ARTERIAL FLOW BASED TRANSFER FUNCTION AND ASCENDING AORTA PRESSURE WAVEFORM ESTIMATION

By

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ABSTRACT OF THE THESIS

Arterial Flow Based Transfer Function and Ascending Aorta

Pressure Waveform Estimation

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Thesis Director:

Professor John K-J. Li

Hypertension has been recognized as a leading cause of cardiovascular diseases. It is principally determined by the amount of the blood ejected by the heart and the properties of the receiving arteries. There is a strong correlation of a reduction in large artery compliance and high blood pressure. Thus, it is important to identify the causative factors that contribute to the severity of hypertension in terms of blood pressure, flow and mechanical properties of arteries.

Numerous methods have been used to measure peripheral arterial blood pressure. As pressure waveform travels away from heart, it is amplified because of increased elastic stiffness which gives rise to wave reflections. As a result, peripheral pressure cannot accurately describe cardiovascular events. On the other hand, central aortic pressure is a much better predictor, but it can only be measured directly with an invasive catheter. For this reason, several pressure-based generalized transfer function methods have been proposed.

In this thesis, a novel flow-based generalized transfer function is established. This new method is tested using carotid flow waveform as an input to predict ascending aortic flow. Additionally a three element windkessel model was used to predict ascending aortic pressure. Results show good correspondence of predicted ascending aortic flow and pressure.

The present approach can be effectively applied in clinical situations where either peripheral arterial flow or ascending aortic flow noninvasively obtained by Doppler ultrasound can be used to obtain ascending aortic pressure. The derived aortic pressure waveform can then be further analyzed in terms of large artery compliance and systolic pressure augmentation, both critical in determining the severity of hypertension.

Acknowledgements

First, I would like to thank my advisor, Dr. John K-J Li, for his guidance and support.

I would also like to thank my parents and my brother and my sister-in-law for their continuous motivation and support. I would like to thank my loving husband for his tremendous contribution and support.

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Chapter 1: Introduction

1.1 Risk factors for Hypertension and Cardiovascular disease:

Blood pressure is the pressure against the walls of that arteries when heart pumps the blood to the body. Blood pressure is determined by amount of the blood the heart ejects and resistance to the blood flow in the arteries. Hypertension is also termed high blood pressure. In hypertension, force of the blood against artery is high. In many cases, cause of hypertension is unknown, but there are several factors identified which can increase your risk of developing blood pressure. Risk factors include family history, age, diabetes (Wang et al., 2006).

Cardiovascular diseases are disease affecting heart and blood vessels. These include arrhythmia, heart failure, coronary heart disease etc. Risk factors for cardiovascular disease include hypertension, diabetes, cholesterol, obesity, age and family history. Hypertension has been known as the leading risk factor for cardiovascular disease. Controlling the risk factors like hypertension, diabetes, unhealthy diet can decrease the risk of the cardiovascular disease.

1.2 Hemodynamics of Hypertension:

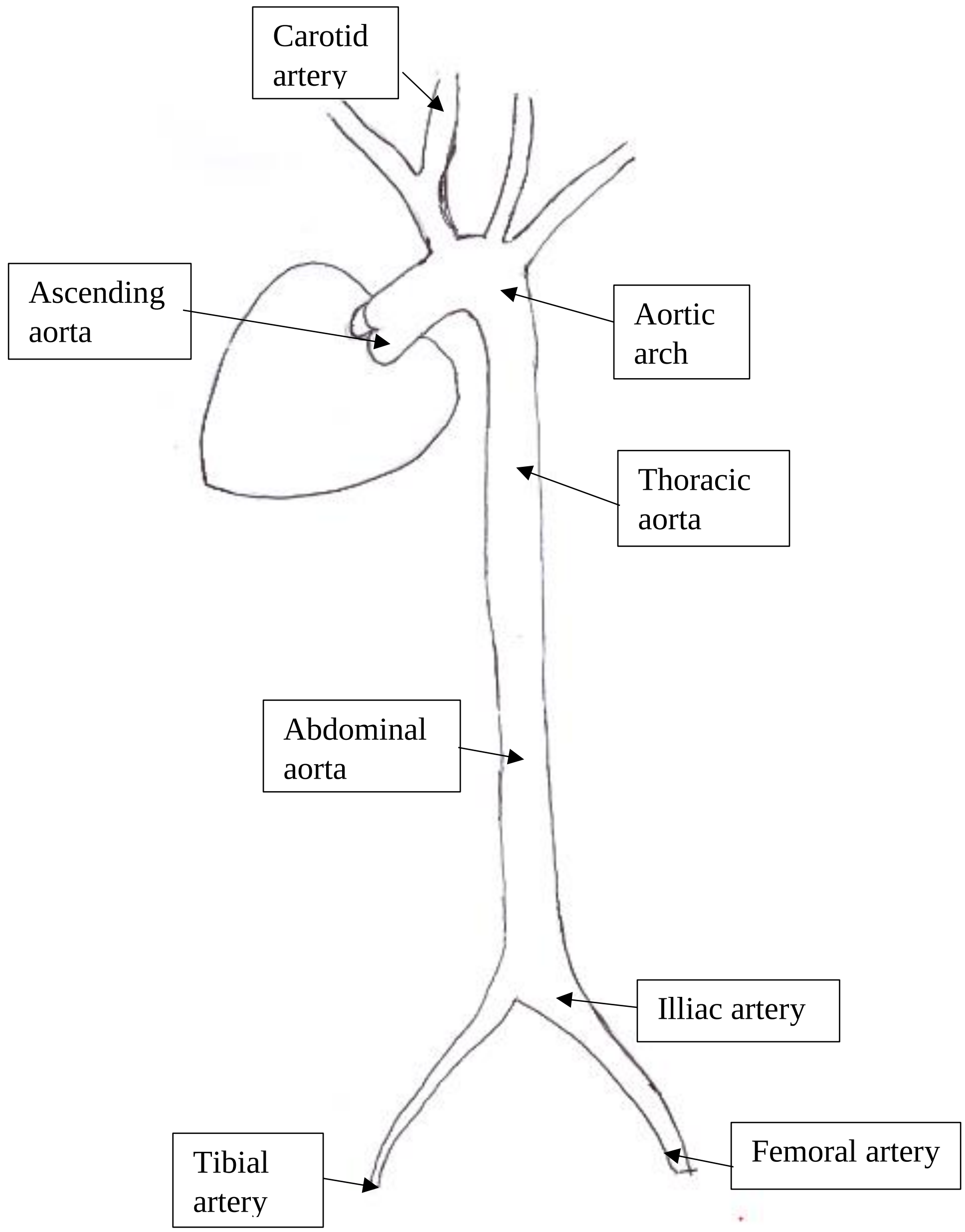


Figure 1.1: Schematic of the systemic arterial tree

1.2.1 The Arterial System:

Circulatory System helps transporting materials throughout the entire body. Circulatory system is made up of heart, arterial system, venous system and microcirculatory system. Heart pumps blood throughout the body. Arterial system is a network between hearts and other organs. Main function of this system is to provide nutrients and oxygen to peripheral tissues in the bed. Main function of venous system is to return blood to atria. Microcirculatory system provides homeostatic environment for cells (Li, 2004). Figure 1.1 shows schematic of arterial tree of dog.

Distribution of branching arteries inside our body resembles a tree structure. There are different arteries that branch off main aorta. Ascending aorta starts after aortic valve. There are many arteries like renal artery, femoral artery that branches off the descending aorta. The arterial system is made up of aorta and these arteries, which connects heart to external tissues. Arteries provide oxygenated blood to the peripheral tissue. Veins provide deoxygenated blood back to heart. Arteries have higher blood pressure to be able to carry blood from heart to distal tissues. The walls of arteries are thicker and elastic to handle high pressure in arteries. Vein are thin walled and have low pressure. Veins have less elastin than arteries. This makes veins stiffer than arteries. Branching and tapering varies from aorta to peripheral arteries. Smaller arteries branch off larger arteries. Smaller arteries are always narrower than larger arteries, but has larger cross sectional area in normal arterial system.

Arterial wall is consist of elastin, collagen and smooth muscle. There are three level of arterial wall. Figure 1.2 shows breakdown of the arterial wall. Tunica intima, the innermost layer of the arterial wall is consist of thin layer of endothelial cells, connective tissue and basement membrane. This layer lines arteries and veins. Medial layer contains arranged elastic lamina. Outermost layer of arterial wall is made up of the collagen fibers. Structure of arterial wall corresponds very well with its function. Large arteries and aorta has more elastic laminae to be able to stand high pressure. These elastic laminae allow them to contract and dilate for pumping action of the heart. On the other hand, Arterioles is actually one of the smallest branch of artery. They have more smooth muscles and less elastic tissue. They have vascular resistance that helps to reduce pressure and velocity of the blood flow. As you go away from the aorta, amount of elastic laminae decrease in the arterial wall, smooth muscle increases. This causes net stiffness to increase and pulse wave velocity increases. Hypertension is defined as a force of the blood flow against your arterial wall. Hypertension can increase arterial wall thickness.

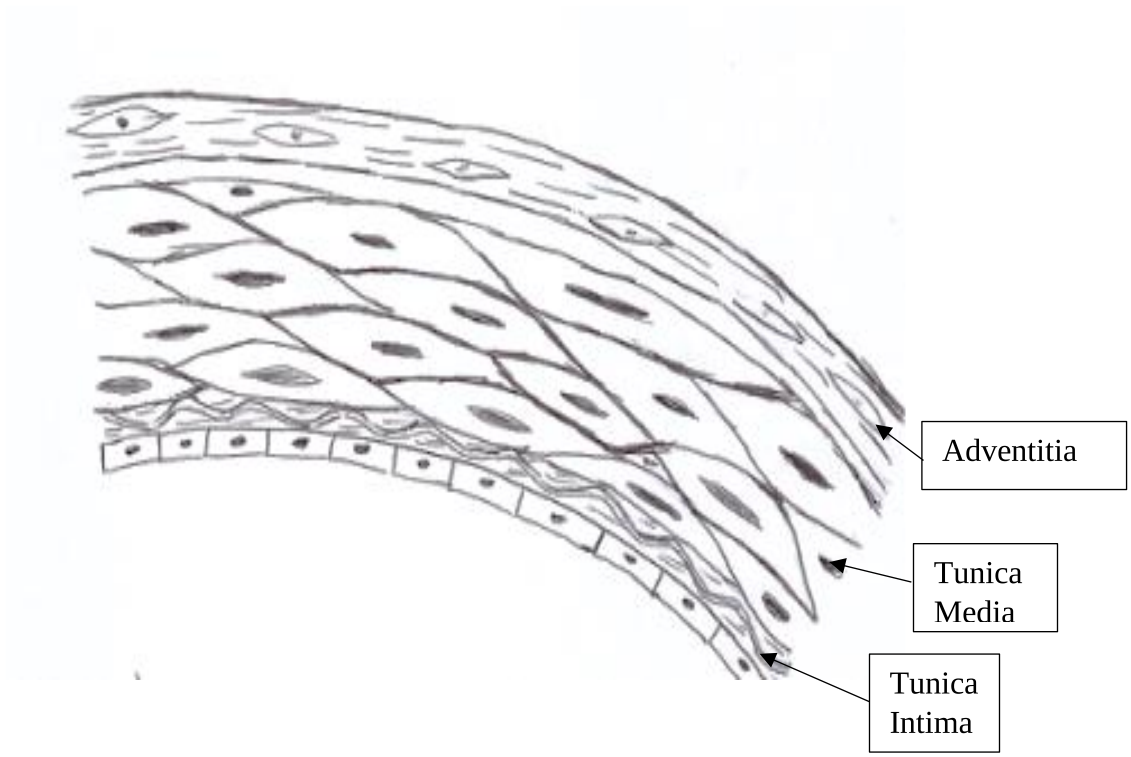


Figure 1.2: Breakdown of the arterial wall showing three principle layers.

1.2.2 Pathology Related to Hypertension:

Cardiovascular diseases are leading cause of the death all over the world. Hypertension is one of the risk factor for cardiovascular disease. Hypertension and diabetes are two of the leading risk factors for atherosclerosis (Cheung et al., 2012). Hypertension actually puts pressure on the arterial wall. This pressure on the arteries can damage arteries. Plaque can build in damaged arteries, which leads to atherosclerosis. Hypertension is more frequent in patients with Arterial Stenosis than in the control population without the disease (Kaden et al., 2008). Association between Aortic Stenosis and Hypertension is not very clear (Bermejo, 2005). Hypertension on the weak arterial wall can cause arterial wall to enlarge and bulge in that area called aneurysm. Aneurysm can rupture and cause internal bleeding. Left ventricular hypertrophy is thickening of wall of left ventricle. Left ventricular hypertrophy and hypertension are correlated (Katholi et al., 2011). Constant pressure on the left ventricle causes left ventricle to be stiff. Constant high pressure on the heart may weaken heart and lead to heart failure.

1.2.3 Mechanical properties of arterial wall:

Mechanical properties:

Young's modulus of elasticity is defined as ratio of force per area to ratio of change in length to original length.

$$E=F/A/\Delta L/L \tag{1.1}$$

F: Force

A: Area

ΔL: Change in length

L: Original Length

Strain can be longitudinal direction or radial direction. Strain can be defined amount of artery that stretched. Young's modulus can give approximation of elasticity of arterial wall.

Compliance can be defined as change in volume over change in pressure.

$$C=\Delta V/\Delta P \tag{1.2}$$

C: Compliance

ΔV: Change in flow

ΔP: Change in pressure

Arterial pressure and pressure waveform provides useful information about vascular stiffness, reflected wave, compliance, and other features (Chen et al., 1997). As pulse travel away from the heart, pressure and flow waveforms at different anatomic locations have differences in waveform due to their structural and geometric non-uniformities (Li, 2004). The arterial pressure waveform is generated when aortic valve opens up and blood ejected from left ventricle to aorta. Systolic pressure in aorta increases as blood flow in the aorta and reaches plateau. Eventually, arterial pressure declines as blood flows from aorta to peripheral arteries. As pulse travel away from heart, amplitude of the pressure pulse increases and flow pulse decreases due to wave reflections (Nichols et al., 2011). Systolic peak in the pressure waveform becomes steeper as pulse travels towards periphery. Flow waveform behaves exactly in opposite manner as pulse travels towards periphery. Dicrotic notch, which appears due to the aortic valve closure becomes rounder and distinct as pulse travels towards periphery. Diastole starts after closure of the aortic valve and it continues till next systole. Decrease in end diastolic pressure can be seen as pulse travels towards periphery. These changes in pressure and flow waveforms from the central to periphery can be seen in Figure 3. These changes in waveform happens due to wave reflections, geometric tapering and changes in the stiffness of the arteries and damping (Li, 2004). Pulse pressure waveform is made up of forward wave and backward wave. Forward wave is generated when blood is ejected from left ventricle. Backward wave (reflected wave) is generated because of differences in the elastic properties of the arteries. Reflective sites include branching points, area where arterial stiffness alters and arterioles (Nichols et al., 2011).

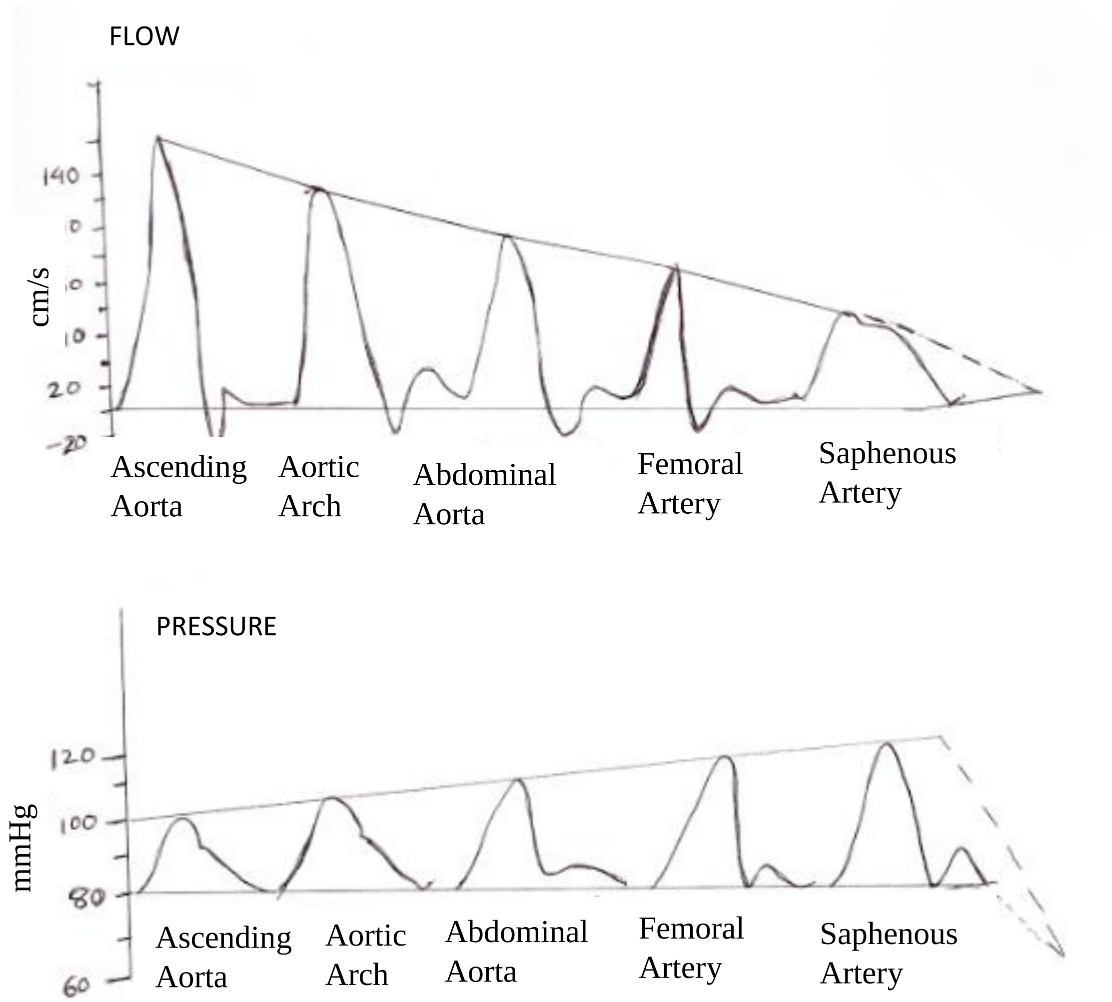


Figure 1.3: Sketch of pressure and flow waveforms in different arteries as you travel away from heart (Redrawn from Nichols et al., 2011)

1.2.4 Lumped Windkessel model:

Windkessel model considers lumped capacitance and resistance elements (Nichols et al., 2011). Windkessel is air filled compression chamber that smooths oscillations of water pump to have continuous flow of water through hose (Nichols et al., 2011). This is similar in terms of arterial system. Heart pumps blood into aorta (elastic element). Blood is actually stored in the aorta in Systole. Blood then travels from aorta to stiff peripheral arteries during elastic recoil. Arterial system acts as a cushion and arterioles acts as a resistance to make pulsatile flow of heart continuous. This representation has been seen in Figure 1.4. This analogy was initially developed by Hales. German scientist Otto Frank is accredited for developing Windkessel model.

Windkessel model takes in account for arterial compliance and peripheral resistance. Arterial compliance is a measure of elasticity of arteries under pressure during cardiac cycle. Peripheral resistance can be defined as resistance of arteries to blood flow. Electrical representation of the windkessel model of the arterial system is shown in Figure 1.5. Two-element windkessel model is the simplest representation in terms of electric analog. Here arterial compliance is illustrated by a capacitor and peripheral resistance is illustrated by a resistor (Li, 2004). Two element model is insufficient to describe vascular impedance and other arterial properties.

