MODELING THE DYNAMICS OF VICIOUS CYCLES INVOLVED IN HEART-RESPIRATORY FAILURE

by

Sema Çömez

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APPROVED BY:

Assoc. Prof. Aybek Korugan (Thesis Supervisor)	.....
Prof. Yaman Barlas (Thesis Co-supervisor)	.....
Assoc. Prof. Gönenç Yücel	.....
Assist. Prof. Cafer Erhan Bozdağ	.....

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ABSTRACT

MODELING THE DYNAMICS OF VICIOUS CYCLES INVOLVED IN HEART-RESPIRATORY FAILURE

Heart failure is a syndrome when the heart is damaged permanently and lost its full functionality. In this case, the tissues cannot be fed sufficiently with blood and oxygen and compensatory mechanisms are triggered. These mechanisms are the sympathetic nervous system, Renin-Angiotensin-Aldosterone, Antidiuretic Hormone and Natriuretic Peptides which help a healthy human body to reach homeostatic balance. When the balance is impaired, they work as negative feedback loops to reach equilibrium. However, these mechanisms can create a vicious cycle for people who have damaged heart and vascular structures. Due to the permanent damage of heart, blood and oxygen supply to the tissues is insufficient and all these mechanisms are activated. Continuous activation of these mechanisms deteriorates the structure and performance of the heart. In this study, a simulation model of Acute Heart Failure Syndrome is constructed. It consists of many subsystems and their complex interactions which are controlled by feedback mechanisms. Excessive accumulation of water and sodium and vasoconstriction are effective in the progress of acute heart failure. Pulmonary edema and increased systolic pressure cause to decrease oxygen supply and to increase cardiac load. Consequently, positive feedback mechanisms are activated and cardiac function loss can occur within hours. Quantitative and qualitative data is obtained from the literature. Healthy individual and patient values are determined and the relationships between the model variables are defined based on investigation. The model is validated after many tests. In the scenario analysis section, various treatment strategies and average hourly sodium intake amounts are simulated. The aim of the study is to minimize the hospital discharge time of the patient. The objective includes pulmonary edema excretion time and time of the stabilization of the variables.

ÖZET

KALP-SOLUNUM YETMEZLİĞİ İÇEREN KISIR DÖNGÜ DİNAMİKLERİNİN MODELLENMESİ

Kalp yetmezliği herhangi bir nedenden dolayı kalbin kalıcı hasar görmesi ve bu hasardan dolayı performans kaybı yaşamasıdır. Bu durumda dokular kan ve oksijen yönünden yeteri kadar beslenemez ve kompanse mekanizmaları tetikler. Bu mekanizmalar sempatik sinir sistemi, Renin-Angiotensin-Aldosterone, Antidiüretik Hormon ve Natriüretik Peptitler'dir. Homeostasinin bozulduğu durumlarda negatif geri besleme mantığı ile çalışırlar. Ancak kalp ve damar yapısı hasar görmüş insanlarda bu mekanizmalar kısır döngü yaratır. Kalpte oluşan kalıcı hasar sebebi ile dokulara hiçbir şekilde yeterli kan ve oksijenin gitmemesi bu mekanizmaların sürekli aktif kalmasına sebep olur. Bu mekanizmaların sürekli aktif olması farklı şekillerde kalbin yapısını ve performansını daha da bozar. Bu çalışma kapsamında, oluşumunda pek çok sistemin rol almasından dolayı kompleks bir yapıya sahip olan ve geri besleme mekanizmaları tarafından kontrol edilen Akut Kalp Yetmezliği sendromunun simülasyon modeli kurulmuştur. Akut Kalp Yetmezliği'nin gelişmesinde vücutta aşırı su ve sodyumun birikmesi ve vazokonstriksiyon etkilidir. Akciğer ödemi ve sistolik basıncın artması kalbin oksijen yönünden beslenememesine ve kardiyak yükün artmasına sebep olur. Bu durumda pozitif geri besleme mekanizmaları devreye girer ve saatler içinde kardiyak fonksiyonda kayıplar meydana gelir. Literatürden elde edilen nicel ve nitel veriler ile sağlıklı ve hasta bireylere ait değerler tayin edilmiş, model değişkenleri arası ilişkiler tanımlanmıştır. Oluşturulan model pek çok testten geçerek valide edilmiştir. Hazırlanan senaryolarda çeşitli tedavi stratejileri ve saatlik alınan ortalama sodyum miktarları simule edilmiştir. Çalışmanın sonucunda hastanın taburcu süresini minimize etmek amaçlanmıştır. Hastanın en kısa sürede akciğer ödemini atması ve takip edilen değişkenlerin stabilize olması kriter kabul edilmiştir.

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LIST OF ACRONYMS/ABBREVIATIONS

Abs	Absorption
ACE	Acute Heart Failure
ADH	Antidiuretic Hormone
ADHF	Acute Decompensated Heart Failure
Adj	Adjustment
AHF	Acute Heart Failure
ALD	Aldosterone
ANG	Angiotensin
ANP	Atrial Natriuretic Peptide
AR	Arterial Resistance
ARB	Angiotensin II Receptor Blocker
AT	Adjustment Time
Avg	Average
Bisop	Bisoprolol
Bioavail	Bioavailability
BNP	Brain Natriuretic Peptide
BV	Blood Volume
Cand	Candesartan
CHF	Chronic Heart Failure
CNP	C-type Natriuretic Peptides
CO	Cardiac Output
Conc	Concentration
CVP	Central Venous Pressure
Dist	Distribution
EDV	End Diastolic Volume
EF	Ejection Fraction
Elim	Elimination
FFV	Free Fluid Volume

Furo	Furosemide
FV	Fluid Volume
GFR	Glomerular Filtration Rate
HBV	Heart Blood Volume
HC	Heart Capability
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Heart Rate
LV	Left Ventricle
LVEDV	Left Ventricular End Diastolic Volume
MAP	Mean Arterial Pressure
Na	Sodium
NAUConc	Urine Sodium Concentration
NYHA	New York Heart Association
O_2	Oxygen
PFV	Pulmonary Fluid Volume
PVP	Peripheral Venous Pressure
RAAS	Renin-Angiotensin-Aldosterone System
RSNS	Renal Sympathetic Nervous System
RV	Right Ventricle
SNS	Sympathetic Nervous System
SP	Systolic Pressure
SV	Stroke Volume
TPR	Total Peripheral resistance
Vol	Volume
VR	Venous Return
VRR	Venous Return Resistance

1. INTRODUCTION

Heart failure (HF) is a syndrome suffered when the loosen its functionality. This condition causes reduced heart perfusion and failure of delivering adequate blood to tissues and organs. Heart failure is a disease that consists of many heterogeneous clinical syndromes and each has a separate clinical presentation, prognosis and management [1]. Due to a variety of symptoms and affected subsystems, it becomes difficult to find the optimal treatment method. In the 2013 ACCF/AHA Guideline for the Management of Heart Failure [2], statistics of mortality rates are given via using results of The Atherosclerosis Risk in Communities Study (ARIC) that is conducted by four U.S. communities for investigating etiology of cardiovascular diseases. The results show that the 30-day, 1-year, and 5-year case mortality rates after hospitalization for HF are 10.4%, 22%, and 42.3%, respectively.

Besides the treatment management of the syndrome, the economic aspect also creates problems. 1-2% of total health care budget is allocated worldwide for heart failure management and treatment [3]. The length of hospital stay is limited for budget constrains of hospitals. However, when the patient is discharged before the hemodynamic and renal parameters are stable causes re-hospitalization [4]. Statistical studies about length of stay and readmission are not sufficient to analyze optimal management of hospitalization period. The general inference is that length of stay is correlated with readmission and mortality rates since patients who are in more severe conditions stay in hospital longer as seen in Figure 1.1.

There are several reasons like cardiovascular disease, heart attack, high blood pressure (hypertension) and heart valve disease that trigger heart failure. When the heart failure is present , several mechanisms are activated. Since there are several mechanisms that play a role in progress of syndrome, it becomes a complex problem and doctors have difficulty to understand the reasons and optimal treatments.

The triggered mechanisms that contribute to the progress of this syndrome is based on the compensating of the hemodynamic parameters. These mechanisms are Renin-Angiotensin-Aldostorene, ADH and Sympathetic nerve activity as seen in Figure 1.2. These mechanisms are beneficial for short term due to increased hemodynamic parameters via sodium and water retention. However, heart failure patients have damaged and dilated hearts. Consequently, hemodynamic parameters never reach their desired levels. Water and sodium retention damages the cardiac system in the long-term since elevated pressure creates tension on heart and respiratory problems occur due to excessive fluid accumulation in lungs. These problems increase myocardial dysfunction and it is irreversible. "Vicious cycle" term comes from these positive feedback mechanisms that causes permanent deterioration in heart.

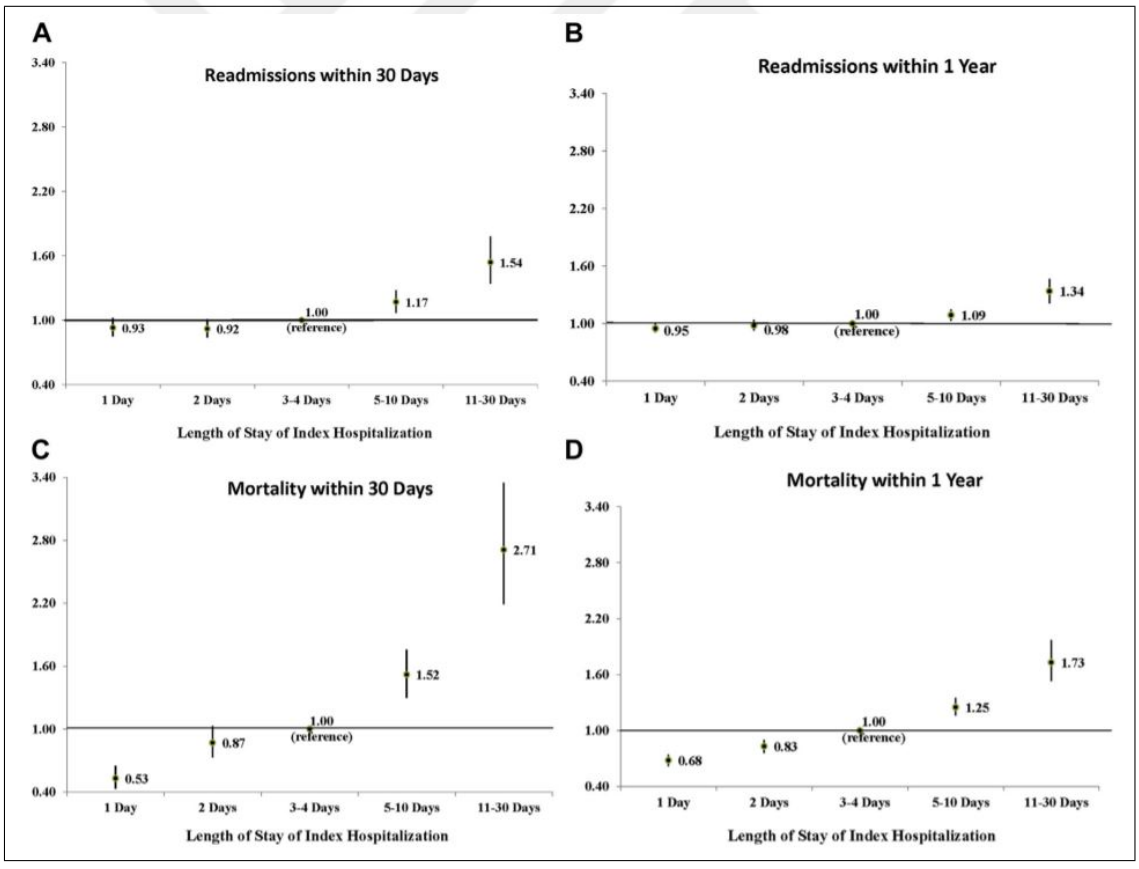


Figure 1.1. Readmission and mortality rates based on length of stay in hospital (reproduced from [5])

Heart failure has many types depending on different classifications. In terms of ventricles, there are two types, left ventricular HF and right ventricular HF. Left sided heart and ventricle supply oxygen-rich blood to peripheral tissues. There are two types of left ventricular (LV) heart failure. One of them is systolic failure that is defined as HF with reduced ejection fraction (HFrEF), another is diastolic that is defined as HF with preserved ejection fraction (HFpEF). Systolic failure means left ventricle loses contractility function in a certain level and enough blood cannot be pumped with enough force into circulation. In case of diastolic failure, heart can't properly fill with blood during the resting period because of loss of relaxing ability. In both conditions, heart must work harder for pumping the same amount of the blood. This condition causes structural change on heart. Right-sided or right ventricular (RV) heart failure usually is a result of left-sided failure. Right side of heart is damaged by increased fluid pressure when left side fails. When it occurs, blood cannot fill the heart at enough level and causes swelling or congestion in the legs, ankles and swelling within the abdomen [6].

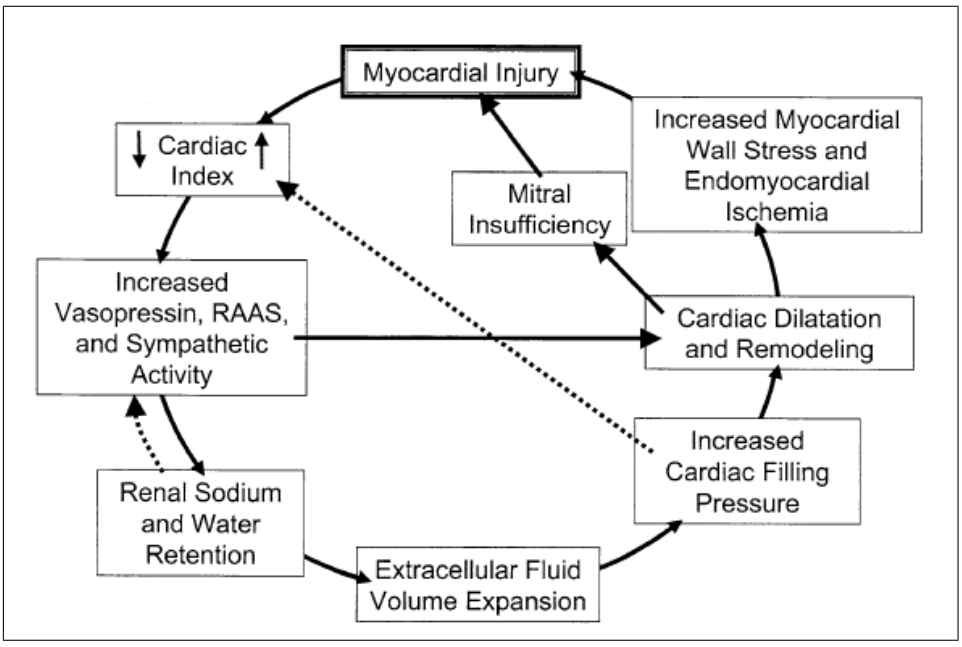


Figure 1.2. Vicious cycle of heart failure (reproduced from [7])

Acute and chronic classification is made in terms of disease progress. Chronic heart failure (CHF) is a type of heart failure that develops due to various cardiovas-

cular diseases such as heart attack, heart disease, hypertension, heart valve diseases and continues lifelong. Acute Heart Failure (AHF) refers to rapid onset or worsening of symptoms of heart failure because of gradual deterioration of heart for days and weeks. It is a life-threatening medical condition that requires urgent evaluation and treatment. In this phase, the admission for emergency care is essential for patient. AHF is frequently a consequence of acute decompensation of chronic HF [8].

The aim of this study is modelling acute decompensated heart failure (ADHF) with system dynamics methodology since physiology of disease is controlled by several positive and negative feedback loops. In progress of acute decompensated heart failure, which is result of respiratory and cardiac failures, consequences are most harmful to body. Due to ventricular systolic dysfunction failures, compensatory mechanisms are triggered to elevate perfusion of the tissues. Both peripheral and pulmonary congestion is observed because of sodium and water retention and reduction of blood flow from lungs to heart [9]. If these symptoms cannot be resolved as soon as possible, death or permanent damage to the heart is inevitable.

First, the studies in the literature about mathematical modeling of heart failure and similar diseases are summarized in the second chapter. In the third chapter, objective of the study and research methodology are explained. Compatibility of methodology with our problem definition is emphasized. In the forth chapter, the general overview of the model that is based on feedback mechanisms are described with causal loop diagram. In the fifth chapter, mathematical expressions of variables and their relationships, that are based on medical fundamentals and assumptions, are defined together with stock flow diagrams. In the sixth chapter, model behaviour is examined and validated with several testing scenarios. In the seventh chapter, treatment strategies are applied on the model in order to minimize hospitalization period. Lastly, the study and results are summarized in conclusion.

2. LITERATURE REVIEW

We focus on the studies that develop mathematical models of heart failure and mechanisms that play role in heart failure. Studies on these topics have addressed the problem in different scopes and used different methodologies. Firstly, studies about mathematical modeling of heart failure are investigated. These studies are significant in understanding important variables and in representing their effects on human body with mathematical expressions. Also, methodologies, that are based on observing time-dependent behaviors of model, are used in some studies. Their results are useful to interpret dynamics of heart failure. Secondly, studies on renal mechanism are examined. Renal mechanisms have an important role in the progress of heart failure since they can lead to sodium and water retention. Sodium and water retention cause peripheral and pulmonary edema and trigger compensating mechanisms. These pathological cases contribute to continued deterioration of heart.

The first model in the literature is developed by Guyton *et al.* [10] and focuses on circulations and regulations of the entire body. This circulatory regulation model consists of 354 blocks, each of them representing one of the parameters of circulatory regulation. The idea behind the study is to create a framework to show how the different regulations operate together in the overall system. The model is divided into 18 different major systems and relationships between them are represented by defining differential equations. This model enables to observe dynamics of circulation variables under several scenarios. One of the pathological cases is congestive heart failure and Figure 2.1 is the simulation output of this syndrome.

In literature, there are several studies that focus on heart failure and models of the heart as an electronic circuit. One of them is by Tsuruta *et al.* [11] [12] and focuses on cardiovascular mechanics for quantitative diagnostic analysis and treatment of heart failure. Systemic and pulmonary circulation are analyzed for both healthy and heart failure patients for each stage. In the treatment section, optimal therapy investigation is conducted with optimal control methodology by defining different objective

functions. The objective functions include the maximization of the cardiac output and minimization of blood pressure, ischemic index and dosage of the drugs. Finding optimal therapy is based on these objectives and on analyzing vascular resistance and capacitance since drug therapy consists of vasodilators and inotropic agent.

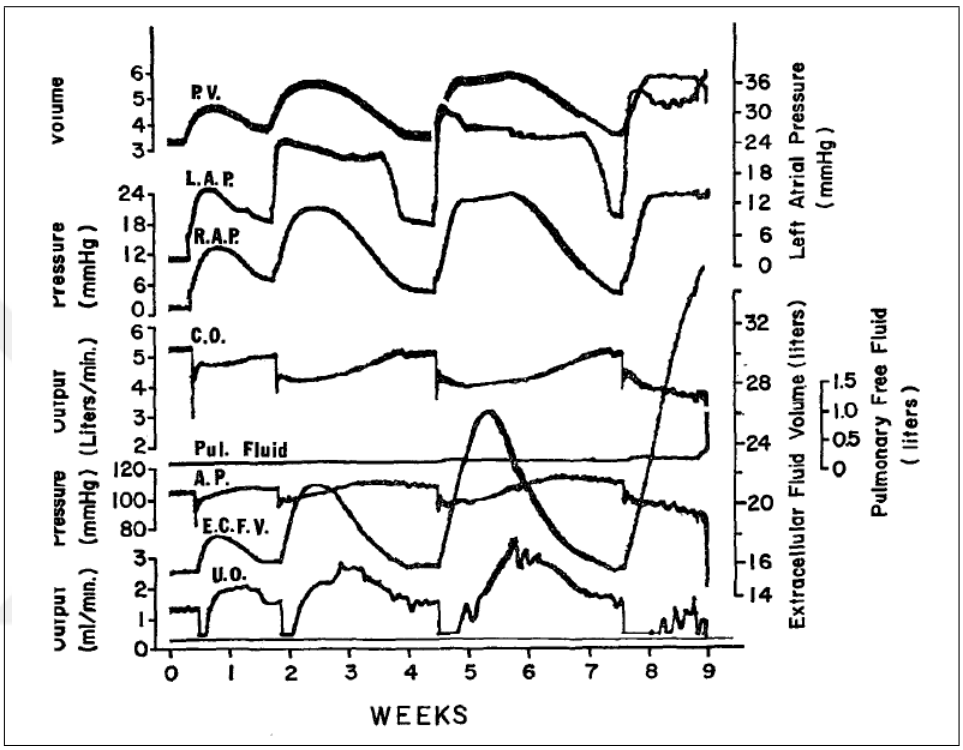


Figure 2.1. Results of congestive heart failure development simulation (reproduced from [10])

Another study where heart is modeled as an electric circuit is conducted by Ellwein *et al.* [13]. They built a coupled cardiovascular-respiratory model. In the study, 5 key cardiovascular parameters and 4 key respiratory parameters were predicted by sensitivity analysis and gradient-based nonlinear optimization. The study considers cardiovascular and respiratory systems together. The compartments of these systems and blood flow between them are represented with mathematical expressions.

Gong *et al.* [14] created a cardiovascular model for simulating left ventricular systolic heart failure. Their model is more comprehensive than previous studies about mathematical modeling of heart failure since it includes carotid baroreflex regulation in

the autonomic nervous system and the renal blood volume adjustment. They modeled heart failure with feedback loops to focus dynamics of deterioration. Several runs were taken under different conditions in terms of cardiac function, vascular property and activity of autonomic nervous system.

Heinke *et al.* [15] focused on cardiovascular system simulation with its control algorithms and related feedback loops. In this study, the relationship between cardiovascular, respiratory and thermoregulatory systems was investigated in the object-oriented modeling environment called Dymola. The model was run with both parameters of healthy individual and heart failure patient. For heart failure patient, ventricular assist device is included to simulate interaction between device and human body. Heart failure simulation that considers thermoregulatory system is a different approach that has not been used before. Also, illustration of interactions between human body and ventricular assist device is useful to study an alternative heart failure therapy and effects on body.

Renal mechanism is one of the effective mechanisms in progress of the heart failure syndrome and mathematical modeling of renal systems helps to understand its contribution to heart failure. The first study belongs to Cameron *et al.* [16] where they modeled how the kidney regulates renal function, blood volume, inter-cellular fluid and hormones. Non-linear first-order differential equations were used to express behavior of variables and the relations between them were defined in a quantitative way. In addition, relationships between renal parameters were illustrated with the causal loop diagram to express feedback mechanisms better. The main variables focused on the study are protein and compartment volumes, electrolytes, hormones, blood pressure and renal dynamics.

Another study about the human renal system was focused on ADH (Antidiuretic hormone) dynamics [17]. Hemodynamic and renal parameters are expressed with mathematical expressions like differential equations. The dynamics of kidneys are described in detail and the mechanisms of secretion and clearance of hormones are formalized. The study is helpful in terms of renal dynamic investigation under extreme conditions

since water load, hypertonic saline load and aldosterone loading are tested and results are well visualized graphically.

Karaarslan *et al.* [18] presented a physiological long-term mathematical model of the cardiovascular system that includes renal sympathetic nerve activity for the first time. The scenarios that cause long term renal sympathetic nerve activation were simulated. These scenarios are hypertension, excessive sodium accumulation in congestive heart failure, nephrotic syndrome and cirrhosis. 36 blocks are defined and each of them represents one effective parameter in renal mechanism. The table that shows relationships with feedback loops and given quantitative definitions of parameters are helpful to understand compensatory mechanisms of heart failure for modeling purpose. Also results that are taken under different scenarios explain the dynamics of hemodynamic and renal parameters and they can be used for validation of this kind of models.

Previous studies related to heart failure are not focused on acute heart failure with cardiogenic pulmonary edema and its treatment strategy. In the study of Guyton *et al.* [10], while the progress of acute heart failure was modeled, the treatment methods were not implemented. Although Tsuruta *et al.* [11] [12] suggested an optimal treatment of acute heart failure, their methodology is focused on point estimation, not dynamics of disease behavior. Furthermore, while Ellwein*et al.* [13], Gong *et al.* [14] and Heinke *et al.* [15] modeled heart failure with a similar approach to system dynamics, cardiogenic pulmonary edema modeling and treatment scenarios lack. In this study, we aim to fill these gaps.

3. PROBLEM DEFINITION AND RESEARCH METHODOLOGY

In the progress of heart failure, several mechanisms play a role. These mechanisms have a complex network structure with many positive and negative feedback loops. Negative loops try to bring the system to an equilibrium. These loops are activated when the tissues are not adequately supplied with blood and oxygen. This triggers feedback control mechanisms that have short-term and medium-term effects on the body. Sympathetic nerve activation and secretion of Renin-Angiotensin-Aldosterone hormones by the kidneys are these compensation mechanisms. Water and sodium retention increases to elevate blood volume. In addition, increased heart rate rises cardiac output. Consequently, blood pressure increases and adequate blood and oxygen are supplied to tissues. These mechanisms become inactive when the system comes back to a desired equilibrium.

However, positive feedback loops come into play in a heart failure patients. Since the negative feedback mechanisms described above cannot reach equilibrium values because of permanent deterioration of heart, excessive water and sodium retention, viz. edema, is observed. This leads to increase in systolic blood pressure which overloads the heart. Besides peripheral edema, increased heart and blood volume also cause pulmonary edema and shortness of breath. Due to lack of supplied oxygen, cardiogenic pulmonary edema causes a rapid deterioration of heart, tissues and hemodynamic parameters [19]. As a result, capability of the heart to pump blood out decreases gradually and this condition becomes irreversible. Decreased capability of the heart deteriorates hemodynamic parameters further. The described harmful positive feedback process is defined as vicious cycle of heart failure as seen in Figure 3.1.

Since many factors have nonlinear relationships with each other, it is hard to find exactly the points where hemodynamic parameters are stabilized in sufficient level. The disorder proceeds as a vicious cycle, so it is necessary to understand the relations

between mechanisms very well. A model that includes these relations in a quantitative way can be useful. No study exists in literature on mathematical modeling of acute heart failure with cardiogenic pulmonary edema and the development of effective treatment strategies. In this study, we aim to fill this gap by modeling the problem using system dynamics approach.

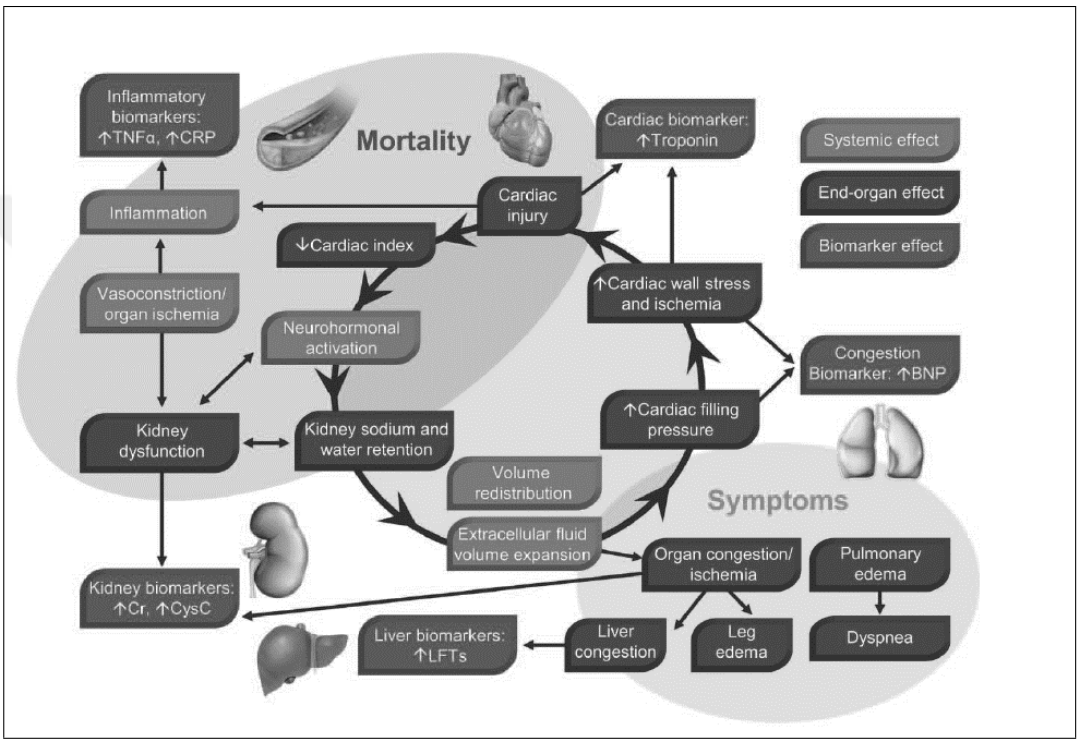


Figure 3.1. Acute heart failure loops with multiple organ dysfunction (reproduced from [20])

This study focuses on quantitative modelling of heart failure. The scope of study is framed around modeling and simulating gradual deterioration of the heart and effectiveness of the treatments in adequate levels. We use the hemodynamic parameters of systolic heart failure patients. When these parameters are given to the model as input, activation of compensatory mechanisms, pulmonary edema and heart deterioration are observed. After establishing a model that creates heart failure patients' dynamics, the model is validated by comparing with outputs of real cases reported in the literature. Finally, we try to find alternative strategies for the effective treatment methods and minimize discharge period.

As seen in Figure 3.1, many subsystems are involved in the progress of acute heart failure. It is very difficult to estimate the behavior of this complex system that has a nonlinear dynamic structure. What is needed is to project the dynamic pattern of the illness evolution, not point estimation of the disease parameters at a given time t. Therefore, system dynamics methodology is a promising tool for the analysis of heart failure. System dynamics methodology that is based on direct circular causality is focused on feedback mechanisms and their resulting dynamics. This methodology allows simulating complex systems with many feedback loops whose behaviors cannot be obtained by mathematical analysis.

Simplification of the real system that presents the problem and creates its dynamics is essential to system modelling [21]. After boundaries of the model are determined, the variables and the relationships between each other are visualized by a causal loop diagram. In the system dynamics method, causal loop diagram illustrates causal relationships between variables with negative or positive causalities. The interactions between subsystems and feedback loops can thus be explained for heart failure syndrome with these modeling tools.

Modeling heart failure with system dynamics methodology requires definition of parameters and relationships with mathematical equations and graphic functions. Stock-flow diagram is a standard system dynamics modeling tool to represent the problem quantitatively. Stocks are central variables to analyze behaviors of system. They cannot change suddenly, time is needed to change them. Flows determine the changes in behavior of stocks in time. There are finally converters that affect flow and other converter variables by equations that originate from stock variables. These effects are typically nonlinear in the complex feedback problems such as heart failure.

4. OVERVIEW OF THE MODEL

Acute heart failure is a disease with high morbidity and mortality rates. These rates are highly related with treatment period of patients in the hospital. In order to determine whether the treatment is successful or not, monitoring of the behaviour of hemodynamic parameters during hospitalization phase is important. These behaviours are predictor of post-discharge their values. Therefore, our study is focused on the period between hospitalization and discharge of a patient who is admitted with pulmonary edema and low cardiac output symptoms. Initial values of the model belong to a patient who has chronic heart failure syndrome. Model considers the acute phase of a patient that is hospitalized.

Chronic heart failure patients' heart volumes are larger than normal and they lose their contractile ability to a certain extent. Acute symptoms occur in the body due to insufficient treatment or any external factors. With respect to this condition, the patient in the model is assumed to have been previously hospitalized one or more times and discharged after hospitalization period because of an improvement in his/her symptoms. When values of the patient had worsened, and he/she had to return to the hospital again.

Since the model we established is about finding the effective treatments to be applied to the patient with acute heart failure and following the process until the discharge, the time unit is in hours and the total time frame of model is around one month. When we start to run the model, the dynamics of the patient's heart deterioration will be observed with the monitoring of several parameters. Hospitalization will be simulated when deterioration reaches a certain level. During the hospitalization period, several suggested medical treatments and strategies are explored to seek treatment strategies that minimize discharge time.

Our model has 5 sectors as hemodynamic sector, hormonal compensatory mechanisms sector, sodium and water sector, cardio-respiratory sector and treatment sec-

tor as described in detail in Chapter 5. Hemodynamic sector parameters decrease due to permanent damage to variables in the cardio-respiratory sector. Consequently, compensating mechanisms try to increase these values to equilibrium level. Although compensating mechanisms contribute to the increase in hemodynamic parameters for healthy people, they have negative effects for HF patients because of excess sodium and water retention. Rising sodium and water level lead to deterioration of respiratory and heart in a vicious cycle. The healthy person model includes these 4 sectors mentioned above and treatment sector is added to simulate patient dynamics.

The causal loop diagram illustrates the relationship between these sectors and the reason behind the vicious cycle as shown in Figure 4.1. The feedback loops can create reinforcing (+) or balancing (-) dynamics that is obtained by multiplication of all relation signs in the feedback loop. The human body system is based on homeostasis that is defined as the balancing loops in our methodology. The small changes in living mechanisms activates the stabilizing mechanism and drive the system to normal values. On the other hand, the reinforcing feedback loops cause growth or collapse dynamics. Steady state condition is not observed and the system variables tend to reach their maximum or minimum levels. In case of diseases, one or more reinforcing loops dominate the system and the dynamics of system are gradually deteriorated. The causal loop diagram given in Figure 4.1 is dominated by reinforcing loops that reflect the worsening of cardio-respiratory systems.

Hemodynamic sector parameters are indicators of whether tissues are properly supplied with blood and oxygen. When the body tissues are not well-fed because of any abnormality in the heart, the blood pressure in the vessels that bring blood to the tissues is reduced and the compensatory mechanisms are activated. These mechanisms, which have short-term effects, allow the secretion of various hormones in the body and help restore the hemodynamic parameters to the desired level. In addition, one of the reasons that hemodynamic parameters are outside of normal values is abnormalities in water and sodium levels. Compensating mechanisms play a role in stabilizing hemodynamic parameters at desired levels by providing water and sodium balance of the body [22].

Respiratory and heart performance of heart failure patients is lower than a healthy person and his/her heart size is larger than the normal heart size. Various drugs are used to inhibit the detrimental effects of mechanisms induced by these abnormalities in hemodynamic parameters for chronic heart failure treatment. However, a sudden deterioration in values of patient can occur which means that the patient has an acute crisis. In case of an acute crisis, treatments are carried out to reduce blood pressure, improve breathing and improve blood circulation. Time is a very important in this situation as there is no chance of recovery if the heart cells cannot be supplied with oxygen over a certain period of time. Pulmonary edema is a negative development that affects the oxygen supply of heart cells, so the treatment is primarily focused on the elimination of it.

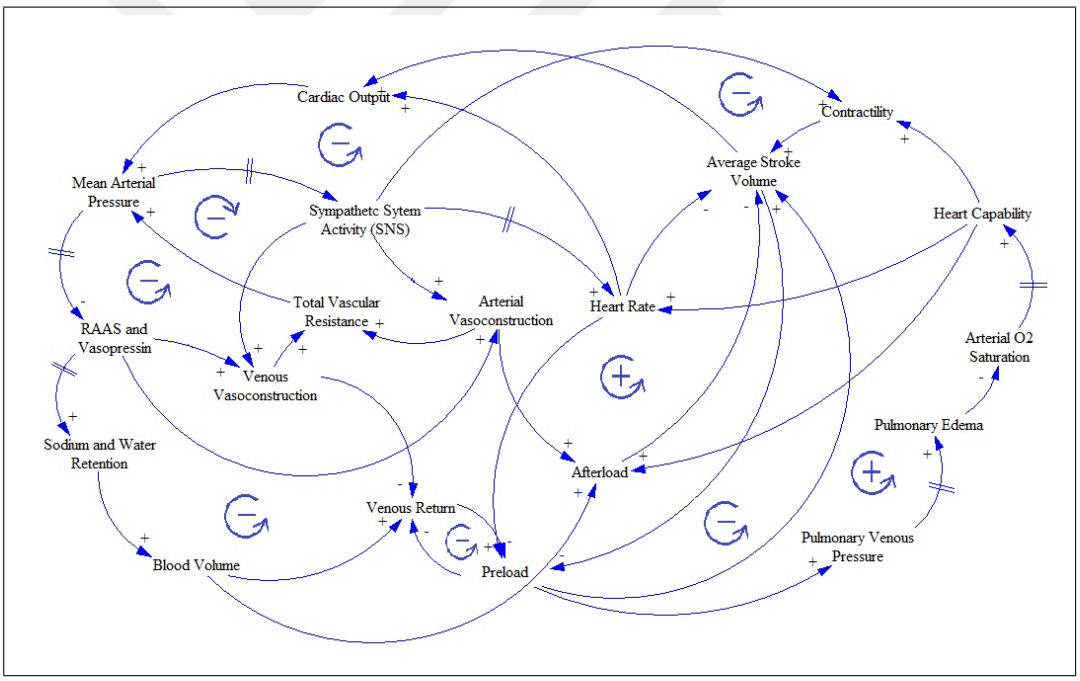


Figure 4.1. Causal loop diagram of the acute heart failure

5. DESCRIPTION OF THE MODEL

The model consists of five sectors; hemodynamic sector, hormonal compensatory sector, sodium and water sector, cardio-respiratory sector and treatment sector. In this section, mathematical model and effect functions of each sector are presented. In addition, the medical aspects behind the model are summarized to explain reasons behind quantitative representation of variables. The steady-state values of the variables are determined based on a healthy male with weight 70 kg.

