ASSOCIATION BETWEEN EIGHT WEEKS OF ISOMETRIC HANDGRIP TRAINING AND ANGIOTENSIN CONVERTING ENZYME INSERTION/DELETION GENE POLYMORPHISM IN HYPERTENSIVE INDIVIDUALS

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by

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mmHg	Millimeters of mercury
µl	Microliter
*****	Indicate significant interaction with $p<0.05$
**	Indicate significant interaction with $p<0.01$

LIST OF ABBREVIATIONS

SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
MAP	Mean Arterial Pressure
PP	Pulse Pressure
HR	Heart Rate
HGS	Handgrip Strength
IHG	Isometric Handgrip Training
CON	Control
BP	Blood Pressure
DNA	Deoxyribonucleic Acid
PEH	Post Exercise Hypotension
ACE	Angiotensin Converting Enzyme
I/D	Insertion/Deletion
D	Day
W	Week
PEH	Post-Exercise Hypotension
PAR-Q	Personal Activity Readiness Questionnaire
MVC	Maximum Voluntary Contraction
RHR	Resting Heart Rate

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HUBUNGKAIT ANTARA LAPAN MINGGU LATIHAN GENGGAMAN ISOMETRIK DAN PENYISIPAN/PENGHAPUSAN GEN ENZIM PENUKAR ANGIOTENSIN PADA INDIVIDU HIPERTENSI

ABSTRAK

Satu kebimbangan kesihatan global yang meluas ialah hipertensi, yang menjejaskan lebih daripada 1 bilion orang di seluruh dunia. Senaman fizikal memainkan peranan penting dalam pengurusan gaya hidup individu yang mengalami tekanan darah tinggi. Kajian ini bertujuan untuk mengaitkan polimorfisme gen *ACE I/D* dengan kesan lapan minggu latihan isometrik genggaman tangan (IHG) dan tanpa latihan ke atas fungsi kardiovaskular dan otot dalam populasi hipertensi yang tidak dirawat di Malaysia. Untuk menilai kesan kardiovaskular dan otot bagi program IHG dan tanpa latihan selama lapan minggu merentasi kumpulan genotip *ACE I/D* yang berbeza, kajian ini melibatkan lima puluh lapan individu dengan hipertensi yang tidak dirawat. Mereka secara rawak dibahagikan kepada dua kumpulan, iaitu kumpulan latihan dan kumpulan kawalan. Kumpulan latihan terdiri daripada 29 peserta (purata umur: 40.45 ± 9.22), yang terdiri daripada 22 lelaki dan tujuh wanita. Pada masa yang sama, kumpulan kawalan termasuk 29 peserta (purata umur: 37.41 ± 9.03), dengan 15 lelaki dan 14 wanita. Peserta dalam kumpulan IHG menerima latihan IHG tiga kali seminggu selama lapan minggu, diikuti dengan lapan minggu lagi tanpa latihan di mana mereka tidak menerima latihan IHG atau sebarang senaman teratur. Selama lapan minggu, mereka dalam kumpulan kawalan (CON) tidak mengambil bahagian dalam sebarang program senaman. Berdasarkan penemuan kajian ini, program IHG selama lapan minggu menghasilkan pengurangan parameter kardiovaskular, seperti yang ditunjukkan oleh penurunan tekanan darah

sistolik (SBP), sambil mengekalkan tahap pembolehubah otot yang konsisten. Tambahan pula, tindak balas kardiovaskular terhadap latihan IHG berbeza-beza dalam kalangan individu hipertensi dengan genotip *ACE I/D* yang berbeza. Hasil SBP menunjukkan perbezaan dalam perubahan nilai SBP merentasi tiga kumpulan genotip. Secara khususnya, kumpulan *DD* dan *ID* menunjukkan tindak balas yang ketara selepas lapan minggu latihan IHG berbanding dengan kumpulan *II*. Sebaliknya, kumpulan *DD* menunjukkan tindak balas SBP yang lebih tinggi selepas 8 minggu detrening IHG, menunjukkan bahawa perubahan tersebut tidak kekal ketara lebih rendah daripada asas untuk lapan minggu berikutnya selepas pemberhentian latihan. Ini menunjukkan bahawa kesan senaman IHG mungkin tidak berterusan selepas tempoh detrening selama 8 minggu dari IHG. Penemuan kajian ini mencadangkan bahawa individu hipertensi mungkin mendapat manfaat daripada pengurangan tekanan darah dalam kalangan individu yang mengalami hipertensi menggunakan program latihan isometrik genggaman tangan selama 8 minggu, dan magnitud tindak balas selepas latihan ini berbeza antara kumpulan genotip. Walau bagaimanapun, kesan penurunan tekanan darah daripada 8 minggu latihan IHG tidak akan berterusan selepas 8 minggu pemberhentian.

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ABSTRACT

A prevalent global health concern is hypertension, affecting over 1 billion people worldwide. Physical exercise plays a crucial role in the lifestyle management of individuals with high blood pressure. This investigation seeks to link *ACE I/D* gene polymorphism with the effects of eight weeks isometric handgrip (IHG) training and detraining regimen on cardiovascular and muscular function in unmedicated hypertensive population in Malaysia. To assess the cardiovascular and muscular impacts of an eight-week IHG and detraining program across different *ACE I/D* genotype groups, this study involved fifty-eight unmedicated individuals with hypertension. They were randomly assigned to two groups, namely the training and control groups. The training group comprised 29 participants (mean age: 40.45 ± 9.22), consisting of 22 males and seven females. Simultaneously, the control group included 29 participants (mean age: 37.41 ± 9.03), with 15 males and 14 females. Participants in the IHG group received IHG training three times per week for eight weeks, followed by another eight weeks of detraining in which they did not receive IHG training or any organized exercise. For eight weeks, those in the control group (CON) did not participate in any exercise regimen. Based on the findings of the present study, an eight-week IHG training program resulted in a reduction of the cardiovascular parameter, as indicated by a decrease in systolic blood pressure (SBP), while maintaining consistent levels of muscle variables. Furthermore, the