The three-element model was then introduced as an improvement on the classical two-element model. Three-element model of Windkessel has been shown in Figure 1.6. It is popular model used to characterize the arterial load of the heart. Resistor is added in series in this model. Three-element model of windkessel also considers arterial compliance and peripheral resistance like two-element model of windkessel. In addition to arterial compliance and peripheral resistance, three-element model also considers impedance of proximal aorta. Hydraulic equivalent of the three-element model is shown in Figure 7. Change in volume of the bottle will cause change in the pressure (Li, 2004). This would represent aortic compliance (Li, 2004). Here resistance to flow can be varied by opening or closing needle valve just like peripheral resistance (Li, 2004). Here finite tube geometry and property represent the characteristic impedance of the aorta (Li, 2004).

Windkessel model is very simple model. It helps us to understand cardiovascular system, but it is unrealistic. Windkessel model do not account for wave reflection and wave propagation (Nichols et al., 2011). Pressure is amplified and pressure waveform changes continuously as it travels away from heart (McEniery et al., 2014). Central and peripheral arteries have different physical properties and they respond to different situations differently like aging and hypertension. Blood flow distribution and changes in the distribution cannot be represented with windkessel model (Westerhof et al., 2008). Windkessel model is simple and accurate, but it fails to describe arterial pressure and flow waveform in term of wave propagation and wave reflection.

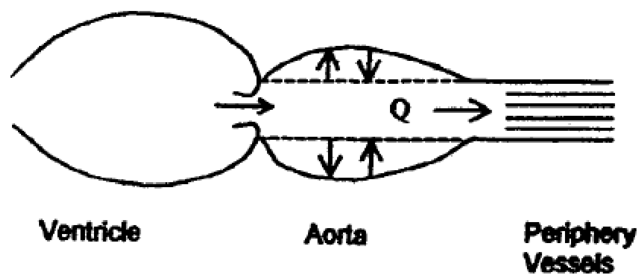


Figure 1.4: Sketch of the left ventricle and arterial circulation based on Windkessel theory. (Li, 2004)

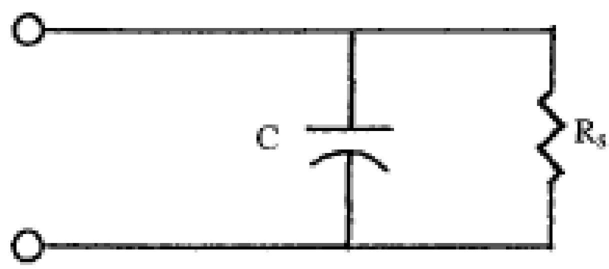


Figure 1.5: Two-element windkessel model (Li, 2004)

In two-element windkessel model,

As per equation (1.2), $C=\Delta V/\Delta P$

$$Rs=\text{Mean } P/\text{Mean } Q \quad (1.3)$$

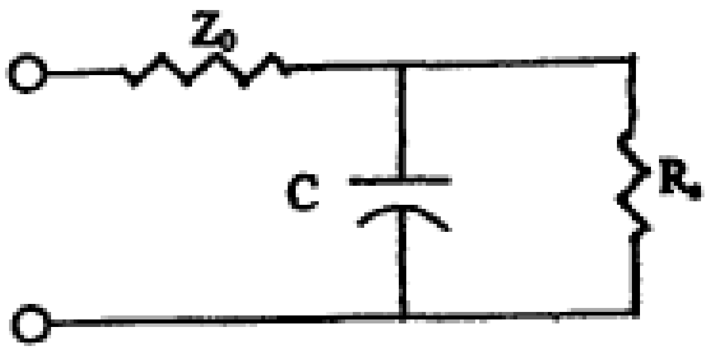


Figure 1.6: Three-element windkessel model (Li, 2004)

In three-element windkessel,

As per equation (1.2), $C=\Delta V/\Delta P$

As per equation (1.3), Rs= Mean P/Mean Q

$Z_0= pc/\pi r^2$ (1.4)

P: Blood density

c: Pulse wave velocity

r: Radius

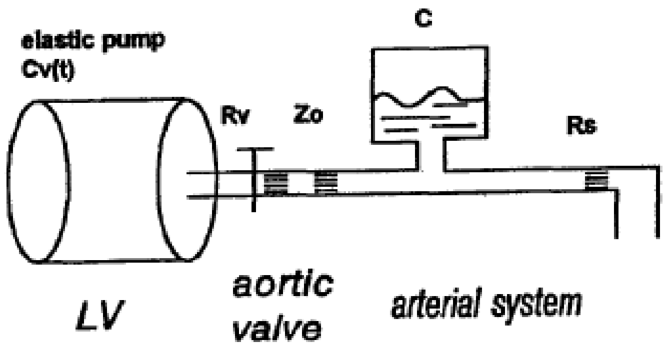


Figure 1.7: Hydrodynamic equivalent of the three-element Windkessel (Li, 2004)

1.3 Blood Pressure Measurement:

Blood pressure assessment is an internal part of clinical practice. Direct and indirect methods exists to measure blood pressure. Direct method include catheter with pressure transducer. In this method, catheter is entered in the artery with pressure transducer attached. This method is invasive. Indirect method includes auscultatory method, oscillometric method and arterial tonometry. Auscultatory method is popular to measure blood pressure in clinical setting. Cuff is allowed to exceed systolic pressure and it collapses artery. Stethoscope is used to listen to Korotkoff sounds in the artery. Oscillometric method measures pressure variation of the cuff caused by oscillation of blood flow. Arterial tonometry method can provide continuous recording of pressure waveform (Drzwiecki et al., 1983). Tonometry is based on compressing and partial flattening of artery against the underlying structure preferably bone (Weiss et al., 1996). All these noninvasive techniques are used to measure peripheral pressure. There are couple of the limitations of measuring peripheral blood pressure. Peripheral arterial blood pressure is amplified due to wave reflections than central arteria blood pressure. As a result, peripheral arterial blood pressure does not accurately reflect central arterial blood pressure. Descending pressure in the large elastic artery like aorta and carotid is a key determinant of degenerative changes due to aging and hypertension than peripheral arteries (Agabiti-Rosei et al., 2007). Central aortic pressure seem to be a more accurate predicator of cardiovascular events than peripheral pressures (Nelson et al., 2010). As a result, it is important to measure central arterial blood pressure.

Central arterial blood pressure can be measured directly with of pressure-sensing catheterization, but it is invasive. There is no direct noninvasive method to measure central arterial blood pressure. There are other noninvasive transfer function based methods exist to measure central arterial blood pressure. These methods generate ascending aortic pressure waveform from peripheral pressure waveform. Transfer function is a mathematical definition of change in pulsatile phenomena between two sites (Söderström et al., 2002). It is expressed in the frequency domain in terms of modulus and phase (Söderström et al., 2002). Generalized transfer function technique exists for deriving the central aortic pressure based on the peripheral pressure. Chen et al. accurately estimated central aortic pressure from radial tonometry with use of generalized transfer function (1997). Reconstructed waveform using generalized transfer function can provide arterial compliance but it may underestimate the augmentation index (Chen et al., 1997). Söderström et al. investigated SphygmoCor™, a commercially available system to synthesize ascending aortic pressure wave from radial pressure wave through generalized transfer function (2002). This system improved monitoring of left ventricular afterload noninvasively (Söderström et al., 2002). Average black box transfer function is created using central aortic and peripheral arterial waveforms from subjects in generalized transfer function. Then peripheral arterial waveform information is used as an input to the transfer function and central aortic transfer pressure waveform is estimated. Generalized transfer function technique allows us to determine central aortic pressure in different conditions. This technique does not take into account physiological differences between patients or age related changes in arterial compliance.

Chapter 2: Aims and Significance of the Thesis

2.1 Objectives of the Thesis:

Hypertension is one of the risk factor for cardiovascular disease. Cardiovascular diseases are leading cause of the death all over the world. As a result, it is important to monitor pressure and flow of central aorta.

Central pressure and flow are more accurate predicator of cardiovascular events than peripheral pressures and flow. Peripheral pressure can be measured directly non-invasively easily, but central pressure can be measured directly invasively only. Noninvasive flow-based transfer function is proposed in this thesis to monitor ascending aortic flow and to derive ascending aortic pressure.

2.2 Specific Aims:

1. Proposed Noninvasive Method for Assessing Cardiovas cular Disease:

Central aortic pressure and flow waveforms have known to be accurate predictor of cardiovascular events than peripheral waveforms. Central aortic pressure waveform can be measured directly with catheters, but this method is invasive. There are no direct noninvasive method for measuring central aortic pressure. Indirect method proposed in this thesis is noninvasive and allows prediction of ascending aortic flow and pressure.

2. Proposed Methodology Flow Based Transfer Function:

Central aortic pressure can be measured directly using catheters, but this technique is invasive. Some pressure based transfer function methods have been proposed before to measure central aortic pressure. Noninvasive flow-based transfer function has been proposed in this thesis to predict ascending aortic flow and to derive ascending aortic pressure.

3. Compare Pressure and Flow Transfer Function:

Flow-based transfer function has been proposed in this thesis to predict ascending aortic flow. This flow-based transfer function can be compared to pressure based transfer functions that has been used to estimate central aortic pressure.

2.3 Proposed Methodology:

Three carotid waveforms and three ascending aorta flow waveforms were obtained. These waveforms were digitalized and averaged. Matlab program was written to find flow based transfer using these waveforms. Carotid waveform is then input into flow based transfer function to predict ascending aortic flow waveform. Three-element windkessel model was used to derive ascending aortic pressure from ascending aortic flow waveform.

2.4 Significance of the Thesis:

Traditionally, peripheral aortic pressure was used to predict cardiovascular events. Many noninvasive techniques have been known to measure pressure and flow of the peripheral arteries. Central aortic pressure and flow are better predictor of the cardiovascular events than peripheral pressure. Central aortic pressure can be measured directly using a catheter, but this method is invasive and can lead to complications. As a result, it is not ideal method for measuring central aortic pressure. Generalized transfer function based non-invasive techniques has been proposed by other investigators to predict central aortic pressure.

Flow-based transfer function based method has been proposed in this thesis to predict ascending aortic flow. Generalized flow based transfer function was established between carotid artery and ascending aorta. Then this generalized transfer function was used to predict ascending aortic flow. This proposed method is non-invasive. Then three-element windkessel model was used to predict ascending aortic pressure from flow. Ascending aortic flow and pressure are critical in predicting cardiovascular events.

Chapter 3: Methods

3.1 Introduction:

Three flow waveforms for carotid and ascending aortic flow waveforms were obtained. These waveforms were digitalized using digitalizing software into equal number of points. Three carotid waveforms were averaged and three ascending aorta waveforms were averaged. Matlab program was written to find flow based transfer function using averaged waveforms for carotid flow and ascending aortic flow. Carotid waveform can be digitalized and this transfer function can be used to predict ascending aortic flow. Then three-element windkessel model was used to predict ascending aortic pressure from flow.

3.2 Data source:

Three carotid waveforms were obtained (Holdsworth et al., 1999; Hirata et al., 2006). Three ascending aorta waveforms were obtained (Sankaranarayanan et al., 2006; Sankaranarayanan et al., 2005; "STACOM 2013 CFD Challenge"). Carotid test waveforms were obtained to test flow based transfer function ("Medison.ru"). Average carotid flow waveform and average ascending aorta flow waveform was used to derive individualized transfer function (Reymond et al., 2009).

3.3 Data Processing:

All waveforms were digitized using webplotdigitizer software. All the waveforms were digitized using webplotdigitizer using x step interpolation into 64 points from 0s to 1s. Carotid artery waveforms were in speed. This waveform was converted to flow by multiplying it by average area of carotid artery. Mean diameter of carotid artery was approximated to be 5.82 mm (Denarié et al., 2000). Area of carotid artery was estimated using π*r^2, where r is radius of carotid artery. Then Fast Fourier Transform (FFT) of these data was taken. Fourier analysis converts a signal form time or space domain to frequency domain. Fourier transform is reversible. Fourier transform was calculated using fft(x) command of matlab. Inverse Fourier Transform was calculated using ifft(x) function of matlab. These transforms can be defined as below:

$$X_n = \sum_{k=0}^{N-1} x_k W_N^{nk} \quad , \quad n = 0, 1, \ldots, N-1 \tag{3.1}$$

Where, $W_N = \exp(-j\, 2\pi/N)$

Inverse Fourier transformation can be described as below:

$$x_k = \frac{1}{N} \sum_{n=0}^{N-1} X_n W_N^{-nk} \quad , \quad k = 0, 1, \ldots, N-1 \tag{3.2}$$

3.4 Transfer Function (TF):

Transfer function is a ratio of output signal to input of the signal. Single-input single output transfer function was used to predict ascending aortic flow. This transfer function is linear and time invariant. Figure 3.1 below shows single-input single output transfer function. If input signal is X and output signal is Y, then transfer function can be defined as a ratio of output signal to input of the signal.

Transfer function=Y/X (3.3)

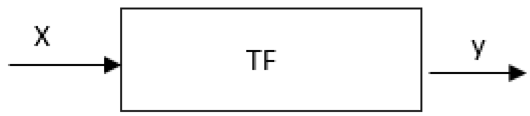


Figure 3.1: Block diagram of transfer function

If carotid artery flow is input for this transfer function and ascending aortic flow is output for the system, then transfer function can be defined as ratio of ascending aortic flow to carotid artery flow.

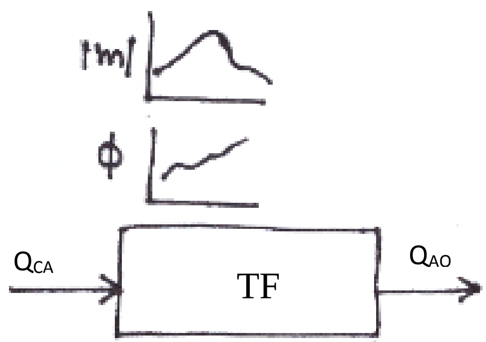


Figure 3.2: Block diagram for TF proposed

Transfer function magnitude :$|H(j\omega)|$ = $|Q_{AO}|$ / $|Q_{CA}|$ (3.4)

Transfer function phase: $\phi(\omega)$=$Phase_{AO}$ – $Phase_{CA}$ (3.5)

This transfer function can be applied to carotid artery flow waveform to obtain ascending aortic flow waveform. Then waveform can be recovered from frequency domain to time domain by taking inverse Fast Fourier Transform of the waveform of all 64 Hz data.

3.5 Windkessel model:

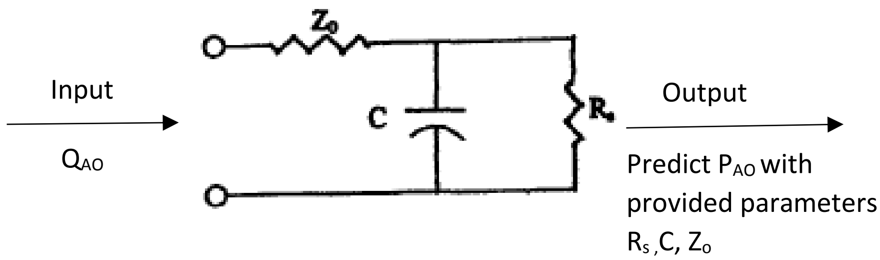


Figure 3.3: Shows electric analogy of three-element windkessel model.

Below equations can be derived from the model:

$$Q_{ao}(t) = Q_{Rs}(t) + Q_C(t) \tag{3.5}$$

$Q_{ao}(t)$: flow through ascending aorta

$Q_{Rs}(t)$: flow through resistive section

$Q_C(t)$: flow through compliance section

$$Q_C(t)=C*\frac{dP(t)}{dt} \tag{3.6}$$

$$Q_{Rs}(t)=\frac{Ps(t)}{Rs} \tag{3.7}$$

$$\frac{dP(t)}{dt} = \frac{1}{C}\left[Qao(t) - \frac{P(t)}{Rs}\right] \tag{3.8}$$

dP(t)/dt : Change in pressure with change in time

C: Compliance

Rs: Peripheral Resistance

Q(t): Flow

P(t): Pressure at time t

$$P_{i+1} = P_i + \frac{dt}{C}(Q_i - \frac{Pi}{Rs}) \qquad (3.9)$$

C: Compliance

Rs: Peripheral Resistance

P_i: Initial pressure (Diastolic pressure)

Q_i: Flow

$$P_a(t)=Q(t)*Z_o+P(t) \qquad (3.10)$$

$P_a(t)$: Aortic Pressure

Q(t): Flow

Z_o: Characteristic Impedance

P(t): Pressure

Equation 3.9 and 3.10 were used to derive ascending aortic pressure waveform from ascending aorta flow waveform. Diastolic pressure was estimated to be 80 mmHg. Peripheral resistance (Rs), Compliance (C) and characteristic Impedance (Z_o) were estimated to best fit pressure waveform.