5.1. Hemodynamic Sector

5.1.1. Medical Fundamentals and Assumptions

Hemodynamics represents the dynamics of blood flow. Since heart failure syndrome is caused by the inability of the heart to deliver enough blood and oxygen to the tissues, tracking and analyzing the hemodynamic parameters is important in problem solving. In order to understand the hemodynamic systems, it is necessary to explain the concepts which are examined together with the disease in the literature. Heart rate (HR) represents the number of times the heart contracts or pumps the blood in one minute. Stroke volume (SV) is the volume of blood in each beat. Cardiac output (CO) is determined by the heart rate and the stoke volume that can be seen in Equation 5.1.

$$CO = HR * SV \tag{5.1}$$

The cardiac output is an important parameter that is used for monitoring the progression of the syndrome based on ejection fraction. The ejection fraction (EF) is the ratio of the amount of blood pumped in each beat to the end-diastolic volume (EDV) of the heart as shown in Equation 5.2.

$$EF = \frac{SV}{EDV} \tag{5.2}$$

Another way of calculating SV is the difference between the volume of heart at contraction state, systole, and volume of heart at relaxation state, diastole. Figure 5.1 shows the relationship between pressure and volume during cardiac cycle and SV is the width between the points B and E. Point A represents the beginning of the state of the diastole and the end of the heart's systole. While the heart valves start to open, the blood begins to fill the ventricles until reaching point B. At B, the diastole ends and the amount of the blood in ventricle reaches to its maximum value. Pressure at this point is called left ventricle end systolic pressure (LVEDP) or the preload.

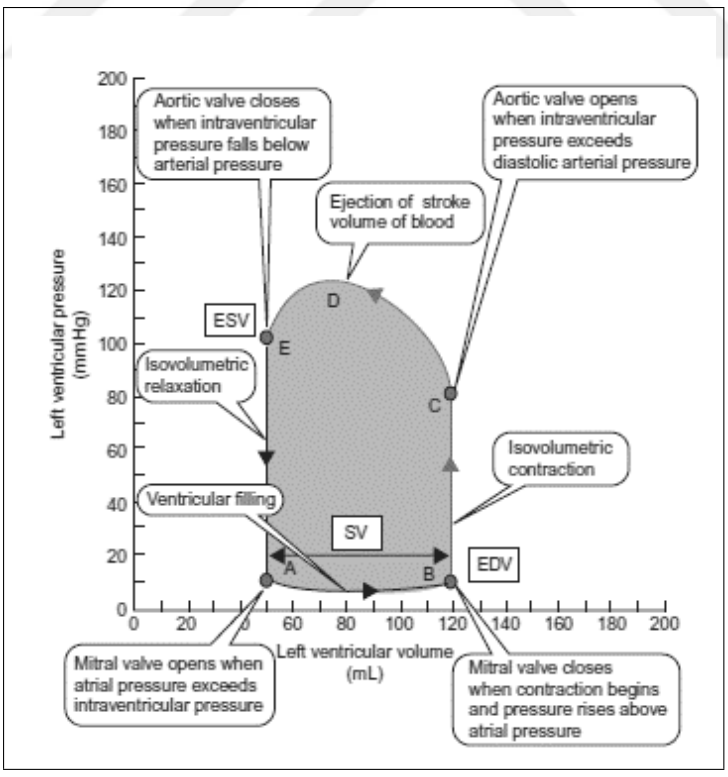


Figure 5.1. Pressure–volume loop of the cardiac cycle (reproduced from [23])

Frank-Starling Mechanism expresses that CO has a strong correlation with left ventricular end diastolic pressure (LVEDP) or preload [24]. There is a positive relationship between the preload and CO as shown in Figure 5.2. In addition, as seen in this figure, a heart failure patient has lower cardiac output than a healthy individual under the same LVEDP. Furthermore, the change in the pressure affects the cardiac output less than healthy people. This means that Frank-Starling mechanism does not work well for the heart failure patients. Also, pulmonary congestion is observed in high levels of preload or LVEDP.

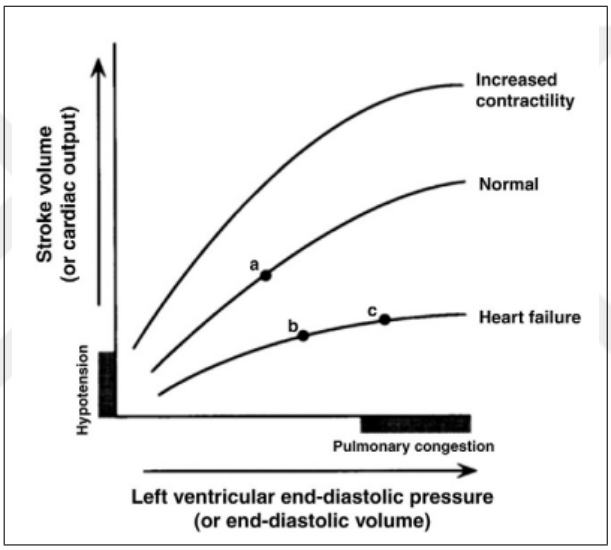


Figure 5.2. The Frank-Starling Mechanism (reproduced from [24])

In Figure 5.1, end systolic volume is given in Point E. At this point the heart valves are closed and the intracardiac pressure is decreased. For the heart to pump blood out, it should exceed the pressure given in D. This pressure is called afterload or arterial blood pressure and is determined by both physiological and physical factors that are shown at Figure 5.3. In addition, myocardial wall stress caused by structural change of a failed heart leads to an increase in afterload. There is a negative relationship between afterload. When afterload increases CO decreases.

Mean arterial pressure (MAP) is a hemodynamic parameter that is used to determine fluctuation of blood pressure and perfusion. It is the mean of systolic and diastolic blood pressure and obtained by multiplying the CO with the total peripheral

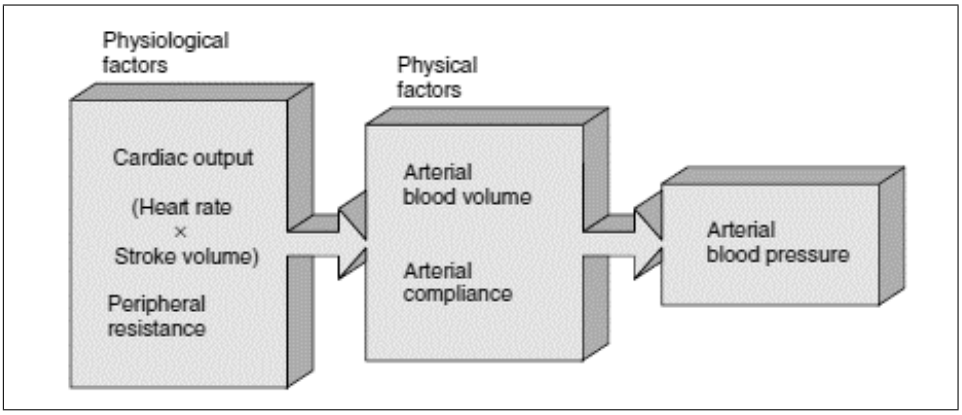


Figure 5.3. Arterial blood pressure components (reproduced from [25])

resistance (TPR) as in Equation 5.3. In case of deviation from normal value, the compensating mechanisms in the body are activated. Total peripheral resistance represents the resistance of the vessels against blood flow. It is inversely proportional to the vessel diameter. In the case of vasoconstriction, the resistance increases and in the case of vasodilation the resistance decreases.

$$MAP = CO * TPR \tag{5.3}$$

Total peripheral resistance consists of arterial resistance (AR) and venous return resistance (VRR). Arterial resistance is around fourteen times higher than venous resistance. As seen in Figure 5.4, the arterial resistance affects arterial blood pressure, while venous resistance determines venous return (VR) and the corresponding central venous pressure (CVP). There must be pressure difference between two compartments for the blood flow. In addition, the resistance is against this flow. The venous return is obtained by dividing the pressure difference between the peripheral and central venous compartments by the resistance as seen in Equation 5.4. Normal values of hemodynamic parameters in the model are shown in Table 5.1.

$$VR = \frac{(Peripheral\,Venous\,Pressure – Central\,Venous\,Pressure)}{Venous\,Return\,Resistance} \tag{5.4}$$

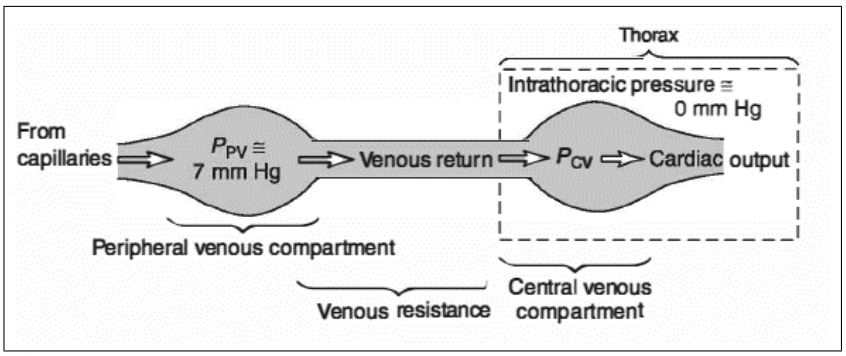


Figure 5.4. Venous Return Factors (reproduced from [26])

Table 5.1. Normal Values of Hemodynamic Sector Variables

Variable	**Normal Steady-State Values**	**Unit**
Heart Rate	75	beat/min
Aortic Pressure	120	mmHg
Heart Blood Volume	125	ml
Cardiac Output	6	l/min
Mean Arterial Pressure	90	mmHg
Average Stroke Volume	80	ml/beat
Venous Return	80	l/min
Total Peripheral Resistance	15	mmHg*min/mL
Ejection Fraction	64%	unitless

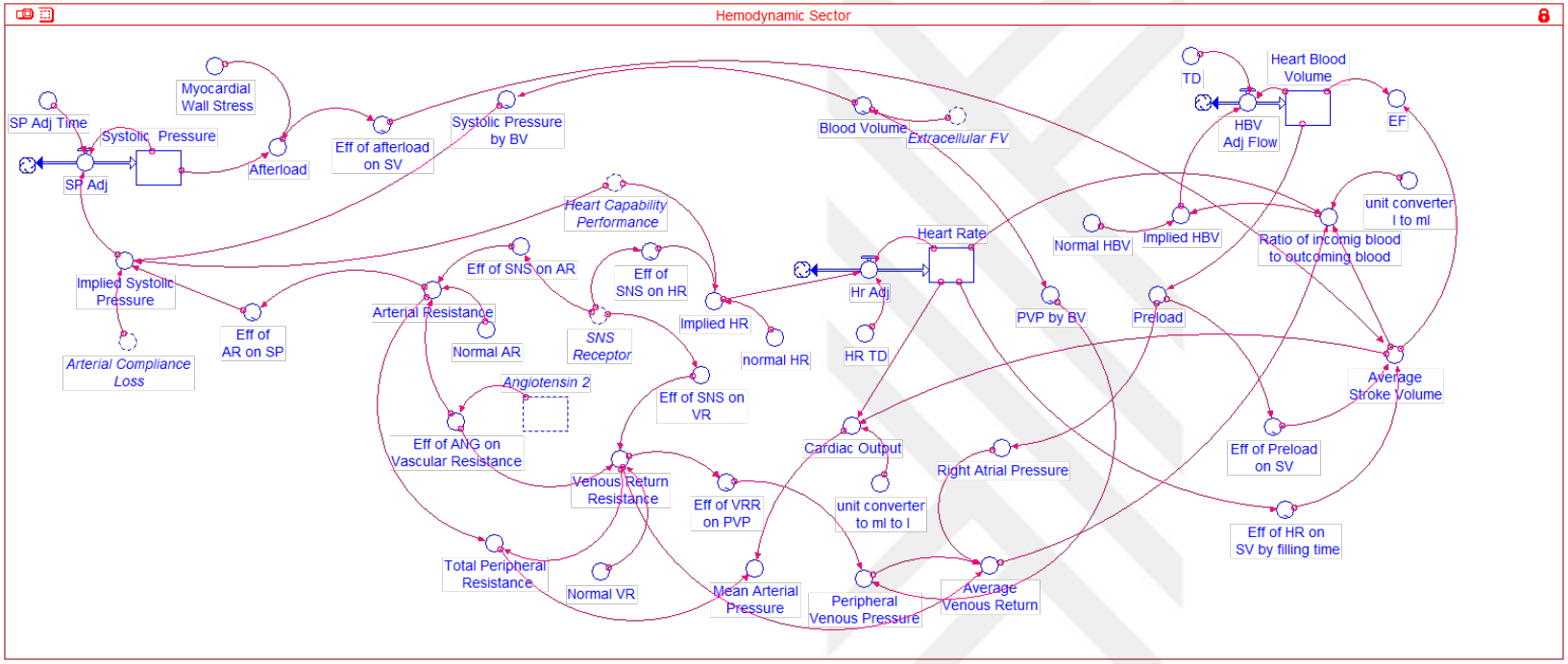


Figure 5.5. Stock Flow Diagram of Hemodynamics

5.1.2. Description of Hemodynamic Structure

The stock-flow diagram of hemodynamic sector is shown in Figure 5.5. It consists of three stocks. These stocks are Heart Blood Volume, Heart Rate and Systolic Pressure.

The heart blood volume (HBV) stock has one bi-flow. The name of the bi-flow is HBV Adjustment Flow as defined in Equation 5.5. The bi-flow is controlled by difference between implied HBV and actual HBV as defined in Equation 5.6.

$$Heart\ Blood\ Vol(t) = Heart\ Blood\ Vol(t - dt) + (HBV\ Adj\ Flow) * dt \tag{5.5}$$

$$HBV\ Adj\ Flow = (Implied\ HBV - Heart\ Blood\ Volume)/HBV\ TD \tag{5.6}$$

Implied HBV is multiplication of a normal HBV and ratio of incoming to outgoing blood flow to the heart as seen in Equation 5.7. This ratio is obtained by division of average venous return to product of average stroke volume and heart rate as shown in Equation 5.8. The unit converter is used to convert l to ml since unit of average venous return is l/min.

$$Implied\ HBV = Normal\ HBV * Ratio\ of\ incomig\ to\ outgoing\ blood\ flow \tag{5.7}$$

$$Ratio\ of\ in\ to\ out\ blood\ flow = \frac{(Average\ Venous\ Return * unit\ con\ l\ to\ ml)}{(Average\ Stroke\ Volume * Heart\ Rate)} \tag{5.8}$$

Average venous return occurs due to pressure difference between peripheral venous and right atrial. Venous return resistance is an opposite force to this flow as

expressed in Equation 5.9.

$$Average\,Venous\,Return = MAX(0.1, \frac{Peripheral\,Venous\,Pressure - Right\,Atrial\,Pressure}{Venous\,Return\,Resistance}) \quad (5.9)$$

Peripheral venous pressure is the blood pressure of veins that transfers dirty blood from peripheral tissue to the heart. So, it is influenced by the blood volume and the resistance of veins as shown in Equation 5.10. There is linear and positive relationship between the peripheral venous pressure and both blood volume and resistance. These relationships are presented in Figure 5.6 and Figure 5.7. They are drawn based on assumptions that are identified in the literature and the medical views of experts.

$$Peripheral\,Venous\,Pressure = PVP\,by\,BV * Eff\,of\,VRR\,on\,PVP \quad (5.10)$$

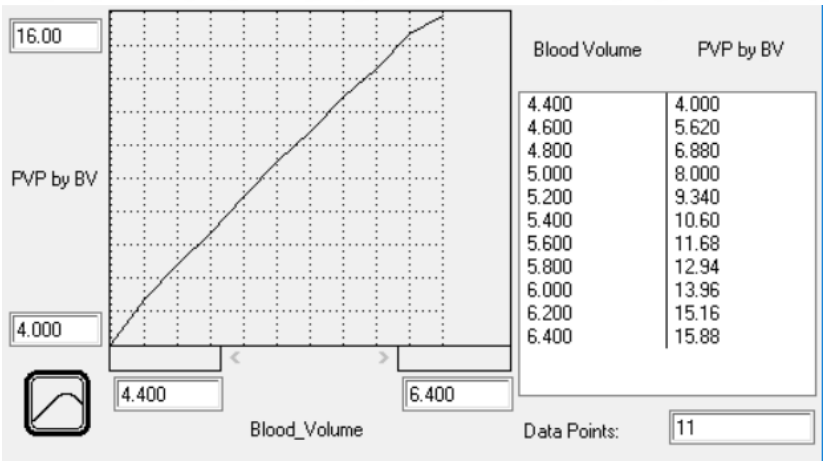


Figure 5.6. Graphical function for the effect of blood volume on peripheral venous pressure

In the model, right atrial pressure is obtained by dividing preload with 3.5 as seen in Equation 5.11. Both right atrial pressure and preload is used for pressure occurs due blood in the heart. The ratio between these two terms is achieved by dividing of steady state values of them for healthy people. When the blood volume in the heart

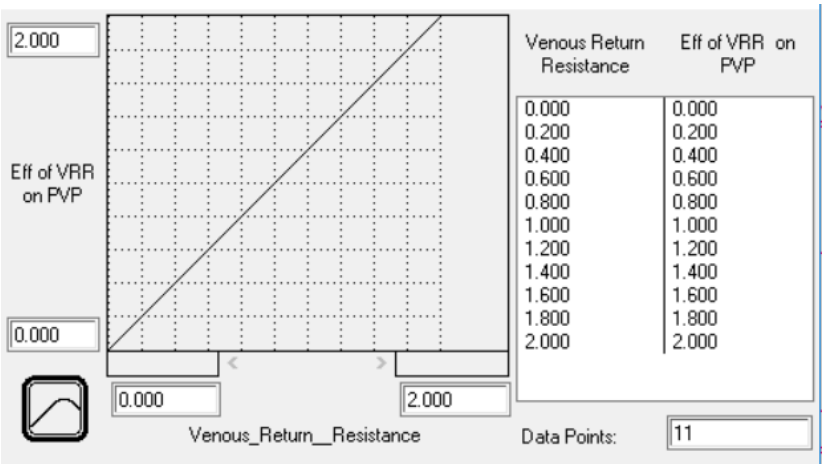


Figure 5.7. Graphical function for the effect of venous return resistance on peripheral venous pressure

is rising, preload is rising as seen in Figure 5.8. It is drawn based on the cardiac cycle given by Feher [23] as shown in Figure 5.1.

$$Right\ Atrial\ Pressure = \frac{Preload}{3.5} \tag{5.11}$$

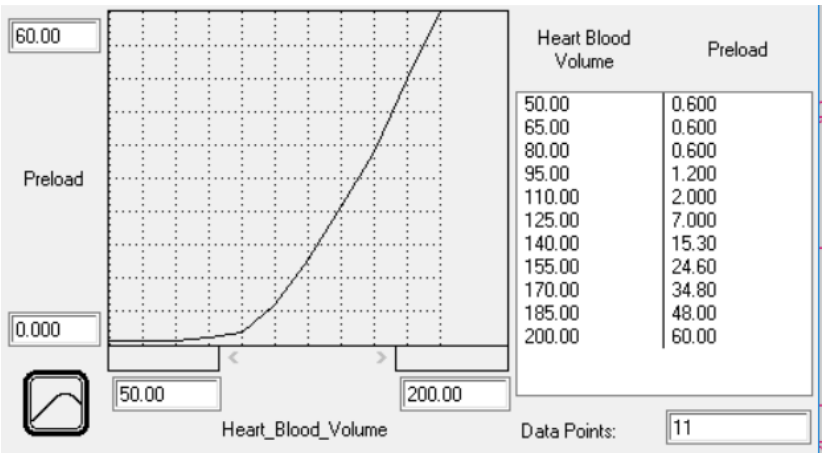


Figure 5.8. Graphical function for the effect of heart blood volume on preload

Normal value of the venous resistance is 1 mmHg*min/l and it is affected by Angiotensin 2 and sympathetic nerve system as shown in Equation 5.12. Secretion of

Angiotensin II and activation of sympathetic nerve system decrease diameter of both arteries and veins. Consequently, arterial and venous return resistance increase. These effects are indicated in Guyton *et al.* [10] with Equation 5.13 and 5.14.

$$\begin{aligned} &Venous\ Return\ Resistance = \\ &\quad Normal\ VR * Eff\ of\ SNS\ on\ VR * Eff\ of\ ANG\ on\ Vascular\ Resistance \end{aligned} \tag{5.12}$$

$$Eff\ of\ SNS\ on\ VR = (SNS * 0.85 + 0.15 - 1) * 0.25 + 1 \tag{5.13}$$

$$\begin{aligned} &Eff\ of\ ANG\ on\ Vascular\ Resistance = \\ &\quad MAX(0.8, ((((Angiotensin\ 2) * 0.15 + 0.85) - 1) * 3 + 1)) \end{aligned} \tag{5.14}$$

There are several factors that affect the average stroke volume. These factors are afterload, preload, contractility and heart rate as shown in Equation 5.15. We suggest that the contractility and the heart capability affect the average stroke volume with linear relationships. When the contractility and heart capability decrease, the stoke volume decreases at the same rate.

$$\begin{aligned} &Average\ Stroke\ Volume = \\ &Eff\ of\ afterload\ on\ SV * Eff\ of\ Preload\ on\ SV * Contractility * \\ &\qquad Eff\ of\ HR\ on\ SV\ by\ filling\ time * Heart\ Capability \end{aligned} \tag{5.15}$$

As shown in the cardiac cycle graph in Figure 5.1, when the blood volume in the heart or its pressure increases, the stroke volume increases. In contrast, when the pressure that the heart has to overcome in order to pump the blood increases, stroke volume decreases. The Figure 5.9 and Figure 5.10 show these relationships. It is drawn based on cardiac cycle given by Feher [23] as shown in Figure 5.1.

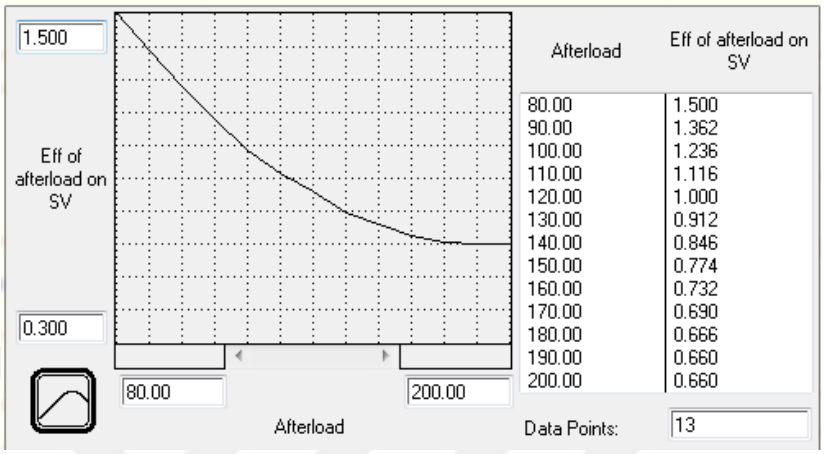


Figure 5.9. Graphical function for the effect of afterload on stroke volume

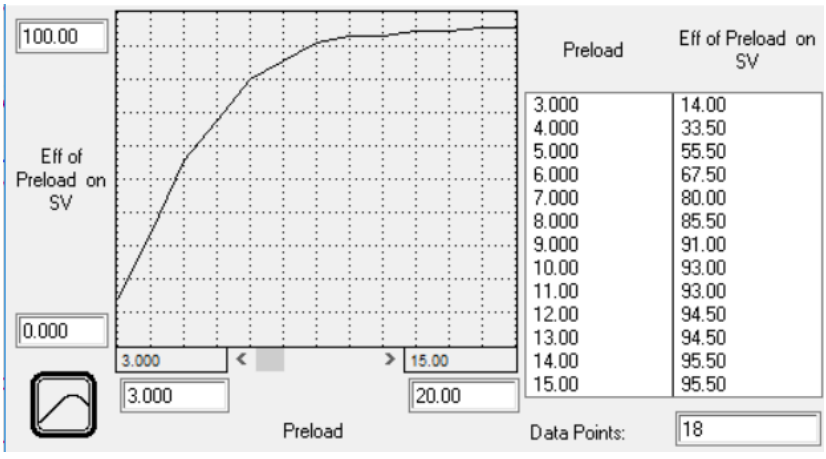


Figure 5.10. Graphical function for the effect of preload on stroke volume

When the heart rate increases, the time for the blood to fill the heart in each cardiac cycle is decreases. This situation affects the stroke volume adversely as seen in Figure 5.11. It is drawn based on assumptions that are identified in the literature and medical views of experts.

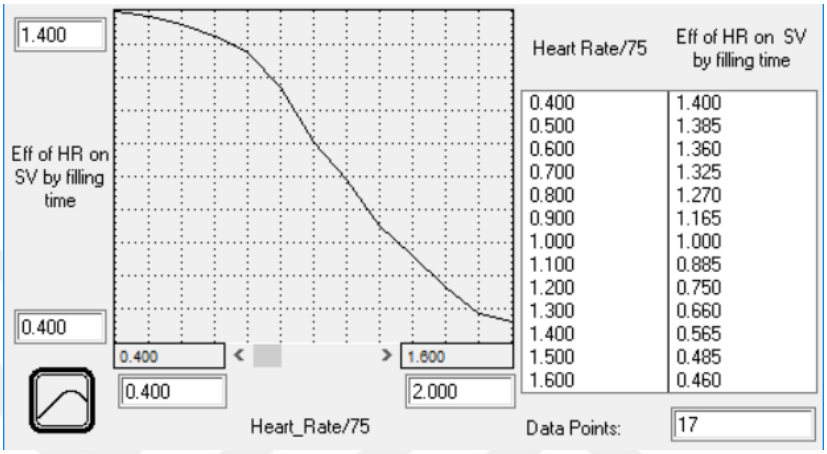


Figure 5.11. Graphical function for the effect of heart rate on stroke volume

Another stock in the hemodynamic sector is the heart rate. It has one bi-flow and this bi-flow is controlled by a heart rate adjustment variable, defined as Hr Adj, and expressed in Equation 5.16.

$$Heart\ Rate(t) = Heart\ Rate(t - dt) + (Hr\ Adj) * dt \tag{5.16}$$

Hr Adj represents difference between implied heart rate and current value of heart rate as defined in Equation 5.17. The implied heart rate is target value of heart rate and determined by SNS, normal value of heart rate and heart capability as seen in Equation 5.18. In addition, the heart rate of chronic HF patients is nearly 75. In the model, heart capability performance converter is defined to describe initial deterioration level of the heart. Its value and heart capability stock value are 0.85 at the beginning of the heart failure patient simulation. Therefore, division operation is applied to eliminate

negative effect of heart capability at the beginning of simulation.

$$Hr\ Adj = \frac{Implied\ HR - Heart\ Rate}{HR\ Adj\ Time} \tag{5.17}$$

$$Implied\ HR = \frac{Normal\ HR * Eff\ of\ SNS\ on\ HR * Heart\ Capability}{Heart\ Capability\ Performance} \tag{5.18}$$

There is a positive relationship between sympathetic nerve activity and heart rate. Figure 5.12 represents this relationship. It is drawn based on SNS effect on cardiac output given by Mohrman *and* Heller [26] as seen in Figure 5.15.

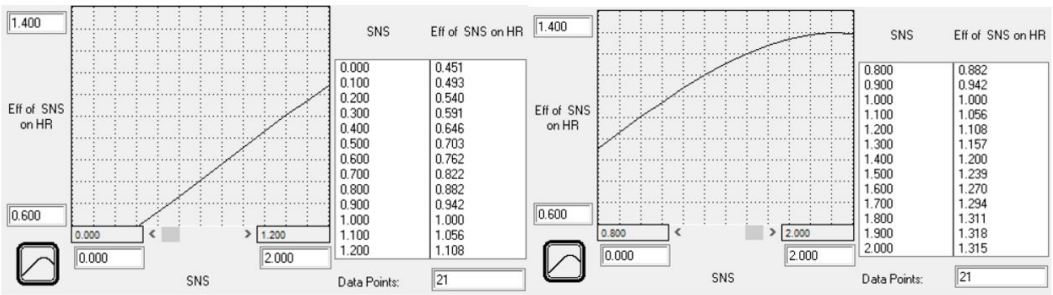


Figure 5.12. Graphical function for the effect of SNS on heart rate

Third stock is the systolic pressure in the hemodynamic sector. It is one of the factors that create afterload. Another factor is wall stress that is related with structure of the heart. As mentioned in the fundamentals of hemodynamics section, cardiac remodeling causes to increase wall stress and consequently afterload in heart failure condition as defined in Equation 5.19.

$$Afterload = Myocardial\ Wall\ Stress * Systolic\ Pressure \tag{5.19}$$

The systolic pressure has one bi-flow, defined as SP Adj. This bi-flow is controlled by difference between implied systolic pressure and actual systolic pressure as shown

in Equation 5.20 and Equation 5.21.

$$Systolic\,Pressure(t) = Systolic\,Pressure(t - dt) + (SP\,Adj) * dt \tag{5.20}$$

$$SP\,Adj = \frac{Implied\,Systolic\,Pressure - Systolic\,Pressure}{SP\,Adj\,Time} \tag{5.21}$$

Implied Systolic Pressure is the desired level of systolic pressure at current condition. This condition is determined by the blood volume, arterial compliance, arterial resistance and heart capability defined in Equation 5.22. The arterial compliance is the ability of arteries to change its volume when the blood pressure increases. When the arteries start to lose this ability, the rise in systolic pressure or afterload is higher in case of blood volume change. In addition, since systolic pressure is created by heart, it reduces when the heart capability decreases.

$$\begin{aligned} &Implied\,Systolic\,Pressure = \\ &Art\,Compl\,Loss * Sys\,Pres\,by\,BV * Eff\,of\,AR\,on\,SP * \frac{Heart\,Cap}{Heart\,Cap\,Perf} \end{aligned} \tag{5.22}$$

Blood volume and arterial resistance are two other factors that play roles in elevated systolic pressure. As seen in Figure 5.13 and Figure 5.14, there are positive relationship between these factors and systolic pressure. They are drawn based on assumptions that are identified in the literature and medical views of experts.

Normal value of arterial resistance is 14 mmHg*min/l. It is also affected by SNS and Angiotensin 2 secretion like venous return resistance. Equation 5.23 represents formulation of the arterial resistance that consists of SNS and Angiotensin 2 effects. Effects of Angiotensin 2 on arterial resistance is the same as the effects of Angiotensin 2 on venous return resistance and defined as Eff of ANG on Vascular Resistance at Equation 5.14. Equation 5.24 presents effect of SNS on arterial resistance that is given

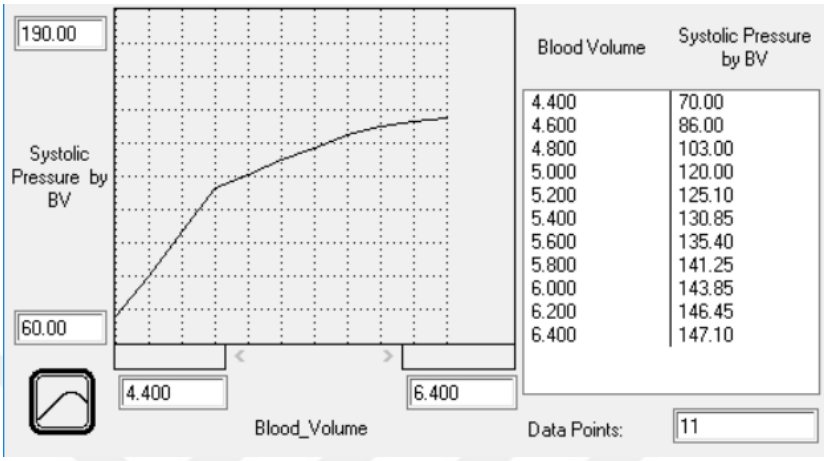


Figure 5.13. Graphical function for the effect of blood volume on systolic pressure

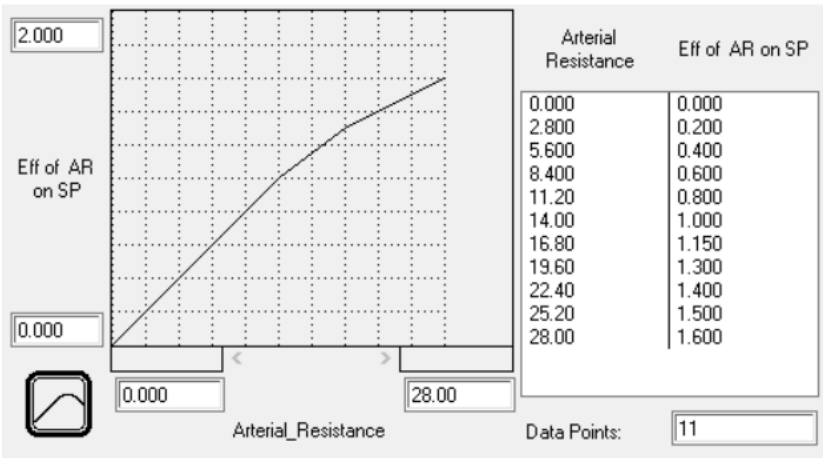


Figure 5.14. Graphical function for the effect of arterial resistance on systolic pressure

by Guyton *et al.* [10].

$$Arterial\ Resistance = \\ Normal\ AR * Eff\ of\ ANG\ on\ Vascular\ Resistance * Eff\ of\ SNS\ on\ AR \tag{5.23}$$

$$Eff\ of\ SNS\ on\ AR = SNS * 0.85 + 0.15 \tag{5.24}$$

5.2. Hormonal Compensatory Mechanisms Sector

5.2.1. Medical Fundamentals and Assumptions

There are many mechanisms that maintain homeostasis in the human body. In case of hypoperfusion and failure of blood supply to tissue, two main systems that have short- and medium-term effects are triggered. One of them is the sympathetic nervous system and the other is Renin-Angiotensin-Aldosterone system (RAAS). In addition, natriuretics and vasopressin, also known as antidiuretic hormone (ADH) are produced. Although they have positive effects in the short term, they support the progress of the vicious cycle in the medium and long term.

As a part of the sympathetic nerve system, alfa and beta-adrenergic receptors are stimulated by decreased mean arterial pressure via baroreceptor and chemoreceptor activity [9]. Both arterial vasoconstriction and venous vasoconstriction are occurred by reduction of vessel diameter. Also, the cardiac output is improved by increasing contractility and heart rate as seen in Figure 5.15. Cardiac output is represented with point A for healthy people. For heart failure patient, it drops to point B and sympathetic activity increases it to point C.

The renal sympathetic nerve system is a part of sympathetic nerve activity that affects kidneys. It is related with renal spillover of Norepinephrine. It is triggered by insufficient kidney perfusion that is result of low level of MAP. The arterial barore-

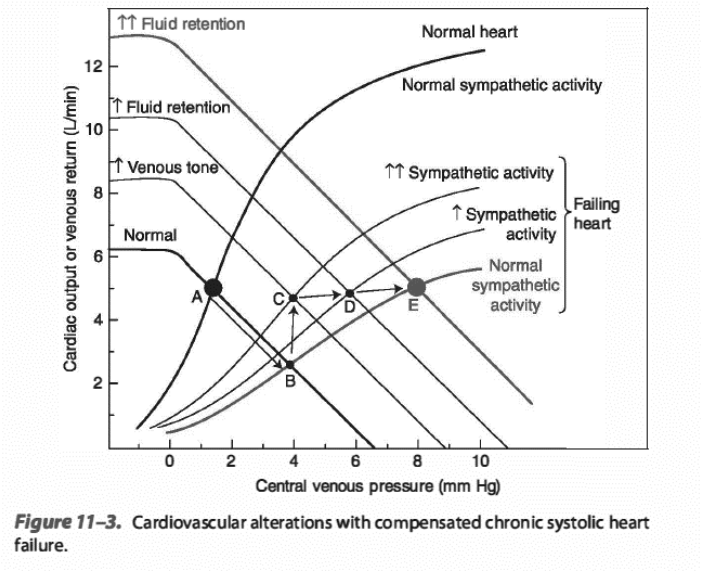


Figure 11–3. **Cardiovascular alterations with compensated chronic systolic heart failure.**

Figure 5.15. Effect of sympathetic activity on cardiac output and central venous pressure (reproduced from [26])

ceptor, peripheral chemoreceptor and cardiopulmonary baroreceptor play a role in its activation mechanism. Renal vasoconstriction, renal sodium retention, Renin secretion and the formation of Angiotensin II and Aldosterone are results of its activation [27].

The Renin-Angiotensin-Aldosterone system is another compensatory mechanism that takes a part in fluid and sodium retention and vasoconstriction. The detailed feedback mechanism of RAAS system with ADH is illustrated in Figure 5.16. The kidneys play a role in secretion of Renin. Decreasing MAP and kidneys perfusion activate Renin secretion. Secretion of Renin leads to increase in sodium concentration and secretion of Angiotensin I [28]. Angiotensin converting enzyme converts Angiotensin I to Angiotensin II. Secretion of Angiotensin II triggers the secretion of Aldosterone. High level of Aldosterone and Angiotensin II decrease urinary flow. Consequently, edema occurs, and the amount of sodium increases.

Vasopressin (ADH) has similar effects with Angiotensin II. It has an important role in water conservation via deciding the urinary sodium concentration as seen in Figure 5.16. There are three types of ADH and two of them, V1a and V2, play

important roles in the heart failure. V1a causes arterial and coroner vasoconstriction, V2 causes water retention [29]. The water retention and arterial vasoconstriction lead to increase in blood pressure. On the other hand, the coroner vasoconstriction leads to decrease coronary blood flow and the cardiac capability [30].

