of Th1 and Th17 cells by suppressing pro-inflammatory cytokine production through secretion of the potent anti-inflammatory cytokine IL-10 [58]. Adoptive transfer of Treg into Ang II infused mice results in lowered systolic blood pressure, reduced small artery stiffness, reduced ROS, and depressed tissue CAM expression and immune cell infiltration in blood vessels all while enhancing the production of anti-inflammatory mediators (i.e., IL-10) of immune cells in the cortex of the kidney [2, 59, 60]. It has not been explicated whether IL-10 has additional functions in the vasculature, aside from moderating immune cell responses.

Effects of Exercise on Systemic Inflammation and Reactive Oxygen Species

Recently, Tousoulis et al. [61] provided a review on novel therapeutic strategies for the management of hypertension. While the authors briefly explain the effects of specific drug treatments, many of their side effects show marked improvements in ROS and inflammatory markers in addition to their blood pressure lowering effects. However, in lieu of the poor effective management of hypertension with multiple pharmacological interventions due to the in vivo variations of drug efficacy, research has been geared toward investigating invasive procedures such as carotid baroreceptor stimulation, renal ablation of sympathetic nerve activity, and even vaccination against angiotensin I and II. With the increased risk that would be associated with invasive procedures, it is imperative to continue building upon the robust justification for the implementation of exercise in the prevention and treatment of CVD and hypertension [62, 63].

Exercise and Its Benefits: The Paradox

There are distinct differences when comparing the effects of different intensities of acute (short-term or immediate) and chronic (long-term or training) exercise on immune function. It has been well established that a strenuous bout of acute exercise suppresses immune function and is directly responsible for increased ROS, while chronic strenuous exercise is associated with an increase in one's susceptibility to infection [64, 65]. Moderate intensity acute exercise elicits increases in circulating populations of immune cell subsets which has been suggested to increase immunosurveillance, while there is a decline in this same population of cells following strenuous acute exercise, where their function is also inhibited. Acute exercise also provides a physiological stress that increase stress hormones (i.e., cortisol), which is known to be immune-suppressive. Further, the pleiotropic cytokine IL-6, where circulating levels are high during acute and chronic inflammation, is also stimulated by exercise and is measurably responsible for the increase in circulating anti-inflammatory mediators [66–68]. However, the effects of moderate exercise have been shown to promote an anti-inflammatory phenotype in multiple tissue depots including the vasculature [62], protect against chronic systemic ROS, provide a physiological stress that is beneficial, and moderate the anti-inflammatory profile of immune cells while mediating overall healthy immune function [17, 69, 70] (see Table 14.1).

Exercise Training and Immune Function

Habitual exercise has been proven to beneficially modify contributing factors to CVD and hypertension. Studies have shown that exercise training reduces local and circulating inflammatory cytokines (e.g., CRP, TNF-α, IL-1β), and oxLDL, increased

Table 14.1 Summary of immune factors and immune cell participation in hypertension and exercise

Immune activating factors & cells	Hypertension	Exercise	
		Acute	Chronic
ROS	↑↑	↑	↓↓
			↑ Antioxidant machinery
Cytokines			
Pro-	↑ (TNF-α, IL-1β, IL-6, CRP)	↑ IL-6	↑ IL-6; ↓ (TNF-α, IL-1β, IL-6, CRP)
Anti-			↑ IL-10, IL-1ra, sTNFr
CAM's	↑ (ICAM, VCAM)	?	↓↓
TLR's	??	↔	↓↓
	Sedentary/obese: ↑	↑ Desensitization	
PPAR-γ	↓	↑	↑↑
	↑ Atherosclerotic plaques		
AMPK	??	↑	↑
	↓ Pulmonary hypertension		
Immune cell types			
Mφ			
M1	↑ Classically Activated Mφ	?	↓ Pro-inflammatory
M2	?? Alternatively Activated Mφ	?	↑ Anti-inflammatory
T_h1, T_h 17	↑↑	?	
T_{reg}	↔	↔	↑↑