3.6 Flow Chart of Methodology:

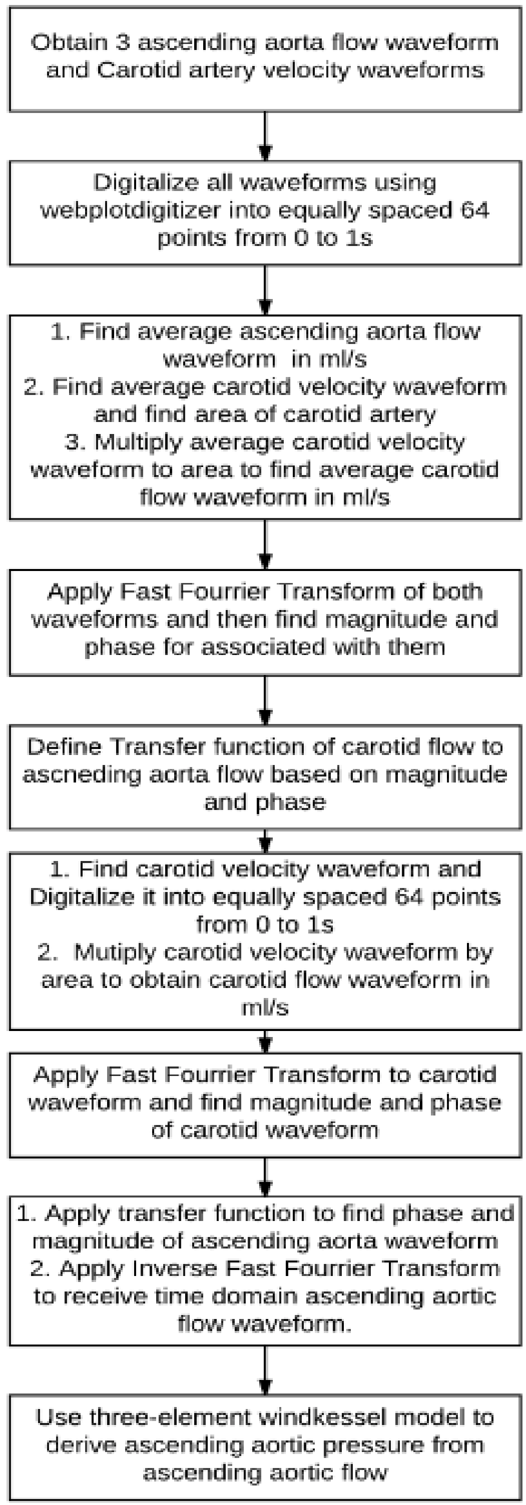


Figure 3.4: Flow chart of the proposed methodology

Chapter 4: Results

4.1 Generalized Transfer function:

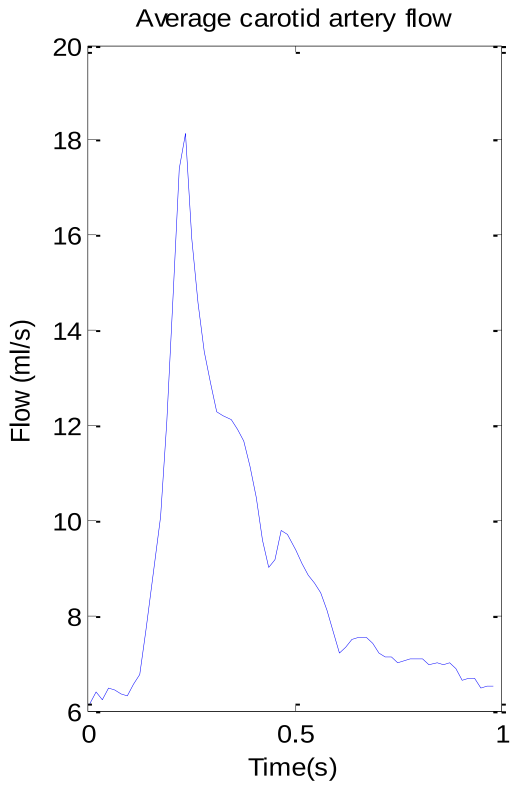


Figure 4.1: Average carotid flow waveform

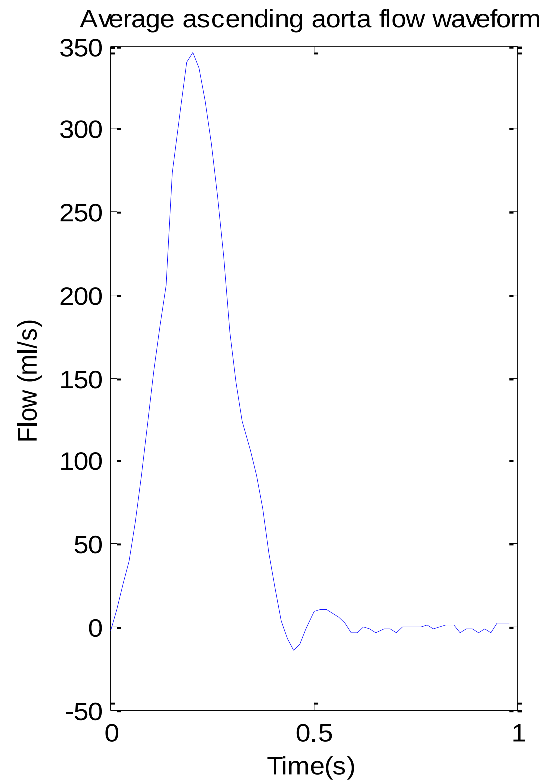


Figure 4.2: Average ascending aorta flow waveform

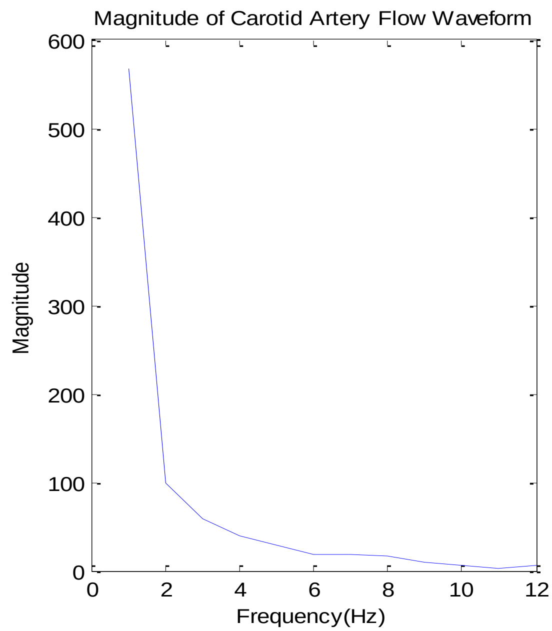


Figure 4.3: Magnitude of carotid artery flow waveform of first 12 harmonics

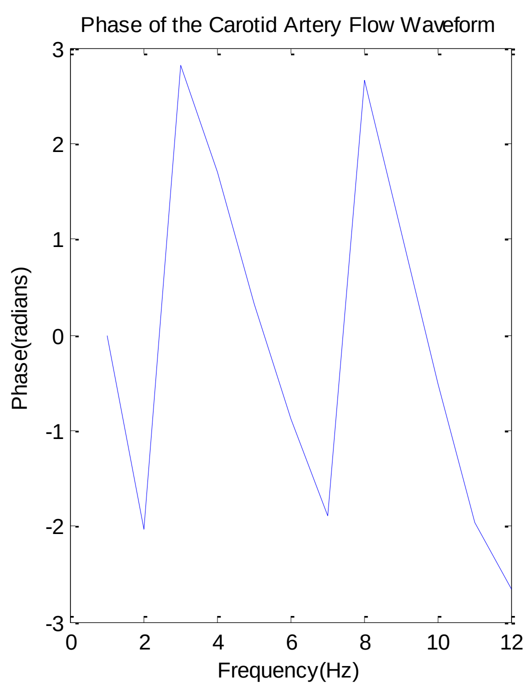


Figure 4.4: Phase of carotid artery flow waveform of first 12 harmonics

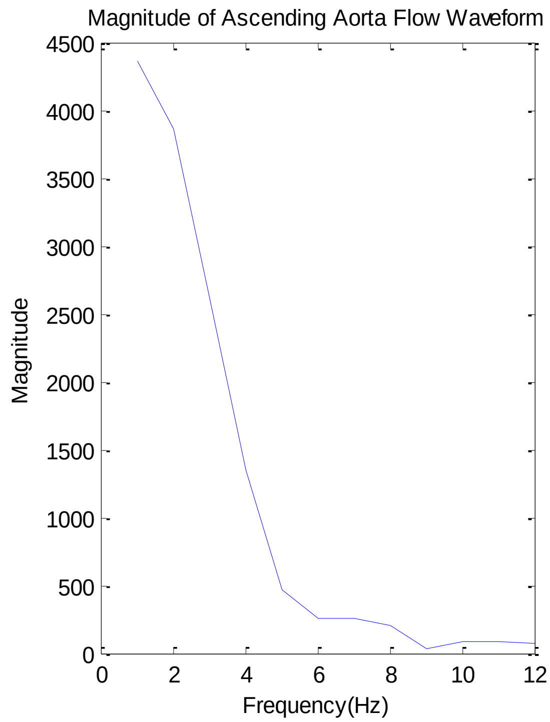


Figure 4.5: Magnitude of ascending aorta flow waveform of first 12 harmonics

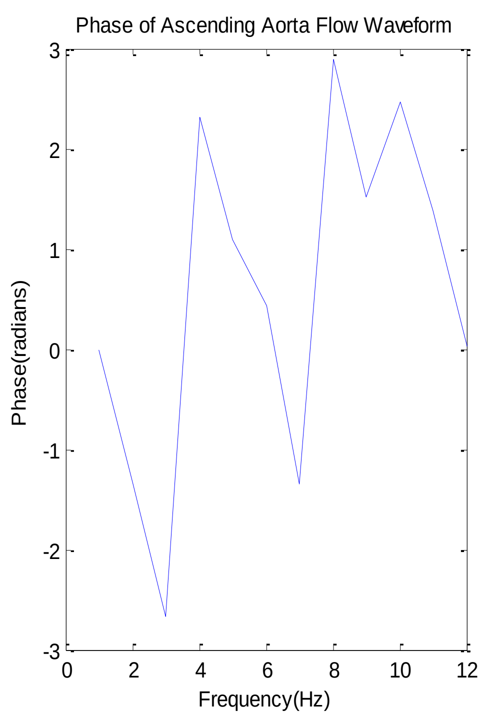


Figure 4.6: Phase of ascending aorta flow waveform of first 12 harmonics

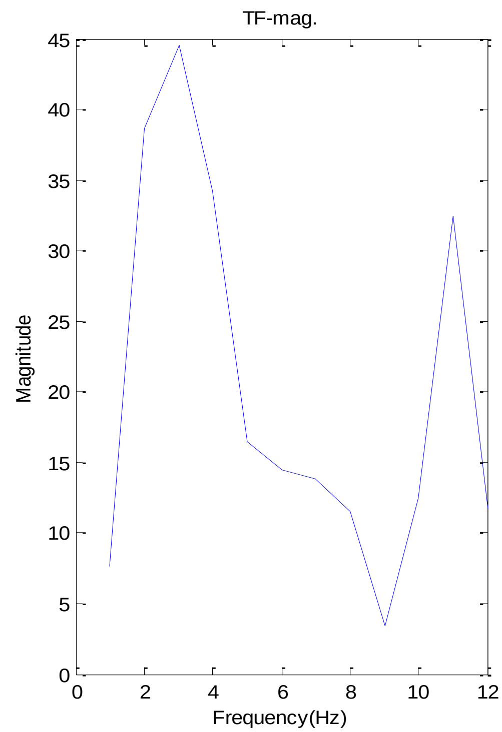


Figure 4.7: Transfer function – magnitude of first 12 harmonics

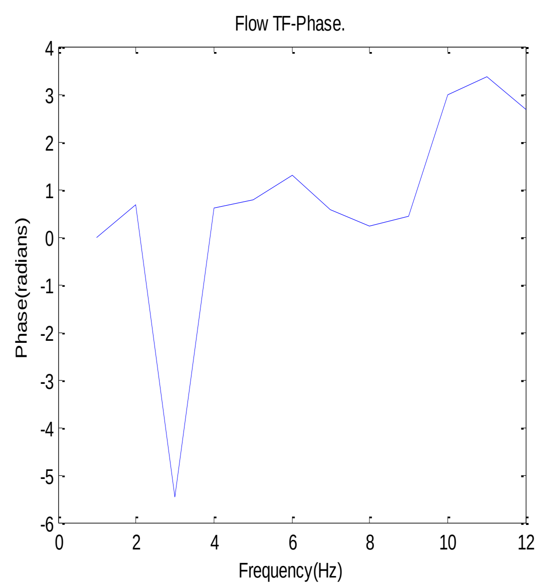


Figure 4.8: Transfer function – phase of first 12 harmonics

Generalized flow based transfer function was derived based on average carotid waveform and average ascending aorta waveform shown in Figure 4.1. Ascending aorta flow waveform has higher magnitude then carotid artery. This can be seen from magnitude plot of carotid artery flow waveform and ascending aortic flow waveforms. Ascending aorta flow phase plot has higher increase in slope than carotid artery flow phase plot. Increase in amplitude of transfer function can be seen from Figure 4.7. Phase plot of the generalized transfer function shows positive slope as seen in Figure 4.8. This transfer function has been used to derive ascending aorta flow waveform as shown in section 4.2.

4.2 Estimated Ascending Aorta Flow and Pressure Waveforms using Generalized Transfer Function:

Section 4.2 show original digitized carotid flow waveforms, estimated ascending aortic flow waveforms and derived ascending aortic pressure waveforms. Overall shape of all five estimated ascending aorta waveforms look very close to the general ascending aortic flow waveform shown in Figure 4.2. They look slightly different because of variability of each waveform. Derived ascending aortic pressure waveforms looks very close to the general shape of the pressure waveform. All ascending aorta pressure waveform shows pressure ranging in 80-120 mmHg, which is normal range of pressure. These pressure waveforms vary slightly due to variability of ascending aorta flow waveforms. Overall, this method can derive ascending aorta flow and pressure waveforms.

