PREDICTIVE MODELING OF ISOLATED SYSTOLIC HYPERTENSION
FROM CHANGES IN ARTERIAL COMPLIANCE AND PERIPHERAL RESISTANCE

By

YUNPING GUO

A thesis submitted to the

School of Graduate Studies

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Master of Science

Graduate Program in Biomedical Engineering

Written under the direction of

Professor John K-J. Li

And approved by

____________________________
____________________________
____________________________

New Brunswick, New Jersey

May 2021
ABSTRACT OF THE THESIS

Predictive Modeling of Isolated Systolic Hypertension from Changes in Arterial Compliance and Peripheral Resistance

by YUNPING GUO

Thesis Director:
Professor John K-J. Li

Hypertension has been recognized as the principal risk factor to cardiovascular diseases (CVD). The condition exists in more than 75 million in the US alone, and is known as the silent killer. Isolated systolic hypertension (ISH) with systolic pressure of 160 mmHg and diastolic pressure of 90 mmHg, is particularly common in the elderly. But its underlying mechanism remains largely unresolved. This thesis investigates the hemodynamic contributing factors to the production of ISH through computational modeling.

Since ISH in the elderly has been found clinically to be due to vascular factors, i.e. reduced artery compliance (C) and increased peripheral resistance (Rs), we utilized the three-element Windkessel model of the arterial system to evaluate its parameter changes in the production of ISH. Experimental aortic pressure (P) and flow (Q) data previously obtained from our lab and from published database were
obtained for the normal, vasoconstrictor induced hypertension and vasodilator induced hypotension conditions. With Q as input to the model, predicted pressure waveform compared well with measured pressure. A variety of combinations of C and Rs are then used to predict the ISH (160/90 mmHg). Significantly larger percentage reduction in C and mild increase in Rs have been found to produce ISH. Comparison of multiple data sets showed that subjects with lower initial blood pressure needed much greater changes in C and Rs to become systolic hypertensive. The opposite was found for those with higher initial pressures.

Findings of the present study agree well with those observed clinically. This model study has the distinct advantage, in that it identifies quantitative alteration in vascular parameter changes (C and Rs) and how they contribute to progressive blood pressure increases. The study can be extended to monitor individual hypertensive patients, as well as evaluated different anti-hypertensive drugs and their effectiveness.
Acknowledgment

First of all, I want to thank my instructor, Dr. John K-J. Li, for his guidance and help to my entire MS Thesis. Dr. Li gave me a lot of practical advice both in school and work. Even in the case of remote, I got many opportunities to practice theoretical knowledge under his guidance.

Besides, I must thank my parents for their psychological and financial support so that I can study and live in Rutgers. Even though we are separated by thousands of rivers and mountains, the understanding and help of my family has brought me endless strength to move forward.

Finally, I would like to thank my friends and my puppy Mibing for their support and happiness during this difficult year. They made me believe that all darkness and suffering will pass, and the future will always be bright.
# Table of Contents

**ABSTRACT** .................................................................................................................... ii

**Acknowledgment** ......................................................................................................... iv

**Table of Contents** .......................................................................................................... v

**Chapter 1. Introduction** ................................................................................................. 1

1.1 Hypertension as Risk Factor of Cardiovascular Disease ........................................... 1

1.1.1 Heart Failure ........................................................................................................... 1

1.1.2 Left Ventricular Factors ........................................................................................ 2

1.1.3 Arteriosclerosis and Atherosclerosis .................................................................. 4

1.2 Systolic Hypertension ............................................................................................... 5

1.2.1 The mechanism of systolic hypertension ............................................................ 5

1.2.2 Pathogenic Factors of Systolic Hypertension ....................................................... 6

1.2.3 Current Treatment Methods and Effects .............................................................. 8

1.3 Arterial Compliance as Index of Vascular Stiffness ................................................. 9

1.3.1 Pulsation Component (PP) .................................................................................. 9

1.3.2 Enhancement Index (AIx) ..................................................................................... 10

1.3.3 Pulse Wave Velocity (PWV) ............................................................................... 11

1.3.4 Quantitative Expression of Arterial Compliance ............................................... 12

1.4 Modeling the Arterial System with the Windkessel ................................................. 13
Chapter 2. Aims and Significance of the Thesis .............................................18

2.1 Overall Objectives of the Thesis..............................................................18

2.2 Specific Aims............................................................................................18

2.2.1 Quantify Arterial System Function in terms of 3-element Windkessel Model
Parameters.................................................................................................18

2.2.2 Analysis of the Mechanisms of Isolated systolic Hypertension based on
Windkessel Model Parameters.....................................................................18

2.2.3 Quantify How Other Hemodynamics Factors Affecting Windkessel Parameters ..............................................................................................................19

2.3 Significance of the Thesis ...........................................................................19

Chapter 3. Methods..........................................................................................20

3.1 Linear and Nonlinear Model Formulations..............................................20

3.1.1 The Linear Lumped Windkessel Model of the Arterial System..............20

3.1.2 Nonlinear Li Model with Pressure-Dependent Compliance or the Li-Model ..........................................................24

3.2 Hypertension..............................................................................................25

3.2.1 Hypertension Modeling.........................................................................25

3.2.2 Isolated Systolic Hypertension...............................................................26

3.3 Experiments and Data Acquisition..........................................................26

3.4 Data Analysis.............................................................................................27

Chapter 4. Results............................................................................................29
4.1. Predictions of Aortic Pressures from Aortic Flows ............................................29

4.1.1. Peripheral resistance (Rs) effects on aortic pressure........................................29

4.1.2. Arterial compliance (C) effects on aortic pressure..........................................35

4.1.3. Rs and C combined changing effects aortic pressure......................................38

4.2. Prediction of ISH with combinations of C and Rs.............................................44

Chapter 5 Discussion and Suggestions for Future Research....................................50

5.1 Advantages of Modeling in the Analysis of Hypertension .................................50

5.2 Contributions of the Present Investigation and Clinical Relevance....................51

5.3 Suggestions for Future Research .......................................................................52

Reference ..................................................................................................................54

Appendix ..................................................................................................................56
List of Tables

Table 4.1: Ps and Pd with different Rs in control case #1. (Constant C and Z0). ...........30

Table 4.2: Ps and Pd with different Rs in control case #3. (Constant C and Z0)............31

Table 4.3: Ps and Pd with different Rs in hypertension case #1. (Constant C and Z0).......33

Table 4.4: Ps and Pd with different Rs in vasodilation case #1. (Constant C and Z0).......35

Table 4.5: Ps and Pd with different C in vasodilation case #1. (Constant Rs and Z0).......37

Table 4.6: Ps and Pd with different Rs in control case #1. (Constant Z0)....................39

Table 4.7: Ps and Pd with different Rs in control case #3. (Constant Z0)...................40

Table 4.8: Ps and Pd with different Rs in hypertensive case #1. (Constant Z0).............42

Table 4.9: Ps and Pd with different Rs in vasodilated case #1. (Constant Z0)...............43

Table 4.10: Comparation of Initial and Predicted Ps, Pd, C and Rs. .........................48
List of Illustrations

Fig. 1.1: Changes and risk factors caused by hypertension................................. 4

Fig. 1.2: Pathophysiologic mechanisms associated with isolated systolic hypertension. ... 7

Fig. 1.3: Lumped electrical analog model of the arterial system..............................14

Fig. 1.4: Two-element Windkessel electrical analog model..................................14