↑ is increased, ↓ is decreased, ↔ is no change, ? is not clear or unknown, cellular adhesion molecules (ICAM-1, VCAM-1), c-reactive protein (CRP), interleukins (IL-1β, IL-1 receptor antagonist (ra), 6, 10), tumor necrosis factor-α (TNF-α), soluble TNF receptor (sTNFr)

production and circulation of anti-inflammatory markers (e.g., IL-10, soluble TNF receptor, and IL-1ra), boosts peripheral and cellular antioxidant capacity (e.g., catalase and superoxide dismutase), and elicits a reduction in the expression of receptors and mediators of endothelial immune activation (e.g., ICAM-1 and VCAM-1) on EC and immune cells [62, 71, 72]. Further, the protective effects of exercise seem to be primarily mediated by reducing tissue specific inflammation (i.e., endothelium, adipose tissue) which aids in the promotion of a systemic anti-inflammatory phenotype of EC and immune cells associated with these tissues [64, 65].

To appropriately relay some of the measurable benefits of exercise on immune function, it is important to briefly review how regular physical activity is protective against the development of chronic inflammatory diseases which as described previously includes hypertension. This involves exploration of the effects of exercise in tissues, which elicit these systemic anti-inflammatory properties. Gleeson et al. [72] focused their review on a few mechanisms by which exercise is anti-inflammatory that include: fat depot reduction, muscle synthesis and release of IL-6, local and peripheral alterations in the expression of proteins that regulate immune interactions and activation, and phenotype switching of immune cell populations within tissues and the circulation.

In the context of EnDy, hypertension, and chronic systemic inflammation, it is important to mention that: (1) exercise of sufficient intensity and volume promotes a reduction in visceral fat mass. This adipose depot produces a substantial amount of pro-inflammatory mediators [73] that drive the activation and migration of inflammatory monocytes and lymphocytes to the tissue and prompt chronic systemic inflammation; (**2**) exercise elicits an increased production and release of anti-inflammatory cytokines from contracting skeletal muscle (IL-6). A short-lived increase in peripheral IL-6 levels after exercise is a potent stimulant of the consequent increase in circulating anti-inflammatory cytokines (e.g., IL-10, IL-1ra, and soluble TNF receptor). These are products of both innate (i.e., Mφ) and adaptive (i.e., T cells, Treg) immune cells that subsequently down-regulate inflammation [66, 67]; (3) exercise inhibits the expression of cell adhesion molecules in vascular tissue and immune cells, therefore mediating the capacity of effector monocytes and T cells to migrate to effector tissues and sustain inflammatory responses [64]; (4) exercise modulates the release of glucocorticoids (e.g., cortisol and adrenaline) which are known to significantly modify immune cell activities [74]. It is well known that chronic stress has deleterious health effects that exacerbate pro-inflammatory diseases while suppressing normal immune function. Exercise training optimizes oscillations in glucocorticoid release which is predicted to be responsible for the adaptations that ameliorate chronically elevated hormonal stress levels; (5) exercise reduces the expression of TLR on Mφ as well as TLR ligand-stimulation of pro-inflammatory cytokines [64]. There is evidence that TLR may be involved in chronic inflammation associated with a sedentary lifestyle [31]; and (6) exercise also provokes phenotype switching of Mφ and T cells to an anti-inflammatory phenotype [75]. For instance, this process initiates decreases in pro-inflammatory cells (i.e., Th17 cells) and increases in circulating Treg [76, 77], therefore promoting a systemic anti-inflammatory phenotype and supporting an antihypertensive environment. See Table 14.1 for a summary of the beneficial effects of exercise on immune function.

Unfortunately, there is not a substantial body of literature that characterizes the responses mentioned above in individuals with hypertension. There is a need for a more complete picture describing the inflammatory status, systemic and vascular, in individuals with hypertension. For instance, it would be clinically relevant and helpful to better understand simple phenomenon such as the activation state of circulating immune cell populations along with a characterization of the ratio of innate to adaptive immune cell populations at differing stages of hypertension to better characterize inflammatory burden. For example, De la Fuente et al. [78] are one of the few that have reported on the interactions of hypertension, immune function, oxidative stress, and exercise in aged women. The reduction in vasoactive peptides (e.g., endothelin-1) and overall systemic antioxidant effects of exercise has been relayed by Beck et al. [79, 80] in young adults with prehypertension and the effects of exercise on circulating inflammatory markers and vascular function in those highly predisposed to hypertension per Heffernan et al. [81] and Cook et al. [82].