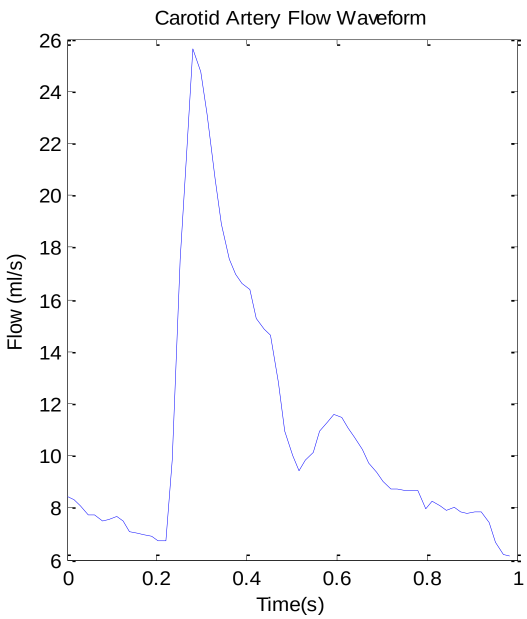


Figure 4.9: Carotid artery flow waveform 1

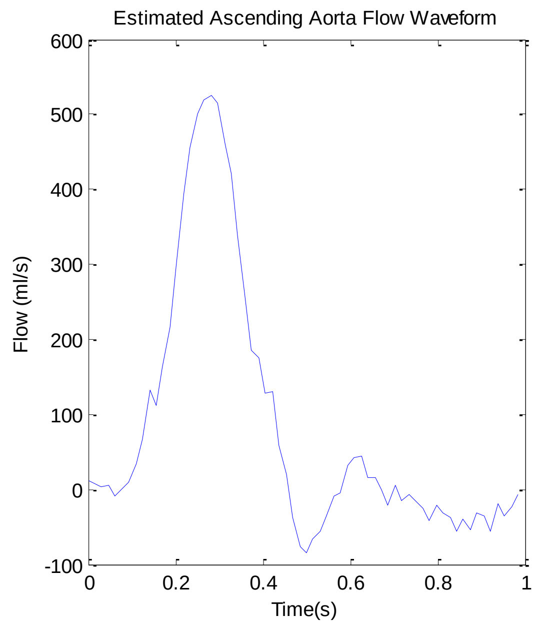


Figure 4.10: Estimated ascending aorta flow waveform 1 using generalized TF

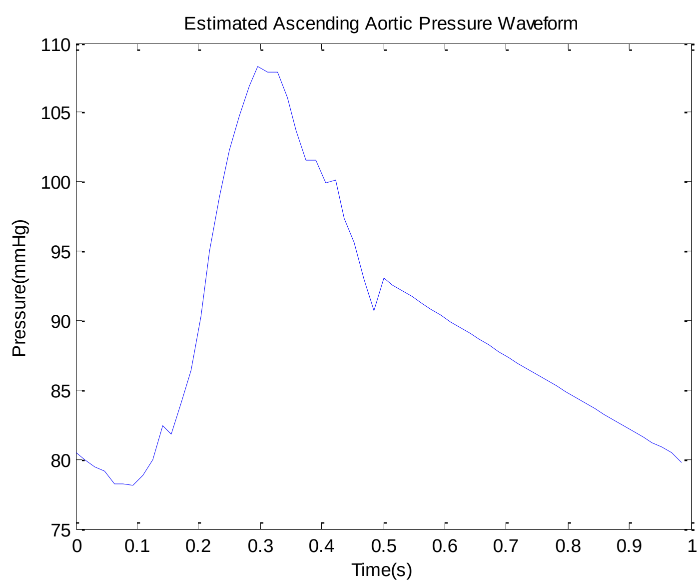


Figure 4.11: Estimated ascending aortic pressure waveform 1

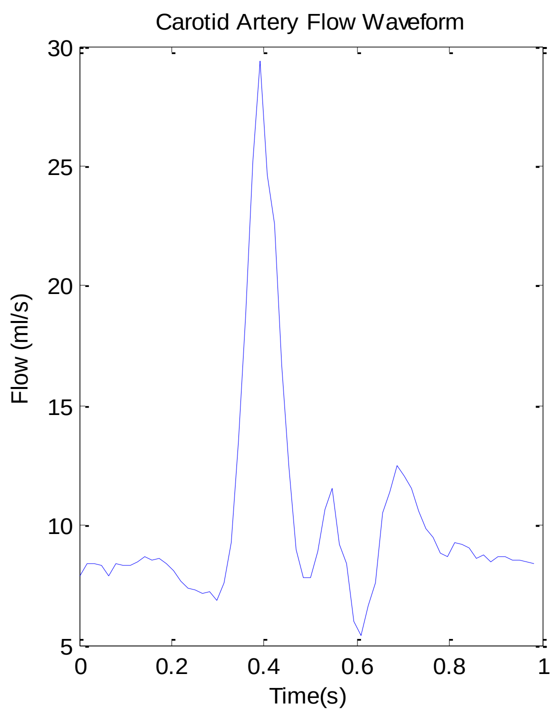


Figure 4.12 : Carotid artery flow waveform 2

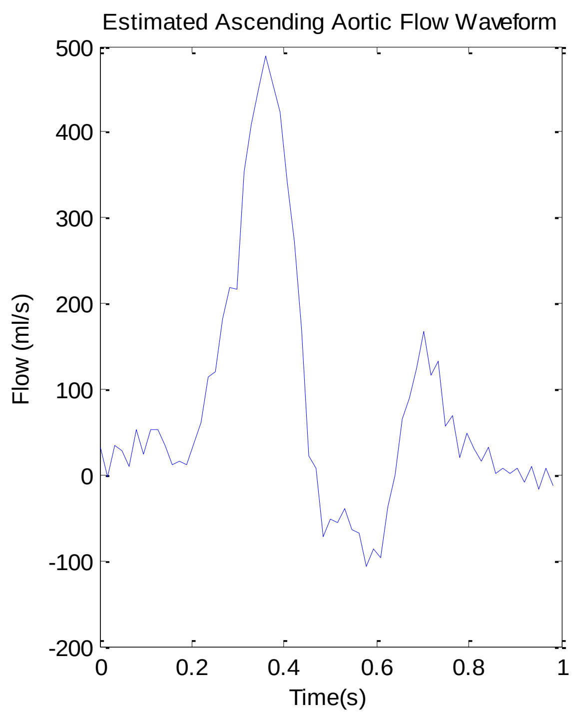


Figure 4.13: Estimated ascending aorta waveform 2 using generalized TF

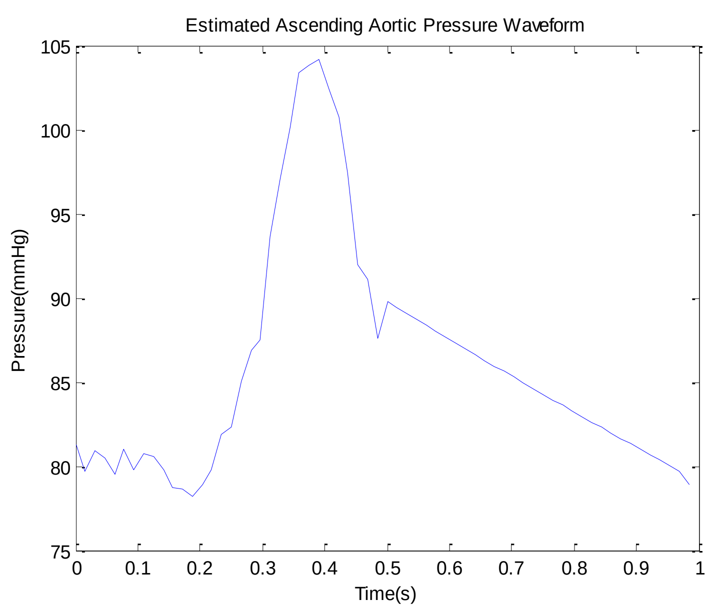


Figure 4.14: Estimated ascending aortic pressure waveform 2

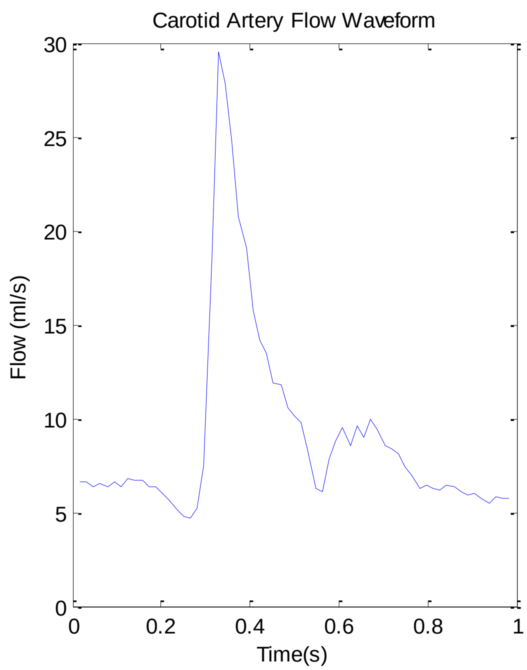


Figure 4.15 : Carotid artery flow waveform 3

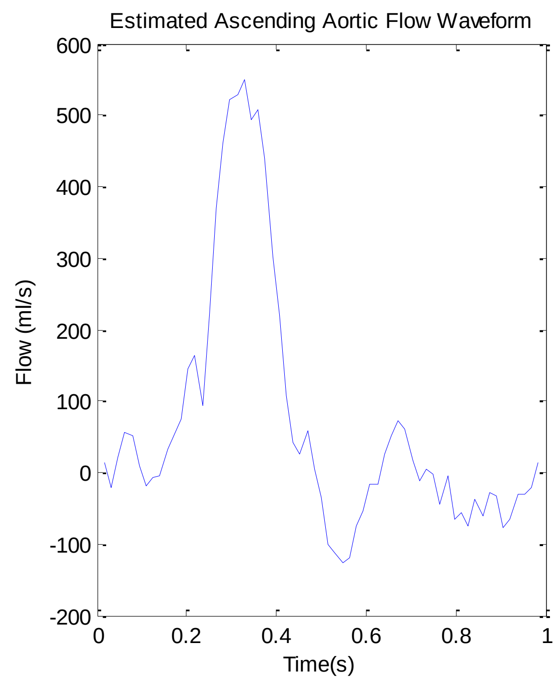


Figure 4.16: Estimated ascending aorta waveform 3 using generalized TF

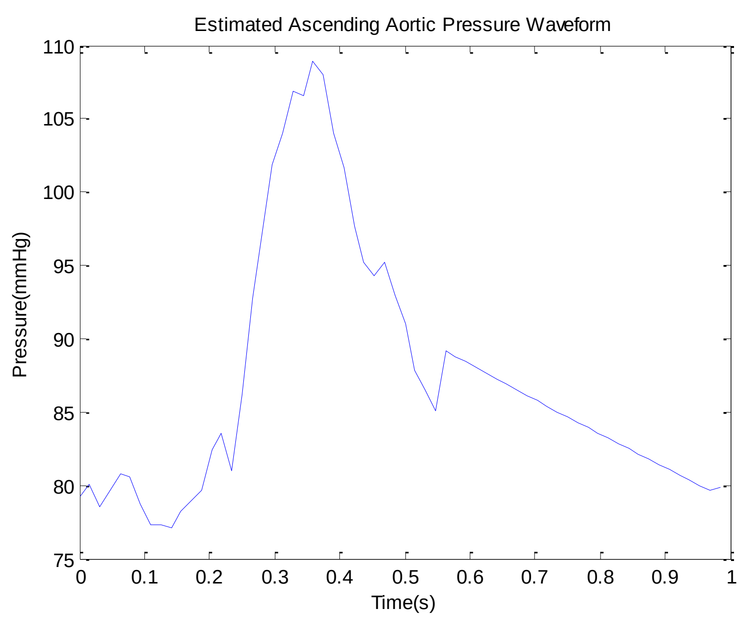


Figure 4.17: Estimated ascending aorta pressure waveform 3

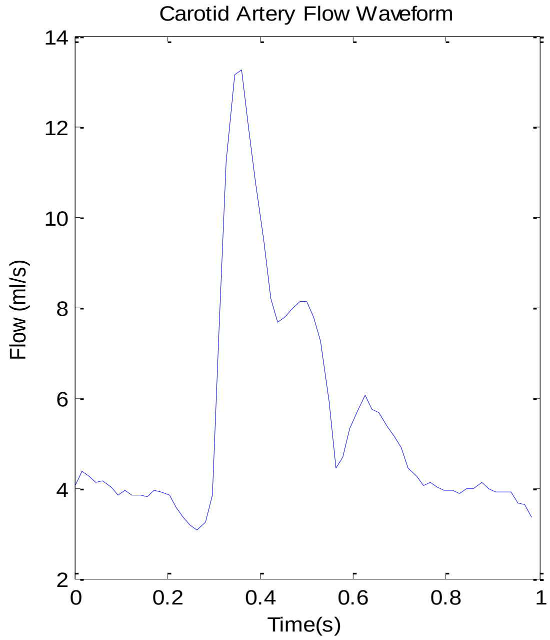


Figure 4.18: Carotid artery flow waveform 4

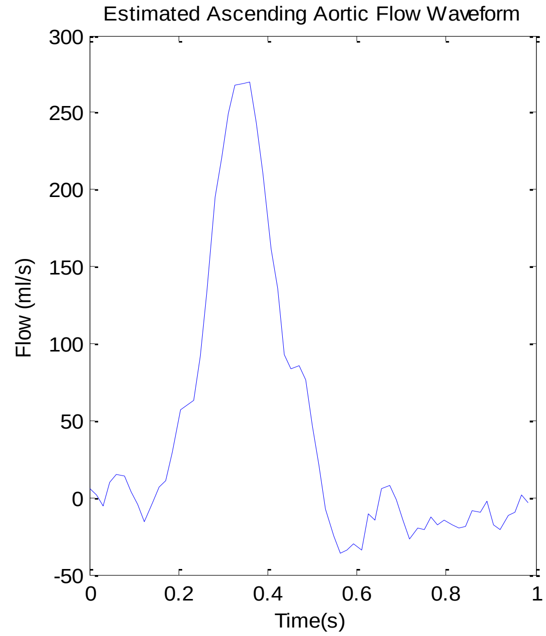


Figure 4.19: Estimated ascending aorta waveform 4 using generalized TF

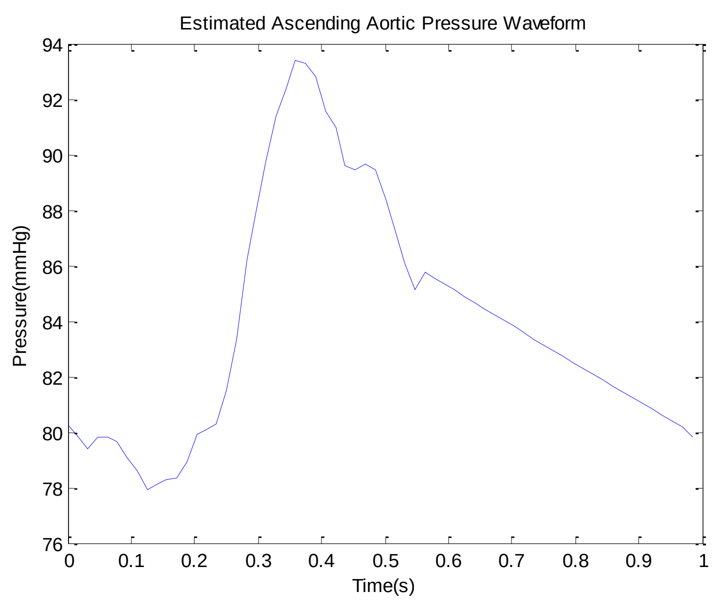


Figure 4.20: Estimated ascending aorta pressure waveform 4

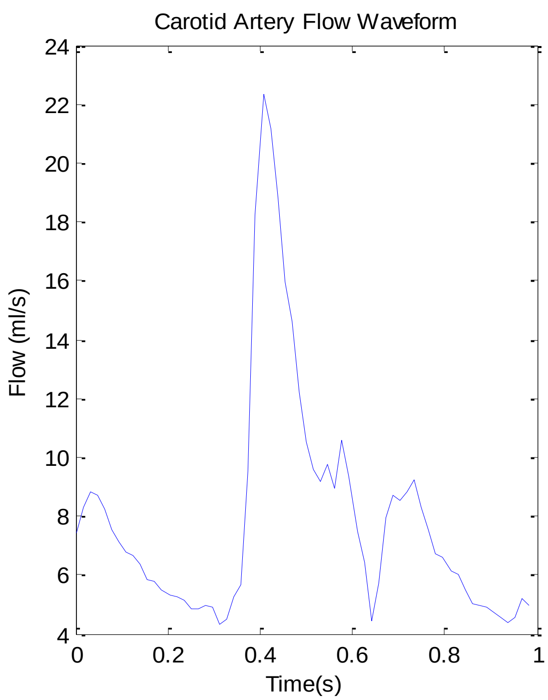


Figure 4.21 : Carotid artery flow waveform 5

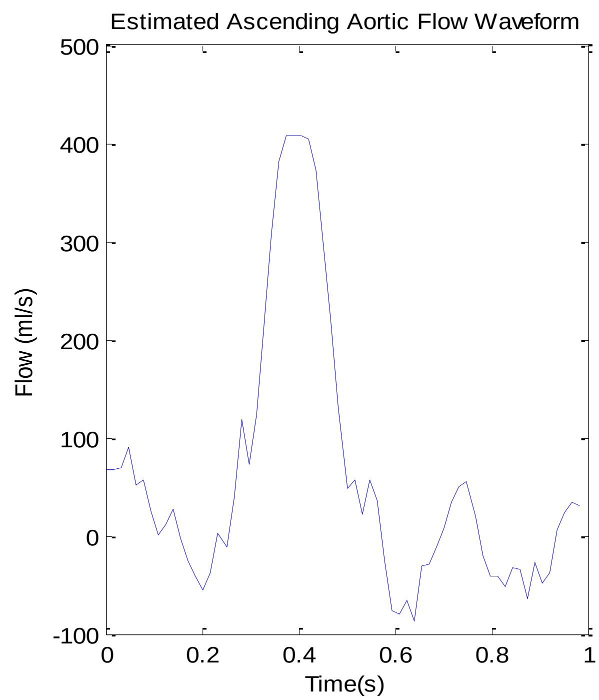


Figure 4.22: Estimated ascending aorta waveform 5 using generalized TF

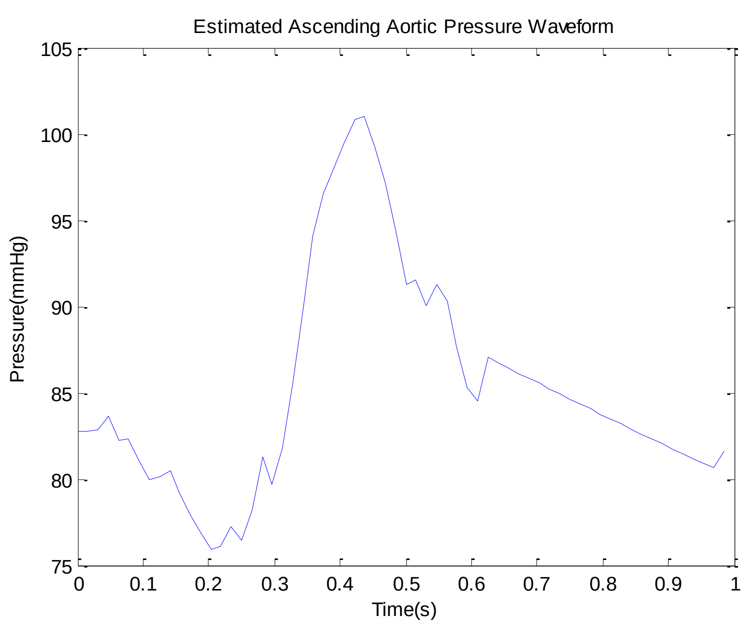


Figure 4.23: Estimated ascending aorta pressure waveform 5

4.3 Individualized transfer function:

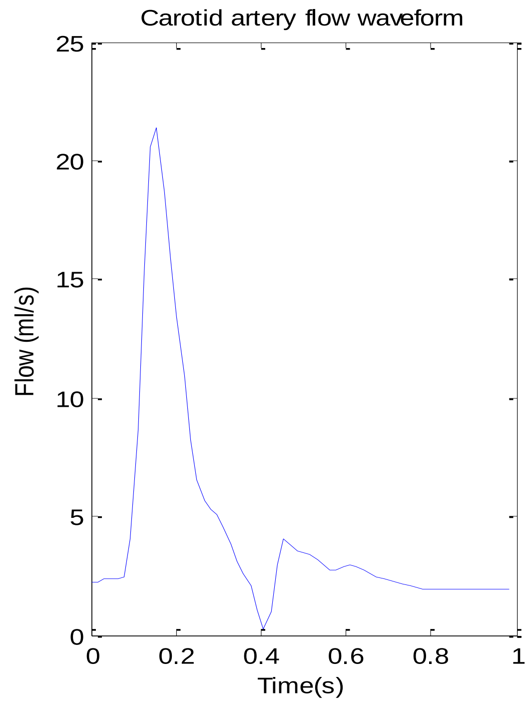


Figure 4.24: Carotid artery flow

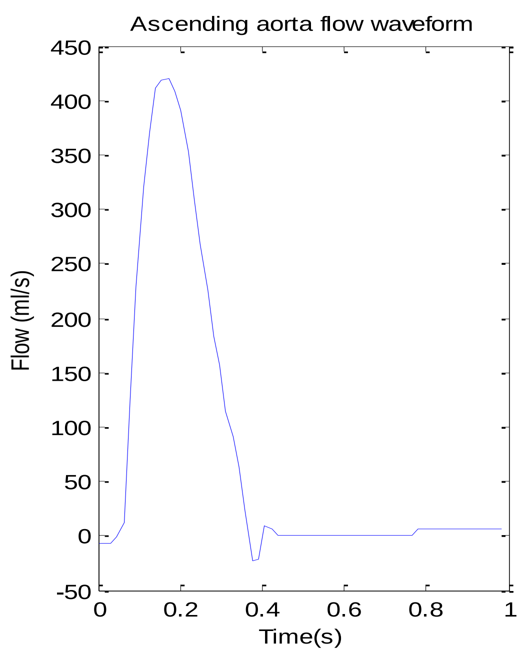


Figure 4.25: Ascending aorta flow waveform

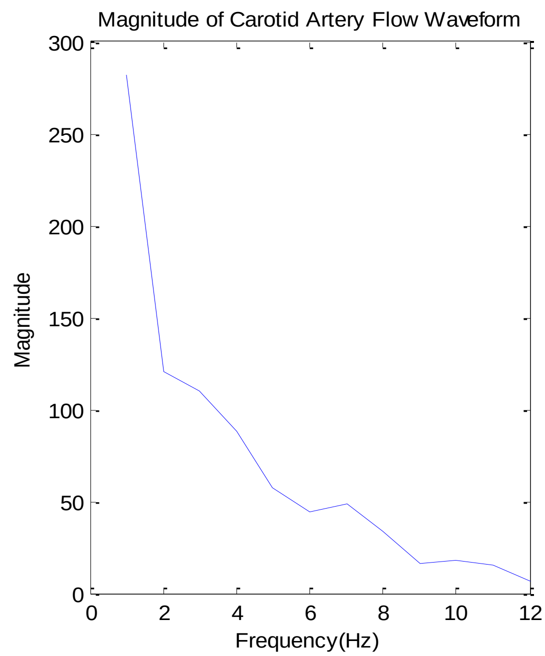


Figure 4.26: Magnitude of carotid flow waveform

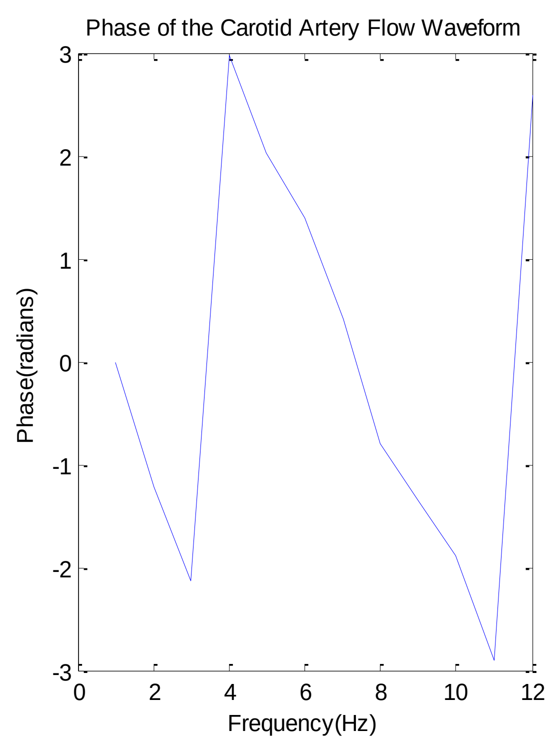


Figure 4.27: Phase of carotid flow waveform

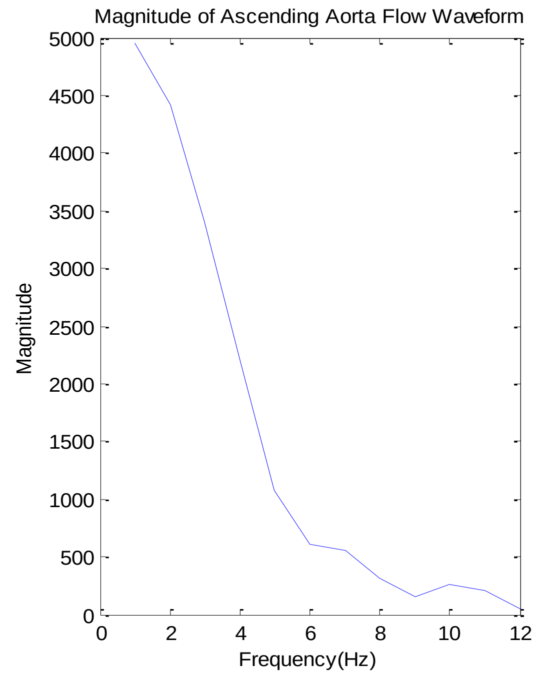


Figure 4.28: Magnitude of ascending aorta flow waveform

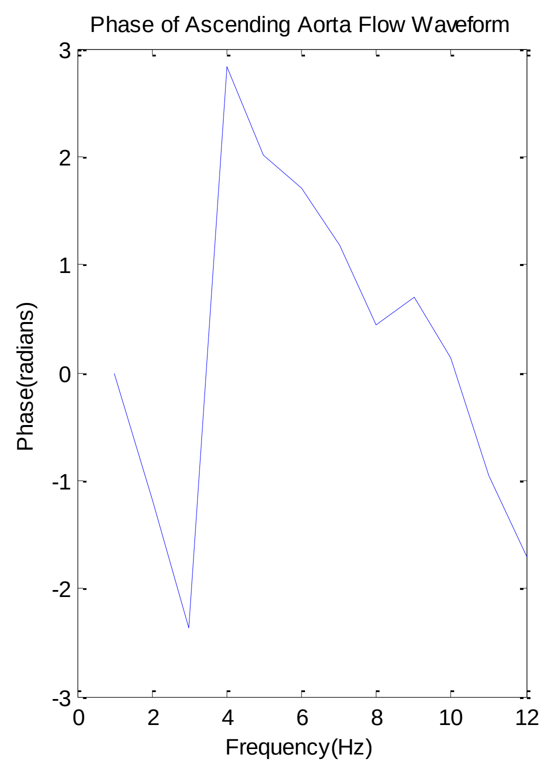


Figure 4.29: Phase of ascending aorta flow waveform

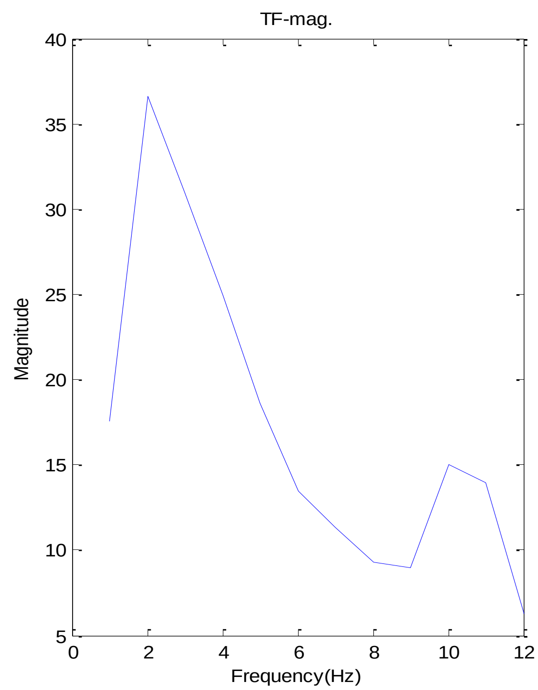


Figure 4.30: Transfer function magnitude

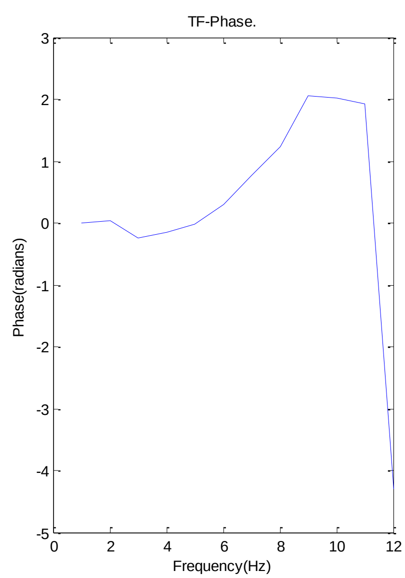


Figure 4.31: Transfer function phase

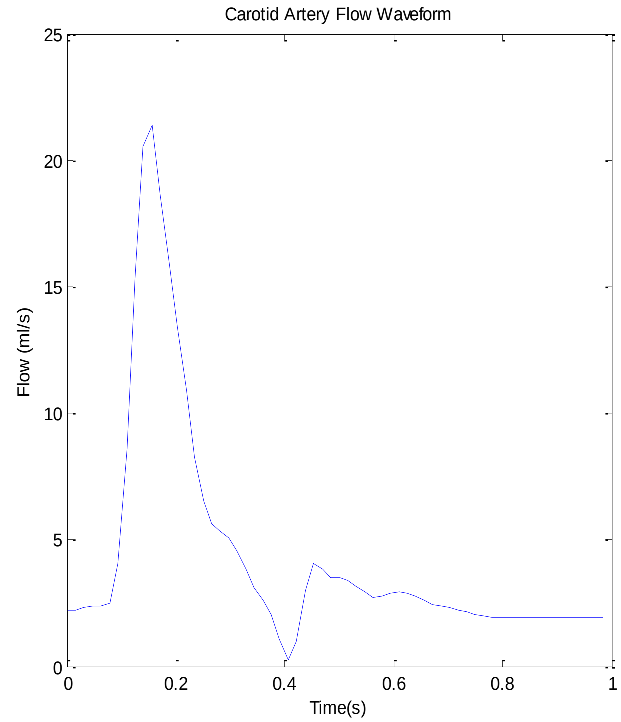


Figure 4.32: Carotid artery flow waveform

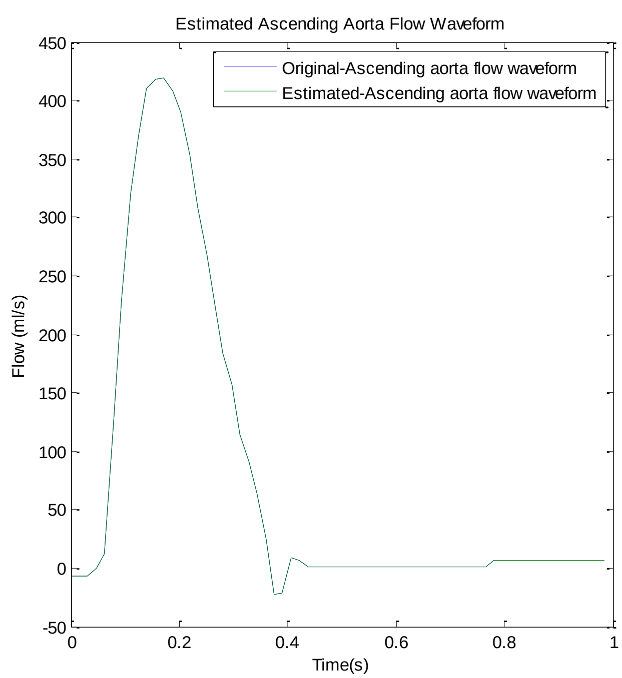


Figure 4.33: Ascending artery flow waveform original and estimate

Figure 4.24 and Figure 4.25 shows average carotid flow waveform and average ascending aorta flow waveform from single source. Individualized transfer function was derived from these waveforms. TF magnitude and TF phase plots can be seen in Figure 4.30 and Figure 4.31. Main characteristics of these plots are similar to generalized transfer function magnitude and phase plots. Original average carotid flow waveform is used as input to this individualized transfer function to estimate ascending aorta flow. Reconstructed ascending aorta waveform looked similar to original ascending aorta waveform. This can be seen in Figure 4.33. Individualized transfer function was derived to make sure that transfer function derivation is working correctly and to make sure that original flow waveform can be retrieved using this method.

Chapter 5: Discussion and Suggestion for Future Research

5.1 Pressure Based Transfer Functions:

There are many direct and indirect methods for the measurement of blood pressure. As pressure waveform travels from central aorta to the periphery, pressure waveform is amplified due to impedance mismatching which gives rise to wave reflections. Central aortic pressure has been recognized as a better predictor of cardiovascular events than peripheral pressure. It can be measured directly using catheter, but this technique is invasive. There is no direct noninvasive method to measure central aortic pressure, but there are several non-invasive techniques that have been proposed to measure central aortic pressure.

Pressure transfer function based techniques have been proposed before to derive central aortic pressure (Karamanoglu et al., 1993; Chen et al., 1997; Hope et al., 2003; Söderström et al., 2002). Peripheral and central pressure waveforms are measured for subjects. Generalized pressure based transfer function is derived from these waveforms. Peripheral pressure waveform is used as an input to transfer function to predict central aortic pressure waveform. This method of predicting central aorta pressure is non-invasive and it can estimate pressure of central aorta in different conditions.

5.2 Comparison of Pressure based Transfer functions and Flow based Transfer function:

Pressure based transfer function to predict central aorta pressure have been proposed and studied before. Generalized flow based transfer function has been proposed in this thesis to predict ascending aortic pressure and flow. Generalized flow based transfer function was derived from three carotid and three ascending aorta flow waveforms, since there were less ascending aorta waveforms available to start with. Ascending aorta pressure was estimated from ascending aorta flow waveform using three element windkessel model. Carotid flow waveform will be input to flow transfer function to estimate flow and pressure of ascending aorta. This is a non-invasive method, which allows you to estimate flow and pressure of ascending aorta. This technique has advantage over pressure transfer function that it allows one to take a look at flow and pressure at the same time.