cardiovascular responses to IHG training varied among hypertensive individuals with different *ACE I/D* genotypes. The SBP results revealed distinctions in the changes of SBP values across the three genotype groups. Specifically, the *DD* and *ID* groups exhibited significant responses after eight weeks of IHG training compared to the II group. Conversely, the *DD* group showed a higher SBP response after 8 weeks of IHG detraining, suggesting that the changes did not remain significantly lower than baseline for the subsequent 8 weeks after the cessation of training. This indicates that the effects of IHG exercise may not be sustained after an 8-week period of detraining from IHG. The findings of this study suggest that hypertensive individuals may benefit from reducing blood pressure in hypertension individuals using an 8-week isometric handgrip training programme, and the magnitude of this post-training response differs between genotype groups. However, the blood pressure lowering effect of 8 weeks of IHG training will not persist after 8 weeks of cessation.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Globally, hypertension is the most important modifiable risk factor for cardiovascular disease and early death. According to predictions, 1.5 billion people worldwide will develop hypertension by 2025, and eighty-two percent of the world's population with hypertension in 2019 lived in low- and middle-income nations (Mills, Stefanescu & He, 2020). The National Health and Morbidity Survey from 2006 and 2011 conducted in Malaysia shows a growing trend in hypertension among people over 30. with 32.9% in 1996, 42.6% in 2006 and 43.5% in 2011 (Naing *et al.*, 2016). Only 1% more people over the age of 18 had hypertension in 2011 (32.7%) compared to 2006 (32.2%) (Naing *et al.*, 2016). Moreover, the Malaysian population with income level RM 3000 to RM 3999 had the highest rate of rise in hypertension (18%) in 2011, and the older age groups generally showed a greater prevalence of hypertension than adults. The prevalence peaked at 74.1% among people age 65 to 69 years old (Naing *et al.*, 2016). According to the most recent National Health and Morbidity Survey report, only half of the 6.4 million people who suffer from hypertension were aware of their condition, and only 45.4% of those using medication had their blood pressure (BP) under control (Majid & Ganapathy, 2020).

Despite taking medicine and changing one's diet, exercise is typically the first lifestyle therapy suggested to prevent, treat, and control hypertension (Majid & Ganapathy, 2020). When compared to other types of exercise, isometric resistance training reduced resting blood pressure the most (Cornelissen & Smart, 2013). Despite it is most effective in reducing blood pressure, isometric training has also referred to be a basic workout because it only utilises a few lower arm muscles and is performed at a moderate intensity (typically 30% of maximum voluntary contraction (MVC) (Goessler, Buys & Cornelissen, 2016).

A few earlier studies suggested a training regimen for four sets of two-minute handgrips training (Millar *et al.*, 2014; Goessler, Buys & Cornelissen, 2016). The previous study found that isometric handgrip (IHG) exercise training lowers resting BP far beyond static legs training (Somani *et al.*, 2018). The observation from previous study (Somani *et al.*, 2018) could be explained by the fact that the contraction of the hand muscles will result in a higher rise in arterial pressure than the contraction of the leg muscles, which will stimulate the baroreceptors and correspond to a larger capability for BP decrease following IHG training than after isometric leg workouts (Somani *et al.*, 2018). Another research found that there was a substantial drop in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) following an IHG programme, supporting the potential efficacy of IHG in treating BP (Ogbutor, Nwangwa & Uyagu, 2019).

Numerous research findings showed that genetics significantly influence BP (Padmanabhan, Newton-Cheh & Dominiczak, 2012; Pazoki *et al.*, 2018). Additionally, because BP is influenced by genes, scientists have focused on finding genes that regulate blood pressure (Ehret & Caulfield, 2013). Due to its involvement in the renin-angiotensin system (RAS), the angiotensin I-converting enzyme (*ACE*) gene has garnered significant consideration as a potential BP candidate gene (Dhanachandra Singh *et al.*, 2014). Based on their preliminary research, Rigat *et al.* (1990) concluded that the *ACE I/D* variants within the ACE gene was strongly correlated with ACE serum levels in the RAS and accounted for 47% of the total phenotypic variation of ACE serum. Rigat *et al.* (1990) also discovered that people with different *ACE I/D* genotypes had progressively higher serum ACE levels (*II* < *ID* < *DD* genotypes). One study found that among Chinese normotensives, those with the *II* genotype had significantly reduce resting BP compared to individuals with the *ID* and *DD* (Wong, Zhao & Koh, 2012). Individuals with the *II* genotype have a lower ACE level, which means they produce less Angiotensin II (a potent vasoconstrictor) and more bradykinin (an effective vasodilator), leading to a lower resting BP (Rigat *et al.* 1990, Kemp *et al.*, 2014). However, ANG II is an important growth factor for heart and blood vessel tissues, and individuals with the *D* allele produced more of it through the RAS in skeletal muscle. This suggests a possible mechanism by which the expansion and proliferation of muscle cells could be promoted (Cabello-Verrugio, Córdova & Salas, 2012). This has led to the assumption that the *D* allele impacts performance in terms of strength or power (Eider *et al.*, 2013).

