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Renin-angiotensin system and its relationship to arterial pressure regulation

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ABSTRACT

RENIN-ANGIOTENSIN SYSTEM AND ITS RELATIONSHIP TO ARTERIAL PRESSURE REGULATION

by
Sami D. Saume

The renal system is known to participate in the natural regulation of blood pressure. A renal system model that simulates interaction responses of renal output to arterial blood pressure was developed. The major components of this model are glomerular filtration rate, tubular sodium reabsorption, the renin-angiotensin system, Aldosterone secretion, and antidiuretic hormone secretion. The model's differential equations were coded using Vissim 1.2 student version. It was found that, the renal output increased as glomerular filtration rate, Aldosterone concentration, and blood pressure increased. Conversely, increasing antidiuretic hormone concentration lead to decreased renal output.

Additionally, Angiotensin II and Aldosterone concentrations increased as the arterial pressure decreased. The model suggests that increasing renal output leads to decreased blood volume, which aids in the long term regulation of blood pressure.

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This thesis is dedicated to my family

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CHAPTER 1

INTRODUCTION

The homeostasis of the human body is what contributes to our well being. Homeostasis results from many organs performing vital functions while preserving the checks and balances of every detail of our system. This is accomplished through production of the carriers we call hormones, synthesized by glands and gland-like organs. The kidney is one of the most important organs in the human body.

The kidney performs three major bodily functions. First, they regulate the water content, mineral composition, and acidity of the body by excreting water, minerals, and acids to achieve total body balance. The second major renal function is the formation of urine through removal of the end products of bodily metabolism and removal of foreign chemicals from the body. The third function is formation and release of certain hormones, such as renin, which regulates sodium excretion, and Aldosterone, which stimulates potassium secretion and sodium reabsorption [1,2].

The kidneys are paired organs that lie in the lower back and contain approximately two million similar units, called nephrons. Each nephron is capable of forming urine by itself. The nephron is composed basically of (1) a glomerulus through which fluid is filtered from the blood, and (2) a long tubule in which the filtered fluid is converted into urine on its way to the pelvis of the kidney. The general plan of the kidney consists of two layers; the inner layer, the medulla, and the outer layer, the cortex.

The basic anatomy of the nephron is described as follows: blood enters the glomerulus through the afferent arteriole and then leaves through the efferent arteriole.

The glomerulus is a network of branching and anastomosing capillaries covered by epithelial cells and encased in Bowman's capsule. Pressure is the major driving force that helps fluid to filter from the blood in the glomerulus into Bowman's capsule. The filtrate who consists of all blood components except red and white cells, fluid flows into the proximal tubule that lies in the cortex of the kidney along with the glomerulus.

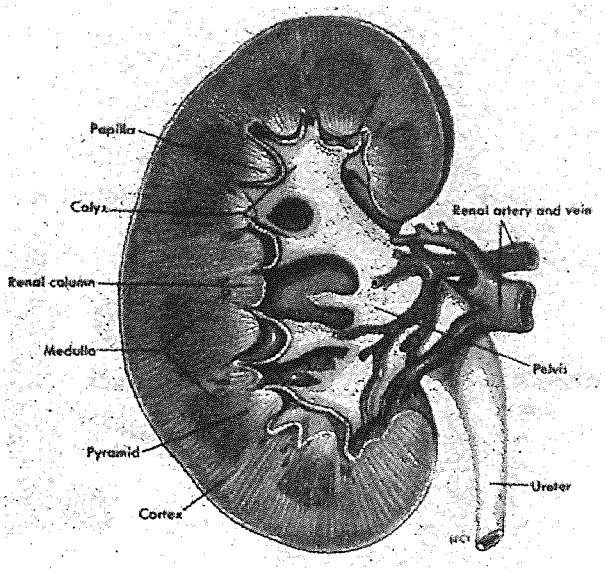

Figure 1: Overall picture of the kidney.