Karamanoglu et al. derived pressure-based generalized transfer function between ascending aorta and carotid artery as seen in Figure 5.1 (1996). Here we have defined generalized flow transfer function between carotid artery and ascending aorta.

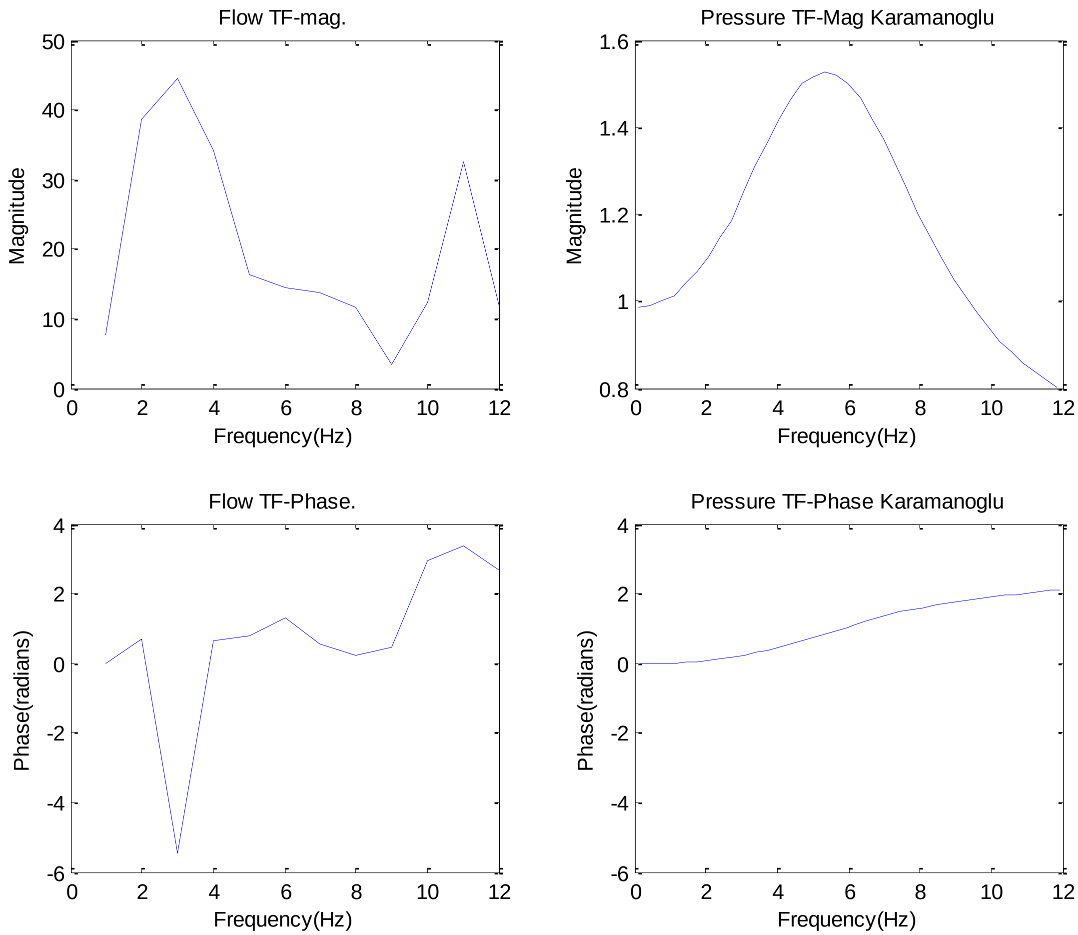
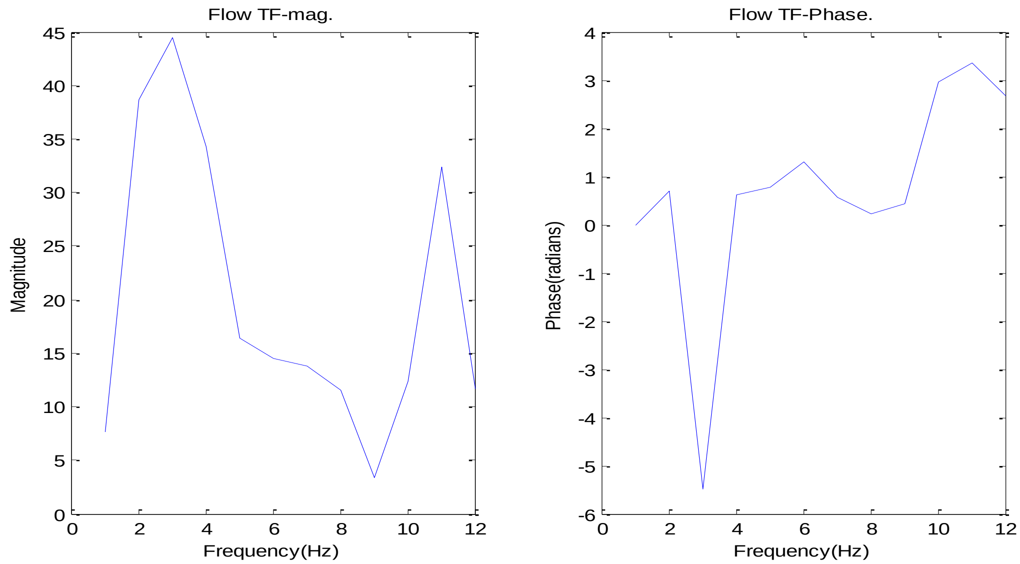


Figure 5.1: In the left, TF-mag and TF-Phase shows magnitude and phase of generalized flow transfer function from carotid to ascending aorta. In the right, magnitude and phase of generalized pressure based transfer function from ascending aorta to carotid (Figure was taken from Karamanoglu et al., 1996 and then it was digitalized and redrawn)

From comparing, magnitude plot of flow based and pressure based transfer function looks different. Increase in amplitude can be seen form both of magnitude plots. As pressure waveform travels away from heart, pressure amplitude increases and this can be seen from magnitude plot of ascending aorta to carotid pressure transfer function. Flow amplitude is highest when pulse is closest to heart. This can be seen from magnitude plot of carotid to ascending aorta flow transfer function. Phase plots of both transfer functions show positive slope. Transfer function magnitude and phase plots are site dependent.

Individualized transfer function from carotid to ascending aorta was also derived to ensure that transfer function is working properly. Average carotid flow waveform and average ascending aorta flow waveforms were taken to derive transfer function using similar methodology. Ascending aorta waveform was then reconstructed using average carotid waveform as a input to the transfer function. Reconstructed ascending aorta flow waveform looks similar to original ascending aorta waveform as seen in Figure 4.33. Figure 5.2 shows flow based generalized and individualized carotid to ascending aorta transfer function magnitude and phase plots. General shape of magnitude plots for generalized transfer function and individualized transfer function looks similar. Phase plots of both transfer functions show positive slope. Differences are due to the different waveforms are being used to derive transfer function.

Generalized Flow TF



Individual Flow TF

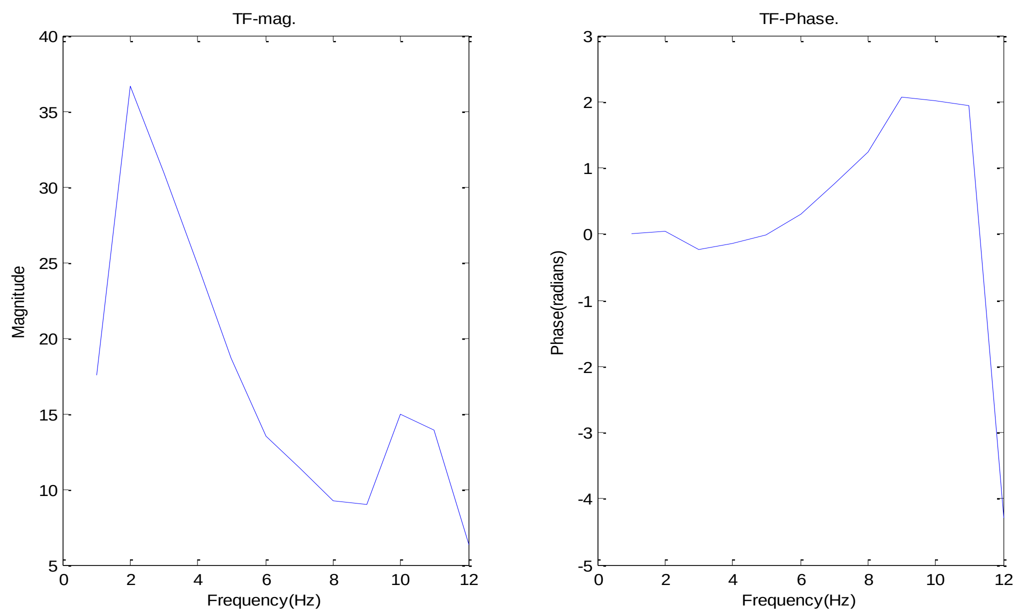


Figure 5.2: Generalized transfer function magnitude and phase plots on the Top and individualized transfer function magnitude and phase plots on the bottom

5.3 Pressure estimation using three-element windkessel model:

	R (mm Hg*s /ml)	C (ml/ mm Hg)	Zo (mm Hg*s /ml)	HR	ESV (ml)	EDV(ml)	SV(ml)	CO(ml/ min)	Systolic pressure (mmHg)	Diastolic Pressure (mmHg)	Mean pressure (mmHg)	Pulse pressure (mmHg)
Waveform 1	0.9	2.3	0.04	60.0	115.5	10.7	104.8	6.3	108.3	79.8	89.3	28.5
Waveform 2	1.1	2.3	0.04	60.0	95.3	34.0	61.3	3.7	104.1	78.9	87.3	25.2
Waveform 3	1.0	2.3	0.04	60.0	124.6	9.4	115.2	6.9	108.9	79.9	89.6	29.0
Waveform 4	1.7	2.3	0.04	60.0	59.0	0.4	58.6	3.5	93.4	79.8	84.4	13.5
Waveform 5	1.3	2.3	0.04	60.0	89.8	5.0	84.9	5.1	101.0	81.6	88.1	19.5
Mean	1.3	2.3	0.04	60.0	96.9	11.9	84.9	5.1	103.2	80.0	87.7	23.2
SD	0.3	0.0	0.00	0.0	25.5	13.0	25.3	1.5	6.3	1.0	2.1	6.6

Table 5.1 Pulsatile hemodynamics derived from waveforms.

After achieving ascending aorta flow waveforms, ascending aorta waveform was converted to pressure waveform using three-element windkessel model. Initial diastolic pressure was estimated to be 80 mmHg. It was also assumed that aortic valve closes in diastole and flow becomes zero. Compliance (C), Resistance(R) and impedance (Zo) were adjusted to minimize error in estimation. See table 1 for Z, C and R values.

Mean Systolic (P_s) and diastolic (P_d) pressures were within normal range. Mean arterial pressure (MAP) was calculated using formula $MAP=[(2* P_d)+ P_s]/3$. Mean arterial pressure was found to be 87.7 ± 2.1mmHg here. Normal mean arterial pressure range has been reported to be 102 ± 3.6 mmHg (Nichols et al, 1986). Mean arterial pressure was slightly lower than normal range. R was reported 1.3 ± 0.3 mmHg*s/ml. mmHg. Normal mean R was reported to be 1344 ± 183 dyne*sec/cm^{-5} (1±0.13 mmHg) (Nichols et al, 1986). R was slightly higher than normal range. Zo mean was estimated to be 0.04 mmHg*s/ml here. Mean of Zo for normal patients was reported to be 63±19 dyne*sec/ cm^{-5} (0.047±0.014 mmHg*sec/ml) (Nichols et al., 1986). Zo mean was within the range of normal patients. Period of each waveforms used in the study was 1sec. As a result, heart rate (HR) was estimated to be 60 beats/sec. Cardiac output was measured based on this heart rate. Cardiac output was calculated based on CO=Stroke volume (SV) / Heart rate (HR). SV was calculated by subtracting end-diastolic volume (EDV) from end-systolic volume (ESV). EDV and ESV were estimated from ascending aorta flow waveforms. For the mean arteria pressure range 87.7 ± 2.1mmHg, mean of the compliance was found to be 2.3 ml/mmHg. Normotensive group at mean aortic pressure of 96.3 ± 5.3 mmHg, aortic compliance was average to be 1.47 ± 0.60 ml/mmHg (Liu et al., 1989). Compliance was slightly overestimated here. Here constant values were changed to best fit the waveform.