Numerous research investigating the relationship between the BP response to exercise training and the *I/D* polymorphism have produced contradictory results (Billinger *et al.*, 2012; Mota *et al.*, 2013). A study found no correlation between this variant and BP response to training in either dynamic resistance exercise or endurance exercise (Mota *et al.*, 2013). The research Billinger *et al.* (2012) demonstrated hypertensives with the *I* allele saw a larger reduction in resting BP following 9 months of high intensity endurance exercise than those with the *D* alelle. Researchers Zhang *et al.* (2002) found that after nine months of endurance exercise training at 75% to 87% of maximal oxygen intake, people with the *I* allele lowered their resting BP more than those with the *DD* genotype. In a related study, Zhang *et* *al.* (2002) looked at64 people from Japan who suffer from essential hypertension and how their BP responded to a 10-week bike ergometer training program in connection to the *I/D* polymorphism. After 12 weeks of a combination aerobic and weight training program, the *DD* genotype of adult females had a greater decrease in DBP compared to the other genotypes (Kim, 2009). This finding contrasts the findings of Hagberg *et al.* (1999) and Zhang *et al.* (2002). Uncertainty about the causes of these contradictory results may stem from limited sample sizes and inadequate exercise amounts to significantly alter resting BP. For instance, research Kim (2009) contrasted the use of mixed cardio and strength training to a research by Hagberg *et al.* (1999) that used endurance training. A previous study among Malaysian normotensive individuals was conducted and discovered a significant reduction in BP among normotensive individuals after eight weeks IHG training with (Yusof, Aziz & Muhamed, 2019). In addition, they revealed that those with the *I* allele improved their cardiovascular performance much more than those with the *D* allele did after IHG training.

1.2 Statement of the Problem

Although it has been demonstrated that isometric exercise training can help reduce BP, it is still unclear how other factors, such as gender and heredity, may impact an isometric exercise program's success. The connection between *I/D* polymorphism and BP response to isometric exercise training and detraining in hypertensive persons has not been published, despite the contradictions of the data. To identify those who might benefit more from this exercise program, it is crucial to determine if the *I/D* polymorphism is linked to the cardiovascular and muscular reactions to isometric handgrip training and detraining. In addition, the study on the potential use of this exercise in Malaysian hypertensive individuals is limited. It is yet uncertain if IHG exercise-related hypotensive effects exist in the Malay population. Given that only half of the 6.4 million people in Malaysia who suffer from hypertension were aware of their condition, and only 45.4% of those using medication had their BP under control (Majid & Ganapathy, 2020), a study among Malaysian hypertensive individuals is warranted to be carried out to support earlier findings reported mainly among the Caucasian population that isometric exercise that are is recommended for avoiding or treating hypertension. The current study's findings may provide some insight into how this type of exercise might be used with the Malay community.

1.3 Research Questions

i. What are the differences in muscular and cardiovascular adaptations between an eight-week IHG training program and a control group?

ii. How do muscular and cardiovascular adaptations differ among hypertensive individuals with various *ACE I/D* genotypes after a single session of IHG exercise, eight weeks of IHG training, and a subsequent detraining period?

1.4 Aims of the Research

General:

This study investigates the relationship between the *I/D* polymorphism of *ACE* gene and the cardiovascular and muscular reactions to eight weeks isometric handgrip training and detraining program among unmedicated hypertensive people in Malaysia.

Specific:

1. To determine whether the presence of the *I* allele is associated with

more excellent cardiovascular response, characterised by significant improvements in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), and resting heart rate (RHR), following eight weeks of IHG training and detraining program.

2. To determine whether the possession of the *D* allele is associated with a significant muscular response, characterised by significant improvements in handgrip strength (HGS) to eight weeks IHG training and detraining program.

3. To determine whether one IHG exercise session and eight weeks IHG training program reduced and improved the cardiovascular and muscular variables, respectively.

1.5 Research Hypotheses

i. Null Hypothesis (H_O): There is no significant relationship between *I/D* polymorphism and the cardiovascular and muscular reactions to eight weeks isometric handgrip training and detraining program among hypertensive people in Malaysia.

Alternative Hypothesis (H_A): There is a significant relationship between *I/D* polymorphism and the cardiovascular and muscular reactions to eight weeks isometric handgrip training and detraining program among hypertensive people in Malaysia.

ii. Null Hypothesis (H_O): There is no significant effect of one IHG exercise session and eight weeks IHG training program on cardiovascular and muscular variables.

Alternative Hypothesis (H_A): There is a significant effect of one IHG exercise session and eight weeks IHG training program on cardiovascular and muscular variables.

iii. Null Hypothesis (H_O): There is no significant association between the presence of the *I* allele and cardiovascular response to eight weeks IHG training and detraining program.

Alternative Hypothesis (H_A): There are significant associations between the *I* allele and cardiovascular response to eight weeks IHG training and detraining program.

iv. Null Hypothesis (H_O): There is no significant association between the presence of the *D* allele with greater muscular response to eight weeks IHG training and detraining program.

Alternative Hypothesis (H_A): There is a significant association between the presence of the *I* allele with greater muscular response to eight weeks IHG training and detraining program.

1.6 Conceptual framework

Figure 1.1 presents the conceptual framework around which this study is organized. The model suggests that *I/D* polymorphism may affect the results of one IHG exercise session, eight weeks of IHG training, and eight weeks of detraining on the cardiovascular and muscular systems, with training responses varying across hypertensive patients with various *ACE I/D* genotypes.