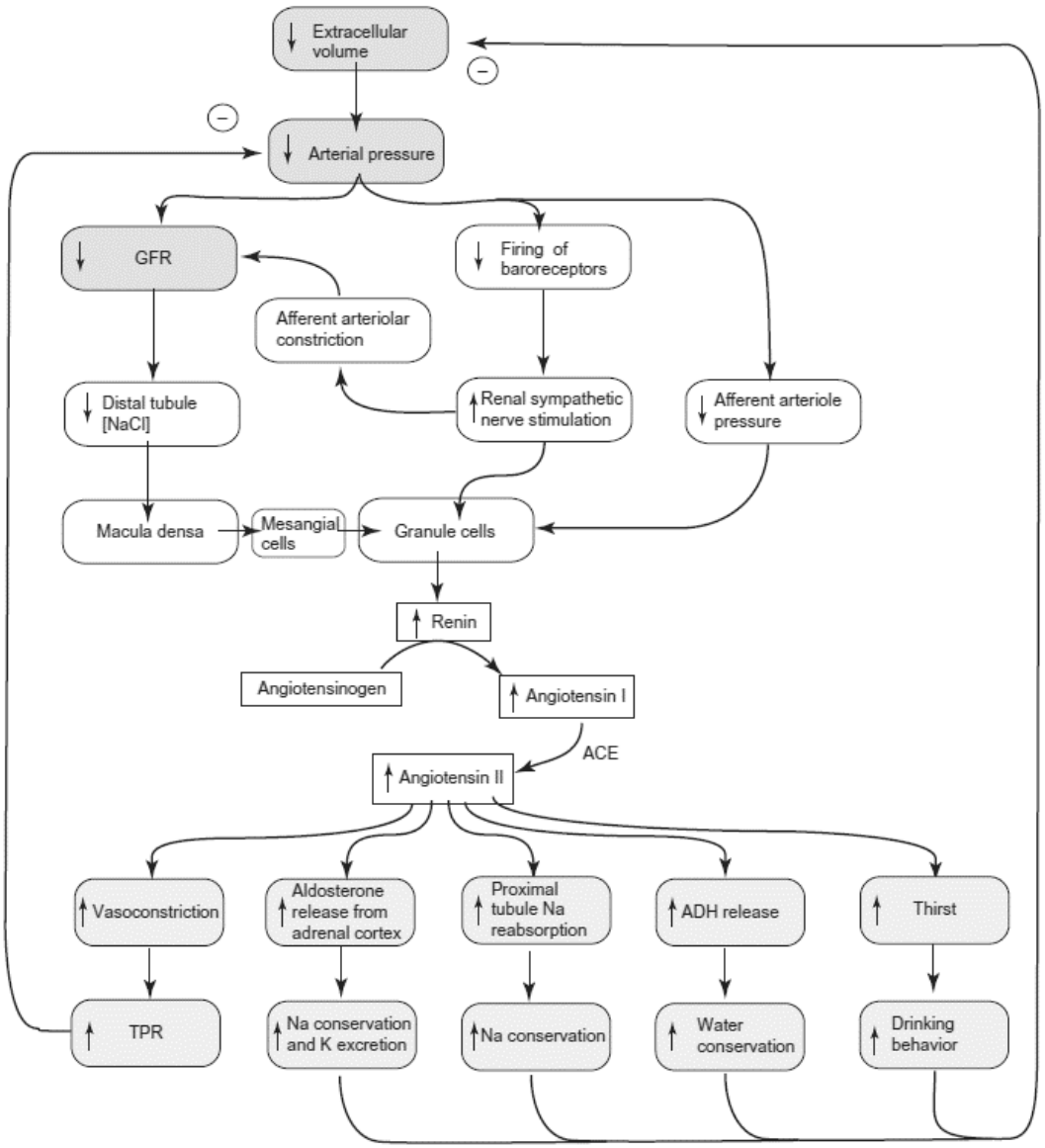


Figure 5.16. The Renin-Angiotensin-Aldosterone and ADH feedback mechanisms (reproduced from [23])

In case of reduction of mean arterial pressure, natriuretic peptides that are ANP, BNP and CNP are also secreted. They play roles in vasodilation, decrease sodium and water reabsorption via increasing GFR, inhibition of RAAS and sympathetic nerve

system [28]. Their effects are intended to stop the effects of other hormones and therefore they are also used as a medicine to prevent vicious cycle progress. They are used very frequently in monitoring the patient's symptoms because their levels are easily measured.

5.2.2. Description of Hormonal Compensatory Structure

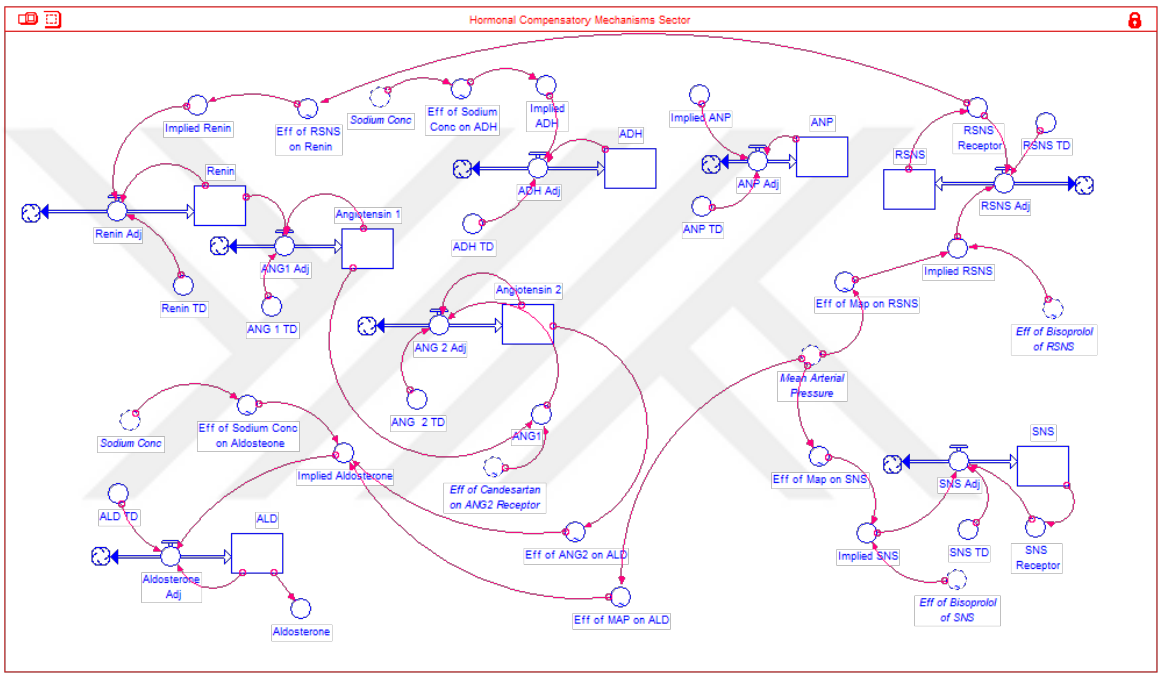


Figure 5.17. Stock Flow Diagram of Hormonal Compensatory Mechanisms

The stock-flow diagram of hormonal compensatory sector is shown in Figure 5.17. It consists of eight stocks. These stocks are SNS, RSNS, Renin, Angiotensin I, Angiotensin II, Aldosterone, ADH and ANP.

SNS and RSNS represent sympathetic nerve system and renal sympathetic nerve system. They are controlled by stock adjustment flows as seen in Equation 5.25 and Equation 5.26. Stock adjustment flows are defined as bi-flow. Bi-flows are defined as difference between implied and current values of these stocks as defined in Equation

5.27 and Equation 5.28.

$$SNS(t) = SNS(t - dt) + (SNS\ Adj) * dt \tag{5.25}$$

$$RSNS(t) = RSNS(t - dt) + (RSNS\ Adj) * dt \tag{5.26}$$

$$SNS\ Adj = \frac{(Implied\ SNS - SNS)}{SNS\ TD} \tag{5.27}$$

$$RSNS\ Adj = \frac{(Implied\ RSNS - RSNS)}{RSNS\ TD} \tag{5.28}$$

Implied SNS and Implied RSNS are product of effect of mean arterial pressure and normal values of them. Effect of mean arterial pressure on SNS and RSNS are illustrated in Figure 5.18 and Figure 5.19. They are drawn based on effect of MAP on SNS and RSNS given by Karaaslan *et al.* [18].

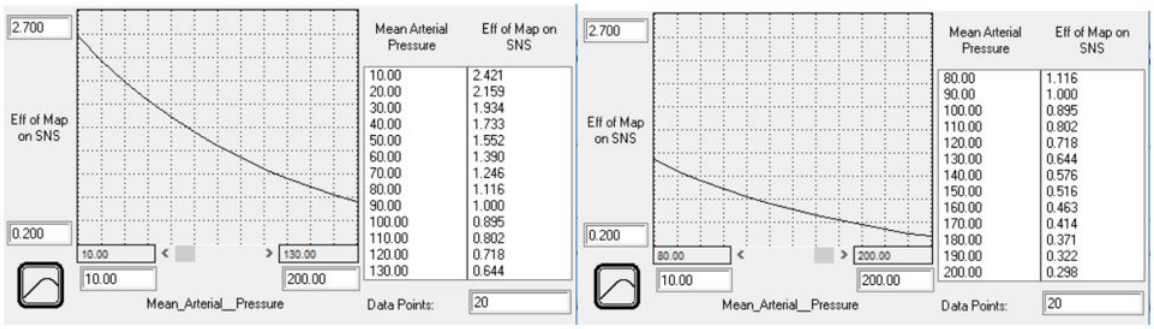


Figure 5.18. Graphical function for the effect of MAP on SNS

Another compensatory system is Renin-Angiotensin-Aldosterone system. Renin secretion is triggered by RSNS and sodium concentration. When Renin level increases, Angiotensin I level also increases. After secretion of Angiotensin I, it is converted to Angiotensin II. This structure that includes three stocks creates third order delay. All

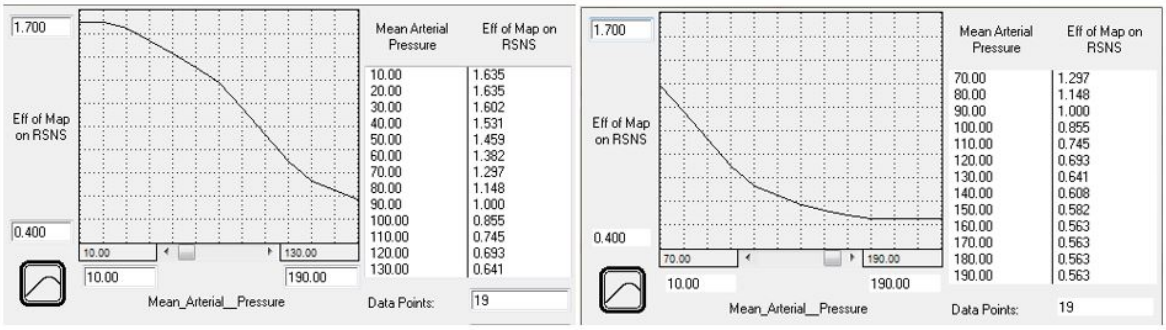


Figure 5.19. Graphical function for the effect of MAP on RSNS

these stocks are controlled by adjustment flows as seen in Equation 5.29, Equation 5.30 and Equation 5.31.

$$Renin(t) = Renin(t - dt) + (Renin\ Adj) * dt \tag{5.29}$$

$$Angiotensin\ I(t) = Angiotensin\ I(t - dt) + (ANG\ I\ Adj) * dt \tag{5.30}$$

$$Angiotensin\ II(t) = Angiotensin\ II(t - dt) + (ANG\ II\ Adj) * dt \tag{5.31}$$

Adjustment flows as defined above are bi-flow. Renin adjustment flow is triggered by the difference between implied and actual values as defined in Equation 5.32. Angiotensin I adjustment flow is triggered by the difference between actual Renin value and actual Angiotensin I value as defined in Equation 5.33. Angiotensin II adjustment flow is triggered by the difference between actual Angiotensin I value and actual Angiotensin II value as defined in Equation 5.34.

$$Renin\ Adj = \frac{Implied\ Renin - Renin}{Renin\ TD} \tag{5.32}$$

$$ANG\ I\ Adj = \frac{Renin - Angiotensin\ I}{ANG\ I\ TD} \tag{5.33}$$

$$ANG\ II\ Adj = \frac{ANG\ I - Angiotensin\ II}{ANG\ II\ TD} \tag{5.34}$$

Implied Renin is obtained by multiplying of effect of RSNS on Renin and normal value of Renin as shown in Equation 5.35. Effect of RSNS on renin are shown in Figure 5.20. It is drawn based on Renin secretion mechanism given by Karaaslan *et al.* [18].

$$Implied\ Renin = normal\ Renin * Eff\ of\ RSNS\ on\ Renin \tag{5.35}$$

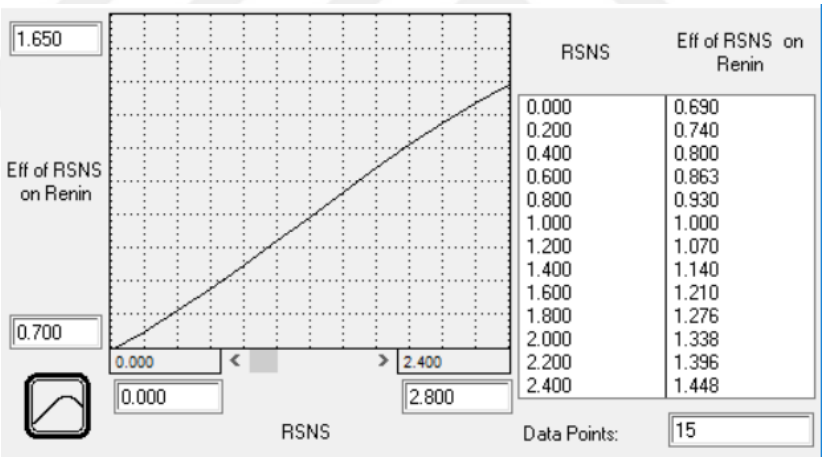


Figure 5.20. Graphical function for the effect of RSNS on renin

Aldosterone, like other hormones, is controlled by adjustment flow. This flow is bi-flow as seen in Equation 5.36. Adjustment flow equals the difference between implied Aldosterone value and actual Aldosterone value as defined in Equation 5.37. Sodium concentration, Angiotensin II and mean arterial pressure play a role in secretion of Aldosterone. This relationship is reflected in Equation 5.38. Figure 5.21, Figure 5.22 and Figure 5.23 illustrate effect of sodium concentration, mean arterial pressure and Angiotensin II on aldosterone secretion. They are drawn based on aldosterone secretion

mechanism given by Guyton *et al.* [10] and Karaaslan *et al.* [18].

$$Aldosterone(t) = Aldosterone(t - dt) + (Aldosterone\ Adj) * dt \tag{5.36}$$

$$Aldosterone\ Adj = \frac{Implied\ Aldosterone - Aldosterone}{ALD\ TD} \tag{5.37}$$

$$\begin{aligned} Implied\ ALD = normal\ ALD * Eff\ of\ NA\ Conc\ on\ ALD * \\ Eff\ of\ MAP\ on\ ALD * Eff\ of\ ANG\ II\ on\ ALD \end{aligned} \tag{5.38}$$

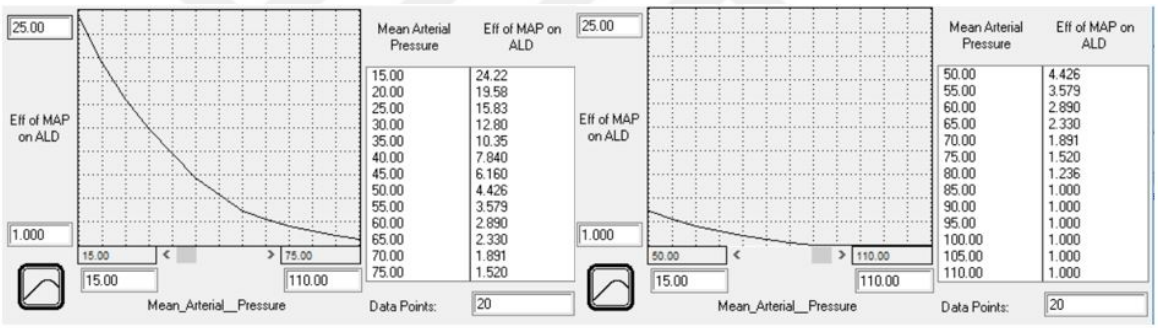


Figure 5.21. Graphical function for the effect of MAP on aldosterone

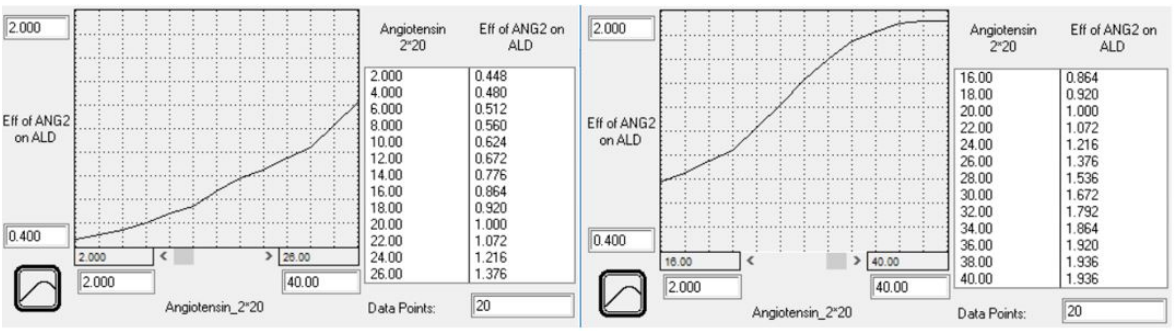


Figure 5.22. Graphical function for the effect ANG II on aldosterone

ANP and ADH are other hormones that play a role in regulation of sodium and water. In the model, ADH is used for adjusting of urine sodium concentration. As

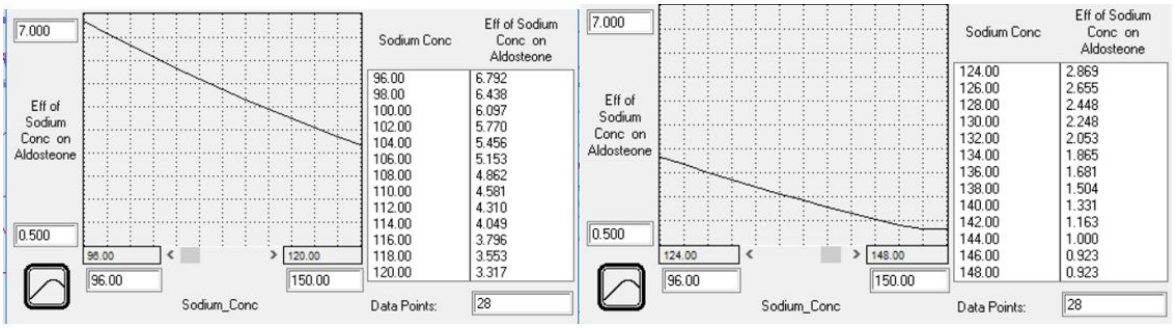


Figure 5.23. Graphical function for the effect of sodium concentration on aldosterone

defined in Equation 5.39, it is controlled by own adjustment flow.

$$ADH(t) = ADH(t - dt) + (ADH\ Adj) * dt \tag{5.39}$$

ADH adjustment flow is bi-flow and it is affected by difference between implied ADH and actual ADH value as seen in Equation 5.40. Implied ADH is defined as a function of sodium concentration (Equation 5.41). When sodium concentration increases, level of ADH in blood increases as seen in Figure 5.24. It is drawn based on ADH function given by Karanfil [31].

$$ADH\ Adj = \frac{Implied\ ADH - ADH}{ADH\ TD} \tag{5.40}$$

$$Implied\ ADH = normal\ ADH * Eff\ of\ Sodium\ Conc\ on\ ADH \tag{5.41}$$

ANP regulates the urine sodium flow by affecting GFR function. It is controlled by own adjustment flow as seen in Equation 5.42. ANP adjustment flow is bi-flow and is affected by difference between implied ANP and actual ANP value as seen in

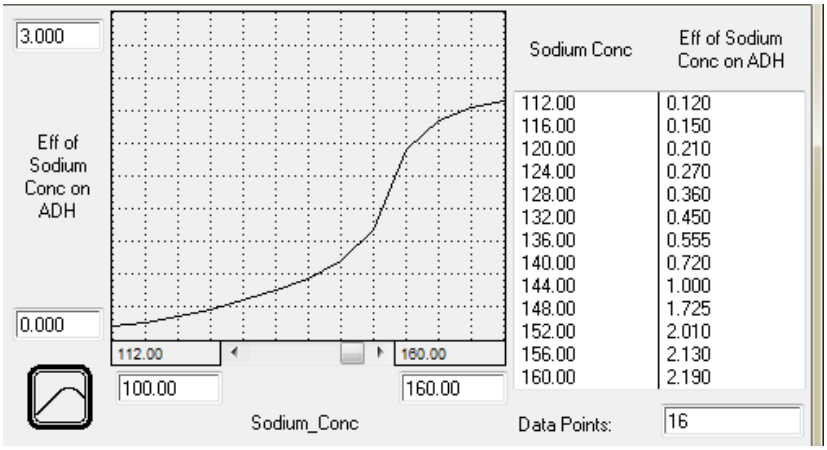


Figure 5.24. Graphical function for the effect sodium concentration on ADH

Equation 5.43.

$$ANP(t) = ANP(t - dt) + (ANP\ Adj) * dt \tag{5.42}$$

$$ANP\ Adj = \frac{Implied\ ANP - ANP}{ANP\ TD} \tag{5.43}$$

ANP is affected by change in fluid volume. Implied ANP is defined by multiplying of normal value of ANP and effect of extracellular fluid volume (EFV) on ANP as seen in Equation 5.44. When EFV increases, level of ANP in blood also increases as seen in Figure 5.25. It is drawn based on ANP function given by Karanfil [31].

$$Implied\ ANP = normal\ ANP * Eff\ of\ EFV\ on\ ANP \tag{5.44}$$

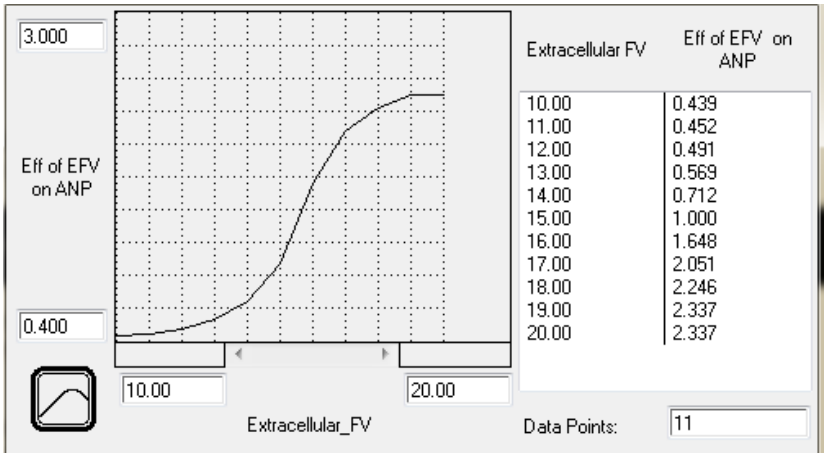


Figure 5.25. Graphical function for the effect extracellular fluid volume on ANP

5.3. Sodium and Water Sector

5.3.1. Medical Fundamentals and Assumptions

Water keeps all biological life and activities alive. Failure to consume adequate water leads to vital defects in organs such as the kidneys, the heart and the liver. The average value of water is indicated in Table 5.2 for average person. Approximately 60% of the fluid volume is intercellular while approximately 40% is extracellular. Extracellular fluid consists of interstitial fluid, plasma and lymph. Interstitial fluid is approximately 70% of extracellular fluid. An average amount of blood in a healthy average body is 5 liters. Increasing in the amount of interstitial fluid causes increasing in the amount of blood.

2% of the body's mineral content is sodium. It is one of the most important element for balancing blood pressure. The average sodium amount is 2160 mEq and the average concentration of sodium is 144 mEq/L. Sodium concentration of less than 135 mEq/L is called hyponatremia. This condition, which is observed in heart failure, is caused by excessive fluid retention and it causes the RAAS activation.

Table 5.2. Normal values of Sodium Water Sector Variables

Variable	**Normal Steady-State Values**	**Unit**
Total Fluid Volume	40	L
Extracellular Fluid Volume	15	L
Sodium Amount	2160	mEq
Sodium Concentration	144	mEq/l
GFR	125	mL/min
Urinary Flow	0,06	l/hour
Urinary Sodium Flow	7,56	mEq/hour

Nephrons, the main unit of kidneys, balance water and sodium levels in the body. The main function of nephrons is eliminating undesirable substances from the plasma by three mechanisms; reabsorption, filtration and secretion [23]. The plasma is substantially filtered in a part called glomeruli. The glomerular filtration rate (GFR) is used as a filtration unit and as a parameter for evaluating the performance of kidneys. When the filtered liquid is circulating through the tubule channels, the necessary substances are reabsorbed. The rest of them are not absorbed and contribute to formation of urine. In addition, some substances in the plasma are secreted directly into the tubular fluid.

Regulation of water and sodium retention is triggered by blood pressure, pH and osmolarity. Hypotension, caused by heart failure, causes the water and sodium retention mechanism. Consequently, water and sodium excretion is decreased. While the amount of fluid excreted from the body is defined as urinary flow, urinary sodium flow is the amount of sodium excreted from the body. They are related each other since the sodium urinary concentration determines amount of water excreted with sodium. This mechanism is controlled by ADH.

Sodium concentration of body is one of the triggering factors in water retention and thirst mechanism. When the sodium concentration decreases, hormonal compen-

satory mechanisms are activated. Consequently, sodium retention increases, and water retention decreases. When the sodium concentration increases, thirst mechanism is activated. It elevates the water intake and consequently sodium concentration reaches an equilibrium point by excessive water intake. In addition, urinary flow is decreased via sodium's ability of water retention.

One of the most common symptoms associated with heart failure is edema, which means the accumulation of excessive interstitial fluid. There are two types of cardiogenic edema in terms of location in the body, peripheral and pulmonary. Pulmonary edema occurs in the lungs, while peripheral edema occurs in the remaining part of the body such as the face, arms, legs, abdomen, etc.

5.3.2. Description of Sodium and Water Structure

The stock-flow diagram of sodium and water sector is shown in Figure 5.26. It consists of three stocks. These stocks are Free Fluid Volume, Sodium Amount and Implied Sodium Sodium Concentration.

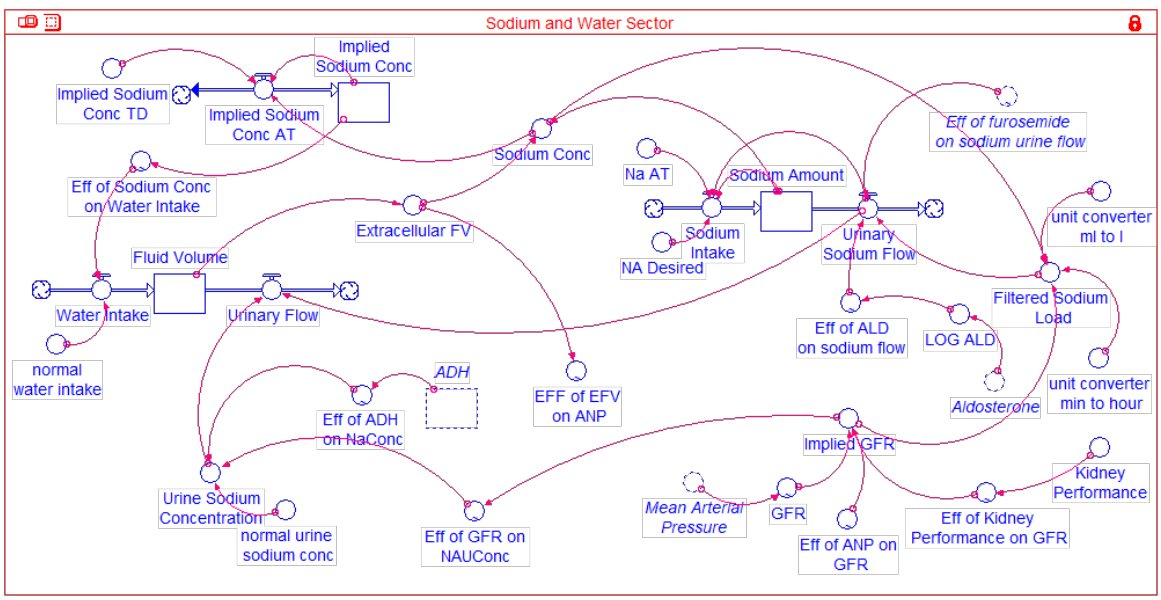


Figure 5.26. Stock Flow Diagram of Sodium and Water Structure

Sodium amount is controlled by the difference between sodium intake and urinary sodium flow as seen in Equation 5.45. Sodium intake is controlled by desired and actual sodium amount and urinary sodium flow to hold sodium amount at desired level. The minimum and maximum levels are defined as 6.5 mEq and 20 mEq as seen in Equation 5.46. Urinary sodium flow is multiplication of filtered sodium load, effect of aldosterone on the flow and 0.007 as shown in Equation 5.47. 0.007 is ratio that is achieved by dividing of normal values of filtered sodium value and urinary sodium flow and it is given by Karaaslan *et al.* [18].

$$\begin{aligned} &Sodium\ Amount(t) = \\ &\quad Sodium\ Amount(t - dt) + (Sodium\ Intake - Urinary\ Sodium\ Flow) * dt \end{aligned} \tag{5.45}$$

$$\begin{aligned} Sodium\ Intake = MIN(MAX(&Urinary\ Sodium\ Flow + \\ &\frac{NA\ Desired - Sodium\ Amount}{Na\ AT}, 6.5), 20) \end{aligned} \tag{5.46}$$

$$\begin{aligned} &Urinary\ Sodium\ Flow = \\ &\quad 0.007 * Filtered\ Sodium\ Load * Eff\ of\ ALD\ on\ sodium\ flow \end{aligned} \tag{5.47}$$

Filtered sodium load is the amount of sodium that is filtered by kidneys in a certain time. It is affected by sodium concentration and glomerular filtration rate (GFR) as shown in Equation 5.48. Implied GFR is defined for reflecting effect of kidney disorder and effect of ANP on GFR (Equation 5.49). The main factor that determines GFR value is MAP. There is positive relationship between them as defined in Figure 5.27. When the perfusion level of kidneys is decreased by low level of MAP, kidney function deteriorates. It is drawn based on MAP function given by Karanfil [31].

$$\begin{aligned} &Filtered\ Sodium\ Load = \\ &\quad Implied\ GFR * Sodium\ Conc * unit\ con\ ml\ to\ l * unit\ con\ min\ to\ hour \end{aligned} \tag{5.48}$$

$$Implied\,GFR = \\ MIN(GFR * Eff\ of\ Kidney\ Perf\ on\ GFR * Eff\ of\ ANP\ on\ GFR, 200) \tag{5.49}$$

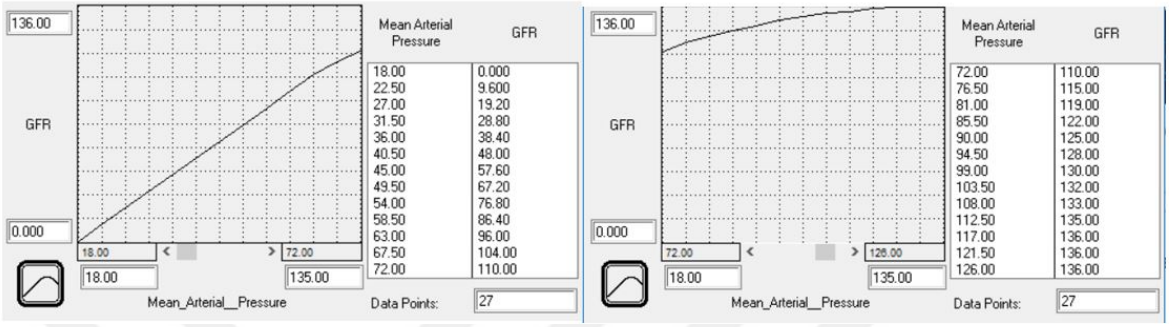


Figure 5.27. Graphical function for GFR based on MAP

Kidney disorder is result of insufficient perfusion of kidneys. Disease progression is observed on a monthly and yearly basis. In our model, it is constant parameter that expresses kidney performance and effect function is used to apply its effect on GFR as seen in Figure 5.28. Another factor that affects GFR is ANP. ANP plays a role in elevating sodium and water retention via increasing GFR. Figure 5.29 explains this relationship and it is drawn based on ANP function on GFR given by Karanfil [31].

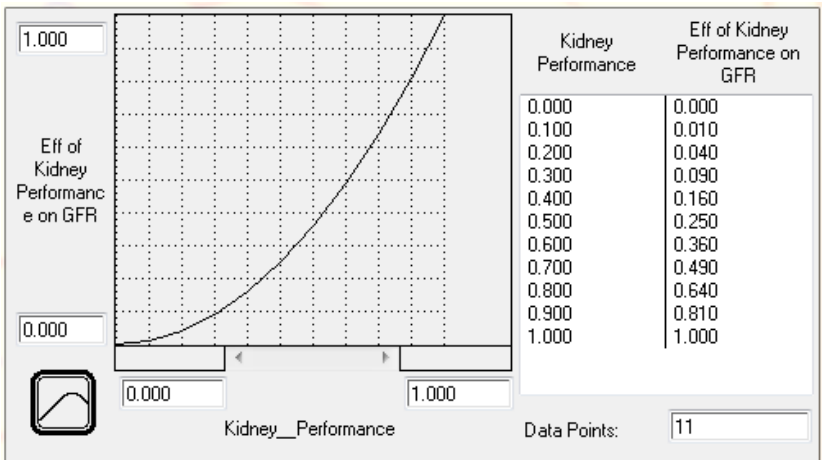


Figure 5.28. Graphical function for effect of Kidney Performance on GFR

Aldosterone is a hormone that has a negative effect on sodium urinary flow. While sodium concentration decreases, it is triggered for retention of sodium. This effect is

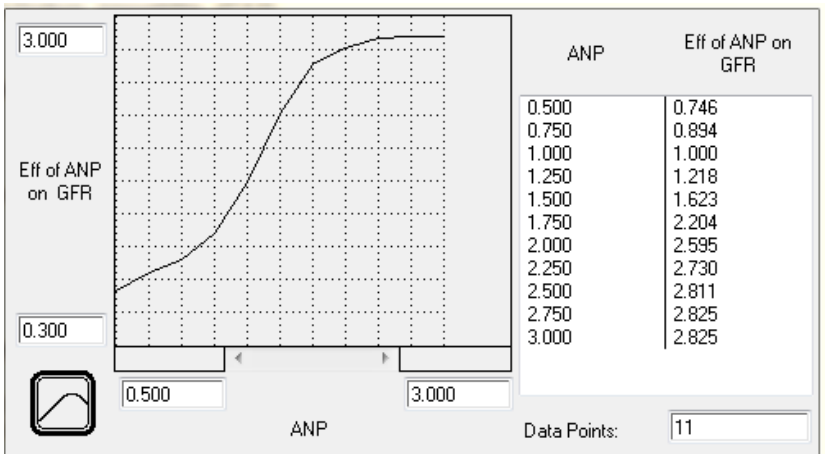


Figure 5.29. Graphical function for effect of ANP on GFR

represented in Figure 5.30. It is drawn based on Aldosterone effect on urinary flow given by Karaaslan *et al.* [18].

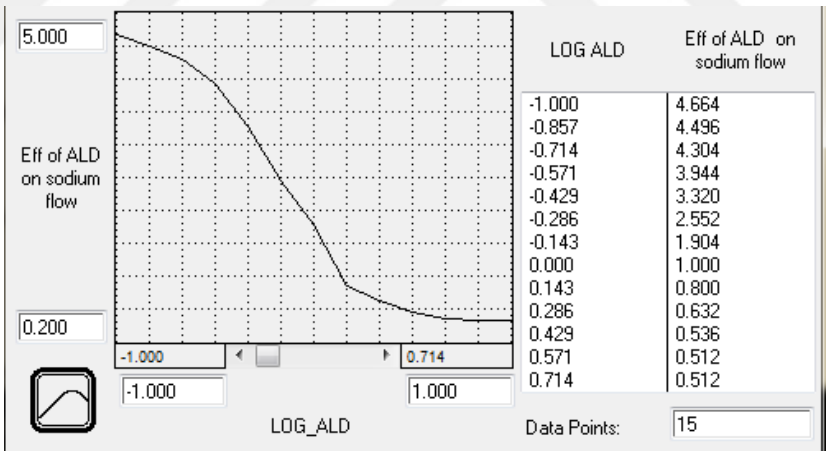


Figure 5.30. Graphical function of effect of aldosterone on sodium flow

Another stock is fluid volume and its net flow is equal to water intake minus urinary flow (Equation 5.50). Water intake is determined by effect of implied sodium concentration (Equation 5.51).

$$FluidVolume(t) = FluidVolume(t-dt)+(WaterIntake-UrinaryFlow)*dt \quad (5.50)$$

$$Water\ Intake = normal\ water\ intake * Eff\ of\ Sodium\ Conc\ on\ Water\ Intake \quad (5.51)$$

There should be delay stock between effect of sodium concentration on water intake and sodium concentration variable since increasing of thirst takes time. Therefore, the implied sodium concentration stock is defined as seen in Equation 5.52. It is controlled by adjustment flow and this adjustment flow is expressed in Equation 5.53.

$$\begin{aligned} &Implied\ Sodium\ Conc(t) = \\ &\quad Implied\ Sodium\ Conc(t - dt) + (Implied\ Sodium\ Conc\ Adj) * dt \end{aligned} \quad (5.52)$$

$$Implied\ Sodium\ Conc\ Adj = \frac{(Sodium\ Conc - Implied\ Sodium\ Conc)}{Implied\ Sodium\ Conc\ TD} \quad (5.53)$$

Figure 5.31 presents effect of implied sodium concentration on water intake. It is drawn based on assumptions that are identified in the literature and medical views of experts.

