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Isometric exercise training for hypertension (Protocol)

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Isometric exercise training for hypertension

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A B S T R A C T

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

We will aim to conduct a systematic review and meta-analysis quantifying the effects of IRT on systolic, diastolic, mean arterial and 24-hour ambulatory blood pressure. We will also quantify changes in heart rate and heart rate variability, and will attempt to determine which patient demographics and exercise program characteristics are associated with the largest blood pressure changes.

BACKGROUND

In light of the global prevalence of hypertension (Heidenreich 2011; Poulter 2015) the associated economic health care costs are significant. Additionally, although anti-hypertensive medications generally have minimal side-effects, they are historically only efficacious in controlling blood pressure in 20-50% of patients, due to poor effectiveness and adherence (Hajjar 2003; Burnier 2019). Both European and North American treatment guidelines for primary and secondary prevention of hypertension recommend non-pharmacological lifestyle modifications as the first line of therapy, including increasing the levels of physical activity performed by patients (Heidenreich 2011; Cornelissen 2013a). There is evidence from meta-analyses of more than 100 randomised controlled trials (RCTs) that 150 minutes weekly of physical activity offers an alternative intervention that may be used to complement anti-hypertensive medication (James 2014). However, the optimal prescription of exercise training remains unclear.

Dynamic aerobic endurance activity is still the preferred exercise modality for blood pressure management (Whelton 2018). However, patient compliance with this type of intervention is often sub-optimal (Pescatello 2004). Isometric resistance training (IRT) involves sustained muscular contraction against an immovable load or resistance, with no change (or minimal change) in the length of the involved muscle group. One important factor that may impact the efficacy of exercise in lowering blood pressure is the type of exercise performed. Analyses suggest that isometric resistance training may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise (Pescatello 2004; Mosca 2011; Cornelissen 2013b; Smart 2019) but with much less time-investment from patients (approximately 20 minutes per week, rather than two to three hours per week).

Description of the condition

Hypertension or high blood pressure is a chronic medical condition in which a person exhibits persistently elevated arterial blood pressure. Often a person is unaware they have high blood pressure, as there are usually no symptoms. Long-term (chronic) high blood pressure, however, is a major risk factor for heart disease, stroke, kidney disease and many other cardiovascular complications (Hajjar 2003).

High blood pressure is classified as either essential (primary), where the cause is uncertain, or secondary, where it is likely the cause is related to a related condition e.g. being overweight. About 90% to 95% of cases are primary (Ferdinand 2017). Lifestyle factors that increase the risk of hypertension include physical inactivity, excess dietary salt, being overweight or obese, smoking, and alcohol consumption (Whelton 2018). The remaining 5% to 10% of cases are categorised as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the renal arteries, endocrine disorders, or the use of contraceptive medication (Charles 2017).

Blood pressure is expressed by two measurements, the systolic and the diastolic pressures. These are the maximum and minimum pressures, taken at the moment the heart beats and taken in-between heartbeats, respectively. Normal blood pressure at rest is within the range of 100 to140 millimetres of mercury (mmHg) systolic pressure and 60 to90 mmHg diastolic pressure. High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults. Different numbers apply to children. Ambulatory blood pressure monitoring (ABPM) over a 24-hour period may be more accurate than office-based measurements, as people may exhibit anxiety when they see their doctor; a phenomenon referred to as 'white coat hypertension.' ABPM is now considered the 'gold standard' blood pressure measurement technique in some countries (Head 2011).

Description of the intervention

IRT involves sustained contraction against an immovable load or resistance with no change or minimal change in the length of the involved muscle group. It can be performed while seated, without changing clothing. and can be performed at any time of day. IRT has been most commonly delivered in the form of unilateral (one arm only) handgrip squeezing activity at 30% of one's maximum voluntary contraction (MVC) for four bouts of two minutes, with a three-minute rest in-between each squeezing bout. Three weekly IRT sessions are recommended. Historically, people with hypertension avoided IRT,due to concerns about hypertensive responses. However, recent work has demonstrated that hypertensive effects during IRT are not as extreme as once thought, and in fact, chronic anti-hypertensive effects have been observed following eight weeks exposure to IRT (Carlson 2014). IRT may reduce blood pressure by a similar magnitude to taking a single anti-hypertensive medication (Wong 2014). The activity does not require much space, requires inexpensive equipment and elicits less physical stress than aerobic activity. The intervention is designed for people with hypertension. In contrast, the usual exercise prescription for treatment of hypertension would involve 30 minutes of aerobic exercise at moderate intensity, five times weekly (ASCM 1993; Brook 2013).

