NOTE TO USERS

This reproduction is the best copy available.

UMI[®]

**Measurement and Prediction of the Hemodynamic Effects
of Passive Leg Elevation**

by

Samira M. Kazan

B. Eng

A thesis submitted to the Faculty of Graduate
Studies and Research in the partial fulfillment
of the requirements for the degree of

Master of Applied Science in Aerospace Engineering

Ottawa-Carleton Institute for Mechanical
and Aerospace Engineering

Department of Mechanical and Aerospace Engineering
Carleton University
Ottawa, Ontario
Canada
October, 2005

Copyright © 2005
Samira M. Kazan

Library and
Archives Canada

Bibliothèque et
Archives Canada

Published Heritage
Branch

Direction du
Patrimoine de l'édition

395 Wellington Street
Ottawa ON K1A 0N4
Canada

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

ISBN: 0-494-13443-7

Our file Notre référence

ISBN: 0-494-13443-7

NOTICE:

The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protègent cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

to my family

This thesis involves the measurement and prediction of the hemodynamic effects of passive leg elevation. The experimental measurements include the mean arterial pressure and the heart rate at the heart level directly after passive leg elevation at different angles using BpTrue automated blood pressure device in normotensive and hypertensive healthy subjects. The computed measurements include the blood pressure and the blood flow rate distribution using a one-dimensional time-mean flow model of the cardiovascular system, where the blood is viewed as an incompressible Newtonian fluid and the vessels as elastic.

The experimental results show that the mean arterial pressure increases momentarily when assuming passive elevation of the legs in both normotensive and hypertensive groups. In normotensive subjects, the mean arterial pressure returns back to its original supine value two minutes after passive leg elevation due to the short term control mechanisms. In the hypertensive group, the mean arterial pressure decreased when measured after two minutes of passive leg elevation. This distinct behavior might be attributed to the different control mechanisms for this group.

The experimental and computational results show that the load on the heart increases momentarily upon passive leg elevation. This brief increase may not be favored by the heart disease patients, and thus this position is not recommended for them.

Acknowledgements

I would like to thank my thesis supervisor, Dr. M.I. Yaras, for his guidance and advice during the course of this work. I extend my thanks to my co-supervisor, Dr. T. Mussivand, for his suggestions and advice on this thesis as well as the staff at the Heart Institute for their help in the experimental work, in particular: Research Nurse: Liz Coletta, Biomedical Engineer: Timothy Zakutnay, Medical doctors: Frans Leenen and Haissam Haddad. Finally, I would like to thank my family for their support and encouragement.

Table of Contents

List of Figures	xiii
List of Tables.....	xviii
Nomenclature.....	xxi
Chapter 1 Introduction	1
Chapter 2 Literature Survey on Blood Pressure and its Measurement.....	4
2.1 Definition of Blood Pressure	4
2.2 Function of Blood Pressure	5
2.3 Regulation of Blood Pressure	6
2.3.1 Nervous System Blood Pressure Regulation	6
2.3.1.1 Sympathetic Effects on the Circulation	7
2.3.1.2 Parasympathetic Effects on the Circulation.....	8
2.3.1.3 Vasomotor Tone	9
2.3.1.4 The Baroreceptor Pressure Control System.....	10
2.3.1.5 The Chemoreceptor Pressure Control System.....	11
2.3.2 Blood Pressure Regulation by Capillary Fluid Shift	12
2.3.3 Blood Pressure Regulation by Kidneys	12
2.3.4 Blood Pressure Regulation by Hormonal Mechanisms	13
2.4 Measurement of Blood Pressure.....	14
2.4.1 Historical Review of Blood Pressure Measurement	15

2.4.2	Physical Characteristics of Direct Techniques	23
2.4.3	Physical Characteristics of Indirect Techniques.....	26
2.4.3.1	The Auscultatory Method.....	26
2.4.3.2	The Oscillometric Method.....	30
2.4.3.3	The Flush Method.....	31
2.4.3.4	The Doppler Ultra-Sound Method.....	33
2.4.4	Comparison between Direct and Indirect Techniques	34
2.4.5	Accuracy of Indirect Measurement Devices.....	36
2.4.5.1	Conventional Sphygmomanometers.....	36
2.4.5.2	Ambulatory Blood Pressure Devices.....	38
2.4.5.3	Electronic Sphygmomanometers	39
2.4.6	Sources of Error in Indirect Techniques	42
2.4.6.1	Auscultatory Gap	42
2.4.6.2	Pseudohypertension	43
2.4.6.3	Arm Position.....	43
2.4.6.4	Cuff Size	47
2.4.6.5	Rate of Cuff Inflation and Deflation.....	48
2.4.6.6	Mechanical Sources of Error	49
2.5	Effects of Different Activities on Blood Pressure.....	49
2.5.1	Exercise.....	50
2.5.2	Post-Exercise Hypotension	51
2.5.3	Eating.....	52

2.5.4	Nicotine.....	53
2.5.5	Alcohol.....	54
2.5.6	Caffeine.....	55
2.5.7	Speech.....	57
2.5.8	Emotion.....	58
2.5.9	Stress.....	58
2.5.10	Variations during Sleep and Wakefulness	59
2.6	Effects of Posture on Blood Pressure	61
2.6.1	Hydrostatic Indifference Point.....	62
2.6.2	Pressures in the Supine Posture	62
2.6.3	Pressures in the Upright Posture	63
2.6.4	Changing Body Posture	65
2.6.5	Therapeutic Postures.....	68
2.6.5.1	Trendelenburg's Posture	69
2.6.5.2	Passive Leg Elevation.....	70
Chapter 3	Measurement of the Effects of Passive Leg Elevation on Blood	
	Pessure.....	73
3.1	Introduction	73
3.2	Measurement of the Effects of Passive Leg Elevation on Systolic and	
	diastolic Blood Pressures	74
3.2.1	Subjects.....	74
3.2.2	Location	75

3.2.3	Measurement Devices.....	75
3.2.4	Experimental Procedure.....	81
Chapter 4	Computation of the Effects of Passive Leg Elevation on Blood Pressure	85
4.1	Introduction	85
4.2	Modeling of the Time-Mean Blood Flow in the Systemic Circulation	86
Chapter 5	Results and Discussion	99
5.1	Measured Effects of Passive Leg Elevation on Blood Circulation	99
5.1.1	Measurements of Systolic, Diastolic and Mean-Arterial Pressures.....	99
5.2	Computation of the Effects of Posture Change on Blood Circulation	102
5.2.1	Computation of the Effects of Head-Down Tilt on Blood Circulation.....	104
5.2.2	Computation of the Effects of Passive Leg Elevation on Blood Circulation	111
5.3	Measured Effects of Passive Leg Elevation on Blood Pressure in Borderline Hypertensive Subjects.....	116
Chapter 6	Conclusions and Recommendations	119
	List of References	121
	Appendices.....	146
Appendix A	Review: The Cardiovascular System	147
A.1	The Cardiovascular Pump	147
A.1.1	Heart Valves.....	150

A.1.2	Heart Sounds	152
A.1.2.1	Heart Murmurs.....	152
A.1.3	Heart Cycle	154
A.2	The Vascular System.....	156
A.2.1	The Systemic Circuit.....	157
A.2.2	The Pulmonary Circuit.....	160
A.2.3	The Lymphatic Circuit.....	160
A.2.4	Comparison of the Series Circuits	161
A.2.5	Vascular Blood vessels	162
A.2.5.1	Functional Categories of the Blood Vessels	164
A.3	The Working Fluid	167
A.3.1	Blood Viscosity.....	168
A.3.2	The Physics of Blood Flow	171
A.3.2.1	Vascular Resistance	171
A.3.2.2	Blood Flow Types.....	172
A.4	Mean Arterial Pressure	174
A.4.1	Cardiac Output	177
A.4.1.1	Stroke Volume	178
A.4.2	Venous Return	179
A.4.2.1	Muscle Pump	180
A.4.2.2	Respiratory Pump	182
A.5	Cardiovascular Control.....	183

A.5.1	Short Term Regulatory Mechanisms	184
A.5.1.1	Arterial Baroreceptor Reflexes	184
A.5.1.2	Cerebral Ischemic Reflex.....	185
A.5.1.3	Adrenalin and Noradrenalin.....	186
A.5.2	Long Term Control Mechanisms	187
A.5.2.1	Renin-Angiotensin Mechanism	187
A.5.2.2	Renal Volume Control Mechanism	190
Appendix B	Derivation of the Hemodynamic Equation	192
Appendix C	Accuracy of Electronic Sphygmomanometers	194
Appendix D	Blood Pressure Protocol	199
D.1	Introduction	203
D.1.1	Objectives of the Blood-Pressure Measurement Study	203
D.2	Equipment.....	203
D.3	Procedural Overview	204
D.4	Preparation of Subjects.....	208
D.5	Sample Selection and Rationale	209
D.6	Quality Control.....	209
D.7	Data Analysis.....	210
D.8	Experimental Success	210
D.9	Record Maintenance	211
D.10	Duration of the Experimental Study.....	211

D.11	Data and Collection Procedure	212
D.12	Clinical Engineering Record	213
Appendix E	Patient Consent Form	217
E.1	Introduction	218
E.2	Procedure	219
E.3	Risks and Discomforts of Participation	224
E.4	Benefits of Participation	224
E.5	Compensation /Remuneration.....	224
E.6	Confidentiality (Where Applicable)	224
E.7	Ethics.....	225
E.8	Participation	225
E.9	Consent to Participate in Research	226
Appendix F	Time Mean Flow Program	227
F.1	Computation Algorithm	227
F.2	Sample Input File	245
F.3	Sample Output File.....	246
F.4	Empirical Data of the blood vessels.....	252
Appendix G	Experimental Results	254

List of Figures

Figure 2.1	Blood pressure as measured in various compartments of the systemic circulation.....	4
Figure 2.2	Sympathetic nervous control of the circulation.....	7
Figure 2.3	Autonomic nervous system regulation of the heart.....	8
Figure 2.4	Effect of spinal anesthesia on arterial blood pressure.	10
Figure 2.5	Location of the baroreceptors and chemoreceptors in the region of the aorta and the carotid artery.....	11
Figure 2.6	Effect of constricting the renal arteries and days later releasing the constriction on blood pressure..	14
Figure 2.7	Galen's belief of the circulatory system.....	16
Figure 2.8	The Reverend Hales demonstrating blood pressure	17
Figure 2.9	Ludwig kymograph.	18
Figure 2.10	Vierordt sphygmograph.....	19
Figure 2.11	Marey sphygmograph.....	19
Figure 2.12	Dudgeon sphygmograph.....	20
Figure 2.13	Von Basch sphygmomanometer.....	21
Figure 2.14	Indicator part of portable Von Basch sphygmomanometer.....	21
Figure 2.15	Riva-Rocci sphygmomanometer.	22
Figure 2.16	Typical direct pressure monitoring system.....	25

Figure 2.17 Auscultatory blood pressure measurement technique.	27
Figure 2.18 Characteristics of Korotkoff sounds.	28
Figure 2.19 Relation between the arterial movement and its transmission to the cuff	31
Figure 2.20 The flush method applied to a finger.	32
Figure 2.21 Ultrasound measurement technique.	33
Figure 2.22 Comparison of direct and indirect blood pressures.	35
Figure 2.23 Effects of different arm positions on blood pressure.	45
Figure 2.24 Effect of different body postures on blood pressure.	46
Figure 2.25 Arterial pressure variation in a normotensive healthy subject during 24 hours.	50
Figure 2.26 Intra-arterial blood pressure changes when lifting barbells	51
Figure 2.27 Systolic, mean arterial and diastolic pressures before, during and 13 hours after a cycling exercise.	52
Figure 2.28 Effect of alcohol on systolic and diastolic pressures in normotensive and hypertensive subjects.	55
Figure 2.29 Effects of cigarette smoking and coffee drinking on systolic pressure.	56
Figure 2.30 Systolic and diastolic pressures of 25 subjects where talking preceded reading a comic book.	58
Figure 2.31 Levels of systolic pressure, diastolic pressure and heart rate in normotensive subjects one hour before and after waking.	60
Figure 2.32 Mean arterial and venous pressures in the supine position.	63
Figure 2.33 Mean arterial and venous pressure in the upright posture.	64

Figure 2.34 Comparison of mean arterial pressure and central venous pressure in an upright human and a young giraffe.....	65
Figure 2.35 TREND posture.....	70
Figure 2.36 Modified Trendelenburg posture.....	71
Figure 3.1 BpTRU blood pressure device.....	76
Figure 3.2 Mobile stand.....	77
Figure 3.3 Regular-Adult blood pressure cuff.....	78
Figure 3.4 First-temp Genius thermometer.....	78
Figure 3.5 Medical bed.....	79
Figure 3.6 Foam leg raisers.....	79
Figure 3.7 Heart pillow.....	80
Figure 3.8 Mobile adjustable stand.....	80
Figure 3.9 Passive leg elevation.....	83
Figure 4.1 (A) Flow rate waveform in the normal femoral artery. (B) Velocity profile in the femoral artery computed from the mean velocity waveforms.....	87
Figure 4.2 Discrete representation of the systemic circulation.....	90
Figure 4.3 Magnetic resonance image of the human arterial tree.....	91
Figure 5.1 Control mechanisms at different time intervals after the onset of a disturbance to the arterial pressure.....	101
Figure 5.2 Passive leg elevation.....	103
Figure 5.3 Trendelenburg's head-down tilt posture.....	104

Figure 5.4	Block diagram of the arterial tree.	107
Figure A.1	Schematic representation of the cardiovascular system.	148
Figure A.2	Layers of the heart.	149
Figure A.3	Internal view of the heart.	149
Figure A.4	Blood path through the heart.	150
Figure A.5	Superior view of the heart valves.	151
Figure A.6	One way flow of blood through the heart valves.	151
Figure A.7	Correlation of events in a cardiac cycle.	153
Figure A.8	Cardiac conduction system.	155
Figure A.9	The lymphatic circuit as it relates to the cardiovascular system.	156
Figure A.10	The arteries of the human body.	158
Figure A.11	The veins of the human body.	159
Figure A.12	The systemic and the pulmonary circulation.	162
Figure A.13	Structure of the wall of a muscular artery.	163
Figure A.14	Anatomy of the terminal capillary bed.	166
Figure A.15	Capillary exchange.	166
Figure A.16	Blood volume distribution.	167
Figure A.17	Viscosity of the whole blood as function of Hematocrit.	169
Figure A.18	Non-Newtonian behavior of human blood.	170
Figure A.19	Factors that determine blood flow.	171
Figure A.20	Schematic representation of laminar viscous fluid flow.	173

Figure A.21 Schematic representations of cross-sectional area, blood distribution, velocity and pressure in different regions of the circulation.....	176
Figure A.22 Distribution of cardiac output to body organs during rest.....	178
Figure A.23 Muscle pump mechanism.	180
Figure A.24 Muscle pump: (A) passive upright rest, (B) active upright posture, (C) muscle relaxation	181
Figure A.25 Venous valves of the leg.....	182
Figure A.26 Respiratory pump.	183
Figure A.27 Blood vessel's receptors.	186
Figure A.28 Comparison of effects of adrenaline and noradrenaline in man.	187
Figure A.29 Renin-Angiotensin-Aldosterone mechanisms.	189
Figure A.30 Renin-Angiotensin-Aldosterone system compensation after hemorrhage	190
Figure A.31 Block diagram of the renal-volume control system.....	191
Figure G.1 Rate of P_{SBP} change with PLE in normotensive healthy subjects.	256
Figure G.2 Rate of P_{DBP} change with PLE in normotensive healthy subjects.....	257
Figure G.3 Rate of HR change with PLE in normotensive healthy subjects.	258
Figure G.4 Rate of P_{SBP} change with PLE in hypertensive healthy subjects.....	259
Figure G.5 Rate of P_{DBP} change with PLE in hypertensive healthy subjects.	260
Figure G.6 Rate of HR change with PLE in hypertensive healthy subjects.	261

List of Tables

Table 2.1	Korotkoff sounds during blood pressure recording by stethoscope.	30
Table 2.2	Differences between the auscultatory and direct measurement techniques (Mean $\pm$ SD) reported in a number of studies.	34
Table 2.3	British Hypertension Society grading criteria.	41
Table 2.4	Recommended ideal arm circumference, arm circumference ranges, and correction of P_{SBP} and P_{DBP} in mmHg for adult cuffs of different bladder widths at various arm circumferences.	48
Table 2.5	Summary of studies on the differences between sitting and supine blood pressure measurements.	67
Table 3.1	Physical characteristics of the subject group (Mean $\pm$ SD).	75
Table 3.2	Accuracy of the BpTRU device.	76
Table 4.1	Grouping of the modeling elements.	91
Table 4.2	Geometric properties and arterial-wall properties of the arterial tree segments..	96
Table 5.1	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 10 seconds after 27 degrees of passive leg elevation.	100

Table 5.2	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects two minutes after 27 degrees of passive leg elevation.	100
Table 5.3	Computed blood flow-rate and resistance distribution in supine versus 15-degrees head-down-tilt postures when values of P_{CV} and Q_{LV} are kept constant during the change in posture.	106
Table 5.4	Computed blood flow-rate and resistance distribution in supine versus 15-degrees head-down-tilt postures when P_{CV} is increased by 2 mmHg while Q_{LV} is kept constant during the change in posture.	109
Table 5.5	Computed blood flow-rate and resistance distribution in supine versus 15-degrees head-down-tilt postures when P_{CV} is increased by 2 mmHg and Q_{LV} by 4.17 ml/sec during the change in posture.	110
Table 5.6	Computed blood flow-rate and resistance distribution in supine versus 27-degree passive-leg-elevation postures when P_{CV} is increased by 2 mmHg and Q_{LV} by 4.17 ml/sec during the change in posture.	112
Table 5.7	Computed blood flow-rate and resistance distribution in supine versus 27-degree passive-leg-elevation postures when P_{CV} is increased by 2 mmHg while Q_{LV} is kept constant during the change in posture.	113
Table 5.8	The effect of uncertainty in the blood-vessel data on the predicted blood flow-rate and resistance distribution in supine versus 27-degree passive-leg-elevation postures.	115

Table 5.9	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate on borderline hypertensive subjects 10 seconds after 27 degrees of passive leg elevation.	116
Table 5.10	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate on borderline hypertensive subjects 2 minutes after 27 degrees of passive leg elevation.	116
Table A.1	Representative rates of shear at vessel walls in the human circulation.	170
Table F.1	Sample output file.	246
Table F.2	Available empirical data of the blood vessels on the literature.	252
Table G.1	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive healthy subjects 10 seconds after 27 degrees of passive leg elevation.	254
Table G.2	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 2 minutes after 9 degrees of passive leg elevation.	255
Table G.3	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 2 minutes after 18 degrees of passive leg elevation.	255
Table G.4	Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 2 minutes after 27 degrees of passive leg elevation.	255

Abbreviations

AAMI	association for the Advancement of Medical Instrumentation
ABPM	ambulatory blood pressure monitoring
AHA	American Heart Association
ANSI	American National Standard Institute
BHS	British hypertension society
BPM	blood pressure measurement
CIR	clinical investigation room
CO	cardiac output (ml/sec)
HIP	hydrostatic indifference point
HR	heart rate (beats/min)
HREB	human research ethics board
IVC	inferior vena cava
PLE	passive leg elevation
RT	resting time
SD	standard deviation
SP	sequence of postures
SV	stroke volume (ml/beat)
SVR	systemic vascular resistance (mmHg/ml/sec)
TREND	Trendelenburg

English Symbols

a	radius of the blood vessel (mm)
Re	Reynolds number
C	compliance of the blood vessel (ml/mmHg)
D	diameter of the blood vessel (mm)
E	Young's modulus of elasticity (mmHg)
g	acceleration due to gravity (m/s^2)
h	height (mm)
h_f	head loss (mm)
h_w	vessel-wall thickness (mm)
l	length of the blood vessel (mm)
P	pressure (mmHg)
P_{MAP}	mean arterial pressure (mmHg)
P_{CV}	central venous pressure (mmHg)
P_{SBP}	systolic blood pressure (mmHg)
P_{DBP}	diastolic blood pressure (mmHg)
q	flow rate (ml/sec)
Q	flow rate (ml/sec)
R	viscous resistance (mmHg/ml/sec)
t	time (sec)
U	average velocity (m/sec)
V	volume (mm^3)

Greek Symbols

μ	dynamic viscosity ($N \text{ sec}/m^2$)
ρ	fluid density (kg/m^3)

ν	kinematic viscosity (m ² /sec)
τ	shear stress (N/m ²)
τ_w	wall shear stress (N/m ²)
γ	rate of shear (1/sec)

Subscripts

j	index identifying a computational block
i	index identifying an element within a computational block

Chapter 1

Introduction

Studying blood pressure and blood flow in the cardiovascular system due to change of body posture and particularly passive leg elevation has been a topic of interest both to theoretical and clinical investigators. Such research is essential since cardiovascular diseases continue to account for the majority of deaths in developed countries, most of which are associated with abnormal blood flow in the arteries.

The purpose of the research presented in this thesis is to obtain a thorough understanding of the hemodynamic changes that occur in the cardiovascular system upon passive leg elevation. The motivation for the experimental study arises from previous and present efforts to examine the effects of passive leg elevation on the blood pressure at the heart in normotensive or hypertensive subjects. At the present time there is no consensus on how the passive elevation of the legs from the supine position affects the blood pressure at the heart level. A reliable answer to this question is deemed useful for patients with cardiovascular diseases since such information might provide guidance on the optimum posture to assume, that would lead to the minimum load on the heart during their recovery in the hospital. Inconsistent results in previous experimental studies on the subject are thought to be related to the limited number of subjects used in the experiments; variations in the experimental procedures amongst the studies, and incomplete documentation of such procedures; and inadequate precision of the equipment used for the measurements, with often insufficient appreciation of the precision of the

measurement results. The present experimental study has thus been designed to alleviate the noted shortcomings as much as possible.

Chapter two is devoted to provide sufficient background on the evolution of blood pressure and its measurements for the purpose of choosing suitable measuring equipment. It also sheds light on all the factors that affect blood pressure and hence should be taken carefully into consideration in blood pressure studies.

Chapter three describes the experimental part of the study. It illustrates the subject group, the equipment used for the measurements, and the measurement procedure.

Chapter four presents a computational model of the cardiovascular system. In order to assist in explaining the experimental results and to gain helpful insights into the effects of passive leg elevation on the blood circulation, this computational model of the cardiovascular system was developed.

The model constitutes a one-dimensional fluid dynamical representation of the cardiovascular system, for it is not possible to make a computationally feasible model of the entire domain in any higher dimension. The blood is viewed as an incompressible Newtonian fluid and the vessels as elastic. The model is split into three parts: the first comprises the arterial part, wherein the arteries are divided into a finite number of elements with viscous, inertia, pressure and gravity forces accounted for; the second the arteriole, capillary and venule network being purely resistive elements; the third is the venous part wherein inertia and viscous effects are neglected.

Chapter five presents the experimental and the computational results including a comparison with both data and other experiments.

Literature Survey on Blood Pressure and its Measurement

2.1 Definition of Blood Pressure

Blood pressure is the force of blood against the walls of the arteries caused when the heart pumps blood to the body parts. The pressure recorded during cardiac ejection is called systolic, P_{SBP} , and correspondingly pressure during ventricular rest is called diastolic, P_{DBP} . The difference between P_{SBP} and P_{DBP} is called the pulse pressure as shown in Figure 2.1.

Figure 2.1 Blood pressure as measured in various compartments of the systemic circulation. Reproduced from Silverthorn (1998).

The mean arterial pressure, P_{MAP} , is the average pressure during a cardiac cycle and is estimated by (Levick, 2003):

$$P_{MAP} = CO \times SVR + P_{CV} \quad (2.1)$$

where CO is the cardiac output, SVR is the systemic vascular resistance, and P_{CV} is the central venous pressure. Eq. 2.1 can be derived from the steady-flow, steady state energy equation as demonstrated in Appendix B.

In medical practice, for practical reasons mean arterial pressure is not determined through Eq. 2.1, but rather by direct or indirect measurements of arterial pressure, and is approximated by:

$$P_{MAP} \approx P_{DBP} + \frac{1}{3}(\text{Pulse Pressure}) \quad (2.2)$$

2.2 Function of Blood Pressure

Blood pressure is needed to counter the forces that resist blood flow through the cardiovascular system. Viscous and inertial forces constitute the resisting forces. It is essential that adequate and uninterrupted blood supply is maintained to all body parts. One organ that is unique in terms of blood supply requirements is the brain. Unlike other organs, its need never varies, and remains at around 750 *ml/min* of freshly oxygenated blood in an adult, regardless of whether the person is sleeping, awake, working, or relaxing (Guyton and Hall, 2000).

Temporary interference with the brain's supply causes a fainting attack. Although other organs may have non-constant blood flow rate requirements, it is necessary for the blood pressure, hence blood supply to remain within a certain range for each organ. Abnormally low blood pressure causes symptoms such as lethargy, weakness, fatigue, and dizziness. Abnormally high blood pressure on the other hand, increases the risk of heart attack, stroke, kidney failure, and development of atherosclerosis* (Moore *et al.*, 2003).

2.3 Regulation of Blood Pressure

The mean arterial blood pressure is regulated by the human body to stay at a value of about 100 mmHg when the body is at rest (Guyton and Hall, 2000). The regulation takes place through four mechanisms: nervous-system mechanisms, the capillary-fluid-shift mechanism, the kidney excretory mechanism, and hormonal mechanisms (Guyton, 1969).

2.3.1 Nervous System Blood Pressure Regulation

Blood vessels in the human body are connected to sympathetic nerve fibers as shown in Figure 2.2. If stimulated, these fibers cause constriction of blood vessels. Constriction of blood vessels increases resistance to blood flow and therefore increases mean arterial pressure (Levick, 2003).

* Hardening of the arteries.

Figure 2.2 Sympathetic nervous control of blood circulation.
Reproduced from Guyton and Hall (2000).

2.3.1.1 Sympathetic Effects on the Circulation

The vasomotor center consists of three major areas as shown in Figure 2.2: the vasoconstrictor, the vasodilator, and the cardioinhibitor. Sympathetic impulses are transmitted from the vasomotor center down the spinal cord into the sympathetic chains as shown in Figure 2.2, and then to the heart and blood vessels via the cardiac accelerator

nerves as shown in Figure 2.3. These impulses innervate the atria and the ventricle, increasing the strength of heart contraction. Moreover, the cardiac accelerator nerves release norepinephrine, which increases the heart rate and subsequently mean arterial pressure. These sympathetic impulses cause vasoconstriction of blood vessels that increases total peripheral resistance, which in likewise fashion increases mean arterial pressure (Berne and Levy, 1981).

Figure 2.3 Autonomic nervous-system regulation of the heart.
Reproduced from Tortora and Grabowski (2003).

2.3.1.2 Parasympathetic Effects on the Circulation

The parasympathetic nervous system plays a minor role in the control of blood circulation (Berne and Levy, 1981). Parasympathetic impulses reach the heart through the vagus nerves shown in Figure 2.3. When the sympathetic fibers are stimulated the parasympathetic fibers are inhibited, and vice versa. Parasympathetic stimulation has the opposite effect on the heart compared to the effect of sympathetic stimulation: parasympathetic stimulation decreases the heart rate and the heart's strength of contraction (Levick, 2003).

2.3.1.3 Vasomotor Tone

Partial contraction of blood vessels due to continuous impulses sent from the vasoconstrictor area of the vasomotor center is known as the vasomotor tone (Berne and Levy, 1981). The sympathetic system decreases mean arterial pressure by decreasing the number of impulses transmitted to the blood vessels. Similarly, the sympathetic system increases mean arterial pressure by increasing the number of impulses above those normally transmitted.

The vasomotor tone plays an important role in regulating blood pressure as can be seen from Figure 2.4. This figure shows the trend in the arterial pressure of an animal with the nerves coming from the spinal cord blocked through local anesthesia. Mean arterial pressure is observed to drop to 50 mmHg, which is the normal pressure in the circulatory system in absence of vasomotor tone. At this state, injecting the animal with

norepinephrine is shown to temporarily raise the arterial blood pressure (Guyton and Hall, 2000).

Figure 2.4 Effect of spinal anesthesia and norepinephrine injections on arterial blood pressure in an animal. Reproduced from Guyton and Hall (2000).

2.3.1.4 The Baroreceptor Pressure Control System

Baroreceptors are sensors located in the major arteries of the body, especially in the aortic arch and the carotid sinus as shown in Figure 2.5. Baroreceptors are stimulated when stretched due to blood pressure changes (Rushmer, 1976). In response to increased number of impulses from the baroreceptors, the vasomotor center increases parasympathetic stimulation and decreases sympathetic stimulation, which results in decreased heart rate, cardiac output, and vascular resistance. Consequently, mean arterial pressure decreases. Similarly, when blood pressure in the arteries drops, the baroreceptors

lower the number of impulses sent, and the vasomotor center reacts accordingly to raise

P_{MAP} .

Figure 2.5 Location of the baroreceptors and chemoreceptors in the region of the aorta and the carotid artery. Reproduced from Milnor (1974).

2.3.1.5 The Chemoreceptor Pressure Control System

Chemoreceptors are nerve endings located mainly in the walls of the carotid arteries, the aorta, and the medullary area of the brainstem. Chemoreceptors monitor the blood levels of O_2 , CO_2 , and H^+ . They are stimulated by hypoxia (low level of O_2), hypercapnia (excess CO_2), and acidosis (excess H^+) (Tortora and Grabowski, 2003). Upon

stimulation, chemoreceptor reflexes send impulses to the cardiovascular center. The cardiovascular center increases sympathetic stimulation of blood vessels, thereby causing vasoconstriction, and increasing blood pressure back to normal. Chemoreceptors are not strongly stimulated until arterial pressure has fallen below 80 mmHg (Guyton and Hall, 2000).

2.3.2 Blood Pressure Regulation by Capillary Fluid Shift

The capillary-fluid-shift mechanism is a non-nervous mechanism that helps in regulating arterial pressure when blood volume tends to become either too low or too high (Guyton, 1969). An increase in blood volume increases blood pressure in capillaries and in arteries. Increased capillary pressure causes fluid to leak out of the circulation into the interstitial spaces. Conversely, a decrease in blood volume decreases blood pressure in capillaries. The decreased capillary pressure causes fluid to be pulled from the interstitial spaces back into circulation due to the osmotic pressure effect of some proteins in the plasma. The capillary fluid shift mechanism is slower to regulate arterial blood pressure than the nervous mechanisms mentioned in the preceding sections. This mechanism requires from 30 minutes to several hours to achieve the desired effect of readjusting the arterial pressure back to normal levels (Guyton and Hall, 2000).

2.3.3 Blood Pressure Regulation by Kidneys

The kidneys regulate the arterial pressure by adjusting the overall blood volume in the body. Blood volume in the body is adjusted by returning water to the blood or eliminating it in the urine. Kidneys perceive any drop in the arterial pressure, and consequently decrease the amount of water secreted in the urine. Steadily, over several hours, the blood volume and thus mean arterial pressure is thereby adjusted back to normal levels (Levick, 2003).

2.3.4 Blood Pressure Regulation by Hormonal Mechanisms

The kidneys also regulate arterial blood pressure by means of hormonal mechanisms. When arterial blood pressure drops substantially, the kidneys secrete a hormone, renin, into the blood. Renin converts one of the plasma proteins to angiotensin. Angiotensin causes vasoconstriction of blood vessels, which brings arterial blood pressure back to normal levels. Furthermore, angiotensin stimulates the secretion of aldosterone, which decreases kidney outputs of salt and water. The amounts of salt and water in the body, in turn, help adjust blood volumes and interstitial fluids in the body. Elevated arterial pressure reverses this mechanism so that fluid volume and arterial pressure decrease (Marieb, 2004).

The remarkable role that kidneys play in the long-term regulation of arterial pressure is demonstrated in Figure 2.6. When a clamp is placed on the renal arteries of the kidneys,

arterial blood pressure rises and continues to rise for several days (Guyton and Hall, 2000). When the constrictions are removed, the arterial blood pressure falls back to normal within a few days.

Figure 2.6 Effect of constricting the renal arteries and days later releasing the constriction on blood pressure. Reproduced from Guyton and Hall (2000).

2.4 Measurement of Blood Pressure

Blood pressure measurement is a clinical procedure performed by physicians, nurses, medical students and even by non specialists at office or at home. Blood pressure

measurement techniques are classified into two categories: direct and indirect techniques. Blood pressure sensors detect mechanical signals of blood pressure waves and convert them into electric signals for further processing and transmission (Geddes, 1970). Before explaining each technique, it is useful to provide the historical evolution of blood pressure measurement.

2.4.1 History of Blood Pressure Measurement

The ancient Egyptians (1500 BC) knew that blood flowed through the body and were aware of the pulsations in different regions of the body (Gispen, 1974). Galen (129-199 AD) believed that blood is created constantly in the liver and is circulated to all body organs through the veins as shown in Figure 2.7. Some of this blood is believed to arrive at the right ventricle from where it diffuses through the septum into the left ventricle, where it catches vital spirits and is then distributed through the arteries to the body organs. Galen's ideas were believed for a thousand years until the seventeenth century. In 1628, Harvey proposed that there is a finite amount of blood that circulates in the body in one direction only, but his views were faced with a lot of resistance and criticism. Hales (1733) was the first to directly record blood pressure by inserting a brass pipe into the artery of a horse as shown in Figure 2.8; the brass pipe was connected to a glass tube of 7.5 *ft* height. Hales observed the blood rising in the pipe and concluded that this must be due to the pressure of the blood being greater than ambient pressure. His discovery was

Figure 2.8 The Reverend Hales demonstrating blood pressure in a horse. Reproduced from Sandwich (1980).

Poiseuille (1828) measured blood pressure in a variety of arteries in animals invasively by connecting a U-shaped mercury manometer with leaden cannulas. Ludwig (1847) was the first to introduce a human blood pressure device by inventing the kymograph. The kymograph consisted of a U-shaped manometer tube connected with a brass pipe cannula into the artery as shown in Figure 2.9. The manometer tube had an ivory float onto which a rod with a quill was attached. This quill would sketch onto a rotating drum, and so

came the name 'Kymograph' which means 'wave writer' in Greek. However, still at that stage, blood pressure could only be measured invasively.

Figure 2.9 Ludwig kymograph.
Reproduced from Booth (1977).

The first non-invasive blood-pressure measurement device was introduced in 1855 by Vierordt who invented the sphygmograph. Vierordt's sphygmograph, shown in Figure 2.10, consisted of a levered system that recorded the movements of a weight resting on the radial artery (O'Brien and O'Malley, 1991). This instrument was not accurate since it gave an estimate of blood pressure by determining the weight required to obliterate the pulse (Booth, 1977). Marey (1863) modified Vierordt's sphygmograph by replacing the lever system and weights with a metal spring the tip of which must be placed over the

radial artery as shown in Figure 2.11, and a recording system that wrote on smoked paper driven by a clockwork mechanism. An adjustable screw altered the pressure exerted by the spring. Marey's design could accurately measure the pulse wave, but was unreliable in determining the blood pressure (O'Brien and O'Malley, 1991). The principal shortcoming of Marey's sphygmograph was the pressure screw, which altered the pressure that the spring exerted on the artery, as it was adjusted to achieve the best pulse trace. The pressure is therefore unknown, and can never be duplicated on a subsequent occasion (Lawrence, 1978).