Fig. 1.5: Three-element Windkessel electrical analog model ..............................15

Fig 1.6: A typical aortic pressure waveform in a single cardiac cycle. ..................16

Fig. 3.1:  Sketch of the physical characteristics of the Windkessel. .........................20

Fig. 3.2: Three-element Windkessel electrical analog model ..............................23

Fig. 3.3: Modified Windkessel model with a pressure-dependent compliance element C(P) (Li model) .................................................................................................................24

Fig. 4.1: Aortic blood pressure prediction with constant C and increased Rs for control #1. ........................................................................................................................................30

Fig. 4.2: Pressure prediction with constant C and increased Rs for control #3. ........31

Fig. 4.3: Aortic blood pressure prediction with constant C and increased Rs for hypertension case #1. ....................................................................................................................32

Fig. 4.4: Pressure prediction with constant C and increased Rs for vasodilation #1. ....34

Fig. 4.5: Pressure prediction with constant Rs and decreased C for vasodilation #1. ....36

Fig. 4.6: Hypertension prediction based on initial normal blood pressure control #1. ...38

Fig. 4.7: Hypertension and ISH prediction for control #3......................................40
Fig. 4.8 Hypertension case

Fig. 4.9 Vasodilator treated case

Fig. 4.10: ISH prediction from control #1 blood pressure levels

Fig. 4.11: ISH prediction from control #3 blood pressure levels

Fig. 4.12: ISH prediction from vasodilation #1 blood pressure levels

Fig. 4.13: ISH prediction for vasodilation #2
Chapter 1. Introduction

1.1 Hypertension as Risk Factor of Cardiovascular Disease

Cardiovascular disease (CVD) is the leading causes of mortality and morbidity in the U.S. and worldwide. Hypertension, as one of the main risk factors in CVDs like sudden cardiac attack (SCA) and irregular heart rate related cardiac arrhythmia, account for the majority of the global health care cost, as well as 9.4 million deaths worldwide. (Pan, Han et al, 2020) More than 25% of people in the U.S. has this condition. (Schiffrin, Ernesto L, 2004)

1.1.1 Heart Failure

Among CVDs, heart failure risk is greatly influenced by hypertension. Chronic hypertension affects the spatial structure of left ventricle which causes left ventricular hypertrophy (LVH) and increased left ventricular mass (LVM), and eventually leading to some high public health burden problems like heart failure (HF).

Basing on epidemiology research, the occurrence of heart failure is closely related to people with hypertension. (Kannel, W. B., & Belanger, A. J., 1991) Specifically, people whose blood pressures are greater than 160/100 mmHg have almost double risk of heart failure when compared to those blood pressure less than 140/90 mmHg. This increased risk also related to the level of hypertension. Mild hypertension patients have 2-3 times risk than people with normal blood pressure, while an extra one-third to one-quarter of people with blood pressure higher than 160 mmHg face development into heart failure. In extreme cases, people with hypertension may have 10 times risk of heart failure than normal. (Di Palo, Katherine
According to Framingham Study research, the relationship between blood pressure and heart failure is also influenced by gender and age. (Ho KK, Pinsky JL et al, 1993) Hypertensive woman has 3 times risk of heart failure than women with normal BP and Hypertensive man has twice the risk.

There are many ways and factors hypertension contribute to heart failure, such as diastolic abnormalities caused by spatial structural changes, left ventricular hypertrophy, and excessive systolic function of the left ventricle caused by hormone changes in the body. These risk factors for heart failure also become more serious with age. (Levy D, Larson MG et al, 1996)

1.1.2 Left Ventricular Factors

Left ventricular hypertrophy plays an important role in the process of other cardiovascular diseases caused by hypertension. Due to the effect of continuous arterial hypertension, the left ventricle expands and changes its shape to adapt to the changing pressure to maintain normal ventricular wall stress. This leads to a positive correlation between the thickness of the ventricular wall and the degree of hypertension, so that cases of left ventricular hypertrophy are very common in a large number of hypertensive patients, especially those with severe hypertension. (Verdecchia, Paolo, et al, 1990) The left ventricular hypertrophy often leads to a decrease in the contractile performance of the myocardium, which brings serious consequences such as heart failure.

In addition to causing left ventricular hypertrophy, hypertension may also cause
cardiac fibrosis by causing continuous increase in myocardial pressure. The human heart muscle can regenerate itself to a certain extent after being injured, and cardiac fibrosis may be a negative result of this repair process. Hypertension-related myocardial damage can exacerbate myocardial fibrosis caused by the repair process.

The myocardium is composed of thick myosin and thin actin to form a structure of sarcomere that overlaps periodically. (Díez J, 2007) The degree of overlap determines the length of the sarcomere, and the length of the sarcomere determines the size of the muscle tension. In order to ensure the ability to generate tension under the continuous stress caused by high blood pressure, myocardial cells will become larger, and the structure of the sarcomere will also change accordingly to adapt to this change. After the myocardium is thickened, its effective marginal fiber density will decrease, causing the maximum tension of the myocardium to fail to reach the original size, resulting in fibrotic consequences. At the same time, the decrease in ATP production under hypertension conditions will also reduce the ion function between myocardial cells, causing the heart to fail to contract and relax normally. All the procession above may cause other chain effects like left ventricular torsion and increasing the risk of stroke.

After the left ventricle is affected by high blood pressure, it may also cause asynchrony and arrhythmia of the left ventricle, and then cause sudden cardiac death. (Pahor M, Bemabei R et al, 1991) Studies have shown that about one-fifth of asymptomatic hypertensive patients have a problem of unsynchronized diastole and contraction of the left ventricle. The remodeling of the left ventricular morphology by
hypertension makes the end-diastolic volume change, which reduces the length of the action potential, so that the resting membrane action potential of the cardiomyocytes is slightly negative. The occurrence of fibrosis also exacerbates the occurrence of arrhythmia. Hypertension leads to abnormal ion channels, impaired communication between myocardial cells, and also affects the activation of neurohormones, which can lead to the development of arrhythmia in hypertensive patients. (Nwabuo, Chike C. et al, 2020)

**Fig. 1.1:** Changes and risk factors caused by hypertension.

1.1.3 Arteriosclerosis and Atherosclerosis

Under the action of hypertension, arterial compliance changes, and blood vessel walls are damaged or narrowed, leading to arteriosclerosis and atherosclerosis. Cardiovascular diseases related to arteriosclerotic hypertension occupy the main
morbidity and mortality factors in the elderly. (Dozono K, Ishii N et al, 1991)

Aortic stiffness can measure the degree of cardiovascular disease risk in the population, and the degree of loss of blood vessel elasticity is affected by age and increased blood pressure. Aortic pulse wave velocity (PWV) is an indicator that can measure the stiffness of the aorta. Many patients will further increase the degree of hypertension after the occurrence of arteriosclerosis. The stiffness of the aorta of these patients increases, which leads to a further increase in systolic blood pressure and pulse pressure. Patients with hypertension and arteriosclerosis are also at risk of some brain-related complications, including stroke and other diseases caused by circulatory insufficiency. (Hollander, William, 1976)

1.2 Systolic Hypertension

Isolated systolic hypertension is defined as systolic blood pressure surpass normal value (160 mmHg) and diastolic blood pressure within the normal range (90 mmHg) or lower. It mainly occurs in elderly hypertension, and its prevalence gradually increases with age. (Staessen, Jan et al, 1990)

1.2.1 The mechanism of systolic hypertension

Systolic hypertension is usually caused by loss of dilation of the large arteries innervated by the aorta. With age, arterial calcium and collagen deposits that can cause arterial elastin abrasion gradually increase, making arterial compliance decrease, arterial stiffness increased, and systolic blood pressure gradually increased. Since most of the smaller arteries do not affect this process, the diastolic blood pressure
remains normal or drops. Affected by this change, the pulse pressure will also increase, so the Windkessel effect is weakened. The pulse wave velocity increases due to the decrease in arterial compliance, producing a faster reflected pressure wave, causing a mismatch between the ventricles and blood vessels, increasing the left ventricular load and systolic pressure. Affected by the increase in systolic blood pressure, the workload of the left ventricle increases, and the possibility of left ventricular hypertrophy increases. At the same time, enzymes and pro-inflammatory effects are increased by the effect of increased systolic blood pressure, causing endothelial dysfunction. The decrease in diastolic blood pressure may impair coronary blood flow and cause other undesirable consequences.

