Acute and Chronic Effects of Resistance Training on Arterial Stiffness in Healthy Adults

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Chapter 1 *Summary*

Aerobic exercise training has been shown to have favorable effects on arterial stiffness. Resistance exercise training has beneficial effects on muscular strength and power. However, its effect on vascular function, in particular arterial stiffness is less certain. A literature review regarding the effects of aerobic and resistance exercise training on arterial stiffness in normotensive and hypertensive adults is presented in **paper 1**. Our review shows that exercise training has varying effects on arterial stiffness depending on the exercise modalities. Aerobic exercise training is more likely to have a beneficial effect on arterial stiffness in normotensive and hypertensive patients, but does not affect arterial stiffness in patients with isolated hypertension. Resistance exercise seems to have no adverse or even beneficial effect on arterial stiffness if the training is of low intensity, in a slow eccentric manner or with lower limbs. However, vigorous concentric resistance exercise increases arterial stiffness in healthy individuals and thus should be avoided in populations with an increased cardiovascular risk. Combined training with resistance training first, followed by endurance training, has neutral or even beneficial effects on arterial stiffness based on limited number of studies available. However, the existing evidence does not allow firm conclusions. The interpretation is hampered by the use of different measures of arterial stiffness, varying exercise programs (modality, duration, intensity and frequency), different population-based variables (age, health status) and several confounding factors (e.g. exercise induced weight loss, daily physical activity, diet, medication). Further longitudinal interventional studies are needed to definitively rule out the effects of confounding factors on arterial stiffness and give conclusive answers to the true effect of aerobic as well as resistance exercise training on arterial stiffness in individuals with and without hypertension.

Arterial stiffness is as an emerging biomarker in the assessment of vascular health. The measurements of arterial stiffness have been recently widely used in sports and exercise medicine research settings to evaluate exercise-induced change in arterial function. However, if it is necessary to standardize the time of the day when performing these measurements is less certain. A methodological study which investigated the variation of the arterial stiffness during the daytime is presented in **paper 2**. We recruited males and females at a wide range of ages and involve both healthy individuals and patients with heart disease. We found that the novel method [cardio-ankle vascular index (CAVI)] and the traditional method [carotid-femoral pulse wave velocity (cfPWV)] were both repeatable. In this study, we demonstrated a lack of diurnal variation of cfPWV. However, there was shown to be a significant diurnal

variation in CAVI, indicative of pronounced vascular stiffening in the morning in healthy young and elderly individuals and patients with heart disease. Therefore, this methodological study provides support to initiate the measurement around the same time of day in order to minimize the diurnal variations in longitudinal studies.

On the basis of the literature review and the methodological study, resistance exercise with lower body seems to have no adverse or even beneficial effect on arterial stiffness. Therefore, we apply an intervention study comparing the acute effect of lower body resistance training (LRT) versus upper body resistance training (URT) on arterial stiffness; it is presented in **paper 3**. High intensity resistance training was recommended for maximizing muscular strength. Studies investigating the effect of acute high intensity resistance exercise on arterial stiffness employed a whole body resistance exercise (WRT) modality and consistently showed an increase in central arterial stiffness. Our study showed acute LRT and URT elicit different systemic arterial stiffness responses in healthy young men. While acute LRT is associated with a lower exercise-induced arterial stiffness than acute URT, differences between LRT and URT diminish within 60 min of exercise cessation. Our results may suggest that LRT should be preferred over URT or even WRT in individuals with impaired arterial stiffness, which may have implications for resistance exercise prescription from a cardiovascular perspective.

Traditional resistance training generally consists of muscular contractions performed at a relatively slow speed. Resistance training with higher velocity and lower intensity, which may result in differing effects on arterial stiffness has recently become more popular in rehabilitation. Resistance training may have no unfavorable effects on arterial stiffness if the training is in a slow eccentric manner. **A study protocol** of an intervention study comparing the chronic effect of resistance training with low intensity high velocity versus high intensity low velocity is presented in **paper 4**.

Chapter 2 *Introduction*

"Man is as old as his arteries."

William Osler

Arterial stiffness is an emerging biomarker in the assessment of vascular health (Laurent et al., 2012). Arterial compliance is the ability of an artery to expand and recoil during cardiac contraction and relaxation while arterial stiffness is the inverse (Nichols et al., 1998). Arterial stiffness is determined by the functional (endothelium, smooth muscle cells) and structural components (elastin, collagen and connective tissue). It is a function of the structure of an artery and may be modified more rapidly or slowly depending on which component is influenced by exercise training (Green et al., 2011; Green et al., 2013; Tinken et al., 2010). Arterial stiffness increases with advancing age in healthy normotensive adults (Vaitkevicius et al., 1993) and hypertensive patients (London et al., 1989). Arterial stiffening with age is more pronounced in central aortic arteries than peripheral muscular arteries (Avolio et al., 1985; Nichols et al., 1998; Wilkinson et al., 2001). Large artery stiffening is independently associated with cardiovascular events and all-cause mortality (Karras et al., 2012; Vlachopoulos et al., 2010; Vlachopoulos et al., 2012; Ben-Shlomo et al., 2014).

There are various techniques for assessing arterial stiffness. The regional and local arterial stiffness can be measured as follows: carotid arterial compliance and carotid β-stiffness index; central arterial stiffness measured as carotid-femoral pulse wave velocity (cfPWV),; peripheral arterial stiffness measured as carotid-radial pulse wave velocity (crPWV), femoral-ankle pulse wave velocity (faPWV), femoral-dorsalis pedis pulse wave velocity (fdPWV); systemic arterial stiffness measured as brachial-ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI). Standardized reference values have recently been published by the "Reference Values for Arterial Stiffness Collaboration" for cfPWV (Mattace-Raso et al., 2010). A higher value of pulse wave velocity, β-stiffness index, CAVI or lower value of arterial compliance denotes a stiffer artery. An increase in cfPWV and baPWV by 1 m/s has been shown to increase risk of cardiovascular events by 7% (Ben-Shlomo et al., 2014) and 12% (Vlachopoulos et al., 2012), respectively.

Therefore, lifestyle modifications aiming at the reduction of arterial stiffness are of great clinical importance. Physical activity is one of the most important lifestyle modifications.

Physical activity is defined as any bodily movement produced by skeletal muscle contractions resulting in a substantial increased energy expenditure above the basal level (Caspersen et al., 1985). Previous studies showed that an active lifestyle with regular physical activity is associated with reductions in cardiovascular disease risk in healthy individuals and patients with cardiovascular disease (Hakim et al., 1999; Sesso et al., 2000; Mons et al., 2014). However, the extreme daily strenuous physical activity may increase cardiovascular mortality in patients with coronary heart disease in a reverse J-shaped association (Mons et al., 2014) showing that the dose-response relationship is still a topic under debate.

Exercise is a physical activity that is planned, structured, repetitive, and purposeful (Caspersen et al., 1985). Exercise training has various effects on arterial stiffness according to its type, duration, frequency and intensity. There are two major types of exercise, aerobic and resistance exercise training. Aerobic exercise training has been defined by the American College of Sports Medicine (ACSM) as any activity that involves major muscle groups and is continuous and rhythmical in nature (Garber et al., 2011). Aerobic exercise has been shown to have favorable effects on cardiorespiratory function as well as on arterial stiffness (Madden et al., 2009; Parnell et al., 2002; Vaitkevicius et al., 1993; Vivodtzev et al., 2010). Resistance exercise training is defined as any activity that involves brief, repeated execution of voluntary muscle contractions against a load that is greater than those normally encountered in activities of daily living (Lee & Carroll, 2007). Resistance training has been suggested as a means of combating the muscular strength declines in a comprehensive exercise program by ACSM and AHA in recent years (Kraemer et al., 2002). However, while typically very effective at increasing muscle mass and strength, the effect of resistance training on arterial stiffness is less certain.

Cross-sectional studies demonstrated that resistance trained men have stiffer central (Miyachi et al., 2003) and peripheral (Bertovic et al., 1999) arteries than their sedentary age-matched peers. While high intensity resistance training was recommended for maximizing muscular strength (Ratamess et al., 2009; Garber et al., 2011), it was found to have unfavorable effects on arterial stiffness, resulting in an increased central arterial stiffness (Miyachi et al., 2004; Cortez-Cooper et al., 2005; Miyachi, 2013). However, this finding is not universal (Rakobowchuk et al., 2005; Okamoto et al., 2006; Casey et al., 2007; Okamoto et al., 2009). Studies investigating the effect of acute high intensity resistance exercise on arterial stiffness employed a whole body resistance training (WRT) and consistently showed an increase in

central arterial stiffness (DeVan et al., 2005; Heffernan et al., 2007). In contrast, peripheral arterial stiffness was unchanged after WRT (Heffernan et al., 2007). There is growing evidence that the effect of exercise training on vascular function differs between arms and legs (Poole et al., 2003; Newcomer et al., 2005). No study so far has assessed the comparative acute effects of LRT and URT in the same study population. In this study, we assessed differences between cardio-ankle vascular index (CAVI) and baPWV in response to a single session of supervised LRT, URT and WRT for healthy young men. We hypothesized that LRT is associated with lower exercise-induced arterial stiffness compared with URT and WRT. Acute exercise-induced change in arterial stiffness in response to lower body versus upper body resistance training has not been investigated.

Further, based on our previous review study, resistance exercise has no unfavorable effects on arterial stiffness if the training is in a slow eccentric manner. Okamoto et al (Okamoto et al., 2006) found that eccentric resistance training seemed to have a neutral effect on arterial stiffness, while concentric training increased arterial stiffness. Therefore, we believe that resistance training with a reduced or shortened concentric phase might be beneficial from the cardiovascular perspective. Power resistance training, whose concentric phase is as fast as possible, might cause less or no impairment of arterial stiffness because of a lower vasopressor response and could be thus a prospective resistance training mode to increase greater muscle power (Fielding et al., 2002) without arterial stiffening. It is not well established whether healthy young and middle-aged adults would gain the similar benefits on arterial compliance using the recommended guidelines program for increasing muscle strength following conventional training (Kraemer et al., 2002; Leszczak et al., 2012; Raj et al., 2012) or for increasing muscle power (Fielding et al., 2002; Leszczak et al., 2012; Porter, 2006) following high velocity training. Furthermore, it is also unknown whether the hemodynamic mechanism of response to high velocity low intensity resistance training and low velocity high intensity resistance training are different. Thus, there is an explicit need of longitudinal randomized controlled trials for assessing and determining the effects of the two resistance training modes on arterial stiffness in healthy young and middle-aged adults, which may contribute to the exercise prescription with particular respect to cardiovascular function in different populations.

This thesis will begin by reviewing the literature examining the changes in arterial stiffness with different resistance exercise training modalities. A methodological study exploring the

diurnal variation and repeatability of two arterial stiffness measures will then be presented. These will be followed by an intervention study comparing the acute effects of lower body versus upper body resistance training in healthy young adults. Finally, a study protocol comparing the high velocity low intensity versus low velocity high intensity resistance training on arterial stiffness will be presented.

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Chapter 3 *Original research*

3.1 Paper 1.

Aerobic, resistance and combined exercise training on arterial stiffness in normotensive and hypertensive adults: a review

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Aerobic, resistance and combined exercise training on arterial stiffness in normotensive and hypertensive adults: A review

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REVIEW ARTICLE

Aerobic, resistance and combined exercise training on arterial stiffness in normotensive and hypertensive adults: A review

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Abstract
Exercise training has different effects on arterial stiffness according to training modalities. The optimal exercise modality for improvement of arterial function in normotensive and hypertensive individuals has not been well established. In this review, we aim to evaluate the effects of aerobic, resistance and combined aerobic and resistance training on arterial stiffness in individuals with and without hypertension. We systematically searched the Pubmed and Web of Science database from 1985 until December 2013 for relevant randomised controlled trials (RCTs). The data were extracted by one investigator and checked by a second investigator. The training effects on arterial stiffness were estimated using weighted mean differences of the relative changes (%) with 95% confidence intervals (CIs). We finally reviewed the results from 17 RCTs. The available evidence indicates that aerobic exercise tends to have a beneficial effect on arterial stiffness in normotensive and hypertensive patients, but does not affect arterial stiffness in patients with isolated systolic hypertension. Resistance exercise has differing effects on arterial stiffness depending on type and intensity. Vigorous resistance training is associated with an increase in arterial stiffness. There seem to be no unfavourable effects on arterial stiffness if the training is of low intensity, in a slow eccentric manner or with lower limb in healthy individuals. Combined training has neutral or even a beneficial effect on arterial stiffness. In conclusion, our review shows that exercise training has varying effects on arterial stiffness depending on the exercise modalities.

Keywords: *Exercise, cardiovascular, health, ageing, lifestyle*

Introduction

Arterial stiffness is as an emerging biomarker in the assessment of vascular health (Laurent, Alivon, Beaussier, & Boutouyrie, 2012). Arterial stiffness increases with advancing age in healthy normotensive adults (Vaitkevicius et al., 1993) and hypertensive patients (London, Marchais, & Safar, 1989). Large artery stiffening is independently associated with cardiovascular events and all-cause mortality (Karras et al., 2012; Vlachopoulos, Aznaouridis, & Stefanadis, 2010; Vlachopoulos, Aznaouridis, Terentes-Printzios, Ioakeimidis, & Stefanadis, 2012). Hypertension has become the leading cause of cardiovascular disease and all-cause mortality (Chow et al., 2013; Danaei et al., 2011; Kearney et al., 2005). The relationship between hypertension and arterial stiffness may be bi-directional (Franklin, 2005). In contrast to conventional understanding, a recent study showed that aortic stiffness may be a precursor of hypertension, rather than being the result of high blood pressure (Kaess et al., 2012). Given that arterial stiffness is a precursor of hypertension, lowering blood pressure alone is not enough to decrease cardiovascular risk. Therefore, lifestyle modifications aiming at the reduction of arterial stiffness are of great clinical importance.

Exercise training is an important component of lifestyle modification. There are two major types of exercise, aerobic and resistance exercise training. Aerobic exercise training has been defined by the American College of Sports Medicine (ACSM) as any activity that involves major muscle groups and is continuous and rhythmical in nature (Garber et al., 2011). Resistance exercise training is defined as any activity that involves brief, repeated execution of voluntary muscle contractions against a load that is

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greater than those normally encountered in activities of daily living (Lee & Carroll, 2007).

Although the blood pressure lowering effect of exercise training has been widely accepted (Cornelissen & Smart, 2013), the effect of exercise training on the vascular system is not fully clarified. Previous studies showed that an active lifestyle with regular physical activity is associated with reductions in cardiovascular disease risk in healthy individuals and patients with cardiovascular disease (Hakim et al., 1999; Mons, Hahmann, & Brenner, 2014; Sesso, Paffenbarger, & Lee, 2000). However, the extreme daily strenuous physical activity may increase cardiovascular mortality in patients with coronary heart disease in a reverse J-shaped association (Mons et al., 2014).

When examining the time course of exercise-induced change on vasculature, shear stress flow-mediated vasodilatation (FMD) was initially altered, followed by other functional and structural adaptations. Arterial compliance is the ability of an artery to expand and recoil during cardiac contraction and relaxation, while arterial stiffness is the inverse (Nichols, O'Rourke, Hartley, & McDonald, 1998). Arterial stiffness is determined by the functional (endothelium, smooth muscle cells) and structural components (elastin, collagen and connective tissue). It is a function of the structure of an artery and may be modified more rapidly or slowly depending on which component is influenced by exercise training (Green et al., 2013; Green, Spence, Halliwill, Cable, & Thijssen, 2011; Tinken et al., 2010). However, the studies investigating the effect of exercise training on arterial stiffness were less uniform. Previous cross-sectional studies showed that aerobic training is associated with improved arterial stiffness (Otsuki et al., 2006; Sugawara et al., 2006; Tanaka et al., 2000), whereas resistance training is associated with an increase of arterial stiffness (Bertovic et al., 1999; Miyachi et al., 2003; Otsuki et al., 2006). However, the combination of aerobic and resistance training in rowers showed either no change (Kawano et al., 2012; Petersen et al., 2006) or improved arterial stiffness (Cook et al., 2006). These cross-sectional studies showed inconsistent results, but they do not suggest cause and effect between exercise and the change of arterial stiffness. Conclusive explanations for the underlying mechanisms are still lacking and the true relationship should be further analysed and confirmed in randomised controlled trials (RCTs). Thus, the aim of this review is to summarise the current evidence based on RCTs regarding the effect of exercise training with a duration >4 weeks on arterial stiffness in normotensive and hypertensive individuals.

Methods

Search methods

We systematically searched for RCTs investigating the effect of exercise training on arterial compliance published from 1985 to December 2013 in the PubMed and Web of Science database. Search terms included "aerobic training" OR "endurance training" OR "resistance training" OR "strength training" OR "weight training" OR "eccentric training" OR "concentric training" OR "exercise" AND "vascular stiffness" OR "arterial stiffness" OR "arterial compliance" OR "arterial stiffening". Abstract, case reports and articles not in English were not considered. The reference lists of published articles and reviews on the topic were checked to identify other eligible studies.

Criteria for study selection

Definition of hypertension. The definition of hypertension is based on recommendations by the American Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. According to the JNC-7 report (2003): prehypertension is defined as SBP ranging from 120–139 mmHg and/or DBP 80–89 mmHg. Hypertension is defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg. Isolated systolic hypertension (ISH) is defined as an elevated SBP of >140 mmHg with a normal (<80 mmHg) DBP (Chobanian et al., 2003).

Types of studies

We included RCTs that involved a non-exercise control group (parallel design) or a non-exercise control phase (cross-over design). The study subjects enrolled should be either healthy normotensive individuals or hypertensive patients without any significant comorbidities.

Types of interventions

RCTs prescribing aerobic or resistance or combined exercise training of at least 4 weeks were included as follows: (1) Aerobic exercise versus non-exercise control group/phase; (2) Resistance exercise versus non-exercise control group/phase; (3) Combined exercise (aerobic exercise plus resistance exercise) versus non-exercise control group/phase; (4) Aerobic, resistance exercise versus non-exercise control group/phase; (5) Aerobic, combined exercise versus non-exercise control group/phase; (6) Resistance, combined exercise versus non-exercise control group/phase; (7) Aerobic, resistance, combined exercise versus non-exercise control group/phase.

Types of outcome measures

There are various techniques for assessing arterial stiffness. We included studies using regional and local arterial stiffness measured as primary or secondary outcome in our review. In particular these were as follows: central arterial stiffness measured as carotid-femoral pulse wave velocity (cfPWV), carotid arterial compliance and carotid β-stiffness index; peripheral arterial stiffness measured as carotid-radial pulse wave velocity (crPWV), femoral-ankle pulse wave velocity (faPWV), femoral-dorsalis pedis pulse wave velocity (fdPWV); systemic arterial stiffness measured as brachial-ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI). Standardised reference values have recently been published by the "Reference Values for Arterial Stiffness Collaboration" (Mattace-Raso et al., 2010). A higher value of pulse wave velocity, β-stiffness index, CAVI or lower value of arterial compliance denotes a stiffer artery. An increase in cfPWV and baPWV by 1 m/s has been shown to increase cardiovascular mortality by 15% (Vlachopoulos et al., 2010) and 13% (Vlachopoulos et al., 2012), respectively.

Quality assessment

The quality of the included studies was assessed using the Jadad scale (Jadad et al., 1996), giving one point each for descriptions of randomisation, blinding, dropouts and appropriateness of randomisation and blinding. Blinding of the investigator administering the intervention and of the participants performing the exercise is almost impossible in exercise intervention trials. Therefore, the Jadad scale was slightly modified by giving one point for proper blinding of the outcome assessor. Since all studies had to be RCTs according to the inclusion criteria, the range of the Jadad score for the included studies in this review was one to five, with higher scores reflecting superior quality.