How the intervention might work

It is unclear how IRT reduces blood pressure. It is postulated that handgrip exercise either completely or partially occludes the brachial arterial, and upon cessation of squeezing, the returning blood flow causes a rebound flow-mediated dilatation (FMD) of the vessel. Progressive exposure to IRT may therefore enhance the vasodilatory response and in time may even increase the vessel diameter. In normotensive or pre-hypertensive participants the effect of IRT on blood pressure may be smaller due to a reduced potential for non-hypertensives to reduce their blood pressure. This assertion is based upon the principle of 'regression to the mean'.

Why it is important to do this review

Previous meta-analyses have examined the effectiveness of endurance training (Cornelissen 2011a), dynamic resistance training (Cornelissen 2011b) and isometric resistance training in lowering resting blood pressure (Inder 2016). The findings showed that isometric resistance exercise does lower blood pressure (McGowan 2006). However, the sample sizes of the trials involving isometric resistance training have generally been small. Recently, several IRT trials have been published (Pagonas 2017; Farah 2018; Goessler 2018; Silva 2018). It is necessary to update the analysis of data from RCTs, controlled clinical trials and crossover trials. Global data suggest hypertension is prevalent, leading to 9.4 million deaths annually (Poulter 2015).

OBJECTIVES

We will aim to conduct a systematic review and meta-analysis quantifying the effects of IRT on systolic, diastolic, mean arterial and 24-hour ambulatory blood pressure. We will also quantify changes in heart rate and heart rate variability, and will attempt to determine which patient demographics and exercise program characteristics are associated with the largest blood pressure changes.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs and cross-over studies comparing isometric resistance training with a sedentary or sham control group in adults.

Types of participants

We will consider studies where participants are persons age 18 years and older, diagnosed with essential hypertension, with resting blood pressure greater than 140/90 mmHg, measured by manual auscultation or automated cuff inflation.

Types of interventions

We will consider studies of IRT at > 10% maximal voluntary contraction (MVC), versus non-IRT control or sham IRT at an intensity of 10% or less of MVC. The IRT should be delivered for a minimum of two weeks or six sessions.

Types of outcome measures

Blood pressure (systolic and diastolic) is an outcome, but also an inclusion criteria, as we will only consider hypertensive participants with blood pressure > 140 mmHg systolic or > 90 mmHg diastolic. We will consider studies that report outcome measures relating to resting and exercise. We will consider exercise response outcome measures that are considered markers of cardiovascular health.

Primary outcomes

- Change in blood pressure from baseline or after intervention
- Blood pressure: daytime, night time or 24-hour systolic, diastolic mean arterial pressure (measured by manual auscultation), 24 hour blood pressure (measured by automated 24-hour ambulatory monitoring)
- Adverse events

Secondary outcomes

- Changes in resting heart rate (measured by resting electrocardiogram (ECG) or other heart rate monitoring device, or manual palpation)
- Heart rate variability and cardiac autonomic modulation (both measured by Holter monitoring for 24 hours)

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist will search the following databases for published, unpublished, and ongoing studies:

- the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web);
- MEDLINE Ovid (from 1946 onwards), Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions;
- Embase Ovid (from 1974 onwards);
- ClinicalTrials.gov (www.clinicaltrials.gov); and
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/).

The subject strategies for databases will be modelled on the search strategy designed for MEDLINE in Appendix 1. Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)).