1.2.2 Pathogenic Factors of Systolic Hypertension

Therefore, compared with diastolic hypertension, systolic hypertension is more harmful to the cardiovascular system. In elderly patients, chronic diseases such as diabetes and chronic kidney disease are often accompanied, which increase the body's burden. (Chobanian, Aram V, 2007) Behaviors such as hyperlipidemia and smoking that accelerate the development of arteriosclerosis and atherosclerosis can also catalyze the appearance of systolic hypertension.
**Fig. 1.2:** Pathophysiologic mechanisms associated with isolated systolic hypertension. RAAS \( \frac{1}{2} \) renin-angiotensin-aldosterone system.

It is estimated that the prevalence of isolated systolic hypertension is much lower than that of the elderly due to the better elasticity of blood vessel walls in adolescents and middle-aged people. The increase in systolic blood pressure in these patients was mainly concentrated in the peripheral arteries rather than the central artery, but it also led to a greater increase in the arterial pressure and pulse pressure of the upper extremities. Studies have shown that, as the prevalence of obesity and metabolic syndrome increases over time, the prevalence of isolated systolic hypertension in young and middle-aged people may continue to rise. The mortality of cardiovascular disease and coronary heart disease caused by hypertension has also increased. (Bavishi, Chirag et al, 2016)
1.2.3 Current Treatment Methods and Effects

The choice of antihypertensive drugs in the pharmacological treatment of isolated hypertension has been controversial from different organizations.

The 1993 guidelines in the United States (Gifford Jr, RW, 1993) pointed out that after long-term controlled clinical trials, the only effective drugs for the treatment of hypertension are diuretics and β-blockers, which can reduce the incidence of hypertension in patients. Morbidity and mortality. Therefore, unless the patient has special indications, contraindications or other unacceptable drugs, non-therapeutic diuretics and beta blockers will be the first choice for treatment.

On the contrary, the joint committee of the World Health Organization and the International Society of Hypertension believes that the blood pressure reduction caused by the combined use of vasodilators, beta blockers, central drugs or diuretics in clinical trials cannot be confirmed by any evidence. The benefit of a particular antihypertensive drug may be due to the decrease in blood pressure itself. The committee gave a list of drugs in the order of their proven effects on the morbidity and mortality of mild persistent hypertension: diuretics, beta-blockers and invertase blockers, calcium channels Blockers and alpha-adrenergic receptor blockers. In other words, both of these confirm the effects of diuretics and β-blockers.

Both of these first-choice recommendations have brought an urgent need to evaluate calcium channel blockers and invertase inhibitors. Their effectiveness in reducing morbidity and mortality in the long-term range in the treatment of hypertension needs to be confirmed. In the placebo-controlled double-blind
experiment "Syst-Eur" (Staessen, Jan A. et al., 1997) conducted by the European Working Group on Hypertension in the Elderly in 1989, nifedipine (calcium channel blocker) and enalapril or Hydrochlorothiazide (or at the same time) is used for treatment. The senile systolic hypertension (SHEP) experiment conducted in 1991 showed that diuretic-based treatment has a preventive effect on stroke, myocardial infarction and congestive heart failure. However, after the results of this trial were announced, due to the uncertainty of the treatment of isolated systolic hypertension in elderly patients, they continued to conduct the Syst-Eur trial. The results show that antihypertensive drugs led by Nitrendipine can reduce cardiovascular complications in elderly patients with isolated systolic hypertension.

1.3 Arterial Compliance as Index of Vascular Stiffness

Arterial compliance is an important parameter to assess the degree of arteriosclerosis, and arterial compliance is often reflected by indicators such as pulse waveform, enhancement index (AIx), and pulse wave velocity (PWV).

1.3.1 Pulsation Component (PP)

Under the combined effect of incident waves and reflected waves along the central artery and peripheral arteries, the pulsation component (PP) increases from the central aorta to the surrounding blood vessels, even though the diastolic pressure (DBP) and mean arterial pressure along the arterial tree gradually decrease. The impedance changes that occur with the branching of blood vessels cause pulse wave (PW) reflections to occur along the vascular tree at unlocated anatomical parts. Small
arterial resistance is one of the main parts of wave reflection. As the reflected wave moves backward, the forward wave increases and is distorted. This process causes the systolic blood pressure to increase abnormally as the wave advances from the start of the aorta to the surrounding blood vessels.

The above process will cause different results in the aorta and surrounding waveform. In the younger population, the pulse pressure between the aortic arch and the brachial artery increased by 18%-31%. As aging occurs, blood vessels become hard, causing traveling waves and reflected waves to accelerate. Since the reflected wave occurs earlier, it returns along the aorta at a faster speed. This advances the time of return from the diastolic period to the systolic period.

Because of this, in a cardiac cycle, the sum of the forward wave and the reflected wave appears earlier, and the aortic systolic pressure is amplified. Therefore, with age, the expansion effect of PP changes drastically. In the young population, the sum of the forward and backward waves at each point on the arterial tree affects the systolic blood pressure of the surrounding arteries, causing it to rise accordingly. In the elderly, the faster the pulse wave propagates, the less PP expands from the central blood vessel to the surrounding blood vessels. Because the reflected wave occurs earlier and travels faster, the peak pressure of the aorta increases, resulting in a similar or close pressure.

1.3.2 Enhancement Index (AIx)

AIx is one of the hemodynamic indicators that can reflect arterial stiffness. It is defined as the pressure increase from the first contraction of the shoulder to the peak
of the aortic pressure waveform, expressed as a percentage of the peak pressure. It is generally believed that AIx is mainly determined by the intensity and duration of the reflected wave.

The central artery PW is composed of the forward traveling wave generated by the left ventricle (LV) pumping blood and the surrounding retroreflected wave. The transmission speed of the forward wave and the reverse wave increases with the increase of the stiffness of the arterial wall. Therefore, as can be seen above, the reflected wave will reach the central aorta earlier and increase the systolic pressure. The increase in arterial pressure generated at this arrival determines AIx. Since AIx reflects the load on the LV caused by wave reflection, it is considered a surrogate sign of arterial stiffness. Like other indicators of arterial stiffness, it is positively correlated with the risk of cardiovascular disease.