Data extraction

The following data were extracted: first author, year of publication, type of study design, characteristics of the study population (health status, age, sex), training programme (duration, frequency, intensity), study sample size, parameters of arterial stiffness, intervention effects (weighted mean difference of relative change with a 95% CI) and Jadad score. The training intensity of aerobic exercise was indicated as heart rate reserve (HRR), maximum heart rate (HR_{max}) or maximal oxygen consumption (VO_{2max}). The intensity of aerobic exercise was defined as follows: moderate, 40–59% heart rate reserve = 64–76% maximal heart rate = 46–63% maximal oxygen uptake; vigorous, 60–89% heart rate reserve = 77–95% maximal heart rate = 64–90% maximal oxygen uptake (Garber et al., 2011). The training intensity of resistance exercise was indicated as a percentage of 1 RM (one repetition maximum). The intensity was defined as follows: light, < 50% 1RM; moderate, 50–69% 1RM; vigorous, 70–84% 1RM (Garber et al., 2011). The primary outcome was resting arterial stiffness in the supine position.

Data synthesis

To summarise the effects of exercise training on arterial stiffness, we estimated the weighted mean differences (WMD) of the relative changes (%) with 95% CIs. We used relative changes in our analysis because the RCTs reviewed had used different arterial stiffness measures and units. The relative change in each group was calculated by subtracting the baseline value ($Mean_{pre}$) from the post intervention value ($Mean_{post}$), divided by the baseline value and multiplied by 100% {$Mean_{rc}$ = [($Mean_{post}$–$Mean_{pre}$)/$Mean_{pre}$] ×100%}; Variances were calculated from the standard deviation (SD) of the changes in the intervention and control group. If the SD of the change was not available, the formula $SD_c = \sqrt{[(SD_{pre})^2 + (SD_{post})^2 - 2 \times corr(pre, post) \times SD_{pre} \times SD_{post}]}$ was used for the calculation, for which we assumed a conservative correlation coefficient of 0.5 between the initial and final values (Cornelissen, Fagard, Coeckelberghs, & Vanhees, 2011; Follmann, Elliott, Suh, & Cutler, 1992). Statistical analysis was performed using the software Review Manager (RevMan 5.1; Cochrane Collaboration, Oxford, United Kingdom).

Results

Our literature search revealed 228 potentially relevant records, of which 36 met our inclusion criteria for outcome variables. Excluding 19 trials with non-random allocation to control group, the remaining 17 RCTs were included in the final analysis. Four RCTs consisted of two studies, therefore, 21 studies were separately reviewed (6 aerobic exercises, 11 resistance exercises and 4 combined aerobic plus resistance exercises). A flow chart of studies identified, included and excluded is shown in Figure 1. All studies used parallel group design except for one study using cross-over design. The characteristics and quality assessment of the included RCTs are shown in Table I.

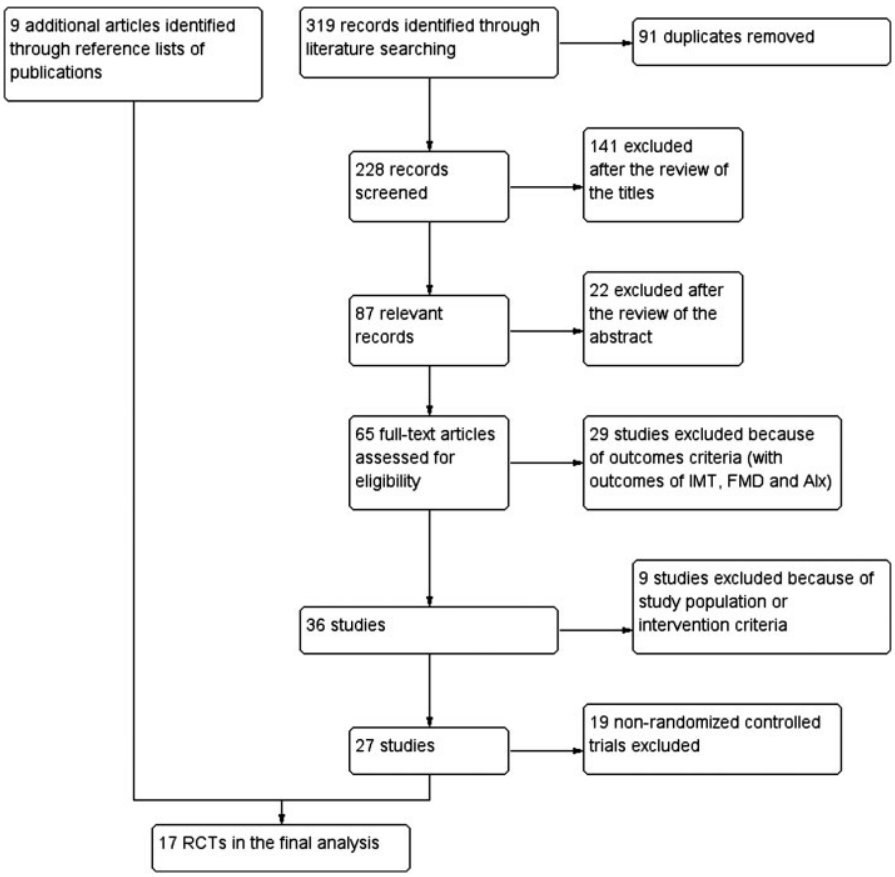

Figure 1. Flow chart of studies identified, included and excluded.

Aerobic exercise and arterial stiffness

Results. We investigated 6 RCTs on the effect of aerobic training on arterial stiffness, involving 8 comparisons and 215 participants. The average age of the participants ranged from 18 to 72 years and 29.3% were male. Training duration varied from 8 to 16 weeks. Training frequency amounted to 2–3 weekly sessions. Training duration per session averaged 30–45 min. Intensity ranged from 50–90% VO_{2max}, 50– 85% HR_{max} or 50–80% HHR. Four of these studies had a Jadad score of ≥3. The combined relative changes in arterial stiffness are reported in Table II.

Two RCTs have measured the changes in arterial stiffness in the context of aerobic training in normotensive young (Ciolac et al., 2010) and middle-aged individuals (Yoshizawa et al., 2009). No RCT was available in the older adults above 60 years old. Combining the data of interval and continuous training, aerobic exercise was associated with a significant reduction in cfPWV by −7.0% (95% CI, −11.3%, −2.6%) in young individuals (Ciolac et al., 2010). Similar result was shown in the middle-aged adults [−6.7% (95% CI, −10.6%, −2.8%)] (Yoshizawa et al., 2009). Comparing the exercise modality of continuous and interval training, the authors showed that vigorous interval training was associated with a significant reduction in cfPWV by −7.5% (95% CI, −13.2%, −1.8%), however, the improvement in arterial stiffness with continuous training was not significant (Ciolac et al., 2010). Regarding the training intensity, combining the data of continuous aerobic exercise (Yoshizawa et al., 2009) and interval aerobic exercise (Ciolac et al., 2010), the vigorous training was associated with a significant improvement in cfPWV by −7.0 (95% CI, −10.2%, −3.8%). However, the improvement of arterial stiffness following moderate continuous aerobic exercise was not significant (Ciolac et al., 2010). All remaining RCTs in this review investigated hypertensive patients with inconsistent results. Three RCTs showed the changes in arterial stiffness in the context of aerobic training in mixed hypertension. In young prehypertensive individuals, peripheral arterial stiffness was significantly reduced [−10.3% (95% CI, −18.4%, −2.2%)] after moderate interval training; however, the central arterial stiffness did not change apparently (Beck, Martin, Casey, & Braith, 2013). In middle-aged hypertensive patients, combining the data of continuous and interval aerobic exercise, vigorous aerobic exercise did not change the central

Table I. Characteristics of the included RCTs: aerobic, resistance and combined exercise training

Study	Design	Participant	Age (years)	Sex	Exercise	Weeks	Frequency/ week	Min/ session	Intensity	N1 (Intervention)	N2 (Control)	Outcome	Mean difference (% change; 95% CI)	Jadad score
Trails including AE														
Yoshizawa et al. (2009)	Parallel	Normotensive	47 ± 2	Female	Cycle ergometer	12	3	30	60–70% VO_{2max}	12	12	cfPWV	−6.74 (−10.64, −2.84)	2
Ciolac et al. (2010)	Parallel	Normotensive females with hypertensive patients	25.0 ± 4.4	Female	Treadmill walking/ running	16	3	40	80–90% VO_{2max} interval training	16	12	cfPWV	−7.5 (−13.21, −1.79)	3
									50–60% VO_{2max} continuous training	16			−6.2 (−12.83, 0.43)	
Beck et al. (2013)	Parallel	Prehypertensive	18–35	Both	Treadmill walking/ running	8	3	45	65–85% HR_{max}	13	15	crPWV	−9.8 (−19.97, 0.37)	3
												cfPWV	−1.00 (−8.52, 6.52)	
												fdPWV	−11.1 (−24.58, 2.38)	
Madden et al. (2009)	Parallel	Hypertension, Hypercholesterolemia	71.4 ± 0.7	Both	Treadmilland cycle ergometer	12	3	40	60–75% HRR	17	17	Radial PWV	−29.2 (−33.54, −24.86)	4
												Femoral PWV	−18.3 (−21.85, −14.75)	
Guimarães et al. (2010)	Parallel	Hypertension	45 ± 9	Both	Treadmill	16	2	40	50–80% HRRinterval training	26	13	cfPWV	−8.6 (−19.35, 2.15)	4
										26			−4.6 (−16.53, 7.33)	
Ferrier et al. (2001)	Cross-over	Isolated systolic hypertension	64 ± 7	Both	Cycle ergometer	8	3	40	65% HR_{max}	10	10	cfPWV	0 (−16.5, 16.5)	1
												fdPWV	2.10 (−16.25, 20.45)	
Trials including RE														
Yasuda et al. (2013)	Parallel	Healthy	61–84	Both	Lower limb	12	2	NG	20–30% 1RM	9	10	CAVI	1.2 (−11.38, 13.78)	1
Okamoto et al. (2008a)	Parallel	Healthy	19.4 ± 0.2	Male	Whole body	8	2	NG	40% 1RM	10	9	baPWV	−6.6 (−13.45, 0.25)	1
Okamoto et al. (2011)	Parallel	healthy	18.5 ± 0.5	Both	Whole body	10	2	NG	50% 1RM	13	13	baPWV	−8.4 (−18.59, 1.79)	3
Kawano et al. (2006)	Parallel	Healthy	20 ± 1	Male	Whole body	16	3	45	50% 1RM	12	16	Carotid arterial compliance	20.0 (7.0, 33.0)	2
												Femoral arterial compliance	−22.5 (−51.38, 6.38)	
Yoshizawa et al. (2009)	Parallel	Healthy	47 ± 2	Female	Whole body	12	2	NG	60% 1RM	11	12	cfPWV	−5.14 (−9.8, −0.48)	2
Beck et al. (2013)	Parallel	Prehypertensive	18–35	Both	Whole body	8	3	45	60% 1RM	15	15	crPWV	−10.5 (−20.20, −0.80)	3
												cfPWV	−2.0 (−9.05, 5.05)	
												fdPWV	−7.9 (−15.26, −0.54)	
Cortez-Cooper et al. (2008)	Parallel	Healthy	52 ± 2	Both	Whole body	13	3	30–45	70% 1RM	13	12	cfPWV	−4.91 (−16.10, 6.28)	2
Okamoto et al. (2006)	Parallel	Healthy	18.9 ± 0.3	Female	Upper limb, eccentric	8	3	NG	100% 1RM	10	9	baPWV	−3.1 (−6.38, 0.18)	3
			19.1 ± 0.3	Female	Upper limb, concentric			NG	80% 1RM	10			10.4 (7.12, 13.68)	
Okamoto et al. (2008b)	Parallel	Healthy	19.6 ± 0.4	Male	Whole body, eccentric	10	2	NG	80% 1RM	10	10	baPWV	−5.55 (−10.37, −0.73)	3
			19.2 ± 0.3	Male	Whole body, concentric			NG		10			8.75 (3.93, 13.57)	
Okamoto et al. (2009)	Parallel	Healthy	20.2 ± 0.4	Both	Upper limb	10	2	NG	80% 1RM	10	10	baPWV	12.18 (5.58, 18.78)	2
			20.0 ± 0.5		Lower limb			NG		10			−1.42 (−8.02, 5.18)	

Table I (*Continued*)

Study	Design	Participant	Age (years)	Sex	Exercise	Weeks	Frequency/ week	Min/ session	Intensity	N1 (Intervention)	N2 (Control)	Outcome	Mean difference (% change; 95% CI)	Jadad score
Miyachi et al. (2004)	Parallel	Healthy	20–38	Male	Whole body	16	3	45	80% 1RM	14	14	Carotid arterial compliance	29.88 (14.17, 45.59)	3
												Femoral arterial compliance	0.00 (−40.34, 40.34)	
Trials including COMB														
Stewart et al. (2005)	Parallel	Mild hypertension	55–75	Both	RE + AE one training session	24	3	RE: NGAE: 45	50% 1RM, 60–90% HR_{max}	40	42	cfPWV	10.5 (−9.08, 30.08)	2
Kawano et al. (2006)	Parallel	Healthy	21 ± 1	Male	RE + AE one training session	16	3	75	80% 1RM, 60% HR_{max}	11	16	Carotid arterial compliance	−12.5 (−26.32, 1.32)	2
												Femoral arterial compliance	12.2 (−15.57, 39.97)	
Cortez-Cooper et al. (2008)	Parallel	Healthy	52 ± 2	Both	RE and AE separate days	13	3	60–90	70% 1RM, 60–75% HR_{max}	12	12	cfPWV	−4.91 (−15.65, 5.83)	2
Figueroa et al. (2011)	Parallel	Healthy	47–68	Female	RE + AE one training session	12	3	40	60% 1RM, 60% HR_{max}	12	12	baPWV	−6.98 (−11.34, −2.62)	1

RE, resistance training; AE, aerobic training; COMB, combined aerobic and resistance training; VO_{2max}, maximal oxygen consumption; HR_{max}, maximal heart rate; HRR, heart rate reserve; NG, not given in the study; 1RM, one repetition maximum; CAVI, cardio-ankle vascular index; baPWV, brachial ankle pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid radial pulse wave velocity; fdPWV, femoral ankle pulse wave velocity; CI, confidence interval; − [Mean difference (% change)], decrease of arterial stiffness or increase of arterial compliance; + [Mean difference (% change)], increase of arterial stiffness or decrease of arterial compliance.

Table II. Combined relative changes in arterial stiffness after aerobic training

	Arterial stiffness	Study	N1 (intervention)	N2 (Control)	Outcome	Combined relative change (%) of arterial stiffness (95% CI)
Normotensive individuals (2 RCTs)						
Intensity						
Moderate	Central	Ciolac et al. (2010)	16	12	cfPWV	−6.2 (−12.8, 0.43)
	Peripheral	No data available				
Vigorous	Central	Yoshizawa et al. (2009) and Ciolac et al. (2010)	28	24	cfPWV	−7.0 (−10.2, −3.8)
	Peripheral	No data available				
Age						
Young (18–39 years)	Central	Ciolac et al. (2010)	32	24	cfPWV	−7.0 (−11.3, −2.6)
	Peripheral	No data available				
Middle-aged (40–59 years)	Central	Yoshizawa et al. (2009)	12	12	cfPWV	−6.7 (−10.6, −2.8)
	Peripheral	No data available				
Old (>60 years)	Central	No data available				
	Peripheral	No data available				
Modality						
Continuous	Central	Ciolac et al. (2010)	16	12	cfPWV	−6.2 (−12.8, 0.4)
	Peripheral	No data available				
Interval	Central	Ciolac et al. (2010)	16	12	cfPWV	−7.5 (−13.2, −1.8)
	Peripheral	No data available				
Mixed hypertension individuals (3 RCTs)						
Intensity						
Moderate	Central	Beck et al. (2013)	13	15	cfPWV	−1.0 (−8.5, 6.5)
	Peripheral	Beck et al. (2013)	26	30	crPWV, fdPWV	−10.3 (−18.4, −2.2)
Vigorous	Central	Guimarães et al. (2010)	52	26	cfPWV	−6.8 (−14.8, 1.2)
	Peripheral	Madden et al. (2009)	34	34	Radial PWV, femoral PWV	−23.7 (−34.4, −13)
Age						
Young (18–39 years)	Central	Beck et al. (2013	13	15	cfPWV	−1.0 (−8.5, 6.5)
	Peripheral	Beck et al. (2013)	26	30	crPWV, fdPWV	−10.3 (−18.4, −2.2)
Middle-aged (40–59 years)	Central	Guimarães et al. (2010)	52	26	cfPWV	−6.8 (−14.8, 1.2)
	Peripheral	No data available				
Old (>60 years)	Central	No data available				
	Peripheral	Madden et al. (2009)	34	34	Radial PWV, femoral PWV	−23.7 (−34.4, −13)
Modality						
Continuous	Central	Guimarães et al. (2010)	26	13	cfPWV	−4.6 (−16.5, 7.3)
	Peripheral	Madden et al. (2009)	34	34	Radial PWV, femoral PWV	−23.7 (−34.4, −13)
Interval	Central	Beck et al. (2013) and Guimarães et al. (2010)	39	28	cfPWV	−3.8 (−11, 3.4)
	Peripheral	Beck et al. (2013)	26	30	crPWV, fdPWV	−10.3 (−18.4, −2.2)
Isolated systolic hypertension individuals (1 RCT)						
	Central	Ferrier et al. (2001)	10	10	cfPWV	0 (−16.5, 16.5)
	Peripheral				fdPWV	2.10 (−16.3, 20.5)

Moderate intensity, 40–59% heart rate reserve = 64–76% maximal heart rate = 46–63% maximal oxygen uptake; Vigorous intensity, 60–89% heart rate reserve = 77–95% maximal heart rate = 64–90% maximal oxygen uptake; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid radial pulse wave velocity; fdPWV, femoral ankle pulse wave velocity; CI, confidence interval; − [Combined relative change of arterial stiffness], decrease of arterial stiffness or increase of arterial compliance; + [Combined relative change of arterial stiffness], increase of arterial stiffness or decrease of arterial compliance.

arterial stiffness significantly (Guimarães et al., 2010). In older hypertensive patients, the vigorous aerobic exercise affected the peripheral arterial stiffness favourably with a combined reduction of radial PWV and femoral PWV by −23.7% (95% CI, −34.4%, −13%) (Madden, Lockhart, Cuff, Potter, & Meneilly, 2009). However, moderate aerobic exercise training did not result in a change of arterial stiffness in patients with isolated systolic hypertension (Ferrier et al., 2001).

Discussion. There is a general agreement that acute aerobic exercise leads to both local (exercising limbs; Kingwell, Berry, Cameron, Jennings, & Dart, 1997) and systemic changes in arterial stiffness (Ranadive et al., 2012). Analogously, for medium to long-term exercise training, similar effects could be speculated.