Searching other resources

The Hypertension Information Specialist will search the Cochrane Hypertension Specialised Register segment (which includes searches of MEDLINE and Epistemonikos for systematic reviews) to retrieve published systematic reviews related to this review title, so that we can scan their reference lists to identify additional relevant trials. The Specialised Register also includes searches of CAB Abstracts & Global Health, CINAHL, ProQuest Dissertations & Theses, SPORTDiscus, and Web of Knowledge.

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials. We will contact experts/organisations in the field to obtain additional information on relevant trials. We may contact original authors for clarification and further data if trial reports are unclear.

Data collection and analysis

Two review authors (CM, VC) will independently assess all identified articles, and will consult a third review author (NS) to resolve any disagreements.

We will record information on outcome measures and archive these data in a database. We will record the following outcome measures; office and ambulatory systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (b.min^{-1}) and heart rate variability (HRV). Where reported, we will not calculate MAP because of potential error in calculating pre-post change in standard deviation.

Selection of studies

We will exclude animal studies, review papers, acute exercise studies, and non-RCTs, except for crossover studies. We will exclude studies that do not report any of the desired outcome measures, or do not have a sedentary control, or sham, group. Where necessary, we will contact study authors to provide missing data or to clarify where data might have been duplicated in multiple publications. We will exclude studies with incomplete data or that report data from a study that we have already included.We will exclude studies using interventions other than solely isometric resistance training (e.g. combined with aerobic or dynamic resistance exercise).

Data extraction and management

We will use a data collection form to collate data (Appendix 2). We will conduct meta-analyses for continuous data by using the change in the mean and standard deviation (SD) of outcome measures. We will calculate change in the pre- versus post-intervention mean by subtracting baseline values from post-intervention values. Review authors DC and RR will extract the data, using an approved data extraction sheet and review author NS will resolve any disagreements. The same three authors will enter the data independently into two separate saved (offline) versions of RevMan 5 (Review Manager 2014) so that comparisons can be made and discrepancies will enable identification of errors. In addition to the primary and secondary outcome data, we will extract the following baseline clinical data for IRT and control or sham groups: age, gender, body mass, body mass index, medication use, smoking status, co-morbid disease. All papers are likely to be English language, but we will seek an interpreter with sufficient scientific knowledge to translate the data for any non-English language papers. We will calculate change in the SD between pre- and post-intervention outcomes using RevMan 5 (Review Manager 2014). We will use either 95% confidence interval (CI) data for pre-post intervention change for each group, or where this is unavailable, actual P values for pre-post intervention change for each group. If only the level of statistical significance is available, we will use precise P values (e.g. P = 0.034) or 95% CIs, where it is possible for us to obtain these from study authors. Where we are unable to obtain these data, we will use default P values (e.g. P < 0.05,which becomes P = 0.049; and where P value is not significant becomes P = 0.05).

Assessment of risk of bias in included studies

We will assess risk of bias using sections 8.9-8.15 of the *Cochrane Handbook for Systematic Reviews of Interventions,* using a narrative description (Higgins 2011). Two review authors will independently assess risk of bias for each study. We will resolve any disagreements by discussion or by involving another author. We will assess the risk of bias according to the following domains.

- Method of randomisation.
- Consideration of confounders.
- Selection of participants into the study.
- Classification of interventions.
- Deviations from intended interventions.
- Missing outcome data (i.e. level of drop out).
- Measurement of the outcome.
- Selection of the reported result.
- Baseline balance between both groups.
- Comparable care received by both groups (excluding the intervention).
- We will assess study quality and reporting using the validated TESTEX scale (maximum score = 15), which has specific criteria for exercise training studies (Smart 2014).

Selective outcome reporting which could overestimate the effects of an intervention will be identifed by cross checking included publications for stated outcomes and assess is any were unreported. We will also assess two further quality criteria: whether the study groups were balanced at baseline; and if the study groups received comparable care (apart from the exercise component of

the intervention). We will assess these two further quality criteria as follows.