1.3.3 Pulse Wave Velocity (PWV)

The definition of pulse wave velocity is the PW velocity along the arterial tree. It is the ratio of the distance between the measurement sites to the time difference between the ECG R wave and the wave reaching the carotid artery and blood vessel of the lower extremity. Measuring PWV can be used to evaluate arterial system damage, vascular adaptability, and therapeutic efficacy of CVDs. In addition, PWV can also be used to indirectly estimate and measure BP. According to research, BP is negatively correlated with PWV, so it can measure the value of BP through a variety of estimation models. Studies have shown that PWV and AIx are similar and can also reflect the age-related characteristics of arterial stiffness.
But the difference is that in addition to age, AIx is also affected by gender, height, heart rate, blood pressure level and vasoactive drugs, and has nothing to do with changes in hardness. For example, taller individuals show smaller AIx. On the contrary, PWV has a weak correlation with these factors, but it is related to the Young's modulus of the thin-walled elastic tube. It can be seen from the definition of pulse wave velocity that pulse wave velocity can provide information about the elastic characteristics of the arterial system. The higher the PWV, the lower the compliance and expansion capacity of the blood vessel. Clinically, the assessment of PWV is often performed between regions. The carotid artery and femoral artery are represented by different combinations of arteries that are prone to pulsation, which can diagnose the local stiffness of the arterial wall at different periods of arterial stiffness. AIx is obtained from the transfer function, which is derived from the peripheral blood vessel, namely the artery or carotid artery, derived from the function. This calculation method makes the transfer function variable, which also brings questions to the accuracy of AIx calculation. According to studies, the correlation between AIx and PWV is weak, and PWV is more accurate in measuring the degree of cardiovascular stiffness. So Local PWV measurement has important clinical significance in analyzing the characteristics of the artery wall locally, and can provide diagnostic information for the biomechanical characteristics of the local artery wall.

1.3.4 Quantitative Expression of Arterial Compliance

From a quantitative point of view, arterial compliance can be expressed by the ratio of the change in blood flow to the synchronous pressure difference:
\[ C = \frac{dV}{dP} \]  \hspace{1cm} (1.3.1)

1.4 Modeling the Arterial System with the Windkessel

The concept of the Windkessel model was first proposed by the British clergymen Stephen Hales in 1733. Its purpose was to imitate the role of a fire hose, which he called an air chamber. Otto Frank named it Windkessel in German a century later, which means air-chambers. Air chambers or reservoirs describe the volumetric elasticity of large arteries. The large arteries expand as the blood pressure rises during the systole, and elastically back seat as the blood pressure decreases during the diastole, thereby helping to relieve blood pressure fluctuations. Otto Frank also developed a quantitative lumped Windkessel model that combines resistance and compliance elements. The heart and the arterial system have very complex interactions and coupling relationships (Li, 2000), so the Windkessel model plays a very precise tool role in the integration, simplification and understanding of the entire arterial circulation function.
Fig. 1.3: Lumped electrical analog model of the arterial system.

In the earliest two-element Windkessel electrical analog model, the resistor (Rs) represents the viscosity of the arteries to blood flow, because the resistance has good blocking characteristics for low-frequency elements and can prevent the passage of current. The capacitor (C) is used to express the arterial compliance with storage characteristics due to its storage characteristics. Frank aims to obtain the stroke amount from the measured pressure pulse profile and predict that when the heart is in diastole, the pressure decays exponentially with a characteristic time constant.

Fig. 1.4: Two-element Windkessel electrical analog model

C = Arterial Compliance.
Rs = Peripheral Resistance.

Although the binary Windkessel model can make a good prediction of the pressure decay process during diastole, it is not enough to describe the relationship between pressure and blood flow during systole. Therefore, another impedance element was added to the binary model to simulate the characteristic impedance of the aorta, and a ternary model was developed. This model is still widely used in research. In the ternary model, the resistance (Z0) is connected in series to the previous binary model to represent the characteristic impedance of the aorta. By defining the characteristic impedance in the time domain as the ratio of the oscillating pressure at the entrance of the aorta to the blood flow under the condition that no reflected wave reaches the input, this is a key factor in determining the left ventricular load during ejection.

![Diagram of three-element Windkessel electrical analog model]

**Fig. 1.5**: Three-element Windkessel electrical analog model

Zo = Characteristic Impedance.

C = Arterial Compliance.

Rs = Peripheral Resistance.
The aortic pressure (Pa) waveform is one of the most important indicators in hemodynamic analysis. This waveform can reflect the situation in a single cardiac cycle and can be used in a variety of research and analysis. Through the Windkessel model, it is possible to simulate the change of aortic pressure over time, and to predict and analyze this waveform.

**Fig 1.6:** An illustration of a typical aortic pressure waveform in a single cardiac cycle. The systolic blood pressure, end systolic blood pressure, mean blood pressure, diastolic blood pressure and pulse pressure are all marked. The duration of a contraction is divided into systolic and diastolic periods (Li, 2004, with approval).

There have not been many studies that utilize arterial system modeling to specifically examine how model parameters can influence the blood pressure development in hypertension in general and isolated systolic hypertension in particular. This aspect is investigated in this thesis study.
Chapter 2. Aims and Significance of the Thesis

2.1 Overall Objectives of the Thesis

The main objective is to utilize the Windkessel arterial system model to explore how its parameters, such as arterial compliance, $C$, and peripheral resistance, $Rs$, and characteristic impedance of the aorta $Zo$, in the prediction of overall arterial function, and in the progression and severity of hypertension.

2.2 Specific Aims

2.2.1 Quantify Arterial System Function in terms of 3-element Windkessel Model Parameters

Changes in vascular stiffness or elastic property will be quantified in terms of Windkessel model compliance, $C$. Along with changes in total peripheral resistance $Rs$, and characteristic impedance of the aorta, $Zo$, we can explain how blood pressure amplitude and waveform change under different conditions.

2.2.2 Analysis of the Mechanisms of Isolated systolic Hypertension based on Windkessel Model Parameters

In elderly hypertensive patients, isolated systolic hypertension (ISH) is more prevalent, i.e. systolic pressure is elevated much higher than normal. It is often caused by age-related aortic sclerosis, resulting in increased vascular stiffness. This thesis will analyze to what extent such changes lead to decreased arterial compliance and increased resistance and whether Windkessel parameters can predict the occurrence of ISH in terms of blood pressure amplitude. ISH is defined by blood
pressure of 160/90 mmHg.

2.2.3 Quantify How Other Hemodynamics Factors Affecting Windkessel Parameters

In addition to arterial compliance, the characteristics of arterial elasticity can be influenced by changes in pulse wave velocity and wave reflections. The increase of the reflected wave increase the systolic blood pressure and pulse pressure (PP). Increased PP decreases arterial compliance. Studies have shown that pulse wave velocity has a negative correlation with arterial compliance. This thesis will investigate the relationship of pulse pressure and wave reflections to model parameters C, Zo and Rs.

2.3 Significance of the Thesis

Hypertension currently has a great impact on human cardiovascular health and life. In the United States, there are more than 75 million adults living with hypertension which is the primary risk factor to many forms of cardiovascular diseases, threatening their lives. Therefore, the development and research needs for blood pressure control drugs are becoming more and more urgent.