Our results demonstrate that aerobic exercise training reduced arterial stiffness in healthy normotensive (Ciolac et al., 2010; Yoshizawa et al., 2009) and hypertensive patients (Beck et al., 2013; Guimarães et al., 2010; Madden et al., 2009). However, aerobic exercise failed to alter large arterial stiffness in older populations with isolated systolic hypertension (Ferrier et al., 2001). The central and peripheral arterial stiffness may differ in response to aerobic exercise. In healthy individuals, central arterial stiffness following aerobic exercise decreased significantly (Ciolac et al., 2010; Yoshizawa et al., 2009). In hypertensive patients, aerobic exercise reduced the peripheral arterial stiffness (Beck et al., 2013; Madden et al., 2009); however, the central arterial stiffness did not change significantly (Beck et al., 2013; Guimarães et al., 2010). Since most of the RCTs investigated the association between exercise training and only one arterial stiffness parameter at one segment of the artery, whether the adaptations differ for central and peripheral arterial stiffness in normotensive and hypertensive is largely unknown and should be investigated in future studies. Further, comparing exercise modalities, vigorous interval training was shown to be superior to traditional moderate continuous training in reducing arterial stiffness in normotensive populations at risk for future cardiovascular events (Ciolac et al., 2010). However, whether high intensity interval training is well tolerated in hypertensive patients is unknown. Interval training with a lower intensity (50–80% HRR) caused a small and non-significant improvement in cfPWV, but the difference of cfPWV at baseline level in the interval training group (9.44 ± 0.91 m/s) and control group (10.23 ± 1.82 m/s) leaves a doubt, as to whether the drop in cfPWV (0.41 m/s) following interval training was due to a superior intervention effect compared to the controls (Guimarães et al., 2010). Further, the lower intensity (50–80% HRR) assigned to the hypertensive patients may also contribute to the blunted reduction of arterial stiffness in hypertensive patients (Guimarães et al., 2010). Therefore, further studies are required to confirm that high intensity interval training is superior to traditional moderate continuous training in reducing arterial stiffness in hypertensive patients. Age alone increased arterial stiffness even in the well-trained individuals (Cameron, Rajkumar, Kingwell, Jennings, & Dart, 1999; Tanaka et al., 2000). Furthermore, the increase of arterial stiffness was more pronounced in hypertensive patients (Vaitkevicius et al., 1993; Wallace et al., 2007). Thus, to determine the effect of aerobic exercise in populations whose arterial stiffness has some alteration is of great clinical importance. The previous thought of a point of no return might be changed by the encouraging results in older hypertensive patients (Madden et al., 2009). However, the low responsiveness of patients with isolated systolic hypertension to exercise, which may be due to an irreversible level of arterial stiffness (Tanaka & Safar, 2005), implied that aerobic training initiated at a younger age may be more effective. In addition, since arterial stiffening seems to precede hypertension (Kaess et al., 2012), studies in normotensive individuals with increased arterial stiffness are warranted in order to show a direct preventive effect of aerobic exercise training on the artery. Finally, different muscle contractions in aerobic training may contribute differently on arterial stiffness. It has been shown that aerobic exercise training (running) involves both eccentric (knee extensors) and concentric contractions (ankle plantar flexors) (Bijker, Groot, & Hollander, 2002). However, no study so far has addressed the question of whether concentric and eccentric muscle contractions in aerobic exercise training contribute to different effects on arterial stiffness.

Resistance exercise and arterial stiffness

Results. We identified 11 randomised controlled trials investigating the effect of resistance training on arterial stiffness, involving 14 study groups and 287 participants totally. The average age of the study groups ranged from 18 to 84 years, 56% of the participants were male. Only one trial was conducted in prehypertensive patients (Beck et al., 2013). Training duration varied from 8 to 16 weeks, training frequency averaged 2–3 weekly sessions and intensity ranged from 20–100% of 1RM. Four studies reported the duration per session which averaged 30–45 min (Beck et al., 2013; Cortez-Cooper et al., 2008; Kawano, Tanaka, & Miyachi, 2006; Miyachi et al., 2004). Of these 11 studies, only 5 had a Jadad score of ≥3 (Beck et al., 2013; Miyachi et al., 2004; Okamoto, Masuhara, & Ikuta, 2006, 2008b, 2011). The combined relative changes in arterial stiffness are reported in Table III.

Table III. Combined relative changes in arterial stiffness after resistance training

Arterial stiffness		Study	N1 (intervention)	N2 (Control)	Outcome	Combined relative change (%) of arterial stiffness (95% CI)
Normotensive individuals (10 RCTs)						
Intensity						
Light	Central	Kawano et al. (2006)	12	16	Carotid arterial compliance	20.0 (7.0, 33.0)
	Peripheral	Kawano et al. (2006)	12	16	Femoral arterial compliance	−22.5 (−51.4, 6.4)
	Systemic	Okamoto et al. (2011), Okamoto et al. (2008a) and Yasuda et al. (2013)	32	32	baPWV, CAVI	−5.7 (−10.9, −0.6)
Moderate	Central	Cortez-Cooper et al. (2008) and Yoshizawa et al. (2009)	24	24	cfPWV	−5.1 (−9.4, −0.8)
	Peripheral	No data available				
	Systemic	No data available				
Vigorous	Central	Miyachi et al. (2004)	14	14	Carotid arterial compliance	29.9 (14.2, 45.6)
	Peripheral	Miyachi et al. (2004)	14	14	Femoral arterial compliance	0 (−40.3, 40.3)
	Systemic	Okamoto et al. (2006), Okamoto et al. (2008b) and Okamoto et al. (2009)	60	58	baPWV	3.1 (1.4, 4.8)
Age						
Young (18 −39 years)	Central	Kawano et al. (2006) and Miyachi et al. (2004)	26	30	Carotid arterial compliance	24.0 (14.0, 34.0)
	Peripheral	Kawano et al. (2006) and Miyachi et al. (2004)	26	30	Femoral arterial compliance	−14.9 (−38.3, 8.6)
	Systemic	Okamoto et al. (2006), Okamoto et al. (2008a), Okamoto et al. (2008b), Okamoto et al. (2009) and Okamoto et al. (2011)	83	80	baPWV	1.1 (−4.5, 6.7)
Middle-aged (40–59 years)	Central	Cortez-Cooper et al. (2008) and Yoshizawa et al. (2009)	24	24	cfPWV	−5.1 (−9.4, −0.8)
	Peripheral	No data available				
	Systemic	No data available				
Old (>60 years)	Systemic	Yasuda et al. (2013)	9	10	CAVI	1.2 (−11.4, 13.8)
Muscle contraction types						
Eccentric	Systemic	Okamoto et al. (2006) and Okamoto et al. (2008b)	20	19	baPWV	−3.9 (−6.6, −1.2)
Concentric		Okamoto et al. (2006) and Okamoto et al. (2008b)	20	19	baPWV	9.9 (7.2, 12.6)
Muscle groups						
Lower limb	Systemic	Okamoto et al. (2009) and Yasuda et al. (2013)	19	20	baPWV, CAVI	−1.0 (−5.7, 3.6)
Upper limb	Systemic	Okamoto et al. (2009)	10	10	baPWV	12.2 (5.6, 18.8)
Prehypertensive patients (1 RCT)						
Intensity	Central	Beck et al. (2013)	15	15	cfPWV	−2 (−9.1, 5.1)
Moderate	Peripheral				crPWV, fdPWV	−8.9 (−14.7, −3)

Intensity "light", <50% 1RM; Intensity "moderate", 50–69% 1RM; Intensity "vigorous", 70–84% 1RM; baPWV, brachial ankle pulse wave velocity; CAVI, cardio-ankle vascular index; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid radial pulse wave velocity; fdPWV, femoral ankle pulse wave velocity; CI, confidence interval; − [Combined relative change of arterial stiffness], decrease of arterial stiffness or increase of arterial compliance; + [Combined relative change of arterial stiffness], increase of arterial stiffness or decrease of arterial compliance.

Light resistance training (≤50%1RM) induced a significant pooled reduction of systemic arterial stiffness measured in baPWV and CAVI of −5.7% (95% CI, −10.9%, −0.6%) in 32 participants in comparison with 32 controls combining 3 studies (Okamoto, Masuhara, & Ikuta, 2008a; Okamoto et al., 2011; Yasuda et al., 2013). However, a relative low intensity of 50% 1RM decreased the carotid arterial compliance by 20% (95% CI, 7.0%, 33%) without changing the femoral arterial compliance (Kawano et al., 2006). Moderate resistance training (>50–70% 1RM) was associated with a reduction of cfPWV by −5.1% (95% CI, −9.4%, −0.8%) in healthy young and middle-age individuals (Cortez-Cooper et al., 2008; Yoshizawa et al., 2009). In contrast, high intensity and concurrent high-volume resistance training was found to have unfavourable effects on arterial stiffness. A training at an intensity of ≥80%1RM, resulted in an increase of central arterial stiffness by 29.9% (95% CI, 14.2%, 45.6%) (Miyachi et al., 2004) and baPWV by 3.1% (95% CI, 1.4%, 4.8%) (Okamoto et al., 2006, 2008b; Okamoto, Masuhara, & Ikuta, 2009) without changing the peripheral arterial stiffness (Miyachi et al., 2004). We further summarised the responses to resistance training in different age groups. In young individuals, resistance training was associated with an increase of central arterial stiffness of 24% (95% CI, 14.0%, 34.0%) (Kawano et al., 2006; Miyachi et al., 2004), but was not associated with changes in peripheral (Kawano et al., 2006; Miyachi et al., 2004) and systemic arterial stiffness (Okamoto et al., 2006, 2008a, 2008b, 2009, 2011). In middle-aged adults, two RCTs showed that resistance training was associated with a reduction of central arterial stiffness by −5.1% (95% CI, −9.4%, −0.8%) (Cortez-Cooper et al., 2008; Yoshizawa et al., 2009). The only existing RCT in older adults showed that light resistance training (20–30% 1RM) with lower limb did not affect the systemic arterial stiffness measured as CAVI (Yasuda et al., 2013). Comparing eccentric and concentric training, eccentric exercise led to a relative change by −3.9% in arterial stiffness (95% CI, −6.6%, −1.2%) and concentric exercise increased arterial stiffness of 9.9% (95% CI, 7.2%, 12.6%) (Okamoto et al., 2006, 2008b). Most of the studies examined dynamic resistance training involving major muscular groups of both the upper and lower limbs. Comparing exercise using upper limb with lower limb, upper limb exercise led to a 12.2% (95% CI, 5.6%, 18.8%) increase of baPWV (Okamoto et al., 2009), while lower limb exercise had not affected the systemic arterial stiffness (baPWV and CAVI)(Okamoto et al., 2009; Yasuda et al., 2013). To our knowledge, the only existing RCT in a small number of prehypertensive patients reported that a 8-week moderate (60% 1RM) whole body resistance training reduced peripheral arterial stiffness (combined crPWV and fdPWV) by −8.9% (95% CI, −14.7%, −3%). However, central arterial stiffness (cfPWV) did not change (Beck et al., 2013).

Discussion. Resistance training has been recommended as an important component in a comprehensive exercise programme by the American College of Sports Medicine in recent years (American College of Sports Medicine, 2009). However, these recommendations were primarily based on its favourable effects on muscular strength (Feigenbaum & Pollock, 1999). Few recommendations with respect to resistance training and cardiovascular function exist so far.

Current evidence suggests that low to moderate intensity resistance training does not result in arterial stiffening measured as carotid-femoral pulse wave velocity (cfPWV) (Cortez-Cooper et al., 2008; Yoshizawa et al., 2009), femoral ankle pulse wave velocity (faPWV) (Yoshizawa et al., 2009) or cardio-ankle vascular index (CAVI) (Yasuda et al., 2013). This is in line with the beneficial blood pressure adaptation to moderate resistance training (Cornelissen et al., 2011). On the other hand, our results show that high intensity and concurrent high-volume resistance training was found to be associated with an increase of arterial stiffness (Miyachi et al., 2004; Okamoto et al., 2006, 2008b, 2009). This is consistent with previous studies reporting blood pressure elevation after vigorous resistance training (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985; Palatini et al., 1989). However, there may be a neutral effect of high intensity resistance training on central arterial stiffness as shown in obese normotensive young men (Croymans et al., 2014). Even a favourable effect on arterial stiffness has been shown for resistance training in a slow eccentric manner (Okamoto et al., 2006, 2008b) or with the lower limbs, although intensity was high (Okamoto et al., 2009). In addition, a non-randomised controlled study showed that progressive high-intensity resistance training without volume increase did not alter arterial stiffness (Casey, Beck, & Braith, 2007). Further, resistance training in young individuals was associated with an increase of central and systemic arterial stiffness, but not peripheral arterial stiffness. However, this was not the case in middle-aged and older adults. One explanation for the divergent effects following eccentric and concentric training could possibly be due to the difference in actively contracting muscle mass, which is lower in eccentric training than concentric training (Komi, Linnamo, Silventoinen, & Sillanpää, 2000; Linnamo, Moritani, Nicol, & Komi, 2003; Madeleine, Bajaj, Søgaard, & Arendt-Nielsen, 2001). The greater amount of active muscle mass in concentric resistance training may cause a stronger

vasopressor response, which again increases the strain on the arteries. Further, compared to eccentric training, concentric training results in a greater increase in blood pressure (Okamoto et al., 2006), which may be associated with a stiffening of the arterial wall (London & Guerin, 1999). The difference in upper limb and lower limb might be explained by higher heart rates (Pivarnik, Grafner, & Elkins, 1988) and higher blood pressure levels (Volianitis & Secher, 2002) induced by upper limb exercises compared to lower limb exercises with the same workload. However, not all RCTs with multiple exercise interventions defined the workloads of eccentric versus concentric exercise or upper versus lower limb exercise to be equivalent for comparison of training effect on arterial stiffness. The results are thus, less convincing. Furthermore, it is of clinical importance to investigate the effects of resistance training on arterial stiffness in hypertension. Noteworthy, the only existing RCT in prehypertensive patients showed that moderate resistance training improved peripheral arterial stiffness (Beck et al., 2013). Further studies are warranted for precise resistance exercise recommendations for hypertensive patients.

Traditional resistance training generally consists of muscular contractions performed at a relatively slow speed. This is different to emerging novel types of resistance training with higher velocity and lower intensity, which may result in differing effects on arterial stiffness. In high-velocity resistance training in which the concentric phase is performed as quickly as possible, force can be produced very fast. This aspect of power production is important in activities of daily living, especially with respect to fall prevention (Orr et al., 2006; Sayers & Gibson, 2014). It has been shown that high-velocity resistance training causes a greater increase in muscle power than low-velocity resistance training (Fielding et al., 2002). However, no study exists on the effect of high-velocity resistance training on arterial stiffness. Compared to lower velocity, higher velocity resistance movements with a quick concentric phase might have a smaller impact on arterial stiffness because of a smaller vasopressor response. In view of an ageing population with an increasing prevalence of hypertension (Kearney et al., 2005), and the progressive reduction in muscular power (Reid & Fielding, 2012) and strength (Doherty, 2003), there is an urgent clinical need to define the optimal type of resistance exercise training. The ideal resistance training should provide muscular benefits without health hazards to the vasculature. At best, the individualised resistance training programme has a destiffening effect on the arteries.

Combined aerobic/resistance exercise and arterial stiffness

We included four RCTs on the effect of combined aerobic and resistance exercise training on arterial stiffness in our analysis. These trials involved 8 study groups and 157 participants. Within the 4 studies, the average age of the study groups ranged from 20 to 75 years and 31% of the participants were male. Only one trial was conducted in patients with untreated milder forms of hypertension (Stewart et al., 2005). Training durations varied from 12 to 24 weeks, training frequency amounted to 3 weekly sessions, the training intensity ranged from 50–80% of 1RM and 60–90% HR_{max} and training duration per session averaged 40–90 min.

The resistance exercises were either directly followed by the aerobic exercise within one training session (Figueroa, Park, Seo, Sanchez-Gonzalez, & Baek, 2011; Kawano et al., 2006; Stewart et al., 2005) or on alternating days (Cortez-Cooper et al., 2008). Combined training either had a small or no positive effect on arterial stiffness, suggesting that combined exercise may be of particular relevance for the prevention of sarcopenia in elderly population without arterial stiffening. Aerobic following resistance training in the same exercise session may favourably affect arterial stiffness, but could decrease the gain in muscular strength (Kawano et al., 2006; Sale, Jacobs, MacDougall, & Garner, 1990). The mammalian target of the rapamycin complex 1 (mTORC1), known as a protein complex that controls protein synthesis, and thus, is important for regulating muscle mass, was induced by resistance training and can be down-regulated by aerobic training (Ogasawara, Sato, Matsutani, Nakazato, & Fujita, 2014). Therefore, in order to minimise the attenuation of strength gain, resistance and aerobic training should preferably be performed on alternating days (Kawano et al., 2006; Sale et al., 1990). However, the portion, intensity and sequence of the aerobic and resistance exercise components in the combined exercise programme may all contribute to the discrepancy of the results. Another aspect worth consideration is the good health status in the studies included in our analysis, whereby the results cannot be generalised to other populations. Furthermore, none of the 4 studies included had a Jadad score of ≥ 3, and thus, all were of lower study quality. Thus, there is an evident need for additional studies on the effect of combined aerobic and resistance training on arterial stiffness in normotensive and hypertensive individuals.

Limitations

There are some limitations that have to be considered. First, we included only the RCTs using the

regional and local arterial stiffness parameters mentioned above. The estimates in this study should be interpreted with caution when compared to other arterial stiffness parameters. Second, we only evaluated studies which reported precise data of change in arterial stiffness in both intervention and control group. Therefore, the estimates were synthesised from the limited data in studies published in English language, and we cannot fully exclude publication bias. Furthermore, the poor methodological quality of some included trials should be acknowledged. We assessed the quality of the included studies using Jadad scale, but we have not excluded the RCTs with a Jadad score <3. We reported all the RCTs that we found according to our inclusion criteria. The existing evidence does not allow firm conclusions. The interpretation is hampered by the use of different measures of arterial stiffness, varying exercise programmes (modality, duration, intensity and frequency), different population-based variables (age, health status) and several confounding factors (e.g. exercise induced weight loss, daily physical activity, diet, medication).

Conclusions

The available evidence indicates that aerobic exercise training is more likely to have a beneficial effect on arterial stiffness in normotensive and hypertensive patients, but does not affect arterial stiffness in patients with isolated hypertension. Resistance exercise seems to have no adverse effect on arterial stiffness if the training is of low intensity, in a slow eccentric manner or with lower limb in healthy individuals. However, intensive concentric resistance exercise increases arterial stiffness in healthy individuals, and thus, should be avoided in populations with an increased cardiovascular risk. Combined training with resistance training first, followed by endurance training, has neutral or even beneficial effects on arterial stiffness based on limited number of studies available.

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3.2 Paper 2

Diurnal variation of arterial stiffness in healthy individuals of different ages and patients with heart disease

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ORIGINAL ARTICLE

Diurnal variation of arterial stiffness in healthy individuals of different ages and patients with heart disease

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Abstract

Background. Arterial stiffness can be measured using various non-invasive methods. It is not well established whether it is necessary to standardize the time of the day when performing these measurements. The aim of the present study is to examine the effect of daytime on arterial stiffness in individuals with and without heart disease. ***Methods.*** We investigated the diurnal variation of cardio-ankle vascular index (CAVI) and carotid femoral pulse wave velocity (cfPWV). CAVI and cfPWV were measured in 70 participants (23 healthy young individuals [HY], 22 healthy elderly individuals [HE], 25 patients with heart disease [HD]) at 09:00, 13:00 and 17:00 h. ***Results.*** There was a significant diurnal variation in CAVI with the highest values at 09:00 h in both univariate and multivariate analysis. After adjusting for age, sex and MAP (mean arterial pressure), CAVI maintained a significant highest values at 09:00 h, which was 4% higher than at 13:00 h ($p = 0.022$) and 5% higher than at 17:00 h ($p = 0.002$). However, a lack of diurnal variation was found in cfPWV in multivariate analysis in our study population. ***Conclusion.*** Our findings suggest that it does not appear mandatory to measure cfPWV at the same time of day. However, standardizing the time of day for CAVI is important in routine clinical practice and longitudinal studies.

Key Words: *Vascular stiffness, blood pressure, circadian rhythm, aging, cardiovascular disease*

Introduction

Arterial stiffness indicates the rigidity of the arterial wall and increases with age and in certain disease states [1,2]. A higher arterial stiffness is associated with a higher risk of cardiovascular disease [1,2]. Various non-invasive methods, which detect the early functional change of the arterial wall have been applied in clinical practice and research to evaluate risk for cardiovascular events [2–6]. It is known that several hemodynamic and humoral regulating parameters such as blood pressure, vascular tone [7,8], endothelial function [7,9,10], plasma renin [11], and epinephrine and norepinephrine [12] display a certain 24-h rhythmicity, partially with impaired function in the early morning [7–9]. Since arterial stiffness is modulated by vascular tone and may be associated with blood pressure and endothelial function, arterial stiffness may also have a diurnal variation [13].