Distinct Mechanisms Involved in the Anti-inflammatory Effects of Exercise

Reactive Oxygen Species and Exercise

As previously discussed, ROS has an integral role in inflammatory processes. There are substantial differences in the immune response to acute and habitual exercise behaviors in relation to ROS production. Sporadic acute exercise is known to promote ROS formation and cause cellular damage while habitual exercise is well documented to reduce ROS. Novel research has illuminated the positive role of the production of ROS during exercise as a key regulator in the advantageous adaptations to exercise. Gomez-Cabrera et al. [83] and Scheele et al. [84] review evidence generated by themselves and others that regular exercise induces ROS which activates an inflammatory response via NF-κB that increases gene expression of cytokines (e.g., IL-6) and upregulates signaling cascades that lead to sustained endogenous expression of important antioxidant enzyme defense mechanisms (e.g., mitochondrial superoxide dismutase, catalase, and glutathione peroxidase). Consequently, blocking ROS during exercise in animals and humans reduces the protective role that exercise has in upregulating endogenous antioxidant capacity. Therefore, the stimulation of ROS during exercise is an essential mechanism by which exercise training facilitates the boost of antioxidant defense.

Peroxisome Proliferator-Activated Receptor-gamma

A key mechanism by which exercise may directly influence vascular ROS production is through its effects on PPAR-γ expression. oxLDL stimulate ROS production in EC. Effective ways of clearing free-fatty acids from the blood stream are necessary to promote vascular homeostasis and reduce this source of ROS production by the endothelium. PPAR-γ is a receptor that mediates the uptake of circulating lipids [85, 86] which is a functional process that occurs in human EC [87] and has direct anti-inflammatory effects on immune cells [88]. PPAR-γ expression has been shown to be increased in atherosclerotic plaques which has been suggested to be a compensatory mechanism to manage local lipid accumulation [89]. PPAR-γ activity reduces vascular and systemic inflammation in vivo [90] and improves endothelial function by reducing apoptosis of endothelial progenitor cells [91]. Further, some angiotensin receptor blocking drugs such as telmisartan, have been shown to facilitate an increase in PPAR- γ expression [92]. Fortunately, exercise also (low to moderate intensity) has favorable effects on PPAR-γ expression that lead to decreased systemic inflammation [93]. Exercise increases immune cell PPAR-γ activity [94] and prompts decreases in the inflammatory response in EC [89], therefore bolstering the anti-inflammatory benefit of exercise within the vasculature and moderating ROS stimulated by oxLDL. Evidence does show that reduced PPAR-γ activity is a

phenotype in pulmonary hypertension [95, 96]. However, it has yet to be definitively proven that depressed PPAR-γ expression and activity in immune cells or EC is a phenotype involved in the pathogenesis of EnDy and peripheral hypertension.

Adenosine Monophosphate-Activated Protein Kinase

AMPK activation is another mechanism by which exercise stimulates and promotes systemic anti-inflammatory effects [97–99]. AMPK is activated by signals that are sensitive to energy deprivation in the cell (↑ ratio of AMP/ATP). Thus, AMPK is important in addressing energy demands by altering cellular metabolism to conserve and replenish energy. Exercise has been shown to be the most powerful stimulus in promoting AMPK upregulation along with its consequential anti-inflammatory effects [100]. Pharmalogical stimulation of this pathway with 5-aminoimidazole-4-carboxamide ribonucleotide (known as AICAR), which is an analog of adenosine monophosphate that can activate AMPK and is considered an exercise mimetic, has both endothelium independent and dependent arterial vasodilatory effects as shown in animal models of hypertension [101], and is associated with drastic improvements in EnDy [102]. The anti-inflammatory mechanism of action of AMPK, in part, consists of its inhibitory effects on pro-inflammatory pathways upstream of and reduced NF-κB activation. In immune cells, AMPK stimulation is associated with reduced TLR-4 induced activation of neutrophils [98] and Mφ [103]. Although AMPK activity is transiently increased following acute exercise [104, 105], exercise training is what maintains the beneficial anti-inflammatory phenotype in cells and tissues (i.e., cardiovascular, skeletal muscle, adipose, immune cells) [99, 100].