Modeling approach as proposed here. i.e. predicting how variations in model parameters are linked to vascular property changes and blood pressure amplitudes in hypertension, can greatly improve the predictable outcome as a much-reduced cost. This can lead to eventual effective evaluation of the effect of anti-hypertensive drugs in controlling hypertension. The overall modeling approach can thus play an important role in faster and more effective drug development.
Chapter 3. Methods

3.1 Linear and Nonlinear Model Formulations

3.1.1 The Linear Lumped Windkessel Model of the Arterial System

In the analysis of the Windkessel model, the blood flow $Q_s$ stored during each contraction is the difference between the flow of $Q_i$ flowing into the aorta and the outflow $Q_0$ flowing into the small peripheral blood vessels. Mathematically, we have:

$$Q_s = Q_i - Q_0$$

(3.1.1)

![Diagram of Windkessel model](image)

Fig. 3.1: Sketch of the physical characteristics of the Windkessel. Aortic flow $Q$ is a result of ventricular ejection which distends the aorta in systole and elastic recoil of the aorta propels blood flow to the peripheral vessels in diastole. From Li (2004) with permission.
Due to the peripheral resistance $R_s$, the outflow is equal to the pressure drop from the arterial side ($P$) to the venous side ($P_v$)

$$Q_0 = (P - P_v)/R_s \quad (3.1.2)$$

Under a stable flow and assuming that $P_v$ is very small, the external resistance can be estimated, and the total inflow $Q = Q_i$

$$R_s = \bar{P}/\bar{Q} \quad (3.1.3)$$

Or mean arterial pressure to mean arterial flow.

The storage characteristics can be described by using an arterial compliance element, which represents the change in blood volume ($dV$) due to changes in the distending pressure ($dP$) in the aortic lumen.

$$C = dV/dP \quad (3.1.4)$$

Due to arterial compliance, the stored blood flow or $Q_s$ is related to the rate of pressure change that causes the artery to expand:

$$Q_s = C dP/dt \quad (3.1.5)$$

Considering the flows, give us:

$$Q_i = Q_s + Q_0 \quad (3.1.6)$$

Substituting (3.1.2) and (3.1.5) into (3.1.6), an expression relating to aortic pressure and flow are obtained, containing the two arterial system model parameters $C$ and $R_s$: 
\[ Q(t) = C \frac{dP}{dt} + \frac{P}{R_s} \quad \text{(3.1.7)} \]

In other words, the total arterial inflow is the sum of the flow stored in the aorta and the flow entering the periphery. In the diastolic phase, when the inflow is zero, for example, after the aortic valve is closed, the aortic blood flow in the diastolic phase is equal to zero,

\[ 0 = C \frac{dP}{dt} + \frac{P}{R_s} \quad \text{(3.1.8)} \]

or

\[ \frac{dP}{P} = -\frac{dt}{R_s C} \quad \text{(3.1.9)} \]

This equation shows that the rate of diastolic aortic pressure drop depends on both the compliance of the arterial system and the total peripheral resistance. Both also determine the flow rate.

Integrate the above formula to get:

\[ \ln P = \frac{t}{R_s C} \quad \text{(3.1.10)} \]

or

\[ P = P_0 e^{-t/R_s C} \quad \text{(3.1.11)} \]

It is valid during diastole, or \( t = t_d \).

Since the diastolic blood pressure decreases approximately exponentially from the end of the systolic period \( (t_s) \) to the diastolic period \( (t_d) \), it can be considered that:
\[ P_d = P_{es} e^{-t_d/\tau} \]  \hspace{1cm} (3.1.12)

Or the change in diastolic aortic pressure from the end-systolic pressure \( P_{es} \) to the end-diastolic pressure \( P_d \) follows a single exponential with a time constant of \( \tau \). The time constant of pressure decay is determined by the product of resistance and compliance, namely

\[ \tau = R_s C \]  \hspace{1cm} (3.1.13)

Or in terms of measured aortic pressure,

\[ \tau = \frac{t_d}{\ln\frac{P_{es}}{P_d}} \]  \hspace{1cm} (3.1.14)

And

\[ C = \frac{t_d}{R_s \ln\frac{P_{es}}{P_d}} \]  \hspace{1cm} (3.1.15)

**Fig. 3.2:** Three-element Windkessel electrical analog model

\( Zo = \) Characteristic Impedance.

\( C = \) Arterial Compliance.

\( Rs = \) Peripheral Resistance.
In a modified 3-parameters Windkessel model (Fig 3.2), the pressure-flow relation can be described by

\[ P_a(t) = P(t) + Z_0 \cdot Q(t) \]  \hfill (3.1.16)

where aortic pressure \( P_a(t) \) and aortic flow \( Q(t) \) are the input of the system. And \( P(t) \) is the pressure associated with compliance.

3.1.2 Nonlinear Li Model with Pressure-Dependent Compliance or the Li-Model

Regarding the three-element Windkessel model, the fixed capacitor represents a constant compliance for a given cardiac cycle. It is known that compliance changes with increasing or decreasing pressure. Thus, a blood pressure-related variable compliance or pressure-dependent compliance as termed by Li et al. (1990) provides a more accurate description, as shown in Figure 3.2. This is also known as the Li-Model.

**Fig. 3.3:** Modified Windkessel model with a pressure-dependent compliance element \( C(P) \) (Li model).
The model consists of pressure-related compliance elements $[C(P)]$, peripheral resistance ($R_s$), and characteristic impedance of the proximal aorta ($Z_0$). $Q_{ao}$, aortic blood flow is the input of this model (Li et al., 1990).

Since arterial compliance changes continuously with blood pressure changes throughout the cardiac cycle, the value of capacitance or compliance $C$ can be represented by $C(P)$,

$$C(P) = a \cdot e^{b(P(t))}$$

This expression was first proposed by Li et al. (1990) and is referred to as the Li model. In this relationship, $a$ and $b$ are empirical constants. This equation well represents the interaction between arterial stiffness and arterial pressure.

### 3.2 Hypertension

#### 3.2.1 Hypertension Modeling

Clinically, blood pressure levels change when aortic compliance and the arterial resistance to blood flow change. Since increased vascular stiffness or decreased compliance is associated with hypertension, and that an increase in total peripheral resistance is also associated with hypertension, the linear Windkessel model can be used to predict what changes in $C$ and $R_s$ can lead to hypertension.

Hypertension is defined by 140/90 mmHg, i.e. systolic/diastolic, which sets the boundaries. We can introduce stepwise reduction in $C$ and stepwise increase in $R_s$ and
observe the computed aortic pressure $P_a(t)$ following eqn. (3.1.7). We will choose to reduce $C$ by 25% increment and increasing $R_s$ by 10% increment to begin the prediction process. Diastolic pressure is used as the initial condition, or $P(t_i=0)$.

3.2.2 Isolated Systolic Hypertension

Similarly, to model isolated systolic hypertension or ISH condition, the decline in aortic compliance is more prominent, so $C$ is reduced more profoundly and $R_s$ is slightly increased. We will also decrease $C$ by 25% increment and increase $R_s$ by 10% each time until $P_a$ reaches 160/90 mmHg to modeling the ISH condition. Reduction in $C$ and increase in $R_s$ can be “tuned” to provide a good prediction of ISH of 160/90 mmHg.

3.3 Experiments and Data Acquisition

With the approval of the Institutional Animal Care and Use Committee (IACUC) of Rutgers University, experimental data was collected from past experiments on anesthetized and ventilated hybrid dogs (Segers et al., 1999; Li et al., 1994; Kaya et al., 2018). The electromagnetic flow probe is placed in the ascending aorta to measure the aortic blood flow. At the same time, a pressure sensor was inserted into the tip of the femoral Millar catheter to record the aortic pressure. Intravenous injection of sodium nitroprusside (50 μg/ml) and methoxyamine (2-5 mg/ml) causes high-dose dilation and vasoconstriction. Subsequently, under normal conditions (control), hypertension (vasoconstriction) and subsequent hypotension (vasodilation), aortic
pressure and aortic blood flow were stably recorded. Lead II electrocardiograph (ECG) is used to monitor the condition of the heart. The collected data was acquired at a frequency of 100 Hz for further calculations. In this study, we selected several data sets, including control or normal blood pressure, hypertension and vasodilator treated conditions, because they provide a wide pressure range and can allow various vascular wall characteristics to be observed and for model parameters computation. This allows a thorough examination of the pressure-dependent compliance properties of the artery as well in the nonlinear Li-model.