Arterial stiffness can be assessed using the measurements of carotid femoral pulse wave velocity (cfPWV) and cardio-ankle vascular index (CAVI). Previous studies showed inconsistent results regarding the diurnal variation of measurements of arterial stiffness [10,14–16]. The inconsistencies could be due to different methods in the assessment of arterial stiffness such as cfPWV, carotid radial pulse wave velocity (crPWV) or augmentation index (AIx). There is currently a lack of data on CAVI. Furthermore, circadian variation of vascular function may depend on age or health status, which has not been analyzed so far. Therefore, the aim of the present study was to examine the effect of daytime on cfPWV and CAVI measurements in healthy young (HY), elderly individuals (HE) and patients with heart disease (HD).

Methods

Subjects

This study was advertised by poster in the outpatient clinic. Seventy-five individuals were recruited for the

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study and were presented in chronologic order. Of the 75 who signed up, one participant dropped out during the study, four participants' data were invalid due to inaccurate measurement. Seventy individuals (aged 21–79) were included into the final data analysis. Participants consisted of three groups: Group 1: HY ($n = 23$), group 2: HE ($n = 22$), group 3: HD patients ($n = 25$; nine hypertensive cardiomyopathy, 13 prior myocardial infarction, two with prior stroke, one compensated heart failure). Healthy individuals were free of clinically relevant cardiovascular diseases or diabetes based on medical history and physical examination. HD patients were in a clinically stable condition with no clinical signs of peripheral arterial occlusive disease. The research protocol was approved by the Ethics Committee of the University of Basel and all the participants provided written informed consent.

Experimental protocol

To assess diurnal variation, volunteers were invited to our vascular laboratory three times within the same visiting day at 09:00, 13:00 and 17:00 h. The arterial stiffness measurements were performed by one trained observer in a quiet, temperature-controlled (22–24°C) room after a resting period of at least 10 min in a supine position. For each participant, four measurements were recorded at 5-min intervals: Two CAVI measurements and two cfPWV measurements. We randomized the order of these two types of measurements for each participant at each time-point (either both CAVI measurements were taken at first, or both cfPWV measurements were taken at first).

As an additional study after the main study phase, we recruited a small sample from the previous study participants to assess the trend of day-to-day variation. Seven healthy volunteers (28.8 ± 5.1 years, randomized chosen from HY) were invited to come to our laboratory two times on two separate days (a week apart) at 09:00 h. CAVI and cfPWV measurements were repeated twice at 5-min intervals.

Various exogenous factors which may influence the arterial stiffness were standardized. Thus, all participants were asked to refrain from caffeine-containing products, alcohol, smoking and exercise training at least 12 h before the first visit (09:00 h) [17–22] and for the entire visiting day. Furthermore, they were asked to fast overnight and 2 h before the second (13:00 h) and third visit (17:00 h). The test procedure complied with the rules of the Helsinki Declaration.

CAVI measurements

CAVI was assessed using VaSera VS-1500 (Fukuda Denshi; Japan). Cuffs were applied to the four extremities with ECG leads attached to the upper arm for electrocardiogram and one microphone placed on the mid sternum for phonocardiography. The CAVI was calculated from the brachial pulse wave obtained from the right and left brachial cuff and pulse waves obtained from the right and left ankle cuffs. PWV from heart to the ankle was obtained by measuring the length from aorta to the ankle and by time taken for the pulse wave to propagate from the aortic valve to the ankle. Vascular length (L) between the heart valve and ankle artery is indirectly calculated from the individual height of the patient using the formula: $L = 0.77685 \times \text{height} - 1.7536$ (in cm) (manufacturer's information). CAVI was obtained by substituting the stiffness parameter β in the following equation for determining vascular elasticity and PWV. The stiffness parameter β is calculated by the following equation:

$$\text{CAVI} = \ln(\text{Ps}/\text{Pd}) \times 2\rho/\Delta\text{P} \times \text{PWV}^2 \qquad (1)$$

where Ps = systolic blood pressure, Pd = diastolic blood pressure, PWV = pulse wave velocity from heart to ankle, ρ = blood density (1.03×10^3 kg/m^3) [23], and ΔP = pulse pressure.

The extremity BP was measured oscillometrically [24]. CAVI measurements were considered to have met the quality control parameter if two consecutive measurements were visually acceptable and the difference between the two measures was less than 1 measurement unit.

cfPWV measurements

cfPWV was assessed using SphygmoCor (AtCor, Medical Pty Ltd, Sydney, Australia). Pulse waves were recorded using a high-fidelity tonometric transducer at two sites (right carotid artery and right femoral artery). cfPWV was determined as the difference in travel time of the pulse wave between the two recording sites and the heart, divided by the transit distance. The transit distance was measured using a scale by subtracting the distance from the carotid recording site to the suprasternal notch from the distance between the suprasternal notch and the femoral recording site [25,26]. The time of the waveforms was compared with that of R wave on a simultaneously recorded ECG [27]. Prior to cfPWV measurement, blood pressure was measured in the right brachial artery using Omron oscillometric standard device (Omron, M9 Premium, Japan). cfPWV measurements were considered to have met the quality control parameters if two consecutive measurements were visually acceptable and within 1.5 m/s of each other with a standard deviation of less than 10% [28].

Laboratory measurements

While fasting, blood was drawn by venipuncture of the antecubital vein 30 min before the first arterial stiffness measurement in the morning to determine cardiovascular risk factors including serum glucose, total cholesterol, low density lipoprotein cholesterol,

high density lipoprotein cholesterol, triglycerides and creatinine using standard laboratory methods.

Statistical analysis

Data were expressed as mean ± SD (standard deviation) unless otherwise stated. Bland-Altman plot was used to assess the agreement between the two repeated measurements for CAVI and cfPWV, respectively [29]. Boxplots were used to visualize the variation of the CAVI, cfPWV and blood pressure, respectively, over the daytime in three groups. Distributions of all the main outcome parameters were assessed using the Shapiro-Wilk test and Q-Q-plots. Data were log-transformed to follow a normal distribution. The overall variations of CAVI and cfPWV during daytime were analyzed using mixed linear model for repeated measures. Factors of time, group and time × group were included in the basic model. Covariates were selected by identifying factors which may confound the results and contribute to arterial stiffness variation. These include age, sex and MAP (mean arterial pressure, MAP = Pd + 1/3(Ps – Pd)). The correlations between CAVI and cfPWV, relationship between CAVI or cfPWV and blood pressure were analyzed using the spearman correlation coefficient. A p values less than 0.05 was considered as statistically significant. Results were presented as changes in the ratio of geometric means of CAVI and cfPWV with 95% confidence intervals. All analysis were done using IBM SPSS 20.0 statistical package.

Results

The characteristics of the study population are reported in Table I. Seven young women in the HY group took contraceptives. Eleven participants in the HE group took medications (two statins, nine other substances like vitamins, calcium, iron or zinc preparation, fish oil in non-effective dosage with regard to vascular function and not on the day of the examination). Medications taken by HD patients were as following: diuretics, $n = 4$; beta-blocker, $n = 13$; calcium channel blocker, $n = 3$; angiotensin-converting enzyme (ACE) inhibitors, $n = 7$; angiotensin receptor blockers (ARB), $n = 6$; aspirin, $n = 16$; statins, $n = 14$; proton-pump inhibitor (PPI), $n = 3$; and others, $n = 14$ (vitamin, calcium, iron or magnesium preparation).

Repeatability of CAVI and cfPWV measurements

The coefficient of variation (CV) for the two repeated measurements at 09:00 h was 3.2% for CAVI and 6.1% for cfPWV. The absolute difference for the repeated measures at 09:00 h was − 0.0429 (− 0.968–0.882, 95% CI) for CAVI and − 0.151 m/s (− 2.022–1.720, 95% CI) for cfPWV. The Bland-Altman plots show the variability of the repeated measurements of CAVI and cfPWV in Figure 1.

Diurnal variation of CAVI

In univariate analysis, CAVI showed a significant morning peak in all participants (5.3% higher at 09:00 h than at the following time-points, $p < 0.001$) (Figure 2). In multivariate analysis, after adjustment for age, sex and MAP, CAVI maintained a significant highest values at 09:00 h, which was 4% higher than at 13:00 h ($p = 0.022$) and 5% higher than at 17:00 h ($p = 0.002$). Age was found as a significant

Table I. Characteristics of study population.

	Healthy young ($n = 23$)	Healthy elderly ($n = 22$)	HD patients ($n = 25$)
Age (yr)	28.3 ± 4.7	61.1 ± 9.1	63.9 ± 11.5
Gender (male/female)	16/7	6/16	18/7
BMI (kg/m^2)	21.1 ± 2.3	23.2 ± 2.3	25.6 ± 4.1
Total cholesterol (mmol/L)	4.8 ± 0.9	5.6 ± 1.3	4.7 ± 1.1
HDL-chol (mmol/L)	1.7 ± 0.6	1.6 ± 0.3	1.5 ± 0.5
Chol./HDL – chol ratio	3.0 ± 0.7	3.6 ± 1.2	3.4 ± 1.1
LDL-chol (mmol/L)	2.6 ± 0.7	3.5 ± 1.2	2.7 ± 1.0
Triglyceride (mmol/L)	1.0 ± 0.5	1.1 ± 0.7	1.2 ± 0.5
Glucose (mmol/L)	4.6 ± 0.7	4.9 ± 0.4	5.0 ± 0.5
Creatinine (mmol/L)	76.1 ± 13.8	69.9 ± 11.7	79.0 ± 13.7
With medication n (%)	7 (30.4%)	11 (50%)	23 (92%)
Diuretics			4
β-blocker			13
Calcium channel blockers			3
ACE inhibitor			7
ARB			6
Aspirin		1	16
Statins		2	14
PPI			3
Others		9	14

Values are mean ± SD. HD, heart disease; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; PPI, proton-pump inhibitor.

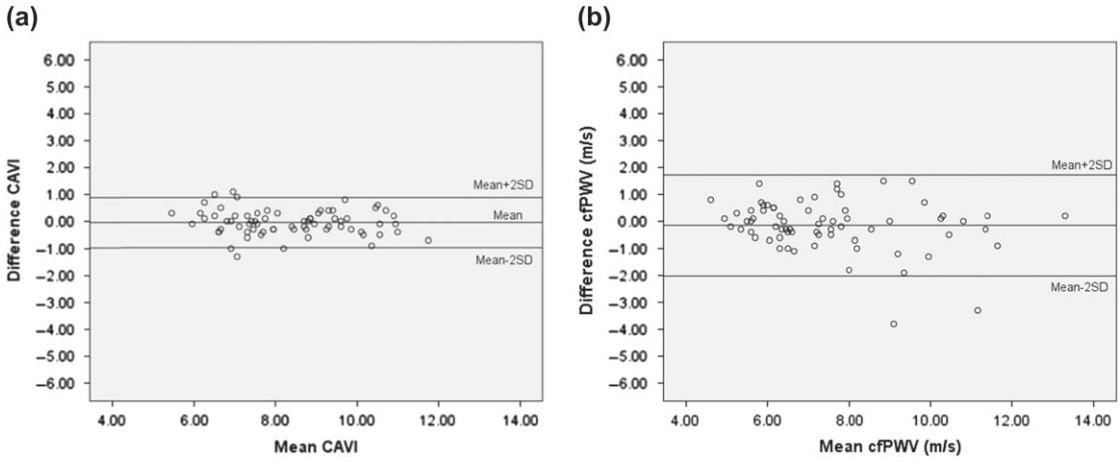

Figure 1. Bland-Altman plots showing the within-observer differences in cardio-ankle vascular index (CAVI) and carotid femoral pulse wave velocity (cfPWV) measurements against the mean value. (a) CAVI; (b) cfPWV.

determinant of CAVI ($p < 0.001$). Furthermore, the patterns of variation showed no significant difference among groups. Variation of CAVI in multivariate analysis is shown in Table II.

Diurnal variation of cfPWV

In univariate analysis, time effect was shown to be significant ($p = 0.007$). However, this significant time effect was shown only in HY. CfPWV was 3.6%

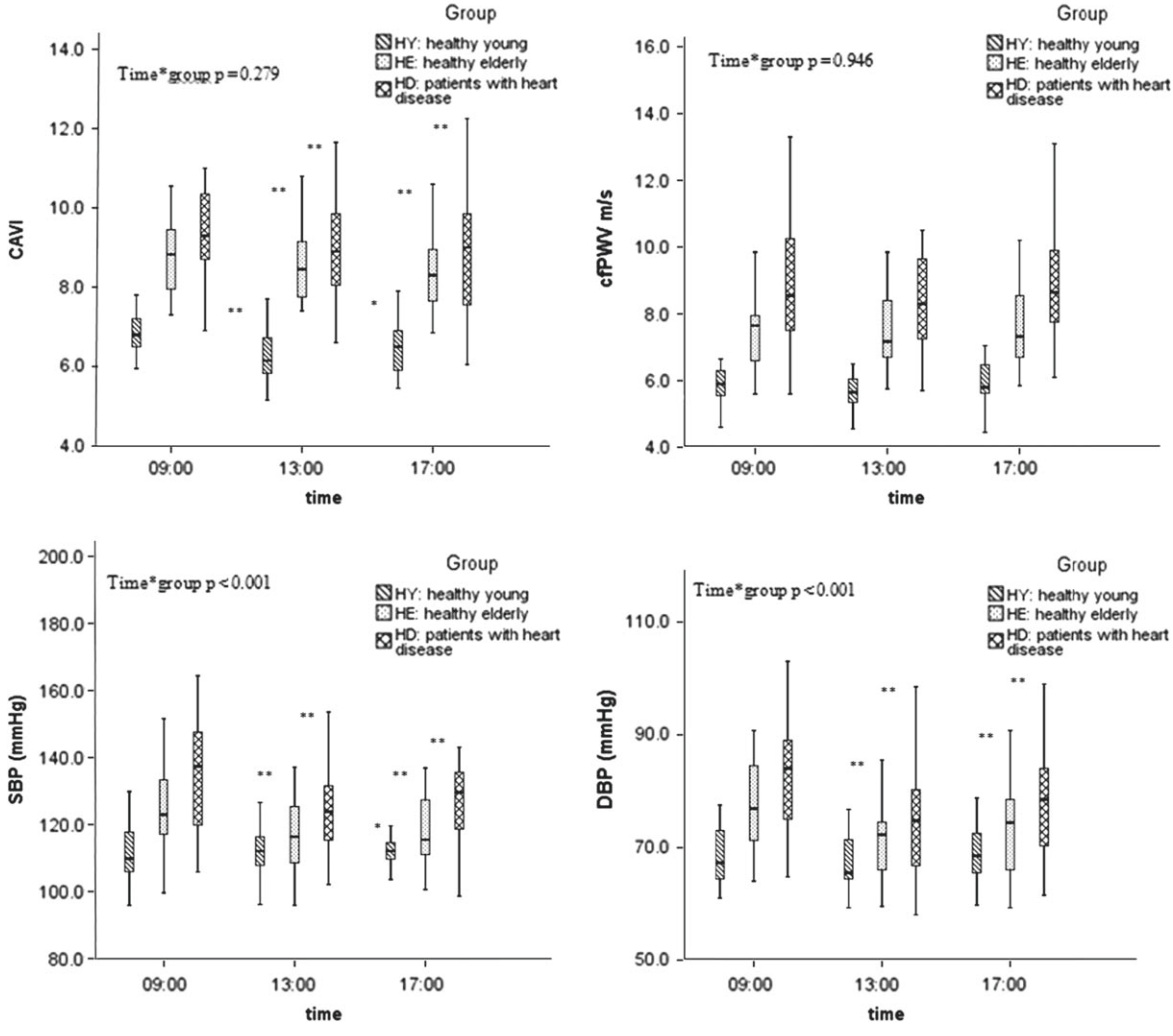

Figure 2. Diurnal variation of cardio-ankle vascular index (CAVI), carotid femoral pulse wave velocity (cfPWV), systolic (SBP) and diastolic blood pressure (DBP). Diurnal variation of CAVI, cfPWV, SBP and DBP. **p<0.01, *p<0.05 compared with 09:00.

Table II. Variation of cardio-ankle vascular index (CAVI) in multivariate analysis.

Parameter	Estimate	*p*-value	95% Confidence interval	
			Lower bound	Upper bound
[Time 1 = 17:00 h]	0.950	0.002	0.919	0.982
[Time 2 = 13:00 h]	0.958	0.022	0.924	0.994
[Time 3 = 09:00 h]	reference	–	–	–
[Group 1 = healthy young]	1.078	0.209	0.958	1.213
[Group 2 = healthy elderly]	0.990	0.761	0.930	1.054
[Group 3 = patients with heart disease]	reference	–	–	–
[Time = 1] × [Group = 1]	0.999	0.956	0.954	1.045
[Time = 1] × [Group = 2]	1.004	0.844	0.961	1.050
[Time = 1] × [Group = 3]	reference	–	–	–
[Time = 2] × [Group = 1]	0.966	0.157	0.922	1.013
[Time = 2] × [Group = 2]	1.013	0.559	0.969	1.059
[Time = 2] × [Group = 3]	reference	–	–	–
[Time = 3] × [Group = 1]	reference	–	–	–
[Time = 3] × [Group = 2]	reference	–	–	–
[Time = 3] × [Group = 3]	reference	–	–	–
Age	1.010	0.000	1.008	1.013
Sex	1.015	0.538	0.967	1.066
MAP	1.000	0.618	0.999	1.002

MAP, mean arterial pressure. Results were presented as changes in the ratio of geometric means of CAVI with 95% confidence intervals.

higher at 17:00 h than at 13:00 h ($p = 0.016$), but the differences between 09:00 and 17:00, 09:00 and 13:00 h were not significant. Furthermore, no significant diurnal variations were found in HE and HD patients (Figure 2).

In multivariate analysis, the time effect lost significance after adjusting for age, sex and MAP. Age ($p < 0.001$) and MAP ($p < 0.001$) were shown to be significant determinants of cfPWV. Variation of cfPWV in multivariate analysis is shown in Table III.

Diurnal variation of blood pressure

The variation of systolic (SBP) and diastolic blood pressure (DBP) are shown in boxplots in Figure 2. Systolic and diastolic blood pressure showed a significant highest value at 09:00 and

Table III. Variation of carotid femoral pulse wave velocity (cfPWV) in multivariate analysis.

Parameter	Estimate	*p*-value	95% Confidence interval	
			Lower bound	Upper bound
[Time 1 = 09:00 h]	0.989	0.571	0.952	1.028
[Time 2 = 17:00 h]	1.022	0.213	0.987	1.059
[Time 3 = 13:00 h]	reference	–	–	
[Group 1 = healthy young]	1.093	0.243	0.941	1.269
[Group 2 = healthy elderly]	0.952	0.215	0.880	1.030
[Group 3 = patients with heart disease]	reference	–	–	
[Time = 1] × [Group = 1]	1.032	0.210	0.982	1.085
[Time = 1] × [Group = 2]	1.009	0.688	0.964	1.057
[Time = 1] × [Group = 3]	reference	–	–	
[Time = 2] × [Group = 1]	1.008	0.753	0.961	1.056
[Time = 2] × [Group = 2]	0.981	0.403	0.936	1.027
[Time = 2] × [Group = 3]	reference	–	–	
[Time = 3] × [Group = 1]	reference	–	–	
[Time = 3] × [Group = 2]	reference	–	–	
[Time = 3] × [Group = 3]	reference	–	–	
Age	1.012	0.000	1.009	1.016
Sex	1.007	0.834	0.946	1.071
MAP	1.004	0.000	1.002	1.007

MAP, mean arterial pressure. Results were presented as changes in the ratio of geometric means of cfPWV with 95% confidence intervals.

lowest value at 13:00 h in both univariate and multivariate analysis after adjustment for age and sex ($p < 0.001$).

The correlation of CAVI and cfPWV and their relationships to blood pressure

There was a significant positive correlation between CAVI and cfPWV ($r = 0.773$, $p < 0.001$). CAVI showed only a weak though significant correlation with both SBP ($r = 0.547$) and DBP ($r = 0.389$), whereas cfPWV was strongly correlated with SBP ($r = 0.701$) and DBP ($r = 0.578$).