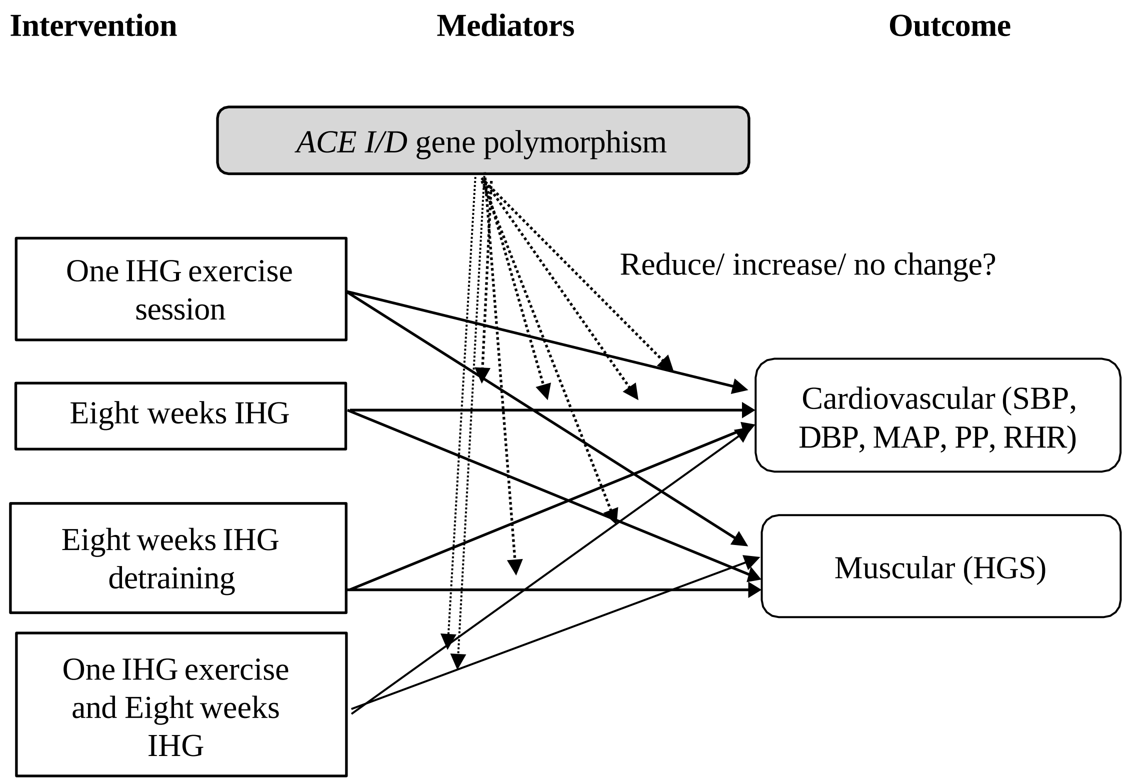

Figure 1.1 Cardiovascular and musculoskeletal adaptations to an IHG bout of exercise, 8 weeks of IHG training, and 8 weeks of detraining are conceptually linked with *ACE I/D* variations in this paradigm. The dependent variables are cardiovascular (SBP, DBP, MAP, PP, RHR) and muscular (HGS). The independent variables are one IHG exercise session, eight weeks IHG and *ACE I/D* gene polymorphism.

1.7 Significance of the Research/ Study Rationale

Previous studies indicate that IHG training considerably affects BP (Badrov *et al.*, 2013). However, the study on the probable use of this exercise in Malaysian hypertensive individuals is limited. Hence this study was conducted to provide additional support for the findings of previous studies that recommended isometric exercise as a method for preventing or managing hypertension. In addition, the factor that influenced the BP reduction following IHG training remained unclear. Multiple research have looked at the relationship between the *I/D* polymorphism and BP response to exercise training, especially endurance training, however the results have been conflicting (Mota *et al.*, 2013). Since no study has examined the effect of *I/D* polymorphism and eight weeks of IHG training and detraining on BP responses in the Malaysian hypertensive population, more research is needed to confirm the findings.

In this study it is expected that an eight-week IHG training would reduce the resting BP of hypertensive individuals. The reduction of resting BP will be more significant in *II* genotype carriers compared to those *ID* and *DD* genotypes carrier. This finding is expected to be consistent with the previous studies where IHG exercise training was demonstrated to reduce resting BP more than other types of isometric training (Badrov *et al.*, 2013; Baross, Wiles & Swaine, 2013). The finding of this study is expected to be beneficial to many people, especially those with hypertension who does not take any medication to manage their BP. The flexibility, simple but not intense kind of exercise described by IHG exercise may increase adherence to exercise intervention among hypertensive individuals, especially those who never engage in any physical activity. This study also look for differences in BP and muscle response to IHG training and detraining across three groups with *ACE I/D* genotypes. This study's results would help hypertension patients with varied *ACE I/D* variations anticipate the extent to which their two variables may vary.

1.8 Operational Definition

The list of operation definitions used in this thesis as shown in Table 1.1.

Table 1.1 Operational definition

Terminology	**Operational Definition**
Isometric handgrip exercise	Exercise that involves muscle contractions without moving the affected body parts such as an extended handgrip.
Single nucleotide polymorphism	Variation in a genetic sequence affects only one of the basic building blocks.
Maximal voluntary contraction	The maximum stress a muscle can produce and maintain.
Post-exercise hypotension	The drop in BP after aerobic exercise to values below normal.
Polymorphism	A given DNA sequence can arise in two or more variant forms in different people or communities.
Detraining	Detraining is the partial or complete loss of training-induced adaptations in response to an insufficient training stimulus. Detraining characteristics may differ depending on the duration of training cessation or insufficient training.
Pre-hypertensives	SBP = 120-129 mmHg and DBP < 80-89 mmHg
Hypertensive stage 1	SBP = 130-139 mmHg or DBP = 80-90 mmHg
Hypertensive stage 2	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg

CHAPTER 2

LITERATURE REVIEW

2.1 Hypertension

Hypertension, also known as high or raised BP, is a condition in which the blood vessels persistently raise pressure (Gande *et al.*, 2020). Blood is carried from the heart to all body parts in the vessels (Gande *et al.*, 2020). Each time the heart beats, it pumps blood into the vessels (Gande *et al.*, 2020). BP is created by the force of blood pushing against the walls of blood vessels known as arteries, as it is pumped by the heart (Gande *et al.*, 2020). The higher the pressure, the more complex the heart must pump (Gande *et al.*, 2020).

Hypertension is classified into different types and stages based on the severity of blood pressure readings. The most common type is Primary (Essential) Hypertension, which has no identifiable cause and develops gradually over many years, influenced by genetic and environmental factors. Secondary Hypertension, on the other hand, is caused by an underlying medical condition such as kidney disease, endocrine disorders, or certain medications, and often appears suddenly with higher blood pressure readings than primary hypertension. Isolated Systolic Hypertension is characterised by elevated systolic blood pressure (SBP) with normal diastolic blood pressure (DBP) and is common in older adults due to arterial stiffening. White Coat Hypertension refers to elevated blood pressure readings in a clinical setting but normal readings outside, often linked to anxiety during medical appointments. Masked Hypertension is the opposite, where normal blood pressure is recorded in a clinical setting, but elevated readings are present outside, making it more challenging to detect and manage. Resistant Hypertension describes blood pressure that remains elevated despite the use of three or more antihypertensive medications, including a diuretic, indicating possible underlying secondary causes or lifestyle factors that need addressing.