3.4 Data Analysis

Experimental data were sampled at 100Hz or 10 msec sampling intervals. This is sufficient as blood pressure and flow waveforms contain highest frequency components to $10^{th}$ harmonic or about 25 Hz (Li, 2000, 2004).

With the normal condition data, $\bar{P}$, $P_{es}$, $P_d$ and $\bar{Q}$ are known, thus initial $R_s$ and $C$ can be calculated by (3.1.3) and (3.1.15). Then the simulation can be carried out on this base.

According to 3.1.7, $P$ and $t$ can be expressed as

$$\frac{dP}{dt} = \frac{Q(t) - P}{R_s/C}$$

(3.4.1)

where $dt = t_{i+1} - t_i$, which in this case is equal to 0.01 s, and $dP = P(t_{i+1}) - P(t_i)$, so eventually $P$ can be expressed as
Thus, to calculate each P and Pa, set a loop to calculate each P value starting from \( P_0 = P_d \) by recursive method, and then substituting formula (3.1.16) to calculate Pa. And for hypertension and ISH condition, set the second loop to decrease C by 25% and increase Rs by 10% each time. Plot all the curves in the same figure to compare each combination of C and Rs with the normal situation.

Model predicted blood pressure waveform is first compared to measured waveform for the normal case to establish the accuracy of the linear model. Root mean square error is noted.

Plot the linear model predicted Pa(t) with measured Pa(t).

Values of C and Rs for each stepwise change are tabulated for comparison.

Since increased vascular stiffness is directly proportional to pulse pressure increases, this relationship is plotted.

\[
C = \frac{SV}{PP} \tag{3.4.3}
\]

A different method of calculating arterial system compliance is also computed.
Chapter 4. Results

4.1. Predictions of Aortic Pressures from Aortic Flows

The three-element Windkessel model of the arterial system was used to evaluate the influence of its parameter changes on blood pressure waveform. Using aortic flow (Q(t)) as input, the normal, vasoconstrictor induced hypertension and vasodilator induced hypotension blood pressure waveforms (P(t)) are predicted under different parameters combinations.

4.1.1. Peripheral resistance (Rs) effects on aortic pressure

Aortic pressure of control was first predicted by three-elements linear Windkessel model and compared with the measured aortic pressure, as shown in Fig. 4.1 (control case #1) and Fig. 4.2 (control case #3). Increases in Rs are also shown. It can be seen that increasing Rs principally increases mean blood pressure levels, lifting up blood pressure in general.
Fig. 4.1: Aortic blood pressure prediction with constant C and increased Rs for control #1.

Table 4.1: Ps and Pd with different Rs in control case #1. (Constant C and Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
<th>Z0(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original</td>
<td>122.8880</td>
<td>96</td>
<td>0.3584</td>
<td>6.3541</td>
<td>0.2208</td>
</tr>
<tr>
<td>#1</td>
<td>123.1967</td>
<td></td>
<td></td>
<td>6.9895</td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>123.5682</td>
<td></td>
<td></td>
<td>7.9426</td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>124.0239</td>
<td></td>
<td></td>
<td>9.5311</td>
<td></td>
</tr>
</tbody>
</table>
**Fig. 4.2:** Pressure prediction with constant C and increased Rs for control #3.

Better prediction of control systolic pressure is seen here than in Fig. 4.1.

**Table 4.2:** Ps and Pd with different Rs in control case #3. (Constant C and Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
<th>Z0(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>132</td>
<td></td>
<td>0.3294</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original</td>
<td>131.9959</td>
<td></td>
<td></td>
<td>4.8511</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>132.8009</td>
<td>105</td>
<td>0.3030</td>
<td>5.3362</td>
<td>0.1597</td>
</tr>
<tr>
<td>2</td>
<td>133.7740</td>
<td></td>
<td></td>
<td>6.0638</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>134.9735</td>
<td></td>
<td></td>
<td>7.2766</td>
<td></td>
</tr>
</tbody>
</table>
Figure 4.3 shows the aortic pressure of vasoconstrictor (methoxamine) induced hypertension case #1 predicted by three-elements linear Windkessel model and compared to the measured aortic pressure. The progressive increases in Rs again increased overall mean blood pressure levels, but the predicted changes in waveform shape were small.
Table 4.3: Ps and Pd with different Rs in hypertension case #1. (Constant C and Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
<th>Z0(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>156</td>
<td></td>
<td>0.3252</td>
<td>6.8130</td>
<td></td>
</tr>
<tr>
<td>Original</td>
<td>156.3513</td>
<td>123</td>
<td>0.3808</td>
<td>7.4943</td>
<td>0.1944</td>
</tr>
<tr>
<td>1</td>
<td>157.0690</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>157.9350</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>159.0006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aortic pressure of vasodilator (nitroprusside) induced hypotension case #1 predicted by three-elements linear Windkessel model is shown in Fig. 4.4 and compared to the measured aortic pressure, as well as those predicted with progressive increases in Rs.

**Fig. 4.4:** Pressure prediction with constant C and increased Rs for vasodilation #1.
Table 4.4: Ps and Pd with different Rs in vasodilation case #1. (Constant C and Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
<th>Z0(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>96</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original</td>
<td>102.5043</td>
<td></td>
<td></td>
<td>2.1364</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>102.5879</td>
<td>67</td>
<td>2.0303</td>
<td>2.3501</td>
<td>0.2292</td>
</tr>
<tr>
<td>2</td>
<td>102.6884</td>
<td></td>
<td></td>
<td>2.6705</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>102.8114</td>
<td></td>
<td></td>
<td>3.2046</td>
<td></td>
</tr>
</tbody>
</table>

4.1.2. Arterial compliance (C) effects on aortic pressure

With progressive reduction in arterial compliance C, considerable changes in morphology of the blood pressure waveforms are observed, together with an increase in pulse pressure. An example of this is seen in Fig. 4.5.
**Fig. 4.5**: Pressure prediction with constant Rs and decreased C for vasodilation #1. Notice the progressive increases in pulse pressure accompany the corresponding decreases in C.
**Table 4.5:** Ps and Pd with different C in vasodilation case #1. (Constant Rs and Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
<th>Z0(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>96</td>
<td>65</td>
<td></td>
<td>2.0303</td>
<td></td>
</tr>
<tr>
<td>Original</td>
<td>102.5043</td>
<td></td>
<td>2.1364</td>
<td>0.2292</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>102.7288</td>
<td>67</td>
<td>1.5227</td>
<td>1.0152</td>
<td>0.2292</td>
</tr>
<tr>
<td>2</td>
<td>103.1790</td>
<td></td>
<td></td>
<td>1.0152</td>
<td>0.2292</td>
</tr>
<tr>
<td>3</td>
<td>105.3579</td>
<td></td>
<td>0.5076</td>
<td></td>
<td>0.2292</td>
</tr>
</tbody>
</table>
4.1.3. Rs and C combined changing effects aortic pressure

Since our goal was to be able to predict hypertension (defined as 140/90 mmHg) from changes in Windkessel model parameters from control, both C and Rs were altered to generate greater blood pressure levels. The level of about 160/90 mmHg defines ISH. Fig. 4.6 illustrates how hypertension is predicted as a combination of reduction in C and increases in Rs.