Day-to-day variation versus daytime variation

The coefficient of variation (CV) of the two visits (with a week apart) was 2.9% for CAVI and 4.1% for cfPWV. There were no significant differences between the first and the second visit for CAVI ($p = 0.965$) and cfPWV ($p = 0.590$).

Discussion

To the best of our knowledge, this is the first study which investigated diurnal variation of arterial stiffness using two devices with the same individuals divided into three different populations. The main findings of the present study are, firstly, that CAVI showed a significant diurnal variation with the highest value at 09:00 h, and secondly, there was a lack of diurnal variation of cfPWV. These findings point out the need to take time of day and type of measurement into consideration when measuring arterial stiffness.

A significant diurnal variation of CAVI with a morning peak pattern was found in 65.7% of the participants. The effect of time on CAVI was shown to be significant in both univariate and multivariate analysis. The absolute differences of the morning-to-evening variation in CAVI in HY and HE in the present study were almost comparable to the differences of CAVI scores between healthy individuals and hypertensive patients of similar age in two different age groups (30–39 and 60–69 years, respectively) [30]. This implies diurnal variation of CAVI is in a clinically relevant range and needs to be taken into consideration when interpreting the results regardless of the measuring time. The phenomenon of the morning peak could be explained by an attenuated vascular response, which may be associated with a reduction of the nitric oxide level and an increase of the vasoconstriction mediated by endothelin-1 [7]. Further, higher arterial stiffness in the morning may be aggravated by higher plasma epinephrine, norepinephrine serum concentration [12] and plasma renin activity [11] in the early morning hours. This has been shown also to be associated with a lower level of blood fibrinolytic activity [31] and higher levels of platelet aggregability [32]. Thus, the morning peak in CAVI may reflect a true diurnal increase in arterial stiffness which is in line with several pathophysiological reactions underscoring the important clinical meaning of the morning surge for cardiovascular events. The absolute CAVI values in HY were significantly lower than those in HE and HD patients, but the variation patterns showed no significant difference among the three groups. A surprising finding was that HD and HE showed no significant differences in both the absolute values and the variation pattern. We cannot exclude possible influences of medication on the results of HD patients in this study. Shirai et al. [33] reported an acute decrease of CAVI after the administration of the alpha1-blocker doxazosin. However, there was no acute effect of beta1-blocker (metoprolol) on CAVI. Further, ARBs have been shown to reduce CAVI [34,35] and cfPWV [36] in hypertensive patients. Thus, the medication intake might have mitigated morning vascular stiffening in HD patients and eliminated the disease-associated differences between HE and HD patients.

Previous studies showed the effect of time of day on arterial stiffness outcomes with inconsistent results. Ter Avest et al. [16] investigated the diurnal variation of cfPWV in 19 healthy individuals and showed no significant difference between 09:00 and 14:00 h. Drager et al. [15] reported consistent results in 15 healthy young individuals with no circadian variation of cfPWV among 08:00, 12:00, 16:00 and 20:00 h. However, Bodlaj et al. [14] showed a significantly higher value of PWV at 08:00 than at 12:00 and at 17:00 h. The discrepancy among studies could be explained by the fact that Bodlaj et al. used carotid-radial PWV instead of carotid-femoral PWV. Further, Kollias et al. [10] showed a progressive increase of cfPWV from the morning until the evening in 35 hypertensive patients without medication treatment. The exact mechanism for this adverse behavior is not clear. But it is known that patients with hypertension may have a disturbed diurnal variation pattern possibly due to endothelial dysfunction [37]. However, there is no study assessing diurnal variation of arterial stiffness using CAVI.

In the present study, the coefficient of variation of cfPWV measured tonometrically by the Sphygmocor device (6.1%) was nearly twice as much as for CAVI (3.2%), which was comparable with that reported by Shirai et al. of 3.8% [24]. Unlike CAVI, there is a lack of diurnal variation in cfPWV after adjusting for age, sex and MAP in our study population. The difference may be reasoned by the measurement of different arterial properties; CAVI reflects both central elastic and peripheral muscular arterial stiffness, while cfPWV measures central arterial stiffness alone. Further, the relative higher intra-observer variability of cfPWV measurements [15]

may mask possible daytime variations. Age and MAP are two significant determinants of cfPWV. When adjusting for age, sex and MAP, the time effect lost significance suggesting that variation of cfPWV may at least partly be attributed to the change in blood pressure, which already has been shown in previous studies [10,15,16].

Furthermore, we think the variation of CAVI and cfPWV cannot be simply explained by the change in blood pressure for the following two reasons: Firstly, the variation patterns were not exactly the same for CAVI, cfPWV and blood pressure. CAVI showed a peak value in the morning and decreased from morning to the evening. Systolic and diastolic blood pressure showed the highest value in the morning and the lowest value at noon. However, variation of cfPWV is not significant during the daytime. Secondly, after adjustment for MAP, the CAVI value maintained significantly different among different measurement time-points during the day suggesting that the variation is not due to blood pressure change.

As an additional result of our study, we found no significant difference between the first and the second visit in CAVI and cfPWV. Contrary to the time of day variation, the day-to-day variation seems to be a minor factor to be taken into consideration when performing these measurements in longitudinal studies. However, day-to-day variation analysis in this study was only done in healthy young individuals. Therefore, the result cannot be extrapolated to patients with cardiovascular diseases or to elderly adults.

Clinical perspectives

Although it is always suggested to standardize the time of the day when performing the non-invasive measurement of arterial stiffness, the exact time effect on the outcomes of CAVI and cfPWV in healthy individuals of different ages and patients with heart disease has not been reported before. In the present study, there was shown to be a lack of diurnal variation of cfPWV after adjusting for age, sex and mean blood pressure in our study population. However, there was shown to be a significant diurnal variation in CAVI, indicative of real and pronounced vascular stiffening in the morning in HY, HE and HD groups. The study provides support to standardize the time of the day of arterial stiffness measurement of CAVI in routine clinical practice and longitudinal studies. Further, care has to be taken in choosing the measuring instruments which might lead to different results and clinical interpretations.

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Authors' contributions

Initial study design was from the primary investigator AST; participant recruitment was done by MC and AST; measurements of CAVI and cfPWV were performed by YL and MC; labor data collection was done by MC, YL and HH; statistical analysis was done by YL and AST; data interpretation was done by YL, AST, MC, JRR, LGO and HH; the first and final draft of manuscript was edited by YL, JRR and LGO and AST. All authors read and approved the final manuscript.

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3.3 Paper 3.

Lower body versus upper body resistance training and arterial stiffness in young men

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Abstract

Resistance training has been shown to increase arterial stiffness. The purpose of the present study was to examine and compare the systemic arterial stiffness responses to acute lower body (LRT) and upper body (URT) resistance training. Twenty healthy young men [median age: 26 years (interquartile range 23, 32)] underwent LRT, URT and whole body resistance training (WRT). Before and immediately after, as well as 20 min, 40 min and 60 min after each training session, we measured the cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV) using VaSera VS-1500N. We used mixed models for repeated measurements to estimate the post-exercise differences in CAVI and baPWV between the three resistance training modes. Immediately after exercise cessation, both CAVI and baPWV were lower for LRT compared with URT [CAVI: -0.93 (95% confidence interval [CI] -1.15, -0.70); baPWV: -2.08 m/s (95% CI -2.48, -1.67)]. Differences between LRT and URT gradually decreased during follow-up. At 60 min post exercise, the difference in CAVI and baPWV between LRT and URT was -0.11 (95% CI -0.33, 0.12) and -0.57 m/s (95% CI -0.97, -0.17), respectively. Compared with WRT, LRT induced a decrease and URT an increase in arterial stiffness across all time points. In conclusion, LRT presents more favorable post-exercise arterial stiffness than URT. Our results suggest that LRT or WRT may be preferred over URT in individuals with impaired arterial stiffness.

Key words: strength training,vascular health, pulse wave velocity,arm and leg training

INTRODUCTION

Arterial stiffness is an emerging biomarker for the assessment of vascular health [16]. It increases with advancing age both in normotensive healthy adults [43] and hypertensive patients [19]. Arterial stiffness is independently associated with cardiovascular disease events and all-cause mortality [15,44].

Aerobic exercise training has beneficial effects on arterial stiffness and is recommended as a preferred exercise modality for improving cardiovascular health [9,39,40]. While muscular strength is known to be associated with reduced mortality and lower blood pressure [1,34] the effects of different resistance training modes on arterial wall properties are unclear. Cross-sectional studies demonstrated that resistance trained men have stiffer central [22] and peripheral [3] arteries than their sedentary age-matched peers. While high intensity resistance training was recommended for maximizing muscular strength [9,33], it was found to have unfavorable effects on arterial stiffness, resulting in an increased central arterial stiffness [6,21,23]. However, this finding is not universal [4,28,29,32].

Studies investigating the effect of acute high intensity resistance exercise on arterial stiffness employed a whole body resistance training (WRT) and consistently showed an exercise-induced increase in central arterial stiffness [7,12]. In contrast, peripheral arterial stiffness was unchanged after WRT [12]. There is growing evidence that the effect of resistance training on vascular function differs between arms and legs [27,29,31]. Maeda and colleagues found that short term lower body resistance training (LRT) did not result in central arterial stiffening [20]. A recent study confirmed this result: a 10-week resistance exercise intervention with LRT did not alter brachial-ankle pulse wave velocity (baPWV), whereas an increase in baPWV was observed for upper body resistance training (URT) [29]. However, other studies examining the vascular response to acute LRT and URT showed inconsistent results [8, 13,17].

No study so far has assessed the comparative acute effects of LRT and URT in the same study population. In this study, we assessed differences between cardio-ankle vascular index (CAVI) and baPWV in response to a single session of supervised LRT, URT and WRT for healthy young men. CAVI is a cuff-based measurement representing the stiffness of the aorta, femoral and tibial artery which has been shown to be less affected by blood pressure at the time of measurement compared to baPWV [37]. We hypothesized that LRT is associated with

lower exercise-induced arterial stiffness than URT or WRT. Our study is the first to examine the acute effects of LRT, URT and WRT on CAVI and baPWV. The effect of the frequently applied whole body resistance training, i.e. a combination of lower and upper limb resistance training, on arterial stiffness is unknown. We aimed to investigate whether a combination of both training modalities neutralizes the expected oppositional effects of each individual resistance exercise. We further investigated whether acute single sessions of lower and upper limb resistance training induce distinguished response patterns of arterial stiffness.

METHODS

Experimental approach to the problem

Study participants were required to come to the laboratory four times. The four visits included the one repetition maximum (1RM) test, followed by LRT, URT and WRT. The wash-out period to exclude any carry-over between the visits was at least 72 hours [5,7,8]. Upon being tested, all participants were at least two hours postprandial. CAVI and baPWV were measured before and immediately after, as well as 20 min, 40 min and 60 min after each training session. For each participant, all training sessions were initiated around the same time of day in order to minimize possible diurnal variations in the outcomes [18] (Figure 1). The study was performed according to the Guidelines for Good Clinical Practice and was approved by the Ethics Committee "Beider Basel" (EKBB: 149/11) of the University of Basel, Switzerland. All participants signed a written informed consent. We have read and understood the IJSM's ethical standards document and we confirm that the study meets the ethical standards of the journal [11].

Subjects

We advertised this study at the Department of Sport, Exercise and Health, University of Basel, on both the university campus and in our outpatient clinic. The inclusion criteria were: 1) male gender; 2) age 20-40 years; 3) normotensive; 4) free of clinically relevant cardiovascular diseases such as diabetes or hypertension or respective medications; 5) without any musculoskeletal, orthopedic or neurological problems that might have limited the participant's ability to exercise. The exclusion criteria were: 1) current smoker or former smoker with <5 years since smoking cessation; 2) any type of structured resistance or aerobic training in the preceding six months; 3) acute illness or active infection.

Procedures

One repetition maximum test

Participants first warmed up for five minutes on a bicycle ergometer at a perceived exertion level 3 (on the CR 10 Borg scale), followed by familiarization with each of the resistance training machines (Cybex Eagle® seated leg press, leg curl, leg extension, chest press, fly backward, fly forward, USA) which was achieved by completing several submaximal repetitions [42]. First, the participants performed 5-10 repetitions with a light load (~40-60% of the estimated 1RM). After three minutes of rest, participants performed 3-5 repetitions with an increased load (~50-70% of the estimated 1RM) through the full range of motion. After another three minutes of rest, participants performed 2-3 repetitions with a load of 60-80% of the estimated 1RM. After these submaximal repetitions, the 1RM was determined within five trials with rest periods of three minutes between the trials. All repetitions were performed at the same speed of movement and the range of motion was consistent between the trials. The final weight lifted successfully was recorded as the participant's 1RM [42].

Acute resistance training

Participants underwent three supervised resistance exercise sessions at least 72 hours apart. The resistance exercise bouts all consisted of a 5-minute warm-up on a bicycle ergometer followed by four sets of 10 repetitions each using 70% of the 1RM. Participants completed seated leg press, leg curl and leg extension in the LRT session, and chest press, fly backward and fly forward in the URT session. For the WRT session, participants completed all six exercises in the order of LRT then followed by URT. Eccentric and concentric phases were timed to be one second each. The recovery time between exercises and between sets of repetitions was two minutes. To avoid valsalva maneuvers, participants were asked to exhale during the process of lifting the weights/ exertion phase and inhale while lowering the weight/ relaxation phase.

CAVI and baPWV measurements

We assessed CAVI and baPWV using a non-invasive and blood pressure-independent device (VaSera VS-1500, Fukuda Denshi, Japan) [14, 36]. Both stiffness parameters were calculated from an electrocardiogram (ECG), phonocardiogram and the brachial as well as the tibial wave forms. Prior to the assessment, participants rested for 10 minutes in a supine position in

a quiet room. Cuffs were wrapped around the upper arms and ankles with ECG leads attached to the wrist and a microphone placed on the mid sternum for phonocardiography. Vascular length (L) between the heart valve and ankle artery was indirectly calculated from the height of the participant using the following formula: L = 0.77685 * height - 1.7536 (in cm) (manufacturer's information). ECG leads at the wrist and a phonocardiogram on the sternal border in the second intercostal space were applied to detect the initial notch of the pulse wave at the heart and the ankle. The time delay of the pulse wave from the heart to the ankle was thereby determined by a foot-to-foot-method [38]. The extremity blood pressure levels were measured using the oscillometric method and heart rate was obtained by electrocardiogram module of VaSera device. In our lab, the coefficient of variation was 3.2% for CAVI [18] and 1.9% for baPWV. We used the average of the left and right CAVI and baPWV for data analysis.

Statistical analyses

We used mixed models for repeated measurements to estimate post-exercise differences in CAVI and baPWV between the three resistance training modes [24]. For the main analysis, we used a direct product structure on the covariance matrices which allowed an unstructured matrix for the covariances among the three levels of resistance training mode and a first-order autoregressive structure for the covariances among the four levels of post-exercise measurement time. The direct product of these two matrices along with a participant random effect gave covariances among the 3*4=12 measurements for each participant, although different participants were still assumed to be independent. In our models, we adjusted for baseline CAVI and baPWV.

We carried out three sensitivity analyses. First, we used a mixed model with random effects that allowed the covariances to vary due to the participant, the resistance training mode, and the post-exercise measurement time. This again gave covariances among the 12 measurements for each participant (although different participants were still assumed to be independent). Second, we removed unusually low and high values of CAVI and baPWV to see whether our estimates were robust to outliers. We considered data points as unusually low and high if they were more than 1.5 times the interquartile range away from the first and third quartile of the CAVI and baPWV values within combinations of resistance training mode and measurement time. Third, we additionally adjusted for concurrent mean arterial pressure

(MAP) to see whether the impact of the resistance training mode on CAVI and baPWV was mediated by its impact on MAP.

For each analysis, we report estimates with 95% confidence intervals in order to emphasize clinical relevance over statistical significance. We used SAS version 9.3 (SAS Institute Inc., Cary, NC) for our analyses and for graphics, we used R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and the R add-on package *lattice* version 0.20-29 [35].

RESULTS

Participant characteristics

Twenty healthy young men with a median age of 26 years (interquartile range [IQR] 23, 32) were enrolled in this study. Table 1 provides an overview of the participants' baseline characteristics. The median time between adjacent visits was seven days (IQR 7, 9; range 3, 25).

Arterial stiffness in response to exercise

Whereas both LRT and WRT induced an initial decrease in CAVI, URT did not induce an apparent change in CAVI (Figure 2(A)). For baPWV, both URT and WRT induced an initial increase, whereas LRT induced a slight decrease (Figure 2(B)). Compared with baseline, pulse pressure initially increased for LRT and WRT, whereas there was no apparent change for URT (Figure 2(C)). At 60 min following exercise cessation, all values had approximately returned to baseline for LRT, URT and WRT.

Hemodynamic parameters in response to exercise

Hemodynamic parameters before and after LRT, URT and WRT are shown in Table 2. Systolic blood pressure was slightly elevated immediately after both LRT and WRT, but was decreased 20 min after URT. Heart rate was elevated immediately after each training session.

Effect of acute LRT versus URT on arterial stiffness

Immediately after exercise cessation, both CAVI and baPWV were lower for LRT compared with URT [CAVI: -0.93 (95% confidence interval [CI] -1.15, -0.70; P<0.001); baPWV: -2.08 m/s (95% CI -2.48, -1.67; P<0.001)]. Differences between LRT and URT then decreased as time since exercise cessation increased. At 60 min following exercise cessation, the difference

in CAVI between LRT and URT was -0.11 (95% CI -0.33, 0.12; P=0.347); and for baPWV, it was -0.57 m/s (95% CI -0.97, -0.17; P=0.007) (Table 3). Compared with WRT, LRT was followed by decreased and URT by increased values of CAVI and baPWV across all post-exercise measurement times (Table 3).

Sensitivity analyses

Our models with random effects, which allowed covariances to vary according to participant, resistance training mode, and post-exercise measurement time, led to a similar pattern of differences in CAVI and baPWV between LRT and URT, with an initial exercise-induced decrease in CAVI and baPWV for LRT compared to URT, as well as decreasing differences between LRT and URT as the time since exercise cessation increased. Compared with WRT, LRT was followed by more favorable and URT by less favorable values of CAVI and baPWV across all post exercise measurement times (data not shown). Estimated differences between resistance training modes appeared robust to outliers. Compared to the main analysis, results after excluding unusually low and high values of CAVI and baPWV exhibited slightly smaller differences in CAVI and baPWV between LRT and URT immediately after exercise cessation [CAVI: -0.87 (95% CI -1.09, -0.65; P<0.001) (7 values excluded); baPWV: -1.78 m/s (95% CI -2.08, -1.47; P=<0.001) (17 values excluded)]. Compared with WRT, LRT was followed by a decrease and URT by an increase in values of CAVI and baPWV across all post-exercise measurement times. When additionally adjusting for concurrent MAP, results remained comparable to those from the main analysis, suggesting that the impact of the resistance training mode on CAVI and baPWV is not mediated by its impact on MAP (data not shown).

DISCUSSION

Our results suggest that acute LRT and URT elicit different vascular responses measured by CAVI and baPWV in healthy young men. Both CAVI and baPWV were lower immediately after LRT compared with URT. LRT and URT carried out one after the other seemed to cumulatively impact CAVI and baPWV, with arterial stiffness following WRT being in the range between those following either LRT or URT alone.

Previous studies showed an increase in arterial stiffness following high intensity resistance training [6,21,23,29]. The increase in arterial stiffness was associated with URT and WRT, but not with LRT [20,29]. An acute bout of high intensity WRT consistently induced an increase in central arterial stiffness [7,12]. It was, however, not certain whether acute bouts of

LRT and URT elicit different effects on arterial stiffness. Heffernan and colleagues found that acute LRT did not alter central arterial stiffness but that it decreased peripheral arterial stiffness in the exercised leg in healthy young adults [13]. On the other hand, URT was shown to increase central arterial stiffness [8,17].