Figure 2.10 Vierordt sphygmograph.
Reproduced from Snellen (1980).

Figure 2.11 Marey sphygmograph.
Reproduced from Snellen (1980).

A more accurate and lighter device, shown in Figure 2.12, developed by Dudgeon (1882) replaced Marey's sphygmograph. A calibrated screw exerted pressure over the radial artery, and a clockwork motor drove a strip of smoked paper under an oscillatory metal tip to produce the pulse wave.

Figure 2.12 Dudgeon sphygmograph.
Reproduced from Dudgeon (1908).

The sphygmograph gave accurate pulse wave measurements, but unreliable blood pressure readings and thus, was considered a disappointment (Lawrence, 1979).

Von Basch (1880) developed the sphygmomanometer shown in Figure 2.13. Von Basch's sphygmomanometer was considered to be the first device for precise clinical blood pressure measurements. It consisted of a rubber bag filled with water and a mercury manometer attached to it. The bag was pressed over the wrist until no pulsations can be felt below, and the height of the mercury manometer at that instant corresponded to systolic pressure. Later on, Von Basch modified this device by replacing the mercury manometer with an aneroid one, and eventually improved it to portable dimensions appropriate for clinical use as shown in Figure 2.14.

Figure 2.13 Von Basch sphygmomanometer.
Reproduced from Janeway (1904).

Figure 2.14 Indicator part of portable Von Basch sphygmomanometer.
Reproduced from de Moulin (1981).

Potain (1889) improved Basch's sphygmomanometer by replacing the liquid contained in the pressure pad with air, and redesigning the pressure pad itself.

Marey (1876) developed the oscillometric method. With deflation of a previously inflated blood pressure cuff, the point of maximal oscillation corresponds to mean arterial pressure, the onset of oscillations to systolic pressure, and below this, the minimal oscillations to diastolic pressure.

Riva-Rocci (1896) developed the mercury sphygmomanometer. It consisted of an inflatable cuff encircling the upper arm to constrict the brachial artery. The cuff was connected to a mercury manometer to measure the pressure exerted onto the arm as shown in Figure 2.15. A pump inflated the cuff until the radial pulse disappeared and the observer recorded the pressure on the mercury manometer which was taken to be systolic pressure. This was the only parameter that could be measured using this device at that time.

Figure 2.15 Riva-Rocci sphygmomanometer.
Reproduced from Janeway (1904).

Korotkoff (1905) introduced auscultation into blood pressure measurement techniques. Korotkoff noticed that there were specific sounds produced at certain points during cuff inflation and deflation. These sounds corresponded to systolic and diastolic pressures, respectively. Korotkoff's technique required the use of a stethoscope placed over the brachial artery to listen to the sounds of blood flowing through it. Since Korotkoff's method in 1905, there has been little development of blood pressure measuring techniques. As a result, most modern blood-pressure measurement devices are based on direct, or indirect auscultatory or oscillometric techniques. Thus, it is useful to explain the physical characteristics of these techniques in greater detail.

2.4.2 Physical Characteristics of Direct Techniques

The direct measurement technique is considered to be the most accurate method of determining blood pressure. This technique is invasive as shown in Figure 2.16, since it involves placing a catheter into an artery. The connecting tubes and the stopcocks connect the intravascular catheter to the monitoring system (Nara *et al.*, 1989). A pressure transducer then converts the mechanical signal of a pressure wave into electrical signal through movement of a displaceable sensing diaphragm. The pressure transducer should be located at the heart level to avoid bias of hydrostatic pressure in blood pressure recordings. The continuous flush device helps prevent blood from clotting in the catheter by continuously flushing fluid through the system at a rate 1-3 ml/hr. An amplifier is used

to increase the low voltage signal from the pressure transducer to a waveform signal that can be displayed on an oscilloscope, and it may include electronic filters to filter out unwanted physiologic noise. The advantage of this system is that pressure is constantly monitored beat-by-beat, and a pressure waveform can be displayed. Patients with invasive arterial monitoring require very close supervision, as there is a danger of severe bleeding if the line becomes disconnected. This invasive measurement technique is generally reserved for critically ill patients where rapid variations in blood pressure are anticipated (O'Brien and O'Malley, 1991).

Figure 2.16 Typical direct pressure monitoring system.
Reproduced from Nara *et al.* (1989).

2.4.3 Physical Characteristics of Indirect Techniques

Indirect measurements of blood pressure are non-invasive in nature. A cuff is usually placed around the upper arm for its closeness to the heart, and is rapidly inflated to a pressure about 30 mmHg greater than the estimated systolic pressure, occluding blood flow in the brachial artery. The cuff is then gradually deflated, while a detector system determines the point at which blood flow is restored to the limb. The detector system may detect sound, oscillation, or blood flow underneath the cuff. Based on the detection method, several indirect means of measurements have been developed. In the subsequent section, the auscultatory, oscillometric, flush and Doppler ultra-sound indirect methods are reviewed.

2.4.3.1 The Auscultatory Method

This technique is the one generally employed clinically. It involves compression of the brachial artery under an elastic, inflatable cuff, and registration of blood pressure levels using a manometer and a stethoscope. Korotkoff sounds heard during auscultation over the brachial artery distal to the cuff are taken as the criteria for the systolic and diastolic pressures as shown in Figure 2.17. These sounds are generated by the turbulent flow of blood and the oscillations of the arterial wall (AHA, 2005). As the pressure in the cuff is gradually lowered, the sound undergoes a series of changes in quality and intensity as shown in Figure 2.18.

Figure 2.17 Auscultatory blood pressure measurement technique.
Reproduced from Nara *et al.* (1989).

Four phases of the sound, each having its distinctive character, presented in Table 2.1, may be heard in succession in the normal subject, as the pressure is gradually reduced. By knowing the correlation between sounds and phase of the blood pressure cycle, one is able to deduce the systolic pressure and the diastolic pressure from the cuff pressure

values. When the Korotkoff sounds start, phase I, a reading is taken from the manometer and noted as systolic pressure. As the cuff pressure falls, these sounds become quieter and finally disappear altogether in phase V. At this moment in time, the cuff pressure reading is taken again as the diastolic pressure (AHA, 2005).

Figure 2.18 Characteristics of Korotkoff sounds.
Reproduced from Geddes (1970).

As shown by the sound intensity curve in Figure 2.18, the Korotkoff sounds may temporarily become inaudible in the absence of arrhythmias* during the latter part of Phase II. This is known as the auscultatory gap and was recognized by Krylov in 1906 only one year after the discovery of the auscultatory technique by Korotkoff in 1905 (King, 1963). This gap may cover a range of 40 mmHg and may cause marked underestimation of systolic pressure if the cuff pressure is increased only to the level at which the sounds are absent. Venous congestion associated with slow cuff deflation or rapidly repeated occlusions increases the occurrence of the auscultatory gap. Rapid cuff deflation at a rate of 2 to 3 mmHg/sec, allowing 2 to 3 minutes to elapse between determinations, and raising the arm to promote venous drainage reduce or eliminate the presence of auscultatory gap.

* Abnormal heart rhythms.

Table 2.1 Korotkoff sounds during blood pressure recording by stethoscope.

Phase	Blood pressure sounds
I	Sudden appearance of a clear sharp tapping sound growing louder during the succeeding 10 to 14 mmHg fall in pressure.
II	The sound takes on a murmuring quality during the next 15 to 20 mmHg fall in pressure.
III	Sound changes little in quality but becomes clearer and louder during the next 5 to 7 mmHg fall in pressure.
IV	Muffled quality lasting throughout the next 5 to 6 mmHg fall; after this all sound disappears.
V	Point at which sounds disappear.

2.4.3.2 The Oscillometric Method

Unlike the auscultatory technique, this technique does not rely on sounds, and is based on the transmission of intra-arterial pulsation to the occluding cuff surrounding the upper arm as shown in Figure 2.19. As the cuff deflates, the artery walls begin to oscillate as the blood flows turbulently through the artery. These oscillations are detected through a pressure sensor that is monitoring cuff pressure. The oscillations reach maximum amplitude which is taken to be mean arterial pressure. The point above mean arterial pressure at which oscillations begin to rapidly change in magnitude correlates to systolic pressure. The point below mean arterial pressure at which oscillations rapidly decrease correlates to diastolic pressure (Geddes, 1984; Mauck *et al.*, 1980). The pressure is then

gradually decreased until the cuff becomes fully deflated. The pressure oscillations are detectable throughout the whole measurement, even at cuff pressures higher than systolic pressure or lower than diastolic pressure.

Oscillometric methods eliminate the need to detect Korotkoff sounds hence, can be used in a noisy environment. However, vibrations and muscle tremors can affect the accuracy of oscillometric devices.

Figure 2.19 Relation between the arterial movement and its transmission to the cuff. Reproduced from Yamakoshi (1991).

2.4.3.3 The Flush Method

The flush method has found practical application in newborn infants, and is applied to the foot or to the finger of the hand, as shown in Figure 2.20. A metal tube (A) consisting of an inflatable annular bladder is placed on a finger. The finger is then pushed without applied pressure into the small cylinder (B) which has a rubber membrane stretched

across its top (Geddes, 1970). The elasticity of this membrane compresses the tip of the finger and forces the blood out of the extremity below the cuff; the cuff is inflated above systolic pressure and the finger is removed from the cylinder. The cuff is then slowly deflated and the systolic pressure is indicated when the pale, bloodless skin flushes (Moss, 1978). Applied to the adult finger, this method gives systolic pressure values below the auscultatory method and is unreliable if vasoconstriction is induced by emotional or temperature changes.

Figure 2.20 The flush method applied to a finger.
Reproduced from Norris (1916).

2.4.3.4 The Doppler Ultra-Sound Method

The Doppler ultra-sound method is used in cases where Korotkoff sounds are hard to detect such as in noisy places and in cases of shock (George *et al.*, 1975). This method involves placing two piezoelectric crystals over the brachial artery beneath the cuff as shown in Figure 2.21. The first crystal transmits ultrasound waves of about 8 MHz towards the arm surface over the brachial artery while the other crystal receives the reflected wave from the brachial artery and the surrounding tissue (Stegall *et al.*, 1968). In absence of arterial vessel-wall motion, the Doppler crystal reflects the wave with no change in frequency. Vibration in the arterial wall causes changes in the reflected ultrasonic frequency which is read as the systolic pressure. When pronounced decrease in arterial vessel wall motion occurs, the diastolic pressure is recorded.

Figure 2.21 Ultrasound measurement technique.
Reproduced from Stegall *et al.* (1968).

2.4.4 Comparison between Direct and Indirect Techniques

Table 2.1 summarizes the result of several studies that compared the auscultatory indirect technique with the direct intra-arterial technique. As is seen from this table, the auscultatory method tends to give systolic pressure values several mmHg lower than the intra-arterial blood pressure values, and diastolic pressure values slightly higher than the intra-arterial blood pressure values.

Table 2.2 Differences between the auscultatory and direct measurement techniques (Mean $\pm$ SD) reported in a number of studies.

Author(s)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Ragan and Bordley (1941)	-0.4 ± 12.1	8.4 ± 8.8
Holland and Humerfelt (1962)	-24.6 ± 14.0	-13.1 ± 9.5
Raftery and Ward (1968)	-5.4 ± 11.6	6.6 ± 9.8
Nielsen (1983)	-8.8 ± 9.0	10.8 ± 6.8
Russell <i>et al.</i> (1989)	-7.6 ± 12.1	7.7 ± 8.3
Gravlee and Brockschmidt (1990)	-9 ± 9.0	8.0 ± 7.0
Weisser <i>et al.</i> (1990)	-5 ± 10.0	15.8 ± 8.0
Byra-Cook <i>et al.</i> (1990)	-7.7 ± 8.9	3.2 ± 6.5
Gorback <i>et al.</i> (1991)	-8.8 ± 11.2	1.6 ± 8.9
Tochikubo <i>et al.</i> (1997)	-7.4 ± 5.6	3.0 ± 7.1

Although the direct technique is considered the standard to which all other indirect techniques are compared, differences exist between these two measurement categories. The direct technique measures the forces at the leading edge of the pressure wave moving down the column of blood in the artery, while the indirect technique measures the lateral forces on the wall of the artery (O'Brien and O'Malley, 1991).

One study that compared the two techniques, and took into account almost all of the factors that can alter the results, is the work of Raftery and Ward (1968). The study was performed on female subjects, on the same arm, at the same time, and under the same conditions. The results showed wide variation between the two measurement techniques. The standard deviation is within 24 mmHg for systolic pressure and as much as 16 mmHg for diastolic pressure as shown in Figure 2.22.

Figure 2.22 Comparison of direct and indirect blood pressures.
Reproduced from Raftery and Ward (1968).

Van Egmond *et al.* (1993) evaluated the accuracy of 30 home blood-pressure monitors in comparison with a direct brachial arterial standard. Twenty-seven monitors were based on the auscultatory technique and three were based on the oscillometric technique. The authors found average offsets of all tested devices amounted to +11.7 mmHg for systolic pressure and -1.6 mmHg for diastolic pressure.

Although the direct technique is more accurate than the indirect technique, due to its invasive nature it will not be considered when choosing an appropriate measuring device

for the present study. Thus, only indirect measurement devices are reviewed for their accuracy in the next section.

2.4.5 Accuracy of Indirect Measurement Devices

The accuracy of blood pressure measurements is of great importance for appropriate therapeutic decisions and for management of hypertensive patients. A 5 mmHg rise in blood pressure may sound trivial, but it results in 21 % rise in the incidence of heart disease and a 34 % rise in the incidence of brain attacks. Cook *et al.* (1995) showed that a 5 mmHg reduction in diastolic pressure would reduce coronary artery disease by 16 % and stroke by 38 %. Therefore, it is essential to research the accuracy of the different indirect measuring devices.

2.4.5.1 Conventional Sphygmomanometers

The utilization of conventional sphygmomanometers is based on the auscultatory technique using a manometer and a stethoscope. The manometer can be either mercury column, or aneroid. The mercury column sphygmomanometer is the golden standard by which the other devices are tested and validated. The main problems that are associated with mercury column are poor visibility of the mercury meniscus in the mercury manometer, faulty calibration of the mercury column, and illegibility of the scale (O'Brien and O'Malley, 1991). Recently, because of environmental concerns about the toxicity of mercury, many countries have banned mercury in sphygmomanometers

(AHA, 2005). In the United States, all hospitals will eliminate mercury by the end of year 2005. However, there is an argument to retain mercury until a satisfactory substitute can be found (Jones *et al.*, 2001).

The aneroid sphygmomanometer is a substitute to mercury column sphygmomanometer, where the mercury column is replaced by a mechanical spring. Unlike the mercury sphygmomanometer, there is considerable variation in the accuracy of these devices even when they are new. Moreover, there are significant differences in the accuracy of different brands (AHA, 2005). Surveys of such devices have shown them to be frequently inaccurate. Their inaccuracy can reach levels up to 44 % (Mion and Pierin, 1998). Fisher (1978) studied the accuracy of 3390 aneroid sphygmomanometers which were calibrated against mercury sphygmomanometers. The author reported differences between aneroid and mercury column sphygmomanometers exceeding ± 3 mmHg in 22 % of the aneroid instruments at 60 mmHg, in 25 % at 120 mmHg, in 29 % at 180 mmHg, and in 34 % at 240 mmHg. Another study performed by Bailey and Bauer (1993) showed that aneroid sphygmomanometers can be as much as 22-60 % inaccurate, while mercury sphygmomanometer can be as much as 2-8 % inaccurate.

Another alternative for the conventional sphygmomanometer is the hybrid sphygmomanometer, which is still under investigation. The hybrid sphygmomanometer combines the features of both electronic and mercury devices (Pickering, 2002). A potential advantage of the hybrid sphygmomanometer is that it is based on the mercury auscultatory method but does not use mercury (AHA, 2005). In this sphygmomanometer, the mercury column is replaced with a transducer. The readings are in principle

equivalent to mercury readings. The device eliminates observer bias; it can be programmed to prevent excessive cuff deflation rate; and it can provide a digital output.

2.4.5.2 Ambulatory Blood Pressure Devices

Ambulatory blood pressure devices monitor blood pressure readings during normal daily activities. They include an upper arm cuff, an electronic monitor with a pressure sensor, and an electrically driven pump that is attached to the patient's belt. The unit is programmed to record the patient's blood pressure over a 24-hour period during normal activities and stores the data for future analysis. Two indirect kinds exist for ambulatory blood pressure monitoring (ABPM): (1) indirect intermittent and (2) indirect continuous.

1. The indirect intermittent ABPM is based on either the auscultatory or the oscillometric techniques.

Auscultatory ABPM devices use one or two microphones in an occlusive arm cuff or taped over the brachial artery to detect Korotkoff sounds and register blood pressure values. The microphones may be very sensitive to record Korotkoff sounds that are not audible to the human ear, resulting in systematic error mainly in the form of high systolic pressure and low diastolic pressure readings (White, 1990).

Oscillometric ABPM devices analyze oscillations as per Section 2.4.3.2. This measurement technique is not very accurate, for pulse pressure is influenced by

cardiac output, peripheral resistance, and abnormalities of the artery (Casadei *et al.*, 1988; Santucci *et al.*, 1988).

2. The indirect continuous ABPM devices, using mostly finger devices, detect the arterial pulsations under a cuff. The systolic pressure and the mean arterial pressures are estimated as the cuff pressures at which finger arterial oscillations commence and become maximal, while the diastolic pressure is derived.

With the use of ABPM devices, one is able to observe the numerous situational and periodic fluctuations of the blood pressure profile (Pickering *et al.*, 1982). These devices play a crucial role in assessing the efficacy of antihypertensive drugs and the validation of drug treatment (Grin *et al.*, 1993). It is also useful for identifying patients with white-coat hypertension also known as isolated clinic hypertension. This is a condition in which blood pressure is persistently elevated in the presence of a doctor, but falls to normal values when the patient leaves the medical environment (AHA, 2005). In spite of its advantages, the cost and practicality of ABPM devices are likely to hinder their replacement of the mercury sphygmomanometer in most applications.

2.4.5.3 Electronic Sphygmomanometers

Electronic sphygmomanometers include semi-automated and automated blood pressure devices and rely on the auscultatory technique (e.g. Remler M2000; Copal UA-231 and UA-251), or the oscillometric technique (e.g. Dinamap). A semi-automated or automated blood pressure device includes an electronic monitor with a pressure sensor, a digital

display, and an upper arm cuff. The semi-automated device includes a hand bulb to manually inflate the cuff, while the automated device includes an electrically driven pump that automatically inflates the cuff on operation of the start button to a preset inflation pressure or the appropriate level, about 30 mmHg above the estimated systolic pressure reading. Electronic sphygmomanometers automatically deflate the cuff and display the values of systolic, diastolic and heart rate. In the auscultatory electronic sphygmomanometers, Korotkoff sounds are amplified by means of piezoelectric microphones mounted within or below the cuff.

The rapidly increasing number of new electronic sphygmomanometers and the necessity of replacing the mercury sphygmomanometer have raised concerns about the accuracy of the blood pressure values measured by these monitors. As a result, several protocols for validation of these devices have been developed.

The Association for the Advancement of Medical Instrumentation and American National Standard Institute, AAMI/ANSI, published a national protocol, SP10, in 1987 (AAMI, 1987) for evaluating electronic sphygmomanometers, which was revised in 1992 (AAMI, 1992) and again in 2002 (AAMI, 2002). This protocol presents the basic requirements for these devices such as manufacturer test methods, performance, safety, and labeling. The SP10 standard requires that the mean difference between the systolic and diastolic pressure measurements of the test device and the reference standard be ± 5 mmHg or less, and the standard deviation be 8 mmHg or less. The reference standard is the mercury sphygmomanometer, but the AAMI also supports the use of invasive methods for the validation of electronic sphygmomanometers.

Similarly, the British Hypertension Society, BHS, published a protocol for testing the accuracy of electronic sphygmomanometers in 1990 (O'Brien *et al.*, 1990) and revised it in 1993 (O'Brien *et al.*, 1993). Their accuracy criteria is based on a grading system (i.e. A, B, C or D) that depends on the percentages of test device measurements differing from the mercury sphygmomanometer measurements falling within 5, 10, and 15 mmHg for systolic and diastolic pressures as shown in Table 2.3. The BHS depends mainly on mercury sphygmomanometer as the reference standard against which all other devices should be tested, and puts particular emphasis on training of observers. Unlike the AAMI, the BHS does not recommend comparison with the intra-arterial blood pressure values.

Table 2.3 British Hypertension Society grading criteria.

Grading Criteria of the BHS Protocol			
Difference between the standard and the test device (mmHg)			
	≤ 5	≤ 10	≤ 15
Grade	Percentage of blood pressure readings		
A	60	85	95
B	50	75	90
C	40	65	85
D	Worse than C		

In order to be validated, both the AAMI and the BHS require that the blood pressure monitor be tested by two trained observers with 85 subjects. As a result, the validation study is difficult to perform (AHA, 2005). A more recent and easier-to-perform international protocol is published by the European Society of Hypertension (O'Brien *et al.*, 2002). This protocol requires comparison of four readings from a device being tested with five readings from the mercury sphygmomanometer obtained by each of the two

trained observers. The device is approved if both systolic and diastolic readings fall within 5 mmHg for at least 50 % of the readings.

Based upon these validation protocols, a survey of most commonly-available blood pressure monitors that were validated was compiled by the author of this thesis and is listed in Appendix C.

Based on this analysis, the mercury sphygmomanometer is the recommended device for accurate blood pressure measurements.

2.4.6 Sources of Error in Indirect Techniques

The procedure under which the measurement is performed is of equal importance as the accuracy of the measurement device. Several sources of error related to the procedure can interfere with the accuracy of measurement. These errors are related to the subject, the observer and / or the measurement technique itself, and will be discussed next.

2.4.6.1 Auscultatory Gap

The auscultatory gap can be a big source of error in the auscultatory electronic sphygmomanometers which function mainly by the Korotkoff sound technique. The presence of auscultatory gap can lead to registration of high diastolic and low systolic pressure.

2.4.6.2 Pseudohypertension

Pseudohypertension is an overestimation of blood pressure (Spence, 1990) and is common in the elderly patients (Kaplan, 1990), longstanding diabetes or chronic renal failure patients (AHA, 2005). It is caused when the brachial artery is stiff due to atherosclerosis and resists blood pressure cuff compression.

2.4.6.3 Arm Position

The position of the arm, on which most indirect blood pressure measurements techniques is performed, is an essential factor to consider. According to several studies (Kahn, 1919; Mitchell *et al.*, 1964; Stein, 1945; Webster *et al.*, 1984) the lower the arm of the subject is placed in comparison to heart level, the higher the systolic and diastolic pressures, as shown in Figure 2.23.

In the standing position, an average difference of about 10 mmHg was found in blood pressure measurements when the arm is placed parallel to the body, versus when the arm is horizontal at the midsternal level (Mariotti *et al.*, 1987; Mitchell *et al.*, 1964; Netea *et al.*, 2002; Webster *et al.*, 1984).

Similarly, in the sitting position, an average difference of 10 mmHg was noted in blood pressure measurements with the arm placed on the arm support of a common chair versus with the arm at the midsternal level (Netea *et al.*, 1999).

The position of the arm relative to the right-atrial level is also critical in the supine position. In this position, Ljungvall *et al.* (1989) recommended that a pillow, known as the heart pillow, be placed under the arm of patients, especially in obesity situations. Failure to follow this guideline can lead to differences up to 5.5 mmHg higher when the arm is placed on the bed than when it is placed on a pillow, hence at the right-atrial level. These pressure changes with respect to arm position are equivalent to hydrostatic pressure changes (Mitchell *et al.*, 1964). Published studies exist that have investigated the effect of posture on blood pressure without paying attention to the position of the arm with respect to the heart (Netea *et al.*, 1998). The results of such studies must be interpreted with caution.

In ABPM, the upper arm position variation can be a big source of error (Terent and Breig-Asberg, 1994). During day time this can be avoided by placing the arm parallel to the trunk (Pickering and Alpert, 1994). However large measurement errors will occur when the subject is sleeping on his/her side. Variations of as much as 10 mmHg have been noted when lying on the right side with the monitored arm above the heart level than when lying on the left side with the monitored arm below the heart level, as shown in Figure 2.24 (Schwan and Pavcek, 1989).

Figure 2.23 Effects of different arm positions on blood pressure.
Reproduced from Pickering and Alpert (1994).

122/67 mm Hg

117/64 mm Hg

107/55 mm Hg

117/67 mm Hg

Figure 2.24 Effect of different body postures on blood pressure.
Reproduced from Pickering and Alpert (1994).

2.4.6.4 Cuff Size

Different characteristics of blood pressure cuff can produce errors. The cuff contains an inflatable bladder within a restrictive cloth sheath. The width of the bladder determines the length of the artery to be occluded. A bladder that is not of suitable width for the arm circumference results in systematic errors. Too wide bladders underestimate blood pressure, while too narrow bladders overestimate blood pressure (AHA, 1988). The correct ratio of bladder width-to-arm circumference is 0.4 (Kirkendell *et al.*, 1967). When highly accurate blood pressure measurements are necessary for research studies, arm circumference should be measured and corrections made as per Table 2.4 (AHA, 1951).

The length of the bladder can also be a source of error. The bladder length determines the area of pressure applied to the artery. Too short bladder overestimates blood pressure readings, since the pressure is not fully transmitted to the artery (BHS, 1987). King (1963) suggested that the most accurate results are obtained if the length of the bladder completely encircles the arm. However, subsequent studies suggested that the bladder length should be 80 % of the arm circumference (AHA, 2005; Nielsen, 1983). In addition to these aspects, careful attention must be taken in placing the center of the bladder over the brachial artery (AHA, 2005).

Table 2.4 Recommended ideal arm circumference, arm circumference ranges, and correction of P_{SBP} and P_{DBP} in mmHg for adult cuffs of different bladder widths at various arm circumferences (AHA, 1951).

Bladder width (cm)	12		15		18	
Ideal arm circumference (cm)	30.0		37.5		45.0	
Arm circumference range (cm)	26 – 33		33 – 41		>41	
Arm circumference (cm)	P_{SBP}	P_{DBP}	P_{SBP}	P_{DBP}	P_{SBP}	P_{DBP}
26	+5	+3	+7	+5	+9	+5
28	+3	+2	+5	+4	+8	+5
30	0	0	+4	+3	+7	+4
32	-2	-1	+3	+2	+6	+4
34	-4	-3	+2	+1	+5	+3
36	-6	-4	0	+1	+5	+3
38	-8	-6	-1	0	+4	+2
40	-10	-7	-2	-1	+3	+1
42	-12	-9	-4	-2	+2	+1
44	-14	-10	-5	-3	1	0
46	-16	-11	-6	-3	0	1
48	-18	-13	-7	-4	-1	-1
50	-21	-14	-9	-5	-1	-1

2.4.6.5 Rate of Cuff Inflation and Deflation

In some patients, cuff inflation alone causes blood pressure to rise up to 40 / 36 mmHg (Mejia *et al.*, 1990; Veerman *et al.*, 1990). This might be due to the white coat hypertension and is thought to be uncommon. The cuff should be inflated up to 30 mmHg above the point at which the radial pulse disappears (AHA, 2005).

Slow deflation rates affect the timing and the intensity of Korotkoff sounds, thus resulting in higher diastolic pressure. Fast deflation rate underestimates systolic pressure and overestimates diastolic pressure. The recommended deflation rate is 2-3 mmHg/sec (King, 1963).

2.4.6.6 Mechanical Sources of Error

Several mechanical sources of error are associated with conventional sphygmomanometers. In the case of mercury sphygmomanometers, the upper curve of the meniscus of the mercury column should always read zero and should rise and fall freely during cuff inflation and deflation (AHA, 2005). When using aneroid sphygmomanometers, it is essential to calibrate them against a mercury column both at zero pressure and when pressure is applied to the cuff. Thus, regular inspection, repair, and calibration are required to ensure reliable blood pressure readings.

2.5 Effects of Different Activities on Blood Pressure

A reading that is representative of the subject's "true" blood pressure cannot be obtained if careful attention and consideration is not paid to the different physical and mental activities that influence those readings. For example, if environmental stimuli and changes in physical activities are minimized, such as during sleep, the blood pressure profile becomes relatively flat (Athanasias *et al.*, 1969). In contrast, the blood pressure profile is higher at work due to physical and mental activity (Clark *et al.*, 1987; Harshfield *et al.*, 1982; Pickering *et al.*, 1982) as illustrated in Figure 2.25. Hence, it is important to shed light on the most common activities and variables that affect blood pressure, and thus should be taken into consideration in blood-pressure studies.

Figure 2.25 Arterial pressure variation in a normotensive healthy subject during 24 hours. Reproduced from Bevan *et al.* (1969).

2.5.1 Exercise

Strenuous exercise increases the body's demand of oxygen. The increased muscular metabolism increases the concentrations of carbon dioxide, lactic acid, and other metabolites in the blood. These chemicals circulate to the vasomotor center and excite the muscle-controlling area in the brain. Upon excitation, the vasomotor center send impulses to the heart resulting in an increase in heart rate, and stroke volume, and consequently cardiac output which increases blood flow rate to the muscles. This allows mean arterial pressure to be raised to the necessary level.

Static exercise such as weight lifting causes extreme elevations of both systolic and diastolic pressures that can reach levels as high as 345 / 245 mmHg as shown in Figure 2.26 (Palatini *et al.*, 1989). The extent of this increase depends on the intensity of the

muscular contraction; mean arterial pressure may increase by 40 mmHg within one minute at 50 % of maximal voluntary muscular contraction (Lind *et al.*, 1964).

Figure 2.26 Intra-arterial blood pressure changes when lifting barbells. Reproduced from Palatini *et al.* (1989).

2.5.2 Post-Exercise Hypotension

Following a prolonged period of exercise, there may be a period of sustained reduction in mean arterial pressure, shown in Figure 2.27, called post exercise hypotension. As soon as the muscular contraction stops, the venous muscular pump is deactivated causing a marked reduction in cardiac output and hence mean arterial pressure. Another factor that contributes to this phenomenon is the elevated body temperature following exercise. In order to dissipate this internal heat load, blood vessels in the skin open, which reduces the

systemic vascular resistance and allows increased blood flow rate to the skin for the off-loading of heat to the environment. This tends to reduce the circulating blood volume causing hypotension. Post exercise hypotension may last for several hours (Kenney and Seals, 1993), and is mediated by the autonomic nervous system and vasodilator substances (Halliwill, 2001).

Figure 2.27 Systolic, mean arterial and diastolic pressures before, during and 13 hours after a cycling exercise. Reproduced from Pescatello *et al.* (1991).

2.5.3 Eating

During digestion, blood shifts away from the arms and legs to the intestines and in response the cardiac output decreases, consequently decreasing mean arterial pressure as per Eq. 2.1. This effect is more common in older people, whose both systolic and

diastolic pressures decrease after eating (Lipsitz *et al.*, 1983). In younger subjects, there is a rise in heart rate, a fall in diastolic pressure, and a slight increase in systolic pressure three hours after a meal (Fagan *et al.*, 1986).

2.5.4 Nicotine

Nicotine is a chemical compound found in tobacco products such as cigarettes, pipe tobacco, chewing tobacco, and cigars (Rippe, 2004). When a subject smokes a tobacco product, he/she inhales the smoke that contains nicotine as well as over 500 other chemicals. Nicotine reaches the brain within 10 seconds after intake. Nicotine decreases the oxygen level in blood and stimulates the production of epinephrine in the adrenal gland. Epinephrine, in turn, causes vasoconstriction of the blood vessels raising mean arterial pressure. Significant increases in heart rate and mean arterial pressure are noticed 5 minutes after smoking a cigarette; the rise in systolic pressure (11 mmHg) has been measured to be approximately twice the rise in diastolic pressure (5 mmHg) (Cellina *et al.*, 1975). It has also been suggested that the elevation in systolic pressure might be due to a reduction in vascular compliance (O'Rourke, 1990). The effects of nicotine on blood pressure are seen within few minutes, and last for about 15 minutes. Such effects are sometimes followed by a transient fall of blood pressure.

2.5.5 Alcohol

Alcohol is an organic chemical containing one or more hydroxyl groups that are made from hydrocarbons by distillation. The physiological effect of alcohol on the nervous system is biphasic. In low doses it acts as a nervous system stimulant, while in high doses it acts as a depressant (Logue, 1986). Alcohol can cause vasodilation of skin vasculature, which is probably sympathetically mediated (Fewings *et al.*, 1966). However, it has a direct vasoconstrictor effect on the arterioles in muscle beds (Gillespie, 1967). Blood pressure rises linearly with increasing alcohol intake (Arkwright *et al.*, 1982; Klatsky *et al.*, 1977). Effects of acute alcohol intake on blood pressure are not clear. Some studies have found a rise in systolic pressure shown in Figure 2.28, and activation of sympathoadrenal function after alcohol consumption (Ireland *et al.*, 1984; Potter *et al.*, 1986), while other studies have found no change in blood pressure (Riff *et al.*, 1969) or a mainly depressor effect (Howes and Reid, 1985; Kupari, 1983). Potter *et al.* (1986) suggested that the alcohol might have a direct vasoconstrictor effect that could result from calcium ion fluxes in arteriolar smooth muscle cells in normotensive subjects. The authors were not sure if the same is true for hypertensive subjects or, whether sympathetic over-activity is responsible.

Figure 2.28 Effect of alcohol on systolic and diastolic pressure in normotensive and hypertensive subjects. Reproduced from Potter *et al.* (1986).

2.5.6 Caffeine

Caffeine is a central nervous system stimulant; it is known chemically as 1,3,7-trimethylxanthine. Caffeine is found in the leaves, seeds, and fruits of more than 63 plant species, but most commonly comes from coffee, coca beans, cola nuts, and tea leaves. For example a 12 oz can of Coca-Cola contains 45 mg of caffeine, 8 oz green tea contains 30 mg of caffeine, and an ounce of milk chocolate candy has 6 mg of caffeine (Piscatella and Franklin, 2003).

The human brain produces a chemical called adenosine. When adenosine binds to the adenosine receptors in the brain, it causes brain activity to slow down and makes a person

feel tired. Caffeine has a structure that is very similar to adenosine, and when consumed binds to the adenosine receptors instead. This stimulates the vasomotor center and causes constriction of blood vessels, raising mean arterial pressure. Experimental studies show that ingesting caffeine increases blood pressure and does not affect heart rate (Smits *et al.*, 1985). The increase in blood pressure starts within 15 minutes of drinking coffee, peaks in 60 minutes, and remains significant for as long as 3 hours. Increases in systolic pressure / diastolic pressure may vary between 5 / 9 and 14 / 10 mmHg (Jeong and Dimsdale, 1990). Combined coffee ingesting and cigarette smoking result in an interactive effect, and causes a sustained rise in blood pressure of about 10 mmHg within 5 min, as shown in Figure 2.29 (Mann *et al.*, 1984).

Figure 2.29 Effects of cigarette smoking and coffee drinking on systolic pressure. Reproduced from Freestone and Ramsay (1982).