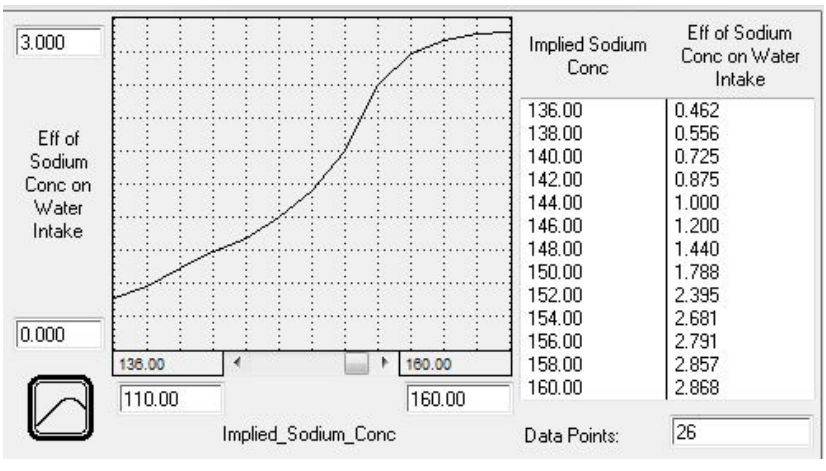


Figure 5.31. Graphical function for the effect of sodium concentration on water intake

Urinary flow is defined as a function of urinary sodium flow and urine sodium concentration as seen in Equation 5.54. The mechanism of excretion of urine is based

on excretion of sodium. Since sodium has a ability of capturing the water, urinary flow is related with sodium urinary flow. Urine sodium concentration determines the amount of water that is discharged with sodium. When the concentration increases, water amount decreases under the same amount of sodium excretion.

$$Urinary\ Flow = MIN(\frac{Urinary\ Sodium\ Flow}{Urine\ Sodium\ Concentration}, 0.06 * 20) \tag{5.54}$$

Normal value of urine sodium concentration is 126 mEq/liter. GFR and ADH have effects on it as seen in Equation 5.55. When GFR increases, filtrated sodium amount increases and urine sodium concentration decreases as defined in Figure 5.32. Besides, rising of level of AHD has positive effect on urine sodium concentration as shown in Figure 5.33. They are drawn based on GFR and ADH functions on urine sodium concentration given by Karanfil [31].

$$\begin{aligned} Urine\ Sodium\ Concentration = normal\ NAU\ Conc* \\ Eff\ \ GFR\ on\ NAUConc * Eff\ of\ ADH\ on\ NAU\ Conc \end{aligned} \tag{5.55}$$

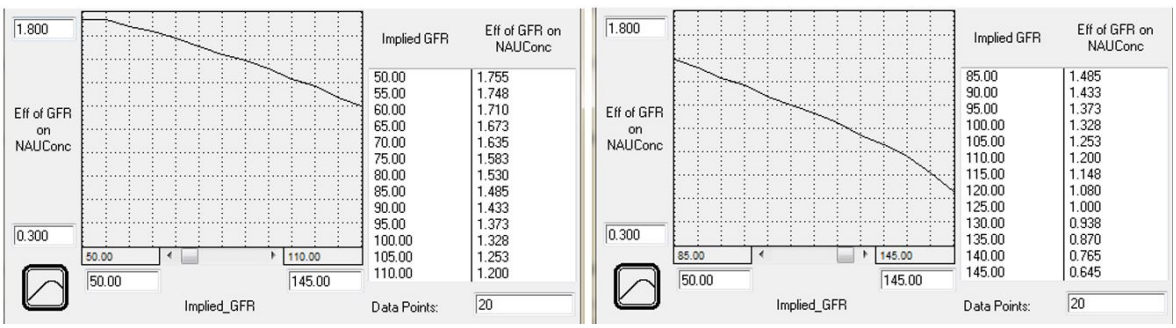


Figure 5.32. Graphical function for the effect of GFR on urinary sodium concentration

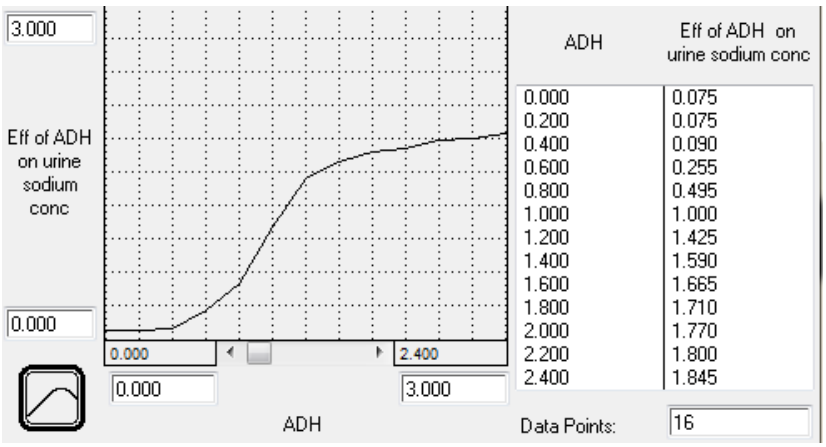


Figure 5.33. Graphical function for the effect of ADH on urinary sodium concentration

5.4. Cardio-Respiratory Sector

5.4.1. Medical Fundamentals and Assumptions

Another compensatory mechanism is cardiac remodeling which progresses throughout the patients life. Remodeling refers to alterations in size, shape, structure and the ventricle activity under the chronic hemodynamic stress. In short term, it works like compensatory mechanism as it elevates stroke volume and contractility. However, in the long term, it leads to diminish contractility by fibrosis and less effective pumping [24]. The effect of cardiac remodeling on cardiac cycle is drawn in Figure 5.34. Pressure-volume loop of heart failure patient appears right side of normal pressure-volume loop. Also, the width of loop is narrowed that indicates reduction of stroke volume.

One of the long-term effects of cardiac remodeling is pulmonary edema. As mentioned in the water and sodium sector, one of the types of edema that is observed in lungs is pulmonary edema. In heart failure, as results of cardiac remodeling and increasing fluid volume, left atrial pressure and pulmonary venous pressure elevate. Since preload and pulmonary venous pressure are elevated, capillary pressure increases. According to Starling's Law of Capillary Interstitial Exchange, the flow of fluid from

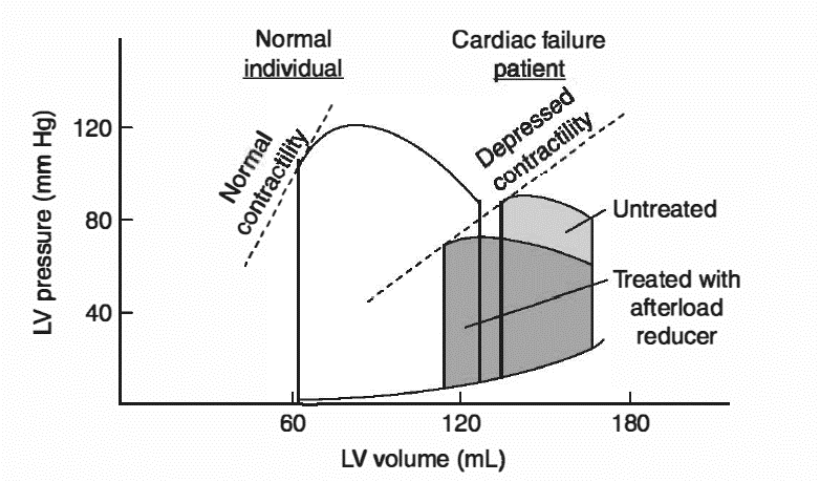


Figure 5.34. Cardiac cycle loop of normal individual and heart failure patient (reproduced from [26])

the pulmonary vasculature into the interstitium is conducted by hydrostatic pressure gradient (capillary pressure – interstitium pressure). Because of pressure gradient, net flow of fluid from the pulmonary vasculature into the interstitium exceeds the capacity of the pulmonary lymphatics. Water in the lung increases and cardiogenic pulmonary edema develops [32]. In Figure 5.35, the relationship between left atrial pressure and lung fluid flow are shown. While fluid in the lung rises, lung level of ventilation is diminished. Level reduction of O_2 saturation leads to vicious cycle of heart failure.

Although our study focuses on cardiogenic edema, there is another type of pulmonary edema in terms of causes. It is defined as non-cardiogenic pulmonary edema. It has the same results as cardiogenic edema. It is less common and generally caused by damage of lung tissues, not caused by increasing heart pressure. In this case, the permeability of lung capillaries increases. Because of this leakage, the fluid begins to fill interstitium. The main reasons of non-cardiogenic pulmonary edema are kidney failure, high altitude, inhaled toxins, pneumonia, acute respiratory distress syndrome (ARDS) and adverse drug reaction. Since kidney failure can be observed in heart failure patients, non-cardiogenic pulmonary edema can occur.

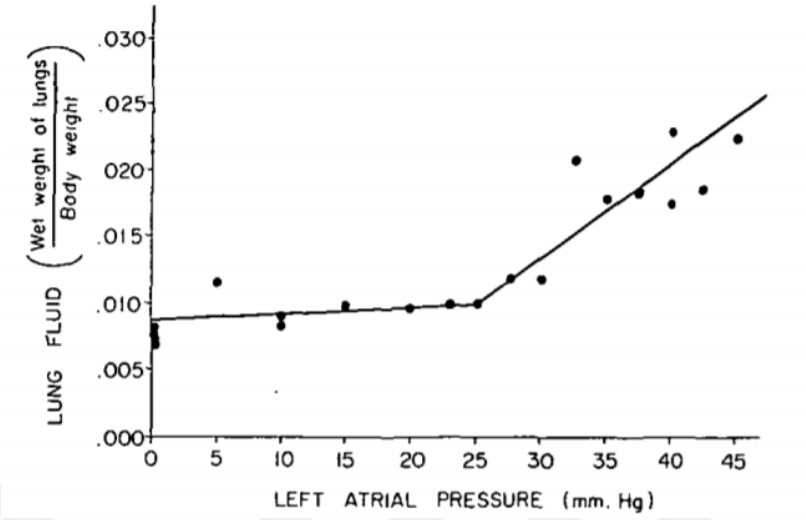
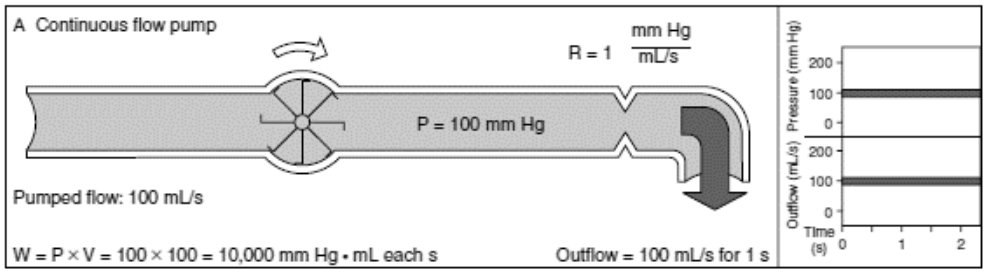


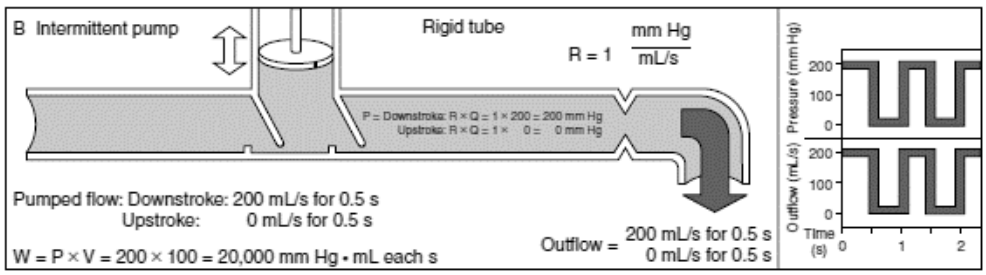
Figure 5.35. Relationship between left atrial pressure and lung fluid flow (reproduced from [33])

Myocardial ischemia is a condition where heart is not supplied with adequate blood and oxygen. With increasing neurohormonal and sympathetic system activation, systemic vasoconstriction, coroner vasoconstriction and rising heart rate are observed. Oxygen demand increases by systemic vasoconstriction and increasing heart rate. Both O_2 saturation of blood and coroner perfusion are decreased by coroner vasoconstriction and pulmonary edema [34]. Also, arteries of heart failure patient lose elasticity at a certain ratio which results in low arterial compliance. Low arterial compliance leads to increase in oxygen demand because of rising cardiac work as explained in Figure 5.36. The simple example in the figure illustrates that compliant tube mechanism stabilizes pressure and minimizes cardiac workload in an intermittent pumping system like heart.

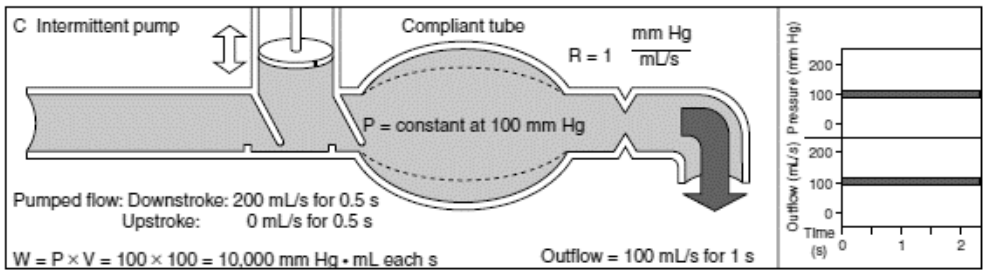
All these conditions mentioned above cause to reduce oxygen supply/demand ratio. Reduction of this ratio contributes to progression of heart dysfunction. In our study, values for a healthy individual are used as given in Table 5.3 for the base run. Lower values are used to simulate dynamics of heart failure since dysfunction of heart reduces these values.



A, The pump flow is steady, and pressure will remain constant regardless of the distensibility of the conduit.



B, The flow *(Q)* produced by the pump is intermittent; it is steady for half the cycle and ceases for the remainder of the cycle. The conduit is rigid and therefore, the flow produced by the pump during its downstroke must exit through the resistance during the same 0.5 s that elapses during the downstroke. The pump must do twice as much work as the pump in **A.**



C, The pump operates as in B, but the conduit is infinitely distensible. This results in perfect filtering of the pressure; that is, the pressure is steady, and the outflow through the resistance is also steady. The work equals that in A.

Figure 5.36. The relationship between pressure and flow for three hydraulic system (reproduced from [25])

Table 5.3. Normal values of Cardio-Respiratory Sector Variables

Variable	**Normal Steady-State Values**	**Unit**
Heart Capability (ratio to normal)	1	unitless
Pulmonary Free Fluid	0	L
Arterial Oxygen Saturation	100%	unitless
Contractility (ratio to normal)	1	unitless

5.4.2. Description of Cardio-Respiratory Structure

The stock-flow diagram of cardio-respiratory sector is shown in Figure 5.37. It consists of three stocks. These stocks are Pulmonary Free Fluid Volume, Heart Capability and Contractility.

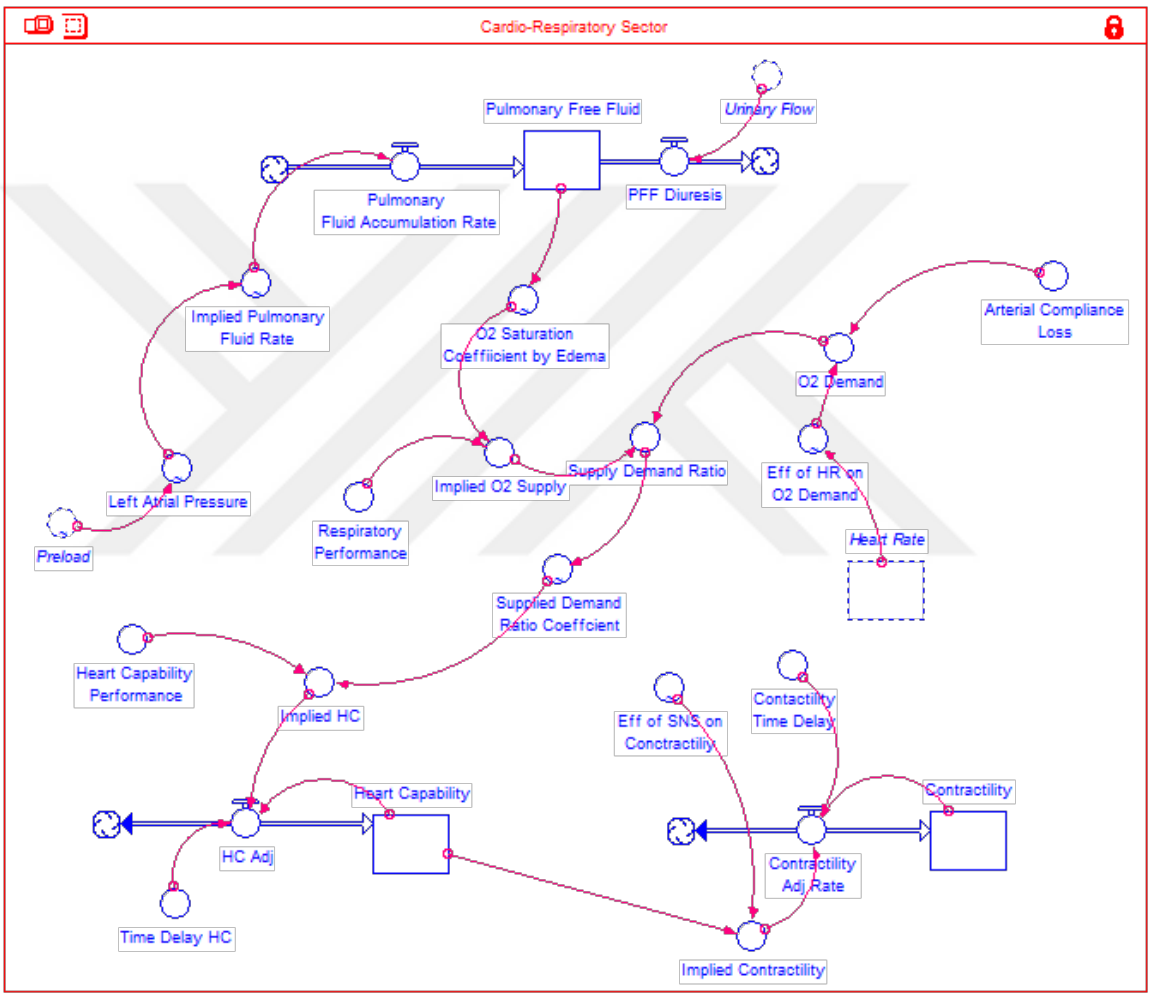


Figure 5.37. Stock Flow Diagram of Cardio-Respiratory Structure

Pulmonary Free Fluid (PFF) represents pulmonary edema that is caused by excessive blood accumulation in the heart. Deviation of pulmonary free fluid is caused by the difference between pulmonary free fluid accumulation rate and PFF diuresis as seen in Equation 5.56. PFF diuresis is assumed to be one third of the urinary flow (Equation 5.57). This assumption is based on ratio of total free fluid accumulation

of body and pulmonary free fluid accumulation. PFF accumulation rate is triggered by implied pulmonary fluid rate as defined in Equation 5.58. It is formulated by the graphical function that depends on left atrial pressure as shown in Figure 5.38. This graphical function is drawn based on lung fluid flow given by Guyton [33] as seen in Figure 5.35.

$$\begin{aligned} &Pulmonary\ Free\ Fluid(t) = \\ &\quad PFF(t - dt) + (PFF\ Accumulation\ Rate - PFF\ Diuresis) * dt \end{aligned} \tag{5.56}$$

$$PFF\ Diuresis = \frac{Urinary\ Flow}{3} \tag{5.57}$$

$$PFF\ Accumulation\ Rate = Implied\ Pulmonary\ Fluid\ Rate \tag{5.58}$$

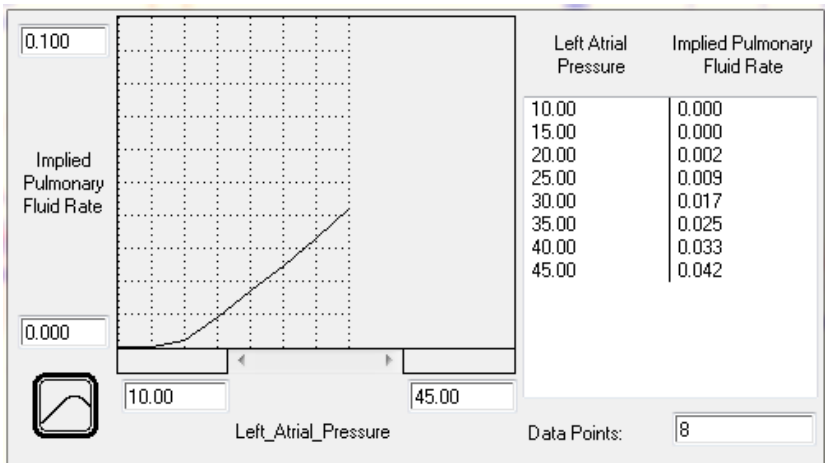


Figure 5.38. Implied pulmonary fluid rate based on left atrial pressure

Left atrial pressure represents the pressure at the point where blood from the lungs enters the heart. It can be represented as a function of preload. Figure 5.39 is drawn based on the ratio of their normal values.

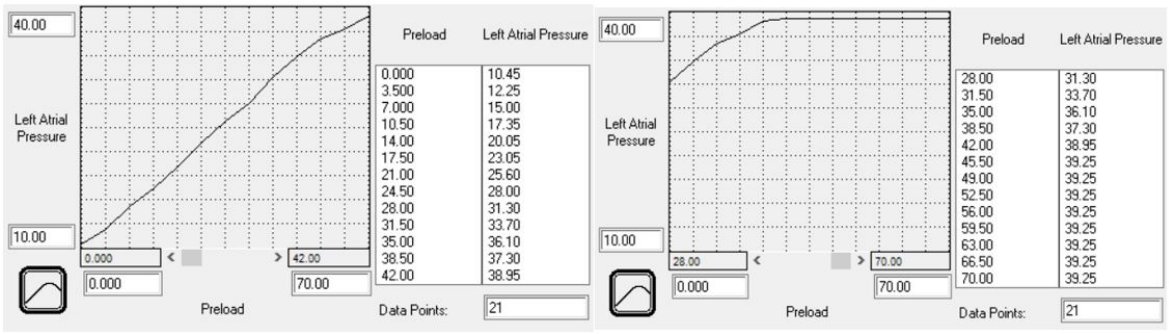


Figure 5.39. Left atrial pressure function based on preload

Another stock is the heart capability (HC) that presents the deterioration level of heart. Its flow is bi-flow. Since heart deterioration is irreversible, this flow behaves just outflow (Equation 5.59).

$$Heart\ Capability(t) = Heart\ Capability(t - dt) + (HC\ Adj) * dt \tag{5.59}$$

HC adjustment is determined by the difference between implied and actual HC values. The values that are lower than 0.005 is ignored (Equation 5.60). This lower bound is defined because of elimination pulmonary edema in case of excessive heart rate. Implied HC is the result of multiplication of O_2 supplied demand ratio coefficient and heart capability performance (Equation 5.61). Heart capability performance is constant. It represents initial degree of heart deterioration at the beginning of the simulation.

$$HC\ Adj = \begin{cases} 0, & \frac{Implied\ HC - Heart\ Capability}{Time\ Delay\ HC} > -0.005 \\ \frac{Implied\ HC - Heart\ Capability}{Time\ Delay\ HC}, & otherwise \end{cases} \tag{5.60}$$

$$Implied\,HC = Supply\,Demand\,Ratio\,Coef * Heart\,Capability\,Performance \quad (5.61)$$

Supply demand ratio coefficient is a function of O_2 supply demand ratio as defined in Figure 5.40. This function is used to moderate the effect of O_2 supply demand ratio on heart deterioration. It is drawn based on assumptions that are identified in the literature and medical views of experts.

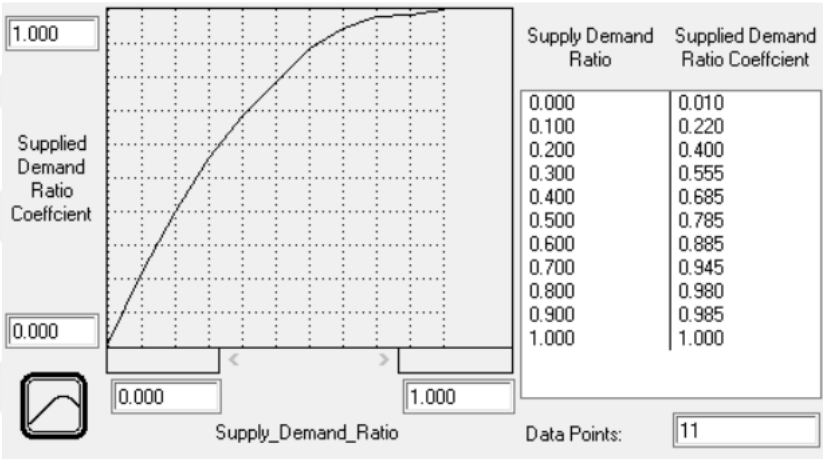


Figure 5.40. Supply demand ratio coefficient based on O_2 supply demand ratio

Supply demand ratio is obtained by dividing implied O_2 supply into O_2 demand. This ratio cannot be greater than 1 (Equation 5.62). Implied O_2 supply is minimum of O_2 saturation coefficient and respiratory performance as defined in Equation 5.63. Respiratory performance is the initial degree of lung deterioration. O_2 saturation coefficient is capability of lungs to enrich blood with oxygen. It is determined with function at Figure 5.41. When PFF increases, the O_2 saturation decreases. This relationship is drawn based on assumptions that are identified in the literature and medical views of experts.

$$Supply\,Demand\,Ratio = MIN(\frac{Implied\,O_2\,Supply}{O_2\,Demand}, 1) \quad (5.62)$$

$$Implied\,O_2\,Supply = MIN(O_2\,Saturation\,Coef, Respiratory\,Performance) \quad (5.63)$$

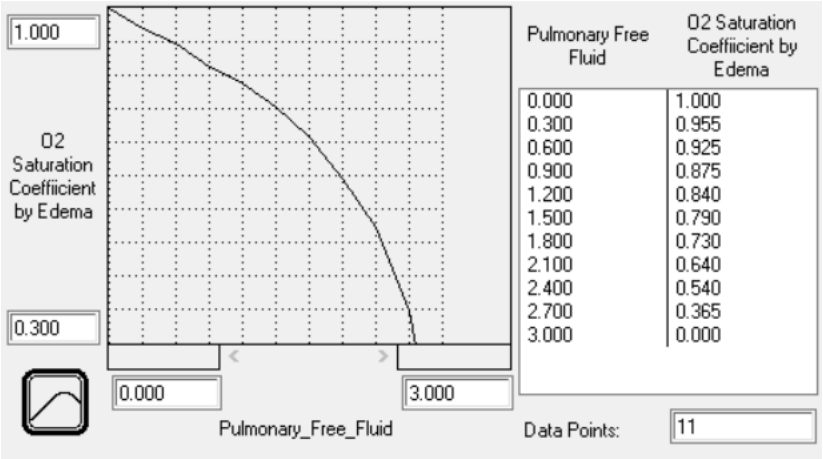


Figure 5.41. O_2 saturation coefficient by PFF function based on PFF

Oxygen demand depends on cardiac work. Heart rate and arterial compliance are critical factors for determining O_2 demand (Equation 5.64). When heart rate increases, cardiac work and O_2 demand increase as seen in Figure 5.42. It is drawn based on assumptions that are identified in the literature and medical views of experts. Also, when arterials lose arterial compliance, O_2 demand increases.

$$O_2\ Demand = Eff\ of\ HR\ on\ O_2\ Demand * Arterial\ Compliance\ Loss \tag{5.64}$$

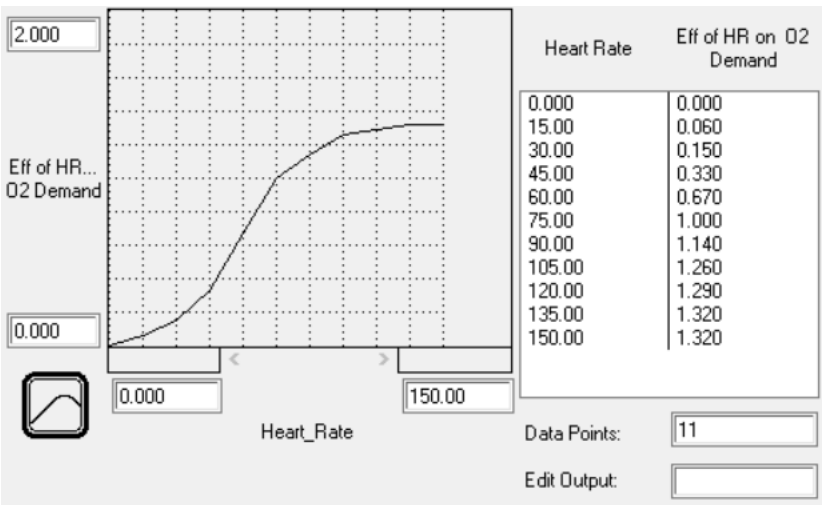


Figure 5.42. Effect of HR on O_2 Demand

The third stock in cardio-respiratory sector is contractility. It is the contraction capability of heart muscles. It is controlled by one bi-flow (Equation 5.65) and this bi-flow is triggered by the difference between implied and actual values of contractility (Equation 5.66).

$$Contractility(t) = Contractility(t - dt) + (Contractility\ Adj\ Rate) * dt \quad (5.65)$$

$$Contractility\ Adj\ Rate = \frac{Implied\,Contractility - Contractility}{Time\ Delay} \quad (5.66)$$

Contractility is affected by heart deterioration level and SNS as seen in Equation 5.67. Since it depends on functionality and structure of heart, heart deterioration level affects it directly. Since SNS plays a role in acceleration of circulation, there is a positive relation between contractility and SNS as illustrated in Figure 5.43. It is drawn based on SNS effect on cardiac output given by Heller *et al.* [26] as seen in Figure 5.15.

$$Implied\,Contractility = Heart\,Capability * Eff\ of\ SNS\ on\ Conctractiliy \quad (5.67)$$

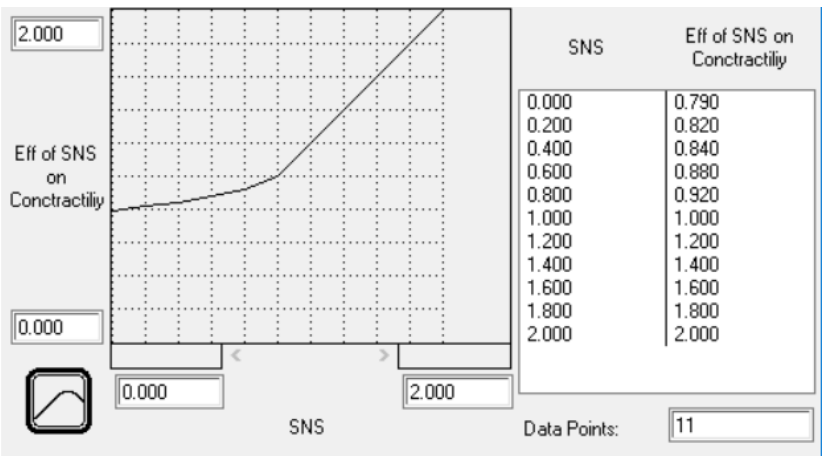


Figure 5.43. Effect of SNS on contractility

5.5. Treatment Sector

5.5.1. Medical Fundamentals and Assumptions

For acute and chronic heart failure, treatments are focused on increasing perfusion. In CHF treatment, medicines play an important role to inhibit mechanisms and to break vicious cycle of heart failure. But in AHF, medicines are used to enhance respiratory system and to diminish the deteriorating clinical picture of heart. In Table 5.4, most common treatment methods are illustrated for both acute and chronic HF.

Table 5.4. Treatment Methods of AHF and CHF [35] [36] [37] [38]

Acute Heart Failure	**Chronic Heart Failure**
Oxygen administration and positive airway pressure	Angiotensin Converting Enzyme (ACE) Inhibitors
Intra aortic balloon pump	Beta Blokers
Vasodilators (natriuretic peptides)	Angiotensin II Receptor Antagonist
Diuretics	Diuretics
Ultrafiltration	Ultrafiltration
Vasopressors and Inotropes	Vasopressin Antagonist
Adenosine Antagonist	LCZ696
Morphine	Aldesterone Receptor Antagonist

In the treatment sector of model, diuretic is used for treatment of acute heart failure. Diuretics increase the excretion of the edema. Therefore, they play a critical role in the treatment of AHF. Vasodilator is another type of drug that is used for treating AHF. When the systolic pressure is more than 120 mmHg, vasodilators are used to reduce the vessel resistance and decrease the pressure by relaxating the of vascular smooth muscle. Venous vasodilation decreases preload by the reduction of venous return. Arterial vasodilation decreases afterload with reduction of systolic pressure [39]. However, according to real hospitalization cases, vasodilators are taken maximum 1 hour continuously. Since time unit of model is hour, its effect can not be observed in

hours. When it is used, sudden decreasing of pressure and resistances are observed. Values of parameters increase quickly when vasodilator usage is cut. Consequently, it is deleted from model.

Ultrafiltration is an alternative method that avoids progressive water and sodium retention, which is the cause of dyspnea and edema. It is an extracorporeal method that can remove extracellular fluid from the body. This method can be used especially in cases when diuretic resistance occurs in patients. Water, sodium and other electrolytes are transferred from the body into this mechanism via ultrafiltration that have 150 mEq/l sodium concentration. Suggested slow ultrafiltration includes removal of 1-2 liters with a rate of 100-200 ml/h [40]. This method is used in the model as an alternative to Furosemide.

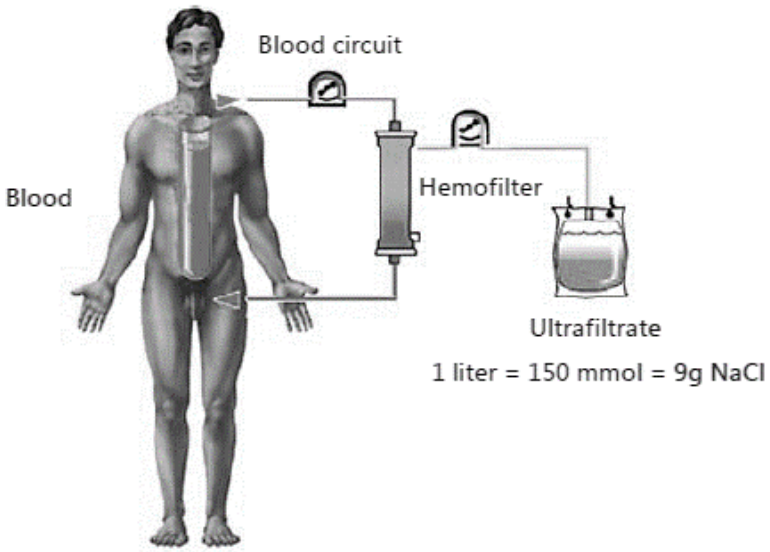


Figure 5.44. Ultrafiltration mechanism (reproduced from [40])

When the patient is stabilized and the desired level of hemodynamic parameters are reached, the treatment continues with the use of chronic heart failure drugs. The main drugs used in this period are ACE (Angiotensin converting enzyme) inhibitors, beta blockers and ARBs (Angiotensin II receptor blocker). These medicines are given to the patient in certain doses and in regular time intervals until patient is discharged.

When the stability is confirmed, the patient is discharged. These drugs are intended to block the effects of hormonal compensatory mechanisms. Patients will continue to use these drugs throughout their life. Bisoprolol is chosen as beta blocker and Candesartan is selected as ARB.

The ARB and ACE inhibitor eliminate the effects of Angiotensin 2 in different ways. Therefore, they are used interchangeably. ACE inhibitor inhibits ACE that converts Angiotensin I to Angiotensin II as seen in Figure 5.45 while the ARB inhibits the binding of Angiotensin II to AT1 receptors. When ACE is inhibited, AT2 and bradykinin that provides vasodilation are also inhibited [41]. In addition, there are different ingredients that play a role on converting Angiotensin II to Angiotensin II. Therefore, ACE inhibitor does not provide 100% blockage of Angiotensin II. Consequently, ARB is used in the model to block the effects of Angiotensin II.

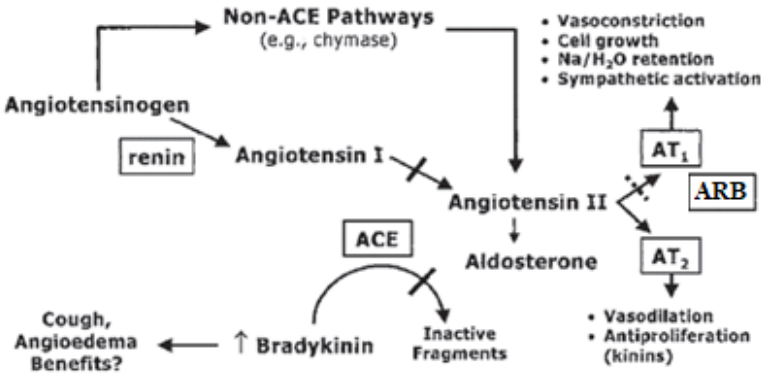


Figure 5.45. Secretion mechanism of Angiotensin II (reproduced from [41])

Pharmacokinetics and pharmacodynamics parameters of drugs are investigated to simulate treatment scenarios. Pharmacodynamics are the effects of drugs on body. Pharmacokinetics are the dynamics of drugs in the body. These dynamics illustrate the time of peak level, required time for removing the drugs and amount of drug remains in the body while it is taken in certain period. The pharmacokinetic parameters of drugs that are used in the model is given in Table 5.5.