According to the American Heart Association 2017 guidelines, hypertension is classified into several stages (Diaz *et al.*, 2017). Normal Blood Pressure is defined as systolic blood pressure (SBP) less than 120 mmHg and diastolic blood pressure (DBP) less than 80 mmHg. Elevated Blood Pressure, or Prehypertension, is characterised by an SBP of 120-129 mmHg and a DBP of less than 80 mmHg. Hypertension Stage 1 occurs when SBP is between 130-139 mmHg and DBP is between 80-89 mmHg. Hypertension Stage 2 is defined by an SBP of 140 mmHg or higher and a DBP of 90 mmHg or higher. A Hypertensive Crisis is when SBP exceeds 180 mmHg and DBP exceeds 120 mmHg, representing a medical emergency that requires immediate attention, as it may lead to severe complications such as stroke or heart attack.

The pathophysiology of hypertension begins with genetic and environmental factors. Genetic predisposition, such as family history and specific genetic mutations, plays a role alongside environmental factors like high salt intake, obesity, lack of exercise, stress, smoking, and alcohol consumption (Muntner *et al.*, 2015; Paul *et al.*, 2018). These factors contribute to the development of primary (essential) hypertension or secondary hypertension. Neurohormonal regulation is crucial in this process, involving sympathetic nervous system activation that increases heart rate and causes vasoconstriction. The Renin-Angiotensin-Aldosterone System (RAAS) is also activated, where the kidneys release renin, converting angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II causes vasoconstriction and aldosterone release, leading to increased sodium and water retention. Additionally, natriuretic peptide dysfunction impairs the body's ability to excrete sodium and water. Vascular changes follow, characterised by endothelial dysfunction, reduced nitric oxide production leading to vasoconstriction, increased peripheral vascular resistance due to narrowing of blood vessels, and vascular remodelling, which thickens arterial walls and reduces elasticity. Cardiac changes also occur, including left ventricular hypertrophy (LVH) due to the increased workload on the heart and initially compensatory increased cardiac output, which eventually leads to heart strain and the potential development of heart failure (Paul *et al.*, 2018). Figure 2.1 illustrating the pathophysiology of hypertension. It outlines the key factors and pathways involved, including genetic and environmental influences, neurohormonal regulation, vascular and cardiac changes, and the potential complications that arise from sustained high blood pressure.

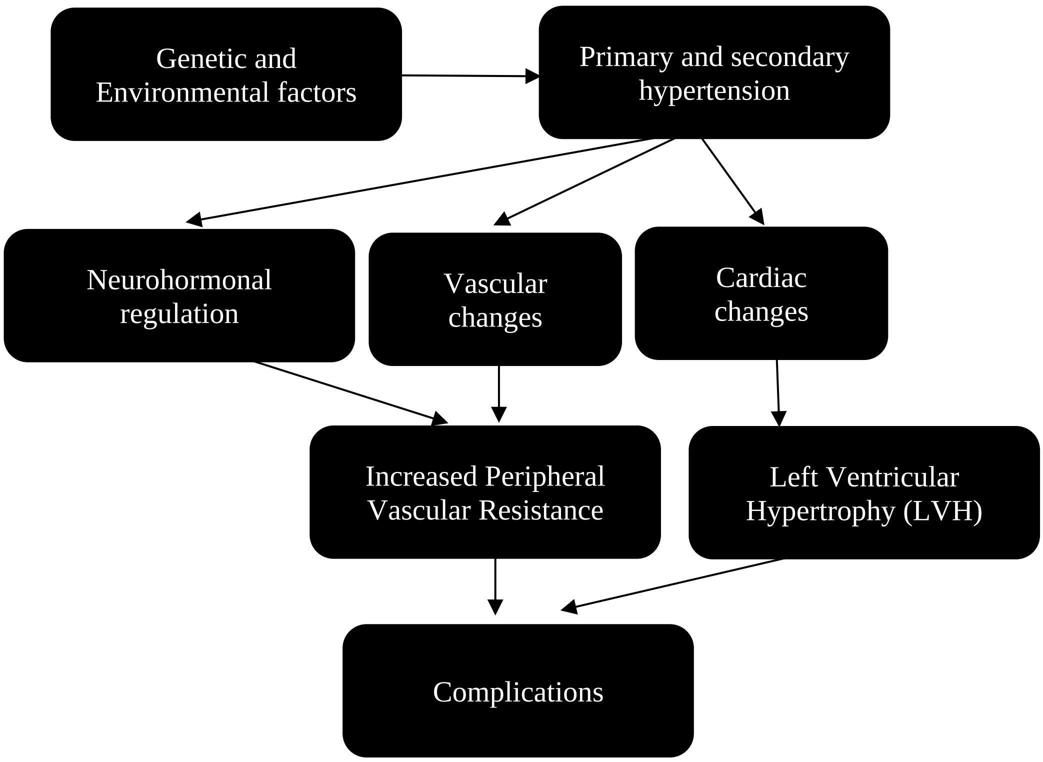

Figure 2.1 The pathophysiology of hypertension

Hypertension is a significant public health problem and an important area of research due to its high prevalence and is a significant risk factor for cardiovascular diseases and other complications. The chance of developing heart, brain, kidney, and other chronic problems might rise due to a significant medical condition known as hypertension. In 2025, 1.56 billion adults are expected to have hypertension, according to predictions (Mills, Stefanescu & He, 2020). Hypertension will be one of the leading causes of early death globally, affecting up to 1 in 4 men and 1 in 5 women (Mills, Stefanescu & He, 2020). High BP is responsible for around 7.5 million fatalities yearly, or 12.8% of all deaths worldwide (Mendis, 2021).