2.5.7 Speech

Talking is a form of speech that results in a remarkable increase in both systolic and diastolic pressures (17 / 13 mmHg) when compared with the preceding period of silence, as shown in Figure 2.30. The rate of the speech has, as well, an additional effect on blood pressure: talking fast produces a larger increase than talking slowly (Friedmann *et al.*, 1982). Reading aloud produces an instant increase in both systolic and diastolic pressures (10 / 7 mmHg), which return to normal levels once silence is resumed. Greater changes in blood pressure were noticed while talking in front of a group than while talking alone in a room. This is due to the psycho-physiological mediating mechanism (Lynch *et al.*, 1980). Moreover, conversation containing a high emotional content showed sharper increase in blood pressure than a less emotional content, in both normotensive (Linden, 1987) and hypertensive subjects (Le Pailleur *et al.*, 1993). This is due to psychological mechanisms in the absence of any physical factors.

Figure 2.30 Systolic and diastolic pressures of 25 subjects where talking preceded reading a comic book. Reproduced from Le Pailleur *et al.* (1998).

2.5.8 Emotion

Different moods have their effects on blood pressure. Anger, anxiety, happiness, and blood pressure are interdependent. In one study, systolic pressure was observed to decrease as the intensity of happiness increased, and diastolic pressure increased with the intensity of anxiety (James *et al.*, 1986).

2.5.9 Stress

Stress is a perturbation of the body's homeostasis. It is a state involving demand on physical or mental energy, which can disturb the normal physiological and psychological

functioning of an individual. In a stressful situation, the brain prepares the body for defensive action; the sympathetic nervous system releases stress hormones, namely, cortisone and adrenaline. These hormones raise the blood pressure through vasoconstriction, and the body prepares to react to the situation. Kulkarni *et al.* (1998) suggested that continual stress eventually leads to hypertension through increased blood pressure levels.

2.5.10 Variations during Sleep and Wakefulness

Sleep is a dynamic process regulated by the brain, and consists of various cycles that repeat themselves during the period of sleep. Blood pressure variations are closely related to the level of awakening. During the first hour of sleep there is a continuous decrease in blood pressure, which reaches its maximum level of reduction of 15 to 20 % two hours after sleep onset (Coccagna *et al.*, 1971). Blood pressure rises immediately upon waking up as shown in Figure 2.31.

Figure 2.31 Levels of systolic, diastolic and heart rate in normotensive subjects one hour before and after waking. Reproduced from Khoury *et al.* (1992).

2.6 Effects of Posture on Blood Pressure

The pressure within the blood vessels of the cardiovascular system is determined by three basic components (Rowell, 1993):

1. A dynamic component created by the pumping action of the heart and is proportional to the product of blood flow rate and resistance to flow. This is the leading component in the arterial system.
2. A static component determined by blood volume and by compliance. This is the leading component in the venous system and pulmonary circulation.
3. A hydrostatic component determined by gravity and physical posture and is proportional to $\rho g h$, where ρ is the blood density, g is the gravitational acceleration, and h is the hydrostatic column of blood.

Hydrostatic pressures are superimposed on pressures generated by the heart, because the three dimensional vascular system is within the earth's field of gravity and therefore, will be the focus of this section. In the passive upright posture, there is a proportional rise in pressure for blood vessels below the heart level, and a proportional decrease in the blood vessels above. When a person is supine, the vertical distances within the vascular system are minimal, hence hydrostatic effects become negligible.

2.6.1 Hydrostatic Indifference Point

The heart is not the only reference point for pressure gradients in the vascular system, since hydrostatic pressure and the elastic properties of blood vessels differ throughout the body, and because there is no linear relationship between hydrostatic pressures and arterial or venous pressures. The hydrostatic indifference point, HIP, is the position where hydrostatic pressures do not change when the circulatory system is rotated around it (Rowell, 1993); this point is located 5-10 cm below the diaphragm. The zero pressure level is the right atrium (Folkow and Neil, 1971). This level is determined by the distribution of venous compliance, which has many controlling mechanisms (Gauer and Thron, 1965).

2.6.2 Pressures in the Supine Posture

In the supine position, mean arterial pressure diminishes slightly from the aorta to the arterial branches, and the same happens to venous pressure along its way from the periphery towards the heart (Ochsner *et al.*, 1951), as shown in Figure 2.32. Venous pressures in the supine position vary from about 15 to 20 mmHg in the smallest veins down to 5 mmHg at the right atrium (Rowell, 1993).

Figure 2.32 Mean arterial and venous pressures in the supine position.

Reproduced from Ochsner *et al.* (1951).

2.6.3 Pressures in the Upright Posture

In the still upright posture, the hydrostatic pressure component substantially affects the blood circulation. In the lower part of the body, it adds to the dynamic component of arterial blood pressure (Greger and Windhorst, 1996). In the upper part of the body, the arterial blood pressure decreases as the hydrostatic column height above heart level increases, as shown in Figure 2.33 (Rowell, 1993). In this body posture of a human, the total mean arterial at the foot is about 200 mmHg in contrast to 60 mmHg in the brain.

Blood pressure in the venous system is also subjected to hydrostatic effects. During still upright posture, leg valves do not prevent the hydrostatic effect produced by the large columns of blood (Folkow and Neil, 1971). During movement (i.e. walking, running),

venous pressure is reduced since external pressure exerted by skeletal muscle which pushes venous blood back towards the heart (Folkow and Neil, 1971).

To illustrate the influence of gravity on the mean arterial pressure and central venous pressure in the upright still posture, Figure 2.34 shows a comparison between a young giraffe and a human. Because the giraffe's head is about 2 meters above its heart, the heart has to generate an aortic pressure of about 250 mmHg, compared to 100 mmHg in humans, to ensure adequate blood flow rate to the brain.

Figure 2.33 Mean arterial and venous pressure in the upright posture. Reproduced from Guyton (1980).

Figure 2.34 Comparison of mean arterial pressure and central venous pressure in an upright human and a young giraffe. Reproduced from Hargens *et al.* (1987).

2.6.4 Changing Body Posture

Changing body posture affects hemodynamics through the redistribution of blood volume. The human circulatory system is most stable in the supine posture because the long columns of blood are near the heart level; moreover, the reflex activity of the

nervous system is low (Rushmer, 1976). When a person in supine posture stands up, about 400-500 ml blood is quickly shifted out of the thoracic section of the circulation into the veins of the legs (Greger and Windhorst, 1996). In healthy subjects, the central nervous system immediately modifies mean arterial pressure and heart rate to prevent postural dizziness (Levick, 2003). In the elderly, dangling the legs before changing from a supine to a standing posture is highly recommended to avoid fainting (Dingle, 2003). Therefore, posture is an important source of blood pressure variability especially in ambulatory blood pressure monitoring studies (Gellman *et al.*, 1990). It has been mentioned in numerous literature that blood pressure readings with the supine and sitting postures can be regarded equivalent if the arm is placed at the heart level (AHA, 1988; American Society of Hypertension, 1992; Ramsay *et al.*, 1999). However, several studies, listed in Table 2.5, contradict this argument, suggesting that the supine and sitting postures cannot be regarded the same even if the arm is precisely positioned at heart level. Nevertheless, inconsistencies still exist among this group of studies. These inconsistencies arise from different procedures followed in each study, such as different definitions for heart level, different sequence of postures, different ways of measurements, and different resting times between blood pressure readings.

Table 2.5 Summary of studies on the differences between sitting and supine blood pressure measurements.

SP: sequence of postures		
RT: resting time		
between postures	Arm position	Results
(Number of subjects)		
Author(s)		
SP: supine / sitting RT: Not defined (365) (Carel <i>et al.</i> , 1983)	At the heart level when sitting	No effect of posture on P_{SBP} P_{DBP} sitting > P_{DBP} supine by 7 mmHg
SP: Random RT: 2 min (166) (Jamieson <i>et al.</i> , 1990)	Not defined	P_{SBP} sitting < P_{SBP} supine P_{DBP} sitting > P_{DBP} supine by 2-3 mmHg
SP: Not defined RT: 5 min (168) (Zachariah <i>et al.</i> , 1990)	Not defined	No effect of posture on P_{SBP} P_{DBP} sitting > P_{DBP} supine by 6 mmHg
SP: Random RT: 5 min (401) (Terent and Breig-Asberg, 1994)	At mid-sternum and on the arm support of chair when sitting; Halfway (sternum-bed) when lying	P_{SBP} sitting arm high < P_{SBP} supine by 8 mmHg P_{DBP} sitting arm high = P_{DBP} supine P_{SBP} sitting arm low = P_{SBP} supine P_{DBP} sitting arm low > P_{DBP} supine by 10 mmHg

Table 2.5 Cont'd Summary of studies on the differences between sitting and supine blood pressure measurements.

SP: Random RT: 5 min (245) (Netea <i>et al.</i> , 1998)	On the arm support of chair when sitting; On the bed when lying	No effect of posture on the P_{SBP} ; P_{DBP} sitting > P_{DBP} supine by 5 mmHg
SP: sitting / supine RT: 5 min (142) (Netea <i>et al.</i> , 2002)	At the heart level	P_{SBP} sitting < P_{SBP} supine by 7 mmHg P_{DBP} sitting < P_{DBP} supine by 7 mmHg
SP: supine / sitting RT: 5 min (57) (Netea <i>et al.</i> , 2003)	At the heart level	P_{SBP} sitting > P_{SBP} supine by 9 mmHg P_{DBP} sitting > P_{DBP} supine by 5 mmHg

2.6.5 Therapeutic Postures

Certain body positions such as body tilts are believed to have improved effects on the circulation and to provide therapeutic benefits. In the following section, two therapeutic positions, (1) Trendelenburg and (2) passive leg elevation are reviewed.

2.6.5.1 Trendelenburg's Posture

Trendelenburg's posture, hereafter referred to as the TREND position, is the head-down tilt position as shown in Figure 2.35. The concept was introduced by Trendelenburg in 1890. At the time, despite lack of evidence, it was believed that this position helped increase mean arterial pressure, improve cerebral blood flow, and improve venous return during shock and hypotension (Morgan *et al.*, 1964). However, this hypothesis has been subjected to significant debate (Sibbald *et al.*, 1979; Wilcox and Vandam, 1988).

Several researchers suggested that mean arterial pressure decreases for animals and humans in TREND position (Guntheroth *et al.*, 1964; Wilkins *et al.*, 1950) with no hemodynamic benefits in normal (Wilkins *et al.*, 1950) or shocked patients (Taylor and Weil, 1967). Moreover, autotransfusion of blood produced by this posture is small (1.8%) and is unlikely to have any important clinical effect (Bivins *et al.*, 1985).

Over the years, inconsistent reports showing controversial findings have been produced from the clinical application of TREND position (Graham and Douglas, 1949; Guntheroth *et al.*, 1964; Kyriakides *et al.*, 1994; Pricolo *et al.*, 1986; Reich *et al.*, 1989; Taylor and Weil, 1967; Wilcox and Vandam, 1988). Asmussen *et al.* (1940) and Sibbald *et al.* (1979) reported beneficial effects of the TREND posture in hypotensive patients. However, Taylor and Weil (1967) showed that the same position induced a reduced mean arterial pressure in the majority of hypotensive patients.

Figure 2.35 TREND posture.

Reproduced from Martin and Warner (1997).

2.6.5.2 Passive Leg Elevation

Passive leg elevation, PLE, sometimes known as the modified TREND posture, is the position where the patient's trunk and head are kept horizontal while the lower extremities are elevated at a specific angle, as shown in Figure 2.36. This posture is used for initial treatment in case of hypovolemic shock* (Ahmad *et al.*, 1977), and cases of acute hypotension (Bertolissi *et al.*, 2003). PLE mimics rapid fluid loading through shifting venous blood from the legs towards the intrathoracic section (Reich *et al.*, 1989; Rutlen *et al.*, 1981), which has been agreed to increase stroke volume and cardiac output (Graftieaux *et al.*, 1998; Thomas and Shillingford, 1965; Wong *et al.*, 1988). Consequently the suggestion is that, PLE increases mean arterial pressure since mean arterial pressure is proportionally related to stroke volume (Boulain *et al.*, 2002; Graftieaux *et al.*, 1998).

* Severe metabolic disturbance caused by a reduction in blood volume.

Yet, only a small volume of blood is shifted from the legs into the intrathoracic section with PLE. Rutlen *et al.* (1981) reported that 150 to 300 ml or less amount of blood is shifted to the central compartment after PLE, which is a relatively small quantity to cause any substantial difference in humans.

Figure 2.36 Modified Trendelenburg posture.

Reproduced from Brunner *et al.* (2004).

In summary, some studies have concluded that there are benefits gained by assuming TREND or PLE postures (Gentili *et al.*, 1988; Pricolo *et al.*, 1986), yet in others, no significant effect of these positions on cardiac performance has been found (Gaffney *et al.*, 1982; Ostrow *et al.*, 1994; Reich *et al.*, 1989; Sibbald *et al.*, 1979; Wilcox and Vandam, 1988).

In view of the fact that there remains conflicting opinions on the clinical benefits of PLE, Dr. Mussivand thinks it is worthwhile to further investigate the effects of PLE. PLE is chosen over TREND body posture due to the discomforting symptoms and sometimes fainting experienced by some subjects when assuming this later body posture and which were reported in several studies. This thesis reports on a study with experimental and computational components, investigating the effects of PLE on the cardiovascular system in normotensive and hypertensive subjects. The experimental component will be presented first, followed by the computational component.

3.1 Introduction

As per the literature survey presented in Section 2.6.5.2, at the present time there is no consensus on how the passive elevation of the legs from the supine position affects the blood pressure at the heart level. A reliable answer to this question is deemed useful, for it would provide guidance on the optimum posture for cardiac patients to assume, that would yield minimum load on the heart during their recovery in the hospital. The reasons for past experimental studies on the subject producing inconsistent results are thought to be related to the limited number of subjects used in the experiments; variations in the experimental procedures amongst the studies, and incomplete documentation of such procedures; and inadequate precision of the equipment used for the measurements, with often insufficient appreciation of the precision of the measurement results. The present experimental study has thus been designed to alleviate the noted shortcomings as much as possible. The size and the composition of the subject group, the equipment used for the measurements, and the measurement procedure are outlined in the following sections, and were approved by the University of Ottawa Heart Institute Ethics Committee. The measurement protocol and the patient consent form that was provided to inform the participants about the procedure of the study and of certain activities that need to be avoided before the scheduled measurement date are given in Appendices D and E,

respectively. Together, the protocol and the patient consent form cover all the aspects that should be carefully taken into consideration in terms of accuracy and reliability of the experiment.

3.2 Measurement of the Effects of Passive Leg Elevation on Systolic and Diastolic Blood Pressures

3.2.1 Subjects

Fifty-four (54) subjects aged between eighteen (18) and forty-five (45) years volunteered to participate in this study. The group consisted of thirty (30) males and twenty-four (24) females, with the majority of the subjects being normotensive. Apart from the fact that four of the subjects were borderline hypertensive, all of the subjects were healthy.

The physical characteristics of the subjects that are deemed potentially relevant to the effect of passive leg elevation on the blood pressure at the heart level are tabulated in Table 3.1.

Table 3.1 Physical characteristics of the subject group (Mean $\pm$ SD).

Parameter	Normotensive <i>n</i> = 50	Hypertensive <i>n</i> = 4
Age (yr)	26.52 $\pm$ 8.16	27.5 $\pm$ 4.04
Weight (kg)	73.15 $\pm$ 14.55	97.4 $\pm$ 28.2
Height (cm)	169.22 $\pm$ 9.34	182.13 $\pm$ 6.17
Arm Circumference (cm)	29.48 $\pm$ 3.18	33.75 $\pm$ 5.25
Body Temperature (°C)	36.23 $\pm$ 0.73	36.83 $\pm$ 0.15
Femur-Tibial Length (cm)	100.63 $\pm$ 4.92	106.75 $\pm$ 6.40
Quadrates-Femora's Circumference (cm)	50.92 $\pm$ 4.59	55 $\pm$ 6.68

3.2.2 Location

The experiments were performed in the clinical investigation room (CIR) of the University of Ottawa Heart Institute*, located on the first floor. The noted room was selected for the experiments, for it provided a quiet and temperature-regulated (22.5°C) environment.

3.2.3 Measurement Devices

- 1) BpTRU automated oscillometric blood-pressure measurement device, shown in Figure 3.1, placed on a mobile stand as illustrated in Figure 3.2. This device was chosen over the alternative blood-pressure measurement devices summarized in Section 2.4.5, as it was deemed to provide the most optimum combination of

* 40 Ruskin Street, Ottawa, Ontario, Canada.

accuracy, speed of measurement, and ease of use. Blood pressure readings obtained with this device are compared to those obtained with an auscultatory mercury sphygmomanometer in Table 3.2. These results are based on measurements by Mattu *et al.* (2001) with the two devices on 85 subjects by two trained observers, with both measurements performed on each of the subjects in sequence, on the same arm, and with the subject remaining in the sitting position.

Table 3.2 The difference between BpTrue and mercury reference readings.

Parameter	Mean $\pm$ SD
Systolic Blood Pressure (mmHg)	-0.62 ± 6.96
Diastolic Blood Pressure (mmHg)	-1.48 ± 4.80
Heart-Rate (Beats/min)	0.14 ± 1.86

Figure 3.1 BpTRU blood pressure device.

Figure 3.2 Mobile stand.

- 2) Blood-pressure cuff, shown in Figure 3.3. Three sizes were used in the experiments (8.9×17.1 cm, 12×22.9 cm, and 15.2×33.0 cm), and the right size of cuff for each subject was determined as per the guidelines summarized in Section 2.4.6.4.

Figure 3.3 Regular-Adult blood pressure cuff.

- 3) First-Temp Genius TM Thermometer with $\pm 1^{\circ}\text{C}$ precision, shown in Figure 3.4.

Figure 3.4 First-Temp Genius TM thermometer.

- 4) Weight-height measuring scale with ± 0.5 kg, ± 1 mm precision.
- 5) Non-elastic measuring tape to measure the subject's antecubital-fossa and quadriceps femoris circumference.
- 6) Medical bed to take blood-pressure measurements in the supine position, shown in Figure 3.5.

Figure 3.5 Medical bed.

- 7) Three foam leg raisers, shown in Figure 3.6, used to passively raise the subject's legs from the supine positions by 9, 18, and 27 degrees.

Figure 3.6 Foam leg raisers.

- 8) A heart pillow, shown in Figure 3.7, to support the arm, on which measurements are taken, at the heart level in the supine position.

Figure 3.7 Heart pillow.

- 9) A stand, shown in Figure 3.8, to support the arm at the heart level in the standing position.

Figure 3.8 Mobile adjustable stand.

3.2.4 Experimental Procedure

The measurements were performed by the author of this thesis, with no one other than the subject and the author being in the room during the measurements.

- 1) A patient consent form (Appendix E) was given to each participant forty-eight hours prior to the blood-pressure measurement session. The consent form explains the experimental procedure and informs the subjects on certain activities that must be performed or avoided prior to the measurement session.
- 2) Upon arrival at the measurement site, certain information was obtained from each subject (Table E.2 of Appendix E) and the consent form (Section E.9 of Appendix E) was signed by the subject if it was not already signed.
- 3) Subject was asked to remove any constrictive clothing that may interfere with the blood-pressure measurements or may artificially affect the subject's blood pressure.
- 4) Subject was given a summary of the procedure.
- 5) Blood pressure was measured in both arms (right and left), and the arm with higher blood pressure was used. Subjects with blood pressure differences larger than 10 mmHg between the two arms were excluded from the study.
- 6) Subject's weight, height, femur-tibial length, body temperature, arm circumference (antecubital-fossa) and quadriceps femoris circumference were measured and recorded.

- 7) The subject was asked to lie on the bed in the supine position. The heart pillow was placed underneath the chosen arm such that the antecubital-fossa was positioned at the fourth intercostal space (heart level) with the palm facing upward.
- 8) The appropriate-size blood-pressure cuff was placed on the subject's arm such that the center of the cuff's bladder is over the brachial artery, and the lower cuff margin is 2.5 cm above the antecubital-fossa. The subject was asked to rest for five minutes before starting the blood-pressure measurements.
- 9) At the end of the rest period, three measurements were taken with a one-minute interval between them. Hereafter, a "measurement" will refer to the measurement of blood-pressure and heart rate.
- 10) Subject's both legs were raised to 9 degrees (relative to examination bed surface) by the observer as shown in Figure 3.9, and a measurement was performed two minutes after raising of the legs.

Figure 3.9 Passive leg elevation.

- 11) Two more measurements were taken with a one-minute interval between them.
- 12) Subject's both legs were raised to 18 degrees (relative to examination bed surface) by the observer, and a measurement was performed two minutes after raising of the legs.
- 13) Two more measurements were taken with a one minute interval between them.
- 14) Subject's both legs were raised to 27 degrees (relative to examination bed surface) by the observer, and a measurement was performed two minutes after raising of the legs.
- 15) Two more measurements were taken with a one-minute interval between them.
- 16) Subject's legs were returned to horizontal position by the observer, and three measurements were performed two minutes after returning to this position with a one-minute interval between them.

- 17) Subject was rested for two minutes. At the end of the rest period, subject's both legs were raised to 27 degrees (relative to examination bed surface) by the observer, and a measurement was performed ten seconds after raising of the legs.
- 18) Subject was asked to switch to a standing position, and his/her arm was positioned at the heart level.
- 19) Three measurements were taken after a period of two minutes in this position.
- 20) The information and consent forms filled by the subject and the data records for the measurement session were catalogued.

For each subject, a total of eighteen (18) measurements (each measurement consisting of recording of systolic and diastolic blood pressures and heart rate) were taken over a period of approximately one hour.

Measurements of blood pressure and of the heart-beat rate will demonstrate any effects of passive leg elevation from the supine positions on these quantities, and thus are of value themselves in establishing posture guidelines for cardiac patients to minimize the load on the heart. Nonetheless, it is beneficial to complement the measurements with computed results, for this synergic approach will allow us to more reliably discern trends that maybe small in comparison to the scatter in the measured results, and will also help us identify the response mechanism(s) of the cardiovascular system to passive leg elevation that yields the observed trends in the blood pressure at the heart level. The next chapter presents the computational model developed for the said purpose. The measured and computed results are then presented and discussed together in Chapter 5.

4.1 Introduction

In the instance of a posture change from supine to that of passively-raised legs, the static pressure distribution throughout the cardiovascular system is altered by the relative increases in the potential energy of the blood within the legs. Since the pressure field is the driving force for the blood flow, any change in this field leads to changes in the flow rates through the blood vessels. The situation is made more complex by the response of the elastic blood vessels to the modified pressure field, leading to a modified field of viscous forces. As was discussed in Section 2.3, short-and long-term control mechanisms strive to counter deviations in blood pressure and blood flow rate from normal levels, such as the noted changes that are expected to occur in the cardiovascular system with the elevation of the legs from the supine position. The objective of the present computational effort is to quantify the extent of changes in the cardiovascular system with the passive elevation of the legs, without accounting for the effects of the control mechanisms. By studying these computational results in the context of the measured effects of passive leg elevation on the blood pressure at the heart level, the role of the cardiovascular control mechanisms during the said posture change can be deduced.

The flow through the cardiovascular system is periodic unsteady, with a flow-rate oscillation amplitude at the discharge from the left ventricle of the heart that is about 40%

of the time-mean flow rate, driven by oscillations in pressure at an amplitude of 200 % of the mean. For modeling purposes, it is most effective to consider this nature of the blood flow as periodic oscillations superimposed on a steady flow. In the evaluation of the passive response of the flow field in the cardiovascular system to a posture change, we shall therefore opt to first model the response of the time-mean flow blood-flow in the systemic circulation to this posture change.

4.2 Modeling of the Time-Mean Blood Flow in the Systemic Circulation

Considering the very large number of blood vessels of complex branching patterns that make up the cardiovascular system, it is not practical to model the whole systemic circulation on the basis of more than one spatial dimension. We shall adopt the well-established practice of taking the blood flow to be one dimensional, aligned with the local axis of the blood vessel, and compute the viscous resistance to blood flow on the assumption of fully-developed laminar flow.

The velocity field in the arteries is unsteady with significant time-periodic variations in pressure hence flow rate, as shown in Fig. 4.1A. As a consequence, the radial distribution of velocity is time dependent, as illustrated in Fig. 4.1B for a location in the arterial tree, corresponding to the femoral artery. The assumption of fully-developed flow for the time-mean velocity field would clearly not be reasonable in light of the extent of temporal variation in the velocity profile in this region. However, such significant time-

periodic variations in blood flow is limited to the larger arteries, which provide only a very small contribution to the overall resistive load that the cardiovascular system imposes on the heart. As such, the error that results from the unjustified approximation of fully-developed flow in modeling these regions is expected to be negligible in the context of the modeling of the cardiovascular system as a whole.

Figure 4.1 (A) Flow rate waveform in the normal femoral artery, (B) velocity profile in the femoral artery computed from the mean velocity waveforms.

Reproduced from: Hoskins et al. (2002) and Ku (1997).

The variation of blood-vessel properties along the length of the cardiovascular tree is continuous, and the interconnectivity of the vessels is highly complicated especially at the arteriole, capillary and venule levels. Thus, in numerical modeling of the flow through this system, the larger blood vessels are commonly approximated by a finite number of segments or elements, with each element having uniform vessel properties, and the vast number of smaller vessels such as arterioles, capillaries and venules are lumped together into few elements such that their substantial resistive effect on the blood flow is accounted for correctly. Viscous and inertia forces in the larger vessels of the venous return portion of the circulation can be neglected all together. This is justified by the relatively large diameter and highly compliant nature of these vessels, and enables the use of basic hydrostatic principles to model this portion of the systemic circulation.

In summary, our mathematical representation of the systemic circulation consists of:

- the arterial portion, wherein the arteries are divided into a finite number of elements, with viscous, inertia, pressure and gravity forces accounted for;
- purely resistive elements representing the arteriole, capillary and venule network;
- the venous return portion wherein inertia and viscous effects are neglected.

Figure 4.2 shows the connectivity of all of these elements comprising the systemic circulation. The arterial elements are shown in red, the purely resistive elements in green and the venous return elements are given in blue. This representation resembles to a great extent the human cardiovascular system as seen in Figure 4.3 which is a magnetic resonance image of the human arterial tree. It is evident that the systemic circulation

consists of various “sub-loops” - arterial feed followed by venous return - , with each loop delivering blood to a major organ or distinct portion of the body, such as each of the limbs, the right and left lobes of the brain, the kidneys, and so on. In order to establish a systematic approach in identifying the various modeling elements in question, they are grouped according to these loops, with each group to be referred to as a computational “block” hereafter. The numbering and identification of these blocks are provided in Table 4.1. The element labels given in Figure 4.2 comprise two indices, $[j,i]$, with the first (j) index denoting the computational block with which the element in question is associated, and the second (i) index identifying the placement of the element within that block. The elements are connected to each other at “nodes”, shown as black circular dots in Figure 4.2, which are the locations where the local pressure and flow-rate values are to be computed. Within each block, each node is indexed based on the i index of the element immediately downstream of that node.

Figure 4.2 Discrete representation of the systemic circulation.

Figure 4.3 Magnetic resonance image of the human arterial tree.

Table 4.1 Grouping of the modeling elements.

Block Number (<i>j</i>)	Anatomical Branch
1	Ascending Aorta
2	Brachiocephalic
3	Right Carotid
4	Right Subclavian I
5	Right Vertebral
6	Right Arm
7	Left Carotid
8	Left Subclavian I
9	Left Vertebral
10	Left arm
11	Abdomen
12	Right Leg
13	Left Leg

With the discretization of the systemic circulation performed as per Figure 4.2 and Table 4.1, the next step is to establish a computational procedure that will yield the distribution of pressure and flow rate at all of the computational nodes, once the boundary conditions of the problem are specified. The cardiac output, i.e. the blood flow rate out of the left ventricle, Q_{LV} , the mean arterial pressure at the exit of the left ventricle, P_{MAP} , and the central venous pressure, which is the pressure at the entrance of the right atrium of the heart, P_{CV} , collectively determine the load imposed upon the heart. In addition to the nodal distributions of flow rate and pressure throughout the modeled systemic circulation, we will be able to quantify one of these three parameters, provided that the remaining two are specified as boundary conditions. In Chapter 5, we shall decide on which two of these three parameters are most convenient to specify as boundary conditions to complement the interpretation of our experimental results on the blood-pressure effects of passive leg elevation. For the purpose of describing the operation of the computational algorithm,

here we shall consider the case where Q_{LV} and P_{CV} are specified. With Q_{LV} and P_{CV} specified, there is a unique value of P_{MAP} that will deliver blood flow at a total rate of Q_{LV} through our modeled system of blood vessels under the influences of body forces (e.g. gravity) and resistive viscous forces. There is also a unique distribution of flow rate amongst our computational blocks, dependent upon the relative magnitudes of the body and viscous forces in these blocks. The algorithm starts with an initial guess for P_{CV} , and proceeds with the calculation of the flow rate and pressure values at each node in sequence. The pressure drop across a given element, bound by nodes i and $i-1$, is computed using one of the following three equations, depending on whether the element belongs to the arterial system, is purely resistive, or is a venous-return vessel (respectively, red, green and blue elements in Figure 4.2):

$$P_i = P_{i-1} - 0.00751 \times 10^{-3} \times \rho \times g \times (h_i - h_{i-1}) - R_i \times q_i \quad (4.1)$$

$$P_i = P_{i-1} - 0.00751 \times 10^{-3} \times \rho \times g \times (h_i - h_{i-1}) - (R_i + R_{Per(i)}) \times q_i \quad (4.2)$$

$$P_i = P_{i-1} - 0.00751 \times 10^{-3} \times \rho \times g \times (h_i - h_{i-1}) \quad (4.3)$$

where 0.00751 is the conversion factor from Pascal to mmHg. $R_i \left(\frac{\text{mmHg}}{\text{ml/sec}} \right)$ is the local vessel resistance and is determined as:

$$R_i = \frac{128 \times 0.00751 \times 10^3 \times \mu \times l}{\pi \times d^4} \quad (4.4)$$

where μ is the blood viscosity and is equal to $0.0035 \left(\frac{\text{g}}{\text{mm sec}} \right)$. h_i (mm) in Eqs. 4.1 to

5.3 is the elevation of node i with respect to an arbitrarily chosen datum, ρ is blood

density and is equal to $1050 \left(\frac{\text{Kg}}{\text{m}^3} \right)$, $g \left(\frac{\text{m}}{\text{sec}^2} \right)$ is gravitational acceleration, P (mmHg) is pressure, $q \left(\frac{\text{ml}}{\text{sec}} \right)$ is flow rate and $R_{per} \left(\frac{\text{mmHg}}{\text{ml/sec}} \right)$ is the peripheral resistance.

All three of these equations are readily derived from the steady-flow energy equation. Equation 4.1 applies to an arterial element, and is obtained by assuming fully-developed laminar flow within the element. Equation 4.2 applies to a resistive element and is obtained by neglecting the inertia terms in the energy equation. The value of the viscous term, R_{per} , appearing in this equation is empirical, and is obtained from published literature. Equation 4.3 applies to a venous-return element, and is obtained by neglecting both the inertia and viscous terms from the steady-flow energy equation.

By default, the principle of conservation of mass is satisfied within each element, but must be enforced explicitly by the algorithm at nodes that are shared by more than two elements (i.e. points of branching and merging). At nodes where the blood stream is split into two or more branches (e.g. the node shared by elements [1,1], [2,1], [7,1] and [8,1] in Figure 4.2), the relative proportions of flow rate for the multiple downstream branches are not known *a priori*. The algorithm thus needs to iterate on the flow-rate distribution amongst the branches until conservation of mass is satisfied at all nodes of the modeled systemic circulation. When this condition is reached, the computed value of the central venous pressure, P_{CV} , is compared to the value specified for P_{CV} as a boundary condition. If the two values differ beyond an acceptable computing tolerance, the series of the computations are repeated with a different value of P_{MAP} . It is to be noted that the arterial

vessels for which the streamwise pressure drop is calculated through Eq. 4.1, are highly elastic and adjust their diameter in response to the local blood pressure. The response of the vessel diameter to local pressure changes is calculated from:

$$d_{adjusted} = \begin{cases} d + \sqrt{\frac{4 \times C \times 10^3 \times |P_0(i) - P_1(i)|}{\pi \times l}} & \text{if } (P_0(i) - P_1(i)) \geq 0 \\ d - \sqrt{\frac{4 \times C \times 10^3 \times |P_0(i) - P_1(i)|}{\pi \times l}} & \text{if } (P_0(i) - P_1(i)) < 0 \end{cases} \quad (4.5)$$

where $P_0(i) - P_1(i)$ is the local pressure change due to posture change, C is the vessel compliance, which can be related to the properties of the vessel wall through:

$$C = \frac{dV}{dP} \approx \frac{3 \pi r^3 L}{2 E h_w} \quad (4.6)$$

where V (mm³) is the volume of the given element, P (mmHg) is pressure, r (mm) is the radius, E (mmHg) is Young's modulus of elasticity, L (mm) is the length of the artery element, and h_w (mm) is the vessel-wall thickness.

The adjustment of the vessel diameter through the local pressure alters the viscous resistance in these elements, which in turn influences the magnitude of the streamwise pressure drop in the element. This mutual interaction between the local blood pressure, vessel geometry and viscous resistance is accounted for in the computational algorithm.

If it were not for the potential-energy terms appearing in Equations 4.1 and 4.3, which are dependent on the relative elevations of the individual nodes affected by the body posture, and for the fact that the arterial vessel diameters are dependent on the local pressure values, closed form solution amongst the cardiac output, Q_{LV} , the pressure at the exit of

the left ventricle, P_{MAP} , and the venous return pressure at the entrance of the right atrium of the heart, P_{CV} could have been obtained.

Table 4.2 lists the diameters of the individual vessel elements depicted in Figure 4.2, the length of the elements, and the vessel-wall properties. These measurements are based on a healthy adult with an average height of 175 cm and weight of 70 Kg measured in the supine position, and obtained from several sources in the literature (Noordergraaf, 1963; Westerhof, 1968; Westerhof et al., 1969)

Table 4.2 Geometric properties and arterial-wall properties of the arterial tree segments.

Branch [j , i]	Internal Diameter (mm)	Wall thickness (mm)	Length (mm)	Elasticity (g cm ⁻¹ s ⁻²)
[1,1]	27.6	1.625	40	4.00E+06
[2,1]	12.46	0.86	34	4.00E+06
[3,1]	7.42	0.63	177	4.00E+06
[3,2]	3.93	0.42	177	8.00E+06
[3,3]	3.93	0.42	177	8.00E+06
[4,1]	8.46	0.67	34	4.00E+06
[5,1]	3.96	0.455	148	8.00E+06
[6,1]	8.06	0.56	422	4.00E+06
[6,2]	3.67	0.43	235	8.00E+06
[6,3]	4.3	0.49	67	8.00E+06
[6,4]	1.99	0.28	79	1.60E+07
[6,5]	4.12	0.46	171	8.00E+06
[7,1]	7.4	0.63	177	4.00E+06
[7,2]	3.93	0.42	177	8.00E+06
[7,3]	3.93	0.42	177	8.00E+06
[8,1]	8.46	0.67	34	4.00E+06
[9,1]	3.96	0.455	148	8.00E+06
[10,1]	8.06	0.56	422	4.00E+06
[10,2]	3.67	0.43	235	8.00E+06
[10,3]	4.3	0.49	67	8.00E+06
[10,4]	1.99	0.28	79	1.60E+07
[10,5]	4.12	0.46	171	8.00E+06
[11,1]	21.87	1.26	111	4.00E+06

Table 4.2 Cont'd. Geometric properties and arterial-wall properties of the arterial tree segments.