In the present study, both CAVI and baPWV were decreased immediately after LRT, reinforcing earlier findings regarding the acute effect of LRT on peripheral arterial stiffness [13]. Our results suggest an initial increase in baPWV following URT and WRT, which is in line with previous studies examining the effect on central arterial stiffness [7, 12].

Our study shows that both CAVI and baPWV are lower after LRT compared with URT. The reasons for this are likely to be manifold but the dilatation of muscular arteries seems to be a key mechanism. It has previously been shown that the exercise-induced reduction of arterial stiffness is accompanied by a dilatation of muscular arteries and an increase in blood flow [25]. In this study, increasing dosage of nitroglycerin provoked similar adaptations of arterial stiffness compared to increasing exercise intensities. Acute exercise induces an increase in nitric oxide production by higher shear stress, leading to a dilatation of muscular arteries and an increase in blood flow [25]. Vasodilatation reduces vascular smooth muscle tone, whereby wall stress is transferred from the stiffer collagen fibers to the more elastic elastin fibers, making the arterial wall more compliant as a consequence [2]. In LRT more muscle mass is involved and the surface area of the muscular arteries involved is greater. It therefore seems plausible that the nitric oxide- induced vasodilatation of the muscle artery beds in the lower body has stronger effects on arterial stiffness than URT. Next to nitric oxide, other factors such as myokines, adenosine, acidity and temperature may also influence alterations of arterial stiffness post exercise. Sympathetic activity may be another key mechanism explaining the differences in limb training. Compared with LRT, URT was shown to elicit higher norepinephrine (NE) concentration [29], MAP [45], heart rate and perceived exertion [30]. LRT and URT seem to induce differential sympathetic tones [10,41]. An increased NE plasma concentration is associated with an elevated sympathetic nervous system activity, which may in turn have a sympathetic vasoconstrictive effect on the arterial wall and lead to an increased arterial stiffness in URT [29].

The estimated mean difference in CAVI between LRT and URT immediately after exercise cessation was comparable to that between normotensive and hypertensive young men of

similar age [26]. A 1 m/s increase in baPWV has been shown to correspond with a 12% increase in the number of cardiovascular disease events, a 13% increase in cardiovascular mortality and a 6% increase in all-cause mortality [44]. The estimated mean difference in baPWV between LRT and URT immediately after exercise cessation may therefore be clinically relevant and should be taken into account when interpreting limb specific resistance exercise. We did not find a higher MAP after URT compared with LRT as this was the case in an earlier study [45]. Thus, changes in blood pressure do not seem to be the reason for differences in arterial stiffness after acute LRT compared with URT. However, an increased heart rate may contribute to the increased arterial stiffness after URT compared with LRT.

Since all study participants completed the WRT session in the order of LRT followed by URT, our results suggest that measurements of arterial stiffness following WRT are typically in the range between those following either LRT or URT alone. It may be concluded that LRT and URT have a cumulative impact on arterial stiffness. While LRT showed a beneficial effect on CAVI, URT showed no apparent effect on CAVI. The beneficial effect of LRT was not superimposed by a detrimental effect of URT so that the post-exercise effect of WRT was still similar to that of LRT. For baPWV, the initial marginally beneficial effect of LRT was, however, superimposed by the detrimental effect of URT, resulting in a post-exercise effect of WRT that was similar to that of URT alone. In contrast to CAVI, baPWV increased after acute bouts of URT, which is in line with previous findings of chronic resistance training [21,29]. It needs to be stated that in the acute setting, the crude baPWV is the more physiologic index of arterial stiffness than the calculated CAVI, with ongoing hemodynamic adaptations to arterial pressure changes in both extremities.

Finally, it should be noted that the same relative intensity (70% of the 1RM) was applied to LRT and URT, but that the total volume of WRT (LRT then followed by URT) was twice that of LRT or URT alone. Our results of an elevated baPWV and therefore an increased systemic arterial stiffness after WRT have not been published before, but they are consistent with previous studies examining the effect of acute high intensity WRT on central arterial stiffness [7,12].

Our study presents some limitations. First, the study population consists of healthy young men only. Women were not eligible in order to (1) allow for a better comparison with previous studies and (2) exclude a potential effect of the menstrual cycle. Second, all

participants received the three different resistance training modes in the same order. It cannot be excluded that our estimated post-exercise differences in CAVI and baPWV between LRT, URT and WRT are confounded by the order of the exercise modes. We focused on measuring CAVI and baPWV since little is known about this part of the vascular bed. Both of these parameters include the central as well as the peripheral vasculature and thus represent systemic arterial stiffness. We did not aim to differentiate between the effects of resistance exercise on local, central or peripheral arterial segments.

Practical Application

In a real-life setting, 70% 1RM resistance training is commonly used for improving muscular strength. However, its effect on the cardiovascular system is less certain. The present study shows the acute exercise-induced change in arterial stiffness. Acute LRT and URT elicit different systemic arterial stiffness responses in healthy young men. While acute LRT is associated with a lower exercise-induced arterial stiffness than acute URT, differences between LRT and URT diminish within 60 min of exercise cessation. Our results suggest that LRT and WRT are less harmful for systemic arterial stiffness compared with URT alone and that LRT or WRT may be preferred over URT in individuals with impaired arterial stiffness. This may have implications for resistance exercise prescription from a cardiovascular perspective. The present study investigated the effect of resistance training on systemic arterial stiffness. Whether the impact of acute LRT, URT and WRT differs for central, peripheral and systemic arterial stiffness and whether and to what extent variation of intensity affects the vascular bed remains to be elucidated in future studies.

Conflict of interest

There are no conflicts of interest or funding to disclose.

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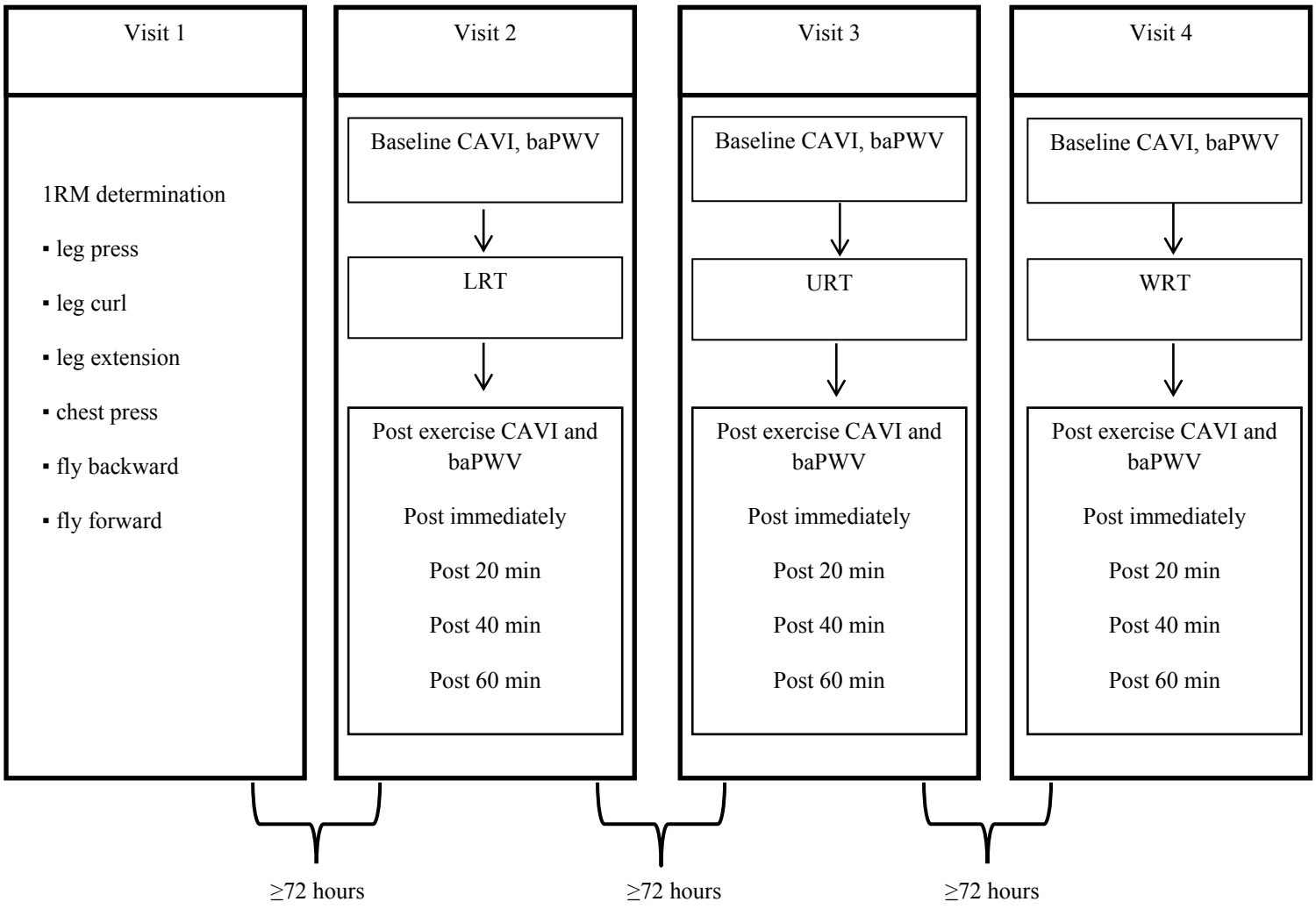
Figure legends

Fig. 1 Flow diagram of the study design. Abbreviations: 1RM, one repetition maximum; CAVI, cardio-ankle vascular index; baPWV, brachial-ankle pulse wave velocity; LRT, lower body resistance training; URT, upper body resistance training; WRT, whole body resistance training.

Fig. 2 Arterial stiffness before and after lower body (LRT), upper body (URT) and whole body resistance training (WRT). The points denote individual measurements, jittered horizontally to avoid over-plotting. The lines join the medians of the points within each resistance training mode. **(A)** Cardio-ankle vascular index (CAVI). **(B)** Brachial-ankle pulse wave velocity (baPWV). **(C)** Pulse pressure (PP).

Figure 1: Flow diagram of the study design



Abbreviations: 1RM, one repetition maximum; CAVI, cardio-ankle vascular index; baPWV, brachial-ankle pulse wave velocity; LRT, lower body resistance training; URT, upper body resistance training; WRT, whole body resistance training.

Figure 2(A):

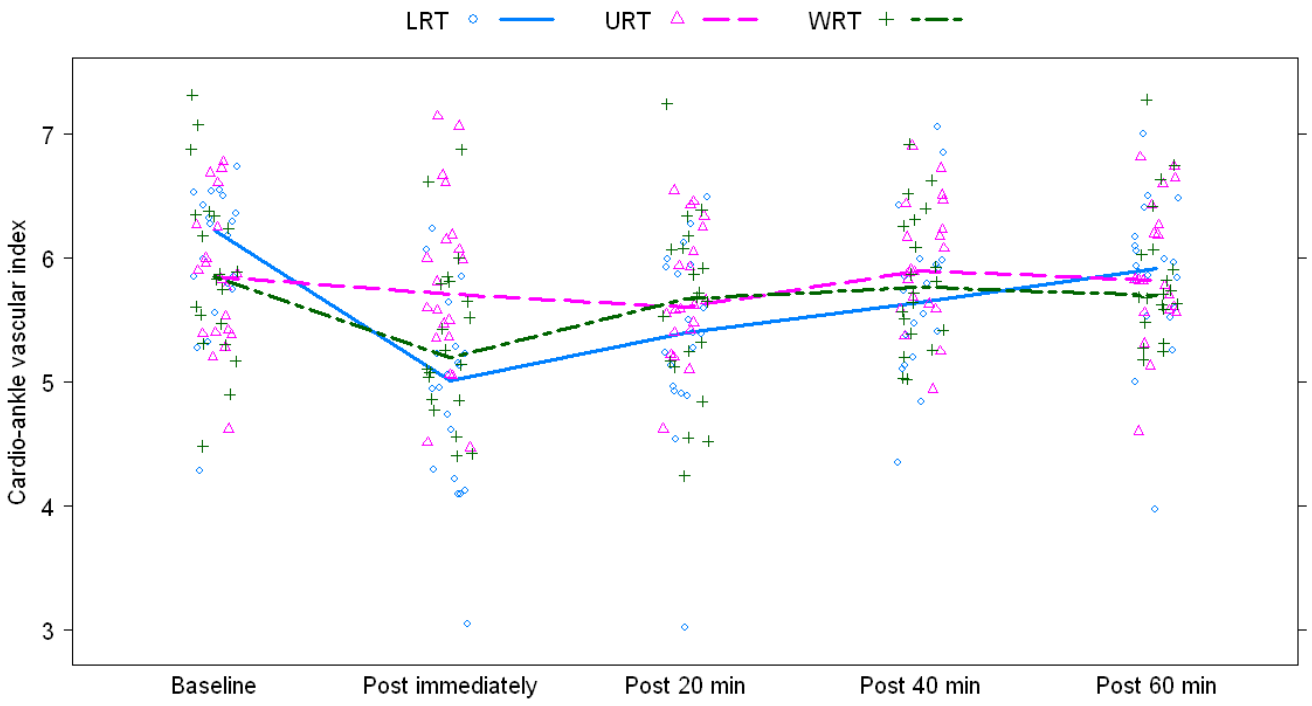

LRT
URT
WRT
Cardio-ankle vascular index
7
6
5
4
3
Baseline
Post immediately
Post 20 min
Post 40 min
Post 60 min

Figure 2(B):

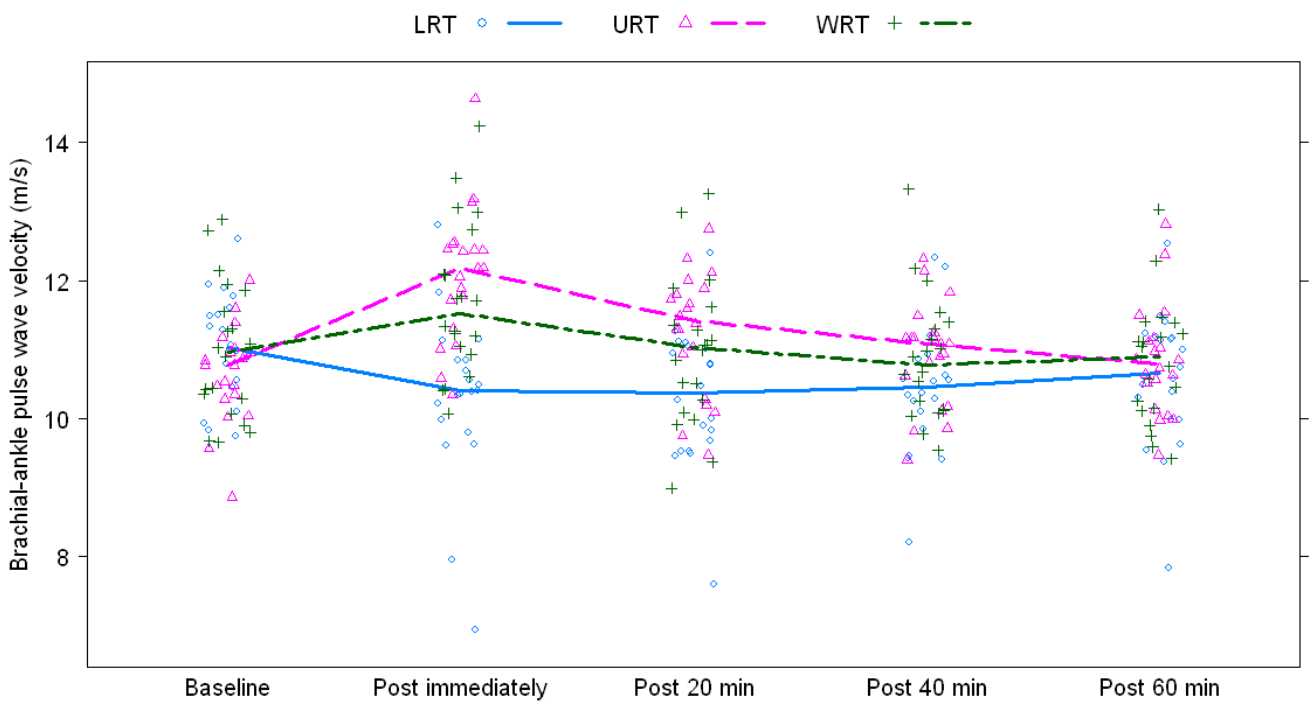

LRT
URT
WRT
Brachial-ankle pulse wave velocity (m/s)
14
12
10
8
Baseline
Post immediately
Post 20 min
Post 40 min
Post 60 min

Figure 2(C):

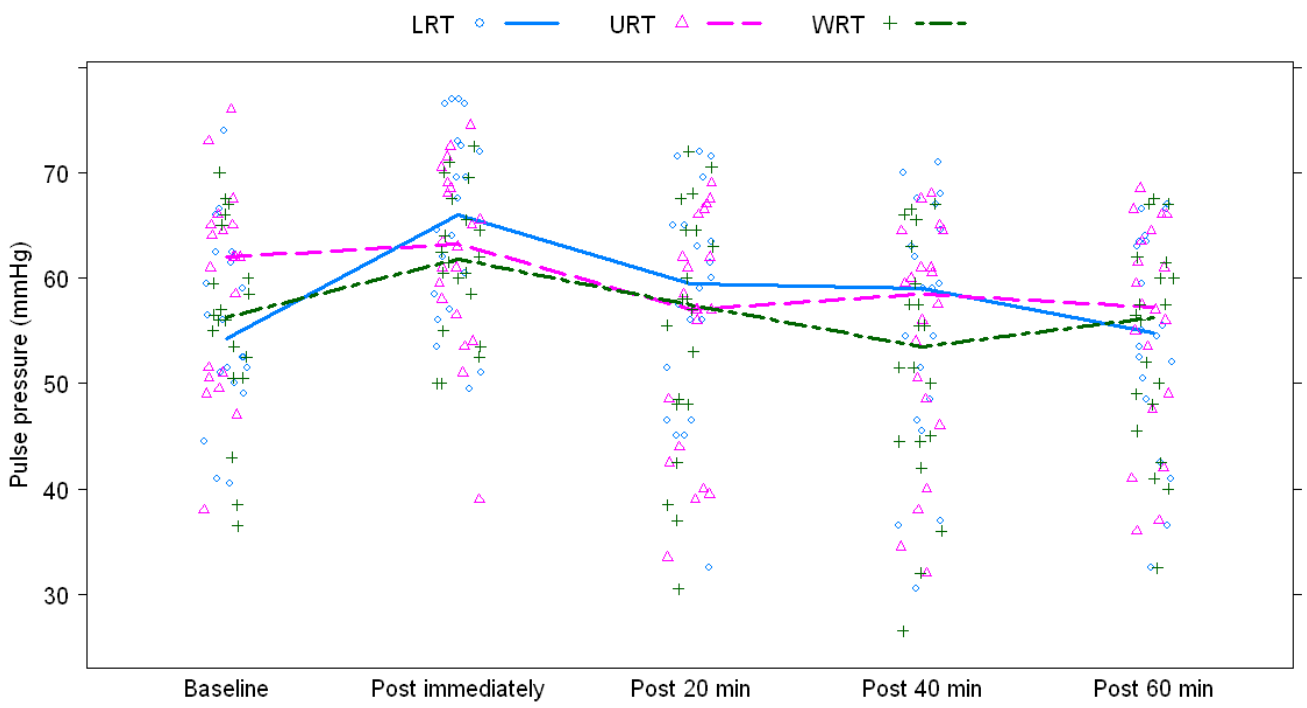

LRT
URT
WRT
Pulse pressure (mmHg)
70
60
50
40
30
Baseline
Post immediately
Post 20 min
Post 40 min
Post 60 min

Table 1: Baseline characteristics of study participants

Characteristic	All participants (n=20)
Male gender, n (%)	20 (100)
Age, years	25.5 (23.0, 32.0)
Height, cm	178 (172, 184)
Weight, kg	75.1 (68.0, 81.5)
BMI, kg/m^2	23.2 (22.4, 25.3)
1RM leg press, kg	220 (187, 223)
1RM leg curl, kg	85.6 (73.8, 89.0)
1RM leg extension, kg	119 (93.1, 133)
1RM chest press, kg	79.0 (69.8, 91.9)
1RM fly backward, kg	62.0 (59.5, 74.6)
1RM fly forward, kg	68.0 (62.0, 81.3)
Cardio-ankle vascular index*	6.23 (5.77, 6.47)
Brachial-ankle pulse wave velocity*, m/s	11.0 (10.5, 11.6)
Pulse pressure*, mmHg	54.3 (50.5, 62.0)
Systolic blood pressure*, mmHg	133 (128, 139)
Diastolic blood pressure*, mmHg	77.3 (74.0, 80.3)
Mean arterial pressure*, mmHg	96.9 (93.7, 98.8)
Heart rate*, bpm	56.0 (49.0, 63.5)

Abbreviations: BMI, body mass index; 1RM, one repetition maximum.