Although other BP variables, such as DBP, pulse pressure (PP), BP variability, and mean arterial pressure (MAP), have also been linked to cardiovascular disease, many studies found that in most age and gender categories, SBP has a more excellent correlation with cardiovascular disease than other variables (Muntner *et al.*, 2015; Paul *et al.*, 2018). A major medical emergency, such as a heart attack, stroke, or chronic renal disease, seldom manifests in the early stages of hypertension, making it a silent killer (Prabakaran, Vijayalakshmi & VenkataRao, 2013). Because most hypertensive patients do not show any symptoms and because most people are not aware of it, the only way to identify high blood pressure is through measurements. Some hypertensive patients report headaches, dizziness, vertigo, impaired vision, or fainting episodes (Tabrizi *et al.*, 2016). The burden of hypertension is disproportionately felt in low- and middle-income nations, where two-thirds of instances are reported. This is partly because risk factors like lifestyle, smoking, and obesity have increased in these populations over the past few decades (Mills, Stefanescu & He, 2020). Given that the rise in risk factors described above is associated with the high risk for hypertension, lowering the risk factor by using antihypertensive drugs and lifestyle changes is the best way to control hypertension.

2.2 Hypertension Management

A difference in BP value of 20/10 mmHg is associated with a 50% difference in cardiovascular risk (Lewington, 2002). This can be achieved using non-pharmacological (lifestyle changes) and pharmaceutical techniques (Kaplan, 2006). Examples of lifestyle changes include dietary adjustments, weight control, smoking cessation, exercise, and stress reduction. Significant randomized clinical investigations have shown that various pharmacological medicines are available for the initial therapy of excessive blood pressure. These include more contemporary drugs such dihydropyridine calcium channel blockers (CCB), angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB), as well as beta-blockers and thiazide diuretics. Comprehensive hypertension care, which strongly emphasizes reducing total cardiovascular risk, is the best course of action for the first therapy of hypertension. Despite the benefits of using medicine to manage hypertension, current data from more than 100 countries show that, on average, fewer than 50% of people with the condition use medication to lower their blood pressure (Geldsetzer *et al.*, 2019; Zhou *et al.*, 2019). Modifying one's lifestyle can reduce cardiovascular risk and delay or halt the emergence of high BP (Piepoli *et al.*, 2016). The mainstay of antihypertensive therapy is lifestyle modification because it can enhance the effects of the medication. The advised lifestyle modifications for hypertension are listed in Table 2.1 (Ashwell, Gunn & Gibson, 2012; He, Li & MacGregor, 2013; Gay *et al.*, 2016; Roerecke *et al.*, 2017; Xie *et al.*, 2018; Cicero *et al.*, 2019; Zhou *et al.*, 2021).

Table 2.1 Lifestyle modification for hypertension management

Lifestyle modification	**Description**	**References**
Salt reduction	Use less salt at the table and when preparing meals. Items high in salt, such as soy sauce, fast food, and prepared foods like salty bread and cereals, should be avoided or consumed in moderation.	(He, Li & MacGregor, 2013)
Healthy diet	Eating more healthy grains, fruits, vegetables, polyunsaturated fats, and dairy products while consuming fewer foods heavy in sugar, saturated fat, and trans fats, as in the dash diet. Increase intake of foods high in nitrates, such as leafy greens and beets, which have been shown to reduce BP. The other nutritious foods and nutrients include avocados, almonds, seeds, legumes, tofu, and other foods high in magnesium, calcium, and potassium.	(Gay *et al.*, 2016; Cicero *et al.*, 2019)
Healthy drinks	Moderate coffee, green, and black tea consumption. Other drinks with health benefits include chocolate, pomegranate juice, beet juice, and hibiscus tea.	(Xie *et al.*, 2018; Cicero *et al.*, 2019)
Alcohol consumption	Men should limit their daily alcohol intake to two standard drinks, while women should limit their daily alcohol intake to 1.5 standard drinks (10 g of alcohol for each standard drink). Quit drinking too much.	(Roerecke *et al.*, 2017)
Weight reduction	Controlling obesity is essential, especially around the abdomen. A waist-to-height ratio of less than 0.5 is suggested for all populations.	(Alberti *et al.*, 2006; Browning, Hsieh & Ashwell, 2010; Ashwell, Gunn & Gibson, 2012)
Regular physical activity	Walking, running, cycling, yoga, or swimming at a moderate level for 30 minutes, 5 to 7 days a week, or high-intensity interval training (HIIT), which includes brief alternating bursts of intensive exercise with following recovery periods of gentler exercise. Additionally, strength exercise helps lower BP. Exercises requiring resistance or strength are performed 1 to 2 days per week.	(Cornelissen & Smart, 2013; Casonatto *et al.*, 2016; Costa *et al.*, 2018)

Reduce stress and induce mindfulness	Chronic stress has been associated with high blood pressure later in life. The transcendental meditation/mindfulness on BP suggests that this practice lowers BP. Stress should be reduced, and mindfulness or meditation should be introduced into the daily routine.	(Matthews *et al.*, 2004; Solano Lopez, 2018)
Complementary, alternative, or traditional medicines	In places like Africa and China, where hypertension is high, many patients use a complementary, alternative, or traditional medicines.	(Wang & Xiong, 2013; Liwa *et al.*, 2014)
Reduce exposure to air pollution and cold temperature	A negative effect of air pollution on BP in the long-term.	(Giorgini *et al.*, 2016; Fedak *et al.*, 2019)

Exercise is one of many individualized management strategies for hypertension. Several systematic reviews demonstrated that for 30 to 60 minutes, five days a week, aerobic exercise at moderate intensity could treat stage 1 hypertension and prevent hypertension (Wong & Wright, 2014; Ghadieh & Saab, 2015). Dynamic resistance exercises, when performed appropriately, can help lower both SBP and DBP in addition to aerobic exercise training. Two to three days a week should be set aside for these workouts (Ghadieh & Saab, 2015). Hypertension Canada and the American Heart Association (James *et al.*, 2014) support isometric exercise as an additional therapy for managing hypertension (Ghadieh & Saab, 2015).