Branch [j, i]	Internal Diameter (mm)	Wall thickness (mm)	Length (mm)	Elasticity ($\text{gcm}^{-1}\text{s}^{-2}$)
[11,2]	5	0.5	80	4.00E+06
[11,3]	19.6	1.16	104	4.00E+06
[11,4]	7.8	0.64	10	4.00E+06
[11,5]	15.6	1.08	53	4.00E+06
[11,6]	7.4	0.69	59	4.00E+06
[11,7]	12.6	0.8	10	4.00E+06
[11,8]	6.5	0.52	32	4.00E+06
[11,9]	11.4	0.8	10	4.00E+06
[11,10]	4.5	0.52	32	4.00E+06
[11,11]	9.42	0.8	106	4.00E+06
[11,12]	3.19	0.43	50	4.00E+06
[11,13]	8.58	0.8	10	4.00E+06
[12,1]	6.46	0.63	58	4.00E+06
[12,2]	4.8	0.4	50	4.00E+06
[12,3]	5.66	0.55	144	4.00E+06
[12,4]	4.01	0.49	126	1.60E+07
[12,5]	4.21	0.49	443	4.00E+06
[12,6]	3.74	0.45	321	1.60E+07
[12,7]	2.76	0.39	343	1.60E+07
[13,1]	6.46	0.63	58	4.00E+06
[13,2]	4.8	0.4	50	4.00E+06
[13,3]	5.66	0.55	144	4.00E+06
[13,4]	4.01	0.49	126	1.60E+07
[13,5]	4.21	0.49	443	4.00E+06
[13,6]	3.74	0.45	321	1.60E+07
[13,7]	2.76	0.39	343	1.60E+07

These parameters, the posture-dependent relative elevations of the nodes, and the values of two of the parameters Q_{LV} , P_{MAP} , and P_{CV} constitutes the complete set of input data required for the algorithm to converge to a unique solution. The data listed in Table 4.2 is empirical, and varies to some extent amongst individuals. Sensitivity analysis has been performed to establish the effect of such uncertainties on the computed results, and will

be presented in Chapter 5. A listing of the computational algorithm, its flowchart, and sample input and output files, are provided in Appendix F.

5.1 Measured Effects of Passive Leg Elevation on Blood Circulation

5.1.1 Measurements of Systolic, Diastolic and Mean-Arterial Pressures

The measurements with passive leg elevations of 9, 18 and 27 degrees were found to yield the same trends in blood pressure. Since the 27 degrees is the steepest position, and since it was the only posture examined for short-term control mechanisms, only the results of this posture are presented in this chapter. The complete set of experimental results is provided in Appendix G.

The changes in systolic pressure, diastolic pressure, mean arterial pressure and heart-beat rate in normotensive patients, measured 10 seconds and 2 minutes after posture change from supine to 27 degrees passive leg elevation, are presented in Tables 5.1 and 5.2, respectively. The mean arterial pressure listed in these tables was calculated as the sum of diastolic pressure and one-third of pulse pressure.

Table 5.1 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 10 seconds after 27 degrees of passive leg elevation.

	Normotensive Healthy Subjects (Mean $\pm$ SD) ($n = 30$)
Systolic pressure (mmHg)	2.51 ± 1.95
Diastolic Pressure (mmHg)	1.54 ± 1.98
Mean arterial pressure (mmHg)	1.87 ± 1.59
Heart rate (Beats/min)	0.34 ± 4.28

Table 5.2 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects two minutes after 27 degrees of passive leg elevation.

	Normotensive Healthy Subjects (Mean $\pm$ SD) ($n = 50$)
Systolic pressure (mmHg)	-0.48 ± 1.97
Diastolic Pressure (mmHg)	-0.27 ± 2.22
Mean arterial pressure (mmHg)	-0.34 ± 1.76
Heart rate (Beats/min)	-0.82 ± 3.33

Immediately after the raising of the legs, before short-term control mechanisms reviewed in Section 2.3 come into effect (Figure 5.1), the mean arterial pressure slightly increases as noted in Table 5.1. Since the mean arterial pressure is directly proportional to cardiac output, systemic vascular resistance, and central venous pressure (Section 2.1), the observed trend in the mean arterial pressure ought to be linked to increases in the cardiac output, the systemic resistance, and/or central venous pressure. This argument is supported by the results of Gaffney *et al.* (1982), who observed transient increases in the cardiac output of normotensive subjects by as much as 10 percent during the first 20 seconds after passive raising of the legs to 60 degrees inclination from the supine

position, with the cardiac output returning to its original level 7 minutes after the said posture change. Gaffney *et al.* (1982) and Nixon *et al.* (1979) also observed slight temporary increases in the systemic resistance following the passive raising of the legs.

Figure 5.1 Control mechanisms at different time intervals after the onset of a disturbance to the arterial pressure. Reproduced from Guyton (1980).

The transient increase in the mean arterial pressure that occurs in response to increases in the cardiac output and systemic resistance immediately after the passive raising of the legs is sensed by the receptors of the cardiovascular control mechanisms, most immediately by the baroreceptors, as shown in Figure 5.1. The carotid-sinus and aortic baroreceptors register the increase in mean arterial pressure, and send impulses to the medullary cardiovascular center. In response, the autonomic nervous system is activated and decreases systemic stimulation of the arterial vessels. The decrease in the systemic stimulation causes vasodilation of the blood vessels, yielding a decrease in the systemic resistance and a consequent reduction in the mean arterial pressure, as per the results tabulated in Table 5.2.

5.2 Computation of the Effects of Posture Change on Blood Circulation

With the cause-and-effect relationship between the increase in mean arterial pressure and the increases in cardiac output and systemic resistance immediately after the passive raising of the legs established, the remaining question pertains to the cause of the increases in cardiac output and systemic resistance. Since these increases occur prior to the activation of the short-term control mechanisms, they are expected to be the result of a passive response of the cardiovascular system to the body posture change. The computational tool for the time-mean properties of cardiovascular flow, described in Chapter 4, can be used to establish the chain of events in the systemic circulation

constituting this passive response. It is important to reiterate that although the computation is referred to as a time-mean prediction, the results correspond to the state that is measured on a subject after the blood flow in the systemic circulation has adjusted to the new boundary conditions, without the control mechanisms having had the time to regulate the hemodynamic conditions.

As was noted in Chapter 2, passive raising of the legs from the supine position (Figure 5.2) is expected to create a fundamentally similar hemodynamic response as the change of posture from supine to head-down tilt (Figure 5.3). Due to the availability of more detailed published empirical data on the transient response of the cardiovascular system to a change from supine to head-down-tilt posture (e.g, Sibbald *et al.*, 1979; Schreiber *et al.*, 2002), the present modeling effort is initially performed for this posture change, enabling the use of published empirical data to support the physics described by the computational results.

Figure 5.2 Passive leg elevation.

Figure 5.3 Trendelenburg's head-down tilt posture.

5.2.1 Computation of the Effects of Head-Down Tilt on Blood Circulation

The computation is performed for a 15-degree head-down tilt position. As was noted in Section 4.2, to start the computations, two out of the three parameters, the cardiac output, Q_{LV} , the pressure at the exit of the left ventricle, P_{MAP} , and the central venous pressure at the entrance of the right atrium of the heart, P_{CV} , need to be specified. We shall choose to specify Q_{LV} and P_{CV} , allowing the algorithm to compute the corresponding value of P_{MAP} . Immediately after a posture change from supine to head-down tilt, an increase in the preload of the heart, P_{CV} , is most likely, which would result from the increased blood drainage from the venous vessels towards the heart under the influence of gravity. This is

confirmed by the measurements of Goldsmith *et al.* (1985) indicating 4 mmHg increase in preload when realizing a posture change from supine to 30-degree head-down tilt.

At this instant, with P_{CV} having increased and P_{MAP} still remaining at its supine value, the heart is temporarily unloaded by the decreased value of afterload minus preload. Whether the heart would respond to this load change by an adjustment in the cardiac output through variation of heart rate, stroke volume, or both is not obvious. In view of the uncertainties in the values of P_{CV} and Q_{LV} immediately following the said body posture change, we shall perform the computations for several scenarios to establish the sensitivity of the computed results to the values of P_{CV} and Q_{LV} .

Table 5.3 presents the computed flow rate distribution amongst the blocks of the discretized systemic circulation for the 15-degree head-down-tilt position with reference to the values for the supine position. These results are obtained with the values of P_{CV} and Q_{LV} remaining constant during the change in posture, at the values noted in the table. The R values given in the table are the overall viscous resistances for each of the blocks presented in the block diagram in Figure 5.4.

It is observed that the general trend that results from the change of posture from supine to head-down tilt is reduced flow rate through the portions of the cardiovascular system that is raised with respect to the heart, and increased flow rate through the portions of the system that is lowered with respect to the heart. This is in response to the changes in viscous resistances, caused by changes in the arterial diameters. In turn, the changes in the arterial diameters are the result of changes in the local blood-pressure values, with the

latter resulting from the change in the local elevation hence potential energy with respect to the heart level.

Table 5.3 Computed blood flow-rate and resistance distribution in supine versus 15-degree head-down-tilt postures when values of P_{CV} and Q_{LV} are kept constant during the change in posture.

		Supine		15 Degree Head-down tilt		
		$Q_{LV} = 83.33 \text{ ml/sec}$ $P_{CV} = 5 \text{ mmHg}$ $P_{MAP} = 91.36 \text{ mmHg}$ $P_{MAP} - P_{CV} = 86.36 \text{ mmHg}$		$Q_{LV} = 83.33 \text{ ml/sec}$ $P_{CV} = 5 \text{ mmHg}$ $P_{MAP} = 92.53 \text{ mmHg}$ $P_{MAP} - P_{CV} = 87.53 \text{ mmHg}$		
Block #	Block Description	Q (ml/sec)	R (mmHg/ml/sec)	Q (ml/sec)	R (mmHg/ml/sec)	ΔQ (%)
1	Ascending Aorta	83.33	1.04	83.33	1.05	0
2	Brachiocephalic	7.87	10.97	7.93	11.04	0.76
3	Right Carotid	1.64	52.66	1.67	52.56	1.83
4	Right Subclavian I	6.23	13.85	6.27	13.97	0.64
5	Right Vertebral	1.89	45.78	1.91	45.78	1.06
6	Right Arm	4.35	19.87	4.35	20.11	0.23
7	Left Carotid	1.64	52.66	1.67	52.56	1.83
8	Left Subclavian I	6.23	13.85	6.27	13.97	0.48
9	Left Vertebral	1.89	45.78	1.91	45.78	1.06
10	Left arm	4.35	19.87	4.35	20.11	0
11	Abdomen	67.57	1.28	67.45	1.30	-0.18
12	Right Leg	7.51	11.44	7.17	12.12	-4.53
13	Left Leg	7.51	11.44	7.17	12.12	-4.53
Total		83.33	1.04	83.33	1.05	0

Figure 5.4 Block diagram of the arterial tree.

The mean arterial pressure, P_{MAP} , is noted to increase slightly in response to the posture change. This is consistent with the slight increase in viscous resistance while P_{CV} and Q_{LV} are kept constant.

The computed results are consistent with published experimental results. For example, Bivins *et al.* (1985) reported 1.8% increase in blood volume in the upper body compartment (from the diaphragm to the top of the head) and 3.2% decrease in blood volume in the lower body compartment (from the greater trochanter to the diaphragm) after a change from supine to 15-degree head-down tilt in ten normovolemic subjects. Yasumasa *et al.* (2002) reported increased cerebral blood flow during the early phase of

45-degree head-down tilt in humans. Hu *et al.* (1999) measured the changes in the internal common carotid artery diameter and the vertebral artery diameter 5 minutes after a change from supine to 30-degree head-down-tilt position. The authors reported an increase of 11 percent in the internal common carotid artery diameter and no change in the vertebral artery diameter. Although this measurement is likely influenced by short-term control mechanisms, given the 5-minute delay between posture change and the measurement, the result is nonetheless in reasonable agreement with the present computations for 15-degree head-down tilt, where the increase in the internal common carotid artery diameter is predicted to be 7 percent, and no change is predicted in the vertebral artery diameter.

The present computations were repeated for the same posture change first assuming that P_{CV} increases by 2 mmHg during the posture change with Q_{LV} remaining constant, and then assuming that both P_{CV} and Q_{LV} respectively increase by 2 mmHg and 4.17 ml/sec (5 %) as per the measurements of Reich *et al.* (1989) who reported 7 % increase in cardiac output 2 minutes after 20-degree head-down tilt. The results of these two simulations are presented in Tables 5.4 and 5.5, respectively. In both instances, the changes in the local resistance values due to the posture change are observed to be similar to those observed in Table 5.3, leading to an increase in P_{MAP} . We therefore conclude that the uncertainty pertaining to the changes in the values of P_{CV} and Q_{LV} during the said posture change does not affect the trends (increase vs decrease) in the adjustment of the local resistances.

Table 5.4 Computed blood flow-rate and resistance distribution in supine versus 15-degree head-down-tilt postures when P_{CV} is increased by 2 mmHg while Q_{LV} is kept constant during the change in posture.

		Supine		15-Degree Head-down tilt		
		$Q_{LV} = 83.33 \text{ ml/sec}$ $P_{CV} = 5 \text{ mmHg}$ $P_{MAP} = 91.36 \text{ mmHg}$ $P_{MAP} - P_{CV} = 86.36 \text{ mmHg}$		$Q_{LV} = 83.33 \text{ ml/sec}$ $P_{CV} = 7 \text{ mmHg}$ $P_{MAP} = 94.29 \text{ mmHg}$ $P_{MAP} - P_{CV} = 87.29 \text{ mmHg}$		
Block #	Block Description	Q (ml/sec)	R (mmHg/ml/sec)	Q (ml/sec)	R (mmHg/ml/sec)	ΔQ (%)
1	Ascending Aorta	83.33	1.04	83.33	1.05	0
2	Brachiocephalic	7.87	10.97	7.93	11.01	0.76
3	Right Carotid	1.64	52.66	1.66	52.53	1.22
4	Right Subclavian I	6.23	13.85	6.27	13.93	0.64
5	Right Vertebral	1.89	45.78	1.91	45.68	1.06
6	Right Arm	4.35	19.87	4.36	20.03	0.46
7	Left Carotid	1.64	52.66	1.66	52.53	1.22
8	Left Subclavian I	6.23	13.85	6.27	13.93	0.64
9	Left Vertebral	1.89	45.78	1.91	45.68	1.06
10	Left arm	4.35	19.87	4.36	20.03	0.46
11	Abdomen	67.57	1.28	67.46	1.29	-0.16
12	Right Leg	7.51	11.44	7.20	12.04	-4.13
13	Left Leg	7.51	11.44	7.20	12.04	-4.13
Total		83.33	1.04	83.33	1.05	0

Table 5.5 Computed blood flow-rate and resistance distribution in supine versus 15-degree head-down-tilt postures when P_{CV} is increased by 2 mmHg and Q_{LV} by 4.17 ml/sec during the change in posture.

		Supine		15-Degree Head-down tilt		
		$Q_{LV} = 83.33$ ml/sec $P_{CV} = 5$ mmHg $P_{MAP} = 91.36$ mmHg $P_{MAP} - P_{CV} = 86.36$ mmHg		$Q_{LV} = 87.50$ ml/sec $P_{CV} = 7$ mmHg $P_{MAP} = 98.14$ mmHg $P_{MAP} - P_{CV} = 91.14$ mmHg		
Block #	Block Description	Q (ml/sec)	R (mmHg/ml/sec)	Q (ml/sec)	R (mmHg/ml/sec)	ΔQ (%)
1	Ascending Aorta	83.33	1.04	87.50	1.04	5
2	Brachiocephalic	7.87	10.97	8.31	10.96	5.59
3	Right Carotid	1.64	52.66	1.74	52.50	6.1
4	Right Subclavian I	6.23	13.85	6.58	13.86	5.62
5	Right Vertebral	1.89	45.78	2.00	45.60	5.82
6	Right Arm	4.35	19.87	4.58	19.90	5.29
7	Left Carotid	1.64	52.66	1.74	52.50	6.1
8	Left Subclavian I	6.23	13.85	6.58	13.86	5.62
9	Left Vertebral	1.89	45.78	2.00	45.60	5.82
10	Left arm	4.35	19.87	4.58	19.90	5.29
11	Abdomen	67.57	1.28	70.87	1.29	4.87
12	Right Leg	7.51	11.44	7.66	11.86	2
13	Left Leg	7.51	11.44	7.66	11.86	2
Total		83.33	1.04	87.50	1.04	5

Having demonstrated the ability of our computational model to capture the passive response of the cardiovascular system to a change in body posture, we are ready to apply the model to our specific problem of a posture change from supine to passive leg elevation.

5.2.2 Computation of the Effects of Passive Leg Elevation on Blood Circulation

In order to compute the effect of 27-degree passive leg elevation starting from the supine position on the systemic circulation, as was noted in Section 4.2, two out of the three parameters, the cardiac output, Q_{LV} , the pressure at the exit of the left ventricle, P_{MAP} , and the central venous pressure at the entrance of the right atrium of the heart, P_{CV} , need to be specified. We shall choose to specify Q_{LV} and P_{CV} , allowing the algorithm to compute the corresponding value of P_{MAP} which we then can compare to the measured values immediately after the posture change, as presented in Table 5.1 in Section 5.1. An increase in the central venous pressure is expected in response to the passive raising of the legs, for this has been observed in the change from supine to the head-down-tilt position (Goldsmith *et al.* 1985; Nixon *et al.* 1979). Using the measured results of Goldsmith *et al.* (1985) for a 15-degree head-down tilt posture, which we deem to correspond qualitatively to our case of 27-degree passive leg elevation, we shall set the value of P_{CV} after the raising of the legs to 2 mmHg higher than the value for the supine position. Gaffney *et al.* (1982) experimentally observed a transient increase in the cardiac output of as much as 10 percent during the first twenty seconds after passive elevation of the legs to 60 degree inclination from the supine position. Guided by this data, we shall set the cardiac output, Q_{LV} , after the raising of the legs to 5 percent higher than the value for the supine position. With these boundary conditions, the computed effect of 27-degree passive leg elevation is presented in Table 5.6.

Table 5.6 Computed blood flow-rate and resistance distribution in supine versus 27-degree passive-leg-elevation postures when P_{CV} is increased by 2 mmHg and Q_{LV} by 4.17 ml/sec during the change in posture.

		Supine		Passive leg elevation		
		$Q_{LV} = 83.33$ ml/sec $P_{CV} = 5$ mmHg $P_{MAP} = 91.36$ mmHg $P_{MAP} - P_{CV} = 86.36$ mmHg		$Q_{LV} = 87.50$ ml/sec $P_{CV} = 7$ mmHg $P_{MAP} = 97.59$ mmHg $P_{MAP} - P_{CV} = 90.59$ mmHg		
Block #	Block Description	Q (ml/sec)	R (mmHg/ml/sec)	Q (ml/sec)	R (mmHg/ml/sec)	ΔQ (%)
1	Ascending Aorta	83.33	1.04	87.50	1.04	5
2	Brachiocephalic	7.87	10.97	8.31	10.90	5.59
3	Right Carotid	1.64	52.66	1.72	52.52	4.88
4	Right Subclavian I	6.23	13.85	6.59	13.75	5.78
5	Right Vertebral	1.89	45.78	1.99	45.61	5.29
6	Right Arm	4.35	19.87	4.60	19.68	5.75
7	Left Carotid	1.64	52.66	1.72	52.52	4.88
8	Left Subclavian I	6.23	13.85	6.59	13.75	5.78
9	Left Vertebral	1.89	45.78	1.99	45.61	5.29
10	Left arm	4.35	19.87	4.60	19.68	5.75
11	Abdomen	67.57	1.28	70.87	1.28	4.87
12	Right Leg	7.51	11.44	7.80	11.58	3.86
13	Left Leg	7.51	11.44	7.80	11.58	3.86
Total		83.33	1.04	87.50	1.04	5

It is noted that the calculations yield an increase of 6 mmHg in the value of the mean arterial pressure, P_{MAP} , when the posture is changed from supine to 27-degree leg elevation. This does not compare very well with the measured results of about 2 mmHg increase in P_{MAP} , as per Table 5.2. The discrepancy may be caused by the assumed value for the increase in cardiac output when the said posture change is realized. If the

computational algorithm is executed without any change in Q_{LV} during the posture change, the increase in P_{MAP} matches the measured value, as presented in Table 5.7.

Table 5.7 Computed blood flow-rate and resistance distribution in supine versus 27-degree passive-leg-elevation postures when P_{CV} is increased by 2 mmHg while Q_{LV} is kept constant during the change in posture.

		Supine		Passive leg elevation		
		$Q_{LV} = 83.33$ ml/sec $P_{CV} = 5$ mmHg $P_{MAP} = 91.36$ mmHg $P_{MAP} - P_{CV} = 86.36$ mmHg		$Q_{LV} = 83.33$ ml/sec $P_{CV} = 7$ mmHg $P_{MAP} = 93.73$ mmHg $P_{MAP} - P_{CV} = 86.73$ mmHg		
Block #	Block Description	Q (ml/sec)	R (mmHg/ml/sec)	Q (ml/sec)	R (mmHg/ml/sec)	ΔQ (%)
1	Ascending Aorta	83.33	1.04	83.33	1.04	0
2	Brachiocephalic	7.87	10.97	7.94	10.92	0.89
3	Right Carotid	1.64	52.66	1.65	52.57	0.61
4	Right Subclavian I	6.23	13.85	6.29	13.79	0.96
5	Right Vertebral	1.89	45.78	1.90	45.68	0.53
6	Right Arm	4.34	19.87	4.39	19.75	1.15
7	Left Carotid	1.64	52.66	1.65	52.57	0.61
8	Left Subclavian I	6.23	13.85	6.29	13.79	0.96
9	Left Vertebral	1.89	45.78	1.90	45.68	0.53
10	Left arm	4.35	19.87	4.39	19.75	0.92
11	Abdomen	67.57	1.28	67.44	1.29	-0.19
12	Right Leg	7.51	11.44	7.29	11.86	-2.93
13	Left Leg	7.51	11.44	7.29	11.86	-2.93
Total		83.32	1.04	83.32	1.04	0

This result is just as plausible as the 5 percent increase in Q_{LV} that was assumed in the original computation described above, for the assumed 5 percent increase was based on a simple linear interpolation from Gaffney *et al.*'s (1982) results, with the linear

relationship between Q_{LV} and leg elevation angle assumed arbitrarily. In addition, the reliability of the thermodilution cardiac output measurement technique used by Gaffney *et al.* (1982) is critically analyzed by Stetz *et al.* (1982), who suggested a minimal difference of 12 to 15 percent to be necessary to indicate a significant change.

It is also important to recognize that the precision of the computed results are dependent on the empirical input to the calculations, which include the diameter, length and compliance information on the blood vessels. Based on information available in the published literature, the uncertainty of these parameters is documented in Appendix F. The effect of these uncertainties on the prediction of the 27-degree passive leg elevation case was established by performing the computations repeatedly with random variations in the noted input parameters within their respective uncertainty ranges, yielding a standard deviation for each of the quantities presented in Table 5.8.

Table 5.8 presents the standard deviation information together with the data of Table 5.7. It is noted that the magnitude of the standard deviation computed for the effect of posture change on P_{MAP} compares quite favorably with the standard deviation of the same quantity observed in the present experiments, as tabulated in Table 5.1. This may suggest that the variation in the measurements were caused to a significant extent by the variations in blood-vessel dimensions amongst the subjects, rather than being dominated by measurement and/or instrumentation errors.

Table 5.8 The effect of uncertainty in the blood-vessel data on the predicted blood flow-rate and resistance distribution in supine versus 27-degree passive-leg-elevation postures.

	Supine		27 Deg-Passive leg elevation	
	$Q_{LV} = 83.33 \text{ ml/sec}$ $P_{CV} = 5 \text{ mmHg}$ $P_{MAP} = 91.24 \pm 0.25 \text{ mmHg}$ $P_{MAP} - P_{CV} = 86.24 \pm 0.25 \text{ mmHg}$		$Q_{LV} = 83.33 \text{ ml/sec}$ $P_{CV} = 7 \text{ mmHg}$ $P_{MAP} = 93.56 \pm 0.29 \text{ mmHg}$ $P_{MAP} - P_{CV} = 86.46 \pm 0.29 \text{ mmHg}$	
Block #	Q Mean $\pm$ SD (ml/sec)	R Mean $\pm$ SD (mmHg/ml/sec)	Q Mean $\pm$ SD (ml/sec)	R Mean $\pm$ SD (mmHg/ml/sec)
1	83.33 $\pm$ 0.00	1.04 $\pm$ 0.01	83.33 $\pm$ 0.00	1.04 $\pm$ 0.00
2	7.84 $\pm$ 0.03	11.00 $\pm$ 0.03	7.91 $\pm$ 0.04	10.95 $\pm$ 0.02
3	1.63 $\pm$ 0.01	52.82 $\pm$ 0.14	1.64 $\pm$ 0.01	52.69 $\pm$ 0.11
4	6.21 $\pm$ 0.03	13.89 $\pm$ 0.03	6.26 $\pm$ 0.03	13.81 $\pm$ 0.03
5	1.88 $\pm$ 0.01	45.84 $\pm$ 0.06	1.89 $\pm$ 0.01	45.73 $\pm$ 0.05
6	4.32 $\pm$ 0.02	19.93 $\pm$ 0.05	4.37 $\pm$ 0.02	19.79 $\pm$ 0.05
7	1.63 $\pm$ 0.01	52.82 $\pm$ 0.14	1.64 $\pm$ 0.01	52.69 $\pm$ 0.11
8	6.21 $\pm$ 0.03	13.89 $\pm$ 0.03	6.27 $\pm$ 0.03	13.81 $\pm$ 0.03
9	1.88 $\pm$ 0.01	45.84 $\pm$ 0.06	1.89 $\pm$ 0.01	45.73 $\pm$ 0.05
10	4.32 $\pm$ 0.02	19.93 $\pm$ 0.05	4.37 $\pm$ 0.03	19.79 $\pm$ 0.05
11	67.64 $\pm$ 0.07	1.27 $\pm$ 0.01	67.51 $\pm$ 0.08	1.28 $\pm$ 0.01
12	7.59 $\pm$ 0.07	11.32 $\pm$ 0.13	7.38 $\pm$ 0.10	11.69 $\pm$ 0.19
13	7.58 $\pm$ 0.07	11.33 $\pm$ 0.13	7.38 $\pm$ 0.10	11.7 $\pm$ 0.19
Total	83.33 $\pm$ 0.00	1.04 $\pm$ 0.01	83.33 $\pm$ 0.00	1.04 $\pm$ 0.00

5.3 Measured Effects of Passive Leg Elevation on Blood Pressure in Borderline Hypertensive Subjects

As was noted in Chapter 4, four of the fifty four subjects used in the present experiments demonstrated signs of borderline hypertension (systolic pressure in the supine position: 120 to 144 mmHg; diastolic pressure in the supine position: 76 to 93 mmHg). The effect of 27-degree passive leg elevation from the supine position on these subjects is documented in Tables 5.9 and 5.10, based on measurements performed 10 seconds and 2 minutes after the posture change, respectively.

Table 5.9 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate on borderline hypertensive subjects 10 seconds after 27 degrees of passive leg elevation.

	Hypertensive Healthy Subjects (Mean $\pm$ SD) ($n = 4$)
Systolic pressure (mmHg)	1.33 $\pm$ 0.88
Diastolic Pressure (mmHg)	2.78 $\pm$ 2.91
Mean arterial pressure (mmHg)	2.30 $\pm$ 1.69
Heart rate (Beats/min)	1.00 $\pm$ 1.2

Table 5.10 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate on borderline hypertensive subjects 2 minutes after 27 degrees of passive leg elevation.

	Hypertensive Healthy Subjects (Mean $\pm$ SD) ($n = 4$)
Systolic pressure (mmHg)	- 8.25 $\pm$ 1.20
Diastolic Pressure (mmHg)	- 3.67 $\pm$ 3.72
Mean arterial pressure (mmHg)	- 5.20 $\pm$ 2.35
Heart rate (Beats/min)	- 4.67 $\pm$ 2.60

Since only four subjects with borderline hypertension were tested, the mean values and the standard deviations presented in these tables are not clearly as reliable as the results for the normotensive subjects. Nonetheless, the results measured 10 seconds after the said posture change are observed to correspond closely with the results for normotensive subjects (Table 5.1), displaying approximately 2 mmHg increase in the mean, diastolic and systolic pressures compared to those recorded in the supine position. This suggests that the response of the cardiovascular system to the posture change before the control mechanisms come into effect is the same for those borderline hypertensive subjects as for the normotensive subjects. On the other hand, the results in Table 5.10 indicate notably lower values of mean, diastolic and systolic pressures measured 2 minutes after the posture change compared to the supine values. This is in contrast with the results of the normotensive subjects, where the said pressures were observed to have returned to the supine-position values when measured 2 minutes after the posture change. This is indicative of a difference in the hemodynamic regulation activities of the control mechanisms between the two groups of subjects.

The difference between the blood-pressure values measured at the 2-minute mark on the normotensive and hypertensive subjects may be due to the augmented function of the cardiopulmonary baroreceptors in hypertensive individuals, as demonstrated by Ueda *et al.* (1989). Another possible answer for the observed difference may be related to the levels of norepinephrine and renin in the system, as documented by Goldsmith *et al.* (1985) during a change from supine to 30-degree head-down-tilt position. Goldsmith *et al.* monitored the plasma norepinephrine and renin activity in six normotensive and one

hypertensive subject during the said posture change. They found that the level of norepinephrine and renin remained unchanged in the normotensive subjects, whereas for the hypertensive subject, the renin level decreased substantially over the first 15 minutes after the posture change, and remained noticeably low when measured at the one-hour mark. Renin acts on angiotensinogen to produce angiotensin I. Together, angiotensin I and angiotensin converting enzyme produce angiotensin II, which in turn causes vasoconstriction of blood vessels, thus raising the arterial pressure. Therefore, if the renin level in the system were to drop during a posture change as per the observation of Goldsmith *et al.* for the hypertensive subject, this would yield dilatation of blood vessel, thereby decreasing the arterial pressure in response to the posture change confirming the blood pressure measurement results in Table 5.10.

Conclusions and Recommendations

The work presented in this thesis has shed light on the hemodynamics effects of passive leg elevation on blood circulation, with emphasis on the variations in the blood pressure at the heart. The chain of events that take place in the cardiovascular system in response to passive leg elevation has been better understood with the aid of the experimental and computational results presented in this thesis.

The experimental results provide quantitative information on the momentary increase in the mean arterial pressure in the ascending aorta, P_{MAP} , observed immediately after passive raising of the legs starting from the supine position. This increase was measured to be about 2 mmHg when the legs were raised to 27 degrees inclination. Computational results demonstrate this temporary increase in P_{MAP} to be the result of changes in the frictional resistance throughout the cardiovascular system. In turn, this change in the resistance field is shown to be the result of the response of viscoelastic blood vessels to local adjustment in blood pressure, induced by the changes in the relative elevation of the various parts of the cardiovascular system as the said posture change is realized.

Experimental observations indicate that the increase in P_{MAP} , noted immediately after passive raising of the legs starting from the supine position (within 2 minutes) offset by the action of the short-term control mechanisms. Borderline hypertensive subjects were observed to differ from normotensive subjects in this regard, with the short-term control

mechanisms overcompensating for the initial increase in P_{MAP} . As a result, the value of P_{MAP} in hypertensive subjects was observed to eventually reach a value slightly (5 mmHg) below the value prevailing before the said posture change is realized. While the number of hypertensive subjects included in the present experiments is relatively small, the observed trend is believed to be correlated with the hypertensive nature of these subjects. Differences in the functioning of the chemoreceptors and baroreceptors between hypertensive and normotensive are argued to be the cause of the noted discrepancy, and the argument is supported by published information on hypertension.

The computational model can be used only to investigate the short term effects of passive leg elevation on blood circulation, but also to lay down the basic ground for more sophisticated models, which can provide a useful tool for clinical analysis and diagnosis of cardiovascular diseases relating to blood flow problems. Improvements to this computational model include taking the control mechanisms into account.

Further recommendations include choosing a larger hypertensive control group particularly due to the distinct behavior noticed in this group which might be due to different control mechanisms.

List of References

- AAMI (1987). "American National Standard for Electronic or Automated Sphygmomanometers. ANSI/AAMI-SP10." Association for the Advancement of Medical Instrumentation, Arlington.
- AAMI (1992). "American National Standard for Electronic or Automated Sphygmomanometers. ANSI/AAMI-SP10." Association for the Advancement of Medical Instrumentation, Arlington.
- AAMI (2002). "Manual, electronic or automated sphygmomanometers. AAMI/CDV-1 SP10." Association for the Advancement of Medical Instrumentation, Arlington.
- AHA (1951). "American Heart Association: Recommendations of human blood pressure determinations by sphygmomanometers." New York.
- AHA (1988). "American Heart Association: Recommendations for human blood pressure determination by sphygmomanometers: report of a special taskforce appointed by the Steering committee." *Hypertension*, 11, 210A-222A.
- AHA (2005). "American Heart Association: Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. Part 1: Blood Pressure Measurement in Humans." *Hypertension*, 45, 142-161.
- Ahmad, M., Blomqvist, C. G., Mullins, C. B., and Willerson, J. T. (1977). "Left ventricular function during lower body negative pressure." *Aviat Space Environ Med*, 48(6), 512-5.

- American Society of Hypertension (1992). "Recommendations for routine blood pressure measurement by indirect cuff sphygmomanometry." *Am J Hypertens*, 5, 207-9.
- Arkwright, P. D., Beilin, L. J., Rouse, I., Armstrong, B. K., and Vandongen, R. (1982). "Effects of alcohol use and other aspects of lifestyle on blood pressure levels and prevalence of hypertension in a working population." *Circulation*, 66(1), 60-6.
- Asmussen, E., Christensen, E. H., and Neilsen, M. (1940). "The regulation of the circulation in different postures." *surgery*, 8, 604.
- Athanassiadis, D., Draper, G. J., Honour, A. J., and Cranston, W. I. (1969). "Variability of automatic blood pressure measurements over 24 hour periods." *Clin Sci*, 36(1), 147-56.
- Bailey, R. H., and Bauer, J. H. (1993). "A review of common errors in the indirect measurement of blood pressure. Sphygmomanometry." *Arch Intern Med*, 153(24), 2741-8.
- Berne, R. M., and Levy, M. N. (1981). *Cardiovascular physiology*, Mosby, St. Louis.
- Bertolissi, M., Broi, U. D., Soldano, F., and Bassi, F. (2003). "Influence of passive leg elevation on the right ventricular function in anaesthetized coronary patients." *Crit Care*, 7(2), 164-70.
- Bevan, A., Honour, A. J., and Scott, F. K. (1969). "Direct arterial pressure recordings in unrestricted man." *Clinical Science*, 36, 329-344.
- BHS (1987). "British Hypertension Society: Recommendations on blood pressure measurement." *British Medical Journal*.