From the proximal tubule the fluid passes into the loop of Henle that dips deeply into the kidney. Each loop is divided into the descending limb and the ascending limb. The wall of the descending limb and the lower end of the ascending limb are very thin and therefore are called the thin segment of the loop of Henle. However, after the ascending limb of the loop has partially returned to the cortical direction, its wall becomes thick. This portion of the loop of Henle is called the thick segment of the ascending limb.

After passing through the loop of Henle, the fluid then enters the distal tubule. The distal tubule is called the collecting duct, and has the following components: connecting tubule, cortical collecting duct and medullar collecting duct [2]. The medullar collecting ducts coalesce to form larger collecting ducts. The largest collecting ducts empty into the renal pelvis. In each kidney there are about 250 of these large collecting ducts, each of which transmits the urine from about 4000 nephrons (see figures 1 and 2 for details).

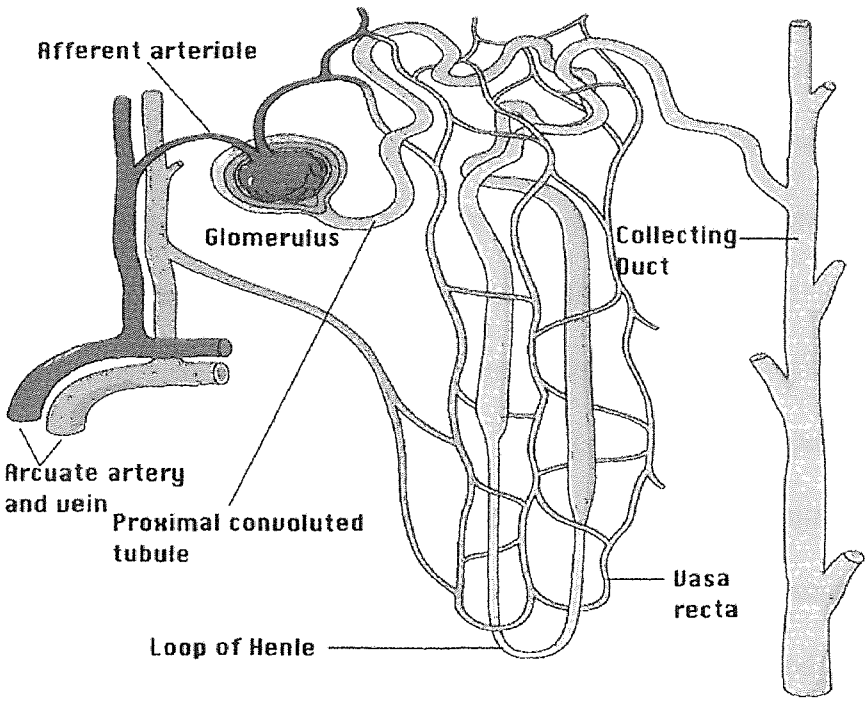

Figure 2: Basic anatomy of the nephron.

As the glomerular filtrate flows through the tubule, over 99 percent of its water, 99.5 percent of its sodium, 100 percent of its glucose, and 44 percent of its urea are normally reabsorbed back into the vascular system. The remaining tubular water and dissolved substances becomes the urine [2, 3].

The basic function of the nephron is to clear unwanted substances from the plasma stream as it passes through the kidney. The cleared substances mainly are the end products of metabolism such as urea, creatinine, uric acid, and urates. In addition, many other substances tend to accumulate in the body in excess quantities such as sodium ions, potassium ions, chloride ions, and hydrogen ions [3].

The principal mechanism by which the nephron cleans the plasma is as follow: (1) blood flows from the renal artery to the glomerulus capillaries through the afferent arteriole. Almost one fifth of afferent plasma is filtered through the glomerular membrane into the tubular system of the nephron in each pass of the blood. (2) Then, as the filtered fluid flows through the nephrons, the unwanted substances are rejected, while important substances are reabsorbed back into the plasma of the peritubular capillaries, which leads to the renal vein and back to the vascular system [2,3].