![Pressure Prediction Control #1](image)

**Fig. 4.6:** Hypertension prediction based on initial normal blood pressure control #1.
Table 4.6 Ps and Pd with different Rs in control case #1. (Constant Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps (mmHg)</th>
<th>Pd (mmHg)</th>
<th>C (ml/mmHg)</th>
<th>Rs (mmHg·s/ml)</th>
<th>Z0 (mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>120</td>
<td>96</td>
<td>0.3584</td>
<td>6.3541</td>
<td></td>
</tr>
<tr>
<td>Original</td>
<td>122.8880</td>
<td>96</td>
<td>0.3584</td>
<td>6.3541</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>127.1613</td>
<td>96</td>
<td>0.2688</td>
<td>6.9895</td>
<td>0.2208</td>
</tr>
<tr>
<td>2</td>
<td>138.3128</td>
<td>96</td>
<td>0.1792</td>
<td>7.9426</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>174.6104</td>
<td>96</td>
<td>0.0896</td>
<td>9.5311</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 4.7: Hypertension (>140/90 mmHg) and ISH (160/90 mmHg) prediction for control #3. Notice the Ps/Pd of this control begins at higher blood pressure levels than control #1.

| Table 4.7 Ps and Pd with different Rs in control case #3. (Constant Z0). |
|-----------------|----------------|-----------------|----------------|-----------------|
|                 | Ps(mmHg) | Pd(mmHg) | C(ml/mmHg) | Rs(mmHg·s/ml) | Z0(mmHg·s/ml) |
| Measured        | 132      | 105      | 0.3294     | 4.8511         |               |
| Original        | 130.5682 | 105      | 0.3294     | 4.8511         |               |
| 1               | 136.9965 | 105      | 0.2470     | 5.3362         | 0.1597        |
| 2               | 150.1893 | 105      | 0.1647     | 6.0638         |               |
| 3               | 190.8389 | 105      | 0.0823     | 7.2766         |               |
Fig. 4.8: The subject is already hypertensive (156/123 mmHg). Progressive reduction in C and increases in Rs rapidly increased overall pulse pressure beyond control.

When the blood pressure level is already hypertensive to begin with (Fig. 4.8), progressive decrease in arterial compliance C and an increase in Rs can rapidly pushing blood pressure to much higher levels, as seen in Fig. 4.8.
Table 4.8 Ps and Pd with different Rs in hypertensive case #1. (Constant Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
<th>Z0(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>156</td>
<td></td>
<td>0.3252</td>
<td>6.8130</td>
<td>0.1944</td>
</tr>
<tr>
<td>Original</td>
<td>159.9529</td>
<td>1</td>
<td>0.2439</td>
<td>7.4943</td>
<td>0.1944</td>
</tr>
<tr>
<td>1</td>
<td>169.2760</td>
<td>123</td>
<td>0.1626</td>
<td>8.5162</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>189.2688</td>
<td></td>
<td>0.0813</td>
<td>10.2195</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>247.4395</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4.9: Windkessel model predicted blood pressure levels with reductions in C and increases in Rs for the vasodilator treated case.
When the subject is pre-treated with vasodilator, blood pressure is low, in this case 96/65 mmHg, any large reduction in arterial compliance with increase in peripheral resistance still cannot push blood pressure to hypertensive (140/90 mmHg) levels. This is illustrated in Fig. 4.9.

**Table 4.9** Ps and Pd with different Rs in vasodilated case #1. (Constant Z0).

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
<th>Z0(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured</td>
<td>96</td>
<td>65</td>
<td>2.0303</td>
<td>2.1364</td>
<td>0.2292</td>
</tr>
<tr>
<td>Original</td>
<td>102.5043</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>102.8400</td>
<td></td>
<td>1.5227</td>
<td>2.3501</td>
<td>0.2292</td>
</tr>
<tr>
<td>2</td>
<td>103.5448</td>
<td></td>
<td>1.0152</td>
<td>2.6705</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>106.9845</td>
<td></td>
<td>0.5076</td>
<td>3.2046</td>
<td></td>
</tr>
</tbody>
</table>

It can be seen from multiple sets of simulation results that the peak systolic pressure increases with the decrease of C, and the diastolic pressure change rate decreases with the increase of Rs, that is, the diastolic pressure increases with the increase of Rs. At the same time, under the same parameter changes, the change in the case of lower initial blood pressure is less significant.
4.2. Prediction of ISH with combinations of $C$ and $R_s$

For the isolated systolic hypertension, we are able to predict the waveforms shown below (red line, while the normal simulation in blue and measured line in dots).

Fig. 4.10: ISH (160/90 mmHg) prediction from control #1 blood pressure levels.
Fig. 4.11: ISH (160/90 mmHg) prediction from control #3 blood pressure levels.
**Fig. 4.12**: ISH (160/90 mmHg) prediction from vasodilation #1 blood pressure levels.
Comparison shows that lower initial blood pressures (vasodilator treated cases) needs greater reductions in C and increases in Rs to achieve ISH of 160/90 mmHg. The higher initial blood pressure (as in hypertensive subject) slight changes in Rs and C can lead to ISH, as expected.
Table 4.10: Comparison of Initial and Predicted Ps, Pd, C and Rs.

<table>
<thead>
<tr>
<th></th>
<th>Ps(mmHg)</th>
<th>Pd(mmHg)</th>
<th>C(ml/mmHg)</th>
<th>Rs(mmHg·s/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control #1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>96.000</td>
<td>120.000</td>
<td>0.4400</td>
<td>6.3541</td>
</tr>
<tr>
<td>Predicted</td>
<td>160.400</td>
<td>87.200</td>
<td>0.0968</td>
<td>6.3541</td>
</tr>
<tr>
<td>%</td>
<td>-78</td>
<td>-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control #3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>131.000</td>
<td>106.580</td>
<td>0.3294</td>
<td>4.8511</td>
</tr>
<tr>
<td>Predicted</td>
<td>161.400</td>
<td>89.700</td>
<td>0.1021</td>
<td>4.2689</td>
</tr>
<tr>
<td>%</td>
<td>-69</td>
<td>-1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX #1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>155.834</td>
<td>124.340</td>
<td>0.3903</td>
<td>6.8130</td>
</tr>
<tr>
<td>Predicted</td>
<td>164.083</td>
<td>85.8367</td>
<td>0.1952</td>
<td>3.8153</td>
</tr>
<tr>
<td>%</td>
<td>-50</td>
<td>-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX #2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>199.915</td>
<td>155.911</td>
<td>0.1303</td>
<td>12.9346</td>
</tr>
<tr>
<td>Predicted</td>
<td>183.143</td>
<td>86.048</td>
<td>0.1303</td>
<td>3.8804</td>
</tr>
<tr>
<td>%</td>
<td>-0</td>
<td>-70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX #3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>164.535</td>
<td>130.109</td>
<td>0.3062</td>
<td>5.2296</td>
</tr>
<tr>
<td>Predicted</td>
<td>164.2039</td>
<td>88.2943</td>
<td>0.1837</td>
<td>2.9286</td>
</tr>
<tr>
<td>%</td>
<td>-40</td>
<td>-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ps(mmHg)</td>
<td>Pd(mmHg)</td>
<td>C(ml/mmHg)</td>
<td>Rs(mmHg·s/ml)</td>
</tr>
<tr>
<td>--------</td>
<td>----------</td>
<td>----------</td>
<td>------------</td>
<td>---------------</td>
</tr>
<tr>
<td>NTP #1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>101.708</td>
<td>64.500</td>
<td>4.0606</td>
<td>1.0682</td>
</tr>
<tr>
<td>Predicted</td>
<td>166.541</td>
<td>86.193</td>
<td>0.0975</td>
<td>3.7388</td>
</tr>
<tr>
<td>%</td>
<td>-97.6</td>
<td>+350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTP #2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>83.000</td>
<td>49.083</td>
<td>0.6770</td>
<td>1.5930</td>
</tr>
<tr>
<td>Predicted</td>
<td>163.588</td>
<td>87.894</td>
<td>0.0812</td>
<td>4.4605</td>
</tr>
<tr>
<td>%</td>
<td>-88</td>
<td>+280</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 5. Discussion and Suggestions for Future Research