- Bivins, H. G., Knopp, R., and dos Santos, P. A. (1985). "Blood volume distribution in the Trendelenburg position." *Ann Emerg Med*, 14(7), 641-3.
- Booth, J. (1977). "A short history of blood pressure measurement." *Proc R Soc Med*, 70(11), 793-9.
- Boulain, T., Achard, J. M., Teboul, J. L., Richard, C., Perrotin, D., and Ginies, G. (2002). "Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients." *Chest*, 121(4), 1245-52.
- Brunner, L. S., Suddarth, D. S., Smeltzer, S. C. O. C., and Bare, B. G. (2004). "Brunner & Suddarth's textbook of medical-surgical nursing." Lippincott Williams & Wilkins, Philadelphia, xxxiv, 2234, 81.
- Byra-Cook, C. J., Dracup, K. A., and Lazik, A. J. (1990). "Direct and indirect blood pressure in critical care patients." *Nurs Res*, 39(5), 285-8.
- Carel, R. S., Silverberg, D. S., Shoenfeld, Y., Eldar, M., Snir, C., and Mor, G. (1983). "Changes in blood pressure in the lying and sitting positions in normotensive, borderline and hypertensive subjects." *Am J Med Sci*, 285(2), 2-11.
- Caro, C. G. (1978). *The Mechanics of the circulation*, Oxford Univ. Press, Oxford; New York.
- Casadei, R., Parati, G., Pomidossi, G., Groppelli, A., Trazzi, S., Di Rienzo, M., and Mancia, G. (1988). "24-hour blood pressure monitoring: evaluation of Spacelabs 5300 monitor by comparison with intra-arterial blood pressure recording in ambulant subjects." *J Hypertens*, 6(10), 797-803.

- Cellina, G. U., Honour, A. J., and Littler, W. A. (1975). "Direct arterial pressure, heart rate, and electrocardiogram during cigarette smoking in unrestricted patients." *Am Heart J*, 89(1), 18-25.
- Chien, S. (1970). "Shear dependence of effective cell volume as a determinant of blood viscosity." *Science*, 168(934), 977-9.
- Chien, S. (1992). "The Benjamin W. Zweifach Award Lecture. Blood cell deformability and interactions: from molecules to micromechanics and microcirculation." *Microvasc Res*, 44(3), 243-54.
- Clark, L. A., Denby, L., Pregibon, D., Harshfield, G. A., Pickering, T. G., Blank, S., and Laragh, J. H. (1987). "A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure." *J Chronic Dis*, 40(7), 671-81.
- Coccagna, G., Mantovani, M., Brignani, F., Manzini, A., and Lugaresi, E. (1971). "Laboratory note. Arterial pressure changes during spontaneous sleep in man." *Electroencephalogr Clin Neurophysiol*, 31(3), 277-81.
- Colin Medical Inst. Corp. (1997). "Colin Service Manual." San Antonio, TX.
- Cook, N., Cohen, J., Hebert, P., Taylor, J., and Hennekens, C. (1995). "Implications of small reductions in diastolic blood pressure for primary prevention." *Arch Intern Med*, 155, 701-9.
- Crombie, A. (1961). *Augustine to Galileo*, Mercury Books, London, G.B.
- de Moulin, D. "A short history of blood pressure measurement." *2nd Einthoven meeting on past and present cardiology: blood pressure measurement and systemic hypertension*, Breda, 28.

- Dingle, M. (2003). "Role of dangling when moving from supine to standing position." *Br J Nurs*, 12(6), 346-50.
- Dudgeon, R. (1882). *The sphygmograph*, Bailliere, Tindall & Cox, London.
- Dudgeon, R. (1908). "wholesale illustrated catalogue of surgical instruments and medical appliances." Fannin and Co., Dublin.
- Fagan, T. C., Conrad, K. A., Mar, J. H., and Nelson, L. (1986). "Effects of meals on hemodynamics: implications for antihypertensive drug studies." *Clin Pharmacol Ther*, 39(3), 255-60.
- Fewings, J. D., Hanna, M. J., Walsh, J. A., and Whelan, R. F. (1966). "The effects of ethyl alcohol on the blood vessels of the hand and forearm in man." *Br J Pharmacol*, 27(1), 93-106.
- Fisher, H. (1978). "The aneroid sphygmomanometer: an assessment of accuracy." *Cardiovasc Med*, 3, 769-771.
- Folkow, B., and Neil, E. (1971). *Circulation*, Oxford University Press, New York.
- Frank, O. (1889). "Die Grundform des arteriellen Pulses erste Abhandlung: mathematische Analyse." *Z.Biol.*, 37, 483-526.
- Freestone, S., and Ramsay, L. E. (1982). "Effect of coffee and cigarette smoking on the blood pressure of untreated and diuretic-treated hypertensive patients." *Am J Med*, 73(3), 348-53.
- Friedmann, E., Thomas, S. A., Kulick-Ciuffo, D., Lynch, J. J., and Suginohara, M. (1982). "The Effects of Normal and Rapid Speech on Blood Pressure." *Psychosom. Med.*, 44(6), 545-553.

Gaffney, F. A., Bastian, B. C., Thal, E. R., Atkins, J. M., and Blomqvist, C. G. (1982).

"Passive leg raising does not produce a significant or sustained autotransfusion effect." *J Trauma*, 22(3), 190-3.

Gauer, O. H., and Thron, H. L. (1965). *Handbook of Physiology. Circulation*, Bethesda.

Geddes, L. (1970). *The direct and indirect measurement of blood pressure*, Year book medical publishers, Chicago.

Geddes, L. (1984). *Cardiovascular devices and their application*, John Wiley and Sons, Inc., New York.

Gellman, M., Spitzer, S., and Ironson, G. (1990). "Posture, place and mood effects on ABP." *Psychophysiology*, 27, 541-555.

Gentili, D. R., Benjamin, E., Berger, S. R., and Iberti, T. J. (1988). "Cardiopulmonary effects of the head-down tilt position in elderly postoperative patients: a prospective study." *South Med J*, 81(10), 1258-60.

George, C., Lewis, P., and Petrie, A. (1975). "Clinical experience with use of ultrasound sphygmomanometer." *Br Heart J*, 37, 804-7.

Gillespie, J. A. (1967). "Vasodilator properties of alcohol." *Br Med J*, 2(547), 274-7.

Gispen, J. (1974). "Measuring the patient in ancient medical texts." *Acta Clin Belg*, 29, 224-227.

Goldsmith, S. R., Francis, G. S., and Cohn, J. N. (1985). "Effect of head-down tilt on basal plasma norepinephrine and renin activity in humans." *J Appl Physiol*, 59(4), 1068-71.

- Gorback, M. S., Quill, T. J., and Lavine, M. L. (1991). "The relative accuracies of two automated noninvasive arterial pressure measurement devices." *J Clin Monit*, 7(1), 13-22.
- Graftieaux, J. P., Lepousse, C., Gomis, P., Barre, J., and Leon, A. (1998). "[Blood volume changes caused by position under general anesthesia]." *Ann Fr Anesth Reanim*, 17(2), 133-9.
- Graham, A., and Douglas, D. (1949). "Effect of the head-down position on the circulation on hypotensive states." *Lancet*, 2, 941.
- Gravlee, G. P., and Brockschmidt, J. K. (1990). "Accuracy of four indirect methods of blood pressure measurement, with hemodynamic correlations." *J Clin Monit*, 6(4), 284-98.
- Greger, R., and Windhorst, U. (1996). *Comprehensive human physiology: from cellular mechanisms to integration*, Springer, Berlin.
- Grin, J. M., McCabe, E. J., and White, W. B. (1993). "Management of hypertension after ambulatory blood pressure monitoring." *Ann Intern Med*, 118(11), 833-7.
- Guntheroth, W. G., Abel, F. L., and Mullins, G. L. (1964). "The effect of Trendelenburg's position on blood pressure and carotid flow." *Surg Gynecol Obstet*, 119, 345-8.
- Guyton, A. C. (1969). *Function of the human body*, Saunders, Philadelphia.
- Guyton, A. C. (1980). *Arterial pressure and hypertension*, Saunders, Philadelphia.
- Guyton, A. C. (1981). *Textbook of medical physiology*, Saunders, Philadelphia.
- Guyton, A. C., and Hall, J. E. (2000). *Textbook of medical physiology*, Saunders, Philadelphia.

- Halliwill, J. R. (2001). "Mechanisms and clinical implications of post-exercise hypotension in humans." *Exerc Sport Sci Rev*, 29(2), 65-70.
- Hargens, A. R., Millard, R. W., Pettersson, K., and Johansen, K. (1987). "Gravitational haemodynamics and oedema prevention in the giraffe." *Nature*, 329, 59-60.
- Harshfield, G. A., Pickering, T. G., Kleinert, H. D., Blank, S., and Laragh, J. H. (1982). "Situational variations of blood pressure in ambulatory hypertensive patients." *Psychosom Med*, 44(3), 237-45.
- Holland, W., and Humerfelt, S. (1962). "Measurement of blood-pressure: comparison of intra-arterial and cuff values." *BMJ*, 2(1241-3).
- Hoskins, P., Thrush, A., Martin, K., Whittingam, T. et al. (2002). "Diagnostic Ultrasound: Physics and Equipment" Cambridge University Press, London.
- Howes, L. G., and Reid, J. L. (1985). "Changes in plasma free 3,4-dihydroxyphenylethylene glycol and noradrenaline levels after acute alcohol administration." *Clin Sci (Lond)*, 69(4), 423-8.
- Hu, Z., Zhao, G., Xiao, Z., Chen, X., Zhong, C., and Yang, J. (1999). "Different responses of cerebral vessels to -30 degrees head-down tilt in humans." *Aviat Space Environ Med*, 70(7), 674-80.
- Imai, Y., Abe, K., Sasaki, S., Minami, N., Munakata, M., Sakuma, H., Hashimoto, J., Sekino, H., Imai, K., and Yoshinaga, K. (1989). "Clinical evaluation of semiautomatic and automatic devices for home blood pressure measurement: comparison between cuff-oscillometric and microphone methods." *J Hypertens*, 7(12), 983-90.

- Imai, Y., Hashimoto, J., Minami, N., Munakata, M., Watanabe, N., Sakuma, H., Sekino, H., and Abe, K. (1994). "Accuracy and performance of the Terumo ES-H51, a new portable blood pressure monitor." *Am J Hypertens*, 7(3), 255-60.
- Ireland, M. A., Vandongen, R., Davidson, L., Beilin, L. J., and Rouse, I. L. (1984). "Acute effects of moderate alcohol consumption on blood pressure and plasma catecholamines." *Clin Sci (Lond)*, 66(6), 643-8.
- James, G. D., Yee, L. S., Harshfield, G. A., Blank, S. G., and Pickering, T. G. (1986). "The influence of happiness, anger, and anxiety on the blood pressure of borderline hypertensives." *Psychosom Med*, 48(7), 502-8.
- Jamieson, M. J., Webster, J., Philips, S., Jeffers, T. A., Scott, A. K., Robb, O. J., Lovell, H. G., and Petrie, J. C. (1990). "The measurement of blood pressure: sitting or supine, once or twice?" *J Hypertens*, 8(7), 635-40.
- Janeway, T. (1904). *The clinical study of blood-pressure.*, D. Appleton & Co., New York and London.
- Jeong, D. U., and Dimsdale, J. E. (1990). "The effects of caffeine on blood pressure in the work environment." *Am J Hypertens*, 3(10), 749-53.
- Jones, D. W., Frohlich, E. D., Grim, C. M., Grim, C. E., and Taubert, K. A. (2001). "Mercury sphygmomanometers should not be abandoned: An advisory statement from the Council for High Blood Pressure Research, American Heart Association." *Hypertension*, 37(2), 185-6.
- Kahn, M. (1919). "The position of the arm in blood pressure measurement." *Am J Med Sci*, 158, 823-29.

- Kaplan, N. M. (1990). *Clinical hypertension*, William and Wilkins, Baltimore.
- Karemaker, J. (1987). "Neurophysiology of the baroreceptor reflex." *The Beat-by-beat Investigation of Cardiovascular Function: Measurement, Analysis, and Applications*, R. Kitney and O. Rompelman, eds., Clarendon Press, Oxford.
- Kenney, M. J., and Seals, D. R. (1993). "Postexercise hypotension. Key features, mechanisms, and clinical significance." *Hypertension*, 22(5), 653-64.
- Khoury, A. F., Sunderajan, P., and Kaplan, N. M. (1992). "The early morning rise in blood pressure is related mainly to ambulation." *Am J Hypertens*, 5(6 Pt 1), 339-44.
- King, G. E. (1963). "Influence of rate of cuff inflation and deflation on observed blood pressure by sphygmomanometry." *Am Heart J*, 65, 303-6.
- Kirkendell, W., Burton, R., Epstein, F., and Freis, E. (1967). "Recommendations for human blood pressure determination by sphygmomanometer." *Circulation*, 36, 980-88.
- Klatsky, A. L., Friedman, G. D., Siegelaub, A. B., and Gerard, M. J. (1977). "Alcohol consumption and blood pressure Kaiser-Permanente Multiphasic Health Examination data." *N Engl J Med*, 296(21), 1194-200.
- Korotkoff, N. (1905). "To the question of methods of determining the blood pressure." *Rep Imp Mil Acad*, 11, 365-7.
- Ku, D. N. (1997). "Blood Flow in Arteries." *Annual Review of Fluid Mechanics*, 29, 399-434.

- Kulkarni, S., O'Farrell, I., Erasi, M., and Kochar, M. S. (1998). "Stress and hypertension." *Wmj*, 97(11), 34-8.
- Kupari, M. (1983). "Acute cardiovascular effects of ethanol A controlled non-invasive study." *Br Heart J*, 49(2), 174-82.
- Kyriakides, Z. S., Koukoulas, A., Paraskevaïdis, I. A., Chrysos, D., Tsiapras, D., Galiotos, C., and Kremastinos, D. T. (1994). "Does passive leg raising increase cardiac performance? A study using Doppler echocardiography." *Int J Cardiol*, 44(3), 288-93.
- Lawrence, C. (1978). "Physiological apparatus in the Wellcome Museum. 1. The Marey sphygmograph." *Med Hist*, 22(2), 196-200.
- Lawrence, C. (1979). "Physiological apparatus in the Wellcome Museum. 3. Early sphygmomanometers." *Med Hist*, 23, 474-8.
- Le Pailleur, C., Feder, J. M., Baubion, N., Landais, P., el Hasnaoui, A., Montgermont, P., Metzger, J. P., Heulin, A., Mounier-Vehier, C., and Vacheron, A. (1993). "["White-coat" effect in 35 consecutive patients with hypertension. Quantification method, role of physician-patient dialogue]." *Arch Mal Coeur Vaiss*, 86(4), 427-33.
- Le Pailleur, C., Helft, G., Landais, P., Montgermont, P., Feder, J. M., Metzger, J. P., and Vacheron, A. (1998). "The effects of talking, reading, and silence on the "white coat" phenomenon in hypertensive patients." *Am J Hypertens*, 11(2), 203-7.
- Levick, J. R. (2003). *An Introduction to Cardiovascular Physiology*, Arnold, London.

- Lind, A. R., Taylor, S. H., Humphreys, P. W., Kennelly, B. M., and Donald, K. W. (1964). "The circulatory effects of sustained voluntary muscle contraction." *Clin Sci*, 27, 229-44.
- Linden, W. (1987). "A microanalysis of autonomic activity during human speech." *Psychosom Med*, 49(6), 562-78.
- Ling, J., Ohara, Y., Orime, Y., Noon, G. P., and Takatani, S. (1995). "Clinical evaluation of the oscillometric blood pressure monitor in adults and children based on the 1992 AAMI SP-10 standards." *J Clin Monit*, 11(2), 123-30.
- Lipsitz, L. A., Nyquist, R. P., Jr., Wei, J. Y., and Rowe, J. W. (1983). "Postprandial reduction in blood pressure in the elderly." *N Engl J Med*, 309(2), 81-3.
- Ljungvall, P., Thorvinger, B., and Thulin, T. (1989). "The influence of a heart level pillow on the result of blood pressure measurement." *J Hum Hypertens*, 3(6), 471-4.
- Logue, A. W. (1986). *The psychology of eating and drinking*, W.H. Freeman, New York.
- Ludwig, C. (1847). "Beitrage zur Kenntnis des Einfluss der Respirations bewegungen auf den Blutlauf im Aortensysteme." *Arch Anat Physiol Wiss Med*, 242-302.
- Lynch, J. J., Thomas, S. A., Long, J. M., Malinow, K. L., Chickadonz, G., and Katcher, A. H. (1980). "Human speech and blood pressure." *J Nerv Ment Dis*, 168(9), 526-34.
- Mader, S. S. (2003). *Inquiry into life*, W. C. Brown Co. Publishers, Dubuque, Iowa.

- Mann, S., Jones, R. I., Millar-Craig, M. W., Wood, C., Gould, B. A., and Raftery, E. B. (1984). "The safety of ambulatory intra-arterial pressure monitoring: a clinical audit of 1000 studies." *Int J Cardiol*, 5(5), 585-97.
- Marey, E. (1863). *Physiologie medicale de la circulation du sang*, Adrien Delahaye, Paris.
- Marey, E. (1876). "Pression et vitesse du sang." *Physiologie experimentale pratique des hautes etudes de M Marey*, Paris.
- Marieb, E. N. (2004). *Human anatomy and physiology*, Benjamin/Cummings, Redwood City, Calif.; Don Mills, Ont.
- Mariotti, G., Alli, C., Avanzini, F., Canciani, C., Di Tullio, M., Manzini, M., Salmoirago, E., Taioli, E., Zussino, A., and Radice, M. (1987). "Arm position as a source of error in blood pressure measurement." *Clin Cardiol*, 10(10), 591-3.
- Martin, J. T., and Warner, M. A. (1997). *Positioning in anesthesia and surgery*, Saunders, Philadelphia.
- Martini, F., Martini, F., and Welch, K. (1998). *Fundamentals of anatomy and physiology. Applications manual*, Prentice Hall, Upper Saddle River, N.J.
- Mattu, G., Perry, T. J., and Wright, J. (2001). "Comparison of the oscillometric blood pressure monitor (BPM-100(Beta)) with the auscultatory mercury sphygmomanometer." *Blood Press Monit*, 6(3), 153-9.
- Mauck, G., Smith, C., Geddes, L., and Bourland, J. (1980). "The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure—part ii." *J Biomech Eng*, 102, 28-33.

- McClintic, J. R. (1985). *Physiology of the human body*, Wiley, New York.
- McDonald, D. A. (1974). *Blood flow in arteries*, Edward Arnold, London.
- Mejia, A. D., Egan, B. M., Schork, N. J., and Zweifler, A. J. (1990). "Artefacts in measurement of blood pressure and lack of target organ involvement in the assessment of patients with treatment-resistant hypertension." *Ann Intern Med*, 112(4), 270-7.
- Milnor, W. R. (1974). "Regional Circulations." *Medical physiology*, V. B. Mountcastle, ed., Mosby, St-Louis, 2v. (xv, 1807, 44).
- Milnor, W. R. (1989). *Hemodynamics*, Williams & Wilkins, Baltimore.
- Mion, D., and Pierin, A. (1998). "How accurate are sphygmomanometers?" *J Hum Hypertens*, 12, 245-8.
- Mitchell, P. L., Parlin, R. W., and Blackburn, H. (1964). "Effect Of Vertical Displacement Of The Arm On Indirect Blood-Pressure Measurement." *N Engl J Med*, 271, 72-4.
- Mohrman, D. E., and Heller, L. J. (2003). *Cardiovascular physiology*, Lange Medical Books/McGraw-Hill, New York.
- Moore, T., Svetkey, L., Pao-Hwa, L., Karanja, N., and Jenkins, M. (2003). *The dash diet for hypertension*, Simon & Schuster, inc., New York.
- Moreno, A. H., and Burchell, A. R. (1982). "Respiratory regulation of splanchnic and systemic venous return in normal subjects and in patients with hepatic cirrhosis." *Surg Gynecol Obstet*, 154(2), 257-67.

- Morgan, B. C., Guntheroth, W. G., and McGough, G. A. (1964). "Effect Of Position On Leg Volume. Case Against The Trendelenburg Position." *Jama*, 187, 1024-6.
- Moss, A. (1978). "Indirect method of blood pressure measurement." *Pediatr Clin North Am*, 25, 3-14.
- Nara, A. R., Burns, M. P., and Downs, W. G. (1989). *Blood pressure*, SpaceLabs, Inc.
- Netea, R. T., Bijlstra, P. J., Lenders, J. W., Smits, P., and Thien, T. (1998). "Influence of the arm position on intra-arterial blood pressure measurement." *J Hum Hypertens*, 12(3), 157-60.
- Netea, R. T., Elving, L. D., Lutterman, J. A., and Thien, T. (2002). "Body position and blood pressure measurement in patients with diabetes mellitus." *J Intern Med*, 251(5), 393-9.
- Netea, R. T., Lenders, J. W., Smits, P., and Thien, T. (1999). "Arm position is important for blood pressure measurement." *J Hum Hypertens*, 13(2), 105-9.
- Netea, R. T., Lenders, J. W., Smits, P., and Thien, T. (2003). "Both body and arm position significantly influence blood pressure measurement." *J Hum Hypertens*, 17(7), 459-62.
- Netea, R. T., Smits, P., Lenders, J. W., and Thien, T. (1998). "Does it matter whether blood pressure measurements are taken with subjects sitting or supine?" *J Hypertens*, 16(3), 263-8.
- Nichols, W. W., and O'Rourke, M. F. (2005). *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*, Arnold; Oxford University Press, London, New York.

- Nichols, W. W., O'Rourke, M. F., Hartley, C., and McDonald, D. A. (1998). *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*, Arnold; Oxford University Press, London, New York.
- Nielsen, P. E. (1983). "The accuracy of auscultatory blood pressure measurement in the elderly." *Acta Med Scand Suppl*, 676, 39-44.
- Nixon, J. V., Murray, R. G., Bryant, C., Johnson, R. L., Jr., Mitchell, J. H., Holland, O. B., Gomez-Sanchez, C., Vergne-Marini, P., and Blomqvist, C. G. (1979). "Early cardiovascular adaptation to simulated zero gravity." *J Appl Physiol*, 46(3), 541-8.
- Noordergraaf, A. (1963). "An analog computer for the human circulatory system.," PhD Thesis.
- Norris, G. W. (1916). *Blood pressure and its clinical application*, Lea & Febiger, Philadelphia.
- O'Brien, E., Mee, F., Atkins, N., and O'Malley, K. (1992). "Short report: accuracy of the CH-Druck/Pressure Scan ERKA ambulatory blood pressure measuring system determined by the British Hypertension Society Protocol." *J Hypertens*, 10(10), 1283-4.
- O'Brien, E., Mee, F., Atkins, N., and O'Malley, K. (1992). "Short report: accuracy of the Profilomat ambulatory blood pressure measuring system determined by the British Hypertension Society Protocol." *J Hypertens*, 10(10), 1285-6.
- O'Brien, E., Mee, F., Atkins, N., and O'Malley, K. (1993). "Short report: accuracy of the Dinamap portable monitor, model 8100 determined by the British Hypertension Society protocol." *J Hypertens*, 11(7), 761-3.

- O'Brien, E., and O'Malley, K. (1991). *Blood pressure measurement*, Elsevier Science Publishers, New York.
- O'Brien, E., Petrie, J., Littler, W. A., and al., e. (1993). "The British Hypertension Society protocol for the evaluation of blood pressure measuring devices." *J Hypertens*, 11(Supp. 2), S43-S62.
- O'Brien, E., Petrie, J., Littler, W. A., Sweit, M., Padfield, P., O'Malley, K., Jamieson, M. J., Altman, D., Bland, M., and Atkins, N. (1990). "The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems." *J Hypertens*, 8, 607-19.
- O'Brien, E., Pickering, T., Asmar, R., Myers, M., Parati, G., Staessen, J., Mengden, T., Imai, Y., Waeber, B., Palatini, P., and Gerin, W. (2002). "Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults." *Blood Press Monit*, 7, 3-17.
- O'Rourke, M. (1990). "Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension." *Hypertension*, 15(4), 339-47.
- O'Rourke, M. F. (1982). *Arterial function in health and disease*, Churchill Livingstone, Edinburgh.
- O'Rourke, M. F., and Taylor, M. G. (1967). "Input impedance of the systemic circulation." *Circ Res*, 20(4), 365-80.

- Ochsner, A. J., Colp, R. J., and Burch, G. (1951). "Normal blood pressure in the superficial venous system of man at rest in the supine position." *Circulation*, 3(5), 674-80.
- Ostrow, C. L., Hupp, E., and Topjian, D. (1994). "The effect of Trendelenburg and modified trendelenburg positions on cardiac output, blood pressure, and oxygenation: a preliminary study." *Am J Crit Care*, 3(5), 382-6.
- Palatini, P., Mos, L., Munari, L., Valle, F., Del Torre, M., Rossi, A., Varotto, L., Macor, F., Martina, S., Pessina, A. C., and et al. (1989). "Blood pressure changes during heavy-resistance exercise." *J Hypertens Suppl*, 7(6), S72-3.
- Palatini P, P. M., Canali C, Pessina, AC. (1991). "Validation of the accuracy of the A&D TM2420 Model 7 for ambulatory blood pressure monitoring and effect of microphone replacement on its performance." *J Ambul Monit*, 4, 281-8.
- Pescatello, L. S., Fargo, A. E., Leach, C. N., Jr., and Scherzer, H. H. (1991). "Short-term effect of dynamic exercise on arterial blood pressure." *Circulation*, 83(5), 1557-61.
- Pickering, T. G. (2002). "Principles and techniques of blood pressure measurement." *Cardiol Clin*, 20(2), 207-23.
- Pickering, T. G., and Alpert, B. S. (1994). *Ambulatory blood pressure*, SpaceLabs Medical Inc., Redmond, Wash.
- Pickering, T. G., Harshfield, G. A., Kleinert, H. D., Blank, S., and Laragh, J. H. (1982). "Blood pressure during normal daily activities, sleep, and exercise. Comparison of values in normal and hypertensive subjects." *Jama*, 247(7), 992-6.

- Piscatella, J.C., and Franklin, B.A. (2003). *Take a load off your heart*, Workman Publishing, New York.
- Poiseuille, J. (1828). "Recherches sur la force du coeur aortique," Didot, Paris.
- Potain, P. (1889). "Du sphygmomanometre et de la mesure de la pression arterielle chez l'homme." *Arch Physiol Norm Pathol*, i, 556-569.
- Potter, J. F., Watson, R. D., Skan, W., and Beevers, D. G. (1986). "The pressor and metabolic effects of alcohol in normotensive subjects." *Hypertension*, 8(7), 625-31.
- Pricolo, V. E., Burchard, K. W., Singh, A. K., Moran, J. M., and Gann, D. S. (1986). "Trendelenburg versus PASG application--hemodynamic response in man." *J Trauma*, 26(8), 718-26.
- Raftery, E. B., and Ward, A. P. (1968). "The indirect method of recording blood pressure." *Cardiovasc Res*, 2(2), 210-8.
- Ragan, C., and Bordley, J. I. (1941). "The accuracy of clinical measurements of arterial blood pressure." *Bull Johns Hopk Hosp*, 69, 504-528.
- Ramsay, L., Williams, B., Johnston, G., MacGregor, G., Poston, L., Potter, J., Poulter, N., and Russell, G. (1999). "Guidelines for management of hypertension: report of the third working party of the British Hypertension Society." *J Hum Hypertens*, 13(9), 569-92.
- Reich, D. L., Konstadt, S. N., Raissi, S., Hubbard, M., and Thys, D. M. (1989). "Trendelenburg position and passive leg raising do not significantly improve

- cardiopulmonary performance in the anesthetized patient with coronary artery disease." *Crit Care Med*, 17(4), 313-7.
- Reid, I. A. (1992). "Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure." *Am J Physiol*, 262(6 Pt 1), E763-78.
- Riff, D. P., Jain, A. C., and Doyle, J. T. (1969). "Acute hemodynamic effects of ethanol on normal human volunteers." *Am Heart J*, 78(5), 592-7.
- Rippe, J.M. (2004). *Heart disease for dummies*, Wiley, New Jersey.
- Riva-Rocci, S. (1896). "Un nuovo sfigmomanometro." *Gazz Med Torino*, 50, 981-996.
- Rowell, L. B. (1986). *Human circulation: regulation during physical stress*, Oxford University Press, New York.
- Rowell, L. B. (1993). *Human cardiovascular control*, Oxford University Press, New York.
- Ruch, T. C., Patton, H. D., and Howell, W. H. (1965). *Physiology and biophysics*, Saunders, Philadelphia.
- Rushmer, R. F. (1976). *Cardiovascular dynamics*, Saunders, Philadelphia.
- Rushmer, R. F. (1976). *Structure and function of the cardiovascular system*, Saunders, Philadelphia.
- Russell, A. E., Wing, L. M., Smith, S. A., Aylward, P. E., McRitchie, R. J., Hassam, R. M., West, M. J., and Chalmers, J. P. (1989). "Optimal size of cuff bladder for indirect measurement of arterial pressure in adults." *J Hypertens*, 7(8), 607-13.

- Rutlen, D. L., Wackers, F. J., and Zaret, B. L. (1981). "Radionuclide assessment of peripheral intravascular capacity: a technique to measure intravascular volume changes in the capacitance circulation in man." *Circulation*, 64(1), 146-52.
- Sandwich. (1980). *History of hypertension series*, Pfizer Ltd., Kent.
- Santucci, S., Steiner, D., Zimble, M., James, G., and Pickering, T. G. (1988). "A validation study of the SpaceLabs 90202 and 5200 ambulatory blood pressure monitors." *J Ambul Monit*, 1, 211-16.
- Schreiber, S. J., Lambert, U. K., Doepp, F., and Valdueza, J. M. (2002). "Effects of prolonged head-down tilt on internal jugular vein cross-sectional area." *Br J Anaesth*, 89(5), 769-71.
- Schwan, A., and Pavsek, K. (1989). "Change in posture during sleep causes errors in noninvasive automatic blood pressure recordings." *J Hypertens*, 7(suppl 6), S62-S63.
- Shepherd, J. T. (1963). *Physiology of the circulation in human limbs in health and disease*, Saunders, Philadelphia.
- Shier, D., Butler, J., and Lewis, R. (2004). *Hole's human anatomy & physiology*, McGraw-Hill Higher Education, Boston, Mass.
- Sibbald, W. J., Paterson, N. A., Holliday, R. L., and Baskerville, J. (1979). "The Trendelenburg position: hemodynamic effects in hypotensive and normotensive patients." *Crit Care Med*, 7(5), 218-24.
- Silverthorn, D. U. (1998). *Human physiology: an integrated approach*, Prentice Hall, Upper Saddle River, N.J.

- Smits, P., Thien, T., and van't Laar, A. (1985). "Circulatory effects of coffee in relation to the pharmacokinetics of caffeine." *Am J Cardiol*, 56(15), 958-63.
- Snellen, H. (1980). *E.J. Marey and cardiology*, Kooyker Scientific Publications, Rotterdam.
- Solomon, E., Smidt, R., and Adragna, P. (1990). *Human Anatomy & Physiology*, Saunders College Publishing, Philadelphia, USA.
- Spence, J. (1990). *Hypertension: Pathophysiology, Diagnosis, and Management*, Raven, New York.
- Spencer, M. P., Okino, H., Denison, A. B. J., and Berry, R. L. "Electronic and mathematical models of the circulatory system." *Dig. Int. Conf. Med. Electron.*, New York.
- Stegall, H., Kardon, M., and Kemmerer, W. (1968). "Indirect measurement of arterial blood pressure by Doppler ultrasonic sphygmomanometry." *J Appl Physiol*, 25, 793-8.
- Stein, I. (1945). "The effect of change of position of the arm upon blood pressure." *Am Heart J*, 31, 477-80.
- Stergiopulos, N., Westerhof, B. E., and Westerhof, N. (1999). "Total arterial inertance as the fourth element of the windkessel model." *Am J Physiol*, 276(1 Pt 2), H81-8.
- Stergiopulos, N., Young, D., and Rogge, T. (1992). "Computer simulation of arterial flow with applications to arterial and aortic stenoses." *Journal of biomechanics*, 25(12), 1477-1488.

- Stetz, C. W., Miller, R. G., Kelly, G. E., and Raffin, T. A. (1982). "Reliability of the thermodilution method in the determination of cardiac output in clinical practice." *Am Rev Respir Dis*, 126(6), 1001-4.
- Sun, M., Tien, J., Jones, R., and Ward, R. (1996). "A new approach to reproducibility assessment: clinical evaluation of SpaceLabs Medical oscillometric blood pressure monitor." *Biomed Instrum Technol*, 30(5), 439-48.
- Taylor, J., and Weil, M. H. (1967). "Failure of the Trendelenburg position to improve circulation during clinical shock." *Surg Gynecol Obstet*, 124(5), 1005-10.
- Terent, A., and Breig-Asberg, E. (1994). "Epidemiological perspective of body position and arm level in blood pressure measurement." *Blood Press*, 3(3), 156-63.
- Thomas, M., and Shillingford, J. (1965). "The circulatory response to a standard postural change in ischaemic heart disease." *Br Heart J*, 27, 17-27.
- Tochikubo, O., Kawano, Y., Miyajima, E., and Ishii, M. (1997). "A new photo-oscillometric method employing the delta-algorithm for accurate blood pressure measurement." *J Hypertens*, 15(2), 147-56.
- Tortora, G. J., and Grabowski, S. R. (2003). *Principles of anatomy and physiology*, Wiley, New York.
- Ueda, M., Nomura, G., Shibata, H., Nishida, H., Moriyama, A., Kumagai, E., and Toshima, H. (1989). "Assessment of cardiopulmonary baroreflex function in hypertensive and normotensive subjects with or without hypertensive relatives." *Clin Exp Pharmacol Physiol Suppl*, 15, 89-92.

- Van Egmond, J., Lenders, J. W., Weernink, E., and Thien, T. (1993). "Accuracy and reproducibility of 30 devices for self-measurement of arterial blood pressure." *Am J Hypertens*, 6(10), 873-9.
- Veerman, D. P., van Montfrans, G. A., and Wieling, W. (1990). "Effects of cuff inflation on self-recorded blood pressure." *Lancet*, 335(8687), 451-3.
- Von Basch, S. (1880). "Ueber die Messung des Blutdrucks am Menschen." *Z Klin Med*, 2, 79-96.
- Wang, J., and Parker, K. (2004). "Wave propagation in a model of the arterial circulation." *Journal of biomechanics*, 37(4), 457-70.
- Webster, J., Newnham, D., Petrie, J. C., and Lovell, H. G. (1984). "Influence of arm position on measurement of blood pressure." *Br Med J (Clin Res Ed)*, 288(6430), 1574-5.
- Weisser, B., Velling, P., Geller, C., Kraft, K., Gobel, B., Vetter, H., and Dusing, R. (1990). "Pseudohypertension in hypertensive patients on multiple drug therapy." *J Hypertens Suppl*, 8(4), S79-81.
- Westerhof, B. E. (1968). "Analog studies of human systemic arterial hemodynamics," PhD thesis.
- Westerhof, N., Bosman, F., DeVries, C. J., and Noordergraaf, A. (1969). "Analog studies of the human systemic arterial tree." *J Biomech*, 2, 121-143.
- White, W. B. (1990). "The assessment of portable, non-invasive blood pressure recorders." *J Hypertens*, 8, 591-3.
- Whitmore, R. L. (1968). *Rheology of the circulation*, Pergamon Press, Oxford, Toronto.