2.3 Exercise Management for Hypertension

Patients with hypertension should receive tailored exercise recommendations. The dosage should be determined using the FITT principle (frequency, intensity, duration, and type); workout needs to be dedicated three to five days a week (Eicher *et al.*, 2010). As stated in Table 2.2, the intensity should be moderate, and the maximum oxygen intake (VO_{2max}) should be between 40% and 70%, or 3 and 6 metabolic equivalents of task (MET) (Manfredini *et al.*, 2009). Each patient should exercise for a minimum of 30 minutes every day, continuously or cumulatively (for instance, in three 10-minute intervals). It should incorporate resistance training in addition to aerobic activity.

Table 2.2 Metabolic equivalents (MET) of several activities

Physical Activity	**MET**
Light intensity	
• Watching television	<3.0
• Walking 2.7 km/h on level ground	1.0
• Strolling very slowly	2.3
Moderate intensity	3.0 to 6.0
• Stationary bicycling is a very light effort, 50 w	3.0
• Walking 4.8 km/h, dancing, gardening, housework	3.3
• Stationary bicycling with light effort, 100 w	5.5
High intensity	
• Jogging	> 6.0
• Vigorous Calisthenics (push-ups, sit-ups, pull-ups, jumping jacks)	7.0
• Running in place	8.0
• Rope jumping, competitive sports	10.0

Abbreviation: MET = Metabolic equivalent task unit; km/h = kilometre per hour; w = watt; Data was from Eicher *et al.* (2010)

2.4 Physiological response during exercise

Cardiovascular output is raised and redistributed during aerobic exercise to maintain the perfusion of working muscles (Nyberg, Gliemann & Hellsten, 2015). Neurohormonal and hydrostatic processes are responsible for this response by first increasing the systolic volume. Then the heart rate and SBP increases when cardiac output increases. In contrast, as peripheral vascular resistance decreases, diastolic blood pressure drops (PVR), allowing for increased perfusion of large muscle groups. Cardiovascular events that result in death are more common in patients with this disease. According to Ruivo and Alcântara (2012), a rise in SBP of more than 7 to 10 mmHg for every MET or a failure of DBP to drop more than 15 mmHg during aerobic activity is both strong indicators of developing hypertension. Due to the exercise pressor reflex from proprioceptors which are mechanoreceptors and metaboreceptors in active muscles, to the cardiovascular center in the medulla, both SBP and DBP increase during resistance exercise to overcome the resistance to muscle perfusion caused by elevated intramuscular pressure interrupting arterial blood flow (Paulo et al., 2020). However, poorly executed resistance exercises for hypertension patients can cause SBP and DBP to increase to 320 mmHg and 250 mmHg, respectively, during a single repetition at maximum load (Ruivo & Alcântara, 2012).

2.4.1 Acute physiological response to exercise

A single workout can result in post-exercise hypotension (PEH) or a dip in blood pressure (de Brito *et al.*, 2019). Repeated acute exercise sessions significantly impact chronic adaptations that could delay or stop the formation of hypertension (de Brito *et al.*, 2019). An earlier study found that before starting an exercise training program, acute exercise might be utilized to assess the intensity of a chronic reaction (Somani *et al.*, 2018). Due to its ability to accurately predict how much blood pressure (BP) will drop after participating in long-term training regimens, acute exercise could have clinically useful implications for pre-hypertension as well as hypertension. People less susceptible to long-term exercise training may show a slight reduction in blood pressure during acute exercise. It may be advised to use an alternative strategy or exercise style for people resistant to this exercise.

A hypotensive response lasting up to 22 hours after exercise is caused by reduced norepinephrine levels and thus by inhibition of sympathetic activity and reduction in circulating angiotensin II, adenosine, and endothelin levels and their receptors in the central nervous system, leading to decreased PVR and increased baroreflex sensitivity (Teodoro de Carvalho *et al.*, 2015). The vasodilator impact of prostaglandins and nitric oxide also causes hypotension (Eicher *et al.*, 2010). The length and type of exercise (but not the intensity), the person's clinical status, age, ethnicity, and level of physical fitness all impact the hypotensive response (Eicher *et al.*, 2010).

2.4.2 Chronic physiological response to exercise

Long-term exercise training results in vascular, immunological, and neuroendocrine alterations (Nyberg, Gliemann & Hellsten, 2015). Some vascular alterations include increased vascular length, expanded lumen diameter, precapillary sphincters, and neoangiogenesis (Nyberg, Gliemann & Hellsten, 2015). Reduced levels of inflammatory cytokines, soluble adhesion molecules, and C-reactive protein, all of which are indicators of mortality and morbidity, are also noted (Nyberg, Gliemann & Hellsten, 2015). Exercise has been shown to lower blood pressure by improving baroreceptor sensitivity, lowering norepinephrine levels, lowering PVR, improving insulin sensitivity, and changing the expression of vasodilator and vasoconstrictor factors (Nyberg, Gliemann & Hellsten, 2015). Exercise, for instance, encourages the development of endothelin 1, which causes vasoconstriction, as well as prostaglandins and nitric oxide, which stimulate vasodilation (Ruivo & Alcântara, 2012). Aerobic exercise also reduces the bulk and thickness of the left ventricle, boosts the levels of significant antioxidants, lowers the levels of pro-oxidants and arterial stiffness, and raises the activity of the central nitric oxide synthase, which enhances endothelial function (Ruivo & Alcântara, 2012).