The quantity of glomerular filtrate formed each minute in all nephrons of both kidneys is called the glomerular filtration rate (GFR). In the normal person, this averages approximately 125 mL/min. There are many factors that determine the glomerular filtration rate such as (1) glomerular pressure, (2) plasma colloid osmotic pressure, and (3) Bowman's capsule pressure. Any increase in the rate of blood flow through the nephron causes an increase in the glomerular filtration rate. One of the reasons for this is that the increasing blood flow elevates the glomerular pressure, and as a result, enhances filtration. In addition, afferent and efferent constrictions have a significant effect on the GFR. Afferent arteriolar constriction decreases the rate of blood flow into the glomerulus, which leads to decreased GFR. On the other hand, efferent arteriolar constrictions increase the glomerular pressure and cause an increase in the GFR [2,3].

The kidney has developed a certain feedback mechanism to control the renal blood flow and glomerular filtration rate. Each nephron is provided with two feedback mechanisms from the distal tubule to the peirglomerular arterioles. These two mechanisms are (1) afferent arteriolar vasodilator and (2) efferent arteriolar vasoconstrictor. These two feedback mechanisms occur entirely at the juxtaglomerular complex.

The initial portion of the distal tubule, which comes after the upper end of the thick segment of the ascending limb of the loop of Henle, and comes in contact with the afferent and efferent arterioles is denser and is called the macula densa. On the other hand, the smooth muscle cells of both the afferent and efferent arterioles are swollen, where they come in contact with the macula densa and they are called juxtaglomerular cells. The whole complex of the macula densa and juxtaglomerular cells is called the juxtaglomerular complex

The significance of the afferent arteriolar vasodilator feedback mechanism is as follows: decreasing the glomerular filtration rate causes sodium and chloride ion concentration to decrease at the macula densa. This reduction of ion concentration causes afferent arteriolar dilation, which allows increased blood flow into the glomerulus and increases the glomerular pressure. As a result, the glomerular filtration rate will increase back toward its normal level [2, 3] Therefore, this is a negative feedback regulator.

In addition, the efferent arteriolar vasoconstrictor feedback mechanism helps in restoring the glomerular pressure in the following manner. Decreasing the glomerular filtration rate causes the juxtaglomerular cells to release renin from their granules. The

renin causes the formation of Angiotensin II, which constricts the efferent arterioles and leads to an increase in glomerulus pressure. Again, this is a negative feedback regulator.

The renin-angiotensin system plays a significant role in cardiovascular homeostasis by indirectly controlling extracellular fluid volume and vascular tone. The system consists of the following components: 1- renin, 2- angiotensinogen, 3- angiotensin converting enzyme (ACE) and 4- Aldosterone. Renin uses angiotensinogen as a substrate to produce Angiotensin I. Angiotensin I is not active biologically and is next converted to Angiotensin II by Angiotensin converting enzyme (ACE). Angiotensin II is the biologically active hormone and is a major stimulator of aldostrone secretion. (See Figure 3)[4,5,6,2]