Flow based transfer function can be used between any two arterial area to predict physiological parameters. This method provides estimation of pressure waveform in ascending aorta under normal conditions. This pressure waveform and flow waveform can be used to predict cardiovascular events. Furthermore, augmentation index (AI) can be calculated. Ps refers to systolic pressure, Pi refers to pressure inflection point.

$\Delta P = Ps - Pi$ (Pi-pressure inflection point) (5.1)

$AI = \Delta P / \text{Pulse pressure}$ (5.2)

Augmentation index can give information about cardiovascular disease and wave reflections. Additionally, forward and backward pressure wave can be calculated also calculated using below equations:

$P_f = (P + Q*Zo)/2$ (5.3)

$P_r = (P - Q*Zo)/2$ (5.4)

5.4 Limitations of the study:

Limitation of this study is that this transfer function is based on 3 carotid and 3 ascending aorta waveforms. Initial ascending aortic flow waveform and carotid flow waveform are not taken from same subjects. This can introduce some error in estimating flow and pressure waveform of ascending aorta. Compliance, resistance and impedance values are estimated to best fit pressure waveform. This can also introduce some error in estimating pressure waveform. Additionally, error in predicting ascending aorta pressure cannot be calculated because there was no measured ascending aorta waveform to compare with. Since this is generalized transfer function, it doesn't take in account for physiological changes between patients.

5.5 Future Research:

Flow based transfer function from carotid to ascending aorta has been proposed in this thesis. Then three element windkessel model was used to derive pressure waveforms from flow waveform of ascending aorta. In future, ascending aorta pressure can be measured and root-mean-square error can be calculated between predicted and measured ascending aortic pressure waveform. Compliance, resistance and impedance values were changed to best fit pressure waveform in this study. In future, ascending aorta flow and pressure waveform can be measured to determine optimal values for C, R and Zo for normal patients. Average of all these parameters can be used as an initial set of parameters to estimate ascending aortic pressure waveform. Then this parameters can be adjusted as needed to best fit pressure waveform. Parameters like arterial compliance and resistance can be derived from these waveforms. Arterial compliance can be predictor of hypertension. Arterial compliance decreases during hypertension. Furthermore, augmentation index can be calculated. Augmentation index can be used to predict cardiovascular risk. Proposed method in this thesis can be used between artery to define transfer function and to derive physiological variables. This method is based on generalized transfer function and it does not consider physiological differences between patients. Additionally, nonlinear pressure dependent compliance instead of linear compliance can be incorporated into three – element windkessel model to predict aortic pressure accurately (Li et al., 1990).

Other adaptive and individualized based transfer function has been proposed to improve accuracy of the measurement (Gao et al., 2016; Sugimachi 2001; Swamy et al. 2009; Mukkamala et al., 2014; Westerhof et al., 2008). These techniques allow us to improve accuracy of the measurement. Such method can be also applied to this approach to derive transfer function to increase accuracy.

References

- Agabiti-Rosei, E., Mancia, G., O'rourke, M. F., Roman, M. J., Safar, M. E., Smulyan, H., . . . Vlachopoulos, C. (2007). Central Blood Pressure Measurements and Antihypertensive Therapy: A Consensus Document. *Hypertension, 50*(1), 154-160. doi:10.1161/hypertensionaha.107.090068
- Bermejo, J. (2005). The effects of hypertension on aortic valve stenosis. *Heart, 91*(3), 280-282. doi:10.1136/hrt.2004.041749
- Chen, C., Nevo, E., Fetics, B., Pak, P. H., Yin, F. C., Maughan, W. L., & Kass, D. A. (1997). Estimation of Central Aortic Pressure Waveform by Mathematical Transformation of Radial Tonometry Pressure : Validation of Generalized Transfer Function. *Circulation, 95*(7), 1827-1836. doi:10.1161/01.cir.95.7.1827
- Cheung, B. M., & Li, C. (2012). Diabetes and Hypertension: Is There a Common Metabolic Pathway? *Curr Atheroscler Rep Current Atherosclerosis Reports, 14*(2), 160-166. doi:10.1007/s11883-012-0227-2
- Denarié, N., Gariepy, J., Chironi, G., Massonneau, M., Laskri, F., Salomon, J., . . . Simon, A. (2000). Distribution of ultrasonographically-assessed dimensions of common carotid arteries in healthy adults of both sexes. *Atherosclerosis, 148*(2), 297-302. doi:10.1016/s0021-9150(99)00276-2
- Drzewiecki, G. M., Melbin, J., & Noordergraaf, A. (1983). Arterial tonometry: Review and analysis. *Journal of Biomechanics, 16*(2), 141-152. doi:10.1016/0021-9290(83)90037-4
- Gao, M., Rose, W. C., Fetics, B., Kass, D. A., Chen, C., & Mukkamala, R. (2016). A Simple Adaptive Transfer Function for Deriving the Central Blood Pressure Waveform from a Radial Blood Pressure Waveform. *Scientific Reports, 6*, 33230. doi:10.1038/srep33230
- Hirata, K., T. Yaginuma, M. F. O'rourke, and M. Kawakami. "Age-Related Changes in Carotid Artery Flow and Pressure Pulses: Possible Implications for Cerebral Microvascular Disease." *Stroke* 37.10 (2006): 2552-556. Web.
- Holdsworth, D. W., Norley, C. J., Frayne, R., Steinman, D. A., & Rutt, B. K. (1999). Characterization of common carotid artery blood-flow waveforms in normal human subjects. *Physiol. Meas. Physiological Measurement, 20*(3), 219-240. doi:10.1088/0967-3334/20/3/301
- Hope, S. A., Tay, D. B., Meredith, I. T., & Cameron, J. D. (2003). Use of arterial transfer functions for the derivation of aortic waveform characteristics. *Journal of Hypertension, 21*(7), 1299-1305. doi:10.1097/00004872-200307000-00017
- Kaden, J. J., & Haghi, D. (2008). Hypertension in aortic valve stenosis--a Trojan horse. *European Heart Journal, 29*(16), 1934-1935. doi:10.1093/eurheartj/ehn306
- Karamanoglu, M., & Feneley, M. P. (1996, December 1). Derivation of the ascending aortic-carotid pressure transfer function with an arterial model. *American Journal of Physiology - Heart and Circulatory Physiology, 271(6 Pt 2):H2399-404.*
- Karamanoglu, M., O'rourke, M. F., Avolio, A. P., & Kelly, R. P. (1993). An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *European Heart Journal, 14*(2), 160-167. doi:10.1093/eurheartj/14.2.160

- Katholi, R. E., & Couri, D. M. (2011). Left Ventricular Hypertrophy: Major Risk Factor in Patients with Hypertension: Update and Practical Clinical Applications. *International Journal of Hypertension, 2011*, 1-10. doi:10.4061/2011/495349
- Li, J., Cui, T., & Drzewiecki, G. (1990). A nonlinear model of the arterial system incorporating a pressure-dependent compliance. *IEEE Transactions on Biomedical Engineering, 37*(7), 673-678. doi:10.1109/10.55678
- Li, J. K. (2004). *Dynamics of the vascular system*. River Edge, NJ: World Scientific.
- Liu, Z. R., Ting, C. T., Zhu, S. X., & Yin, F. C. (1989). Aortic compliance in human hypertension. *Hypertension, 14*(2), 129-136. doi:10.1161/01.hyp.14.2.129
- Mceniery, C. M., Cockcroft, J. R., Roman, M. J., Franklin, S. S., & Wilkinson, I. B. (2014). Central blood pressure: Current evidence and clinical importance. *European Heart Journal, 35*(26), 1719-1725. doi:10.1093/eurheartj/eht565
- MEDISON.RU - Sonography of vessels. (n.d.). Retrieved October 31, 2016, from http://www.medison.ru/uzi/eng/all/vessels.htm
- Nelson, M. R., Stepanek, J., Cevette, M., Covalciuc, M., Hurst, R. T., & Tajik, A. J. (2010). Noninvasive Measurement of Central Vascular Pressures With Arterial Tonometry: Clinical Revival of the Pulse Pressure Waveform? *Mayo Clinic Proceedings, 85*(5), 460-472. doi:10.4065/mcp.2009.0336
- Mukkamala, R., Gao, M., Rose, W., Fetics, B., Cheng, H., Chen, C., & Kass, D. (2014). An adaptive transfer function for deriving the central blood pressure waveform from a peripheral blood pressure waveform: Validation in patients. *Journal of the American Society of Hypertension, 8*(4). doi:10.1016/j.jash.2014.03.096
- Nichols, W. W., O'rourke, M. F., Avolio, A. P., Yaginuma, T., Pepine, C. J., & Conti, C. R. (1986). Ventricular/vascular interaction in patients with mild systemic hypertension and normal peripheral resistance. *Circulation, 74*(3), 455-462. doi:10.1161/01.cir.74.3.455
- Nichols, W. W., O'Rourke, M. F., & Vlachopoulos, C. (2011). *McDonald's blood flow in arteries: Theoretical, experimental and clinical principles*.
- Reymond, P., Merenda, F., Perren, F., Rufenacht, D., & Stergiopulos, N. (2009). Validation of a one-dimensional model of the systemic arterial tree. *AJP: Heart and Circulatory Physiology, 297*(1). doi:10.1152/ajpheart.00037.2009
- Sankaranarayanan, M., Chua, L., Ghista, D., & Tan, Y. (2005, March 4). Computational model of blood flow in the aorto-coronary bypass graft. *Biomed Eng Online*. doi:10.1186/1475-925X-4-14
- Sankaranarayanan, M., Ghista, D., Poh, C. L., Seng, T. Y., & Kassab, G. S. (2006). Analysis of blood flow in an out-of-plane CABG model. *AJP: Heart and Circulatory Physiology, 291*(1). doi:10.1152/ajpheart.01347.2005
- Soderstrom, S. (2002). Can a clinically useful aortic pressure wave be derived from a radial pressure wave?dagger. *British Journal of Anaesthesia, 88*(4), 481-488. doi:10.1093/bja/88.4.481
- STACOM 2013 CFD Challenge. (n.d.). Retrieved October 31, 2016, from http://vascularmodel.org/miccai2013/

- Sugimachi, M., Shishido, T., Miyatake, K., & Sunagawa, K. (2001). A New Model-Based Method of Reconstructing Central Aortic Pressure from Peripheral Arterial Pressure. *The Japanese Journal of Physiology JJP, 51*(2), 217-222. doi:10.2170/jjphysiol.51.217
- Wang, W., Lee, E. T., Fabsitz, R. R., Devereux, R., Best, L., Welty, T. K., & Howard, B. V. (2006). A Longitudinal Study of Hypertension Risk Factors and Their Relation to Cardiovascular Disease: The Strong Heart Study. *Hypertension, 47*(3), 403-409. doi:10.1161/01.hyp.0000200710.29498.80
- Westerhof, B. E., Guelen, I., Stok, W. J., Lasance, H. A., Ascoop, C. A., Wesseling, K. H., . . . Spaan, J. A. (2008). Individualization of transfer function in estimation of central aortic pressure from the peripheral pulse is not required in patients at rest. *Journal of Applied Physiology*, *105*(6), 1858-1863. doi:10.1152/japplphysiol.91052.2008
- Westerhof, N., Lankhaar, J., & Westerhof, B. (2009, February). Arterial Windkessel. *Medical &Biological Engineering & Computing, 47*(2), 131-141. doi:10.1007/s11517-008-0359-2
- Weiss, B. M., Spahn, D. R., Rahmig, H., Rohling, R., & Pasch, T. (1996). Radial artery tonometry: Moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement. *British Journal of Anaesthesia, 76*(3), 405-411. doi:10.1093/bja/76.3.405

Appendix I – Matlab Code

```
clc;
clear all;
close all;
%Derivation of generalized TF-Mag and TF-Phase
%Signal carotid
A = xlsread('ave_carotid_1.xlsx',1);
t1=A(:,1);
q1=A(:,2);
figure (1)
subplot(1,2,1)
plot(t1,q1)
title('Average carotid artery flow')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

B = xlsread('ave_aorta_1.xlsx',1);
t2=B(:,1);
q2=B(:,2);
subplot(1,2,2)
plot(t2,q2)
title('Average ascending aortic flow waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Taking FFT of caratoid artery
yc = fft(q1);
 %Compute DFT of x
 mc = abs(yc);          % Magnitude
 pc =angle(yc);
 figure (2)
subplot(1,2,1)
plot(mc(1:12))
title('Magnitude of Carotid Artery Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(pc(1:12))
title('Phase of the Carotid Artery Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

% %Taking FFT of aorta
ya = fft(q2);                                   % Compute DFT of x
ma = abs(ya);                                   % Magnitude
pa = angle(ya);
figure (3)
subplot(1,2,1)
plot(ma(1:12))
title('Magnitude of Ascending Aorta Flow Waveform')
```

```
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(pa(1:12))
title('Phase of Ascending Aorta Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

% % %Transfer function
  TF=ma./mc;
  TFP=pa-pc;

  TF_amp_chen=xlsread('TF-Amplitude-Karamanoglu et al..xls',1)
  freq1=TF_amp_chen(:,1);
 Ampl=TF_amp_chen(:,2);

 TF_phase_chen=xlsread('TF-Phase-Karamanoglu et al..xls',1)
  freq2=TF_phase_chen(:,1);
 phase=TF_phase_chen(:,2);

 figure (4)
subplot(2,2,1)
plot(TF(1:12))
title('Flow TF-mag.')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(2,2,3)
plot(TFP(1:12))
title('Flow TF-Phase.')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')


 subplot(2,2,2)
plot(freq1,Ampl)
title('Pressure TF-Mag Karamanoglu')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(2,2,4)
plot(freq2,phase)
title('Pressure TF-Phase Karamanoglu')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')
ylim([-6 4])

%Estimation of Carotid waveform 1
C = xlsread('Test 1.xlsx',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
```

```
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

yc = fft(q3);
 %Compute DFT of x
 new_mc = abs(yc);          % Magnitude
 new_pc =angle(yc);

newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new);

subplot(1,2,2)
plot(t3,X_new)
title('Estimated Ascending Aorta Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Pressure estimation of flow waveform 1
q_est=real(X_new);%flow measured
dt=0.01;%Delta T
Rs=0.9;
C=2.3;
Zo=0.04;
t=0:0.015625:.9844;
for i=1:(length(q_est)-1)%Estimate all till length of P
   pestimated(1)=80;%Take 1st measured pressure as Pe(1)
    if t(i)>=0.5%Change this variable depending on when flow becomes
zero.
         q_est(i)=0;%Flow becomes zero after valve closes
     end
       pestimated(i+1)=pestimated(i)+(dt*(q_est(i)-
(pestimated(i)/Rs))./C);
end
Estimate_pressure=pestimated'+(q_est*Zo);
figure (6)
 plot(t1,Estimate_pressure)
 title('Estimated Ascending Aortic Pressure Waveform')
ylabel('Pressure(mmHg)')
xlabel('Time(s)')

%%
%Carotid waveform 2
C = xlsread('test2.xls',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')
```

```
yc = fft(q3);
 %Compute DFT of x
 new_mc = abs(yc);         % Magnitude
 new_pc = angle(yc);
 %figure (5)
%subplot(1,3,1)
%plot(new_mc)
%title('Mag. of the Caratoid artery')
%subplot(1,3,2)
%plot(new_pc)
%title('Phase of the Caratoid artery')
newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new);
%subplot(1,3,3)
subplot(1,2,2)
plot(t3,X_new)
title('Estimated Ascending Aortic Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Pressure estimation of flow waveform 2
q_est=real(X_new);%flow measured
dt=0.01;%Delta T
Rs=1.10;
C=2.3;
Zo=0.04;
t=0:0.015625:.9844;
for i=1:(length(q_est)-1)%Estimate all till length of P
   pestimated(1)=80;%Take 1st measured pressure as Pe(1)
    if t(i)>=0.5%Change this variable depending on when flow becomes
zero.
         q_est(i)=0;%Flow becomes zero after valve closes
     end
       pestimated(i+1)=pestimated(i)+(dt*(q_est(i)-
(pestimated(i)/Rs))./C);
end
Estimate_pressure=pestimated'+(q_est*Zo)
figure (6)
 plot(t1,Estimate_pressure)
title('Estimated Ascending Aortic Pressure Waveform')
ylabel('Pressure(mmHg)')
xlabel('Time(s)')

%%
%Estimate Carotid waveform 3
C = xlsread('test 3.xls',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
```

```
ylabel('Flow (ml/s)')
xlabel('Time(s)')

yc = fft(q3);
 %Compute DFT of x
 new_mc = abs(yc);         % Magnitude
 new_pc =unwrap(angle(yc));
 %figure (5)
%subplot(1,3,1)
%plot(new_mc)
%title('Mag. of the Caratoid artery')
%subplot(1,3,2)
%plot(new_pc)
%title('Phase of the Caratoid artery')
newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new);
%subplot(1,3,3)
subplot(1,2,2)
plot(t3,X_new)
title('Estimated Ascending Aortic Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Pressure estimation of flow waveform 3
q_est=real(X_new);%flow measured
dt=0.01;%Delta T
Rs=1;
C=2.3;
Zo=0.04;
t=0:0.015625:.9844;
for i=1:(length(q_est)-1)%Estimate all till length of P
   pestimated(1)=80;%Take 1st measured pressure as Pe(1)
    if t(i)>=0.55%Change this variable depending on when flow becomes
zero.
         q_est(i)=0;%Flow becomes zero after valve closes
     end
       pestimated(i+1)=pestimated(i)+(dt*(q_est(i)-
(pestimated(i)/Rs))./C);
end
Estimate_pressure=pestimated'+(q_est*Zo)
figure (6)
 plot(t1,Estimate_pressure)%Pressure estimation of flow waveform 3
title('Estimated Ascending Aortic Pressure Waveform')
ylabel('Pressure(mmHg)')
xlabel('Time(s)')

%%
%Estimate Carotid waveform 4
C = xlsread('test 4.xls',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
```

```
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

yc = fft(q3);
 %Compute DFT of x
 new_mc = abs(yc);         % Magnitude
 new_pc =unwrap(angle(yc));
 %figure (5)
%subplot(1,3,1)
%plot(new_mc)
%title('Mag. of the Caratoid artery')
%subplot(1,3,2)
%plot(new_pc)
%title('Phase of the Caratoid artery')
newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new);
%subplot(1,3,3)
subplot(1,2,2)
plot(t3,X_new)
title('Estimated Ascending Aortic Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Pressure estimation of flow waveform 4
q_est=real(X_new);%flow measured
dt=0.01;%Delta T
Rs=1.68;
C=2.3;
Zo=0.04;
t=0:0.015625:.9844;
for i=1:(length(q_est)-1)%Estimate all till length of P
   pestimated(1)=80;%Take 1st measured pressure as Pe(1)
    if t(i)>=0.5625%Change this variable depending on when flow becomes
zero.
         q_est(i)=0;%Flow becomes zero after valve closes
     end
       pestimated(i+1)=pestimated(i)+(dt*(q_est(i)-
(pestimated(i)/Rs))./C);
end
Estimate_pressure=pestimated'+(q_est*Zo)
figure (6)
 plot(t1,Estimate_pressure)%Pressure estimation of flow waveform 4
  title('Estimated Ascending Aortic Pressure Waveform')
ylabel('Pressure(mmHg)')
xlabel('Time(s)')

 %%

 %Estimate Carotid waveform 5
C = xlsread('Test 5.xls',1);
t3=C(:,1);
```

```
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

yc = fft(q3);
 %Compute DFT of x
 new_mc = abs(yc);        % Magnitude
 new_pc =unwrap(angle(yc));
 %figure (5)
%subplot(1,3,1)
%plot(new_mc)
%title('Mag. of the Caratoid artery')
%subplot(1,3,2)
%plot(new_pc)
%title('Phase of the Caratoid artery')
newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new);
%subplot(1,3,3)
subplot(1,2,2)
plot(t3,X_new)
title('Estimated Ascending Aortic Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Pressure estimation of flow waveform 5
q_est=real(X_new);%flow measured
dt=0.01;%Delta T
Rs=1.25;
C=2.3;
Zo=0.04;
t=0:0.015625:.9844;
for i=1:(length(q_est)-1)%Estimate all till length of P
   pestimated(1)=80;%Take 1st measured pressure as Pe(1)
    if t(i)>=0.6094%Change this variable depending on when flow becomes 
zero.
         q_est(i)=0;%Flow becomes zero after valve closes
     end
       pestimated(i+1)=pestimated(i)+(dt*(q_est(i)-
(pestimated(i)/Rs))./C);
end
Estimate_pressure=pestimated'+(q_est*Zo)
figure (6)
 plot(t1,Estimate_pressure)%Pressure estimation of flow waveform 5
  title('Estimated Ascending Aortic Pressure Waveform')
ylabel('Pressure(mmHg)')
xlabel('Time(s)')
```

```
%individual transfer function derivation
clc;
clear all;
close all;
%Signal carotid
A = xlsread('Individual TF_Carotid artery.xls',1);
t1=A(:,1);
q1=A(:,2);
figure (1)
subplot(1,2,1)
plot(t1,q1)
title('Carotid artery flow waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

B = xlsread('Individual TF_Ascending aorta.xls',1);
t2=B(:,1);
q2=B(:,2);
subplot(1,2,2)
plot(t2,q2)
title('Ascending aorta flow waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Taking FFT of carotid artery
yc = fft(q1);
 %Compute DFT of x
 mc = abs(yc);        % Magnitude
 pc =angle(yc);
 figure (2)
subplot(1,2,1)
plot(mc(1:12))
title('Magnitude of Carotid Artery Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(pc(1:12))
title('Phase of the Carotid Artery Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

% %Taking FFT of aorta
ya = fft(q2);                                  % Compute DFT of x
ma = abs(ya);                                  % Magnitude
pa = angle(ya);
figure (3)
subplot(1,2,1)
plot(ma(1:12))
title('Magnitude of Ascending Aorta Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(pa(1:12))
title('Phase of Ascending Aorta Flow Waveform')
```

```
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

% % %Transfer function
  TF=ma./mc;
  TFP=pa-pc;

 figure (4)
subplot(1,2,1)
plot(TF(1:12))
title('TF-mag.')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(TFP(1:12))
title('TF-Phase.')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')
%%
%Carotid waveform 1
C = xlsread('Individual TF_Carotid artery.xls',1);
t3=C(:,1);
q3=C(:,2);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

B = xlsread('Individual TF_Ascending aorta.xls',1);
t2=B(:,1);
q2=B(:,2);


yc = fft(q3);
 %Compute DFT of x
 new_mc = abs(yc);        % Magnitude
 new_pc = angle(yc);
newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new);
%subplot(1,3,3)
subplot(1,2,2)
plot(t2,q2,t3,X_new)
title('Estimated Ascending Aorta Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')
legend('Original-Ascending aorta flow waveform ','Estimated-Ascending
aorta flow waveform')
```