Additionally, AMPK activation has also been shown to be initiated by glucocorticoid stimulation [106], and exercise elicits increases in circulating glucocorticoids, relative to intensity [107]. Importantly, glucocorticoids themselves utilize a multitude of pathways to promote an anti-inflammatory phenotype in immune cells through the upregulation of anti-inflammatory proteins and down-regulation of pro-inflammatory proteins, all while being an important mediator in the development and homeostasis of immune cells [108–111]. Thus, the interconnected pathways by which exercise promotes this systemic anti-inflammatory phenotype (↑ AMPK) is, at best, complicated but necessary to continue to explore in the context of EnDy and hypertension.

Clinical Implications and Importance

Maintaining Immune Health

The position statement on exercise and maintenance of immune function has reviewed evidence for the importance of exercise in preserving healthy immune function [64, 65]. The beneficial effects of moderate intensity exercise and detrimental effects

of strenuous exercise have on immunity have been intensely reviewed and outlined. Although there have been no specific exercise recommendations for maintaining healthy immunity in adults with hypertension, implementation of the physical activity guidelines that maintain healthy immune function in these position statements from Walsh et al. [64, 65], superimposed with the recommendations for adults with hypertension mentioned throughout this book, would be highly effective in reducing the inflammatory burden and cellular dysfunction that participates in the pathology of this chronic condition. However, patient populations with EnDy and hypertension are in dire need of systematic clinical and experimentally controlled investigations that will provide evidence-based physical activity guidelines that would substantially improve their immune health. Trials are also necessary because there is no consensus of the varying degrees of inflammatory burden this population may have. In general, the consensus for exercise considerations in the maintenance of healthy immune function are to perform exercise at a low to moderate intensity and to avoid prolonged exercise sessions (>1.5 h) of moderate to high intensity, which may increase physiological stress and suppress immune function.

Conclusion

EnDy perpetuates a feed forward cycle of NF-κB activation and EC immune activation that is characterized by increased pro-inflammatory cytokine production establishing the endothelium as a tissue depot that can promote systemic inflammation. While the beneficial systemic and cardio-protective effects of exercise are not fully understood, we do know the positive effects that exercise has on the immune system as being overall anti-inflammatory, reducing ROS [83], and most importantly depressing morbidity and all-cause mortality associated with CVD, including hypertension [62]. Cellular mechanisms that highlight the effect of exercise on anti-inflammatory cascades such as those briefly mentioned above (PPAR-γ and AMPK activity) may only be the tip of the iceberg in regards to chronic inflammatory diseases.

In relation to hypertension, there is a distinct gap in the research concerning the mechanistic interactions between exercise and immune activities related to the pathogenesis, and to some extent, the mitigation of hypertension. It is important that we efficiently utilize what has been proven about the systemic and cellular effects of exercise in shaping treatment strategies to alleviate the burden of hypertension. For instance, there is still a substantial need to explore the role PPAR-γ and AMPK may have in the pathogenesis and progression of EnDy and hypertension. It is well know that altered activity of enzymes and proteins such as these are directly related to the onset and progression of multiple diseases in which exercise is effective in altering activity of these pathways and improving health status [7, 100]. Concerning endothelial dysfunction and hypertension, rigorous in vitro and in vivo investigations are essential to uncover hidden mechanisms by which exercise improves EnDy in the scope of immune activities within the vasculature and effector organs.