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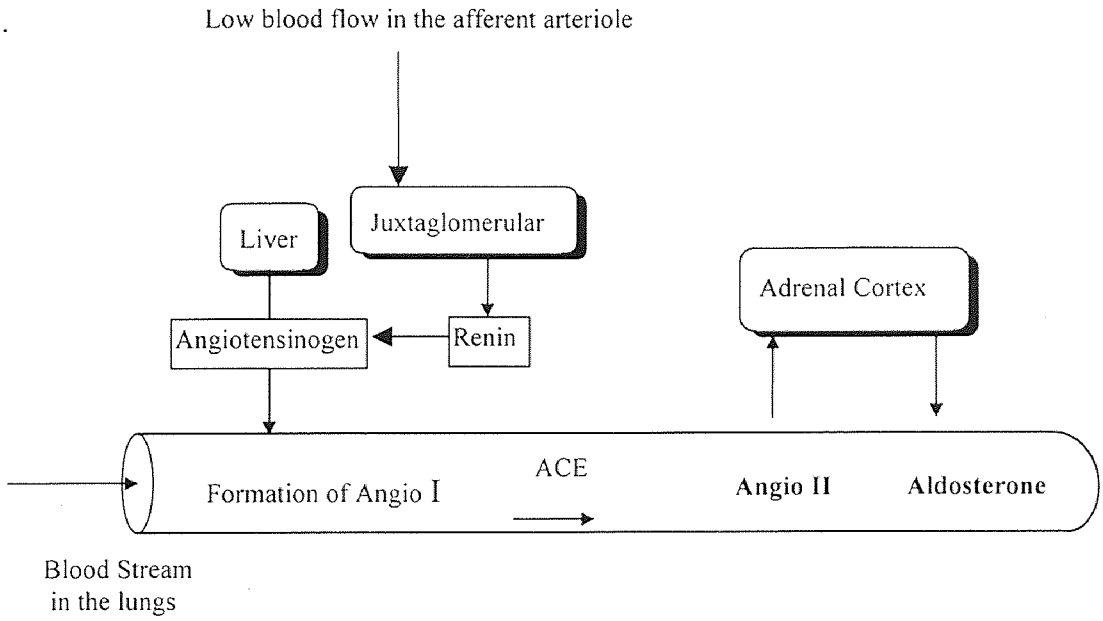


Figure 3: Summary of the renin-angiotensin system.

Renin: Renin is synthesized in the Juxtaglomerular cells of the afferent arterioles, where it is stored in special granules. The renin is released into the blood stream in response to a number of inputs to the Juxtaglomerular cells, which trigger three types of

mechanisms: 1) renal baro-receptors; 2) the renal sympathetic nerves ; and 3) the macula densa. Low blood pressure in the circulation is the signal for activating the renin-releasing elements [2,6].

Angiotensinogen: Angiotensinogen is a glycoprotein synthesized in the liver. In much lower quantities, it is also synthesized, in the kidney, brain, adrenal gland, aorta, heart, and testis [6]. Renin acts on this substrate, convertimg the larger glycoprotein into smaller decapeptide angiotensin I [2,6]. Angiotensin I stimulates the production of angiotensin II.

Angiotensin II has two major functions: 1) it has vasoconstrictor properties and can cause a marked increase in the blood pressure. 2) It stimulates aldosterone production through the adrenal gland. Angiotensin also controls the release of renin through a feed-back mechanism [6].

When angiotensin II is present in the blood, it acts rapidly to elevate blood pressure. Angiotensin II binds with specific receptors on the vascular smooth muscles, leading to constriction of the vascular muscles and increasing peripheral resistance. Arterial pressure will increase rapidly in response to the resistance change,.

Sodium intake plays a major role in the regulation of the angiotensin receptors in the smooth muscles. When sodium supply decreases, the number of available receptors also decreases, and vascular sensitivity to angiotensin decreases. Meanwhile, an increase in sodium intake leads to an increase in the number of receptors, which leads to an increase in blood pressure. [5]

Angiotensin converting enzyme (ACE): ACE is a zinc-containing glycoprotein, found in the lungs, proximal renal tubule, vascular endothelium, brain, and testes. This

enzyme removes two amino acids from angiotensin I to produce Angiotensin II. Many studies show that the synthesis of ACE is increased in patients with Reno-vascular diseases [6]

Aldosterone: Aldosterone is secreted by the zona glomerulosa cells in the outer cortex of the adrenal glands. There are three different factors that stimulate aldosterone secretion: 1) increased angiotensin II in the blood, (2) increased potassium ion concentration in the extracellular fluid, and (3) decreased sodium ion concentration in the extracellular fluid.