- Wilcox, S., and Vandam, L. D. (1988). "Alas, poor Trendelenburg and his position! A critique of its uses and effectiveness." *Anesth Analg*, 67(6), 574-8.
- Wilkins, R. W., Bradley, S. E., and Friedland, C. K. (1950). "The acute circulatory effects of the head-down position, negative G in normal man, with a note on some measures designed to relieve cranial congestion in this position." *J Clin Invest*, 29(7), 940-9.
- Wong, D. H., Tremper, K. K., Zaccari, J., Hajduczek, J., Konchigeri, H. N., and Hufstedler, S. M. (1988). "Acute cardiovascular response to passive leg raising." *Crit Care Med*, 16(2), 123-5.
- Yamakoshi, K. (1991). "Non-invasive Techniques for Ambulatory Blood Pressure Monitoring and Simultaneous Cardiovascular Measurement." *J. Ambulat. Mont.*, 4, 123-143.
- Yasumasa, A., Inoue, S., Tatebayashi, K., Shiraishi, Y., and Kawai, Y. (2002). "Effects of head-down tilt on cerebral blood flow in humans and rabbits." *J Gravit Physiol*, 9(1), 89-90.
- Zachariah, P. K., Sheps, S. G., and Moore, A. G. (1990). "Office blood pressures in supine, sitting, and standing positions: correlation with ambulatory blood pressures." *Int J Cardiol*, 28(3), 353-60.

Appendices

Review: The Cardiovascular System

The cardiovascular system is like a highway network. It consists of a pumping station (heart), a distribution system (blood vessels), a working fluid (blood), and a control system as shown in Figure A.1.

The cardiovascular system provides for the exchange of mass (nutrients, oxygen, carbon dioxide, metabolic waste products, etc), and energy (including heat) between every living cell of the body and the environment.

A.1 The Cardiovascular Pump

The heart is the cardiovascular pump and is made up of a powerful cardiac muscle called the myocardium as shown in Figure A.2 (Levick, 2003). The myocardium contracts and causes a wringing type of action. The heart consists of four chambers and four valves shown in Figure A.3. The heart chambers function as separate pumps. These chambers intermittently pump blood to the aorta and continuously to the capillaries, carrying nutrients, oxygen, and helping removing harmful waste. The right atrium receives blood from the body, pumps it into the right ventricle, and then the right ventricle pumps it into the pulmonary artery, and finally to the lungs. Gas exchange takes place in the lungs. Blood picks up oxygen and travels back to the heart through the pulmonary veins into the left atrium, to the left ventricle and out to the body's cells through the aorta (Figure A.4).

Figure A.1 Schematic representation of the cardiovascular system.
Reproduced from Levick (2003).

Figure A.2 Layers of the heart.
Reproduced from Marieb (2004).

Figure A.3 Internal view of the heart.
Reproduced from Mader (2003).

Figure A.4 Blood path through the heart.
Reproduced from Mader (2003).

A.1.1 Heart Valves

The heart valves are composed of tough connective tissue sheets, which act like flaps as shown in Figure A.5. These valves play a significant role in helping the heart to efficiently pump the blood around the body. Heart valves ensure a one-way blood flow through the heart. The valves open and close simultaneously and passively due to pressure differentials. That is to say, when pressure is greater in front of the valve, it closes, and when pressure is greater behind the valve, it opens as illustrated in Figure A.6 (Marieb, 2004).

Figure A.5 Superior view of the heart valves.
Reproduced from Tortora and Grabowski (2003).

Figure A.6 One way flow of blood through the heart valves.
Reproduced from Tortora and Grabowski (2003).

A.1.2 Heart Sounds

The closing of heart valves causes normal heart sounds. As valves snap shut, the walls of the chambers and major arteries vibrate. When atrioventricular valves close, a first “lub” sound is produced. When semilunar (aortic and pulmonary) valves close, a second “dub” sound is produced (Figure A.7).

A.1.2.1 Heart Murmurs

Blood flow through the heart must take place in a smooth laminar fashion where heart valves fully open or fully close. However, if the heart valves fail to fully open or to fully close, then turbulent flow occurs, and abnormal heart sounds are produced. Abnormal heart sounds are called murmurs. Heart murmurs are closely related to heart disease (Mohrman and Heller, 2003).

Figure A.7 Correlation of events in a cardiac cycle.
Reproduced from McClintic (1985).

A.1.3 Heart Cycle

The Cardiac cycle consists of systole and diastole. The systole part refers to heart contractions, while the diastole part refers to heart relaxation. The amount of blood pumped out of a ventricle during each systole is called the stroke volume and it is equal to approximately 70 ml per heart beat in the average adult (Guyton and Hall, 2000). The amount of blood pumped out per minute is known as the cardiac output, and it is approximately equal to 5 to 6 l/min in a resting individual (Mohrman and Heller, 2003). Blood flow through the heart is controlled by pressure changes.

The sinoatrial node, also known as the pace maker and located at the junction of the superior vena cava and the right atrium, initiates the cardiac cycle. Impulses from this node cause the atria to contract (Figure A.8) and are represented in the P wave in Figure A.7. After a momentary pause represented by the PQ wave, impulses from the P wave stimulate the AV node, which is located near the tricuspid valve above the ventricular septum. Impulses pass from the AV node to the bundle of His and Purkinje fibers, and cause the ventricle to contract. These contractions are represented by the QRS wave. Recovery of the ventricles is represented by the T wave (Shier *et al.*, 2004).

Figure A.8 Cardiac conduction system.
Reproduced from Nara *et al.*(1989).

A.2 The Vascular System

The human circulatory system consists of two circuits arranged in series one after the other, known as the systemic and pulmonary circuits, and an additional lymphatic sub-circuit shown in Figure A.9.

Figure A.9 The lymphatic circuit as it relates to the cardiovascular system.
Reproduced from Tortora and Grabowski (2003).

A.2.1 The Systemic Circuit

The systemic circuit has the left ventricle as its pump. In this circuit, blood is propelled during systole from the left ventricle into the aorta, then on to the various arteries (Figure A.10), then to arterioles, and finally to the capillary bed. The capillary bed is a network of very narrow blood vessels, where exchange of chemicals between the blood and the body cells takes place. Capillaries merge to form venules, which in turn join to form veins (Figure A.11). As the merging progresses, there is a steady decrease in the number and an increase in the diameter of the vessels. Eventually, only the superior and inferior vena cava, remain to pass low-oxygen, residual loaded blood into the right atrium.

Figure A.10 The arteries of the human body.

Reproduced from Tortora and Grabowski (2003).

Figure A.11 The veins of the human body.
Reproduced from Tortora and Grabowski (2003).

A.2.2 The Pulmonary Circuit

The pulmonary circuit has the right ventricle as its pump. In the pulmonary circuit, blood passes from the right ventricle through the pulmonary trunk into the vascular system of the lungs. In the lung capillaries, the exchange of carbon dioxide and oxygen takes place. Fresh, oxygen-rich blood enters the pulmonary veins and, it then returns to the heart, re-entering through the left atrium. The oxygen-rich blood later passes through a one-way valve into the left ventricle, and the blood journey starts again in a closed loop.

A.2.3 The Lymphatic Circuit

The lymphatic circuit is a supplementary transport circuit. It is the defense system, a one-way system, which consists of lymph, lymphatic ducts, and lymphatic nodes. Lymph is a clear fluid that contains white blood cells and antibodies, and it is circulated throughout the body by the lymphatic system. Lymphatic ducts drain away the fluid that fills the spaces between the cells (interstitial or tissue fluid) and the miniscule particles in the lymph. The nodes store large quantities of white blood cells and act as filters for germs and impurities. Lymphatic flow depends on pressure from the blood system and the massaging effect of muscles. Most of the interstitial fluid enters the lymphatic capillaries to become lymph. The lymph moves into the larger lymphatic ducts, the lymphatic nodes, and eventually enters the blood through the veins as can be seen in Figure A.9. The lymphatic system is thus a secondary transport system. Lymph has no pump of its own.

Its flow depends on pressure gradients related to the blood stream (Berne and Levy, 1981).

A.2.4 Comparison of the Series Circuits

The major differences between the two series circuits (systemic and pulmonary) lie in the function, organization, and environment of their two beds.

The systemic circuit is a high resistance circuit providing for a wide variety of tissues over a long distance from the heart (long hydrostatic columns) (Figure A.12), and that differs in function and level of activity from the pulmonary circuit. The systemic circuit maintains steep pressure gradients, and blood flow into the tissues is regulated by various control mechanisms.

The pulmonary circuit, on the other hand, is a low pressure, low resistance circuit that serves only the lungs over a short distance from the heart (short hydrostatic columns) (Figure A.12) providing for gas exchange and heat dissipation. The pulmonary circuit has slight control capacity to monitor and control blood flow through the lungs (Ruch *et al.*, 1965).

Figure A.12 The systemic and the pulmonary circulation.
Reproduced from Ruch *et al.* (1965).

A.2.5 Vascular Blood vessels

The vascular system consists of a large network of blood vessels, some of which (arteries) transport blood away from the heart to body tissues and organs, and the others (veins) transport blood back to the heart. All blood vessels except blood capillaries consist of three different layers: the tunica intima (inner layer), tunica media (middle layer), and tunica adventitia (outer layer) as shown in Figure A.13 (Levick, 2003).

Figure A.13 Structure of the wall of a muscular artery.
Reproduced from Levick (2003).

The tunica intima consists of endothelial cells and a variable number of elastic fibers, and it can be expanded to many times its original length. Elastin is the major protein present in elastic fibers, and it is six times more extensible than rubber (Levick, 2003).

The tunica media is the thickest layer; it supplies mechanical and contractile power, and it consists of smooth muscle and collagen fibers. The smooth muscle fibers can contract to regulate blood pressure and flow (Mader, 2003). The collagen fibers join the tunica media to the tunica intima and to the tunica adventitia (Martini *et al.*, 1998). Collagen is 100 times stiffer than elastin preventing over-distension of blood vessels (Levick, 2003).

The tunica adventitia consists of connective tissue forming a sheath around the blood vessels. They bind the blood vessels to the surrounding tissue.

A.2.5.1 Functional Categories of the Blood Vessels

Blood vessels are classified into six categories according to their function: windkessel vessels, resistance vessels, sphincter vessels, exchange vessels, capacitance vessels, and shunt vessels (Folkow and Neil, 1971):

- **Windkessel vessels:** These are arteries with a large quantity of elastic fibers such as the aorta, the pulmonary arteries, and other neighboring large arteries. In the aorta, large elasticity is responsible for the windkessel effect, by which the phasic systolic inflow of blood is converted into a smoother outflow.
- **Resistance vessels:** These consist of the terminal arteries and arterioles. They play a remarkable role in regulating blood flow from arteries into capillaries (Tortora and Grabowski, 2003). During vasoconstriction, local resistance is increased thus reducing local blood flow. During vasodilation, local resistance is decreased thus increasing blood flow (Levick, 2003).
- **Sphincter vessels:** These are the terminal segments of the precapillary arterioles (Figure A.14). They control blood flow into capillaries and

determine the size of the capillary exchange surface. When they dilate, more blood flows into the capillaries, and the reverse is true.

- **Exchange vessels:** These are the capillaries, where diffusion (O_2 , CO_2 , proteins, hormones) and filtration take place (Figure A.15). The capillaries are not contractile; capillary diameter changes passively as a result of pressure changes in the region of pre-and post capillary resistance and sphincter vessels.
- **Capacitance vessels:** These represent veins and venules. They contain about two-thirds of the total blood volume Figure A.16; therefore, they act as blood reservoirs, especially the veins in abdominal organs (such as the liver and spleen) and the skin (Tortora and Grabowski, 2003). During severe conditions, capacitance vessels constrict and displace blood into the heart and arteries (Levick, 2003).
- **Shunt vessels:** These are found in certain tissues and act as bypass valves, diverting blood away from tiny capillaries. When these vessels are open, flow through the capillaries is diminished or fully hindered.

Figure A.14 Anatomy of the terminal capillary bed.
Reproduced from Mader (2003).

Figure A.15 Capillary exchange.
Reproduced from Tortora and Grabowski (2003).

Figure A.16 Blood volume distribution.

Reproduced from Folkow and Neil (1971).

A.3 The Working Fluid

Blood is a heterogeneous fluid that circulates in the body and contains red blood cells, white blood cells, platelets, proteins, plasma, and other elements. Blood volume in liters can be estimated for any given individual by calculating 7 % of the body weight in kilograms; an average adult of weight 70 Kg has approximately 5 Liters of blood (Martini *et al.*, 1998). Blood transports oxygen from the lungs to body cells and carbon dioxide from body cells back to the lungs. Moreover, blood transports nourishment from

digestion and hormones from glands throughout the body, as well as disease fighting substances to body tissues, and waste to the kidneys (Tortora and Grabowski, 2003).

A.3.1 Blood Viscosity

Viscosity is a fluid property. It dictates the extent of friction between adjacent fluid layers sliding past one another, as well as the friction between the fluid and the vessel walls (Levick, 2003). Hematocrit* is an important determinant of blood viscosity. Viscosity varies linearly with cell concentration from 0 % hematocrit (plasma) to about 45 % hematocrit (Figure A.17), and it increases very rapidly above this value (Nichols et al., 1998). Viscosity is expressed in relative units (ratio of whole blood to plasma viscosity), plasma viscosity is about 1.2 cP (1.2×10^{-3} Pa.s) (Chien, 1970). Human blood viscosity values vary from 3 to 4 cP at 37 °C (McDonald, 1974). Temperature also has a significant effect on viscosity. Viscosity of blood increases approximately by 2 % for each 1 degree Celsius decrease in temperature.

* The percentage by volume of the blood that is cells (Guyton and Hall, 2000).

Figure A.17 Viscosity of the whole blood as function of Hematocrit.
Reproduced from Whitmore (1968).

For a Newtonian fluid, the shear stress (τ : shear force per unit area) is related to the rate of shear (γ) through:

$$\tau = \mu \gamma \quad (\text{A. 1})$$

Where μ is the viscosity (independent of shear rate). For non-Newtonian fluids, such as blood, μ is dependent on the shear rate. However, the composition of blood, consisting of red blood cells, white blood cells, platelets, proteins, plasma, and other elements, makes it a non-Newtonian fluid. The dependence of the viscosity of blood on the rate of shear (γ) is shown in Figure A.18. Based on the range of shear rates encountered in the

cardiovascular system, as given in Table A.1, the error in μ when the effect of shear rate is neglected remains below 2 %. This error is very small compared to other errors when modeling the cardiovascular system. Thus, it is common practice to approximate blood behavior as that of a Newtonian fluid (i.e. neglecting the effect of shear rate on viscosity).

Figure A.18 Non-Newtonian behavior of human blood.
Reproduced from Whitmore (1968).

Table A.1 Representative rates of shear at vessel walls in the human circulation.

Reproduced from Milnor (1989).

Vessel	Rate of shear at vessel wall (sec^{-1})
Ascending aorta	50
Femoral artery	150
Arteriole	400

A.3.2 The Physics of Blood Flow

Blood flow through the vascular system is produced by an overall pressure differential between vascular sections (Figure A.19).

Figure A.19 Factors that determine blood flow.
Reproduced from Mohrman and Heller (2003).

The factors determining flow can be summarized in an equation analogous to Ohm's law:

$$\dot{Q} = \Delta P / R \quad (\text{A. 2})$$

Where $\dot{Q}$ is the volumetric flow rate describing the organ's blood supply, ΔP is the pressure differential between vascular parts of the system, and R is the resistance to flow in the region concerned.

A.3.2.1 Vascular Resistance

Resistance to flow is the difficulty or effort involved into forcing blood through the vessels. Resistance falls with increasing radius of blood vessels, and increases with

increased blood viscosity. The resistance of a blood vessel is described by Poiseuille's law:

$$R = \frac{8 \mu L}{\pi a^4} \quad (\text{A. 3})$$

Where μ is the viscosity of the blood, L is the length of the blood vessel, and a is the inner radius of the vessel. Vascular resistance increases sharply in the resistance vessels. The resistance to flow in capillaries is very low and becomes even lower in the venules.

A.3.2.2 Blood Flow Types

One important factor that determines the energy consumed in the cardiovascular system is the nature of the flow. Fluid flow can take place as laminar or turbulent flow.

◆ Laminar flow

Blood flows throughout most of the circulatory system in a laminar fashion, which is characterized by concentric layers of blood moving in parallel down the length of the vessels, and showing a parabolic distribution of velocities as shown in Figure A.20. The highest velocity is found right at the center of the vessel.

Figure A.20 Schematic representation of laminar viscous fluid flow.
Reproduced from Chien (1992).

Laminar flow through a vessel helps minimize energy losses in the flowing blood due to adjacent viscous dissipation. Disruption of laminar flow leads to turbulence and increased energy losses.

◆ Turbulent Flow

Turbulence occurs when smooth laminar flow is disrupted. Turbulence occurs at stenotic heart valves or arterial vessels, at vessel branch points, and in the ascending aorta at high cardiac ejection velocities (e.g., during exercise). The onset of turbulence is dictated by the flow:

$$\text{Re} = \frac{\rho U D}{\mu} \quad (\text{A.4})$$

where ρ is the blood density, U is the mean velocity, D is the vessel diameter, and μ is the blood viscosity. There is a critical Reynolds number, above which laminar flow is disrupted and transition into turbulence occurs. Under ideal conditions

(e.g., long, straight, smooth blood vessels), transition from laminar into turbulent flow is approximately at $Re = 2300$ for a pipe flow. However, in branching vessels, or in vessels with atherosclerotic plaques protruding into the lumen, the transitional Re is much lower such that turbulence exists even at normal physiological flow velocities. The typical Reynolds number range of blood flow in the body varies from 1 in small arterioles to approximately 4000 in the largest artery, the aorta (Ku, 1997). Thus, blood flow is turbulent in the aorta.

A.4 Mean Arterial Pressure

Pressure is generated when blood is pumped by the heart against the resistive network of the systemic circulation. Since cardiac output is intermittent, pressure is pulsatile. The mean arterial pressure (P_{MAP}) can be approximated to be the product of the cardiac output (CO) and the systemic vascular resistance (SVR) minus the central venous pressure (P_{CV}):

$$P_{MAP} = CO \times SVR - P_{CV} \quad (A. 5)$$

In medical practice, mean arterial pressure is not determined by establishing values for the cardiac output and the systemic vascular resistance, but rather by direct or indirect measurements of arterial pressure. The central venous pressure is usually 0 to 25 mmHg (Figure A.21). The form of the pressure v.s. time curve yields a time mean pressure value that is less than the arithmetic average of the systolic and diastolic pressures. At normal resting heart rates, P_{MAP} can be approximated by the following equation:

$$\text{MAP} \approx \text{DBP} + \frac{1}{3}(\text{Pulse Pressure}) \quad (\text{A. 6})$$

where P_{DBP} is the diastolic pressure, and $P_{SBP} - P_{DBP}$ is the Pulse Pressure.

Figure A.21 Schematic representations of cross-sectional area, blood distribution, velocity and pressure in different regions of the circulation. Reproduced from Levick (2003).

A.4.1 Cardiac Output

The volume of blood pumped by the left ventricle into the aorta per minute is called the cardiac output (CO), and it is equal to the product of the stroke volume (SV) and the heart rate (HR). For an average sized adult at rest, CO would be about 5 L/min (Marieb, 2004). During exercise CO may increase to 30-35 L/min (Silverthorn, 1998). The distribution of the cardiac output to the body organs varies according to the organ's demand and activity level (Figure A.22).

Figure A.22 Distribution of cardiac output to body organs during rest.
Reproduced from Silverthorn (1998).

A.4.1.1 Stroke Volume

Stroke volume is the total volume of blood ejected by the heart in a single beat. It can be calculated by taking the difference between the volume of blood in the ventricles before

contraction (end diastolic volume) and the volume of blood after contraction (end systolic volume) (Marieb, 2004). For an average sized adult (70 Kg) at rest, stroke volume is equal to 70 ml and can increase to as much as 100 ml during exercise (Silverthorn, 1998). Stroke volume is increased by increased strength of the cardiac contraction. Two significant influences on cardiac contraction are the venous return and the sympathetic mediators.

A.4.2 Venous Return

Venous return is the volume of blood flowing back from the veins into the right atrium per minute. Under steady-state conditions, venous return is generally equal to the cardiac output since the cardiovascular system is a closed loop (Guyton and Hall, 2000). Otherwise, blood would accumulate in either the systemic or pulmonary circuits. A change in either cardiac output or venous return will affect the other at steady state. Although cardiac output and venous return are interdependent, each can be independently regulated. Different factors reduce venous return, such as the hydrostatic effects on blood vessels below the heart level in the erect position, exercise, and thermal stress. Venous return can be improved by two main mechanisms: the muscle pump, and the respiratory pump.

A.4.2.1 Muscle Pump

The skeletal muscles of the leg, together with proper venous valves form an efficient pump that drives the blood back into the heart. This pump, shown in Figure A.23, is referred to as the muscle pump or the second heart (Rowell, 1993).

Figure A.23 Muscle pump mechanism.
Reproduced from Martini (1998).

In passive upright posture, both leg venous valves are opened and blood flows upward towards the heart with a net driving pressure into the veins of 80 mmHg (Figure A.24A).

In active upright posture such as walking or standing on tiptoes (Figure A.23, Figure A.24B), the muscle pump contracts, and compresses the veins. As a result, blood is pushed upward towards the heart with a driving pressure of 90 mmHg (Shepherd, 1963) via the valve closer to the heart which opens; the other valve closes as blood is pushed against it (Figure A.23), and thus preventing any blood back-flow as illustrated in Figure A.25.

After muscle relaxation, pressure is decreased near zero in the previously compressed vein (Figure A.24C). Consequently, the valve closer to the heart closes, and the valve further from the heart opens for the pressure in foot is higher than in the leg.

Figure A.24 Muscle pump: (A) passive upright rest, (B) active upright posture, (C) muscle relaxation. Reproduced from Rowell (1986).

Figure A.25 Venous valves of the leg.
Reproduced from Guyton (1981).

A.4.2.2 Respiratory Pump

During inspiration the diaphragm moves downward resulting in a pressure drop in the thoracic cavity, and a pressure rise in the abdominal cavity. As a result, the hepatic veins are compressed stopping hepatic venous outflow (liver outflow), and speeding up the inferior vena caval (IVC) flow into the thorax as illustrated in Figure A.26 (Moreno and Burchell, 1982). Consequently, a larger volume of blood moves from the compressed abdominal veins into the decompressed thoracic veins, and then into the right atrium (Figure A.26). The reverse process occurs during expiration; the venous valves prevent the backflow of blood from the thoracic to the abdominal veins (Tortora and Grabowski,

2003). This pumping action is very important especially during heavy exercise, when respirations are deep and frequent (Martini *et al.*, 1998).

Figure A.26 Respiratory pump.

Reproduced from Moreno and Burchell (1982).

A.5 Cardiovascular Control

Instantaneous blood flow is controlled by a combination of local and remote, more elaborate mechanisms. The cardiovascular center, in the medulla oblongata, adjusts heart rate and stroke volume, and it controls the neural and hormonal systems that regulate blood pressure and blood flow. The cardiovascular center receives impulses from receptors located at various places in the cardiovascular system; it also provides output to both, the parasympathetic and the sympathetic divisions of the autonomic nervous system (Tortora and Grabowski, 2003).

Systemic arterial pressure regulation is one of the most important mechanisms for the proper operation of the cardiovascular system. Arterial pressure variation from its normal value is controlled through the regulation of the total peripheral resistance and cardiac output (Mohrman and Heller, 2003).

The various regulatory mechanisms are classified according to their time of action into two groups: short-term regulation mechanisms (seconds), and long-term regulation mechanisms (minutes to days)(Guyton and Hall, 2000).

A.5.1 Short Term Regulatory Mechanisms

Short-term regulatory mechanisms are characterized by rapid (few seconds) onset of action. They include arterial baroreceptor reflexes, chemoreceptor reflexes, and cerebral ischemic reflexes. They are supplemented by hormonal mechanisms involving adrenalin, noradrenalin and, with a delayed action, vasopressin.

A.5.1.1 Arterial Baroreceptor Reflexes

The arterial baroreceptors are sensors found in the major arteries of the body especially in the aortic arch and the carotid sinus. They are stimulated by the stretching of the vessel wall caused by the transmural pressure (Karemaker, 1987).

Baroreceptor reflexes play a significant role during changes in body posture. Changing from supine to standing position results in a pressure drop in the upper part of the body. The baroreceptor reflexes counteract this pressure drop by sending immediate reflexes

resulting in a strong sympathetic discharge throughout the body, which regulates the pressure drop in the head and upper body (Guyton and Hall, 2000). In older people, baroreceptor reflexes tend to operate slower than normal. The blood pressure drop on assuming the standing position may lead to orthostatic intolerance (i.e. dizziness and/or fainting) (Dingle, 2003). Dangling the legs when moving from supine to standing position is highly recommended for individuals with diabetes mellitus, cardiovascular disease, and older people (Dingle, 2003). This action helps to prevent notable reductions in blood pressure.

A.5.1.2 Cerebral Ischemic Reflex

The cerebral ischemic reflex is an emergency arterial pressure control mechanism. It is not stimulated until arterial pressure drops below 60 mmHg. When blood flow to the brain decreases severely resulting in cerebral ischemia, the neurons in the vasomotor center respond directly to the ischemia and become strongly excited, bringing arterial pressure to levels as high as 250 mmHg. This reflex is activated primarily by chemoreceptors that sense an ischemic increase in CO_2 and H^+ in the brain. The reflex raises the heart rate, cardiac output, and stroke volume very strongly in order to return mean arterial pressure back to normal. This increase in arterial blood pressure in response to the ischemia is known as the central nervous system ischemic response (Guyton and Hall, 2000).

A.5.1.3 Adrenalin and Noradrenalin

Adrenaline and noradrenaline are hormones secreted mainly by the adrenal gland. When the sympathetic circulatory centers in the medulla are excited, secretion of adrenaline and noradrenaline is increased stimulating receptors found on vascular smooth muscles.

Adrenalin traveling in the bloodstream reduces total peripheral resistance because it acts on β receptors that produce vessel dilatation once stimulated (Figure A.27). Noradrenaline causes vasoconstriction increasing total peripheral resistance, which in turn increases arterial blood pressure (Silverthorne, 1998).

Figure A.27 Blood vessel's receptors.
Reproduced from Silverthorne (1998).

Under severe conditions such as hemorrhage, anxiety, terror, rage, adrenalin secretion increases to such a degree that vasoconstriction dominates due to the excitation of α receptors (Figure A.27). In humans, adrenaline and noradrenaline have opposite effects on skeletal muscle as shown in Figure A.28 (Levick, 2003).

Figure A.28 Comparison of effects of adrenaline and noradrenaline in man.
Reproduced from Levick (2003).

A.5.2 Long Term Control Mechanisms

A.5.2.1 Renin-Angiotensin Mechanism

Renin is an enzyme synthesized and stored in the kidneys. When arterial pressure falls, renin is released; most of the renin passes out of the kidney and circulates throughout the body. Renin acts on angiotensinogen, a protein in plasma, to produce angiotensin I

(Greger and Windhorst, 1996). Together, angiotensin I and angiotensin converting enzyme (ACE) produce angiotensin II. Angiotensin II causes vasoconstriction of blood vessels (Reid, 1992), which results in increase in blood pressure (Figure A.29). Furthermore, angiotensin II stimulates the secretion of aldosterone from the adrenal cortex (i.e. the outer shell of two small endocrine glands), which increases reabsorption of sodium ions and water by the kidneys. As a result, total blood volume increases increasing blood pressure (Levick, 2003).

The renin-angiotensin mechanism is a very powerful system, especially in cases of circulatory shock, such as hemorrhage as illustrated in Figure A.30. It takes about 20 minutes for the renin-angiotensin mechanism to come into effect (Guyton and Hall, 2000).

Figure A.29 Renin-Angiotensin-Aldosterone mechanisms.
Reproduced from Levick (2003).

Figure A.30 Renin-Angiotensin-Aldosterone system compensation after hemorrhage. Reproduced from Guyton and Hall (2000).

A.5.2.2 Renal Volume Control Mechanism

The renal volume control mechanism is an important system that maintains balance between fluid intake and output (Mohrman and Heller, 2003). As the blood pressure increases, the renal fluid output increases and reduces the extra cellular fluid volume and consequently, the blood volume. The reduced blood volume results in a decreased mean filling pressure, which reduces both, venous return and cardiac output. The reduced cardiac output brings the blood pressure back to normal level. The reverse process occurs in case of blood pressure drops. The renal volume control mechanism is summarized in Figure A.31.

Figure A.31 Block diagram of the renal-volume control system.
Reproduced from Guyton and Hall (2000).

Appendix B

Derivation of the Hemodynamic Equation

Using the energy equation between the left and right ventricles:

$$\frac{P_{MAP}}{\rho g} + \frac{U_1^2}{2g} + Z_1 = \frac{P_{CVP}}{\rho g} + \frac{U_2^2}{2g} + Z_2 + h_f \quad (\text{B. 1})$$

where h_f is the head loss due to friction and is equal to:

$$h_f = \frac{4 f L U^2}{2 g D} \quad (\text{B. 2})$$

For laminar flow, f is a function of Reynolds number and is equal to:

$$f = \frac{16}{\text{Re}} = \frac{16 \mu}{\rho U D} \quad (\text{B. 3})$$

Assuming that $Z_1 = Z_2$ and assuming no change in kinetic energy and no tethering in blood vessel thus, $U_1 = U_2$, and using Eqs. B.2 and B.3, Eq. B.1 can then be manipulated through the following steps:

$$\frac{P_{MAP} - P_{CVP}}{\rho g} = h_f \quad (\text{B. 4})$$

$$\Delta P = \rho g h_f \quad (\text{B. 5})$$

$$\Delta P = \rho g \left(\frac{4 f L U^2}{2 g D} \right) \quad (\text{B. 6})$$

$$\Delta P = \rho g \left(\frac{16 \mu}{\rho U D} \right) \left(\frac{4 L U^2}{2 g D} \right) \quad (\text{B. 7})$$

$$\Delta P = \left(\frac{32 \mu L U}{D^2} \right) \quad (\text{B. 8})$$

$$\Delta P = \left(\frac{8 \mu L U}{a^2} \right) \quad (\text{B. 9})$$

Assuming parabolic flow in a tube with circular cross-section, the flow rate and the velocity are related through:

$$\dot{q} = UA = U(\pi a^2) \quad (\text{B. 10})$$

$$\Delta P = \dot{q} \left(\frac{8 \mu L}{\pi a^4} \right) \quad (\text{B. 11})$$

$$\Delta P = \dot{q} R \quad (\text{B. 12})$$

where R is Poiseuille resistance and is equal to:

$$R = \frac{8 \mu L}{\pi a^4} \quad (\text{B. 13})$$

Accuracy of Electronic Sphygmomanometers

Model (Manufacturer)	Technique	Reference Standard (MC/AC)	Accuracy			
			(Device-reference) (mmHg)		Device Validation	Reference
			P_{SBP}	P_{DBP}		
ES-H51 Semiautomatic (Terumo, Tokyo, Japan)	Auscultatory (Primary Mode)	MC	0.7±2.9	0.3±2.6	Followed the AAMI and BHS protocols. BHS grades are A for both P_{SBP} & P_{DBP} for Primary mode. B & A for backup mode for both P_{SBP} & P_{DBP} .	Imai et al. (1994)
	Oscillometry (Back up mode)	MC	-0.3±5.7	-0.3±4.3		
HEM 439 Semiautomatic (Omron, Tokyo, Japan)	Auscultatory	MC	-0.21±5.26	6.23±9.85		Imai et al. (1989)
HEM 719K Automatic (Omron, Tokyo, Japan)	Auscultatory	MC	-2.26±5.58	2.42±4.67		Imai et al. (1989)
DS 91 Semiautomatic (Nissei, Tokyo, Japan)	Auscultatory	MC	-2.45±7.42	2.82±10.79		Imai et al. (1989)

Table C.1 Survey of indirect blood pressure measurement devices in terms of accuracy and validation.

Model (Manufacturer)	Technique	Reference Standard (MC/AC)	Accuracy			Reference
			(Device-reference)		Device Validation	
			(mmHg)			
			P_{SBP}	P_{DBP}		
TM-2420 Version 7 (A&D, Tokyo, Japan)	Auscultatory (Ambulatory)	MC	-1.8± 5	-3.5±6.8	Followed the AAMI and BHS protocols. BHS grades are B for both P_{SBP} & P_{DBP} .	Palatini et al. (1991)
CH Druck / Pressure Scan ERKA Disetronic Medical Systems AG Burgdorf, Switzerland	Auscultatory (Ambulatory)	MC	-3± 4	-2±4	Followed the AAMI and BHS protocols. BHS grades are A for both P_{SBP} & P_{DBP} .	O'Brien et al. (1992)
Profilomat Disetronic Medical Systems AG, Burgdorf, Switzerland	Auscultatory (Ambulatory)	MC	-3± 5	-1±5	Followed the AAMI and BHS protocols. BHS grades are B for P_{SBP} & A for P_{DBP} .	O'Brien et al. (1992)

Table C.2 Survey of indirect blood pressure measurement devices in terms of accuracy and validation.