Groups balanced at baseline

- Low risk of bias: The characteristics of the participants in the intervention and control groups at baseline are reported to be comparable or can be judged to be comparable (e.g. baseline data reported in the study's Table 1) in terms of likely main prognostic factors.
- Unclear risk of bias: Whether the characteristics of the participants in the intervention and control groups are balanced at baseline is not reported, and reported information is inadequate to assess this (e.g. the study does not include a Table 1).
- High risk of bias: There is evidence of substantive imbalance in the baseline characteristics of the intervention and control groups with regard to likely major prognostic factors.

Groups received comparable treatment (except physical activity or exercise)

- Low risk of bias: Check that all additional or co-interventions were delivered equally across intervention and control groups.
- Unclear risk of bias: Information to assess whether co-interventions were delivered equally across groups was insufficient.
- High risk of bias: The co-interventions were not delivered equally across intervention and control groups.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with an author, we will note this in the 'Risk of bias' table. When analysing treatment effects, we will consider the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

We will complete meta-analyses for continuous data by using mean difference (MD), calculated from the change in the mean and SD of outcome measures. Although we do not anticipate analysis of any dichotomous data, as adverse events have not previously been reported, we will analyse dichotomous data as odds ratios (OR) or risk ratios (RR) with their 95% CIs.

Unit of analysis issues

In accordance with Section 16.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we will aim to include data from both periods of any cross-over trials identified, assuming that there has been a wash-out period considered long enough to reduce carry-over, no irreversible events such as mortality have occurred, and appropriate statistical approaches have been used.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (for example, when a study is identified as abstract-only).

Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies on the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will assess heterogeneity using the Cochrane Q test as per sections 9.5 and 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing a random-effects model.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot and use the Egger test to explore possible small study biases for the primary outcomes (Egger 1997).

Data synthesis

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. Continuous data will be analyzed using mean difference (MD), calculated from the change in the mean and SD of outcome measures. Dichotomous outcomes for each comparison will be expressed as ORs or RRs with 95% CIs. Continuous data will be expressed as MD with 95% CIs, or, where an outcome is measured and reported in more than one way, as standardised mean difference (SMD) with 95% CIs. We will enter data presented as a scale with a consistent direction of effect. Where appropriate, we will pool data from each study using a fixed-effect model, except where substantial heterogeneity exists. If there is substantial evidence of clinical heterogeneity or statistical heterogeneity (P value less than 0.10, I^2 greater than 50%) associated with an effect estimate, we will apply a random-effects model, which provides a more conservative statistical comparison of the difference between intervention and control groups. This is because a CI around the effect estimate with a random-effects model is wider than a CI around the estimate obtained with a fixed-effect model. If a statistically significant difference is still present using the random-effects model, we will also report the fixed-effect pooled estimate and 95% CI because of the tendency of smaller trials, which are more susceptible to publication bias, to be over-weighted with a random-effects analysis (Heran 2008).

We will process data in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will complete data synthesis and analyses using Review Manager Web software (RevMan Web 2019). We will explore the impact of studies with high or variable risk of bias on the overall assessment of results by a sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

We will conduct the following sub-analyses where possible.

- Male versus female (because sex may be a confounding variable).
- Age (as a continuous variable because blood pressure rises with age).
- Intervention > 8 weeks vs ≤ 8 weeks (because prolonged intervention should intuitively lower blood pressure more than shorter intervention periods).
- Unilateral versus bilateral limb training (because the effect of IRT is thought to work locally rather than systemically).
- Arm versus leg training (because arm exercise is likely to elicit greater blood pressure responses due to lower active muscle mass).
- Body mass index <25 $kg.m^{-2}$ versus >25 $kg.m^{-2}$ (because greater body mass has been shown to increase blood pressure).
- Medicated versus non-medicated patients (because some medications may attenuate the effects of the intervention).
- Training intensity (percentage of MVC) and total training volume the product of the 4 exercise parameters (intensity X weekly frequency X duration of contraction X duration of total intervention) because these intervention dose parameters may have a bearing on effect size.

Sensitivity analysis

We will conduct the following sensitivity analyses.

- Studies exhibiting high risk of bias.
- Studies where TESTEX quality scores are < 11 versus a study quality score of 11 or more.