Data are medians (interquartile range) unless stated otherwise.

*Baseline measurements taken at the second visit before the start of lower limb resistance training.

Table 2: Hemodynamic parameters before and after lower body resistance training (LRT), upper body resistance training (URT) and whole body resistance training (WRT)

	Baseline	Post immediately	Post 20 min	Post 40 min	Post 60 min
Lower body resistance training (LRT)					
SBP, mmHg	133	139	136	135	137
	(128, 139)	(135, 145)	(127, 140)	(123, 140)	(128, 140)
DBP, mmHg	77.3	72.3	73.8	75.0	76.5
	(74.0, 80.3)	(68.3, 77.3)	(70.0, 79.0)	(71.5, 76.5)	(75.3, 79.8)
MAP, mmHg	96.9	95.8	94.1	94.5	96.4
	(93.7, 98.8)	(91.9, 97.8)	(91.0, 98.7)	(92.2, 97.0)	(94.0, 98.1)
HR*, bpm	56.0	71.5	65.5	61.0	63.0
	(49.0, 63.5)	(64.0, 82.0)	(57.0, 76.5)	(55.0, 68.0)	(53.0, 68.5)
Upper body resistance training (URT)					
SBP, mmHg	139	138	128	133	134
	(130, 142)	(132, 142)	(121, 139)	(123, 140)	(127, 142)
DBP, mmHg	75.8	71.8	74.0	75.3	77.3
	(74.3, 78.8)	(68.8, 79.8)	(68.5, 79.8)	(73.5, 81.3)	(72.5, 81.8)
MAP, mmHg	97.3	93.7	92.6	95.2	96.2
	(93.9, 99.7)	(90.3, 99.4)	(86.3, 98.1)	(89.7, 99.7)	(92.1, 101)
HR, bpm	60.5	74.0	67.5	63.0	65.5
	(52.5, 66.5)	(66.5, 84.5)	(57.5, 77.0)	(56.0, 69.0)	(53.5, 70.0)
Whole body resistance training (WRT)					
SBP, mmHg	135	138	131	131	133
	(129, 140)	(134, 142)	(125, 140)	(120, 138)	(126, 140)
DBP, mmHg	77.5	77.5	75.0	75.8	77.5
	(73.5, 81.5)	(72.0, 80.5)	(71.0, 81.8)	(71.5, 80.0)	(75.3, 82.3)
MAP, mmHg	97.2	97.6	95.2	94.3	97.9
	(91.9, 102)	(93.4, 100)	(89.6, 99.0)	(88.9, 98.5)	(90.7, 101)
HR†, bpm	58.0	78.0	69.5	62.0	58.0
	(51.0, 62.0)	(62.0, 84.0)	(57.0, 76.0)	(50.0, 70.0)	(51.5, 66.0)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate.

Data are medians (interquartile range).

*Available in 19 (95%) participants at 40 min of LRT cessation.

†Available in 19 (95%) participants at 40 min of WRT cessation.

Table 3: Baseline-adjusted differences in average cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV)

	Estimate (95% CI)	P-value
Difference in CAVI		
Post immediately		
LRT-URT	-0.93 (-1.15, -0.70)	<0.001
LRT-WRT	-0.48 (-0.75, -0.21)	0.001
URT-WRT	0.44 (0.18, 0.71)	0.002
Post 20 min		
LRT-URT	-0.39 (-0.62, -0.17)	0.001
LRT-WRT	-0.24 (-0.52, 0.03)	0.077
URT-WRT	0.15 (-0.12, 0.41)	0.276
Post 40 min		
LRT-URT	-0.33 (-0.56, -0.11)	0.004
LRT-WRT	-0.18 (-0.45, 0.09)	0.187
URT-WRT	0.15 (-0.11, 0.42)	0.260
Post 60 min		
LRT-URT	-0.11 (-0.33, 0.12)	0.347
LRT-WRT	-0.04 (-0.31, 0.23)	0.779
URT-WRT	0.07 (-0.20, 0.33)	0.610
Difference in baPWV (m/s)		
Post immediately		
LRT-URT	-2.08 (-2.48, -1.67)	<0.001
LRT-WRT	-1.48 (-1.87, -1.09)	<0.001
URT-WRT	0.60 (0.33, 0.88)	<0.001
Post 20 min		
LRT-URT	-1.22 (-1.63, -0.82)	<0.001
LRT-WRT	-0.70 (-1.09, -0.31)	0.001
URT-WRT	0.52 (0.25, 0.80)	<0.001
Post 40 min		
LRT-URT	-0.77 (-1.18, -0.37)	<0.001
LRT-WRT	-0.50 (-0.89, -0.11)	0.013
URT-WRT	0.27 (-0.00, 0.55)	0.052
Post 60 min		
LRT-URT	-0.57 (-0.97, -0.17)	0.007
LRT-WRT	-0.31 (-0.70, 0.08)	0.122
URT-WRT	0.26 (-0.01, 0.54)	0.061

Abbreviations: CI, confidence interval; CAVI, cardio-ankle vascular index; LRT, lower body resistance training; URT, upper body resistance training; WRT, whole body resistance training; baPWV, brachial-ankle pulse wave velocity.

3.4 Paper 4

Study protocol: The effect of high velocity low intensity versus low velocity high intensity resistance training on arterial stiffness

Introduction

Age and pathological related arterial stiffening in elderly individuals and patients with cardiovascular disease has been recognized in clinical studies (O'Rourke et al., 2011). Decreased arterial compliance and increased arterial stiffness is associated with an increased risk of cardiovascular disease (Laurent et al., 2006; Mattace-Raso et al., 2006). Resistance training has been suggested as an important component in a comprehensive exercise program by ACSM and AHA in recent years (Kraemer et al., 2002). However, these recommendations were primarily based on its favorable effects on muscular strength, muscle power (Kraemer et al., 2002). There are by so far few recommendations particularly with respect to resistance training and cardiovascular function. Based on our previous review study, resistance exercise has no unfavorable effects on arterial stiffness if the training is of low intensity, in a slow eccentric manner or using lower limbs only. Therefore, a properly designed resistance training program may keep the above established benefits while minimizing the arterial stiffening.

Previous studies showed controversial results on arterial stiffness following different types of resistance trainings. These controversies were mainly in healthy young individuals. A preliminary meta-analysis in our laboratory showed that low intensity (40%1RM) was associated with a 6.6% (-13.4%, 0.3)(P=0.06) decrease of brachial-ankle PWV (baPWV) in comparison with the control group (Okamoto et al., 2008a). Five studies (Cortez-Cooper et al., 2005; Miyachi et al., 2004; Okamoto et al., 2006; Okamoto et al., 2008b; Okamoto et al., 2009) that involved high intensity exercise demonstrated a significant increase of arterial stiffness of 9.8% (3.1%, 16.4%) (P=0.004) in comparison with control groups. One of these five showed a differing effect following resistance training with different muscle groups; upper limb resistance exercise training led to a 12.9% increase of baPWV, while baPWV following lower limb resistance exercise training caused no change (Okamoto et al., 2009). Based on our previous review study, resistance exercise has no unfavorable effects on arterial stiffness if the training is of low intensity, in a slow eccentric manner or using lower limbs only.

However, studies in middle-aged adults showed comparable effects on arterial stiffness;. Yoshizawa et al. demonstrated no change in both central (aortic PWV) and peripheral arterial stiffness (femoral-ankle PWV) following a 12-week resistance training (6 whole body exercises, 60%1RM, 3 sets, 10 repetitions, 2d/w) in middle-aged women (32-59 yr)(Yoshizawa et al., 2009). Cortez-Cooper et al. showed a non-significant change in carotid

artery compliance and carotid-femoral pulse wave velocity following a 13-week strength training (10 whole body exercises, 70%1RM, 1 set, 8-12 repetitions, 3d/w) in middle-aged and older adults (52±2yr) (Cortez-Cooper et al., 2008). On this point, further studies are needed to figure out the difference of the cardiovascular response following resistance training between healthy young and middle-aged adults.

Further, Okamoto et al (Okamoto et al., 2006) found that eccentric resistance training seemed to have a neutral effect on arterial stiffness, while concentric training increased arterial stiffness. Therefore, we believe that resistance training with a reduced or shorten concentric phase might be prospective from the cardiovascular perspective. Power resistance training, whose concentric phase is as fast as possible, might cause less or no impairment of arterial stiffness because of a lower vasopressor response and could be thus a prospective resistance training mode to increase greater muscle power (Fielding et al., 2002) without arterial stiffening.

It is not well established whether healthy young and middle-aged adults would gain the similar benefits on arterial compliance using the recommended guidelines program for increasing muscle strength following conventional training (Kraemer et al., 2002; Leszczak et al., 2012; Raj et al., 2012) or for increasing muscle power (Fielding et al., 2002; Leszczak et al., 2012; Porter, 2006) following high velocity training. Furthermore, it is also unknown whether the hemodynamic mechanism of response to high velocity low intensity resistance training and low velocity high intensity resistance training are different.

Thus, there is an explicit need of longitudinal randomized controlled studies for assessing and determining the effects of the two resistance training modes on arterial stiffness in healthy young and middle-aged adults, which may contribute to the exercise prescription with particular respect to cardiovascular function in different populations.

Methods

Subjects

Inclusion criteria: (i) 18-45 years old (ii) currently healthy (iii) BMI<=30 (iv) BP<=140/90mmHg (v) no musculoskeletal, orthopedic or neurological problems which may limit their ability to exercise.

Exclusion criteria: (i) current smokers or former smokers with <5 years smoking cessation (ii)

pregnancy (iii) patients with prior myocardial infarction or any other cardiac disease being a contraindication against resistance training (iv) undertook any type of structured resistance or aerobic training in the preceding 6 months.

This study was advertised in the Department of Sports, Exercise and Heath, on university campus as well as in our outpatient clinic. The research protocol was approved by the Ethics Committee of the University of Basel and all the participants provided written informed consent.

One Repetition maximum test

Participants warmed up prior to testing for 5 minutes on ergometer. After a 1 minute rest period, participants were familiarized with each of the resistance machines by performing 8-10 repetitions of a light load (~50% of predicted 1RM). After a 1 minute of rest, participants performed a load (~80% of estimated 1RM) through the full range of motion. After each successful performance, the weight increased until a failed attempt occurred. One minute rests were given between each attempt and the 1-RM was attained within 5 attempts and 5 minutes rest separated each test. In order to facilitate the recovery and reduce the effect of fatigue, exercises will be alternated between the upper and lower body (Thompson et al., 2010).

High velocity low intensity (HVLI) versus low velocity high intensity (LVHI) resistance training

Participants in the intervention group underwent supervised resistance-training. During each training session, they were required to complete 6 exercises in the following order: chest press, fly backward, abdominal, seated leg press, leg extension, leg curl. Recovery time between each exercise was controlled for 2 minutes (Leszczak et al., 2012).Volume load was calculated using the equation: volume load = sets*repetitions*relative intensity (Raj et al., 2012) and the total volume was matched in HVLI and LVHI. For the HVLI resistance training, all the participants are required to do their concentric phase as fast as possible. Eccentric phase was controlled for 2 seconds (Henwood et al., 2008; Sayers & Gibson, 2010). Recovery time between sets was controlled for 2 minutes (Kraemer et al., 2002). Participants completed 4 sets of 8-10 repetitions of their 30%-50% 1RM (1-2 week: 30%1RM, 3-6week: 40%1RM, 7-10 week: 50% 1RM). For the LVHI resistance training, eccentric and concentric phase were controlled for 2 seconds (Tanimoto & Ishii, 2006). Recovery time between sets was controlled

for 2 minutes (Kraemer et al., 2002). Participants completed 3 sets of 8-12 repetitions of their 50-70% 1RM (1-2 week: 50%1RM, 3-6week: 60%1RM, 7-10 week: 70% 1RM).

Arterial stiffness

All the arterial stiffness measurements were performed and analyzed with the following noninvasive devices by one experienced observer blinded to the group assignments

CAVI and baPWV measurements

CAVI was assessed based on the oscillometric measurement of the baPWV using blood-cuffs at each upper arm and above each ankle (VaSera VS-1500, Fukuda Denshi; Japan)(Shirai et al., 2006) . Cuffs were applied to the four extremities with ECG leads attached to the wrist for electrocardiogram and one microphone placed on the mid sternum for phonocardiography. The baPWV is defined as the velocity with which the pulse wave propagates along the arterial wall from the heart to the ankle (I would still call it baPWV since this is the term used in the literature). Vascular length (L) between the heart valve and ankle artery is indirectly calculated from the individual height of the patient using the formula: L=0.77685*height - 1.7536 (in cm) (manufacturer's information). Electrocardiogram leads at each wrist and a phonocardiogram on the sternal border in the second intercostal space are applied to detect the initial notch of the pulse wave at the heart and the ankle. Thereby the time delay of the pulse wave from the heart to the ankle is determined by a foot-to-foot-method. The baPWV is then calculated by dividing the vascular length by the time delay of the pulse wave. CAVI is mathematically derived from Bramwell-Hill´s equation and the stiffness parameter ß with an inclusion of the baPWV using the following equation: $CAVI= \ln(Ps/Pd)*2\rho/\Delta P*PWV^2$ (Ps=systolic blood pressure, Pd=Diastolic blood pressure, PWV= Pulse wave velocity from heart to ankle, ρ=blood density(1.03×10^3 kg/m^3), ΔP=pulse pressure) (Shirai et al., 2006). By this procedure, CAVI is argued to be less dependent on the blood pressure at time of measurement (Ibata et al., 2008; Shirai et al., 2006; Shirai et al., 2011; Takaki et al., 2008).The extremity BP levels were measured oscillometrically.

cfPWV

cfPWV was assessed using SphygmoCor (AtCor, Medical Pty Ltd, Sydney, Australia). Pulse waves were recorded using a high-fidelity tonometric transducer at two sites (right carotid artery and right femoral artery). cfPWV was determined as the difference in travel time of the

pulse wave between the two recording sites and the heart, divided by the transit distance. The transit distance was measured using a scale by subtracting the distance from the carotid recording site to the suprasternal notch from the distance between the suprasternal notch and the femoral recording site (Weber et al., 2009). The time of the waveforms was compared with that of R wave on a simultaneously recorded ECG (Van Bortel et al., 2012). Prior to cfPWV measurement, blood pressure was measured in the right brachial artery using Omron oscillometric standard device (Omron, M9 Premium, Japan). cfPWV measurements were considered to have met the quality control parameters if two consecutive measurements were visually acceptable and within 1.5 m/s of each other with a standard deviation of less than 10% (Sigrist et al., 2010).

Study design

Prior to the 10-week training, participants were invited to the training center 2 times for familiarization. Familiarization included completing one or two sets of each exercise with a very light weight under supervision. After completing this familiarization period, participants were invited to the lab for 1 repetition maximum (1RM) test followed by group randomization (HVLI, LVHI and CON) before the intervention phase.

Participants in the intervention group underwent 2 supervised resistance-training sessions per week for 10 weeks. The training intensity was progressively increased to the target percent of 1RM to keep a consistent relative intensity considering the new individual adaption during the training period.

CAVI, baPWV, aortic PWV, 1RM and Body Composition (BC) in HVLI, LVHI and CON group were measured 2 times: before training (baseline) and at 10 weeks (completion of the training). All the participants will be instructed to do the training at the similar time of day to avoid the diurnal variation in physical activity and arterial stiffness parameters. Participants should refrain from all the other exercise training except their HVLI or LVHI session or daily activity (CON) during the study period.

Hypothesis

1) A single session of HVLI resistance training would not change or even decrease the CAVI, while LVHI resistance training would reversely increase the CAVI.

2) A single session of HVLI resistance training would not change or even decrease the baPWV, while LVHI resistance training would reversely increase the baPWV.

Current status of this project

However, due to the difficulty of recruitment and high dropout rate (nearly 20%), we had involved 49 participants, which is far less than the required sample size (87 participants, 29 per group). Therefore, data analysis and publication of this study is pending and this project is now awaiting an additional round of recruitment.

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Main findings

The literature review (paper 1) has provided substantial evidences that aerobic exercise training can be assigned as a de-stiffening exercise. Resistance exercise may not have unfavorable effects with training of low intensity, in a slow eccentric manner or using lower limbs only. These results may also have implications in the exercise prescription for general population as well as hypertensive patients.

The results of the methodological study (paper 2) show that under standardized condition, outcome measures of CAVI and cfPWV have sufficient reliability to be used in intervention studies, allowing the results from the subsequent studies to be interpreted with confidence when investigating changes in arterial stiffness in groups of healthy adults and patients with heart disease.

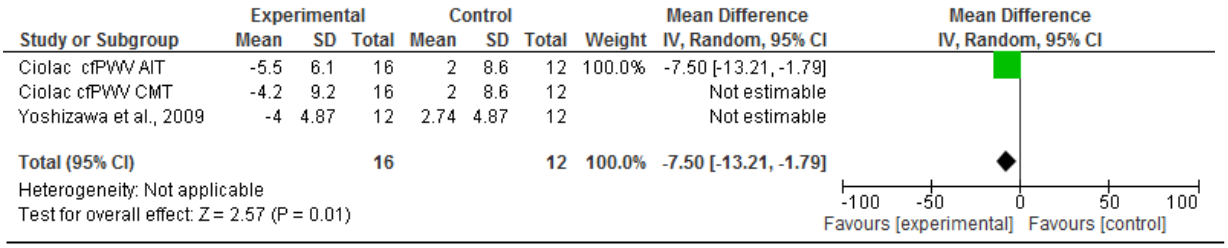
The results of the acute intervention study (paper 3) demonstrated that LRT or WRT may be preferred over URT in individuals with impaired arterial stiffness.