Table 5.5. Pharmacokinetic parameters of drugs [42] [43] [44] [45]

Drug	Bioavailability	Volume Dist	Abs Ratio	Clearance	Binding Ratio
Furosemide	0.6	9	0.65	6	0.9
Bisoprolol	0.95	3.5	0.8	0.32	0.3
Candesartan	0.4	0.13	0.33	0.014	0.99

Bioavailability (bioavail), volume of distribution (dist), absorption (arb) ratio, clearance ratio and binding (bind) ratio are used to replicate the dynamics of drugs on simulation. Bioavailability is the absorption fraction of the active substance of a drug into the body. It is the first factor that is used to arrange the dosage of drug. Volume of distribution is the measure that the area in which the drug is absorbed and spread in the body [43]. The flow of non-absorbed concentration is determined by these two factors with drug dosage. There is the absorption ratio that controls transition from non-absorbed drug to free drug in the blood. Free drug concentration determines the pharmacodynamics of drug. Therefore, drug dosage with a high absorption ratio is lower than drug dosage for low absorption rate.

The drug in the body is discharged with a certain flow. One of the parameters that determines this flow is clearance. Capability of the body to remove the drug defines as clearance. Multiplication of clearance and volume of distribution create elimination constant [46]. Elimination (elim) of drug is proportional to elimination constant and free drug concentration. The drugs also have the ability to bind the plasma proteins from free drug concentrations with binding ratio. Bind drug cannot be eliminated by clearance. If free drug concentration decreases, some bind drugs in the plasma protein come back to increase free drug concentration since desired concentration drug to plasma bind is defined. When free drug concentration reduces, desired concentration drug to plasma bind reduces.

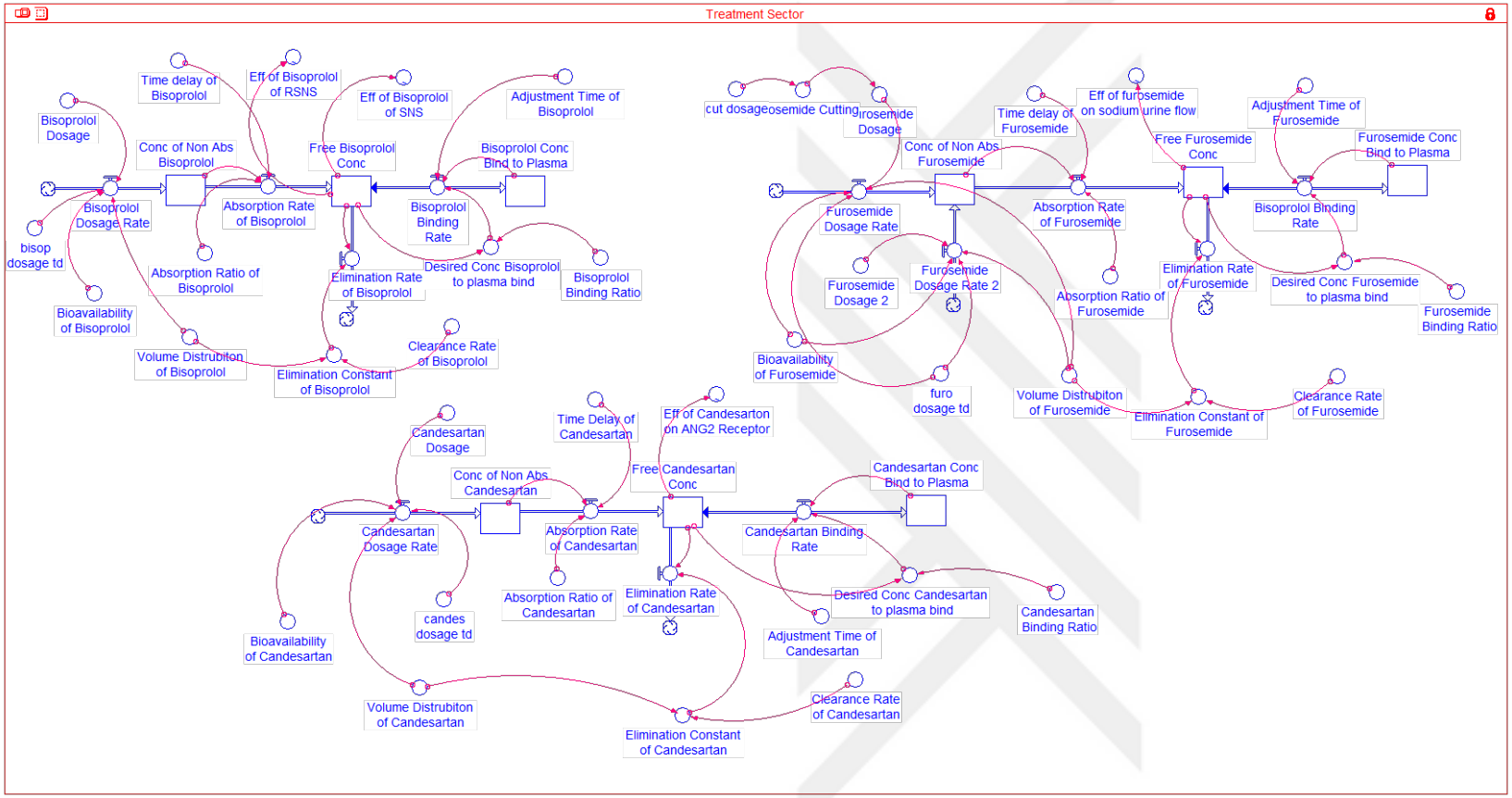


Figure 5.46. Flow Diagram of Treatment Structure

5.5.2. Description of Treatment Structure

The stock-flow diagram of treatment sector is shown in Figure 5.46. It consists of three drugs and each of them has three stocks. These drugs are Furosemide (Furo) as a diuretic, Bisoprolol (Bisop) as a beta-blocker and Candesartan (Cand) as a ARB. Their stocks are non-absorbed drug, free drug concentration and drug bind to plasma.

Conc of Non Abs Bisoprolol, Conc of Non Abs Candesartan and Conc of Non Abs Furosemide represent concentration of drugs that are already taken into body and they are waiting to be absorbed. Each of them has one inflow that is defined as Drug Dosage Rate and one outflow that is defined as Absorption Rate of Drug shown in Equation 5.68, Equation 5.69 and Equation 5.70.

$$\begin{aligned} Conc\,of\ Non\ Abs\ Bisop(t) = Conc\,of\ Non\ Abs\ Bisop(t - dt) + \\ (Bisop\ Dosage\ Rate - Absorp\ Rate\,of\ Bisop) * dt \end{aligned} \tag{5.68}$$

$$\begin{aligned} Conc\,of\ Non\ Abs\ Cand(t) = Conc\,of\ Non\ Abs\ Cand(t - dt) + \\ (Cand\ Dosage\ Rate - Absorp\ Rate\,of\ Cand) * dt \end{aligned} \tag{5.69}$$

$$\begin{aligned} Conc\,of\ Non\ Abs\ Furo(t) = Conc\,of\ Non\ Abs\ Furo(t - dt) + \\ (Furo\ Dosage\ Rate - Absorp\ Rate\,of\ Furo) * dt \end{aligned} \tag{5.70}$$

Bisoprolol Dosage Rate, Candesartan Dosage Rate and Furosemide Dosage Rate are represented with pulse function because of reflecting behavior of drugs on model as seen in Equation 5.71, Equation 5.72 and Equation 5.73. There are three parameters in the pulse function that help to create this behavior. One of them is pulse volume and it depends on bioavailability of drug, dosage intake and volume of distribution. The other is first pulse time that represents first time to take drug into body. Last

parameter is internal that presents time between each usage of drug.

$$Bisop\ Dosage\ Rate = PULSE(\frac{Bioavail\ of\ Bisop * Bisop\ Dosage}{Vol\ Dist\ of\ Bisop * bdosage\ td}, 92, 24) \quad (5.71)$$

$$Cand\ Dosage\ Rate = PULSE(\frac{Bioavail\ of\ Cand * Bisop\ Dosage}{Vol\ Dist\ of\ Cand * cdosage\ td}, 92, 24) \quad (5.72)$$

$$Furo\ Dosage\ Rate = PULSE(\frac{Bioavail\ of\ Furo * Furo\ Dosage}{Vol\ Distn\ of\ Furo * fdosage\ td}, 92, 24) \quad (5.73)$$

Free Bisoprolol Conc, Free Candesartan Conc and Free Furosemide Conc are controlled by one inflow that is Absorption Rate of Drug, one outflows that is Elimination Rate of Drug and one bi-flow that is Drug Binding Rate as defined in Equation 5.74, Equation 5.75 and Equation 5.76. These stocks are the effective drug concentration in the blood and pharmacodynamics are depending on values of these stock.

$$\begin{aligned} Free\ Bisop\ Conc(t) &= Free\ Bisop\ Conc(t - dt) + \\ &(Abs\ Rate\ of\ Bisop - Elim\ Rate\ of\ Bisop - Bisop\ Bind\ Rate) * dt \end{aligned} \quad (5.74)$$

$$\begin{aligned} Free\ Cand\ Conc(t) &= Free\ Cand\ Conc(t - dt) + \\ &(Abs\ Rate\ of\ Cand - Elim\ Rate\ of\ Cand - Cand\ Bind\ Rate) * dt \end{aligned} \quad (5.75)$$

$$\begin{aligned} Free\ Furo\ Conc(t) &= Free\ Furo\ Conc(t - dt) + \\ &(Abs\ Rate\ of\ Furo - Elim\ Rate\ of\ Furo - Furo\ Bind\ Rate) * dt \end{aligned} \quad (5.76)$$

Absorption Rate of Bisoprolol, Absorption Rate of Candesartan and Absorption Rate of Furosemide are flows that transfer to volume of drug from non-absorbed drug

stock to free drug concentration stock with defined function in Equation 5.77, Equation 5.78 and Equation 5.79. They are created by multiplying constant absorption ratio and concentration of non-absorbed drug concentration.

$$Abs\ Rate\ of\ Bisop = Abs\ Ratio\ of\ Bisop * Conc\ of\ Non\ Abs\ Bisop \tag{5.77}$$

$$Abs\ Rate\ of\ Cand = Abs\ Ratio\ of\ Cand * Conc\ of\ Non\ Abs\ Cand \tag{5.78}$$

$$Abs\ Rate\ of\ Furo = Abs\ Ratio\ of\ Furo * Conc\ of\ Non\ Abs\ Furo \tag{5.79}$$

Elimination Rate of Bisoprolol, Elimination Rate of Candesartan and Elimination Rate of Furosemide are excreted volume of drug per hour. Free drug concentration and elimination constant of drug are effective factors on calculation of them as seen in Equation 5.80, Equation 5.81 and Equation 5.82.

$$Elim\ Rate\ of\ Bisop = Free\ Bisop\ Conc * Elim\ Constant\ of\ Bisop \tag{5.80}$$

$$Elim\ Rate\ of\ Cand = Free\ Cand\ Conc * Elim\ Constant\ of\ Cand \tag{5.81}$$

$$Elim\ Rate\ of\ Furo = Free\ Furo\ Conc * Elim\ Constant\ of\ Furo \tag{5.82}$$

Elimination Constant of Bisoprolol, Elimination Constant of Candesartan and Elimination Constant of Furosemide depend on clearance ratio and volume of distribution of drugs as shown in Equation 5.83, Equation 5.84 and Equation 5.85. Increase in clearance ratio affects elimination constant positively, although increase in volume

of distribution affects this constant negatively.

$$Elim\ Constant\ of\ Bisop = \frac{Clearance\ Ratio\ of\ Bisop}{Volume\ Dist\ of\ Bisop} \tag{5.83}$$

$$Elim\ Constant\ of\ Cand = \frac{Clearance\ Ratio\ of\ Cand}{Volume\ Dist\ of\ Cand} \tag{5.84}$$

$$Elim\ Constant\ of\ Furo = \frac{Clearance\ Ratio\ of\ Furo}{Volume\ Dist\ of\ Furo} \tag{5.85}$$

Bisoprolol Conc Bind to Plasma, Candesartan Conc Bind to Plasma and Furosemide Conc Bind to Plasma represent drug concentration that bind to plasma. They have one bi-flow that is defined as Drug Binding Rate seen in Equation 5.86, Equation 5.87 and Equation 5.88.

$$Bisop\ Conc\ Bind(t) = Bisop\ Conc\ Bind(t - dt) + (Bisop\ Binding\ Rate) * dt \tag{5.86}$$

$$Cand\ Conc\ Bind(t) = Cand\ Conc\ Bind(t - dt) + (Cand\ Binding\ Rate) * dt \tag{5.87}$$

$$Furo\ Conc\ Bind(t) = Furo\ Conc\ Bind(t - dt) + (Furo\ Binding\ Rate) * dt \tag{5.88}$$

Bisoprolol Binding Rate, Candesartan Binding Rate and Furosemide Binding Rate are defined as bi-flow for controlling drug concentration bind to plasma. Flow is the difference between desired and actual values of drug concentration bind to plasma shown in Equation 5.89, Equation 5.90 and Equation 5.91.

$$Bisop\ Binding\ Rate = \frac{(Desired\ Bisop\ Cond\ Bind - Bisop\ Conc\ Bind)}{Adj\ Time\ of\ Bisop} \tag{5.89}$$

$$Cand\ Binding\ Rate = \frac{(Desired\ Cand\ Cond\ Bind - Cand\ Conc\ Bind)}{Adj\ Time\ of\ Cand} \tag{5.90}$$

$$Furo\ Binding\ Rate = \frac{(Desired\ Furo\ Cond\ Bind - Furo\ Conc\ Bind)}{Adj\ Time\ of\ Furo} \tag{5.91}$$

Desired Bisoprolol Cond Bind, Desired Candesartan Cond Bind and Desired Furosemide Cond Bind represent desired level of drug concentration bind to plasma. They are obtained by multiplying with drug binding rate and free drug concentration in Equation 5.92, Equation 5.93 and Equation 5.94. Drug binding ratio is constant variable and demonstrates the tendency of drug to bind to plasma.

$$Desired\ Bisop\ Cond\ Bind = Bisop\ Binding\ Ratio * Free\ Bisop\ Conc \tag{5.92}$$

$$Desired\ Cand\ Cond\ Bind = Cand\ Binding\ Ratio * Free\ Cand\ Conc \tag{5.93}$$

$$Desired\ Furo\ Cond\ Bind = Furo\ Binding\ Ratio * Free\ Furo\ Conc \tag{5.94}$$

After detailed explanation of pharmacokinetics of drugs with mathematical formulas, pharmacodynamics of drugs are expressed below with revised compensation mechanisms equations and effects of drug on them.

Bisoprolol is used for blocking the sympathetic nerve activity. Eff of Bisoprolol of RSNS and Eff of Bisoprolol of SNS are defined to reflect this effect on the model. They are added to the function of SNS and RSNS as seen in Equation 5.95 and Equation 5.96. The graphical functions of Bisoprolol effect on RSNS and SNS are shown in Figure 5.47 and Figure 5.48. They are drawn based on assumptions that are identified

in the literature and medical views of experts.

$$Implied\,RSNS = 1 * Eff\ of\ Map\ on\ RSNS * Eff\ of\ Bisoprolol\ of\ RSNS \quad (5.95)$$

$$Implied\,SNS = 1 * Eff\ of\ Map\ on\ SNS * Eff\ of\ Bisoprolol\ of\ SNS \quad (5.96)$$

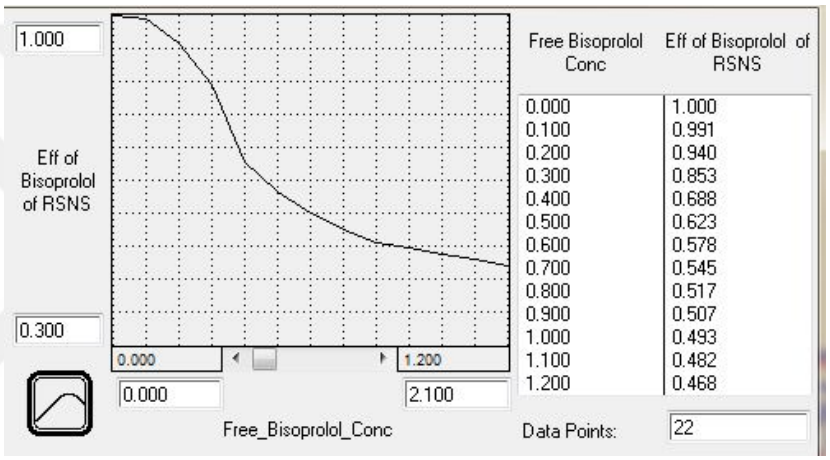


Figure 5.47. Effect of Bisoprolol on RSNS

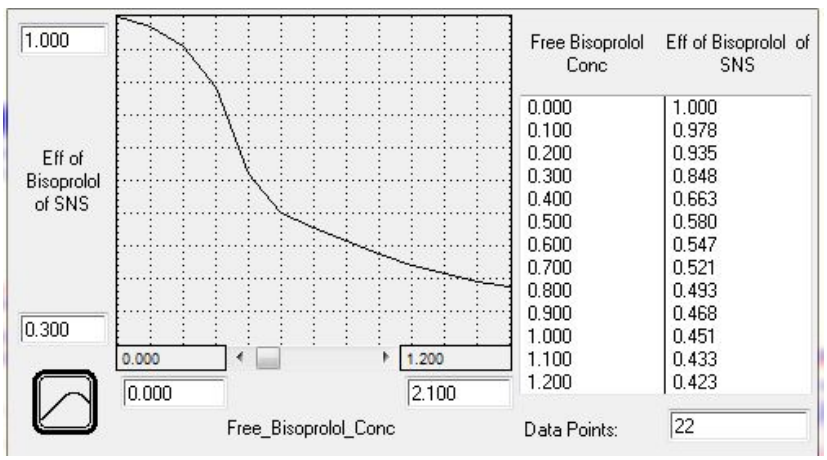


Figure 5.48. Effect of Bisoprolol on SNS

Candesartan is used for blocking Angiotensin II effects in the body. Eff of Candesartan on ANG II Receptor is defined to apply effect of Candesartan on Angiotensin II receptor. It is added in the Angiotensin I formulation since Angiotensin I is utilized as the desired level of Angiotensin II in the model as expressed in Equation 5.97. The graphical function of this effect is shown in Figure 5.49. It is drawn based on assumptions that are identified in the literature and medical views of experts.

$$ANG1 = Angiotensin\ 1 * Eff\ of\ Candesartan\ on\ ANG2\ Receptor \tag{5.97}$$

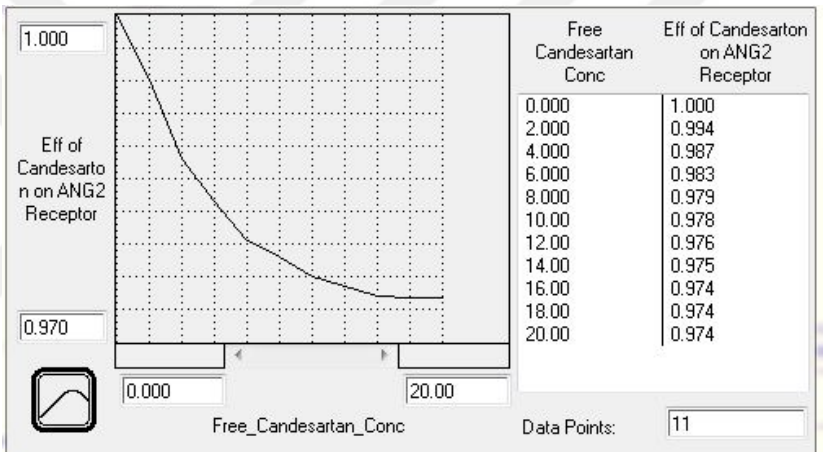


Figure 5.49. Effect of Candesartan on ANG2 Receptor

Furosemide is used for increasing urinary sodium flow to excrete sodium and water. Eff of furosemide on sodium urine flow is defined to create diuretic effect on sodium flow. Revised urinary sodium flow formula is seen in Equation 5.98. The graphical function of this effect is shown in Figure 5.50. It is drawn based on pharmacodynamics of furosemide given by Hammarlund-Udenaes and Benet [42].

$$\begin{aligned} Urinary\ Sodium\ Flow = MAX(&0.007 * Filtered\ SodiumLoad * Eff \\ &of\ ALD\ on\ sodium\ flow, 0.007 * Filtered\ SodiumLoad * Eff\ of \\ &ALD\ on\ sodium\ flow * Eff\ of\ furosemide\ on\ sodium\ urine\ flow) \end{aligned} \tag{5.98}$$

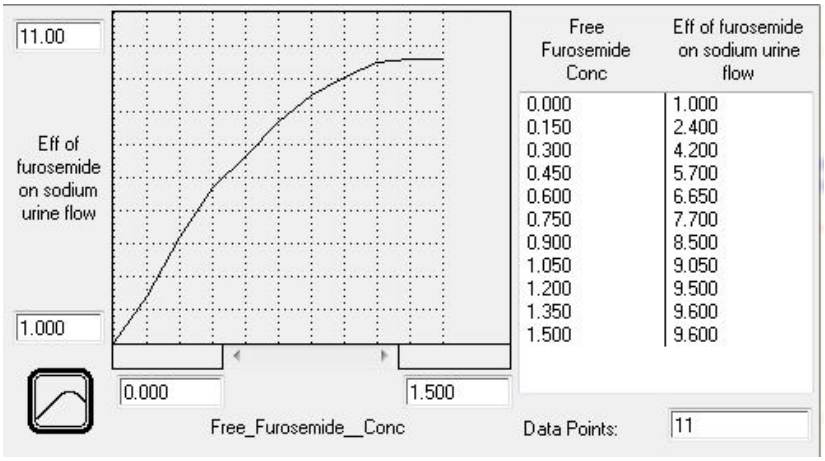


Figure 5.50. Effect of Furosemide on Urinary Sodium Flow

Ultrafiltration is another diuresis method that is used as a alternative to Furosemide for acute phase of heart failure when diuresis resistance occurs in the patients. It elevates urinary sodium flow to desired level with constant flow. Since it is a continuous and constant flow, a step function is used as seen in Equation 5.99. Revised urinary sodium flow formula is seen in Equation 5.100.

$$Ultrafiltration = STEP(25, 160) + Ultrafiltration\ cut \tag{5.99}$$

$$\begin{aligned} &Urinary\ Sodium\ Flow = \\ &MAX(MAX(0.007 * Filtered\ Sodium\ Load * Eff\ of\ ALD\ on \\ &sodium\ flow, 0.007 * Filtered\ Sodium\ Load * Eff\ of\ ALD\ on\ sodium \\ &flow * Eff\ of\ furosemide\ on\ sodium\ urine\ flow), Ultrafiltration) \end{aligned} \tag{5.100}$$

6. MODEL BEHAVIOR AND VALIDATION

Stella 9.0.3 software is used to model and simulate heart failure dynamics. Stella is a simulation and differential equation solver software. It is utilized to obtain how the system variables will behave in the time horizon of interest using both graphical and tabular outputs. In addition, how subsystems interact with each other and the response of the system in case of changes can be observed with this simulation program easily.

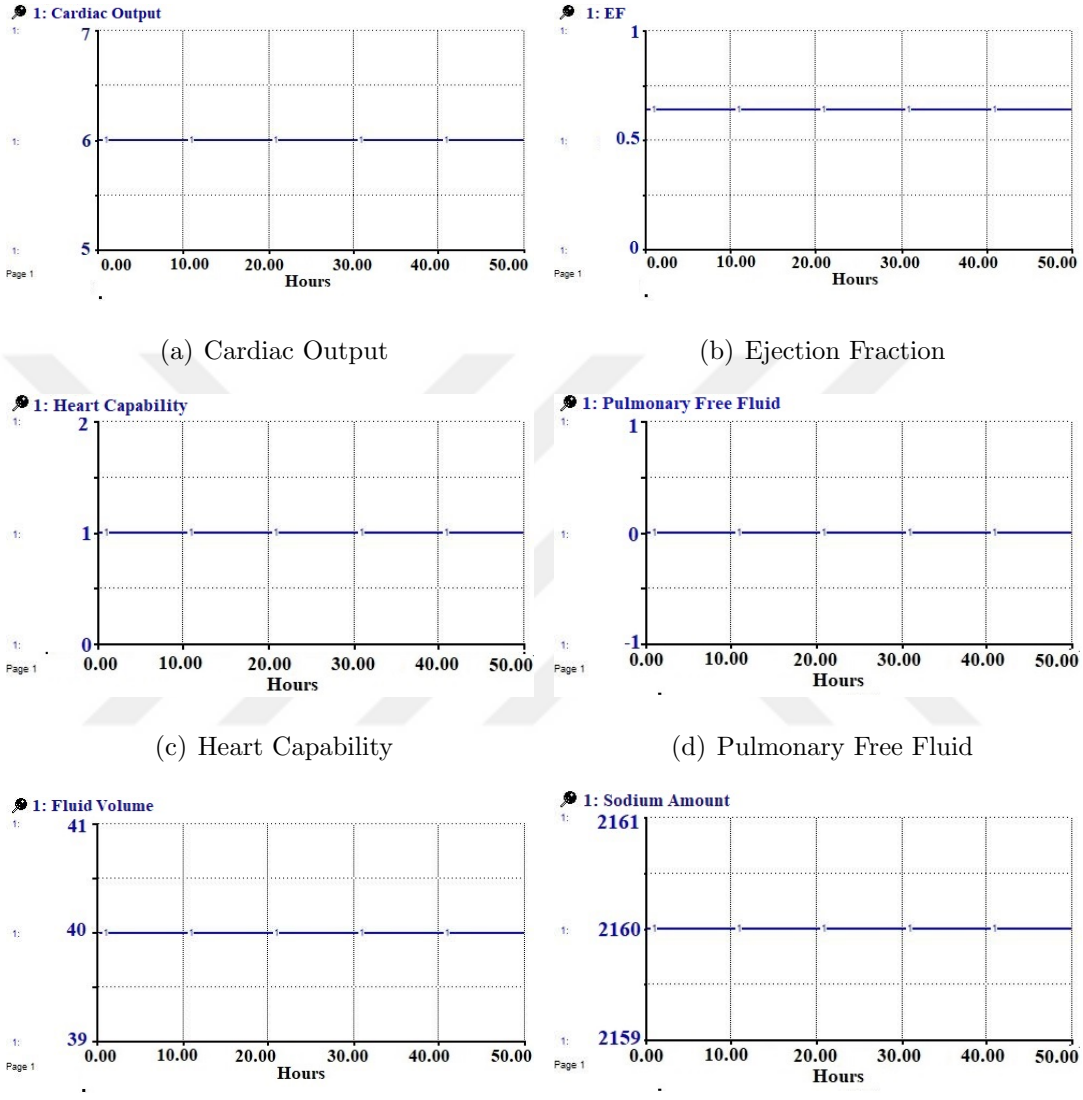
The time unit of our model is in hours and the time step is selected as 0.02 hour. The equations and graph functions used in the model are defined based on quantitative information obtained from literature. Assumptions are based on qualitative expressions of behaviors of body. Unit consistency is satisfied in all equations. Each equation is given in Appendix A. The minimum and maximum values in the graphical functions are defined according to parameter ranges in the literature.

Since certain mechanisms are known to play a role in the development of the heart failure, the conditions that trigger these mechanisms have been tested and the outputs are interpreted. In this way, it is determined whether the mechanisms respond to the effect correctly. Firstly, healthy individual that has normal parameter values is simulated and equilibrium behavior is observed. Then,higher and lower values are given to the sodium and fluid stocks as initial values and results are interpreted. Thirdly, Renin and SNS are triggered with pulse function and dynamics are interpreted. Fourthly, noncardiogenic pulmonary edema is tested with impaired kidney function. Finally, pharmacokinetic behaviors of drugs in the model are compared with results of several study in the literature in terms of drug behaviors.

6.1. Equilibrium Run

We run the model by inputting healthy individual values without adding any external factors as a first step in validation. The expected condition is that the body

stays in homeostasis. As a result, we observe that values of variables are constant and in their healthy equilibrium levels as seen in Figure 6.1.



(a) Cardiac Output (b) Ejection Fraction

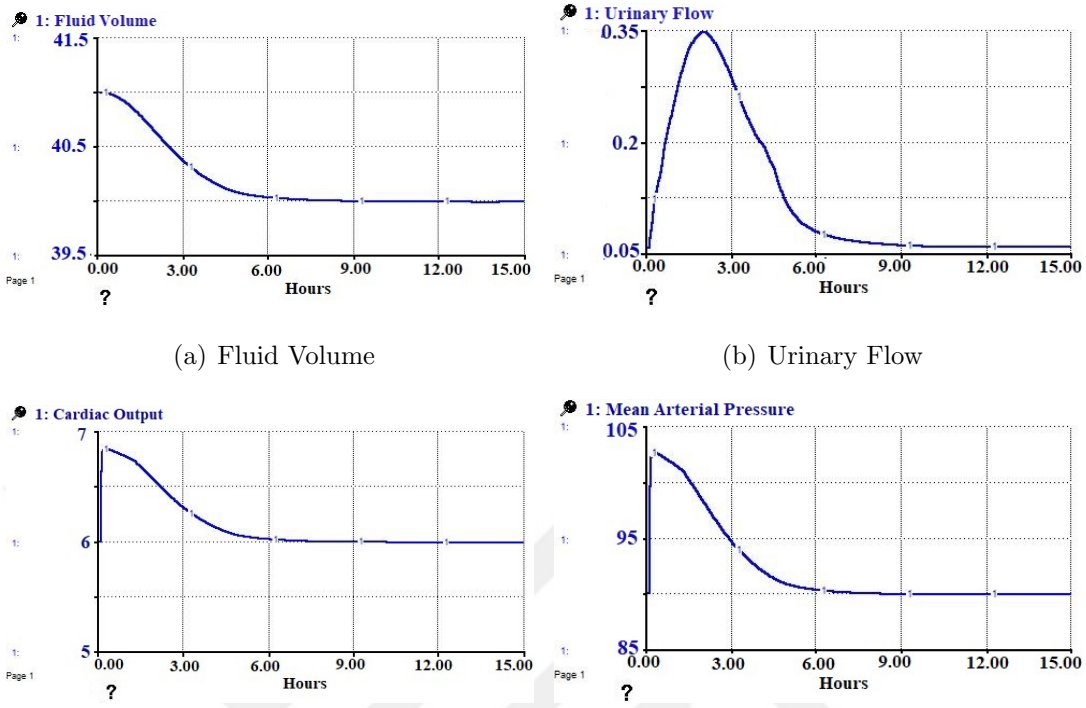
(c) Heart Capability (d) Pulmonary Free Fluid

(e) Fluid Volume (f) Sodium Amount

Figure 6.1. Equilibrium behaviors of the major variables for healthy individuals

6.2. Change in Initial Values of Fluid Volume and Sodium Amount

Initial values of fluid volume and sodium amount are set to lower and higher than normal levels separately in the base runs. When we make these runs, the expected result is that these stocks and other variables that are affected by these stocks reach the level of equilibrium after a certain period of time. Then the steady-state behaviour should be observed. The negative feedback mechanisms work on these dynamics.



(a) Fluid Volume

(b) Urinary Flow

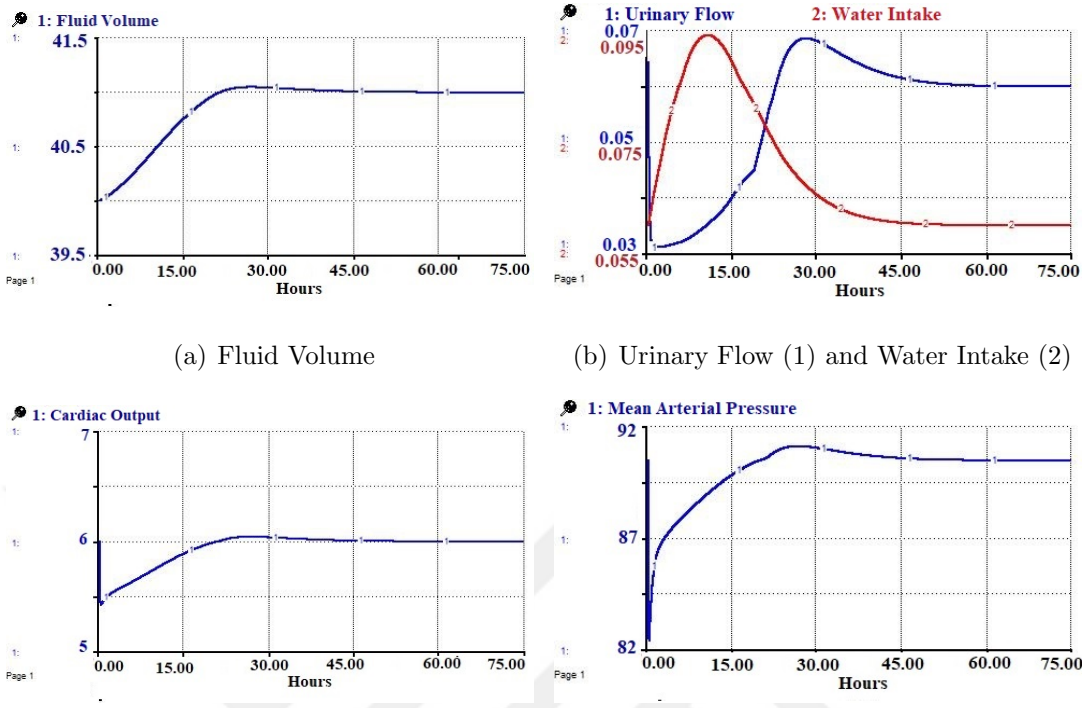
(c) Cardiac Output

(d) Mean Arterial Pressure

Figure 6.2. Dynamics of important variables when initial fluid volume is 41 liters

In this run, initial fluid volume is set to 41 liters. As seen in Figure 6.2, fluid volume stock comes back to its equilibrium level in approximately 6 hours. Compensatory mechanisms, especially ADH and ANP, are triggered by high level of fluid volume. Increasing of ANP enhances sodium urinary flow and decreasing of ADH reduces urine sodium concentration. Both of these two conditions cause urine flow to elevate. Consequently, fluid volume reaches its equilibrium of 40 liters. In addition, since blood volume is a function of fluid volume, cardiac output and mean arterial pressure are affected by fluid volume. They have the same dynamics as fluid volume as shown in Figure 6.2. The results are consistent with the study that is given by Uttamsingh *et al.* [17].

Second run of fluid volume is setting of its initial value on 39 liters. As seen in Figure 6.3, it reaches its equilibrium level in approximately 20 hours. In this situation, water intake is triggered by high level of sodium concentration. In addition, urine flow reduces half of its normal value in a short time. It increases gradually with increasing ANP level and decreasing ADH level. Consequently, fluid volume reaches 40 liters under



(a) Fluid Volume

(b) Urinary Flow (1) and Water Intake (2)

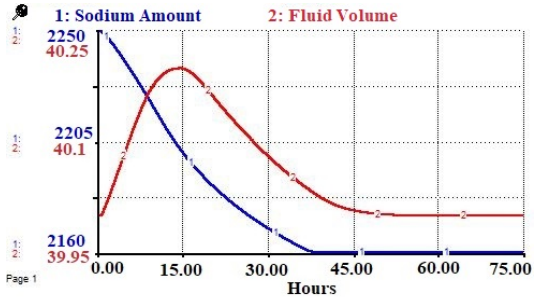
(c) Cardiac Output

(d) Mean Arterial Pressure

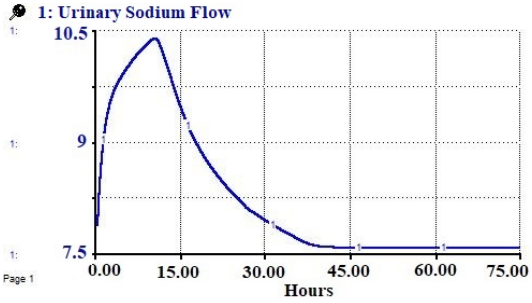
Figure 6.3. Dynamics of important variables when initial fluid volume is 39 liters

balancing feedback loops. Furthermore, cardiac output and mean arterial pressure have same dynamics with fluid volume shown in Figure 6.3. The results are consistent with literature and the medical views of experts.

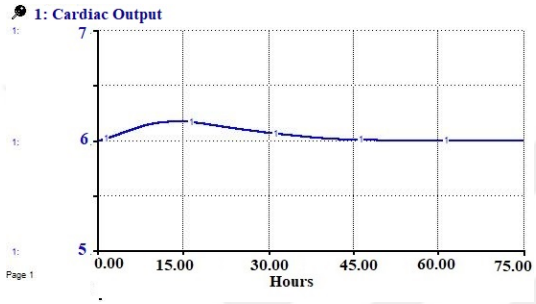
Accumulation of sodium in the body causes fluid accumulation. When the initial sodium amount is set on 2250 mEq, sodium concentration increases. High sodium concentration triggers both water intake and urine sodium flow. Urine sodium flow is regulated by Aldosterone. Under the high level of sodium concentration, Aldosterone level reduces and urine flow increases. As seen in Figure 6.4, while sodium amount is decreasing, fluid volume is elevated by water intake. Rising of fluid volume affects cardiac output and mean arterial pressure positively. After approximately 40 hours, the sodium amount is in equilibrium level, 2160 mEq, and follows its steady state condition. The results are consistent with literature and the medical views of experts.