Appendix II – Extended Research

Noise reduction:

There was some noise seen in estimated ascending aorta flow waveforms as well as estimated pressure waveform. To reduce noise in the estimated signal, mean of the average carotid flow and average ascending aorta flow was subtracted from average carotid flow and average ascending aorta flow. Then 1st order butterworth low pass filter was used to reduce noise in both average carotid flow and average ascending aorta flow. Then fft of the both waveforms were taken. Mean of the ascending aorta flow was added back to the signal after taking inverse fft. Phase of the waveforms were found using angle(x) function in matlab. Angle function in matlab returns angles that jumps between ± pi. This can be corrected with using unwrap function. This function corrects the radian phase angles in the vector by adding multiple of the ± 2*pi. Previously, we used all 64hz data to retrieve ascending aorta flow waveform in time domain. We can use data up to Nyquist frequency to retrieve the signal back in time domain to avoid high frequency noise. See below for the results of generalized transfer function for estimating ascending aorta flow. Ascending aorta pressure can be measured from improved ascending aorta flow waveforms as described earlier in the thesis. Similar approach can be applied to individualized transfer function to derive ascending aorta flow waveform.

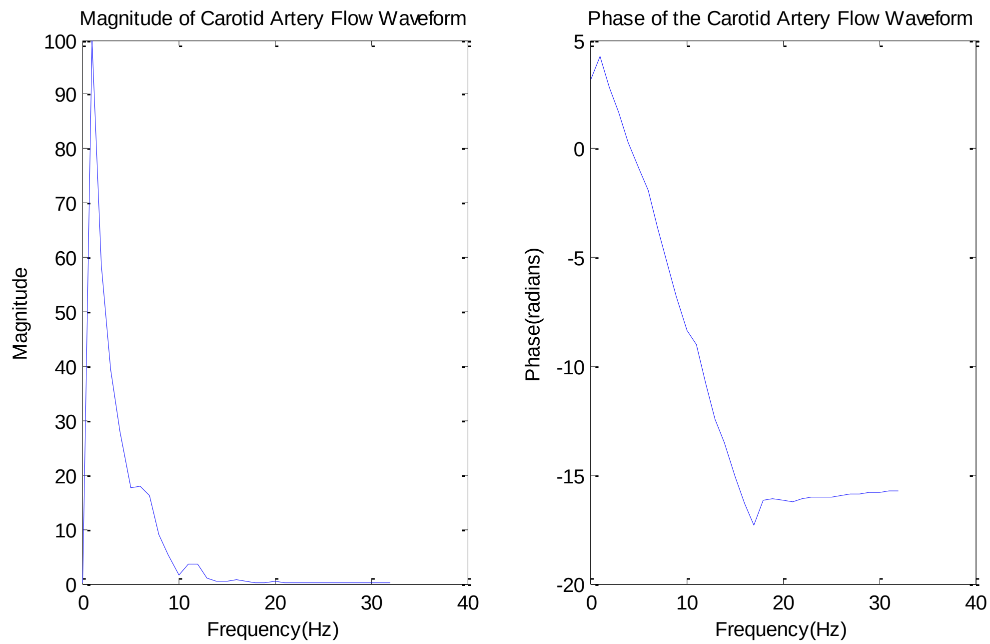


Figure II.I : Magnitude and phase of average carotid waveform up to Nyquist frequency

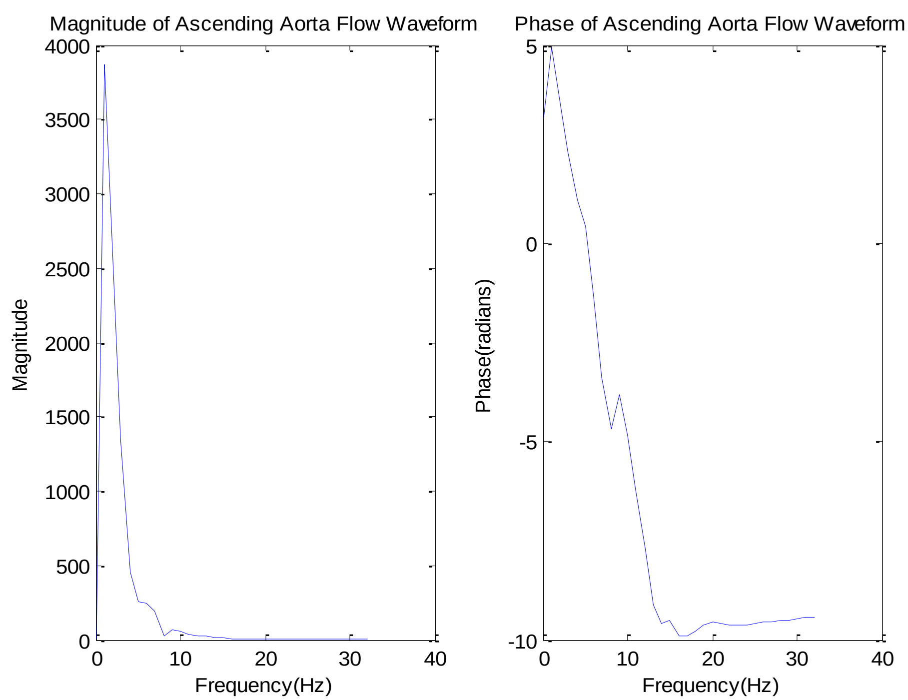


Figure II.II : Magnitude and phase of average ascending waveform up to Nyquist frequency

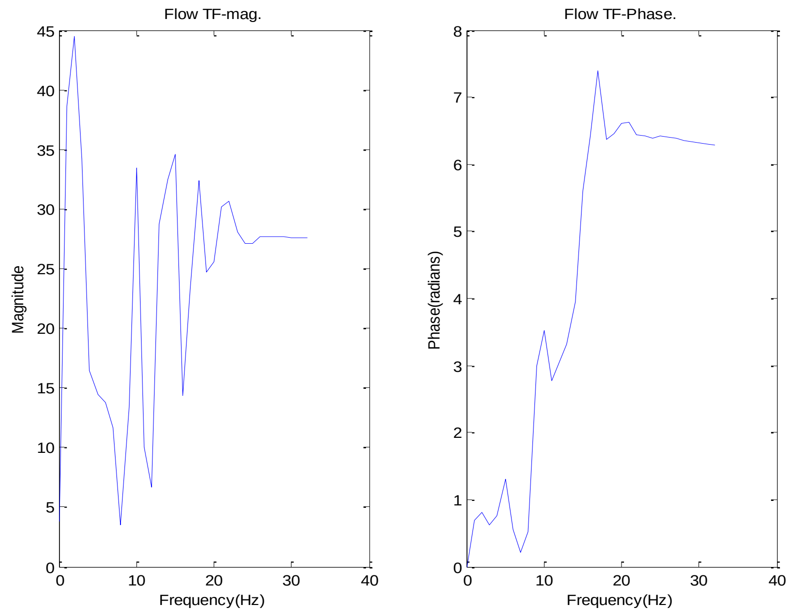


Figure II.III : Magnitude and phase of Transfer function up to Nyquist frequency

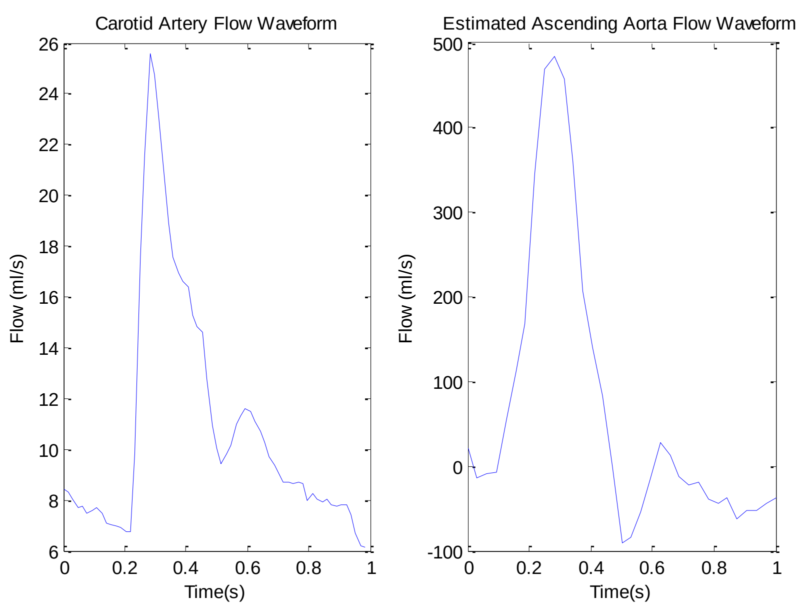


Figure II.IV : Carotid flow waveform 1 and estimated ascending aorta flow waveform using data up to Nyquist frequency

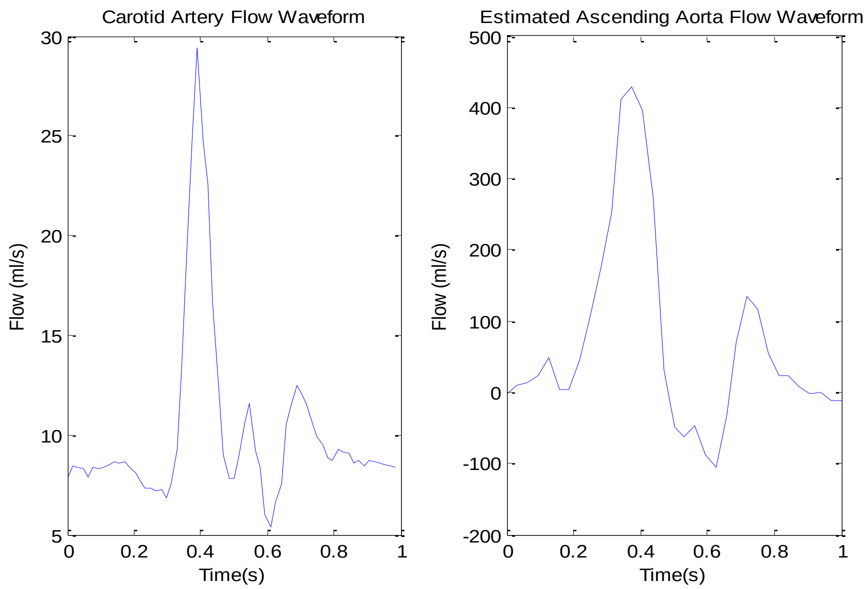


Figure II.V : Carotid flow waveform 2 and estimated ascending aorta flow waveform using data up to Nyquist frequency

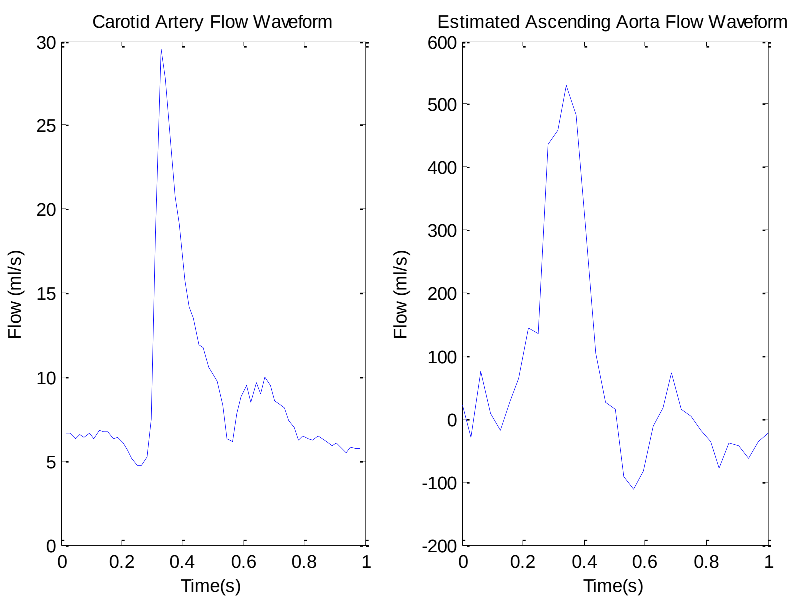


Figure II.VI : Carotid flow waveform 3 and estimated ascending aorta flow waveform using data up to Nyquist frequency

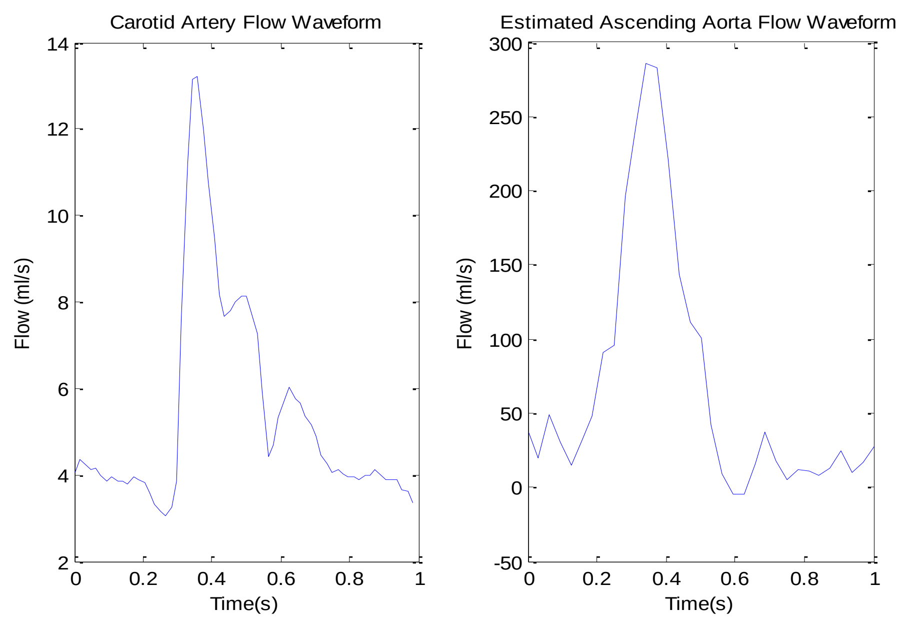


Figure II.VII : Carotid flow waveform 4 and estimated ascending aorta flow waveform using data up to Nyquist frequency

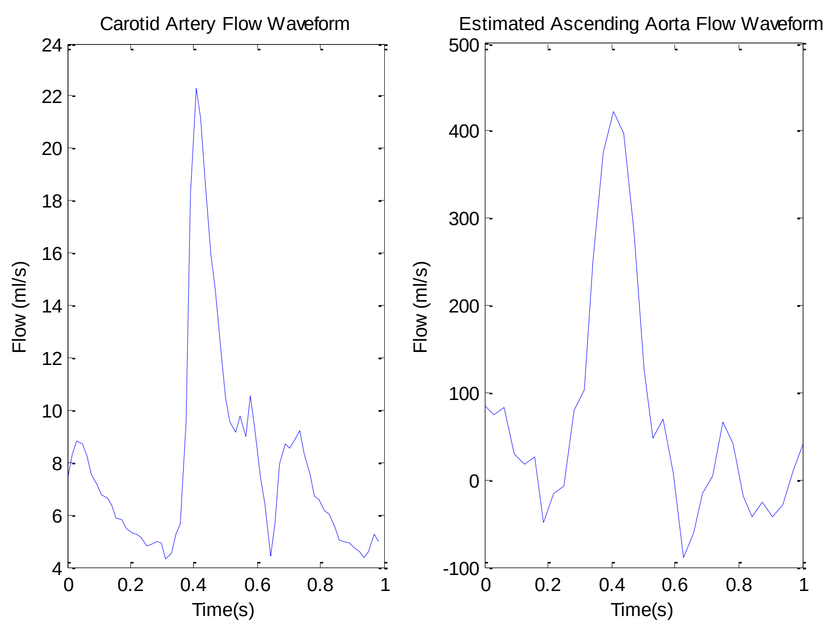


Figure II.VIII : Carotid flow waveform 5 and estimated ascending aorta flow waveform using data up to Nyquist frequency

Transfer function estimation:

Transfer function can be also estimated using tfestimate function in matlab. Transfer function derived in this thesis was compared to transfer function derived using tfestimate. General shape of magnitude plots derived using both methods looks similar. General shape of phase plots derived using both plots looks similar. Transfer function magnitude and phase plot derived using our method shows some noise at high frequency. Transfer function magnitude and phase plots derived using tfestimate function looks much smoother. In future, transfer function can be derived using tfestimate will provide smoother ascending aorta flow and pressure plots.

Furthermore, we also derived flow based transfer function from ascending aorta (AA) to carotid artery (CA). Magnitude plot of transfer function (AA-CA) is reciprocal magnitude plot of transfer function (CA-AA). Phase plot of transfer function (CA-AA) has positive slope. Phase plot of transfer function (AA-CA) has negative slope. These characteristics can be seen in below figures of transfer function. These characteristics may look slightly different depending on the set of data that is used to derive it.