Model		Accuracy				Reference
		Reference Standard (MC/AC)	(Device-reference) (mmHg)		Device Validation	
			P_{SBP}	P_{DBP}		
Dinamap 1846SX (Critikon, Tampa, Fl)	Oscillometry	AC	-8.8±11.2	1.6±8.9		Gorback et al. (1991)
Dinamap 8100 portable monitor (Critikon, Tampa, Fl)	Oscillometry	MC	-1±7	-6±7	Fulfills the criteria of AAMI for P_{SBP} , but not for P_{DBP} . BHS grades are B& D for SBP & DBP.	O’Brien et al. (1993)
Oscillometric Blood Pressure monitor (SpaceLabs Medical,	Oscillometry	MC	-0.6±5.9	0.9±6.4	Followed the AAMI and BHS protocols. BHS grades are B for both P_{SBP} &	Sun et al. (1996)
Denko EW 260 Automatic (Matsushita, Osaka, Japan)	Oscillometry	MC	1.78±5.17	-1.69±5.51		Imai et al. (1989)
401C Semiautomatic (Omron, Tokyo, Japan)	Oscillometry	MC	-1.61±7.67	2.37±6.11		Imai et al. (1989)

Cont’d-Table C.1 Survey of indirect blood pressure measurement devices in terms of accuracy and validation

			Accuracy			
			Reference Standard (MC/AC)	(Device-reference) (mmHg)	Device Validation	Reference
Model				P_{SBP}	P_{DBP}	
MB 500A						Imai et al.
Automatic	Oscillometry	MC	-1.80±6.70	0.71±6.30		(1989)
Takeda UA 751						
Automatic	Oscillometry	MC	-4.11±5.60	0.40±7.75		Imai et al.
(A&D, Tokyo, Japan)						(1989)
						Ling et al.
BP8800MS	Oscillometry	MC	2.8±5.4	0.0±4.9		(1995)
(Colin Medical Instruments, San Antonio, TX)						

Cont'd-Table C.1 Survey of indirect blood pressure measurement devices in terms of accuracy and validation

Appendix D
Blood Pressure Protocol

PROTOCOL COVER SHEET

Title: Effects of Leg Position on Blood-Pressure Measurements

Study Sponsor

Cardiovascular Devices Division
University of Ottawa Heart Institute
40 Ruskin Street
Ottawa, Ontario
Canada K1Y 4W7

Test Facilities

Ottawa Hospital and University of Ottawa Heart Institute
40 Ruskin Street
Ottawa, Ontario
Canada K1Y 4W7

Carleton University
Mechanical & Aerospace Engineering Department
1125 Colonel By Dr.
Ottawa, Ontario
Canada K1S 5B6

Responsible Personnel/Approvals:

	Date:	Title: Masters Student
Samira Kazan		Mechanical & Aerospace Engineering Carleton University

	Date:	Title: Co-investigator
Metin Yaras		Professor of Mechanical & Aerospace Engineering Carleton University

	Date:	Title: Primary Investigator
Tofy Mussivand		Professor of Surgery & Engineering University of Ottawa Chairman and Director Cardiovascular Devices Division and Medical Devices University of Ottawa Heart Institute

_____ Date: _____ Title: Co-investigator
Haissam Haddad
University of Ottawa
Professor of Cardiology
Heart Failure and Transplant Program
University of Ottawa Heart Institute

_____ Date: _____ Title: Co-investigator
Frans Leenen
Professor of Medicine & Pharmacology
University of Ottawa
Director
Hypertension Unit
University of Ottawa Heart Institute

_____ Date: _____ Title: Co-investigator
Timothy Zakutnay
Biomedical Engineer
University of Ottawa Heart Institute

_____ Date: _____ Title: Co-investigator
Liz Coletta
Research Nurse
University of Ottawa Heart Institute

This document contains information proprietary to the Cardiovascular Devices Division of the Ottawa Heart Institute Research Corporation or to a third party to which the Cardiovascular Devices Division of the Ottawa Heart Institute Research Corporation may have a legal obligation to protect such information from unauthorized disclosure, use or duplication. Any disclosure, use or duplication of this document or any of the information contained herein for other than the specific purpose for which it was disclosed is expressly prohibited, except as the Director, Cardiovascular Devices Division of the Ottawa Heart Institute Research Corporation may otherwise agree to in writing.

D.1 Introduction

This protocol applies to the study of blood pressure variation due to body position, especially to leg(s) elevation, and examines its potential impact (disadvantages) or benefits for patients.

D.1.1 Objectives of the Blood-Pressure Measurement Study

The specific goals for the study are to:

- 1) experimentally determine blood-pressure reduction or increase due to leg elevation ranging from 15 cm to 45 cm as compared to supine position.
- 2) use the experimental data to help validate a computer model of the blood pressure system.

D.2 Equipment

This section describes the equipment that will be used for the study.

- 1) Mercury sphygmomanometer
 - a) Mercury manometer (minimum 1 mmHg resolution on the scale)
 - b) Stethoscope (Littmann Master Cardiology or equivalent)
 - c) Blood-pressure cuff (three (3) sizes required: 12×35 cm, 15×35 cm, and 18×42 cm)
- 2) Heart rate monitor (Polar A3TM or equivalent with ± 0.6 bpm precision)

- 3) Thermometer (Braun ThermoScan Plus IRT 3520 or equivalent with $\pm 1^{\circ}\text{C}$ precision)
- 4) Weight, height, and femur-tibial length measurement (Detecto Model 339 Eye-Level Beam Scale or equivalent with ± 0.5 kg, ± 1 cm precision)
- 5) Non-elastic measuring tape to measure the subject's antecubital fossa and quadriceps femoris circumference
- 6) Hydraulic bed to take blood-pressure measurements and to raise the subject's legs to specific heights in the supine position (15 cm, 30 cm, and 45 cm)
- 7) A heart pillow to support the arm at the heart level in the supine position
- 8) A stand to support the arm at the heart level in the standing position

This study will be undertaken at the Ottawa Heart Institute. It is highly desirable to make use of the same equipment throughout the study. The noted equipment is to be made available in a quiet, air conditioned ($21\text{-}23^{\circ}\text{C}$) environment for undertaking the study.

D.3 Procedural Overview

The measurement procedure will be as follows:

- 1) The subject is to complete and sign the Conset Form (Section 13).
- 2) Subject will be given a sheet of instructions (Section 4) at least 24 hrs before the measurement session, informing him/her on certain activities that must be performed or avoided prior to the measurements.

- 3) Upon arrival at the measurement site, certain information will be obtained from the subject (Section 11) and a consent form (Section 13) will be signed by the subject if it is not already signed.
- 4) Subject will be asked to remove any constrictive clothing that may interfere with the blood-pressure measurements or may artificially affect the subject's blood pressure.
- 5) Subject will be given a summary of the procedure.
- 6) Blood pressure will be measured in both arms (right and left). Subjects with blood pressure differences larger than 10 mmHg between the two arms will be excluded from the study.
- 7) Subject's weight, height, femur-tibial length, body temperature, arm circumference (antecubital fossa) and quadriceps femoris circumference will be measured and recorded.
- 8) Subject will be asked to rest for five minutes on the examination bed (in the supine position) before starting the blood-pressure measurements.
- 9) At the end of the rest period, a heart pillow will be placed underneath the right arm such that the antecubital fossa is positioned at the fourth intercostal space (heart level) with the palm facing upward.
- 10) The appropriate-size blood-pressure cuff will be placed on the subject's right arm such that the center of the cuff's bladder is over the brachial artery, and the lower cuff margin is 2.5 cm above the antecubital fossa.
- 11) The bell of the stethoscope will be placed lightly over the brachial artery.

- 12) The heart-rate monitor will be placed on the subject's left arm.
- 13) Initially, three measurements will be taken with a one-minute interval between them. Hereafter, a "measurement" will refer to the measurement of blood-pressure and heart rate.
- 14) Subject's both legs will be raised to 15 cm elevation (relative to examination bed surface) by the observer, and a measurement will be performed two minutes after raising of the legs.
- 15) Two more measurements will be taken with a one-minute interval between them.
- 16) Subject's both legs will be raised to 30 cm elevation (relative to examination bed surface) by the observer, and a measurement will be performed two minutes after raising of the legs.
- 17) Two more measurements will be taken with a one minute interval between them.
- 18) Subject's both legs will be raised to 45 cm elevation (relative to examination bed surface) by the observer, and a measurement will be performed two minutes after raising of the legs.
- 19) Two more measurements will be taken with a one-minute interval between them.
- 21) Subject's legs will be returned to horizontal position by the observer, and three measurements will be performed two minutes after returning to this position with a one-minute interval between them.
- 22) Subject will be asked to switch to a standing position, and his/her arm will be positioned at the heart level.
- 23) Three measurements will be taken after a period of two minutes in this position.

- 24) The information and consent forms filled by the subject and the data records for the measurement session will be catalogued.

For each subject, a total of eighteen (18) measurements (each measurement consisting of recording of blood pressure and heart rate) will be taken over a period of approximately 45 minutes. An additional 15 minutes is expected for preliminary assessment of the subject. The measurements will be taken during the period from 9AM to 1PM. According to published studies, the morning period is most suitable for obtaining blood pressure readings that are uninfluenced by specific daily activities of a subject. The measurements will be taken by a nurse or student under supervision.

D.4 Preparation of Subjects

Subject should follow the noted guidelines before participating in the blood-pressure study:

report the use of any drugs or emotional distress
not ingest alcohol at least 12 hours before blood pressure measurement (BPM)
not wear constrictive clothing that may occlude blood in the arm
not undertake heavy physical activities at least three hours before BPM
not eat heavy meals two hours before BPM
not ingest caffeine two hours before BPM
empty his/her bladder before BPM
be comfortable and relaxed

D.5 Sample Selection and Rationale

Size of Control Group: 30
Control: 30 healthy volunteers
Gender: Mixed

The size of the control group for the present study is tentatively set to 30. This is considered for the first study; measurement will be discontinued once a distinct and reliable trend in blood pressure with leg position is established. It is not known whether the blood-pressure response to leg-position changes is the same for male and females. As such, the control group will include an equal number of members of each gender.

D.6 Quality Control

Quality control during the study will include two parts: checking of the measurement equipment and performance monitoring of the blood pressure observer. The calibration of the measurement equipment will be verified at the beginning of the study. The blood-pressure measurements of the trained observed will be cross-checked against those of a nurse at least twice during the course of the study.

The quality of the data will be closely monitored throughout the study, and any adjustments to the measurement procedure that are required to ensure data of adequate quality will be implemented promptly. In this context, a number of subjects will be passed through the measurement procedure several times throughout the study.

Inconsistency in the results of these subjects will be used to quantify the repeatability of the measurements.

There may be changes to the measurement procedure, equipment and/or measurement environment during the course of the study, brought about by factors that are beyond the control of the investigators. The effects of any such changes on the quality of the measurement results will be promptly evaluated to ensure consistency of the results.

D.7 Data Analysis

The results of the measurements will be used to establish trends in blood-pressure changes with adjustments of leg elevation in the supine position. This will be done by plotting the blood-pressure readings against the range of leg elevations considered in the study, with the data divided into subgroups accordingly.

The results will then be used in the evaluation of a mathematical model of the cardiovascular system, with the objective of identifying the minimum level of model complexity required to reproduce the experimentally-observed trends.

D.8 Experimental Success

Perspective	Criteria
Studying the effects of leg elevation on blood pressure in the supine position	Experimental success will be reached when either a trend or no trend is obtained

D.9 Record Maintenance

Original experiment records, protocols, and final reports will be maintained in the Cardiovascular Devices Division of the University of Ottawa Heart Institute archives.

D.10 Duration of the Experimental Study

The experimental study will be carried out at the University of Ottawa Heart Institute and computer modeling will be done at the Department of Mechanical and Aerospace Engineering at Carleton University. The study will be performed on a continuous basis, in the following manner. During each day of a five-day week (M-F), the hours from 9AM-1PM will be allotted for the measurements, as per Section 3. These four hours on each day will be divided into four one-hour sessions. In each one-hour session, preliminary assessments and measurements will be performed for one subject. With a control group of thirty (30) subjects (as per Section 5), the study is estimated to last about two (2) weeks, provided no unforeseen problems arise during the measurements. The measurement equipment and measurement locations will therefore be reserved for a conservative duration of four (4) weeks.

D.11 Data and Collection Procedure

The following information will be obtained (measured) for each subject prior to the blood-pressure measurements (Table 1).

Table 1 Preliminary information to be obtained from subjects

Subject ID Number	Parameters
Gender	
Age	
Weight (kg)	
Height (cm)	
Length of femur-tibal region (cm)	
Body temperature (°C)	
Arm circumference (antecubital fossa) (cm)	
Quadriceps femoris circumference (cm)	
Emotional distress	
Current illnesses that may affect blood pressure	
Medication that may affect blood pressure	
Smoking Habit	
Female subjects : Pregnancy / Menstrual Period	

Subsequent to obtaining this information, blood-pressure and heart rate readings will be taken as per the procedure outlined in Section 3, and the information will be recorded as presented in the next section.

D.12 Clinical Engineering Record

Data Collection Schedule

Sample number	
Date	
Time	
Room temperature (°C)	
Gender	
Age	
Body Temperature (°C)	
Weight (kg)	
Height (cm)	
Femur-Tibal Length (cm)	
Quadriceps femoris Circumference (cm)	
Arm Circumference (cm)	
Cuff used	

		Blood Pressure Measurements	Estimated Duration
1st position 5 min	{ Supine	S ₁ = -----	1 min
		D ₁ = -----	procedure
		HR ₁ = -----	1 min rest
		S ₂ = -----	1 min
		D ₂ = -----	procedure
		HR ₂ = -----	1 min rest
2nd position 5 min	{ Supine (leg up by 15 cm from horizontal)	S ₃ = -----	1 min
		D ₃ = -----	procedure
		HR ₃ = -----	
		S ₄ = -----	1 min
		D ₄ = -----	procedure
		HR ₄ = -----	1 min rest
		S ₅ = -----	1 min
		D ₅ = -----	procedure
		HR ₅ = -----	1 min rest
		S ₆ = -----	1 min
		D ₆ = -----	procedure
		HR ₆ = -----	

		$S_7 =$ -----	1 min
		$D_7 =$ -----	procedure
		$HR_7 =$ -----	
			1 min rest
3rd position 5 min	{	Supine	$S_8 =$ -----
		(leg up by 30 cm	$D_8 =$ -----
		from horizontal)	$HR_8 =$ -----
			1 min rest
		$S_9 =$ -----	1 min
		$D_9 =$ -----	procedure
		$HR_9 =$ -----	
			1 min rest
		$S_{10} =$ -----	1 min
		$D_{10} =$ -----	procedure
		$HR_{10} =$ -----	
			1 min rest
4th position 5 min	{	Supine	$S_{11} =$ -----
		(leg up by 45 cm	$D_{11} =$ -----
		from horizontal)	$HR_{11} =$ -----
			1 min rest
		$S_{12} =$ -----	1 min
		$D_{12} =$ -----	procedure
		$HR_{12} =$ -----	
			1 min rest
		$S_{13} =$ -----	1 min
		$D_{13} =$ -----	procedure
		$HR_{13} =$ -----	
			1 min rest
5th position 5 min	{	Supine	$S_{14} =$ -----
			$D_{14} =$ -----
			$HR_{14} =$ -----
			1 min rest
		$S_{15} =$ -----	1 min
		$D_{15} =$ -----	procedure
		$HR_{15} =$ -----	
			1 min rest

6th position 5 min	{	Standing	$S_{16} =$ -----	1 min
			$D_{16} =$ -----	procedure
			$HR_{16} =$ -----	
				1 min rest
			$S_{17} =$ -----	1 min
			$D_{17} =$ -----	procedure
			$HR_{17} =$ -----	
				1 min rest
			$S_{18} =$ -----	1 min
			$D_{18} =$ -----	procedure
	$HR_{18} =$ -----			
			Total: 45 minutes	

Appendix E
Patient Consent Form

Patient Information Sheet & Consent Form
Effects of Leg Position on Blood-Pressure Measurements
UOHI Protocol # 05-127

Principal Investigator and telephone number:

Tofy Mussivand 761-5000 Ext.:14545

Co-Investigator(s)/ Supervisor/Coordinators and telephone numbers:

Samira Kazan	721-6555
Metin Yaras	520-2600 Ext.: 1174
Haissam Haddad	761-5000 Ext.: 15165
Frans Leenen	761-5000 Ext.: 14521
Timothy Zakutnay	761-5000 Ext.: 16773
Liz Coletta	761-5000 Ext.: 14385

Please read this Patient Information Sheet and Consent Form carefully and ask as many questions as you like before deciding whether to participate.

E.1 Introduction

You have been invited to participate in a research project entitled: Effects of Leg Position on Blood-Pressure Measurements. The purpose of this project is to examine the potential impact (disadvantages or benefits) of this position for patients. Your participation will help the Investigators to (1) experimentally determine heart-level-blood-pressure reduction or increase due to leg elevation ranging from 15 cm to 45 cm as compared to

supine position, (2) use the experimental data to help validate a computer model of the blood pressure system. The entire experimental study is estimated to last about two (2) weeks. The study for each patient is estimated to last about one (1) hour.

E.2 Procedure

If you agree to participate in the study, the procedure you will follow consists of the steps listed below:

- 1) You will be given a sheet of instructions (Table 1) at least 24 hrs before the measurement session, informing you on certain activities that must be performed or avoided prior to the measurements.
- 2) Upon arrival at the measurement site, certain information will be obtained from you (Table 2) and a consent form (Page 6 of 6) will be signed by yourself if it is not already signed.
- 3) You will be asked to remove any constrictive clothing that may interfere with the blood-pressure measurements or may artificially affect your blood pressure.
- 4) You will be given a summary of the procedure.
- 5) Blood pressure will be measured in both arms (right and left). If you have blood pressure differences larger than 10 mmHg between your two arms, you will be excluded from the study.
- 6) Your weight, height, femur-tibial length, body temperature, arm circumference (antecubital fossa) and quadriceps femoris circumference will be measured and recorded.

- 7) You will be asked to rest for five minutes on the examination bed (in the supine position) before starting the blood-pressure measurements.
- 8) At the end of the rest period, a heart pillow will be placed underneath your right arm such that the antecubital fossa is positioned at the fourth intercostal space (heart level) with the palm facing upward.
- 9) The appropriate-size blood-pressure cuff will be placed on your right arm such that the center of the cuff's bladder is over the brachial artery, and the lower cuff margin is 2.5 cm above the antecubital fossa.
- 10) The bell of the stethoscope will be placed lightly over the brachial artery.
- 11) The heart-rate monitor will be placed on your left arm.
- 12) Initially, three measurements will be taken with a one-minute interval between them. Hereafter, a "measurement" will refer to the measurement of both blood pressure and heart rate.
- 13) Your both legs will be raised to 15 cm elevation (relative to examination bed surface) by the observer, and a measurement will be performed two minutes after raising of the legs.
- 14) Two more measurements will be taken with a one-minute interval between them.
- 15) Your both legs will be raised to 30 cm elevation (relative to examination bed surface) by the observer, and a measurement will be performed two minutes after raising of the legs.
- 16) Two more measurements will be taken with a one minute interval between them.

- 17) Your both legs will be raised to 45 cm elevation (relative to examination bed surface) by the observer, and a measurement will be performed two minutes after raising of the legs.
- 18) Two more measurements will be taken with a one-minute interval between them.
- 19) Your legs will be returned to horizontal position by the observer, and three measurements will be performed two minutes after returning to this position with a one-minute interval between them.
- 20) You will be asked to switch to a standing position, and your arm will be positioned at the heart level.
- 21) Three measurements will be taken after a period of two minutes in this position.
- 22) The information and consent forms filled by yourself and the data records for the measurement session will be catalogued.

Table E.1 Instruction sheet.

report the use of any drugs or emotional distress
not ingest alcohol at least 12 hours before blood pressure measurement (BPM)
not wear constrictive clothing that may occlude blood flow in the arm
not undertake heavy physical activities at least three hours before BPM
not eat heavy meals two hours before BPM
not ingest caffeine two hours before BPM
empty his/her bladder before BPM
be comfortable and relaxed

Table E.2 Preliminary information to be obtained from you (the subject).

Subject ID Number	Parameters
Gender	
Age	
Weight (kg)	
Height (cm)	
Length of femur-tibial region (cm)	
Body temperature (°C)	
Arm circumference (antecubital fossa) (cm)	
Quadriceps femoris circumference (cm)	
Emotional distress	
Current illnesses that may affect blood pressure	
Medication that may affect blood pressure	
Smoking habit	
Female patients : Pregnancy Risk / Menstrual Period	

E.3 Risks and Discomforts of Participation

There are no risks and discomforts associated with participation in this experiment.

E.4 Benefits of Participation

You may not receive any direct benefit from your participation in this experiment. Your participation may allow the researchers to examine the potential impact (disadvantages or benefits) of this position to future patients.

E.5 Compensation /Remuneration

In the event of research-related side-effects or injury, you will be provided with appropriate medical treatment. By participating in the study and signing this Consent, you are not waiving your legal rights that may be available to you. If you park in the parking lot in front of the Heart Institute, a parking voucher will be given to you.

E.6 Confidentiality (Where Applicable)

As part of this research protocol, the Principal Investigator and their clinical research staff will review your health records. Your records may also be reviewed by representatives of *Sponsor Name*, Health Canada, the Food and Drug Administration (USA), as well as by representatives of the Heart Institute Human Research Ethics Board under the supervision of the Investigator.

You and your health records will not be identifiable in publications or presentations. No identifying information will leave the hospital, and your initials will not be used to identify you.

E.7 Ethics

The Human Research Ethics Board (HREB) of the University of Ottawa Heart Institute has approved this protocol. The HREB considers the ethical aspects of all Heart Institute research projects involving human subjects. If you wish, you may talk to the Chair, Human Research Ethics Board at (613) 761-4417.

E.8 Participation

Participation in research is completely voluntary. You are free to choose to participate or not to participate in this research study. If you agree to participate in this study, you may choose to withdraw your participation at any time. This will not affect your present or future care at the Heart Institute, or at any hospital. You may also refuse to answer any specific questions.

E.9 Consent to Participate in Research

I understand that I am being asked to participate in a research study about *The effects of leg position on blood-pressure measurements.*

This study has been explained to me by _____ .

I have read and understood this Patient Information Sheet and Consent Form. All my questions at this time have been answered to my satisfaction. If I or any of my family members have any further questions about this study, we may contact _____ at _____.

I will receive a signed copy of this Patient Information Sheet and Consent Form.

I voluntarily agree to participate in this study.

Patient's Name

Patient's Signature

Date

Signature of Person Obtaining Consent

(Co-)Investigator's Signature

Date

Appendix F

Time Mean Flow Program

F.1 Computation Algorithm

```
#include <stdio.h>
#include <stdlib.h>
#include <string.h>
#include <math.h>
#include <iostream.h>

#define INDEX_J 0
#define INDEX_I 1
#define LENGTH 2
#define DIAMETER_POS1 3
#define DIAMETER_POS2_COMP 4
#define RESISTANCE_PER 5
#define RESISTANCE_L_POS1 6
#define RESISTANCE_L_POS2_COMP 7
#define RESISTANCE_T_POS1 8
#define RESISTANCE_T_POS2_COMP 9
#define RESISTANCE_B 10
#define FLOWRATE_POS1 11
#define FLOWRATE_POS2_RIGID 12
#define FLOWRATE_POS2_COMP 13
#define HEIGHT_POS1 14
#define HEIGHT_POS2 15
#define PRESSURE_OUTLET_POS1 16
#define PRESSURE_OUTLET_POS1_CAL 17
#define PRESSURE_INLET_POS1 18
#define PRESSURE_OUTLET_POS2 19
#define PRESSURE_OUTLET_POS2_CAL 20
#define PRESSURE_INLET_POS2 21
#define COMPLIANCE_C 22

#define RHO 1050
#define GRAVITY 9.8
#define MU 0.0035
```

```

#define PI 3.14
#define SUCCESS 0
#define FAIL 1
#define K 18
FILE *fp,*output_fp;

/*Global declaration of all the functions*/
void update_cardiac_output(int pos);
void update_pressure_inlet(int pos);
void update_pressure_outlet(int pos);
void update_Local_Resistance(int pos);
void update_Total_Resistance(int pos);
void position(int pos);
void Pressure_Block(float num,float assumed_flowrate, int pos);
void update_diameter();
void Flow_rate_checkup1(int pos);
void Flow_rate_checkup2(int pos);
void Flow_rate_checkup3(int pos);
int Begin_of_block(float num);
int End_of_block(float num);
float initial_flowrate (int pos, float num);
float block_height(int pos,float num);
float Resistance_block(float num, int pos);

/*Global variable declaration*/
static int maxRows = 0;
float** data;
float CO, paorta, pright_atrium;
int f,r,s,t,v,u,c,d;

/*Read data from input file*/
int read_data(int m, int n) {
FILE *fp;
char line[100];
if ((fp = fopen("leg27", "r")) == NULL) {
printf("\nError opening input file for reading ..");
return FAIL;
} else {
while ((maxRows < n*m) && fgets(line, 100, fp) != NULL) {
data[maxRows]= (float *)malloc(23*sizeof(float));
sscanf(line, "%f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f %f",
%f %f",

```

```

&data[maxRows][INDEX_J],&data[maxRows][INDEX_I],&data[maxRows][LENGTH]
,&data[maxRows][DIAMETER_POS1],&data[maxRows][DIAMETER_POS2_COMP],
&data[maxRows][RESISTANCE_PER],

&data[maxRows][RESISTANCE_L_POS1],&data[maxRows][RESISTANCE_L_POS2_
COMP],&data[maxRows][RESISTANCE_T_POS1],&data[maxRows][RESISTANCE_
T_POS2_COMP],&data[maxRows][RESISTANCE_B],

&data[maxRows][FLOWRATE_POS1],&data[maxRows][FLOWRATE_POS2_RIGID],
&data[maxRows][FLOWRATE_POS2_COMP],&data[maxRows][HEIGHT_POS1],&da
ta[maxRows][HEIGHT_POS2],&data[maxRows][PRESSURE_OUTLET_POS1],&data[
maxRows][PRESSURE_OUTLET_POS1_CAL],

&data[maxRows][PRESSURE_INLET_POS1],&data[maxRows][PRESSURE_OUTLET
_POS2],&data[maxRows][PRESSURE_OUTLET_POS2_CAL],&data[maxRows][PRES
SURE_INLET_POS2],&data[maxRows][COMPLIANCE_C]);
    maxRows++;
}
}
return(SUCCESS);
}

void position(int pos) {
    if (pos==1) {
        f=FLOWRATE_POS1;
        r=PRESSURE_INLET_POS1;
        s=PRESSURE_OUTLET_POS1;
        t=HEIGHT_POS1;
        v=RESISTANCE_L_POS1;
        u=RESISTANCE_T_POS1;
        c=PRESSURE_OUTLET_POS1_CAL;
        d=DIAMETER_POS1;
    }
    else if (pos==2) {
        f=FLOWRATE_POS2_RIGID;
        r=PRESSURE_INLET_POS2;
        s=PRESSURE_OUTLET_POS2;
        t=HEIGHT_POS2;
        v=RESISTANCE_L_POS1;
        u=RESISTANCE_T_POS1;
        c=PRESSURE_OUTLET_POS2_CAL;
        d=DIAMETER_POS1;
    }
}

```

```

else if (pos==3) {
    f=FLOWRATE_POS2_COMP;
    r=PRESSURE_INLET_POS2;
    s=PRESSURE_OUTLET_POS2;
    t=HEIGHT_POS2;
    v=RESISTANCE_L_POS2_COMP;
    u=RESISTANCE_T_POS2_COMP;
    c=PRESSURE_OUTLET_POS2_CAL;
    d=DIAMETER_POS2_COMP;
}
}

int Begin_of_block(float num) {
    int i;
    for (i=0;i<=maxRows-1;i++) {
        if (data[i][INDEX_J]==num){
            break;
        }
    }
    return(i);
}

int End_of_block(float num) {
    int i;
    for (i=Begin_of_block(num)+1;i<=maxRows-1;i++) {
        if (data[i][INDEX_I]==1){
            break;
        }
    }
    return(i-1);
}

/*Boundary Condition, Flowrate (ml/sec)*/
void update_cardiac_output(int pos) {
    float SV = 0 , HR = 0;
    printf("\nPlease enter the stroke volume in millimeters per beat for position %d > ",pos);
    scanf("%f", &SV);
    printf("\nPlease enter the heart rate in beats per minute for position %d > ", pos);
    scanf("%f", &HR);
    CO=(SV*HR)/60;
    return;
}

```

```

/*Boundary Condition, Inlet Pressure (mmHg)*/
void update_pressure_inlet(int pos) {
    position(pos);
    printf("\nplease enter an initial guess for the mean arterial pressure in mmHg for
position %d > ", pos);
    scanf("%f",&paorta);
    data[Begin_of_block(1)][r] = paorta;
    return;
}

/*Boundary Condition, Outlet Pressure (mmHg)*/
void update_pressure_outlet(int pos) {
    int i;
    position(pos);
    printf("\nplease enter the central venous pressure in mmHg for position %d >
",pos);
    scanf("%f",&pright_atrium);
    for (i = 0; i <= maxRows-1; i++) {
        if (data[i][RESISTANCE_PER]!=-1) {
            data[i][s] = (pright_atrium -
((float)RHO*(float)GRAVITY*(float)0.00751*data[i][t]*(float)(1.e-3)));
        }
    }
}

/*Calculate the local resistance for each position (mmHg/ml/sec)*/
void update_Local_Resistance(int pos) {
    int i;
    position(pos);
    for (i = 0; i <= maxRows - 1; i++) {
        data[i][v] =
((float)128*(float)MU*(float)0.00751*((float)1.e+3)*data[i][LENGTH])/((float)PI*(float)
pow(data[i][d],4));
    }
    return;
}

/*Calculate total resistance for each position (mmHg/ml/sec)*/
void update_Total_Resistance(int pos) {
    int i;
    position(pos);
    for (i = 0; i <= maxRows - 1; i++) {
        if (data[i][RESISTANCE_PER]==-1){

```



```

        data[i][u]=data[i][v];
    }
    else if (data[i][RESISTANCE_PER]!=-1) {
        data[i][u]=data[i][RESISTANCE_PER]+data[i][v];
    }
}

return;
}

/*calculate the total resistance for each block (mmHg/ml/sec)*/

/*peripheral blocks (3,5,6,7,9,10,12,13)*/
float Resistance_block(float num, int pos) {
    float res;
    int i;
    position(pos);
    if (data[End_of_block(num)][u]!=0) {

        data[End_of_block(num)][RESISTANCE_B]=data[End_of_block(num)][u];
    }
    for (i=End_of_block(num);i>Begin_of_block(num);i=i-2) {
        data[i-2][RESISTANCE_B]=data[i-
2][u]+(data[i][RESISTANCE_B]*data[i-1][u])/(data[i][RESISTANCE_B]+data[i-1][u]);
    }
    res=data[Begin_of_block(num)][RESISTANCE_B];
    return(res);
}

/*not peripheral block but depends on peripheral blocks (4,8,11)*/
float Resistance_block_notper(float num, int pos) {
    float res;
    int i;
    position(pos);
    if ((num==11)||((num==4)||((num==8)) {

        data[End_of_block(num)][RESISTANCE_B]=(Resistance_block((num+1),pos)*
Resistance_block((num+2),pos))/(Resistance_block((num+1),pos)+Resistance_block((nu
m+2),pos));
    }
    for (i=End_of_block(num);i>Begin_of_block(num);i=i-2) {
        data[i-2][RESISTANCE_B]=data[i-
2][u]+(data[i][RESISTANCE_B]*data[i-1][u])/(data[i][RESISTANCE_B]+data[i-1][u]);
    }
    res=data[Begin_of_block(num)][RESISTANCE_B];

```

```

        return(res);
    }

/*not a peripheral block but depends on a peripheral and a not peripheral block (2)*/
float Resistance_block_pernotper(float num, int pos) {
    float res;
    position(pos);
    data[End_of_block(num)][RESISTANCE_B]=(Resistance_block((num+1),pos)*
Resistance_block_notper((num+2),pos))/(Resistance_block((num+1),pos)+Resistance_block_notper((num+2),pos));
    res=data[Begin_of_block(num)][RESISTANCE_B];
    return(res);
}

/*peripheral resistance of the main block (1)*/
float Resistance_main_block(float num, int pos) {
    float x,y,res;
    position(pos);
    x=(Resistance_block(7,pos)*Resistance_block_notper(8,pos))/(Resistance_block(7,pos)+Resistance_block_notper(8,pos));
    y=(x*Resistance_block_pernotper(2,pos))/(x+Resistance_block_pernotper(2,pos));
    data[End_of_block(num)][RESISTANCE_B]=(y*Resistance_block_notper(11,pos))/(y+Resistance_block_notper(11,pos));
    res=data[Begin_of_block(num)][RESISTANCE_B];
    return(res);
}

/*Pressure calculations for each block (mmHg)*/
void Pressure_Block(float num,float assumed_flowrate, int pos) {
    int i;
    float x=1.0, k=0.0, y=0.0;
    position(pos);
    data[Begin_of_block(num)][f]=assumed_flowrate;
    data[Begin_of_block(2)][r]=data[End_of_block(1)][s];
    data[Begin_of_block(3)][r]=data[End_of_block(2)][s];
    data[Begin_of_block(4)][r]=data[Begin_of_block(3)][r];
    data[Begin_of_block(5)][r]=data[End_of_block(4)][s];
    data[Begin_of_block(6)][r]=data[Begin_of_block(5)][r];
    data[Begin_of_block(7)][r]=data[End_of_block(1)][s];
    data[Begin_of_block(8)][r]=data[Begin_of_block(7)][r];
    data[Begin_of_block(9)][r]=data[End_of_block(8)][s];
    data[Begin_of_block(10)][r]=data[Begin_of_block(9)][r];
    data[Begin_of_block(11)][r]=data[End_of_block(1)][s];
}

```

```

data[Begin_of_block(12)][r]=data[End_of_block(11)][s];
data[Begin_of_block(13)][r]=data[End_of_block(11)][s];

while ((x>=0.1) || (x<=-0.1)) {
    if (Begin_of_block(num)!=End_of_block(num)) {
        for (i=Begin_of_block(num);i<End_of_block(num);i=i+1) {
            if ((data[i][RESISTANCE_PER]==-1)&&(i==Begin_of_block(num))) {
                if (num==3) k=data[End_of_block(2)][t];
                if (num==6) k=data[End_of_block(4)][t];
                if (num==7) k=data[End_of_block(1)][t];
                if (num==10) k=data[End_of_block(8)][t];
                if (num==11) k=data[End_of_block(1)][t];
                if (num==12) k=data[End_of_block(11)][t];
                if (num==13) k=data[End_of_block(11)][t];

                data[i][s]=data[i][r]-((float)RHO*(float)GRAVITY*(float)0.00751*(data[i][t]-
                k)*((float)1.e-3))-data[i][u]*data[i][f];
                data[i+1][r]=data[i][s];
                data[i+2][r]=data[i][s];
            }
            if ((data[i][RESISTANCE_PER]==-1)&&(i!=Begin_of_block(num))) {
                data[i][s]=data[i][r]-((float)RHO*(float)GRAVITY*(float)0.00751*(data[i][t]-
                data[i-2][t])*((float)1.e-3))-data[i][u]*data[i][f];
                data[i+1][r]=data[i][s];
                data[i+2][r]=data[i][s];
            }
            else if ((data[i][RESISTANCE_PER]!=-1)&&(i!=End_of_block(num))) {
                data[i][f]=(data[i][r]-data[i][s]-((float)RHO*(float)GRAVITY*(float)0.00751*
                (data[i][t]-data[i-1][t])*((float)1.e-3)))/data[i][u];
                data[i+1][f]=data[i-1][f]-data[i][f];
            }
            else if ((data[i][RESISTANCE_PER]!=-1)&&(i==End_of_block(num))) {
                data[i][f]=(data[i][r]-data[i][s]-((float)RHO*(float)GRAVITY*(float)0.00751*
                (data[i][t]-data[i-2][t])*((float)1.e-3)))/data[i][u];
                data[i+1][f]=data[i-1][f]-data[i][f];
            }
        }
        if (data[End_of_block(num)][RESISTANCE_PER]!=-1) {
            data[End_of_block(num)][c]=data[End_of_block(num)][r]-
            (float)RHO*(float)GRAVITY*(float)0.00751*(data[End_of_block(num)][t]-
            data[End_of_block(num)-2][t])*((float)1.e-3)-
            data[End_of_block(num)][u]*data[End_of_block(num)][f];
            x=data[End_of_block(num)][c]-data[End_of_block(num)][s];
        }
    }
}