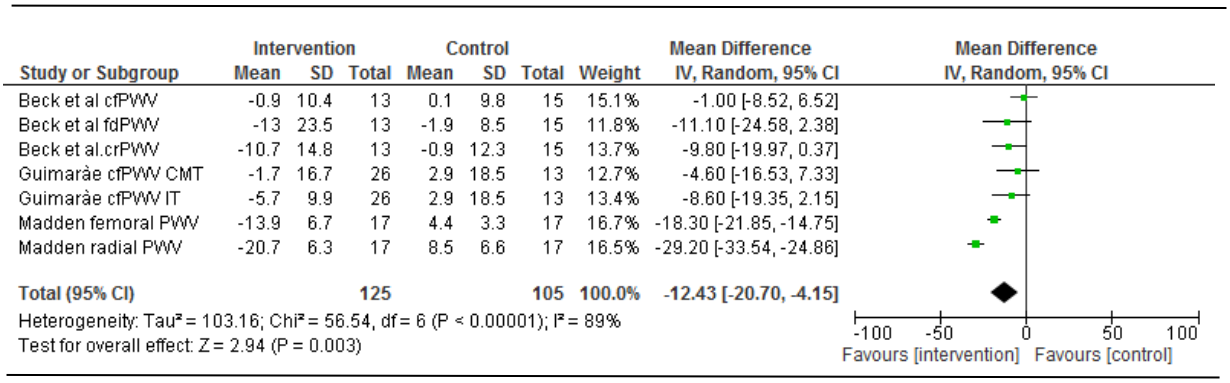
Effect of exercise training on arterial stiffness (paper 1)

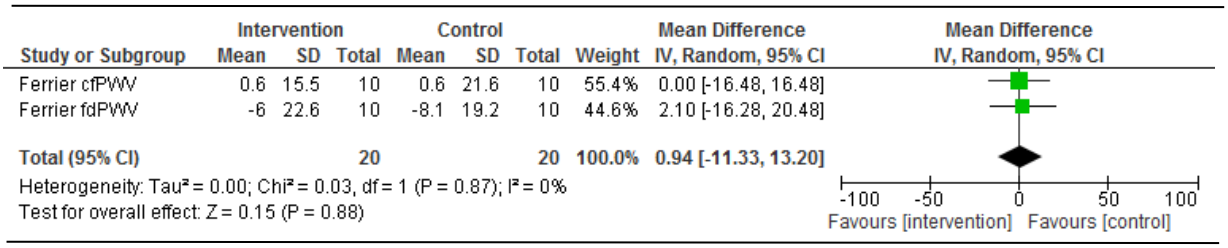
Our results demonstrate that aerobic exercise training reduced arterial stiffness in healthy normotensive (Ciolac et al., 2010; Yoshizawa et al., 2009), and hypertensive patients (Beck et al., 2013; Guimarães et al., 2010; Madden et al., 2009). However, aerobic exercise failed to alter large arterial stiffness in older populations with isolated systolic hypertension (Ferrier et al., 2001) (Figure 1. Arterial stiffness following aerobic exercise training). Further comparing exercise modalities, vigorous interval training was shown to be superior to traditional moderate continuous training in reducing arterial stiffness in normotensive populations at risk for future cardiovascular events (Ciolac et al., 2010). However, whether high intensity interval training is well tolerated in hypertensive patients is unknown. Further studies are required to confirm that high intensity interval training is superior to traditional moderate continuous training in reducing arterial stiffness in hypertensive patients. Age alone increased arterial stiffness even in the well trained individuals (Cameron et al., 1999; Tanaka et al., 2000). Furthermore, the increase of arterial stiffness was more pronounced in hypertensive patients (Vaitkevicius et al., 1993; Wallace et al., 2007). Thus, to determine the effect of aerobic

exercise in populations whose arterial stiffness has some alteration is of great clinical importance and aerobic training initiated at a younger age may be more effective. In addition, since arterial stiffening seems to precede hypertension (Kaess et al., 2012), studies in normotensive individuals with increased arterial stiffness are warranted in order to show a direct preventive effect of aerobic exercise training on the artery.

Figure 1. Arterial stiffness following aerobic exercise training: healthy adults (upper panel), patients with mixed hypertension (middle panel), patients with isolated systolic hypertension (lower panel)







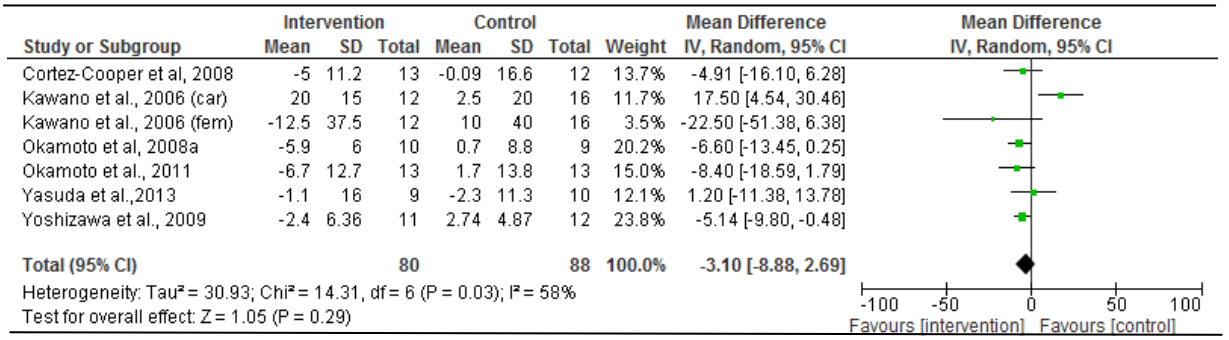
As is shown in the forest plot (Figure 2. Arterial stiffness following resistance training: intensity), low to moderate intensity resistance training does not result in arterial stiffening measured as carotid-femoral pulse wave velocity (cfPWV) (Cortez-Cooper et al., 2008; Yoshizawa et al., 2009), femoral ankle pulse wave velocity (faPWV) (Yoshizawa et al., 2009) or cardio-ankle vascular index (CAVI) (Yasuda et al., 2013). This is in line with the beneficial

blood pressure adaptation to moderate resistance training (Cornelissen et al., 2011). On the other hand, our review showed that high intensity and concurrent high-volume resistance training was found to be associated with an increase of arterial stiffness (Miyachi et al., 2004; Okamoto et al., 2006, 2008b, 2009). This is consistent with previous studies reporting blood pressure elevation after vigorous resistance training (MacDougall et al., 1985; Palatini et al., 1989). However, there may be a neutral effect of high intensity resistance training on central arterial stiffness as shown in obese normotensive young men (Croymans et al., 2014).

Even a favorable effect on arterial stiffness has been shown for resistance training in a slow eccentric manner (Okamoto et al., 2006, 2008b) or with the lower limbs, although intensity was high (Okamoto et al., 2009). (Figure 3. Arterial stiffness following resistance training: eccentric versus concentric training). In addition, a non-randomised controlled study showed that progressive high intensity resistance training without volume increase did not alter arterial stiffness (Casey et al., 2007). Further, resistance training in young individuals was associated with an increase of central and systemic arterial stiffness, but not peripheral arterial stiffness. However, this was not the case in middle-aged and older adults. One explanation for the divergent effects following eccentric and concentric training could possibly be due to the difference in actively contracting muscle mass, which is lower in eccentric training than concentric training (Komi et al., 2000; Linnamo et al., 2003; Madeleine et al., 2001). The greater amount of active muscle mass in concentric resistance training may cause a stronger vasopressor response, which again increases the strain on the arteries. Further, compared to eccentric training, concentric training results in a greater increase in blood pressure (Okamoto et al., 2006), which may be associated with a stiffening of the arterial wall (London & Guerin, 1999).

The difference in upper limb and lower limb resistance training (Figure 4. Arterial stiffness following resistance training: lower versus upper limb training) might be explained by higher heart rates (Pivarnik et al., 1988) and higher blood pressure levels (Volianitis & Secher, 2002) induced by upper limb exercises compared to lower limb exercises with the same workload. Furthermore, it is of clinical importance to investigate the effects of resistance training on arterial stiffness in hypertension. Noteworthy, the only existing RCT in prehypertensive patients showed that moderate resistance training improved peripheral arterial stiffness (Beck et al., 2013). Further studies are warranted for precise resistance exercise recommendations for hypertensive patients.

Figure 2. Arterial stiffness following resistance training: low to moderate intensity (upper panel), high intensity (lower panel).



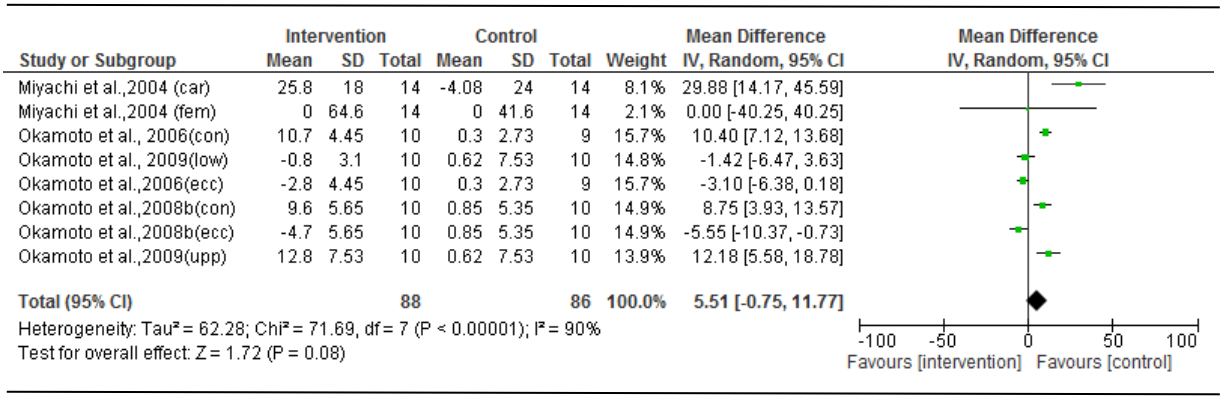
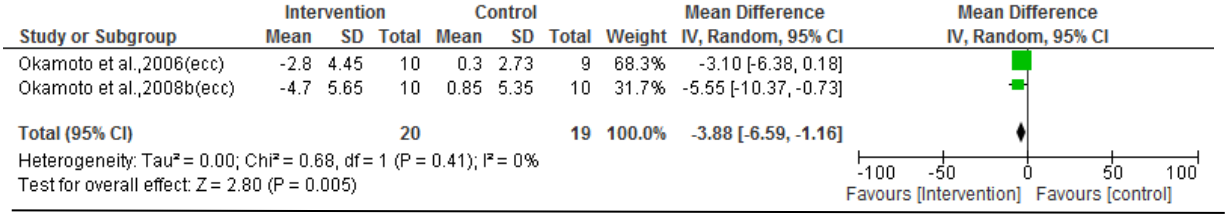


Figure 3. Arterial stiffness following resistance training: eccentric (upper panel) versus concentric training (lower panel)



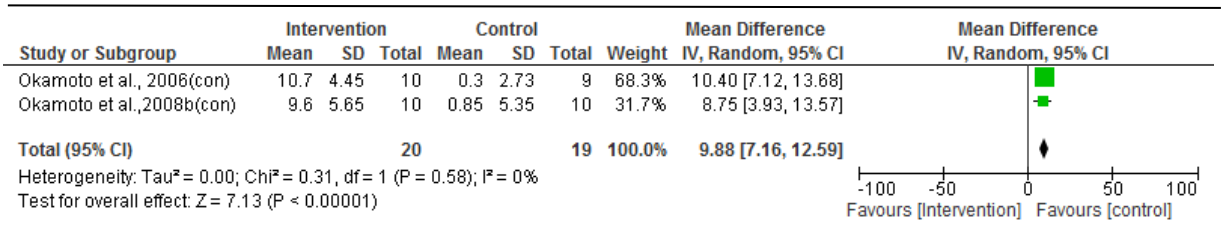
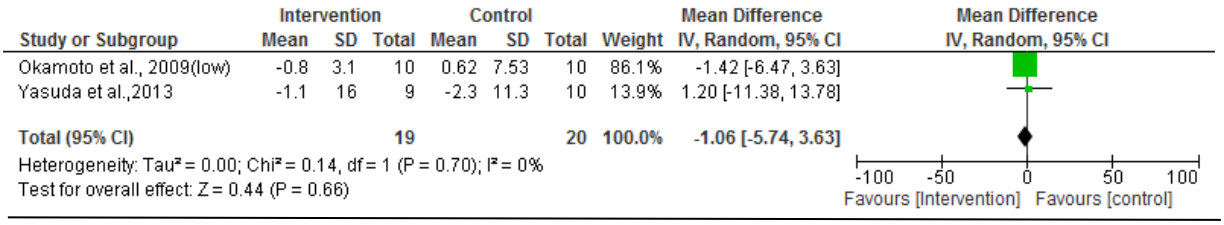
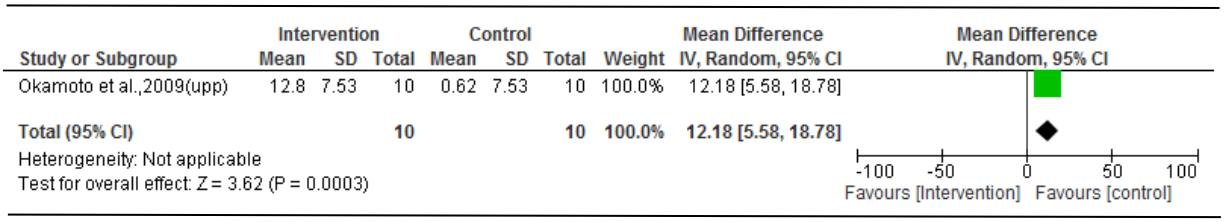


Figure 4. Arterial stiffness following resistance training: lower (upper panel) versus upper limb training (lower panel)





Diurnal variation of arterial stiffness (paper 2)

Although it is always suggested to standardize the time of the day when performing the non-invasive measurement of arterial stiffness in research, the exact time effect on the outcomes of CAVI and cfPWV in healthy individuals of different ages and patients with heart disease has not been reported before. In our methodological study, there was shown to be a lack of diurnal variation of cfPWV after adjusting for age, sex and mean blood pressure in our study population. However, there was shown to be a significant diurnal variation in CAVI, indicative of real and pronounced vascular stiffening in the morning in healthy young, healthy elderly and patient groups. The absolute differences of the morning-to-evening variation in CAVI in healthy young and healthy elderly in the present study were almost comparable to the differences of CAVI scores between healthy individuals and hypertensive patients of similar age in two different age groups (30-39yr and 60-69yr, respectively) in the study of Namekata and colleagues (Namekata et al., 2011). This implies diurnal variation of CAVI is in a clinically relevant range and needs to be taken into consideration when interpreting the results regardless of the measuring time. The study provides support to standardize the time of the day of arterial stiffness measurement of CAVI in our intervention study.

Effect of lower versus upper body resistance training on arterial stiffness (paper 3)

In the intervention study, both CAVI and baPWV were decreased immediately after LRT, which is in contrast to the results of previous studies that have observed an increase in arterial stiffness (Miyachi et al., 2004; Cortez-Cooper et al., 2005; Okamoto et al., 2009; Miyachi, 2013), but reinforcing earlier findings regarding the acute effect of LRT on peripheral arterial

stiffness (Heffernan et al., 2006). One reason for this discrepancy could be that previous studies that observed increases in arterial stiffness following resistance exercise measured central arterial stiffness, while the method used in the current study takes into account a combination of peripheral and central arteries. Therefore, there is a possibility that if opposing changes in central and peripheral arterial stiffness occurred, they may have nullified each other and consequently no overall changes in arterial stiffness were detected. Also, differences in the resistance training protocols may partly explain the difference in results. The increase in arterial stiffness was associated with URT and WRT, but not with LRT in previous studies (Maeda et al., 2006; Okamoto et al., 2009). An acute bout of high intensity WRT consistently induced an increase in central arterial stiffness (DeVan et al., 2005; Heffernan et al., 2007). It was, however, not certain whether acute bouts of LRT and URT elicit different effects on arterial stiffness. Heffernan and colleagues found that acute LRT did not alter central arterial stiffness but decreased peripheral arterial stiffness in the exercised leg in healthy young adults (Heffernan et al., 2006). On the other hand, URT was shown to increase central arterial stiffness (Fahs et al., 2009; Lefferts et al., 2014).

Our study shows that both CAVI and baPWV are lower after LRT compared with URT. The estimated mean difference in CAVI between LRT and URT immediately after exercise cessation (-0.93 (-1.15, -0.70)) was comparable to that between normotensive and hypertensive young men of similar age (Namekata et al., 2011). A 1 m/s higher in baPWV has been shown to correspond with a 12% increase in of the relative risk of cardiovascular disease events, a 13% increase in cardiovascular mortality and a 6% increase in all-cause mortality (Vlachopoulos et al., 2012). The estimated mean difference in baPWV between LRT and URT immediately after exercise cessation (-2.08 (-2.48, -1.67) m/s) (paper 3, Table 3.) may therefore be clinically relevant and should be taken into account when interpreting limb specific resistance exercise. Compared with LRT, URT was shown to elicit higher norepinephrine concentration (Okamoto et al., 2009), mean arterial pressure (Volianitis et al., 2003), heart rate and perceived exertion (Pivarnik et al., 1988). LRT and URT may induce differential sympathetic tones with higher values for URT (Green et al., 2002; Thijssen et al., 2009). An increased norepinephrine concentration may be associated with an elevated sympathetic nervous system activity, which may in turn have a sympathetic vasoconstrictive effect on the arterial wall and lead to an increased arterial stiffness (Okamoto et al., 2009). However, we did not find a higher mean arterial pressure or heart rate after URT compared

with LRT as this was the case in an earlier study (Pivarnik et al., 1988; Volianitis et al., 2003). Thus, changes in blood pressure or heart rate do not seem to be the reason for differences in arterial stiffness after acute LRT compared with URT.

Effect of high velocity resistance training on arterial stiffness (study protocol)

The available evidence from the literature review indicates that resistance exercise seems to have no adverse effect on arterial stiffness if the training is in a slow eccentric manner in healthy individuals. Traditional resistance training generally consists of muscular contractions performed at a relatively slow speed. This is different to emerging novel types of resistance training with higher velocity and lower intensity, which may result in differing effects on arterial stiffness. In high velocity resistance training, in which the concentric phase is performed as quickly as possible, force can be produced very fast. This aspect of power production is important in activities of daily living, especially with respect to fall prevention (Orr et al., 2006; Sayers & Gibson, 2014). It has been shown that high velocity resistance training causes a greater increase in muscle power than low velocity resistance training (Fielding et al., 2002). However, no study exists on the effect of high velocity resistance training on arterial stiffness. Compared to lower velocity, higher velocity resistance movements with a quick concentric phase might have a smaller impact on arterial stiffness because of a smaller vasopressor response. In view of an aging population with an increasing prevalence of hypertension (Kearney et al., 2005), and the progressive reduction in muscular power (Reid & Fielding, 2012) and strength (Doherty, 2013), there is an urgent clinical need to define the optimal type of resistance exercise training. The ideal resistance training should provide muscular benefits without health hazards to the vasculature. At best, the individualized resistance training program has a destiffening effect on the arteries.

Limitations

There are some limitations of the literature review (paper 1) to be mentioned. First, the estimates in this study should be interpreted with caution when compared to other arterial stiffness parameters which were not discussed in this review. Furthermore, the poor methodological quality of some included trials should be acknowledged. We assessed the quality of the included studies using Jadad scale, but we have not excluded the RCTs with a Jadad score<3. We reported all the RCTs that we found according to our inclusion criteria. The existing evidence does not allow firm conclusions. The interpretation is hampered by the

use of different measures of arterial stiffness, varying exercise programs (modality, duration, intensity and frequency), different population-based variables (age, health status) and several confounding factors (e.g. exercise induced weight loss, daily physical activity, diet, medication).

In the methodological study (paper 2), 23 patients (92% of the participants in the patient group) took medications (diuretics, beta-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, statins, proton-pump inhibitor, vitamin, calcium, iron or magnesium). Therefore, we cannot exclude possible influences of medication on the results of those patients in this study. Especially beta blockers are under debate to impair cfPWV (Ting et al., 1995; Williams et al., 2006) which were taken by 13 out of 23 patients in our study.

The acute intervention study (paper 3) presents some limitations. First, the study population consists of healthy young men only. Second, all participants received the three different resistance training modes in the same order. It cannot be excluded that our estimated post exercise differences in CAVI and baPWV between LRT, URT and WRT are confounded by the order of the exercise modes. We focused on measuring CAVI and baPWV since little is known about this part of the vascular bed. Both of these parameters include the central as well as the peripheral vasculature and thus represent systemic arterial stiffness. We did not aim to differentiate between the effects of resistance exercise on central and peripheral arterial segments.

Perspectives

The study on the effect of lower versus upper body resistance training on arterial stiffness contributes to our understanding of two different resistance training modalities, which have been commonly used in a real-life setting for improving muscular strength, from a cardiovascular perspective.

However, the exercise recommendations for improving overall cardiovascular health are varying from young to elderly adults, from healthy adults to patients with cardiovascular disease. Furthermore, whether the training modality which induced acute favorable effect on arterial stiffness can be equally effective in a long-term training modality, also needs to be confirmed.

Therefore, future longitudinal studies with regards to the prescriptions of novel resistance training modalities for older adults or patients with cardiovascular disease are needed.

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