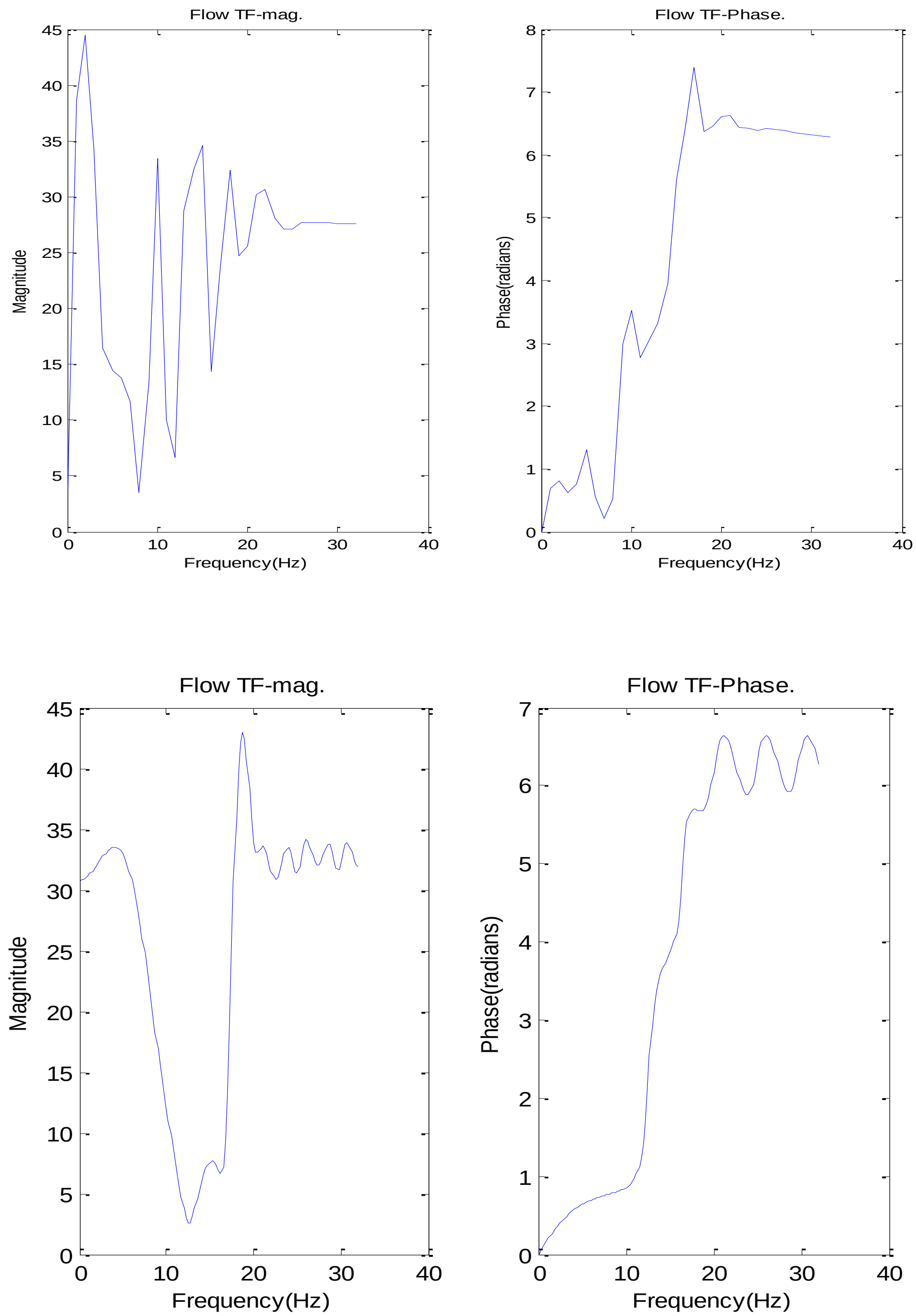


Figure II.IX : Magnitude and phase of flow based transfer function from carotid artery to ascending aorta on the top was derived using method described in this thesis. Magnitude and phase plot of flow based transfer function from carotid artery to ascending aorta on the bottom was derived using tfestimate function in matlab.

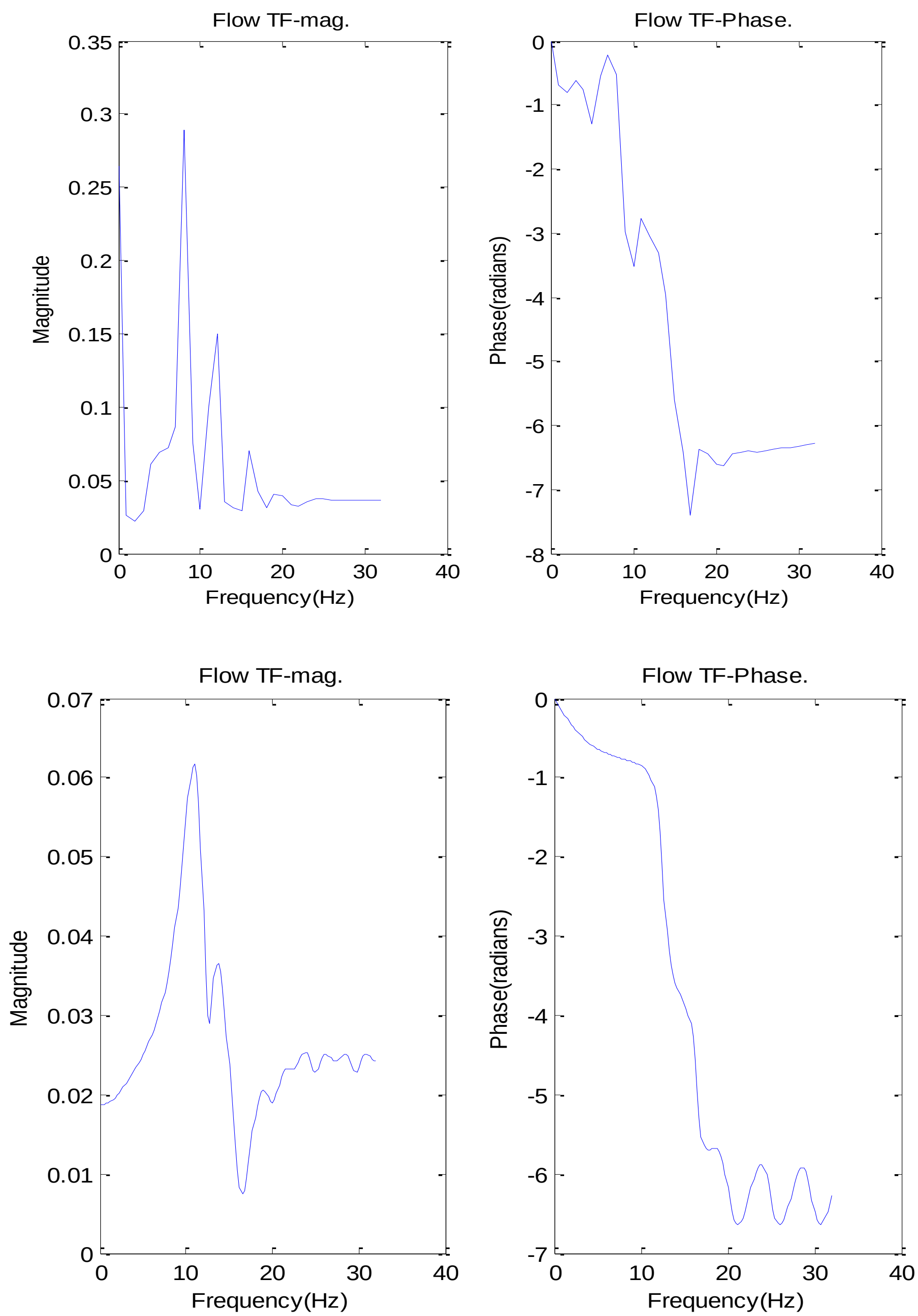


Figure II.X : Magnitude and phase of flow based transfer function from ascending aorta to carotid artery on the top was derived using method described in this thesis. Magnitude and phase plot of flow based transfer function from ascending aorta to carotid artery on the bottom was derived using tfestimate function in matlab.

Matlab code:

```
 n=input('Enter a number:');

switch n
   case 1
       %Deriving flow based transfer function from Carotid artery to
ascending
       %aorta using method described in this thesis.
    A = xlsread('ave_carotid_1.xlsx',1);
    t1=A(:,1);
    q1=A(:,2);
    figure (1)
    subplot(1,2,1)
    plot(t1,q1)
    title('Average carotid artery flow')
    ylabel('Flow (ml/s)')
    xlabel('Time(s)')

    B = xlsread('ave_aorta_1.xlsx',1);
    t2=B(:,1);
    q2=B(:,2);
    subplot(1,2,2)
    plot(t2,q2)
    title('Average ascending aortic flow waveform')
    ylabel('Flow (ml/s)')
    xlabel('Time(s)')

    %Taking FFT of caratoid artery
    nq1=q1-mean(q1);%Minus out mean.
    fs = 64; % sampling freq = 64Hz
    fnorm = 12/32; % normalized cut off freq
    [b1,a1] = butter(2,fnorm,'low');
    low_pass_data_nq1 = filtfilt(b1,a1,nq1);

    yc = fft(low_pass_data_nq1);
     %Compute DFT of x
     mc = abs(yc);         % Magnitude
     pc =unwrap(angle(yc));
     figure (2)
    subplot(1,2,1)
    f=0:1:32;
    plot(f',mc(1:33))
    title('Magnitude of Carotid Artery Flow Waveform')
    xlabel('Frequency(Hz)')
    ylabel('Magnitude')

    subplot(1,2,2)
    plot(f',pc(1:33))
    title('Phase of the Carotid Artery Flow Waveform')
    xlabel('Frequency(Hz)')
    ylabel('Phase(radians)')
```

```
% %Taking FFT of aorta
nq2=q2-mean(q2);
%data=q1; % this is your data
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq2 = filtfilt(b1,a1,nq2);

ya = fft(low_pass_data_nq2);
ma = abs(ya);% Magnitude
pa = unwrap(angle(ya));
figure (3)
subplot(1,2,1)
plot(f',ma(1:33))
title('Magnitude of Ascending Aorta Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(f',pa(1:33))
title('Phase of Ascending Aorta Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

%Transfer function
  TF=ma./mc;
  TFP=pa-pc;

 figure (4)
subplot(1,2,1)
plot(f',(TF(1:33)))
title('Flow TF-mag.')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(f',(TFP(1:33)))
title('Flow TF-Phase.')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

case 2
%Estimate ascending aorta flow waveform 1
C = xlsread('Test 1.xlsx',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

nq3=q3-mean(q3);
```

```
%data=q1; % this is your data
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq3 = filtfilt(b1,a1,nq3);

yc = fft(nq3);
 %Compute DFT of x
 new_mc = abs(yc);         % Magnitude
 new_pc =unwrap(angle(yc));

newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new,33);
New_signal=real(X_new)+mean(q2);

subplot(1,2,2)
t4=linspace(0,1,33);
plot(t4,New_signal)
title('Estimated Ascending Aorta Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

case 3
    %Estimate ascending aorta flow waveform 2
 C = xlsread('test2.xls',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

nq3=q3-mean(q3);
%data=q1; % this is your data
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq3 = filtfilt(b1,a1,nq3);

yc = fft(nq3);
 %Compute DFT of x
 new_mc = abs(yc);         % Magnitude
 new_pc =unwrap(angle(yc));

newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new,33);
New_signal=real(X_new)+mean(q2);
```

```
subplot(1,2,2)
t4=linspace(0,1,33);
plot(t4,New_signal)
title('Estimated Ascending Aorta Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

case 4
    %Estimate ascending aorta flow waveform 3
 C = xlsread('test 3.xls',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

nq3=q3-mean(q3);
%data=q1; % this is your data
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq3 = filtfilt(b1,a1,nq3);

yc = fft(nq3);
 %Compute DFT of x
 new_mc = abs(yc);        % Magnitude
 new_pc =unwrap(angle(yc));

newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new,33);
New_signal=real(X_new)+mean(q2);

subplot(1,2,2)
t4=linspace(0,1,33);
plot(t4,New_signal)
title('Estimated Ascending Aorta Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

case 5
     %Estimate ascending aorta flow waveform 4
C = xlsread('test 4.xls',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
```

```
ylabel('Flow (ml/s)')
xlabel('Time(s)')

nq3=q3-mean(q3);
%data=q1; % this is your data
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq3 = filtfilt(b1,a1,nq3);

yc = fft(nq3);
 %Compute DFT of x
 new_mc = abs(yc);         % Magnitude
 new_pc =unwrap(angle(yc));

newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);

X_new=ifft(XF_new,33);
New_signal=real(X_new)+mean(q2);

subplot(1,2,2)
t4=linspace(0,1,33);
plot(t4,New_signal)
title('Estimated Ascending Aorta Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

case 6
       %Estimate ascending aorta flow waveform 5
C= xlsread('Test 5.xls',1);
t3=C(:,1);
q3=C(:,3);
figure (5)
subplot(1,2,1)
plot(t3,q3)
title('Carotid Artery Flow Waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

nq3=q3-mean(q3);
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq3 = filtfilt(b1,a1,nq3);

yc = fft(nq3);
 %Compute DFT of x
 new_mc = abs(yc);         % Magnitude
 new_pc =unwrap(angle(yc));

newma=TF.*new_mc;
newpa=TFP+new_pc;
XF_new=newma.*exp(1i.*newpa);
```

```
    X_new=ifft(XF_new,33);
    New_signal=real(X_new)+mean(q2);

    subplot(1,2,2)
    t4=linspace(0,1,33);
    plot(t4,New_signal)
    title('Estimated Ascending Aorta Flow Waveform')
    ylabel('Flow (ml/s)')
    xlabel('Time(s)')

     case 7
      %Deriving transfer function from Carotid artery flow to ascending
       %aorta flow using tfestimate function
    A = xlsread('ave_carotid_1.xlsx',1);
    t1=A(:,1);
    q1=A(:,2);
    figure (1)
    subplot(1,2,1)
    plot(t1,q1)
    title('Average carotid artery flow')
    ylabel('Flow (ml/s)')
    xlabel('Time(s)')

    B = xlsread('ave_aorta_1.xlsx',1);
    t2=B(:,1);
    q2=B(:,2);
    subplot(1,2,2)
    plot(t2,q2)
    title('Average ascending aortic flow waveform')
    ylabel('Flow (ml/s)')
    xlabel('Time(s)')

    %Taking FFT of caratoid artery
    nq1=q1-mean(q1);%Minus out mean.
    fs = 64; % sampling freq = 64Hz
    fnorm = 12/32; % normalized cut off freq
    [b1,a1] = butter(2,fnorm,'low');
    low_pass_data_nq1 = filtfilt(b1,a1,nq1);

    %Taking FFT of aorta
    nq2=q2-mean(q2);
    %data=q1; % this is your data
    fs = 64; % sampling freq = 64Hz
    fnorm = 12/32; % normalized cut off freq
    [b1,a1] = butter(2,fnorm,'low');
    low_pass_data_nq2 = filtfilt(b1,a1,nq2);



[Txy,f]=tfestimate(low_pass_data_nq1,low_pass_data_nq2,[],[],[],fs);
    TF=abs(Txy)
    TFP=unwrap(angle(Txy))
```

```
 figure (2)
subplot(1,2,1)
plot(f,TF)
title('Flow TF-mag.')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(f,TFP)
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')
title('Flow TF-Phase.')


 case 8
 %Deriving flow based transfer function from ascending aorta flow
to
 %carotid artery using method described in this thesis.
A = xlsread('ave_carotid_1.xlsx',1);
t1=A(:,1);
q1=A(:,2);
figure (1)
subplot(1,2,1)
plot(t1,q1)
title('Average carotid artery flow')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

B = xlsread('ave_aorta_1.xlsx',1);
t2=B(:,1);
q2=B(:,2);
subplot(1,2,2)
plot(t2,q2)
title('Average ascending aortic flow waveform')
ylabel('Flow (ml/s)')
xlabel('Time(s)')

%Taking FFT of caratoid artery
nq1=q1-mean(q1);%Minus out mean.
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq1 = filtfilt(b1,a1,nq1);

yc = fft(low_pass_data_nq1);
 %Compute DFT of x
 mc = abs(yc);         % Magnitude
 pc =unwrap(angle(yc));
 figure (2)
subplot(1,2,1)
f=0:1:32;
plot(f',mc(1:33))
title('Magnitude of Carotid Artery Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Magnitude')
```

```
subplot(1,2,2)
plot(f',pc(1:33))
title('Phase of the Carotid Artery Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

% %Taking FFT of aorta
nq2=q2-mean(q2);
%data=q1; % this is your data
fs = 64; % sampling freq = 64Hz
fnorm = 12/32; % normalized cut off freq
[b1,a1] = butter(2,fnorm,'low');
low_pass_data_nq2 = filtfilt(b1,a1,nq2);

ya = fft(low_pass_data_nq2);
ma = abs(ya);% Magnitude
pa = unwrap(angle(ya));
figure (3)
subplot(1,2,1)
plot(f',ma(1:33))
title('Magnitude of Ascending Aorta Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(f',pa(1:33))
title('Phase of Ascending Aorta Flow Waveform')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

%Transfer function
  TF=mc./ma;
  TFP=pc-pa;

 figure (4)
subplot(1,2,1)
plot(f',(TF(1:33)))
title('Flow TF-mag.')
xlabel('Frequency(Hz)')
ylabel('Magnitude')

subplot(1,2,2)
plot(f',(TFP(1:33)))
title('Flow TF-Phase.')
xlabel('Frequency(Hz)')
ylabel('Phase(radians)')

case 9
 %Deriving flow based transfer function from ascending aorta
 %to carotid artery using tfestimate function
A = xlsread('ave_carotid_1.xlsx',1);
t1=A(:,1);
q1=A(:,2);
figure (1)
```

```
    subplot(1,2,1)
    plot(t1,q1)
    title('Average carotid artery flow')
    ylabel('Flow (ml/s)')
    xlabel('Time(s)')

    B = xlsread('ave_aorta_1.xlsx',1);
    t2=B(:,1);
    q2=B(:,2);
    subplot(1,2,2)
    plot(t2,q2)
    title('Average ascending aortic flow waveform')
    ylabel('Flow (ml/s)')
    xlabel('Time(s)')

    %Taking FFT of caratoid artery
    nq1=q1-mean(q1);%Minus out mean.
    fs = 64; % sampling freq = 64Hz
    fnorm = 12/32; % normalized cut off freq
    [b1,a1] = butter(2,fnorm,'low');
    low_pass_data_nq1 = filtfilt(b1,a1,nq1);

    %Taking FFT of aorta
    nq2=q2-mean(q2);
    %data=q1; % this is your data
    fs = 64; % sampling freq = 64Hz
    fnorm = 12/32; % normalized cut off freq
    [b1,a1] = butter(2,fnorm,'low');
    low_pass_data_nq2 = filtfilt(b1,a1,nq2);



[Txy,f]=tfestimate(low_pass_data_nq2,low_pass_data_nq1,[],[],[],fs);
    TF=abs(Txy)
    TFP=unwrap(angle(Txy))


     figure (2)
    subplot(1,2,1)
    plot(f,TF)
    title('Flow TF-mag.')
    xlabel('Frequency(Hz)')
    ylabel('Magnitude')

    subplot(1,2,2)
    plot(f,TFP)
    xlabel('Frequency(Hz)')
    ylabel('Phase(radians)')
    title('Flow TF-Phase.')

end
```