5.1 Advantages of Modeling in the Analysis of Hypertension

Hypertension has been recognized as a major risk factor for cardiovascular disease (CVD). In the United States alone, there are more than 75 million of this disease, and it is called the silent killer. The global health care cost spending was most on hypertension related disease, as well as led to 9.4 million deaths worldwide. (Boutouyrie and Bruno, 2019). Isolated systolic hypertension (ISH) is defined as a systolic blood pressure of 160 mmHg and a diastolic blood pressure of 90 mmHg, which is especially common in the elderly. But its basic mechanism is still unresolved.

Clinicians and cardiovascular researchers in the world have been working tirelessly in an attempt to solve the origination and to generate the treatment of the hypertension problem. (Oparil, and Schmieder, 2015). The current research provides a new method of modeling the underlying physiology of reduced arterial compliance C (or increased vascular stiffness) in combination with increased peripheral resistance Rs, to predict the outcome and progressive changes. Through the combination of multiple parameters, we were able to simulate multiple conditions with varying blood pressure levels.

ISH is mostly caused by the decrease in vascular compliance caused by the loss of distensibility of the large arteries such as the aorta. With age, the arterial calcium
and collagen deposits caused by arterial elastin abrasion gradually increase, resulting in decreased arterial compliance, increased arterial stiffness, and systolic blood pressure. For this reason, ISH is more prevalent in the elderly who also have suffer from similar physiologic changes. Therefore, vascular stiffness plays an important role in the production of ISH. Since increased arterial stiffness is closely associated with hypertension and the degree of generation of ISH, a variety of anti-hypertension drugs focus on improving vascular compliance to relieve pressure inside the blood vessel. This makes the present modeling study of predicting the relationship between blood vessel stiffness and ISH production especially important.

5.2 Contributions of the Present Investigation and Clinical Relevance

This study provided quantitative analysis of index of vascular stiffness parameter (arterial compliance) and how its change is related to arterial wall properties and overall arterial system function. In other words, this study quantified the relationship between hypertension and systolic hypertension and arterial compliance, and intuitively demonstrated the effect of changes in blood vessel wall elasticity on blood pressure. This allows us to predict how the increase in peripheral resistance (Rs) and arterial compliance (C) can lead to hypertension, especially the production of Isolated Systolic Hypertension (ISH) in particular.

Since the study uses arterial flow as input, the modeling approach presented here can be applied to any single individual. C and Rs can be obtained from peak systolic
pressure (Ps) and diastolic pressure (Pd) and these model parameters are used to predict the probability and the progression individuals may suffer from hypertension or ISH during their elderly years.

5.3 Suggestions for Future Research

According to the nonlinear arterial compliance or the pressure-dependent compliance model described in (3.1.2), this study can be extended to the nonlinear Li model (Li et al., 1990). Since arterial compliance is related to changes in blood pressure, arterial compliance can be represented by C(P) instead of constant C used in this study. This can improve the overall accuracy of model predictions of hypertension and ISH.

This research can be applied to the self-monitoring of some hypertensive patients. Active participation in the management of hypertension is very important to improve self-management behavior and clinical outcomes. (Kim et al. 2016). Therefore, this application is effective for blood pressure control and combination therapy for people with hypertension.

In addition, the model in this study can also be used to evaluate different anti-hypertensive drugs and their effectiveness. Some drugs reduce blood pressure by increase artery compliance (C). For example, angiotensin receptor blockers (ARB: valsartan), angiotensin converting enzyme inhibitors (ACE-I: temocapril). (Takami and Shigemasa, 2003). ARB caused the greatest decrease in pulse pressure (PP) and
brachial-ankle pulse wave velocity (baPWV), followed by ACE-1 and L-type and N-type Ca channel blockers. Therefore, the effects on arterial stiffness and PP vary with the properties of the drug. ARB can further reduce arteriosclerosis in elderly hypertensive patients. The effects of these drugs can be reflected by increasing C while maintaining Rs, and vice versa. Therefore, this model can bring benefits to the overall analysis of drug efficacy.
Reference


systematic review and meta-analysis of cohort studies." European journal of epidemiology, 2020
Appendix

Original Codes:

close all
figure(1)
clear

LPant = readvars('JKL-N MTX NTP-3
sets.xlsx','Sheet','NTP1','Range','B2:B40');
LQant = readvars('JKL-N MTX NTP-3
sets.xlsx','Sheet','NTP1','Range','C2:C40');
% Import of raw data, according to different data groups

Q = LQant';
Pd = LPant(1);
dt = 0.01;
Zo =
((LPant(3)-LPant(2))/(LQant(3)-LQant(2))+(LPant(2)-LPant(1))/(LQant(2)-LQant(1))))/2;
% Calculate Zo by initial P

td = 0.19;
Pes = 70;
% According to each data group

Ps0 = max(LPant)
M = 1;
N = 1;
Rs0 = mean(LPant(:))/mean(LQant(:))*M;
C0 = -td./(Rs0.*log(Pd./Pes))*N;
% C0 and Rs0 adjusted by M and N to be close to measured figure.

Rs(1) = Rs0;
C(1) = C0;

t = 0.01:0.01:0.39;
P = zeros(1);'
Pa = zeros(1);'
X = 1;
Y = 1;
% Parameters to give adjust C and Rs to ISH condition. X for Rs. Y for C.
for j = 1:4
    P(1) = Pd - Zo.*Q(1);
    n = 0;
    for i = 1:39
        if Q(i)<0
            Q(i) = 0;
        end
        P(i+1) = P(i) + dt.*(Q(i)-(P(i))./(Rs(j)*X))./(C(j)*Y);
    end
    Pa(i) = Q(i).*Zo + P(i);
end
Ps = max(Pa)
plot(t,Pa,'-')
hold on
C(j+1) = (1-0.25*j)*C0;
%change C by loop
if j == 1
    Rs(2) = Rs0*1.1;
end
if j == 2
    Rs(3) = Rs0*1.25;
end
if j == 3
    Rs(4) = Rs0*1.5;
end
%change Rs by loop.
end
C1=C'
Rs1=Rs'
Zo
%obtain calculated values
plot(t,LPant,'r:')
hold on
legend('Original Prediction','C -25%','C -50%','C -75%','Measured Pressure')
title('Pressure Prediction Vasodilation #1')
xlabel('Time(s)'),ylabel('Pressure(mmHg)')
%labels can be different for each simulation aim.