Key Points and Resources

- Chronic inflammation potentiates vascular dysfunction at the level of the endothelium.
- Immune cell subsets (i.e., Mφ and T cells) have distinct roles in the pathogenesis and pathology of hypertension.
- The anti-inflammatory effects of habitual low to moderate intensity exercise significantly modifies contributing factors of CVD and hypertension by reducing circulating pro-inflammatory cytokines and oxLDL, while increasing circulating anti-inflammatory mediators and systemic antioxidant capacity. Exercise also reduces pro-inflammatory ligand (i.e., TLR) and adhesion molecules (i.e., ICAM-1, VCAM-1) on both immune cells and EC.
- Research addressing the effects of exercise in individuals with hypertension that characterize inflammatory burden is severely limited and essential to provide effective therapeutic pharmacological and lifestyle treatment options such as exercise for the resolution of hypertension.
- The American College of Sports Medicine: http://www.acsm.org/ for access to ACSM certified news regarding exercise immunology http://certification.acsm.org/files/file/CNews22_3pp4_webready.pdf
- International Society of Exercise Immunology: http://www.isei.dk/index.php?pageid=3 for access to the Exercise Immunology Review journal.
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ERRATUM

Effects of Exercise on Hypertension

Linda S. Pescatello

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Molecular and Translational Medicine, DOI 10.1007/978-3-319-17076-3

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The original version of this book was inadvertently published with incorrect acknowledgements. The publisher would like to apologize for this mistake. The original versions have been corrected accordingly online and in print (see DOI 10.1007/978-3-319-17076-3).

Michael Brown, Ph.D., F.A.C.S.M., F.A.H.A.

I became interested in hypertension when I did an internship in cardiac rehabilitation. I was able to sit in the cardiologists' meetings in which they discussed their patients' cases. I noticed a trend, most of the patients had hypertension. A bit later, I learned that African Americans had the highest prevalence of hypertension in the United States and that at the time, there were no studies on the effects of exercise on hypertension in African Americans. My mission crystallized at that point.

The online version of the original book can be found at
http://dx.doi.org/10.1007/978-3-319-17076-3

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Being accepted into the doctoral program at the University of Maryland College Park gave me the opportunity to train under Dr. James Hagberg. The research he was doing in exercise and hypertension was a fertile training environment for me. Under his mentorship, I received a National Institutes of Health predoctoral training grant. The grant was on the effects of short-term daily aerobic exercise on insulin sensitivity in African Americans with hypertension and led to my first author publication in the journal Hypertension. I completed a postdoctoral fellowship at the University of Michigan, Department of Internal Medicine, Division of Geriatric Medicine, under the mentorship of Dr. Mark Supiano and Dr. Don Dengel. The general focus of our research was age-associated Hypertension and specifically mechanisms of hypertension such as insulin resistance, sympathetic nervous system activity, and sodium sensitivity. Under the guidance of Drs. Supiano and Dengel and the tremendous resources at the University of Michigan, I greatly expanded my research techniques and fine-tuned my experience with conducting exercise training studies. My work has continued to evolve and now includes basic science experiments in endothelial cells.

Throughout my career, I have been fortunate to learn and collaborate with scientists that helped to shape my career. Dr. Joon Park, first my doctoral student, is now a leading researcher on the effects of shear stress on mitochondrial function as it relates to endothelial dysfunction. Dr. Park is a superb young scientist who brought me into the area of endothelial cell research. Dr. Robert Ferrell, a noted geneticist, was a mentor on my National Institutes of Health Career Award. I learned a great deal from Dr. Ferrell and valued his support. Dr. Matthew Weir, a nephrologist and leading expert on renal mechanism of hypertension, was also a mentor of my Career Award. Dr. Weir helped me to sharpen my focus, and I always appreciated his support of exercise research. Dr. Steve Houser, an eminent cardiovascular scientist, was important during the middle stages of my career as he provided invaluable guidance and insight on both research and career development matters. Lastly, I want to thank Dr. Bo Fernhall for giving me the opportunity to continue to evolve my career in the Department of Kinesiology and Nutrition at the University of Illinois at Chicago. To all of these individuals and others I did not mention, I am forever grateful for your support.

Michael's Dedication

I dedicate this book to two people for without them I would not be in a position to contribute to this book. My mother, Ferne Brown, has been there for me through the ups and downs. My first mentor, Dr. James Hagberg, set me on a path of success for which I will always be grateful. We would also like to thank Gregory Tsongalis, Ph.D., from the Dartmouth Hitchcock Medical Center, who facilitated our communications with the publisher, and Patrick Carr at Springer US/Humana in shepherding this book to print, as well as the many dedicated staff who had a part in making this book an important contribution to the field of exercise and hypertension.

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