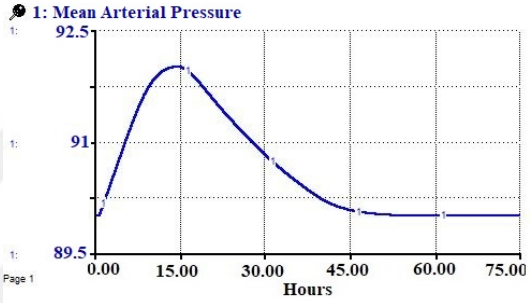
(a) Sodium Amount (1) and Fluid Volume (2)



(b) Urinary Sodium Flow



(c) Cardiac Output



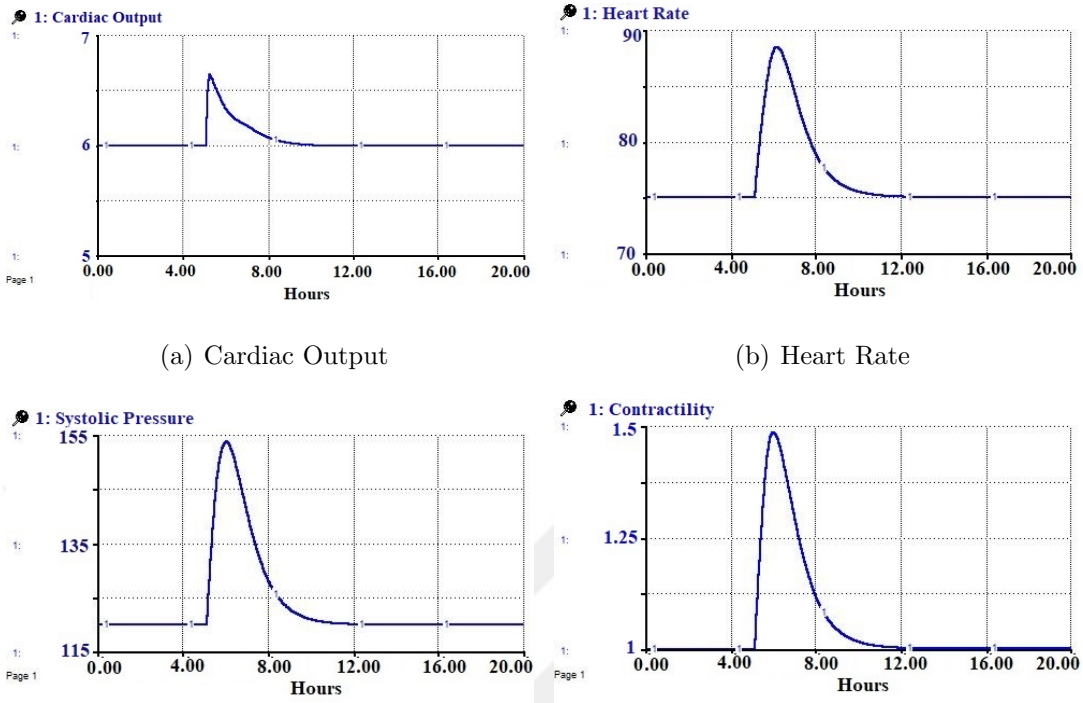
(d) Mean Arterial Pressure

Figure 6.4. Dynamics of important variables when initial sodium amount is 2250 mEq

6.3. Activation of Hormonal Compensatory Mechanisms

Regulation of hemodynamic parameters are based on compensatory mechanisms as mentioned in Chapter 5.2. Analyzing of the reaction of the body is important in case of activation of these mechanisms. SNS and Renin are selected for testing scenarios since they are dominant variables in the compensatory mechanisms.

SNS plays a role in accelerating blood circulation. When the positive pulse function is applied on implied SNS variable, rising of hemodynamic parameters is observed as seen in Figure 6.5. Most important hemodynamic parameters that are affected by it are cardiac output, systolic pressure, heart rate and contractility. SNS affects these parameters in minutes and causes the deviation from equilibrium levels. Since the effect of SNS disappears in approximately 3 hours, steady state condition of values of hemodynamic parameters can be observed. The results are consistent with literature and the medical views of experts.



(a) Cardiac Output

(b) Heart Rate

(c) Systolic Pressure

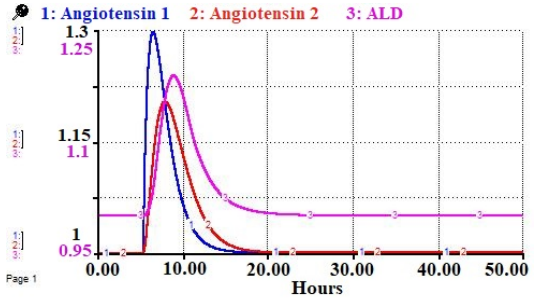
(d) Contractility

Figure 6.5. Dynamics of important variables when a positive pulse function is input on Implied SNS.

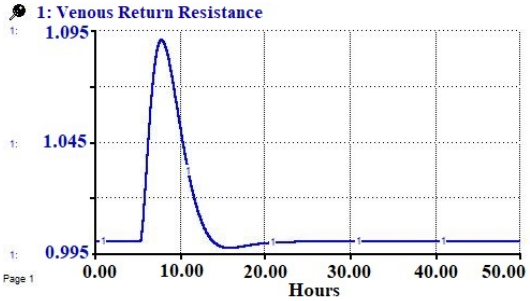
Another compensatory mechanism is Renin that is first hormone triggered in RAA (Renin-Angiotensin-Aldosterone) system. When renin level is increased with positive pulse function, level of Angiotensin I, Angiotensin II and Aldosterone are elevated in sequence as seen in Figure 6.6. In case of elevated Angiotensin II, vascular resistances, venous return and arterial, and blood pressure increase. Their secretion occurs in hours and their effects disappear in nearly 15 hours. They are in the negative feedback loop mechanisms. When the equilibrium point is reached, their values continue at this level. The results are consistent with literature and the medical views of experts.

6.4. Impaired Kidney Performance and Non-cardiogenic Pulmonary Edema

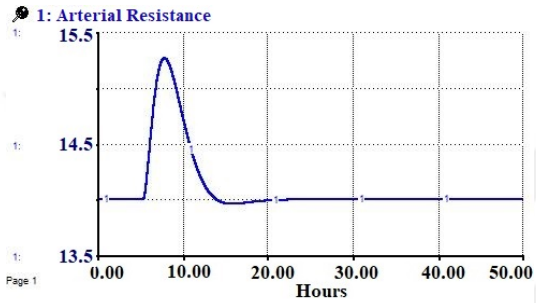
In the sodium and water sector, kidney performance is defined to present the functionality of kidney. As a result of renal failure, noncardiogenic pulmonary edema is observed without cardiogenic failure as mentioned in Chapter 5.4. This scenario is



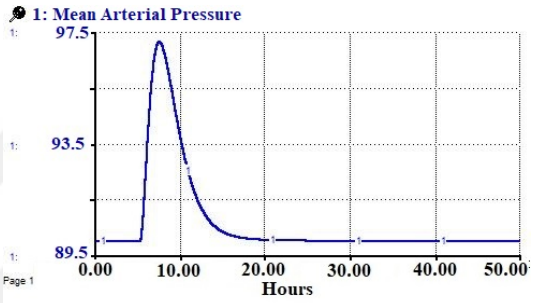
(a) ANG I (1), ANG II (2) and ALD (3)



(b) Venous Return Resistance



(c) Arterial Resistance



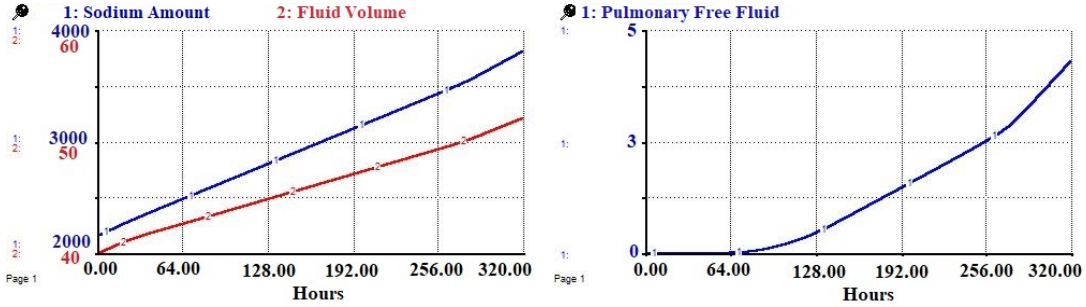
(d) Mean Arterial Pressure

Figure 6.6. Dynamics of important variables when the positive pulse function is applied on Implied Renin.

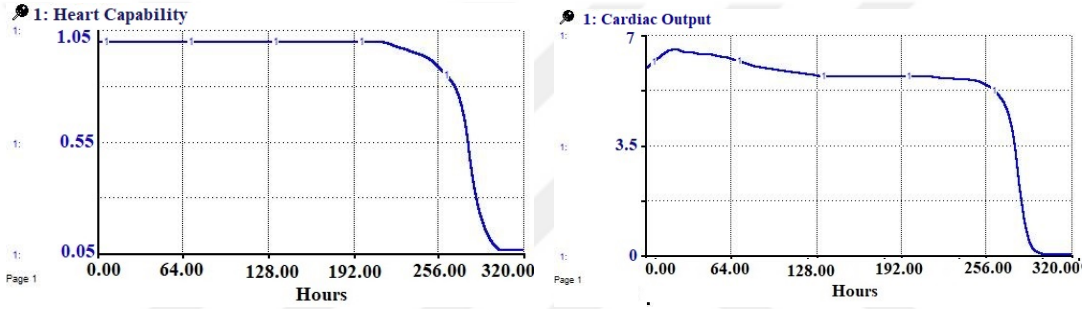
tested to validate model behaviour in terms of both effect of kidney performance in the model and effect of pulmonary fluid volume on heart performance. As shown in Figure 6.7 pulmonary edema and deterioration of heart are observed while fluid volume and sodium amount are increasing. The results are consistent with literature and the medical views of experts.

6.5. Pharmacokinetics of Drugs

Furosemide, Bisoprolol and Candesartan are defined as stocks in the model. The pharmacokinetic parameters are collected to create dynamics of drugs when they are in body. The creation of right pharmacokinetic behaviour is important to reflect effects of drugs on parameters. As seen in Figure 6.8, Figure 6.9 and Figure 6.10, the comparison of dynamics in simulation and dynamics of drug that is obtained from literature is compared. The figures show that very similar behaviours are captured by using pharmacokinetic parameters and stock-flow structure of treatment sectors.

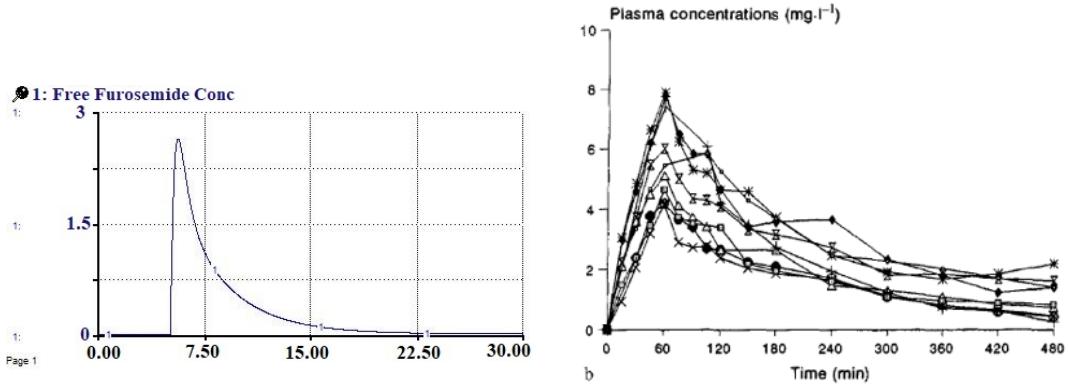


(a) Sodium Amount (1) and Fluid Volume (2) (b) Pulmonary Free Fluid



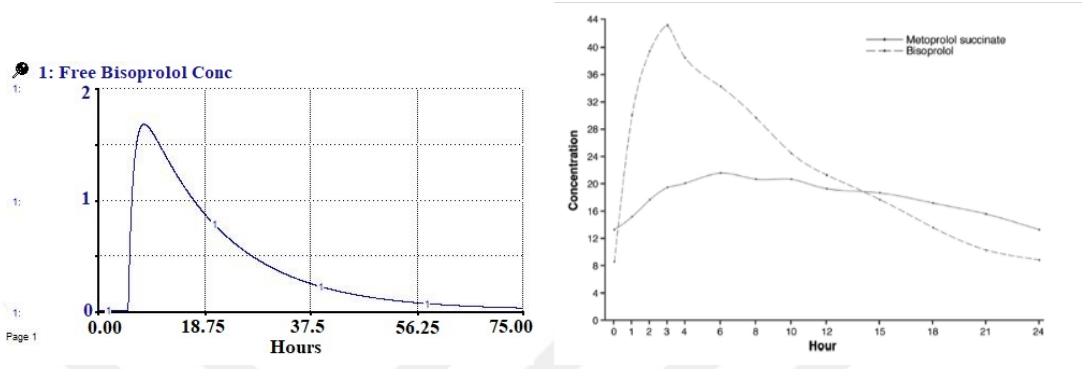
(c) Heart Capability (d) Cardiac Output

Figure 6.7. Dynamics of important variables when the kidney performance value is low (0.3).



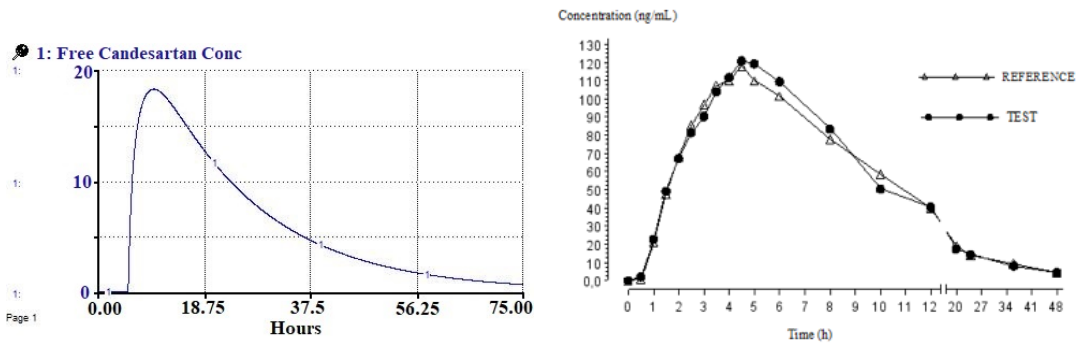
(a) Furosemide Dynamics in Simulation Run (b) Furosemide Pharmacokinetics [47]

Figure 6.8. Comparison of Furosemide dynamics of simulation run when it is used once and dynamics from literature



(a) Bisoprolol Dynamics in Simulation Run (b) Bisoprolol Pharmacokitenics [48]

Figure 6.9. Comparison of Bisoprolol dynamics of simulation run when it is used once and dynamics from literature



(a) Candesartan Dynamics in Simulation Run (b) Candesartan Pharmacokitenics [49]

Figure 6.10. Comparison of Candesartan dynamics of simulation run when it is used once and dynamics from literature

7. SCENARIO ANALYSIS

7.1. Acute Decompensated Heart Failure with Cardiogenic Pulmonary Edema

Heart of chronic heart failure patient suffers a structural change and it is dilated. This change negatively affects the functionality of the heart and causes to decrease contractility. In addition, this deterioration increases myocardial wall stress that creates a force on the heart. Vascular compliance of patients decreases because of arteriosclerosis that is elasticity loss of vessels. It causes to elevate cardiac load.

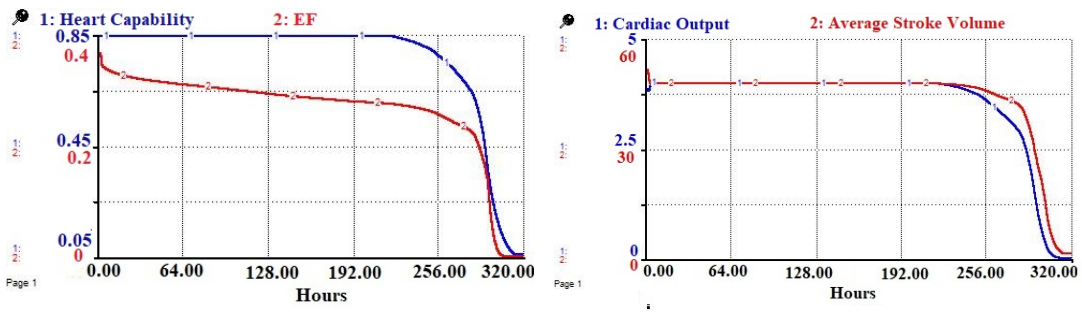
Other organs lose their performance to a certain degree as a result of inadequate blood supply from the heart to tissues. In the scope of our study, kidneys and lungs belong to this organ group. All these mentioned conditions are implemented by changes in the initial values of some parameters in the model.

When the hemodynamic parameters of a heart failure patient are selected, initial degree of heart deterioration should be determined. Doctors generally use an evaluation method that depends on the level of severity of patient's physical symptoms for early diagnosis. The New York Heart Association (NYHA) classification has been developed for this purpose. It is the most commonly used classification system to understand the daily life effects of heart failure. Doctors classify their patients in one of the four categories by assessing restrictions during physical activity. These classes are stage A, B, C and D. Stage A patients don't have any symptoms or limitations on physical activity. Stage B patients have mild symptoms of cardiovascular disease and minor limitations on physical activity. Stage C and D patients have severe disease symptoms and high limitations on daily activities. The results of studies indicate that average survival rate for stage A, B, C, and D are 97%, 96%, 75%, and 20%, respectively in 5-years [2]. C-stage patient values are put on the model as seen in Table 7.1.

Table 7.1. Impaired Parameters of C-Stage HF Patient

Variable	Value	Unit
Heart Capability	0.85	Unitless
Heart Capability Performance	0.85	Unitless
Heart Blood Volume	140	ml
Myocardial Wall Stress	1.3	Unitless
Arterial Compliance Loss	1.05	Unitless
Contractility	0.85	Unitless
Respiratory Performance	0.93	Unitless
Kidney Performance	0.6	Unitless

When we start the simulation with impaired parameters, hemodynamic parameters have exhibit collapse behaviours as seen in Figure 7.1. Compensatory mechanisms try to increase them since they are lower than the healthy individual values. Simultaneously, pulmonary edema occurs because of blood accumulation in the heart and this edema deteriorates oxygen supply. This condition decreases heart capability performance gradually. Loss of heart capability reduces contractility function and the accumulation of blood increases. These sequential physiologic actions create a vicious cycle. Consequently, hemodynamic parameters go down and patient dies.

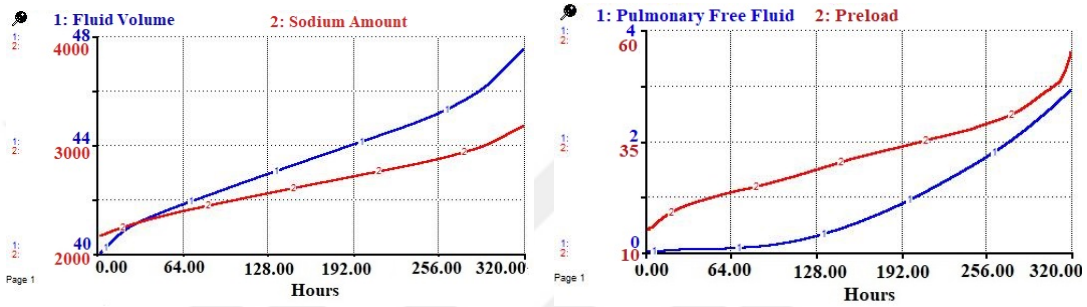


(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.1. Dynamics of Important Hemodynamic Parameters for C Stage Systolic HF Patient without treatment

In Figure 7.2, increasing of free fluid and sodium amount can be seen. When free fluid in the body increases, blood volume increases. Dilated heart has already

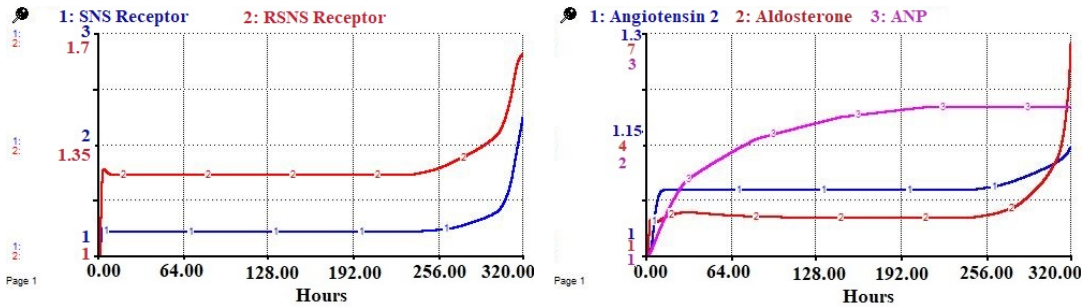
tendency to accumulate blood because of loss of contractility. Since blood volume increases, blood volume in the heart rises. Consequently, preload is elevated. In case of high preload, blood congestion in the lungs occurs since blood flow from lungs to heart decreases. Blood congestion breaks the fluid balance in the lungs and fluid passes the interstitial area. The correlated dynamics between preload and pulmonary free fluid volume can be seen in Figure 7.2.



(a) Fluid Volume (1) and Sodium Amount (2) (b) Pulmonary Free Fluid (1) and Preload (2)

Figure 7.2. Dynamics of accumulation of fluid and sodium in periphery and lungs for C Stage Systolic HF Patient without treatment

The levels of hormones that try to compensate effects of heart deterioration on hemodynamic parameters are shown in Figure 7.3. All the hormone levels are higher than their normal values. This condition causes to increase vascular resistance and blood pressure. In addition, they affect the urine sodium flow. Consequently, sodium and water accumulation is observed. In summary, the model simulates realistically the life-threatening dynamics of a hospitalized C-stage HF patient.



(a) SNS (1) and RSNS (2) (b) ANG II (1), ALD (2) and ANP (3)

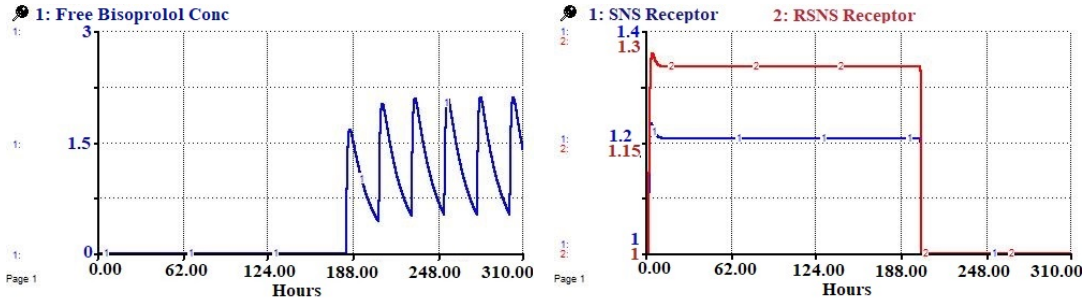
Figure 7.3. Dynamics of compensatory mechanisms for C Stage Systolic HF Patient without treatment

7.2. Treatment Strategies for ADHF with Cardionegic Pulmonary Edema

In this section, first, three drugs, given to patients with acute heart failure, are applied in the model one by one during the hospitalization. After evaluating the results, two different combinations of the three drugs are tested and the results are compared. For a scenario that may give better results, ultrafiltration method is implemented instead of diuretic for a patient that has diuretic resistance. The difference between the outcomes is examined for ultrafiltration and diuretic intake. In addition, a scenario is prepared to see the effect of deterioration ratio before hospitalization on length of hospital stay and the post-discharge values of hemodynamics. Finally, the sodium intake with different hourly doses is tested to find the ideal sodium intake strategy for HF patients.

7.2.1. Drug Intake One by One

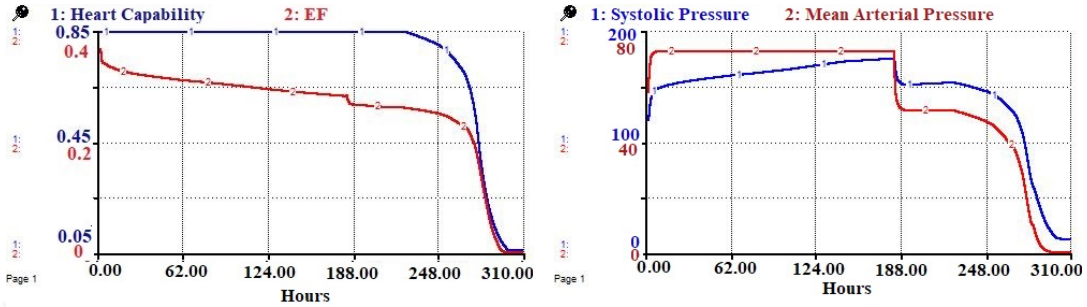
7.2.1.1. Bisoprolol Intake and Pharmacodynamics. In this scenario, only 10 mg Bisoprolol is given to the patient who has AHF with Cardiogenic Pulmonary Edema at t = 180. This drug that blocks sympathetic nerve activity is taken every 24 hours. Figure 7.4 shows the dynamics of the free Bisoprolol in the blood and its effects on SNS and RSNS. The drug shows its effect within a hours and reduces RSNS and SNS to their normal levels.



(a) Bisoprolol Pharmacokinetics (b) SNS (1) and RSNS (2)

Figure 7.4. After Bisoprolol intake each 24 hours after t=180, Bisoprolol, SNS and RSNS Dynamics

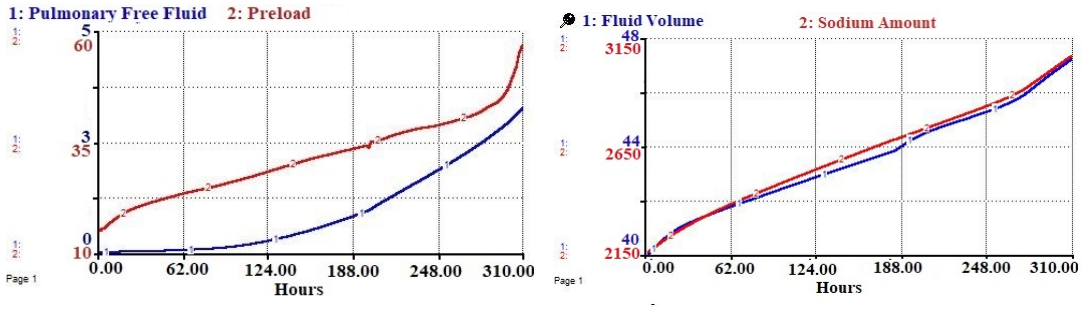
As seen in Figure 7.5, heart capability continues to decrease until reaches zero. Bisoprolol causes to keep mean arterial pressure and systolic pressure at lower levels by reducing vasoconstriction. However, this is not enough to stop deterioration.



(a) Heart Capability (1) and EF (2) (b) Systolic Pressure (1) and MAP (2)

Figure 7.5. After Bisoprolol intake each 24 hours after t=180, Hemodynamic Parameters Dynamics

The reason that Bisoprolol cannot stop the heart deterioration is that it cannot extract pulmonary edema as shown in Figure 7.6. Although overload on heart caused by excessive systolic pressure is decreased, oxygen supply of the heart is still insufficient. In addition, the total fluid and sodium accumulated in the body increases gradually. Consequently, heart loses its functionality gradually until patient eventually dead.

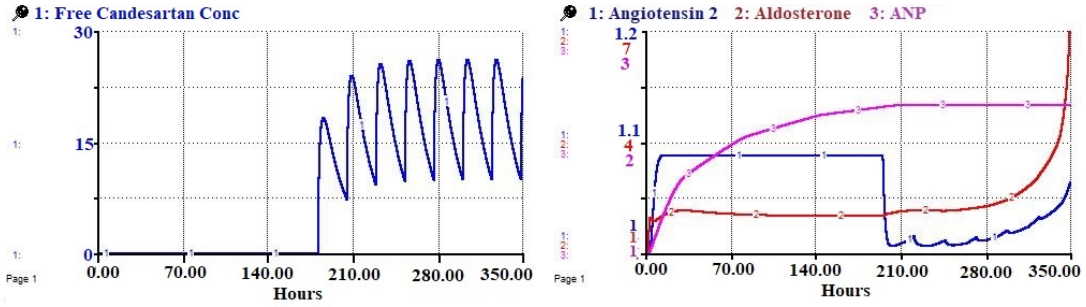


(a) PVV (1) and Preload (2) (b) Fluid Volume (1) and Sodium Amount (2)

Figure 7.6. After Bisoprolol intake each 24 hours after t=180, Sodium and Fluid Volume Dynamics

7.2.1.2. Candesartan Intake and Pharmacodynamics. In this scenario, only 16 mg Candesartan is given to the patient who has AHF with Cardiogenic Pulmonary Edema at t = 180. This drug that blocks Angiotensin II receptor is taken every 24 hours. Figure 5.49 shows the dynamics of the free Candesartan in the blood and its effects on

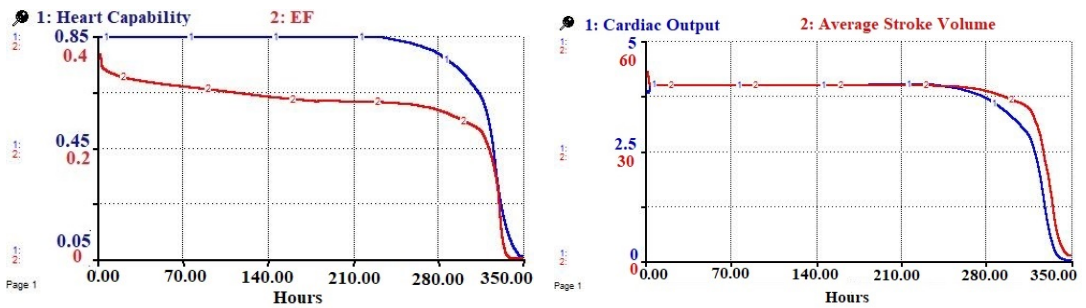
Angiotensin II. The drug shows its effect within hours and reduces Angiotensin II to their normal levels. After t = 235, the dosage is insufficient and Angiotensin II level increases gradually.



(a) Candesartan Pharmacokinetics (b) ANG II (1), ALD (2) and ANP (3)

Figure 7.7. After Candesartan intake each 24 hours after t=180, Candesartan, ANG II, ALD and ANP Dynamics

As seen in Figure 7.8, heart capability decreases until it reaches zero at t= 260. Candesartan decreases Angiotensin II receptor activity. It causes to reduce arterial and venous vasoconstriction and secretion of Aldosterone. However, Aldosterone continues at same level because of low MAP and Sodium Concentration. Consequently, only Candesartan is not sufficient to stop vicious cycle of acute heart failure and death.

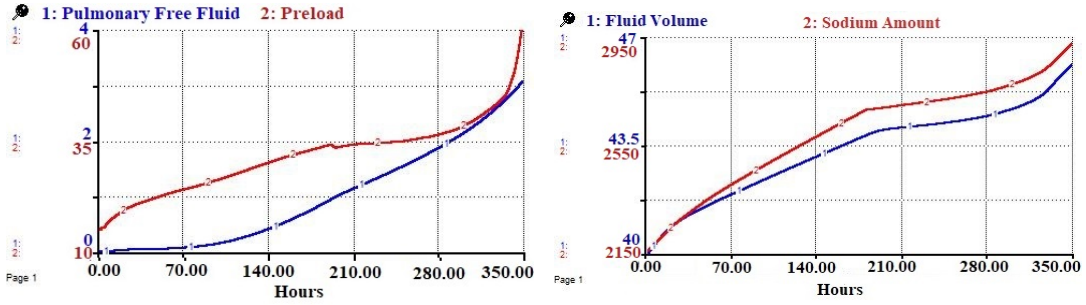


(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.8. After Candesartan intake each 24 hours after t=180, Hemodynamic Parameters Dynamics

Candesartan can not increases urinary sodium flow and accumulation of peripheral edema, sodium and pulmonary edema continues as seen in Figure 7.9. This situation causes unbalanced supply demand ratio of oxygen and consequently impairment of heart. Low heart performance affects all hemodynamic parameters and dead is

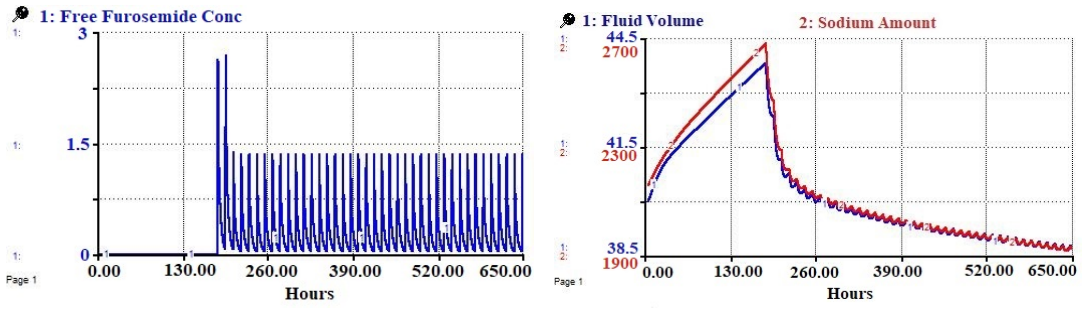
inevitable for patient.



(a) PVV (1) and Preload (2) (b) Fluid Volume (1) and Sodium Amount (2)

Figure 7.9. After Candesartan intake each 24 hours after t=180, Sodium and Fluid Volume Dynamics

7.2.1.3. Furosemide Intake and Pharmacodynamics. There are two different doses, 80 mg and 40 mg, in this scenario that includes only Furosemide taken. Firstly, 80 mg furosemide is given to the patient at t=180. This drug is taken every 12 hours. The doses is reduced to 40 mg when pulmonary edema disappears at t= 204 as seen in as seen in Figure 7.11. Furosemide decreases fluid volume and sodium amount gradually.After they reach at their normal values, their value continue to decrease below their normal values as shown in Figure 7.10. In this condition, stability can not be achieved. Furthermore, the continuous decrease of water and sodium after reaching normal levels is risky for maintaining metabolic activities.

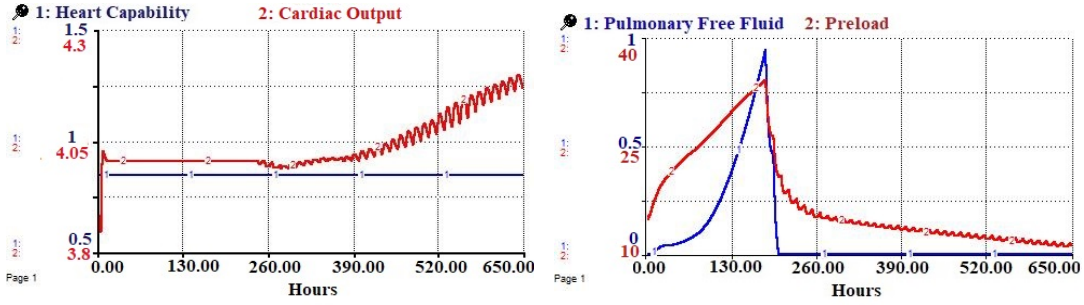


(a) Furosemide Pharmacokinetics (b) Fluid Volume (1) and Sodium Amount (2)

Figure 7.10. After Furosemide intake each 12 hours after t=180, Furosemide, Sodium and Fluid Volume Dynamics

As shown in Figure 7.11, heart capability stays its initial value due to the excretion of pulmonary edema. In addition, decrease in both preload and afterload is observed with the removal of excess water and sodium in the body. Reduction of afterload

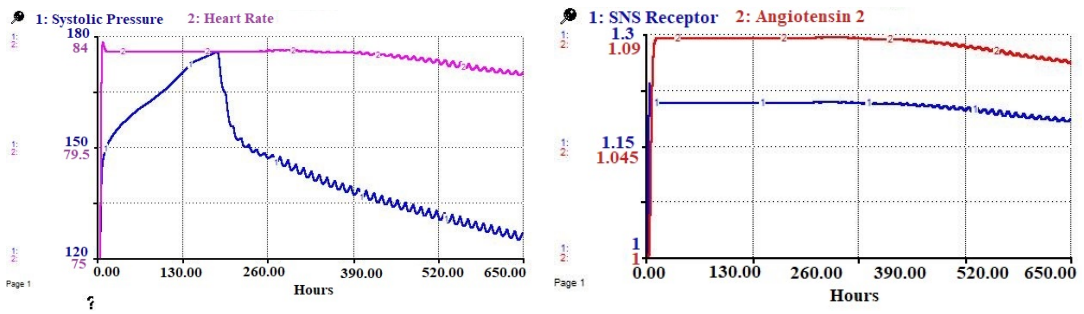
positively affects cardiac output. However, since fluid volume in the body decreases below its normal values, it is expected that cardiac output would decrease in next weeks.



(a) Heart Capability (1) and CO (2) (b) PVV (1) and Preload (2)

Figure 7.11. After Furosemide intake each 12 hours after t=180, Hemodynamic and PVV Dynamics

As shown in Figure 7.12, both sympathetic activity and Angiotensin II levels are decreased with improvement in hemodynamic parameters. However, they are still higher than their normal levels even if they decrease gradually. Consequently, values of systolic pressure and heart rate are above their normal values. This condition increases workload of heart and encourages to change structure of heart via cardiac remodeling.



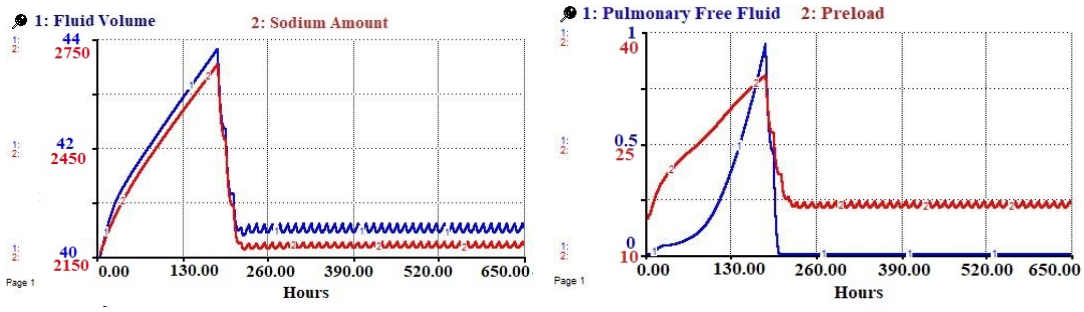
(a) Systolic Pressure (1) and HR (2) (b) SNS Receptor (1) and ANG II (2)

Figure 7.12. After Furosemide intake each 12 hours after t=180, Compensatory Mechanism Dynamics

7.2.2. Alternative Combined Treatment Strategies

After analyzing the scenarios of separate drug intakes, the scenario analysis continues with two different strategies of combination the drugs. In these scenarios, the time of admission to the hospital is t = 180, where oxygen saturation is between 90% and 85%, because most of heart failure patients go to the hospital when their oxygen saturation level is in this range. The doses and drug combinations are determined according to guidelines given by Yancy *et al.* [2] and Ponikowski *et al.* [8].