2.5 Aerobic Exercise and Hypertension

Regular aerobic exercise has been demonstrated to lower blood pressure at rest and during stressful situations (Boutcher & Boutcher, 2016). Aerobic exercise reduces inflammation and lowers blood pressure during the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (Ghadieh & Saab, 2015). When not prohibited, aerobic exercise nearly never has any adverse side effects. Joints and big muscle groups are regularly and purposefully moved during this workout. Table 2.3 summarises research that has undergone meta- analyses to examine the relationship between aerobic exercise and BP response.

Table 2.3 Meta-analyses studies examine the relationship between aerobic activity and BP response

Research	**Methods**	**Results**
(Fagard & Cornelissen, 2007)	• 72 trials with an average of 40 participants per trial • 40-min sessions three times per week for 16 weeks at an average intensity of 65% of HR reserve	• A 6.9 mmHg drop in SBP, and a 4.9 mmHg drop in DBP
(Lee *et al.*, 2010)	• 27 RCTs with 1842 participants • Walking for a mean of 19 weeks (range four days to 26 weeks), 4.4 days/week, and • 36.5 minutes/day	• The effect is more significant when exercising more frequently and intensely for more extended periods • A mean decrease of 3.8 to 7.7 mmHg in • DBP and 5.2 to 11.0 mmHg in SBP
(Cornelissen & Smart, 2013)	• 15 trials with 633 participants • Study duration: 6 to 52 weeks; 30 to 60 minutes sessions, 2 to 5 times per week, at 50% to 75% HR • reserve	• A drop in SBP of 3.2 mmHg and a reduction in DBP of • 2.7 mmHg during the day
(Cornelissen & Smart, 2013)	• 105 trials with 3957 participants • Moderate aerobic exercise (walking and jogging) 3 to 5 times per week, 30 to 60 • minutes per session for 4 to 52 weeks	• Reduction in SBP of • 3.5 mmHg and DBP of 2.5 mmHg

2.6 Resistance Exercise and Hypertension

To gradually build muscle strength, dynamic resistance training involves exerting effort against an opposing force while purposefully moving joints and major muscle groups (MacDonald *et al.*, 2016). Muscles are contracted either eccentrically or concentrically. A few of instances of dynamic resistance training are weightlifting and circuit training using machines for resistance training. Training regimens include two to three weekly sessions of eight to ten weightlifting exercises that target the major muscle groups. The resistance (weight) for upper-body exercises is 30% to 40% of the one-repetition maximum, and for lower-body exercises, it is 50% to 60% of the one-repetition maximum. The recommended number of repetitions for each set of exercises is 10 to 15. (Ruivo & Alcântara, 2012). Dynamic resistance exercise should not involve extended breath-holding for patients (Ruivo & Alcântara, 2012). The program should be reassessed if the resistance training program raises the DBP by more than 20 mmHg above baseline or more than 120 mmHg.

Overall, the data points to a modest blood pressure-lowering effect of dynamic resistance training, notably in stage 1 hypertension, without any evidence of damage, acute cardiovascular event triggering during exercise, or chronic BP worsening (Cornelissen *et al.*, 2011). The same contraindications apply to dynamic resistance training as to aerobic exercise. Before starting training, patients with stage 2 hypertension should receive pharmaceutical treatment. Table 2.4 overviews the meta-analysis research of resistance exercise and bp response.

Table 2.4 Meta-analyses studies examine the relationship between resistance exercise and BP response

Research	Methods	Results
(Cornelissen *et al.*, 2011)	• 25 trials with 1043 adults • Median duration eight weeks (range 6 to 52 weeks) and frequency three sessions per week • Weight- or resistance- training machines were used to train the muscles of the upper or lower body • 1 to 6 (median 3) sets per exercise session for each muscle • 6 to 30 repetitions for each set	• There is no correlation between training intensity and the amount of BP reduction • Reduction in SBP of 2.7 mmHg and DBP of 2.9 mmHg • Dynamic resistance exercise enhanced peak oxygen consumption and decreased body fat and blood triglyceride levels • Resistance training was shown to be safe
(Cornelissen & Smart, 2013)	• 29 trials with 750 participants • 8 to 52 weeks, three sessions per week at 60% to 80% of 1 RM using weightlifting and resistance machines, three sets per session for each muscle, and 10 to 14 repetitions per set	A 1.8 mmHg drop in SBP and a 3.2 mmHg drop in DBP

2.6.1 Isometric Exercise and Hypertension

Exercises with isometric resistance entail prolonged static contractions of the muscles without causing any change in the length of the muscle groups engaged or any movement of the joints (Cornelissen & Smart, 2013). Most isometric resistance experiments were of limited duration and recruited only a small number of subjects (Cornelissen & Smart, 2013). Isometric resistance training has nevertheless been shown to have a distinct, albeit little, cardiovascular benefit, which includes slight increases in blood pressure (Kelley & Kelley, 2010; Owen, Wiles & Swaine, 2010; Cornelissen *et al.*, 2011; Cornelissen & Smart, 2013). However, the hazards to cardiovascular health brought on by the temporary increase in blood pressure that results from muscle contractions still need to be more precisely defined. Very high-risk or unstable cardiovascular patients, as well as people with more advanced stages of hypertension, have not been investigated with isometric workouts.

For 12 to 15 minutes every session, at least three times per week over an eight to twelve-week period, isometric hand-grip training regimens involve many intermittent bouts of hand-grip contractions at 30% maximum strength lasting two minutes each. Therefore, compared to other exercise kinds (which generally require 150 minutes per week with aerobic or dynamic resistance training), it requires less time commitment to generate an effective reduction in BP (33 minutes per week in total) (Cornelissen *et al.*, 2011). The US Food and Drug Administration has approved a brand-new hand-held dynamometer that ambulatory and non-ambulatory patients can use at home. The dynamometer enhances endothelial function by increasing nitric oxide generation and vagal activity (Owen, Wiles & Swaine, 2010). Table 2.5 summarises the meta-analysis research on the relationship between isometric exercise and BP responses.