Summary of findings and assessment of the certainty of the evidence

We will use GRADEpro GDT to assess the certainty of the evidence and we will summarise the results of all primary and secondary outcomes in a 'Summary of findings' table. We will follow methods outlined by the GRADE Working Group (Schunemann 2013).

ACKNOWLEDGEMENTS

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A P P E N D I C E S

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

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1 exp exercise therapy/
2 resistance training/
3 isometric contraction/
4 ((isometric or resistance or strength or weight) adj3 (contraction? or exercis$ or training)).mp.
5 isometrics.tw,kf.
6 IRT.tw.
7 or/1-6
8 hypertension/
9 (antihypertens$ or hypertens$).tw,kf.
10 ((elevat$ or high or lower$ or reduc$) adj3 (blood pressure or bp)).tw,kf.
11 or/8-10
12 randomized controlled trial.pt.
13 pragmatic clinical trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 or/12-20
22 animals/ not (humans/ and animals/)
23 21 not 22
24 7 and 11 and 23

Appendix 2. Data Collection Form

STUDY/YEAR:_____

CHECKED BY:_____ DATE:_____

NUMBER INTERVENTION 1:_____ Details of Intervention 1:_____

NUMBER INTERVENTION 2:_____ Details of Intervention 2:_____

NUMBER CONTROL PARTICIPANTS:_____ Details of Control Care:_____

Setting:_____

Intervention 1 Intervention 2 Control

Inclusion Criteria

Mean Age/SD _____ _____ _____

Male/Female (N/N) _____ _____ _____

Base SBP mean/SD _____ _____ _____

Post SBP mean/SD _____ _____ _____

Base DBP mean/SD _____ _____ _____

Post DBP mean/SD _____ _____ _____

Base MAP mean/SD _____ _____ _____

Post MAP mean/SD _____ _____ _____

Base HR mean/SD _____ _____ _____

Post HR mean/SD _____ _____ _____

H I S T O R Y

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CONTRIBUTIONS OF AUTHORS

Draft the protocol:	Smart wrote the initial draft. Cornelissen, Swaine, Ritti-Dias, Baross and Millar all provided comments on primary and secondary outcome measures. McGowan and Carlson commented on outcome measures but also the types of studies to be considered for inclusion.
Develop and run the search strategy:	Neil Smart, with assistance provided by Douglas Salzwedel, Information Specialist for Cochrane Hypertension
Obtain copies of studies:	Neil Smart, Ian Swaine, Tony Baross, Deb Carlson, Veronique Cornelissen, Philip J. Millar, Cheri McGowan, Anthony Baross
Select which studies to include (2 people):	Cheri McGowan, Veronique Cornelissen
Extract data from studies (2 people):	Deb Carlson, Rapheal Ritti-Dias
Enter data into RevMan:	Neil Smart, Deb Carlson
Carry out the analysis:	Neil Smart, Ian Swaine
Interpret the analysis:	Veronique Cornelissen, Neil Smart
Draft the final review:	Neil Smart
Update the review:	Neil Smart

DECLARATIONS OF INTEREST

- Neil A. Smart has no conflicts of interest to declare.
- Debra J. Carlson has no conflicts of interest to declare.
- Philip J. Millar has no conflicts of interest to declare.
- Ian L Swaine has no conflicts of interest to declare.
- Anthony W. Baross has no conflicts of interest to declare.
- Rapheal Ritti-Dias received funding from 'Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPQ' (#448759/2014-4), 'Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco' – FACEPE (#APQ-0695-4.09/14), and 'Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES'.
- Veronique Cornelissen has no conflicts of interest to declare.
- Cheri L. McGowan has no conflicts of interest to declare.

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Internal sources

- Neil Smart, Australia

  Salary from the University of New England enabled Profeessor Smart to write the protocol.
- Debra Carlson, Australia

  PhD Scolarship from the University of New England enabled Debra Carlson to contribute to the protocol editing.
- Ian Swaine, UK

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- Cheri McGowan, Canada

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External sources

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