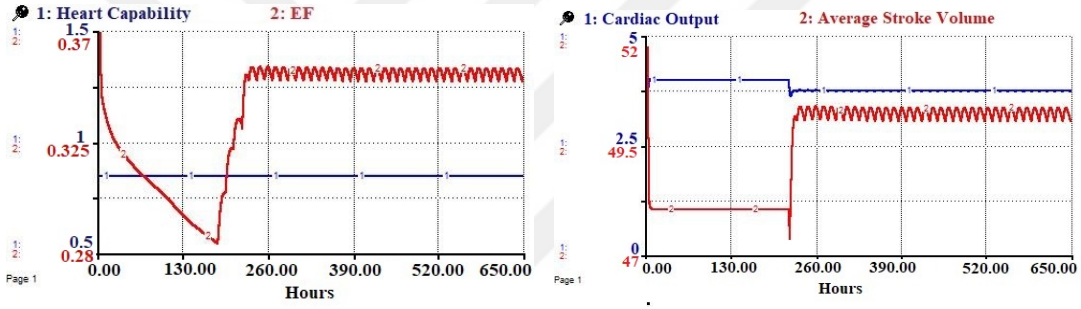
7.2.2.1. Treatment Strategy 1: Bisoprolol & Candesartan Intake After Stabilization.
Diuretic is the first step of the treatment for patients who have acute heart failure with pulmonary edema. It is started with high dose diuretics and this treatment is terminated when the values of patient reach the desired levels. The treatment continues with drugs that are used as chronic heart failure medication. Treatment strategy 1 is designed according to this procedure. This procedure is conventional treatment method that is based on acute heart failure guidelines. Firstly, 80 mg Furosemide is given to the patient each 12 hours until pulmonary edema is completely excreted. As shown in Figure 7.13, pulmonary edema decrease to zero at t = 202. In addition, fluid volume and sodium amount is reached slightly above their normal levels. Treatment is continued with 40 mg Furosemide every 12 hours, 10 mg Bisoprolol and 16 mg Candesartan every 24 hours.



(a) Fluid Volume (1) and Sodium Amount (2) (b) PVV (1) and Preload (2)

Figure 7.13. Dynamics of Fluid and Sodium Amount when Treatment Strategy 1 is applied

After t = 216, the combination of three drugs provide stabilization which includes fluctuation of patient's values in an acceptable range. This fluctuation occurs because of variation of the value of free Furosemide in the blood. The body's water and sodium levels are stable at the desired levels at t=230. As seen in Figure 7.14, the patient's hemodynamic values are elevated by the elimination of pulmonary edema. Average stroke volume is 48 ml/beat at the beginning of hospitalization and it reaches 50.2 ml/beat after treatment. Ejection fraction is 0.284 at the beginning of hospitalization and it reaches 0.353 after treatment. Cardiac output is 3.77 liter/min after treatment. The heart capability does not decrease because of hospitalization on time and successful treatment strategy.

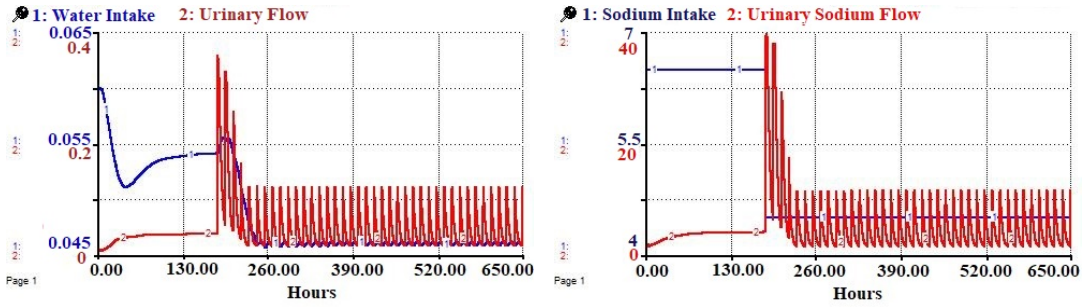


(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.14. Dynamics of Hemodynamic Parameters when Treatment Strategy 1 is applied

Furthermore, the hourly sodium intake after hospitalization is reduced from 6.5 mEq to 4.5 mEq, which is continued after discharge. According to results of this scenario, the average hourly water intake is found 0.046 liter/hour to ensure that the patient's values remain stable as shown in Figure 7.15. Based on these results, it is claimed that it is necessary to restrict the patient in terms of both sodium and water intake during hospitalization and after discharge.

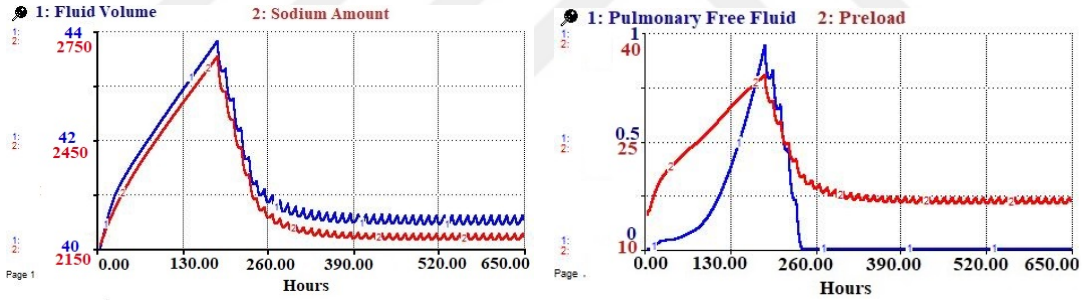
7.2.2.2. Treatment Strategy 2: Bisoprolol & Candesartan Intake Before Stabilization. As an alternative to Treatment Strategy 1, a scenario that includes Bisoprolol and Candesartan intake since the beginning of the hospitalization is designed. In this scenario, 10 mg Bisoprolol and 16 mg Candesartan are given every 24 hours together with 80 mg



(a) Water Intake (1) and Urine Flow (2) (b) Sodium Intake (1) and Urine Na Flow (2)

Figure 7.15. Dynamics of Fluid and Sodium Flows when Treatment Strategy 1 is applied

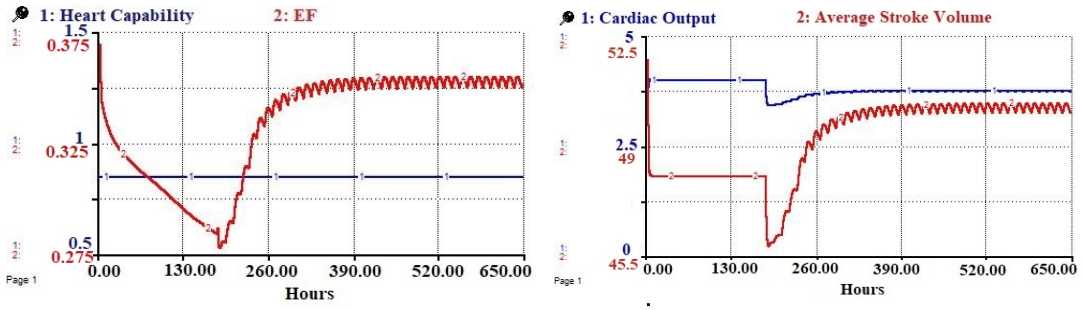
Furosemide given every 12 hours. According to the results, the patient's pulmonary edema disappears at t = 240 as seen in Figure 7.16. At that moment, the amount of Furosemide is reduced from 80 mg to 40 mg and continued every 12 hours. Stabilization of the patient's fluid volume and sodium amount is achieved after t = 390.



(a) Fluid Volume (1) and Sodium Amount (2) (b) PVV (1) and Preload (2)

Figure 7.16. Dynamics of Fluid and Sodium Amount when Treatment Strategy 2 is applied

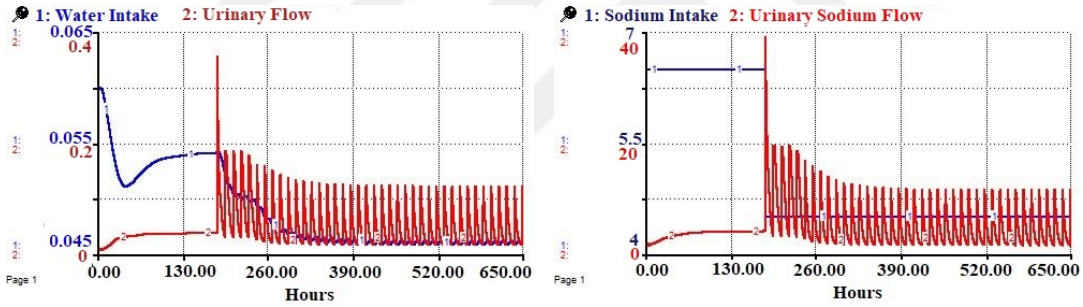
The dynamics of the heart capability and hemodynamic parameters are similar to the results of Treatment Strategy 1. Ejection fraction and average stroke volume increase since pulmonary edema decreases as shown in Figure 7.17. Average stroke volume is 48 ml/beat at the beginning of hospitalization and it reaches 50.2 ml/beat after treatment. Ejection fraction is 0.284 at the beginning of hospitalization and it reaches 0.353 after treatment. Cardiac output is 3.77 liter/min after treatment. These parameters are stable after stabilization of fluid volume and sodium. In conclusion, heart deterioration is not observed.



(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.17. Dynamics of Hemodynamic Parameters when Treatment Strategy 2 is applied

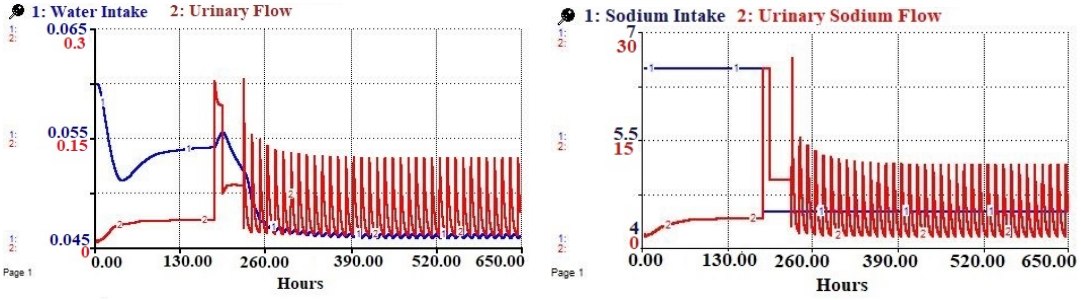
Sodium intake is restricted after hospitalization and decreased to 4.5 mEq. According to simulation results, the hourly water intake that provides stabilization is again 0.046 liter/hour as in the previous strategy as seen in Figure 7.18.



(a) Water Intake (1) and Urine Flow (2) (b) Sodium Intake (1) and Urine Na Flow (2)

Figure 7.18. Dynamics of Fluid and Sodium Flows when Treatment Strategy 2 is applied

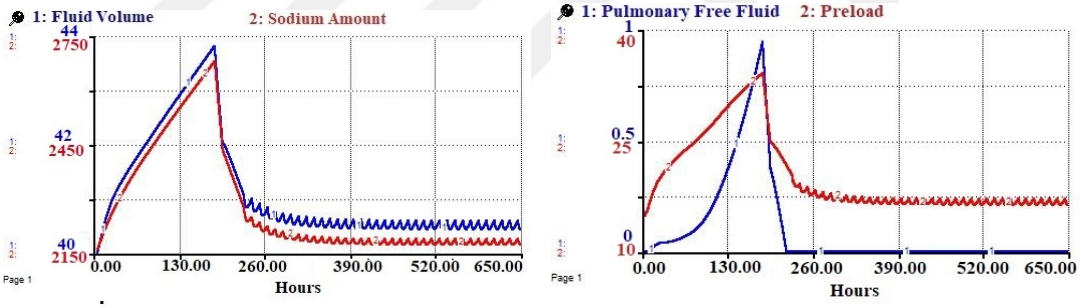
7.2.2.3. Ultrafiltration Usage in case of Diuretic Resistance. Diuretic resistance may occur patients who use diuretics for a long time. In this case, rapid excretion of pulmonary edema may not be realized by high-dose diuretics. Ultrafiltration method is applied as a solution for acute period based on ultrafltration strategy given by Costanzo *et al.* [50]. According to these guidelines, average 25 mEq sodium and 0.2 liter water are excreted between t=180 and t=192. Then, the dose is reduced to average 9.4 mEq sodium and 0.085 liter water at t=192 and this process continues between t=192 and t=225 as seen in Figure 7.19.



(a) Water Intake (1) and Urine Flow (2) (b) Sodium Intake (1) and Urine Na Flow (2)

Figure 7.19. Dynamics of Fluid and Sodium Flows when Ultrafiltration is applied

According to the results, pulmonary edema is eliminated at t = 220 as seen in Figure 7.20. After the elimination of pulmonary edema, conventional treatment is started. 40 mg Furosemide is taken every 12 hours, 10 mg Bisoprolol and 16 mg Candesartan are taken every 24 hours. After t=390, fluid volume and sodium amount is stabilized.



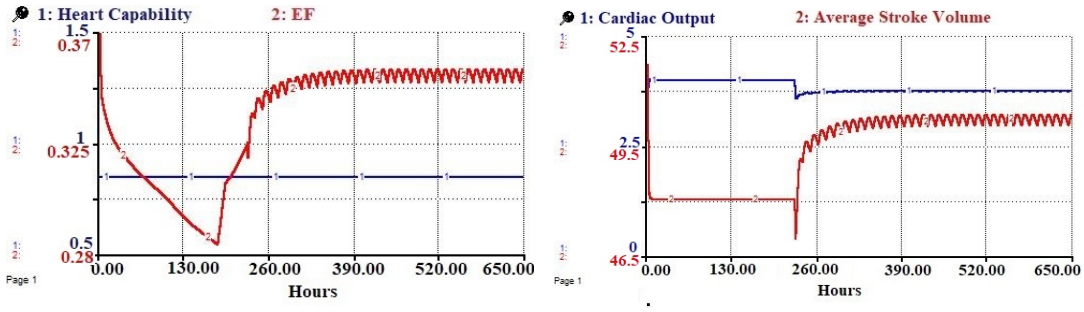
(a) Fluid Volume (1) and Sodium Amount (2) (b) PVV (1) and Preload (2)

Figure 7.20. Dynamics of Fluid and Sodium Amount when Ultrafiltration is applied

The results are same as usage of high-dose diuretics in terms of the values of hemodynamic parameters and stability of heart deterioration as seen in Figure 7.21. Therefore, it can be said that ultrafiltration is an effective method for patients with diuretic resistance. In addition, water and sodium restrictions are applied. The amount of sodium taken per hour is 4.5 mEq and the amount of water is 0.046 liter/hour.

7.2.3. Late Hospitilization Scenario

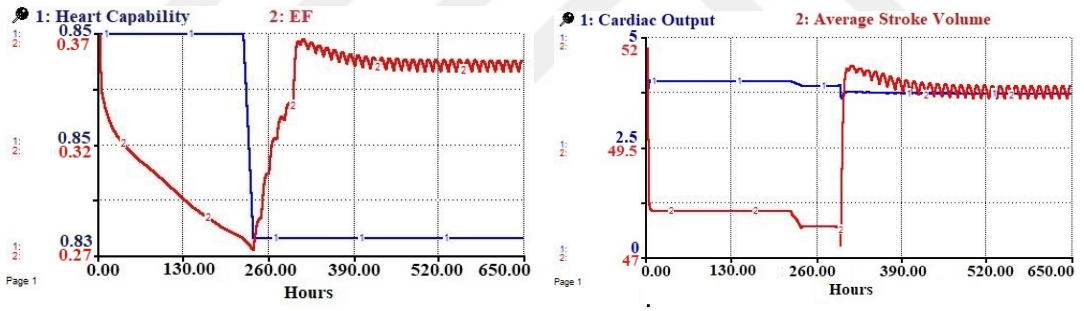
In the previous scenarios, the time of going to the hospital is t = 180 that is determined based on O_2 saturation. In this scenario, it is assumed that patient does



(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.21. Dynamics of Hemodynamic Parameters when Ultrafiltration is applied

not keep track of his/her O_2 saturation and comes to the hospital at t = 235 when his/her respiration is impaired. When he/she arrives the hospital, O_2 saturation is 0.75 and, heart capability reduces from 0.85 to 0.83 as shown in Figure 7.22. Treatment strategy 1 is applied to patient. However, since heart deterioration is permanent, CO is 3.72 liter/minute after acute treatment.

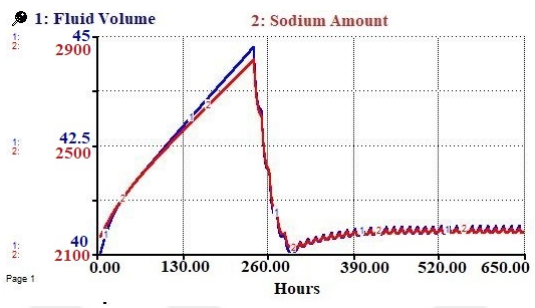


(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

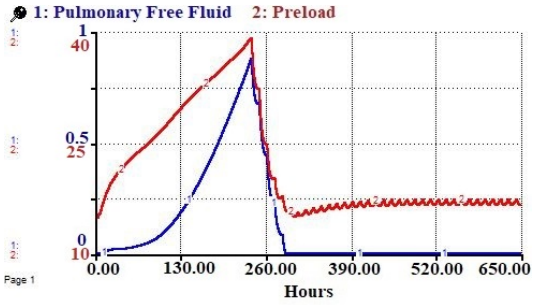
Figure 7.22. Dynamics of Hemodynamic Parameters when Treatment Strategy 1 is applied with late hospitalization at t=235

At t = 230, 80 mg Furosemide intake is started and five doses are taken until t=290. This dose is reduced to 40 mg at this moment. In addition, 16 mg Candesartan and 10 mg Bisoprolol are added that are given every 24 hours. As seen in Figure 7.23, pulmonary edema disappears at t = 270. In addition, water and sodium amounts reach to steady state position at t = 410.

Sodium restriction is applied and hourly sodium intake is determined as 4.5 mEq. According to simulation results, the hourly water intake that provides the stabilization is again 0.046 liter/hour as in the previous scenarios as seen in Figure 7.24.

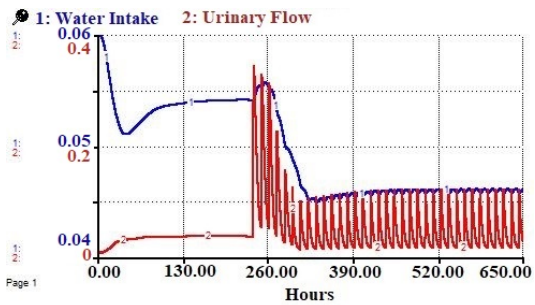


(a) Fluid Volume (1) and Sodium Amount (2)

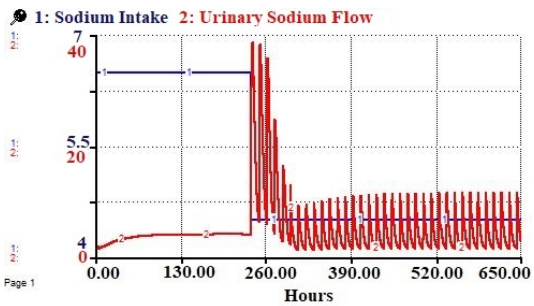


(b) PVV (1) and Preload (2)

Figure 7.23. Dynamics of Fluid and Sodium Amount when Treatment Strategy 1 is applied with late hospitalization at t=235



(a) Water Intake (1) and Urine Flow (2)



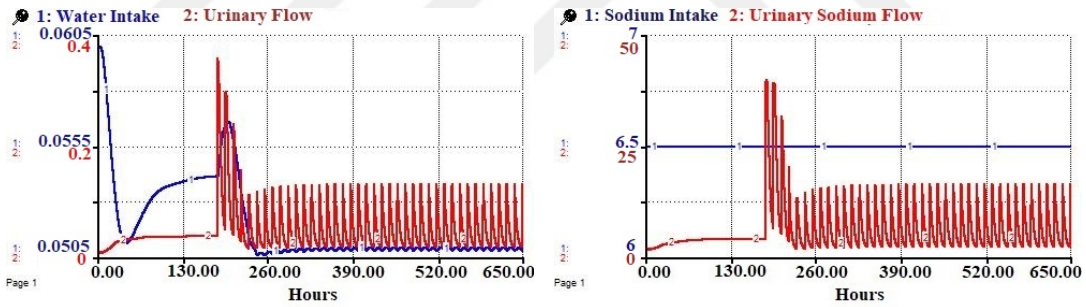
(b) Sodium Intake (1) and Urine Na Flow (2)

Figure 7.24. Dynamics of Fluid and Sodium Flows when Treatment Strategy 1 is applied with late hospitalization at t=235

7.2.4. Different Amount of Sodium Intake Scenarios

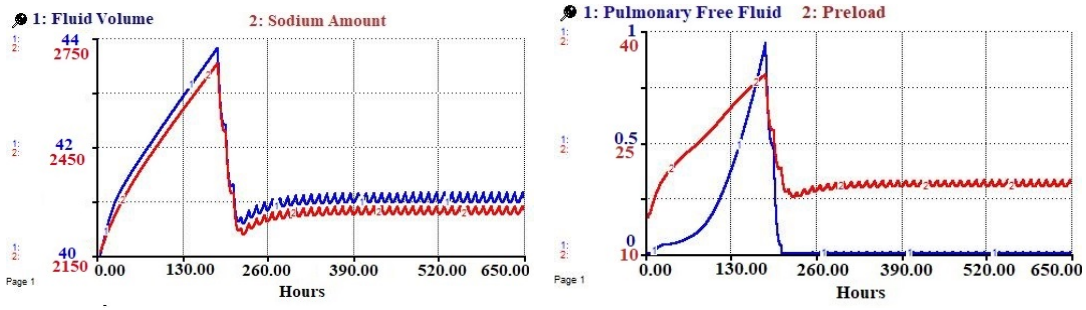
In the alternative treatment scenarios, the patient takes 6.5 mEq sodium per hour before hospitalization. After hospitalization and discharge, hourly sodium intake is reduced to 4.5 mEq. In this section, different scenarios are created in order to analyze the effect of hourly sodium intake during hospitalization and after discharge on stability of hemodynamic parameters. Defined sodium amounts are based on study that is given by Parrinello *et al.* [51]. Strategy of drug intake is same with Treatment Strategy 1.

7.2.4.1. Hourly 6.5 mEq Sodium Intake after Hospitalization. This first scenario is that the patient always takes 6.5 mEq sodium per hour as seen in Figure 7.25. According to simulation results, hourly average water intake is 0.0508 liter/hour.



(a) Water Intake (1) and Urine Flow (2) (b) Sodium Intake (1) and Urine Na Flow (2)

Figure 7.25. Dynamics of Fluid and Sodium Flows when hourly sodium intake is 6.5 mEq after hospitalization

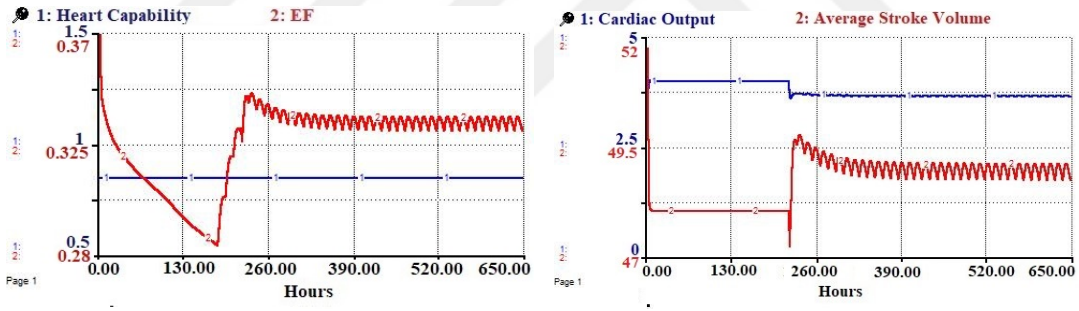


(a) Fluid Volume (1) and Sodium Amount (2) (b) PVV (1) and Preload (2)

Figure 7.26. Dynamics of Fluid and Sodium Amount when hourly sodium intake is 6.5 mEq after hospitalization

Pulmonary edema extraction is completed at t = 207 and it is very similar with 4.5 mEq sodium intake scenario. However, the time of stabilization for fluid and sodium is longer. At t = 335, fluid volume and sodium stabilize as seen in Figure 7.26. In addition, total fluid volume is 40.98 liter and sodium amount is 2275 mEq. High sodium amount explains more fluid accumulation in the body. These values are higher than the scenario with 4.5 mEq sodium intake. In that scenario, the sodium and fluid levels were 40.48 liters and 2178 mEq respectively.

Hourly 6.5 mEq sodium intake does not affect heart capability negatively as shown in Figure 7.27. The heart preserves its performance without damage. However, the average stroke volume and ejection fraction are slightly lower than the scenario of 4.5 mEq sodium intake. Their values are 49 ml/beat and 0.335 respectively since the blood volume increases systolic pressure that creates load on heart.

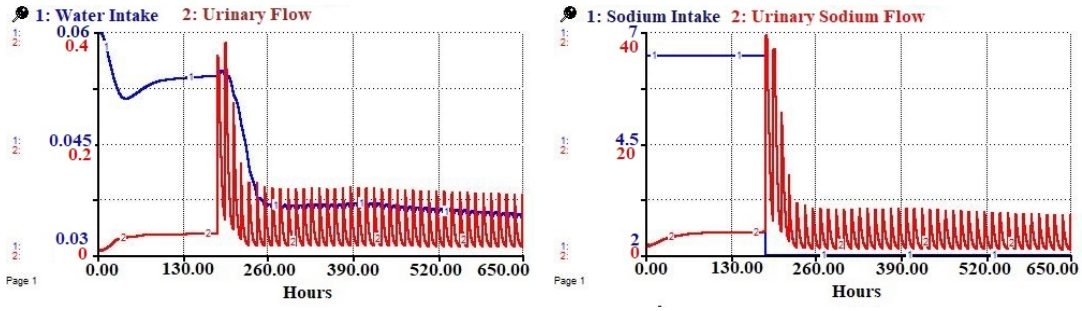


(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.27. Dynamics of Hemodynamic Parameters when hourly sodium intake is 6.5 mEq after hospitalization

7.2.4.2. Hourly 2 mEq Sodium Intake after Hospitalization. The second scenario is that the patient takes 2 mEq sodium per hour after hospitalization as seen in Figure 7.28. According to simulation results, hourly average water intake is 0.036 liter/hour but it has a tendency to fall and it can be observed in weeks.

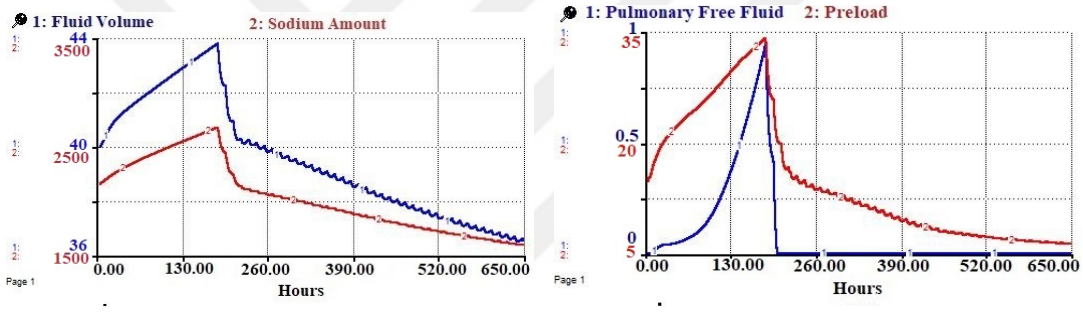
Low sodium intake with usage of diuretic lead to a gradual decrease in sodium and fluid volume as seen in Figure 7.29. At t = 200, after the pulmonary edema is completely removed, stabilization of free fluid and sodium values can not be achieved. After t = 208, the sodium amount falls to below its normal value and after t = 240,



(a) Water Intake (1) and Urine Flow (2) (b) Sodium Intake (1) and Urine Na Flow (2)

Figure 7.28. Dynamics of Fluid and Sodium Flows when hourly sodium intake is 2 mEq after hospitalization

fluid volume also falls below its normal value.

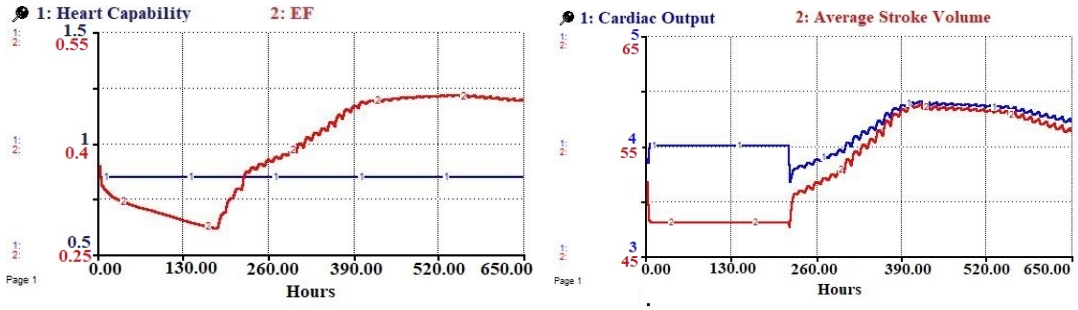


(a) Fluid Volume (1) and Sodium Amount (2) (b) PVV (1) and Preload (2)

Figure 7.29. Dynamics of Fluid and Sodium Amount when hourly sodium intake is 2 mEq after hospitalization

As expected, low level of sodium intake does not adversely affect heart capability as seen in Figure 7.30. Decrease in fluid volume causes to decrease systolic pressure. Consequently, this situation increases hemodynamic parameters up to t = 530 since systolic pressure reduces. Average stroke volume reaches 58.7 ml/beat. However, after this point, the decrease in blood volume begins to be effective. Since blood volume decreases, hemodynamic parameters diminish gradually. Although, low sodium intake is beneficial for hemodynamic parameters in a short time, it affects negatively in long term.

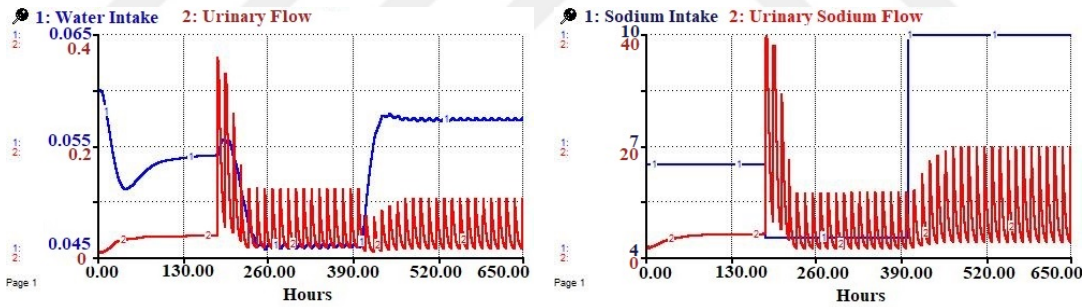
7.2.4.3. Hourly 10 mEq Sodium Intake after Discharge. Last scenario is 10 mEq sodium intake after discharge. It is a common situation that heart failure patients ignore the importance of sodium restriction and take excessive sodium. In Figure 7.31, values



(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.30. Dynamics of Hemodynamic Parameters when hourly sodium intake is 2 mEq after hospitalization

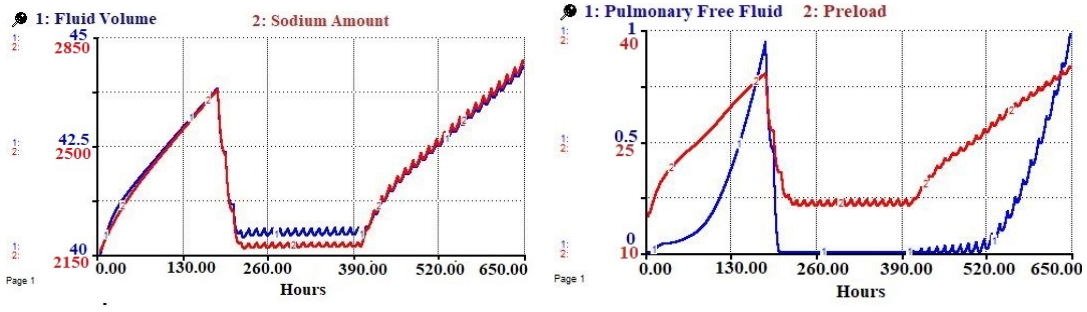
of hourly sodium and water intake can be seen. When sodium intake increases after t=400, water intake also increases. Although hourly water intake is 0.046 liter/hour during hospitalization, it reaches 0.0574 liter/hour after discharge. In addition, when sodium amount increases, filtered sodium amount increases. This condition elevates urine sodium flow.



(a) Water Intake (1) and Urine Flow (2) (b) Sodium Intake (1) and Urine Na Flow (2)

Figure 7.31. Dynamics of Fluid and Sodium Flows when hourly sodium intake is 10 mEq after discharge

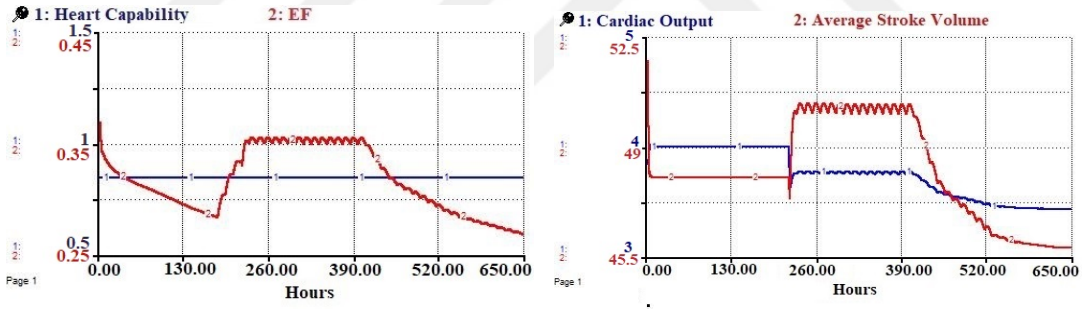
When the patient starts to take excessive sodium after t = 400, high amount of sodium accumulates in the body. Due to the water retention function of sodium, fluid volume also increases as shown in Figure 7.32. Consequently, blood volume elevates and it affects preload positively. This condition causes pulmonary edema after t=500. Heart capability does not affect accumulation of water yet as shown in Figure 7.33. However, pulmonary edema starts to increase after t=500 and will cause deterioration of heart. On the other hand, since blood volume increases, systolic pressure increases. Elevation of systolic pressure decreases hemodynamic parameters. Cardiac output reduces from



(a) Fluid Volume (1) and Sodium Amount (2) (b) PVV (1) and Preload (2)

Figure 7.32. Dynamics of Fluid and Sodium Amount when hourly sodium intake is 10 mEq after discharge

3.77 liter/minute to 3.43 liter/minute. Average stroke volume decrease from 50.36 ml/beat to 45.8 ml/beat. Ejection fraction reduces from 0.355 liter/minute to 0.27. All these conditions reflect that excessive sodium amount deteriorates functionality of heart.



(a) Heart Capability (1) and EF (2) (b) CO (1) and Avg Stroke Volume (2)

Figure 7.33. Dynamics of Hemodynamic Parameters when hourly sodium intake is 10 mEq after discharge

8. CONCLUSION

In this study, the dynamics of acute heart failure syndrome with pulmonary edema is modelled with system dynamics methodology. The model consists of four subsystems that play role in the progress of syndrome. These are hormonal compensatory mechanisms, hemodynamic variables, water and sodium and cardio-respiratory sectors. Interactions between these sectors are based on balancing feedback mechanisms for healthy person. When homeostasis is disturbed, subsystems affect each other to restore equilibrium conditions. However, when the heart failure disease occurs, reinforcement feedback loops become involved. These reinforcing loops create vicious cycles of eventual heart failure. In order to stop the progress of syndrome and to stabilize patient condition in minimum time, the treatment sector is included in the model as the fifth sector. It contains three drugs that are commonly used in acute heart failure treatment.

In model validation phase, initial values of sodium and water are changed in order to test the response of the model. Changing these values triggers compensating mechanisms and the values reach their steady state in realistic time intervals. Next, the activation of compensating mechanisms due to external factors are tested and their effects on the model are examined. In addition, the deterioration of the kidney performance is tested to examine the dynamics of non-cardiogenic pulmonary edema. Finally, the dynamics of the drugs in the body after intake are compared with the data in the literature and the results are found to be consistent.

In the scenario analysis section, firstly the values of C-stage systolic heart failure patient are given to the model as input. The results show the gradual deterioration of the heart and hemodynamic parameters. Then, three drugs are added to the model and one by one intake scenarios are applied. After the reliability of effects of three drugs are demonstrated, two different combined drug treatments are simulated. The aim is to find the treatment strategy that minimizes pulmonary edema excretion time and stabilization time of patient parameters. In the first treatment strategy, only diuretics

are given when patient arrives at the hospital. When pulmonary edema disappears within 22 hours, the diuretic dose is reduced and angiotensin II receptor blocker and betablocker are added to the treatment. According to the results, stabilization is achieved within 50 hours. As a second scenario, three drugs are simultaneously given together when patient is admitted. This strategy is less efficient than the first strategy due to pulmonary edema being completely excreted in 60 hours and stabilization being reached in 210 hours.