```

```

else if (data[End_of_block(num)][RESISTANCE_PER]==-1) {

    data[End_of_block(num)][s]=data[End_of_block(num)][r]-
(float)RHO*(float)GRAVITY*(float)0.00751*(data[End_of_block(num)][t]-
data[End_of_block(num)-2][t])*((float)1.e-3)-
data[End_of_block(num)][u]*data[End_of_block(num)][f];
    break;
    }
}
else if ((Begin_of_block(num)==End_of_block(num)) &&
(data[End_of_block(num)][RESISTANCE_PER]!=-1)) {
    data[End_of_block(num)][c]=data[End_of_block(num)][r]-
(float)RHO*(float)GRAVITY*(float)0.00751*(data[End_of_block(num)][t]-
data[End_of_block(num-1)][t])*((float)1.e-3)-
data[End_of_block(num)][u]*data[End_of_block(num)][f];
    x=data[End_of_block(num)][c]-data[End_of_block(num)][s];
    }
else if ((Begin_of_block(num)==End_of_block(num)) &&
(data[End_of_block(num)][RESISTANCE_PER]==-1)) {
    if (num==1) y=0.0;
    if (num==2) y=data[End_of_block(1)][t];
    if (num==4) y=data[End_of_block(2)][t];
    if (num==8) y=data[End_of_block(1)][t];

    data[Begin_of_block(num)][s]=data[Begin_of_block(num)][r]-
(float)RHO*(float)GRAVITY*(float)0.00751*(data[Begin_of_block(num)][t]-
y)*((float)1.e-3)-data[Begin_of_block(num)][u]*data[Begin_of_block(num)][f];
    break;
    }
/*Convergence Criteria*/
if (x>0) {
    data[Begin_of_block(num)][f]=data[Begin_of_block(num)][f]+(float)0.0001*data
[Begin_of_block(num)][f];
    }
else if (x<0) {

    data[Begin_of_block(num)][f]=data[Begin_of_block(num)][f]-
(float)0.0001*data[Begin_of_block(num)][f];
    }
}

/*Accounting for the Compliance of the blood vessels*/
void update_diameter() {

```

```

int i;
for (i = 0; i <= maxRows - 1; i++) {
if ((data[i][PRESSURE_INLET_POS2]-data[i][PRESSURE_INLET_POS1])>=0) {

data[i][DIAMETER_POS2_COMP]=data[i][DIAMETER_POS1]+(float)sqrt((4*data[i][
COMPLIANCE_C]*((float)1.e+3)*abs(data[i][PRESSURE_INLET_POS2]-
data[i][PRESSURE_INLET_POS1]))/(data[i][LENGTH]*PI));
        }
if ((data[i][PRESSURE_INLET_POS2]-data[i][PRESSURE_INLET_POS1])<0) {

data[i][DIAMETER_POS2_COMP]=data[i][DIAMETER_POS1]-
(float)sqrt((4*data[i][COMPLIANCE_C]*((float)1.e+3)*abs(data[i][PRESSURE_INLET
_POS2]-data[i][PRESSURE_INLET_POS1]))/(data[i][LENGTH]*PI));
        }
    }
}

/*Block height calculations used to allow for an initial flowrate guess for the blocks*/

float block_height(int pos,float num) {
/*Supine position*/
    if (pos==1) {
        return ((float)0);
    }
/*27 degrees leg elevation*/
    else if ((pos==2)|| (pos==3)) {
if ((num==2)|| (num==3)|| (num==4)|| (num==5)|| (num==6)|| (num==7)|| (num==8)||
(num==9)|| (num==10)|| (num==11)) {
return ((float)0);
        }
if ((num==12)|| (num==13)) {
return ((float)450);
        }
    }
}
/*15 degrees TREND position*/
    else if ((pos==2)|| (pos==3)) {
        if ((num==3)|| (num==7)) {
            return ((float)-102);
        }
        if ((num==5)|| (num==9)) {
            return ((float)-49);
        }
        if ((num==6)|| (num==10)) {

```

```

        return ((float)160);
    }
    if ((num==12)|| (num==13)) {
        return ((float)350);
    }
}

}*/

/*Initial flow rate caculation*/
float initial_flowrate(int pos, float num) {
    float assumed_flowrate1;
    position(pos);
    data[Begin_of_block(2)][r]=data[End_of_block(1)][s];
    data[Begin_of_block(3)][r]=data[End_of_block(2)][s];
    data[Begin_of_block(4)][r]=data[Begin_of_block(3)][r];
    data[Begin_of_block(5)][r]=data[End_of_block(4)][s];
    data[Begin_of_block(6)][r]=data[Begin_of_block(5)][r];
    data[Begin_of_block(7)][r]=data[End_of_block(1)][s];
    data[Begin_of_block(8)][r]=data[Begin_of_block(7)][r];
    data[Begin_of_block(9)][r]=data[End_of_block(8)][s];
    data[Begin_of_block(10)][r]=data[Begin_of_block(9)][r];
    data[Begin_of_block(11)][r]=data[End_of_block(1)][s];
    data[Begin_of_block(12)][r]=data[End_of_block(11)][s];
    data[Begin_of_block(13)][r]=data[End_of_block(11)][s];
    if (num==2) {
        assumed_flowrate1=(data[Begin_of_block(num)][r]-
        data[End_of_block(num)][s]-
        (float)RHO*(float)GRAVITY*(float)0.00751*block_height(pos,num)*((float)1.e-
        3))/(Resistance_block_pernotper(num,pos));
        return assumed_flowrate1;
    }
    else if
    ((num==3)|| (num==5)|| (num==6)|| (num==7)|| (num==9)|| (num==10)|| (num==12)|| (num==
    13)) {
        assumed_flowrate1=(data[Begin_of_block(num)][r]-
        data[End_of_block(num)][s]-
        (float)RHO*(float)GRAVITY*(float)0.00751*block_height(pos,num)*((float)1.e-
        3))/(Resistance_block(num,pos));
        return assumed_flowrate1;
    }
    else if ((num==4)|| (num==8)) {
        assumed_flowrate1=(data[Begin_of_block(num)][r]-
        data[End_of_block(num)][s]-

```

```

(float)RHO*(float)GRAVITY*(float)0.00751*block_height(pos,num)*((float)1.e-
3))/(Resistance_block_notper(num,pos));
    return assumed_flowrate1;
    }
}

/*Flowrate checkup for the three major loops shown in the block diagram of the arterial
tree*/
void Flow_rate_checkup1(int pos) {
    float j,w;
    position(pos);
    j=data[Begin_of_block(3)][f]+data[Begin_of_block(5)][f]+data[Begin_of_block(
6)][f];
    w=j-data[Begin_of_block(2)][f];
    while ((w>=0.001) || (w<=-0.001)) {
        if (w>0) {

            data[Begin_of_block(2)][f]=data[Begin_of_block(2)][f]+(float)0.001*data[Begin
_of_block(2)][f];

        }
        else if (w<0) {

            data[Begin_of_block(2)][f]=data[Begin_of_block(2)][f]-
(float)0.001*data[Begin_of_block(2)][f];

        }
        Pressure_Block(2,data[Begin_of_block(2)][f],pos);
        Pressure_Block(3,initial_flowrate(pos,3),pos);
        Pressure_Block(4,data[Begin_of_block(2)][f]-data[Begin_of_block(3)][f],pos);
        Pressure_Block(5,initial_flowrate(pos,5),pos);
        Pressure_Block(6,initial_flowrate(pos,6),pos);

        j=data[Begin_of_block(3)][f]+data[Begin_of_block(5)][f]+data[Begin_of_block(6)][f];
        w=j-data[Begin_of_block(2)][f];
    }
}

void Flow_rate_checkup2(int pos) {
    float j,w;
    position(pos);
    j=data[Begin_of_block(9)][f]+data[Begin_of_block(10)][f];
    w=j-data[Begin_of_block(8)][f];
    while ((w>=0.001) || (w<=-0.001)) {
        if (w>0) {

```

```

        data[Begin_of_block(8)][f]=data[Begin_of_block(8)][f]+(float)0.001*data[Begin
_of_block(8)][f];
    }
    else if (w<0) {
        data[Begin_of_block(8)][f]=data[Begin_of_block(8)][f]-
(float)0.001*data[Begin_of_block(8)][f];
    }
    Pressure_Block(8,data[Begin_of_block(8)][f],pos);
    Pressure_Block(9,initial_flowrate(pos,9),pos);
    Pressure_Block(10,data[Begin_of_block(8)][f]-data[Begin_of_block(9)][f],pos);

    j=data[Begin_of_block(9)][f]+data[Begin_of_block(10)][f];
    w=j-data[Begin_of_block(8)][f];
    }
}

void Flow_rate_checkup3(int pos) {
    position(pos);
    data[Begin_of_block(11)][f]=data[Begin_of_block(12)][f]+data[Begin_of_block(
13)][f]+(data[Begin_of_block(11)][f]-data[End_of_block(11)][f]);
    Pressure_Block(11,data[Begin_of_block(11)][f],pos);
    Pressure_Block(12,data[Begin_of_block(12)][f],pos);
    Pressure_Block(13,data[Begin_of_block(13)][f],pos);
}

/*Checkup pressure among all the blocks*/
void Inlet_pressure_checkup(int pos) {
    position(pos);
    data[Begin_of_block(1)][r]=data[Begin_of_block(1)][f]*Resistance_main_block(
1,pos)+pright_atrium;
    Pressure_Block(1,(float)CO,pos);
    Pressure_Block(2,(float)0.07596*CO,pos);
    Pressure_Block(3,initial_flowrate(pos,3),pos);
    Pressure_Block(4,(float)0.058319*CO,pos);
    Pressure_Block(5,initial_flowrate(pos,5),pos);
    Pressure_Block(6,initial_flowrate(pos,6),pos);
    Flow_rate_checkup1(pos);
    Pressure_Block(7,initial_flowrate(pos,7),pos);
    Pressure_Block(8,(float)0.058319*CO,pos);
    Pressure_Block(9,initial_flowrate(pos,9),pos);
    Pressure_Block(10,initial_flowrate(pos,10),pos);
    Flow_rate_checkup2(pos);
}

```



```

        Pressure_Block(11,((float)CO-data[Begin_of_block(2)][f]-
        data[Begin_of_block(7)][f]-data[Begin_of_block(8)][f]),pos);
        Pressure_Block(12,initial_flowrate(pos,12),pos);
        Pressure_Block(13,initial_flowrate(pos,13),pos);
        Flow_rate_checkup3(pos);
    }

/*print the results*/
void print_output() {
    if ((output_fp = fopen("output.txt", "w")) == NULL) {
        printf("\nError opening output file for writing ..");
        return;
    } else {
        int i;
        fprintf(output_fp,"\n\n*****
        *****
        *****
        *****");
        fprintf(output_fp,"\n      I      J      L      D_P1  D_P2_C  RES_PER
        RES_L_P1  RES_L_P2C  RES_T_P1  RES_T_P2C  RES_B  FLOW_P1
        FLOW_P2_RIGID  FLOW_P2_CMP  H_P1   H_P2   P_OUT_P1  P_OUT_P1_C
        P_IN_P1  P_OUT_P2  P_OUT_P2_C  P_IN_P2_R      COMP_C");
        fprintf(output_fp,"\n*****
        *****
        *****
        *****\n");
        for (i = 0; i <= maxRows - 1; i++) {
            fprintf(output_fp,"\n%10.0f\t%10.0f  %10.2f %10.2f %10.2f %10.2f %10.2f
            %10.2f %10.2f %10.2f %10.2f %10.2f %10.2f %10.2f %10.2f %10.2f
            %10.2f %10.2f %10.2f %10.2f \t%10.5f",

            data[i][INDEX_J],data[i][INDEX_I],data[i][LENGTH],data[i][DIAMETER_POS1],data
            [i][DIAMETER_POS2_COMP],data[i][RESISTANCE_PER],data[i][RESISTANCE_L_
            POS1],

            data[i][RESISTANCE_L_POS2_COMP],data[i][RESISTANCE_T_POS1],data[i][RESI
            STANCE_T_POS2_COMP],data[i][RESISTANCE_B],data[i][FLOWRATE_POS1],data
            [i][FLOWRATE_POS2_RIGID],

            data[i][FLOWRATE_POS2_COMP],data[i][HEIGHT_POS1],data[i][HEIGHT_POS2],d
            ata[i][PRESSURE_OUTLET_POS1],data[i][PRESSURE_OUTLET_POS1_CAL],data[i]

```



```

Flow_rate_checkup3(1);
Inlet_pressure_checkup(1);

update_cardiac_output(2);
update_pressure_inlet(2);
update_pressure_outlet(2);
update_Local_Resistance(2);
update_Total_Resistance(2);
Pressure_Block(1,(float)CO,2);
Pressure_Block(2,(float)0.07596*CO,2);
Pressure_Block(3,initial_flowrate(2,3),2);
Pressure_Block(4,(float)0.058319*CO,2);
Pressure_Block(5,initial_flowrate(2,5),2);
Pressure_Block(6,initial_flowrate(2,6),2);
Flow_rate_checkup1(2);
Pressure_Block(7,initial_flowrate(2,7),2);
Pressure_Block(8,(float)0.058319*CO,2);
Pressure_Block(9,initial_flowrate(2,9),2);
Pressure_Block(10,initial_flowrate(2,10),2);
Flow_rate_checkup2(2);
Pressure_Block(11,((float)CO-data[Begin_of_block(2)][f]-data[Begin_of_block(7)][f]-
data[Begin_of_block(8)][f]),2);
Pressure_Block(12,initial_flowrate(2,12),2);
Pressure_Block(13,initial_flowrate(2,13),2);
Flow_rate_checkup3(2);
Inlet_pressure_checkup(2);

/*Calculations for the second position (TREND15 or LEGUP27)*/
update_diameter();
update_Local_Resistance(3);
update_Total_Resistance(3);
Pressure_Block(1,(float)CO,3);
Pressure_Block(2,(float)0.07596*CO,3);
Pressure_Block(3,initial_flowrate(2,3),3);
Pressure_Block(4,(float)0.058319*CO,3);
Pressure_Block(5,initial_flowrate(3,5),3);
Pressure_Block(6,initial_flowrate(3,6),3);
Flow_rate_checkup1(3);
Pressure_Block(7,initial_flowrate(3,7),3);
Pressure_Block(8,(float)0.058319*CO,3);
Pressure_Block(9,initial_flowrate(3,9),3);
Pressure_Block(10,initial_flowrate(3,10),3);
Flow_rate_checkup2(3);

```

```

Pressure_Block(11,((float)CO-data[Begin_of_block(2)][f]-data[Begin_of_block(7)][f]-
data[Begin_of_block(8)][f]),3);
Pressure_Block(12,initial_flowrate(3,12),3);
Pressure_Block(13,initial_flowrate(3,13),3);
Flow_rate_checkup3(3);
Inlet_pressure_checkup(3);

print_output();
for (i = 0; i <= maxRows - 1; i++) {
    free(data[i]);
}
free(data);
return 0;
}

```

F.2 Sample Input File

Please enter the stroke volume in millimeters per beat for position 1: 83.33

Please enter the heart rate in beats per minute for position 1: 60

Please enter an initial guess for the mean arterial pressure in mmHg for position 1: 83

Please enter the central venous pressure in mmHg for position 1: 5

Please enter the stroke volume in millimeters per beat for position 2: 83.33

Please enter the heart rate in beats per minute for position 2: 60

Please enter the mean arterial pressure in mmHg for position 2: 83

Please enter the central venous pressure in mmHg for position 2: 7

F.3 Sample Output File

Table F.1 Sample output file.

I	J	L (mm)	d(p1) (mm)	d(p2) (mm)	R(total-p1) (mmHg/ml/sec)	R(total-p2) (mmHg/ml/sec)
1	1	40	27.6	30.14	0	0
2	1	34	12.46	13.52	0	0
3	1	177	7.42	7.99	0.06	0.05
3	2	177	3.93	4.12	105.19	105.05
3	3	177	3.93	4.12	105.19	105.05
4	1	34	8.46	9.13	0.01	0.01
5	1	148	3.96	4.14	45.78	45.68
6	1	422	8.06	8.74	0.11	0.08
6	2	235	3.67	3.84	41.04	40.81
6	3	67	4.3	4.5	0.21	0.17
6	4	79	1.99	2.05	638.49	637.89
6	5	171	4.12	4.31	40.29	40.18
7	1	177	7.4	7.97	0.06	0.05
7	2	177	3.93	4.12	105.19	105.05
7	3	177	3.93	4.12	105.19	105.05
8	1	34	8.46	9.13	0.01	0.01
9	1	148	3.96	4.14	45.78	45.68
10	1	422	8.06	8.74	0.11	0.08
10	2	235	3.67	3.84	41.04	40.81
10	3	67	4.3	4.5	0.21	0.17
10	4	79	1.99	2.05	638.49	637.89
10	5	171	4.12	4.31	40.29	40.18
11	1	111	21.87	23.91	0	0
11	2	80	5	5.35	10.58	10.54
11	3	104	19.6	21.4	0	0
11	4	10	7.8	8.41	8.42	8.42
11	5	53	15.6	16.92	0	0
11	6	59	7.4	7.94	7	7
11	7	10	12.6	13.72	0	0
11	8	32	6.5	7.01	8.51	8.5
11	9	10	11.4	12.36	0	0
11	10	32	4.5	4.8	8.57	8.55

Cont'd- Table F.1 Sample output file.

I	J	L (mm)	d(p1) (mm)	d(p2) (mm)	R(total-p1) (mmHg/ml/sec)	R(total-p2) (mmHg/ml/sec)
11	11	106	9.42	10.14	0.01	0.01
11	12	50	3.19	3.38	52.19	52.08
11	13	10	8.58	9.21	0	0
12	1	58	6.46	6.92	0.04	0.03
12	2	50	4.8	4.8	59.7	59.7
12	3	144	5.66	5.66	0.15	0.15
12	4	126	4.01	3.81	36.34	36.46
12	5	443	4.21	3.77	1.51	2.34
12	6	321	3.74	3.36	37.58	38.52
12	7	343	2.76	2.5	48.31	51.38
13	1	58	6.46	6.92	0.04	0.03
13	2	50	4.8	4.8	59.7	59.7
13	3	144	5.66	5.66	0.15	0.15
13	4	126	4.01	3.81	36.34	36.46
13	5	443	4.21	3.77	1.51	2.34
13	6	321	3.74	3.36	37.58	38.52
13	7	343	2.76	2.5	48.31	51.38

Cont'd- Table F.1 Sample output file.

I	J	Q(P1) (ml/sec)	Q(P2) (ml/sec)	H(P1) (mm)	H(P2) (mm)	Pin(P1) (mmHg)	Pout(P1) (mmHg)
1	1	83.33	83.33	0	0	91.36	91.36
2	1	7.87	7.94	0	0	91.36	91.35
3	1	1.64	1.65	0	0	91.35	91.24
3	2	0.82	0.82	0	0	91.24	5
3	3	0.82	0.82	0	0	91.24	5
4	1	6.23	6.29	0	0	91.35	91.3
5	1	1.89	1.9	0	0	91.3	5
6	1	4.34	4.39	0	0	91.3	90.84
6	2	2.09	2.12	0	0	90.84	5
6	3	2.25	2.27	0	0	90.84	90.36
6	4	0.13	0.13	0	0	90.36	5
6	5	2.12	2.14	0	0	90.36	5
7	1	1.64	1.65	0	0	91.36	91.26
7	2	0.82	0.82	0	0	91.26	5
7	3	0.82	0.82	0	0	91.26	5
8	1	6.23	6.29	0	0	91.36	91.31
9	1	1.89	1.9	0	0	91.31	5
10	1	4.35	4.39	0	0	91.31	90.85
10	2	2.09	2.12	0	0	90.85	5
10	3	2.26	2.28	0	0	90.85	90.38
10	4	0.13	0.13	0	0	90.38	5
10	5	2.12	2.14	0	0	90.38	5
11	1	67.57	67.44	0	0	91.36	91.32
11	2	8.16	8.22	0	0	91.32	5
11	3	59.41	59.22	0	0	91.32	91.28
11	4	10.24	10.29	0	0	91.28	5
11	5	49.17	48.93	0	0	91.28	91.23
11	6	12.32	12.38	0	0	91.23	5
11	7	36.85	36.54	0	0	91.23	91.22
11	8	10.13	10.19	0	0	91.22	5
11	9	26.72	26.36	0	0	91.22	91.2
11	10	10.05	10.12	0	0	91.2	5

Cont'd- Table F.1 Sample output file.

I	J	Q(P1) (ml/sec)	Q(P2) (ml/sec)	H(P1) (mm)	H(P2) (mm)	Pin(P1) (mmHg)	Pout(P1) (mmHg)
11	11	16.66	16.24	0	0	91.2	90.96
11	12	1.65	1.66	0	0	90.96	5
11	13	15.02	14.58	0	0	90.96	90.93
12	1	7.51	7.29	0	26.33	90.93	90.66
12	2	1.43	1.44	0	49.03	90.66	5
12	3	6.07	5.84	0	91.7	90.66	89.75
12	4	2.33	2.34	0	148.9	89.75	5
12	5	3.74	3.5	0	292.82	89.75	84.09
12	6	2.1	2	0	438.55	84.09	5
12	7	1.64	1.5	0	448.54	84.09	5
13	1	7.51	7.29	0	26.33	90.93	90.66
13	2	1.43	1.44	0	49.03	90.66	5
13	3	6.07	5.84	0	91.7	90.66	89.75
13	4	2.33	2.34	0	148.9	89.75	5
13	5	3.74	3.5	0	292.82	89.75	84.09
13	6	2.1	2	0	438.55	84.09	5
13	7	1.64	1.5	0	448.54	84.09	5

Cont'd- Table F.1 Sample output file.

I	J	Pin(P2) (mmHg)	Pout(P2) (mmHg)	Compliance (ml/sec/mmHg)
1	1	93.73	93.72	0.101
2	1	93.72	93.71	0.015
3	1	93.71	93.64	0.0225
3	2	93.64	7	0.00251
3	3	93.64	7	0.00251
4	1	93.71	93.68	0.00603
5	1	93.68	7	0.00198
6	1	93.68	93.34	0.0774
6	2	93.34	7	0.00265
6	3	93.34	92.94	0.00107
6	4	92.94	7	0.00011
6	5	92.94	7	0.00255
7	1	93.72	93.64	0.0223
7	2	93.64	7	0.00251
7	3	93.64	7	0.00251
8	1	93.72	93.69	0.00603
9	1	93.69	7	0.00198
10	1	93.69	93.35	0.0774
10	2	93.35	7	0.00265
10	3	93.35	92.95	0.00107
10	4	92.95	7	0.00011
10	5	92.95	7	0.00255
11	1	93.72	93.7	0.181
11	2	93.7	7	0.00392
11	3	93.7	93.67	0.132
11	4	93.67	7	0.00145
11	5	93.67	93.63	0.0365
11	6	93.63	7	0.00679
11	7	93.63	93.62	0.0049
11	8	93.62	7	0.00331
11	9	93.62	93.61	0.00363
11	10	93.61	7	0.0011

Cont'd- Table F.1 Sample output file.

I	J	Pin(P2) (mmHg)	Pout(P2) (mmHg)	Compliance (ml/sec/mmHg)
11	11	93.61	93.44	0.0217
11	12	93.44	7	0.00074
11	13	93.44	93.41	0.00155
12	1	93.41	91.18	0.00487
12	2	91.18	3.21	0.00271
12	3	91.18	85.25	0.00931
12	4	85.25	-4.51	0.00081
12	5	85.25	61.52	0.0132
12	6	61.52	-26.89	0.00183
12	7	61.52	-27.66	0.00091
13	1	93.41	91.18	0.00487
13	2	91.18	3.21	0.00271
13	3	91.18	85.25	0.00931
13	4	85.25	-4.51	0.00081
13	5	85.25	61.52	0.0132
13	6	61.52	-26.89	0.00183
13	7	61.52	-27.66	0.00091

F.4 Empirical Data of the blood vessels

Based on information available in the published literature (Noordergraaf, 1963; Stergiopoulos et al., 1992; Wang and Parker, 2004; Westerhof, 1968; Westerhof et al., 1969), the diameter, length and compliance information on the blood vessels are documented together with the uncertainty of these parameters on Table F.2.

Table F.2 Available empirical data of the blood vessels on the literature.

Branch [j, i]	Internal Diameter Mean $\pm$ SD (mm)	Compliance Mean $\pm$ SD (ml/mmHg)	Length Mean $\pm$ SD (ml/mmHg)	Peripheral Resistance Mean $\pm$ SD (mmHg/ml/sec)
[1,1]	27.44 $\pm$ 3.33	0.10148 $\pm$ 0.04134	40 $\pm$ 0.00	-1
[2,1]	11.78 $\pm$ 1.42	0.015 $\pm$ 0.00573	34 $\pm$ 0.00	-1
[3,1]	7.17 $\pm$ 0.57	0.02251 $\pm$ 0.0056	177 $\pm$ 0.45	-1
[3,2]	2.86 $\pm$ 0.57	0.00251 $\pm$ 0.00126	176 $\pm$ 2.68	104.35 $\pm$ 0.06
[3,3]	2.93 $\pm$ 0.55	0.00251 $\pm$ 0.00121	176 $\pm$ 26.28	104.35 $\pm$ 0.06
[4,1]	7.62 $\pm$ 1.09	0.00603 $\pm$ 0.00264	34 $\pm$ 0.00	-1
[5,1]	3.73 $\pm$ 0.15	0.00198 $\pm$ 0.00023	148 $\pm$ 0.00	45.18 $\pm$ 0.06
[6,1]	7.41 $\pm$ 0.9	0.07737 $\pm$ 0.02892	352 $\pm$ 0.00	-1
[6,2]	3.23 $\pm$ 0.22	0.00265 $\pm$ 0.00051	235 $\pm$ 0.45	39.68 $\pm$ 0.04
[6,3]	4.23 $\pm$ 0.12	0.00107 $\pm$ 0.00009	67 $\pm$ 0.00	-1
[6,4]	1.83 $\pm$ 0.09	0.00011 $\pm$ 0.00002	79 $\pm$ 0.00	633.35 $\pm$ 0.36
[6,5]	3.87 $\pm$ 0.13	0.00255 $\pm$ 0.00025	171 $\pm$ 0.45	39.68 $\pm$ 0.04
[7,1]	7.17 $\pm$ 0.57	0.02232 $\pm$ 0.00557	177 $\pm$ 17.17	-1
[7,2]	2.86 $\pm$ 0.57	0.00251 $\pm$ 0.00126	176 $\pm$ 0.45	104.35 $\pm$ 0.06
[7,3]	2.93 $\pm$ 0.55	0.00251 $\pm$ 0.00121	176 $\pm$ 26.39	104.35 $\pm$ 0.06
[8,1]	8.45 $\pm$ 0.03	0.00603 $\pm$ 0.00006	34 $\pm$ 0.00	-1
[9,1]	3.73 $\pm$ 0.15	0.00198 $\pm$ 0.00023	148 $\pm$ 0.00	45.18 $\pm$ 0.06
[10,1]	7.41 $\pm$ 0.9	0.07737 $\pm$ 0.02892	352 $\pm$ 0.00	-1
[10,2]	3.23 $\pm$ 0.22	0.00265 $\pm$ 0.00051	235 $\pm$ 0.45	39.68 $\pm$ 0.04
[10,3]	4.23 $\pm$ 0.12	0.00107 $\pm$ 0.00009	67 $\pm$ 0.00	-1
[10,4]	1.83 $\pm$ 0.09	0.00011 $\pm$ 0.00002	79 $\pm$ 0.00	633.35 $\pm$ 0.36
[10,5]	3.87 $\pm$ 0.13	0.00255 $\pm$ 0.00025	171 $\pm$ 0.45	39.68 $\pm$ 0.04
[11,1]	23.04 $\pm$ 1.43	0.1807 $\pm$ 0.04092	111 $\pm$ 0.00	-1
[11,2]	4.25 $\pm$ 1.06	0.00392 $\pm$ 0.00306	80 $\pm$ 0.00	10.45 $\pm$ 0.01

Cont'd –Table F.2 Available empirical data of the blood vessels on the literature.

Branch [j, i]	Internal Diameter Mean $\pm$ SD (mm)	Compliance Mean $\pm$ SD (ml/mmHg)	Length Mean $\pm$ SD (ml/mmHg)	Peripheral Resistance Mean $\pm$ SD (mmHg/ml/sec)
[11,3]	15.7 $\pm$ 3.3	0.13237 $\pm$ 0.07875	104 $\pm$ 0.00	-1
[11,4]	7.54 $\pm$ 0.63	0.00145 $\pm$ 0.00038	12 $\pm$ 0.00	8.42 $\pm$ 0.00
[11,5]	13.28 $\pm$ 2.83	0.03653 $\pm$ 0.02371	53 $\pm$ 0.45	-1
[11,6]	8.18 $\pm$ 0.77	0.00679 $\pm$ 0.00235	59 $\pm$ 0.00	6.99 $\pm$ 0.01
[11,7]	11.52 $\pm$ 1.16	0.0049 $\pm$ 0.00148	10 $\pm$ 0.00	-1
[11,8]	5.3 $\pm$ 0.66	0.00331 $\pm$ 0.00112	32 $\pm$ 0.00	8.52 $\pm$ 0.04
[11,9]	10.96 $\pm$ 1.04	0.00363 $\pm$ 0.00109	10 $\pm$ 0.00	-1
[11,10]	4.96 $\pm$ 0.37	0.0011 $\pm$ 0.00029	32 $\pm$ 0.00	8.52 $\pm$ 0.04
[11,11]	10.35 $\pm$ 1.32	0.02172 $\pm$ 0.01047	106 $\pm$ 0.00	-1
[11,12]	3.14 $\pm$ 0.15	0.00074 $\pm$ 0.00011	50 $\pm$ 0.00	51.71 $\pm$ 0.05
[11,13]	9.49 $\pm$ 1.29	0.00155 $\pm$ 0.00081	10 $\pm$ 0.00	-1
[12,1]	7.32 $\pm$ 1.73	0.00487 $\pm$ 0.00505	58 $\pm$ 0.45	-1
[12,2]	4.27 $\pm$ 0.46	0.00271 $\pm$ 0.00086	50 $\pm$ 0.00	59.6 $\pm$ 0.00
[12,3]	5.68 $\pm$ 0.28	0.00931 $\pm$ 0.00145	144 $\pm$ 33.41	-1
[12,4]	4.48 $\pm$ 0.36	0.00081 $\pm$ 0.00024	126 $\pm$ 28.17	35.84 $\pm$ 0.02
[12,5]	4.57 $\pm$ 0.31	0.01323 $\pm$ 0.00314	443 $\pm$ 0.00	-1
[12,6]	3.69 $\pm$ 0.17	0.00183 $\pm$ 0.00026	321 $\pm$ 0.45	35.84 $\pm$ 0.02
[12,7]	2.55 $\pm$ 0.16	0.00091 $\pm$ 0.00017	343 $\pm$ 8.05	41.99 $\pm$ 0.04
[13,1]	7.32 $\pm$ 1.73	0.00487 $\pm$ 0.00505	58 $\pm$ 0.00	-1
[13,2]	4.27 $\pm$ 0.46	0.00271 $\pm$ 0.00086	50 $\pm$ 0.00	59.6 $\pm$ 0.00
[13,3]	5.79 $\pm$ 0.09	0.00931 $\pm$ 0.00145	144 $\pm$ 33.41	-1
[13,4]	4.48 $\pm$ 0.36	0.00081 $\pm$ 0.00024	126 $\pm$ 28.17	35.84 $\pm$ 0.04
[13,5]	4.57 $\pm$ 0.31	0.01323 $\pm$ 0.00314	443 $\pm$ 0.00	-1
[13,6]	3.69 $\pm$ 0.17	0.00183 $\pm$ 0.00026	343 $\pm$ 0.45	35.84 $\pm$ 0.04
[13,7]	2.55 $\pm$ 0.16	0.00091 $\pm$ 0.00017	343 $\pm$ 8.05	41.99 $\pm$ 0.04

Appendix G

Experimental Results

Measured changes in P_{SBP} , P_{DBP} , P_{MAP} , and HR in normotensive healthy subjects 10 seconds after 27-degree passive leg elevation are presented in Table G.1. Measured changes for the same parameters 2 minutes after 9-degree, 18-degree and 27-degree of passive leg elevation are presented in Tables G.2, G.3 and G.4.

The rate of P_{SBP} change (mmHg / °), P_{DBP} change (mmHg / °) and HR change (Beats /min/ °) for normotensive healthy subjects are presented graphically in Figures G.1, G.2 and G.3, and for hypertensive healthy subjects in Figures G.4, G.5 and G.6.

Table G.1 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive healthy subjects 10 seconds after 27 degrees of passive leg elevation.

	Normotensive Healthy Subjects ($n = 30$) Mean $\pm$ SD
Systolic pressure (mmHg)	2.51 ± 1.95
Diastolic Pressure (mmHg)	1.54 ± 1.98
Mean arterial pressure (mmHg)	1.87 ± 1.59
Heart rate (Beats/min)	0.34 ± 4.28

Table G.2 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 2 minutes after 9 degrees of passive leg elevation.

	Normotensive Healthy Subjects (<i>n</i> = 50) Mean $\pm$ SD
Systolic pressure (mmHg)	-0.91 ± 1.47
Diastolic Pressure (mmHg)	-0.41 ± 1.84
Mean arterial pressure (mmHg)	-0.56 ± 1.78
Heart rate (Beats/min)	-0.69 ± 2.31

Table G.3 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 2 minutes after 18 degrees of passive leg elevation.

	Normotensive Healthy Subjects (<i>n</i> = 50) Mean $\pm$ SD
Systolic pressure (mmHg)	-0.71 ± 1.71
Diastolic Pressure (mmHg)	-0.38 ± 2.47
Mean arterial pressure (mmHg)	-0.49 ± 1.83
Heart rate (Beats/min)	-0.78 ± 2.84

Table G.4 Measured changes in systolic pressure, diastolic pressure, mean arterial pressure and heart rate in normotensive subjects 2 minutes after 27 degrees of passive leg elevation.

	Normotensive Healthy Subjects (<i>n</i> = 50) Mean $\pm$ SD
Systolic pressure (mmHg)	-0.48 ± 1.97
Diastolic Pressure (mmHg)	-0.27 ± 2.22
Mean arterial pressure (mmHg)	-0.34 ± 1.76
Heart rate (Beats/min)	-0.82 ± 3.33

Figure G.1 Rate of P_{SBP} change with PLE in normotensive healthy subjects.

Figure G.2 Rate of P_{DBP} change with PLE in normotensive healthy subjects.

Figure G.3 Rate of HR change with PLE in normotensive healthy subjects.

Figure G.4 Rate of P_{SBP} change with PLE in hypertensive healthy subjects.

Figure G.5 Rate of P_{DBP} change with PLE in hypertensive healthy subjects.

Figure G.6 Rate of HR change with PLE in hypertensive healthy subjects.