Treatment by ultrafiltration of a patient with diuretic resistance is also analyzed. The ultrafiltration method is applied with the recommended doses. Although it is slower than high dose diuretics, it is successful for improving the symptoms and stopping the deterioration. In another scenario, late hospitalization is simulated, and it is shown that this would increase the risk of death and prolong the hospital stay. For this reason, it is important for chronic heart failure patients to monitor their O_2 saturation levels. When the O_2 saturation level falls below 90%, they should be hospitalized immediately in order to discharge without permanent damage and shorten hospitalization period.

In each scenario described above, the hourly sodium intake is determined 4.5 mEq/hour as an input after hospitalization and discharge. The hourly water intake is calculated by the model as 0.046 liter/hour. The effect of higher or lower sodium intake is investigated as another scenario analysis. Firstly, the amount of sodium intake per hour is increased to 6.5 mEq/hour. Consequently, stabilization time increases in the hospital. In addition, water and sodium accumulation elevates in the body after hospital discharge. When we decrease sodium intake to 2 mEq/hour, water and sodium values persistently decrease and stabilization cannot be achieved. Finally, hourly sodium intake is tested as 10 mEq / hour after discharge. There is excessive water and sodium accumulation in the body and it affects hemodynamic parameters negatively and causes pulmonary edema. Therefore, it is emphasized that the adjustment of water and sodium intake is important as well as using the medicines.

In future studies, more comprehensive and detailed models can be developed to simulate other types of heart failure and multiple organ failure. Different treatment methods, different drugs and several doses of these drugs that affect different mechanisms can be tested. In the model, graphical functions and equations that are report in the literature are used. Model validation can be performed more rigorously by using real data and data-sets that include the values of patient's parameters during hospitalization. Furthermore, working with multidisciplinary groups and joint studies with doctors and physiologists would be the most effective way to increase the awareness and dissemination of such studies.

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APPENDIX A: MODEL EQUATIONS

**********Cardio-Respiratory Sector**********

Contractility(t) = Contractility(t - dt) + (Contractility Adj Rate) * dt

INIT Contractility = 1

UNITS: Unitless

INFLOWS:

Contractility Adj Rate = (Implied Contractility-Contractility)/Contactility Time Delay

UNITS: 1/hr

Heart Capability(t) = Heart Capability(t - dt) + (HC Adj) * dt

INIT Heart Capability = 1

UNITS: Unitless

INFLOWS:

HC Adj = IF ((Implied HC-Heart Capability)/Time Delay HC)>-0.005 THEN 0 ELSE (Implied HC-Heart Capability)/Time Delay HC

UNITS: 1/hr

Pulmonary Free Fluid(t) = Pulmonary Free Fluid(t - dt) + (Pulmonary Fluid Accumulation Rate - PFF Diuresis) * dt

INIT Pulmonary Free Fluid = 0

UNITS: l

INFLOWS:

Pulmonary Fluid Accumulation Rate = Implied Pulmonary Fluid Rate

UNITS: l/hr

OUTFLOWS:

PFF Diuresis = Urinary Flow/3

UNITS: l/hr

Arterial Compliance Loss = 1

UNITS: Unitless

Contactility Time Delay = 1

UNITS: hr

Heart Capability Performance = 1

UNITS: Unitless

Implied Contractility = Heart Capability*Eff of SNS on Conctractiliy

UNITS: Unitless

Implied HC = Supplied Demand Ratio Coeffcient*Heart Capability Performance

UNITS: Unitless

Implied O2 Supply = MIN(O2 Saturation Coeffiicient by Edema,Respiratory Performance)

UNITS: Unitless

O2 Demand = Eff of HR on O2 Demand*Arterial Compliance Loss

UNITS: Unitless

Respiratory Performance = 1

UNITS: Unitless

Supply Demand Ratio = MIN(Implied O2 Supply/O2 Demand,1)

UNITS: Unitless

Time Delay HC = 10

UNITS: hr

Eff of HR on O2 Demand = GRAPH(Heart Rate)

(0.00, 0.00), (15.0, 0.06), (30.0, 0.15), (45.0, 0.33), (60.0, 0.67), (75.0, 1.00), (90.0, 1.14), (105, 1.26), (120, 1.29), (135, 1.32), (150, 1.32)

UNITS: Unitless

Eff of SNS on Conctractiliy = GRAPH(SNS Receptor)

(0.00, 0.9), (0.2, 0.92), (0.4, 0.94), (0.6, 0.96), (0.8, 0.98), (1.00, 1.00), (1.20, 1.20), (1.40, 1.40), (1.60, 1.60), (1.80, 1.80), (2.00, 2.00)

UNITS: Unitless

Implied Pulmonary Fluid Rate = GRAPH(Left Atrial Pressure)

(10.0, 0.00), (15.0, 0.00), (20.0, 0.0017), (25.0, 0.009), (30.0, 0.0167), (35.0, 0.0245), (40.0, 0.033), (45.0, 0.0417))

UNITS: l/hr

Left Atrial Pressure = GRAPH(Preload)

(0.00, 10.4), (3.50, 12.3), (7.00, 15.0), (10.5, 17.4), (14.0, 20.0), (17.5, 23.0), (21.0, 25.6), (24.5, 28.0), (28.0, 31.3), (31.5, 33.7), (35.0, 36.1), (38.5, 37.3), (42.0, 38.8),

(45.5, 39.1), (49.0, 39.7), (52.5, 39.5), (56.0, 39.7), (59.5, 39.5), (63.0, 39.5), (66.5, 39.5), (70.0, 40.0)

UNITS: mmHg

O2 Saturation Coeffiicient by Edema = GRAPH(Pulmonary Free Fluid)

(0.00, 1.00), (0.3, 0.955), (0.6, 0.925), (0.9, 0.875), (1.20, 0.84), (1.50, 0.79), (1.80, 0.73), (2.10, 0.64), (2.40, 0.54), (2.70, 0.365), (3.00, 0.00)

UNITS: Unitless

Supplied Demand Ratio Coeffcient = GRAPH(Supply Demand Ratio) (0.00, 0.01), (0.1, 0.22), (0.2, 0.4), (0.3, 0.555), (0.4, 0.685), (0.5, 0.785), (0.6, 0.885), (0.7, 0.945), (0.8, 0.98), (0.9, 0.985), (1, 1.00)

UNITS: Unitless

**********Hemodynamic Sector**********

Heart Blood Volume(t) = Heart Blood Volume(t - dt) + (HBV Adj Flow) * dt

INIT Heart Blood Volume = 125

UNITS: ml

INFLOWS:

HBV Adj Flow = (Implied HBV-Heart Blood Volume)/TD

UNITS: ml/hr

Heart Rate(t) = Heart Rate(t - dt) + (Hr Adj) * dt

INIT Heart Rate = 75

UNITS: beat/min

INFLOWS:

Hr Adj = (Implied HR-Heart Rate)/HR TD

UNITS: beat/hr-min

Systolic Pressure(t) = Systolic Pressure(t - dt) + (SP Adj) * dt

INIT Systolic Pressure = 120

UNITS: mmHg

INFLOWS:

SP Adj = (Implied Systolic Pressure-Systolic Pressure)/SP Adj Time

UNITS: mmhg/hr

Afterload = Myocardial Wall Stress*Systolic Pressure

UNITS: mmHg

Arterial Resistance = Normal AR*Eff of ANG on Vascular Resistance*Eff of SNS on AR

UNITS: mmhg-min/l

Average Venous Return = MAX(0.1,(Peripheral Venous Pressure-Right Atrial Pressure)/(Venous Return Resistance))

UNITS: l/min

Average Stroke Volume = Eff of afterload on SV*Eff of Preload on SV*Contractility* Eff of HR on SV by filling time*Heart Capability

UNITS: ml/beat

Cardiac Output = Average Stroke Volume*Heart Rate*unit converter ml to l

UNITS: l/min

EF = Average Stroke Volume/Heart Blood Volume

UNITS: Unitless

Eff of ANG on Vascular Resistance = MAX(0.8, ((((Angiotensin 2)*0.15+0.85)-1)*3+1))

UNITS: Unitless

Eff of SNS on AR = SNS Receptor*0.85+0.15

UNITS: Unitless

Eff of SNS on VR = (SNS Receptor*0.85+0.15-1)*0.25+1

UNITS: Unitless

HR TD = 1

UNITS: hr

Implied HBV = Normal HBV*Ratio of incomig blood to outgoing blood

UNITS: ml

Implied HR = normal HR*Eff of SNS on HR*Heart Capability/Heart Capability Performance

UNITS: beat/min

Implied Systolic Pressure = Arterial Compliance Loss*Systolic Pressure by BV* Eff of AR on SP*Heart Capability/Heart Capability Performance

UNITS: mmHg

Mean Arterial Pressure = Cardiac Output*Total Peripheral Resistance

UNITS: mmHg

Myocardial Wall Stress = 1

UNITS: Unitless

Normal AR = 14

UNITS: mmhg-min/l

Normal HBV = 125

UNITS: ml

normal HR = 75

UNITS: beat/min

Normal VR = 1

UNITS: mmhg-min/l

Peripheral Venous Pressure = PVP by BV*Eff of VRR on PVP

UNITS: mmHg

Ratio of incomig blood to outgoing blood = (Average Venous Return*unit converter l to ml)/(Average Stroke Volume*Heart Rate)

UNITS: Unitless

Right Atrial Pressure = Preload/3.5

UNITS: mmHg

SP Adj Time = 1

UNITS: hr

TD = 1

UNITS: hr

Total Peripheral Resistance = Venous Return Resistance+ Arterial Resistance

UNITS: mmhg-min/l

unit converter l to ml = 1000

UNITS: ml/l

unit converter ml to l = 0.001

UNITS: l/ml

Venous Return Resistance = Normal VR*Eff of SNS on VR*Eff of ANG on Vascular Resistance

UNITS: mmhg-min/l

Blood Volume = GRAPH(Extracellular FV)

(9.00, 4.50), (11.0, 4.55), (13.0, 4.72), (15.0, 5.00), (17.0, 5.46), (19.0, 6.03), (21.0, 6.50), (23.0, 6.77), (25.0, 6.90), (27.0, 6.96), (29.0, 6.98)

UNITS: l

Eff of afterload on SV = GRAPH(Afterload)

(80.0, 1.50), (90.0, 1.28), (100, 1.15), (110, 1.03), (120, 1.00), (130, 0.966), (140, 0.93), (150, 0.882), (160, 0.84), (170, 0.792), (180, 0.732), (190, 0.684), (200, 0.66)

UNITS: Unitless

Eff of HR on SV by filling time = GRAPH(Heart Rate/75)

(0.4, 1.40), (0.5, 1.38), (0.6, 1.36), (0.7, 1.32), (0.8, 1.27), (0.9, 1.17), (1, 1.00), (1.10, 0.885), (1.20, 0.75), (1.30, 0.66), (1.40, 0.565), (1.50, 0.485), (1.60, 0.46), (1.70, 0.445), (1.80, 0.43), (1.90, 0.41), (2.00, 0.41)

UNITS: Unitless

Eff of Preload on SV = GRAPH(Preload)

(3.00, 14.0), (4.00, 33.5), (5.00, 55.5), (6.00, 67.5), (7.00, 80.0), (8.00, 85.5), (9.00, 91.0), (10.0, 93.0), (11.0, 93.0), (12.0, 94.5), (13.0, 94.5), (14.0, 95.5), (15.0, 95.5), (16.0, 96.0), (17.0, 96.0), (18.0, 96.0), (19.0, 96.0), (20.0, 96.0)

UNITS: ml

Eff of VRR on PVP = GRAPH(Venous Return Resistance)

(0.00, 0.00), (0.2, 0.2), (0.4, 0.4), (0.6, 0.6), (0.8, 0.8), (1.00, 1.00), (1.20, 1.20), (1.40, 1.40), (1.60, 1.60), (1.80, 1.80), (2.00, 2.00)

UNITS: Unitless

Eff of AR on SP = GRAPH(Arterial Resistance)

(0.00, 0.00), (2.80, 0.2), (5.60, 0.4), (8.40, 0.6), (11.2, 0.8), (14.0, 1.00), (16.8, 1.15), (19.6, 1.30), (22.4, 1.40), (25.2, 1.50), (28.0, 1.60)

UNITS: Unitless

Eff of SNS on HR = GRAPH(SNS Receptor)

(0.00, 0.451), (0.1, 0.493), (0.2, 0.54), (0.3, 0.591), (0.4, 0.646), (0.5, 0.703), (0.6, 0.762), (0.7, 0.822), (0.8, 0.882), (0.9, 0.942), (1, 1.00), (1.10, 1.06), (1.20, 1.11), (1.30, 1.16), (1.40, 1.20), (1.50, 1.24), (1.60, 1.27), (1.70, 1.29), (1.80, 1.31), (1.90, 1.32), (2.00, 1.32)

UNITS: Unitless

Preload = GRAPH(Heart Blood Volume)

(50.0, 0.6), (65.0, 0.6), (80.0, 0.6), (95.0, 1.20), (110, 2.00), (125, 7.00), (140, 15.3), (155, 24.6), (170, 34.8), (185, 48.0), (200, 60.0)

UNITS: mmHg

PVP by BV = GRAPH(Blood Volume)

(4.40, 4.00), (4.60, 5.62), (4.80, 6.88), (5.00, 8.00), (5.20, 9.34), (5.40, 10.6), (5.60, 11.7), (5.80, 12.9), (6.00, 14.0), (6.20, 15.2), (6.40, 15.9)

UNITS: mmHg

Systolic Pressure by BV = GRAPH(Blood Volume)

(4.40, 70.0), (4.60, 86.0), (4.80, 103), (5.00, 120), (5.20, 125), (5.40, 131), (5.60, 135), (5.80, 141), (6.00, 144), (6.20, 146), (6.40, 147)

UNITS: mmHg

**********Hormonal Compensatory Mechanisms Sector**********

ADH(t) = ADH(t - dt) + (ADH Adj) * dt

INIT ADH = 1

UNITS: Unitless

INFLOWS:

ADH Adj = (Implied ADH-ADH)/ADH TD

UNITS: 1/hr

ALD(t) = ALD(t - dt) + (Aldosterone Adj) * dt

INIT ALD = 1

UNITS: Unitless

INFLOWS:

Aldosterone Adj = (Implied Aldosterone-ALD)/ALD TD

UNITS: 1/hr

Angiotensin 1(t) = Angiotensin 1(t - dt) + (ANG1 Adj) * dt

INIT Angiotensin 1 = 1

UNITS: Unitless

INFLOWS:

ANG1 Adj = (Renin-Angiotensin 1)/ANG 1 TD

UNITS: 1/hr

Angiotensin 2(t) = Angiotensin 2(t - dt) + (ANG 2 Adj) * dt

INIT Angiotensin 2 = 1

UNITS: Unitless

INFLOWS:

ANG 2 Adj = (ANG1-Angiotensin 2)/ANG 2 TD

UNITS: 1/hr

ANP(t) = ANP(t - dt) + (ANP Adj) * dt

INIT ANP = 1

UNITS: Unitless

INFLOWS:

ANP Adj = (Implied ANP-ANP)/ANP TD

UNITS: 1/hr

Renin(t) = Renin(t - dt) + (Renin Adj) * dt

INIT Renin = 1

UNITS: Unitless

INFLOWS:

Renin Adj = (Implied Renin-Renin)/Renin TD

UNITS: 1/hr

RSNS(t) = RSNS(t - dt) + (RSNS Adj) * dt

INIT RSNS = 1

UNITS: Unitless

INFLOWS:

RSNS Adj = (Implied RSNS-RSNS Receptor)/RSNS TD

UNITS: 1/hr

SNS(t) = SNS(t - dt) + (SNS Adj) * dt

INIT SNS = 1

UNITS: Unitless

INFLOWS:

SNS Adj = (Implied SNS-SNS Receptor)/SNS TD

UNITS: 1/hr

ADH TD = 1

UNITS: hr

Aldosterone = MIN(ALD,7)

UNITS: Unitless

ALD TD = 1

UNITS: hr

ANG1 = Angiotensin 1*Eff of Candesarton on ANG2 Receptor

UNITS: Unitless

ANG 1 TD = 1.5

UNITS: hr ANG 2 TD = 1.5

UNITS: hr

ANP TD = 1

UNITS: hr

Implied Aldosterone =

Eff of Sodium Conc on Aldosteone*Eff of MAP on ALD*Eff of ANG2 on ALD*normal ALD

UNITS: Unitless

Implied ANP = normal ANP*EFF of EFV on ANP

UNITS: Unitless

Implied Renin = normal Renin*Eff of RSNS on Renin

UNITS: Unitless

Implied RSNS = normal RSNS*Eff of Map on RSNS*Eff of Bisoprolol of RSNS

UNITS: Unitless

Implied SNS = normal SNS*Eff of Map on SNS*Eff of Bisoprolol of SNS

UNITS: Unitless

Renin TD = 1

UNITS: hr

normal ADH = 1

UNITS: Unitless

normal ALD = 1

UNITS: Unitless

normal ANP = 1

UNITS: Unitless

normal Renin = 1

UNITS: Unitless

normal RSNS = 1

UNITS: Unitless

normal SNS = 1

UNITS: Unitless

RSNS TD = 1

UNITS: hr

RSNS Receptor = MAX(RSNS,1)

UNITS: Unitless

SNS TD = 1

UNITS: hr

SNS Receptor = MAX(SNS,1)

UNITS: Unitless

Eff of ANG2 on ALD = GRAPH(Angiotensin 2*20)

(2.00, 0.448), (4.00, 0.48), (6.00, 0.512), (8.00, 0.56), (10.0, 0.624), (12.0, 0.672), (14.0, 0.776), (16.0, 0.864), (18.0, 0.92), (20.0, 1.00), (22.0, 1.07), (24.0, 1.22), (26.0, 1.38), (28.0, 1.54), (30.0, 1.67), (32.0, 1.79), (34.0, 1.86), (36.0, 1.92), (38.0, 1.94), (40.0, 1.94)

UNITS: Unitless

Eff of MAP on ALD = GRAPH(Mean Arterial Pressure)

(15.0, 24.2), (20.0, 19.6), (25.0, 15.8), (30.0, 12.8), (35.0, 10.4), (40.0, 7.84), (45.0, 6.16), (50.0, 4.43), (55.0, 3.58), (60.0, 2.89), (65.0, 2.33), (70.0, 1.89), (75.0, 1.52), (80.0, 1.24), (85.0, 1.00), (90.0, 1.00), (95.0, 1.00), (100, 1.00), (105, 1.00), (110, 1.00)

UNITS: Unitless

Eff of Map on RSNS = GRAPH(Mean Arterial Pressure)

(10.0, 1.63), (20.0, 1.63), (30.0, 1.60), (40.0, 1.53), (50.0, 1.46), (60.0, 1.38), (70.0, 1.30), (80.0, 1.15), (90.0, 1.00), (100, 0.855), (110, 0.744), (120, 0.692), (130, 0.64), (140, 0.608), (150, 0.582), (160, 0.563), (170, 0.563), (180, 0.563), (190, 0.563)

UNITS: Unitless

Eff of Map on SNS = GRAPH(Mean Arterial Pressure)

(10.0, 2.42), (20.0, 2.16), (30.0, 1.93), (40.0, 1.73), (50.0, 1.55), (60.0, 1.39), (70.0, 1.25), (80.0, 1.12), (90.0, 1.00), (100, 0.895), (110, 0.802), (120, 0.718), (130, 0.644), (140, 0.576), (150, 0.516), (160, 0.463), (170, 0.414), (180, 0.371), (190, 0.322), (200, 0.298)

UNITS: Unitless

Eff of RSNS on Renin = GRAPH(RSNS Receptor)

(0.00, 0.69), (0.2, 0.74), (0.4, 0.8), (0.6, 0.863), (0.8, 0.93), (1, 1.00), (1.20, 1.07), (1.40, 1.14), (1.60, 1.21), (1.80, 1.28), (2.00, 1.34), (2.20, 1.40), (2.40, 1.45), (2.60, 1.50), (2.80, 1.54)

UNITS: Unitless

Eff of Sodium Conc on Aldosteone = GRAPH(Sodium Conc)

(96.0, 6.79), (98.0, 6.44), (100, 6.10), (102, 5.77), (104, 5.46), (106, 5.15), (108, 4.86), (110, 4.58), (112, 4.31), (114, 4.05), (116, 3.80), (118, 3.55), (120, 3.32), (122, 3.09), (124, 2.87), (126, 2.65), (128, 2.45), (130, 2.25), (132, 2.05), (134, 1.86), (136, 1.68), (138, 1.50), (140, 1.33), (142, 1.16), (144, 1.00), (146, 0.922), (148, 0.922), (150, 0.922)

UNITS: Unitless

Implied ADH = GRAPH(Sodium Conc)

(100, 0.12), (104, 0.12), (108, 0.12), (112, 0.12), (116, 0.15), (120, 0.21), (124, 0.27), (128, 0.36), (132, 0.45), (136, 0.555), (140, 0.72), (144, 1.00), (148, 1.73), (152, 2.01), (156, 2.13), (160, 2.19)

UNITS: Unitless

**********Sodium and Water Sector**********

Fluid Volume(t) = Fluid Volume(t - dt) + (Water Intake - Urinary Flow) * dt

INIT Fluid Volume = 40

UNITS: l

INFLOWS:

Water Intake = normal water intake*Eff of Sodium Conc on Water Intake

UNITS: l/hr

OUTFLOWS:

Urinary Flow = MIN(Urinary Sodium Flow/Urine Sodium Concentration,0.06*20)

UNITS: l/hr

Implied Sodium Conc(t) = Implied Sodium Conc(t - dt) + (Implied Sodium Conc AT)*dt

INIT Implied Sodium Conc = 144

UNITS: mEq/l

INFLOWS:

Implied Sodium Conc Adj = (Sodium Conc-Implied Sodium Conc)/Implied Sodium Conc TD

UNITS: meq/hr-l

Sodium Amount(t) = Sodium Amount(t - dt) + (Sodium Intake - Urinary Sodium Flow)*dt

INIT Sodium Amount = 2160

UNITS: mEq

INFLOWS:

Sodium Intake = MIN(MAX(Urinary Sodium Flow+ (NA Desired-Sodium Amount)/ Na AT,6.5),20)

UNITS: meq/hr

OUTFLOWS:

Urinary Sodium Flow = MAX(0.007*Filtered Sodium Load*Eff of ALD on sodium flow, 0.007*Filtered Sodium Load*Eff of ALD on sodium flow*Eff of furosemide on sodium urine flow)

UNITS: meq/hr

Extracellular FV = Fluid Volume-25

UNITS: l

Filtered Sodium Load = unit converter min to hour*Implied GFR*Sodium Conc*unit converter ml to l

UNITS: meq/hr

Implied GFR = MIN(GFR*Eff of Kidney Performance on GFR*Eff of ANP on GFR,200)

UNITS: ml/min

Implied Sodium Conc TD = 10

UNITS: hr

Kidney Performance = 1

UNITS: Unitless

LOG ALD = LOG10(Aldosterone)

Na AT = 1

UNITS: hr

NA Desired = 2160

UNITS: mEq

normal urine sodium conc = 126

UNITS: mEq/l

normal water intake = 0.06

UNITS: l/hr

Sodium Conc = Sodium Amount/Extracellular FV

UNITS: mEq/l

unit converter min to hour = 60

UNITS: min/hour

unit converter ml to l = 0.001

UNITS: l/ml

Urine Sodium Concentration = normal urine sodium conc*Eff of GFR on NAUConc*
Eff of ADH on NaConc

UNITS: mEq/l

Eff of ADH on NaConc = GRAPH(ADH)

(0.00, 0.075), (0.2, 0.075), (0.4, 0.09), (0.6, 0.255), (0.8, 0.495), (1.00, 1.00), (1.20, 1.43), (1.40, 1.59), (1.60, 1.67), (1.80, 1.71), (2.00, 1.77), (2.20, 1.80), (2.40, 1.85), (2.60, 1.86), (2.80, 1.88), (3.00, 1.88)

UNITS: Unitless

Eff of ALD on sodium flow = GRAPH(LOG ALD)

(-1.00, 4.66), (-0.857, 4.50), (-0.714, 4.30), (-0.571, 3.94), (-0.429, 3.32), (-0.286, 2.55), (-0.143, 1.90), (-2.22e-016, 1.00), (0.143, 0.8), (0.286, 0.632), (0.429, 0.536), (0.571, 0.512), (0.714, 0.512), (0.857, 0.587), (1, 0.587)

UNITS: Unitless

Eff of ANP on GFR = GRAPH(ANP)

(0.5, 0.746), (0.75, 0.894), (1.00, 1.00), (1.25, 1.22), (1.50, 1.62), (1.75, 2.20), (2.00, 2.60), (2.25, 2.73), (2.50, 2.81), (2.75, 2.82), (3.00, 2.82)

UNITS: Unitless

EFF of EFV on ANP = GRAPH(Extracellular FV)

(10.0, 0.439), (11.0, 0.452), (12.0, 0.491), (13.0, 0.569), (14.0, 0.712), (15.0, 1.00), (16.0, 1.65), (17.0, 2.05), (18.0, 2.25), (19.0, 2.34), (20.0, 2.34)

UNITS: Unitless

Eff of GFR on NAUConc = GRAPH(Implied GFR)

(50.0, 1.75), (55.0, 1.75), (60.0, 1.71), (65.0, 1.67), (70.0, 1.64), (75.0, 1.58), (80.0, 1.53), (85.0, 1.49), (90.0, 1.43), (95.0, 1.37), (100, 1.33), (105, 1.25), (110, 1.20), (115, 1.15), (120, 1.08), (125, 1.00), (130, 0.938), (135, 0.87), (140, 0.765), (145, 0.645)

UNITS: Unitless

Eff of Kidney Performance on GFR = GRAPH(Kidney Performance)

(0.00, 0.00), (0.1, 0.01), (0.2, 0.04), (0.3, 0.09), (0.4, 0.16), (0.5, 0.25), (0.6, 0.36), (0.7, 0.49), (0.8, 0.64), (0.9, 0.81), (1, 1.00)

UNITS: Unitless

Eff of Sodium Conc on Water Intake = GRAPH(Implied Sodium Conc)

(110, 0.105), (112, 0.105), (114, 0.135), (116, 0.12), (118, 0.135), (120, 0.105), (122, 0.105), (124, 0.135), (126, 0.18), (128, 0.21), (130, 0.21), (132, 0.225), (134, 0.33), (136, 0.462), (138, 0.556), (140, 0.725), (142, 0.875), (144, 1.00), (146, 1.20), (148, 1.44), (150, 1.79), (152, 2.40), (154, 2.68), (156, 2.79), (158, 2.86), (160, 2.87)

UNITS: Unitless

GFR = GRAPH(Mean Arterial Pressure)

(18.0, 0.00), (22.5, 9.60), (27.0, 19.2), (31.5, 28.8), (36.0, 38.4), (40.5, 48.0), (45.0, 57.6), (49.5, 67.2), (54.0, 76.8), (58.5, 86.4), (63.0, 96.0), (67.5, 104), (72.0, 110), (76.5, 115), (81.0, 119), (85.5, 122), (90.0, 125), (94.5, 128), (99.0, 130), (104, 132), (108, 133), (113, 135), (117, 136), (122, 136), (126, 136), (131, 136), (135, 136)

UNITS: ml/min

**********Treatment Sector**********

Bisoprolol Conc Bind to Plasma(t) = Bisoprolol Conc Bind to Plasma(t - dt) + (Bisoprolol Binding Rate) * dt

INIT Bisoprolol Conc Bind to Plasma = 0

UNITS: mg/l

INFLOWS:

Bisoprolol Binding Rate = (Desired Conc Bisoprolol to plasma Bind-Bisoprolol Conc Bind to Plasma)/Adjustment Time of Bisoprolol

UNITS: mg/hr-l

Candesartan Conc Bind to Plasma(t) = Candesartan Conc Bind to Plasma(t - dt) + (Candesartan Binding Rate) * dt

INIT Candesartan Conc Bind to Plasma = 0

UNITS: mg/l

INFLOWS:

Candesartan Binding Rate = (Desired Conc Candesartan to plasma Bind-Candesartan Conc Bind to Plasma)/Adjustment Time of Candesartan

UNITS: mg/hr-l

Conc of Non Abs Bisoprolol(t) = Conc of Non Abs Bisoprolol(t - dt) + (Bisoprolol Dosage Rate - Absorption Rate of Bisoprolol) * dt

INIT Conc of Non Abs Bisoprolol = 0

UNITS: mg/l

INFLOWS:

Bisoprolol Dosage Rate = PULSE(Bioavailability of Bisoprolol*Bisoprolol Dosage/ (Volume Distrubiton of Bisoprolol*bisop dosage td),7,0)

UNITS: mg/hr-l

OUTFLOWS:

Absorption Rate of Bisoprolol = Absorption Ratio of Bisoprolol*Conc of Non Abs Bisoprolol/Time delay of Bisoprolol

UNITS: mg/hr-l

Conc of Non Abs Candesartan(t) = Conc of Non Abs Candesartan(t - dt) + (Candesartan Dosage Rate - Absorption Rate of Candesartan) * dt

INIT Conc of Non Abs Candesartan = 0

UNITS: mg/l

INFLOWS:

Candesartan Dosage Rate = PULSE(Bioavailability of Candesartan*Candesartan Dosage/(Volume Distrubiton of Candesartan*candes dosage td),5,0)

UNITS: mg/hr-l

OUTFLOWS:

Absorption Rate of Candesartan = (Absorption Ratio of Candesartan*Conc of Non Abs Candesartan)/Time Delay of Candesartan

UNITS: mg/hr-l

Conc of Non Abs Furosemide(t) = Conc of Non Abs Furosemide(t - dt) + (Furosemide Dosage Rate + Furosemide Dosage Rate 2 - Absorption Rate of Furosemide) * dt

INIT Conc of Non Abs Furosemide = 0

UNITS: mg/l

INFLOWS:

Furosemide Dosage Rate = PULSE(Bioavailability of Furosemide*Furosemide Dosage/(Volume Distrubiton of Furosemide*furo dosage td),5,0)

UNITS: mg/hr-l

Furosemide Dosage Rate 2 = PULSE(Bioavailability of Furosemide*Furosemide Dosage 2/(Volume Distrubiton of Furosemide*furo dosage td),150,0)

UNITS: mg/hr-l

OUTFLOWS:

Absorption Rate of Furosemide = Absorption Ratio of Furosemide*Conc of Non Abs Furosemide/Time delay of Furosemide

UNITS: mg/hr-l

Free Bisoprolol Conc(t) = Free Bisoprolol Conc(t - dt) + (Absorption Rate of Bisoprolol - Elimination Rate of Bisoprolol - Bisoprolol Binding Rate) * dt

INIT Free Bisoprolol Conc = 0

UNITS: mg/l

INFLOWS:

Absorption Rate of Bisoprolol = Absorption Ratio of Bisoprolol*Conc of Non Abs Bisoprolol/Time delay of Bisoprolol

UNITS: mg/hr-l

OUTFLOWS:

Elimination Rate of Bisoprolol = Free Bisoprolol Conc*Elimination Constant of Bisoprolol

UNITS: mg/hr-l

Bisoprolol Binding Rate = (Desired Conc Bisoprolol to plasma Bind-Bisoprolol Conc Bind to Plasma)/Adjustment Time of Bisoprolol

UNITS: mg/hr-l

Free Candesartan Conc(t) = Free Candesartan Conc(t - dt) + (Absorption Rate of Candesartan - Elimination Rate of Candesartan - Candesartan Binding Rate) * dt

INIT Free Candesartan Conc = 0

UNITS: mg/l

INFLOWS:

Absorption Rate of Candesartan = (Absorption Ratio of Candesartan*Conc of Non Abs Candesartan)/Time Delay of Candesartan

UNITS: mg/hr-l

OUTFLOWS:

Elimination Rate of Candesartan = Free Candesartan Conc*Elimination Constant of Candesartan

UNITS: mg/hr-l

Candesartan Binding Rate = (Desired Conc Candesartan to plasma Bind-Candesartan Conc Bind to Plasma)/Adjustment Time of Candesartan

UNITS: mg/hr-l

Free Furosemide Conc(t) = Free Furosemide Conc(t - dt) + (Absorption Rate of Furosemide - Elimination Rate of Furosemide - Bisoprolol Binding Rate) * dt

INIT Free Furosemide Conc = 0

UNITS: mg/l

INFLOWS:

Absorption Rate of Furosemide = Absorption Ratio of Furosemide*Conc of Non Abs Furosemide/Time delay of Furosemide

UNITS: mg/hr-l

OUTFLOWS:

Elimination Rate of Furosemide = Free Furosemide Conc*Elimination Constant of Furosemide

UNITS: mg/hr-l

Bisoprolol Binding Rate = (Desired Conc Furosemide to plasma Bind-Furosemide Conc Bind to Plasma)/Adjustment Time of Furosemide

UNITS: mg/hr-l

Furosemide Conc Bind to Plasma(t) = Furosemide Conc Bind to Plasma(t - dt) + (Bisoprolol Binding Rate) * dt

INIT Furosemide Conc Bind to Plasma = 0

UNITS: mg/l

INFLOWS:

Bisoprolol Binding Rate = (Desired Conc Furosemide to plasma Bind-Furosemide Conc Bind to Plasma)/Adjustment Time of Furosemide

UNITS: mg/hr-l

Absorption Ratio of Bisoprolol = 0.8

UNITS: Unitless

Absorption Ratio of Candesartan = 0.45

UNITS: Unitless

Absorption Ratio of Furosemide = 0.65

UNITS: Unitless

Adjustment Time of Bisoprolol = 1

UNITS: hr

Adjustment Time of Candesartan = 1

UNITS: hr

Adjustment Time of Furosemide = 1

UNITS: hr

Bioavailability of Bisoprolol = 0.95

UNITS: Unitless

Bioavailability of Candesartan = 0.4

UNITS: Unitless

Bioavailability of Furosemide = 0.6

UNITS: Unitless

Bisoprolol Binding Ratio = 0.3

UNITS: Unitless

Bisoprolol Dosage = 0

UNITS: mg

bisop dosage td = 1

UNITS: hr

Candesartan Dosage = 0

UNITS: mg

Candesartan Binding Ratio = 0.99

UNITS: Unitless

candes dosage td = 1

UNITS: hr

Clearance Rate of Bisoprolol = 0.318

UNITS: l/hr

Clearance Rate of Candesartan = 0.0144

UNITS: l/hr

Clearance Rate of Furosemide = 6

UNITS: l/hr

cut dosage = 80

UNITS: mg

Desired Conc Bisoprolol to plasma Bind = Bisoprolol Binding Ratio*Free Bisoprolol Conc

UNITS: mg/l

Desired Conc Candesartan to plasma Bind = Candesartan Binding Ratio*Free Candesartan Conc

UNITS: mg/l

Desired Conc Furosemide to plasma Bind = Furosemide Binding Ratio*Free Furosemide Conc

UNITS: mg/l

Elimination Constant of Furosemide = Clearance Rate of Furosemide/Volume

Distrubiton of Furosemide

UNITS: 1/hr

Elimination Constant of Bisoprolol = Clearance Rate of Bisoprolol/Volume Distrubiton of Bisoprolol

UNITS: 1/hr

Elimination Constant of Candesartan = Clearance Rate of Candesartan/Volume Distrubiton of Candesartan

UNITS: 1/hr

Furosemide Cutting = STEP(-cut dosage,150)

UNITS: mg

Furosemide Binding Ratio = 0.90

UNITS: Unitless

Furosemide Dosage = 0+Furosemide Cutting

UNITS: mg

Furosemide Dosage 2 = 0

UNITS: mg

furo dosage td = 1

UNITS: hr

Time delay of Bisoprolol = 1

UNITS: hr

Time Delay of Candesartan = 1

UNITS: hr

Time delay of Furosemide = 0.25

UNITS: hr

Volume Distrubiton of Bisoprolol = 3.5

UNITS: l

Volume Distrubiton of Candesartan = 0.13

UNITS: l

Volume Distrubiton of Furosemide = 9

UNITS: l

Eff of Bisoprolol of RSNS = GRAPH(Free Bisoprolol Conc)

(0.00, 1.00), (0.1, 0.991), (0.2, 0.94), (0.3, 0.853), (0.4, 0.688), (0.5, 0.623), (0.6, 0.578), (0.7, 0.552), (0.8, 0.55), (0.9, 0.542), (1, 0.54), (1.10, 0.53), (1.20, 0.53), (1.30, 0.525), (1.40, 0.522), (1.50, 0.52), (1.60, 0.522), (1.70, 0.52), (1.80, 0.522), (1.90, 0.52), (2.00, 0.525), (2.10, 0.527)

UNITS: Unitless

Eff of Bisoprolol of SNS = GRAPH(Free Bisoprolol Conc)

(0.00, 1.00), (0.1, 0.978), (0.2, 0.935), (0.3, 0.848), (0.4, 0.662), (0.5, 0.58), (0.6, 0.547), (0.7, 0.522), (0.8, 0.52), (0.9, 0.522), (1, 0.52), (1.10, 0.525), (1.20, 0.522), (1.30, 0.527), (1.40, 0.522), (1.50, 0.525), (1.60, 0.52), (1.70, 0.517), (1.80, 0.517), (1.90, 0.515), (2.00, 0.507), (2.10, 0.507)

UNITS: Unitless

Eff of Candesarton on ANG2 Receptor =

GRAPH(Free Candesartan Conc)

(0.00, 1.00), (2.00, 0.762), (4.00, 0.615), (6.00, 0.478), (8.00, 0.37), (10.0, 0.325), (12.0, 0.328), (14.0, 0.325), (16.0, 0.328), (18.0, 0.328), (20.0, 0.328)

UNITS: Unitless

Eff of furosemide on sodium urine flow =

GRAPH(Free Furosemide Conc)

(0.00, 1.00), (0.15, 2.40), (0.3, 4.20), (0.45, 5.70), (0.6, 6.65), (0.75, 7.70), (0.9, 8.50), (1.05, 9.05), (1.20, 9.50), (1.35, 9.60), (1.50, 9.60)

UNITS: Unitless

Not in a sector