Aldosterone plays an important role in sodium reabsorption. In the presence of large amounts of aldosterone, almost all the tubular sodium is reabsorbed so that essentially none of the sodium enters the urine. On the other hand, in the absence of aldosterone, almost all of the sodium that enters the late distal tubules is excreted with the urine.

Aldosterone enters the tubular epithelial cells and combines with a receptor protein. This combination diffuses within minutes into the nucleus, where it activates the DNA molecules to form one or more types of messenger RNA. The RNA causes formation of protein enzymes. These specific protein enzymes increase the permeability to sodium at the luminal border of the cell [3].

One of the most important functions of the kidney is controlling the osmolality of the body fluids. When the osmolality is low, the fluids are dilute, which causes the kidneys to excrete the excess of water in the urine. In addition, if the osmolality is too high, the kidney excretes the excess solutes, thereby reducing the body fluid osmolality back toward normal, while excreting concentrated urine.

The signal that tells the kidney whether to excrete dilute or concentrated urine is a hormone called antidiuretic hormone, ADH (also called Vasopressin) that is secreted by the posterior pituitary gland.

An increase in osmolality due to increased sodium ions excites osmoreceptors located in the anterior hypothalamus near the supraoptic nuclei. This excitation in turn stimulates the supraoptic nuclei, which then causes the posterior pituitary gland to release ADH. ADH increases the permeability of water in the cortical collecting ducts and therefore causes increased conservation of water by the kidneys. The conservation of water and loss of sodium ions in urine causes dilution of the sodium and other substances in the extracellular fluid, and results in a more concentrated extracellular fluid. Conversely, when the extracellular fluid becomes too dilute, less ADH is synthesized and excess water is lost in the urine.

The kidneys have developed a very complex mechanism, called the counter-current mechanism for concentrating the urine. The first step of this mechanism is to create a very high osmotic pressure in the medullar interstitial fluid. The normal osmolality of the fluids range from 300 mOsm/liter in the cortex to 1200 mOsm/liter in the pelvic tip of the medulla. Three different solute-concentrating mechanisms are responsible for this increase; these are as follows:

The first mechanism is the active transport of sodium ions out of the ascending limb of the loop of Henle into the interstitium. The second mechanism, smaller quantities of ions are also transported into the medullary interstitial fluid from the collecting duct, mainly resulting from active transport of sodium ions and electrogenic passive absorption of Chloride ions along with sodium ions. The last mechanism is the reabsorpion of urea

into the fluids of the medulla from the collecting duct, due to presence of antidiuretic hormone, ADH.

CHAPTER 2

LITERATURE REVIEW

Laboratory experiments show a consistent relationship between angiotensin II and arterial blood pressure. The simple experimental procedure consists of infusing a certain amount of angiotensin II into the blood stream and observing the changes in blood pressure. [4,5]

In his experiment, White used a simple dynamic infusion model to achieve better understanding of the relationship between angiotensin II and blood pressure [4]. Many subjects were injected at the pulmonary artery with a constant rate of angiotensin II over a period lasting from several minutes to 1 hour. Different correlations were recorded at the carotid artery and at the right atrium. The following mathematical model was developed to simulate the system response:

$$\frac{dx_1}{dt} = -\frac{1}{\tau_1}x_1 + \frac{K_1}{\tau_1}x_2 \qquad (1A)$$

$$\frac{dx_2}{dt} = \frac{K_2}{\tau_2}x_1 - \frac{1}{\tau_2}x_2 + \frac{K_2}{\tau_2}u \qquad (2A)$$

$$\frac{dx_3}{dt} = \frac{1}{\tau_3}\left(\frac{\alpha x_2}{\beta + x_2}\right) - \frac{1}{\tau_3}x_3 \qquad (3A)$$

The state variables x_1, x_2, and x_3 represent, respectively, venous plasma angiotensin II concentration measured at the right atrium ($pg.mL^{-1}$), arterial plasma angiotensin II concentration measured at the carotid artery ($pg.mL^{-1}$), and arterial blood pressure (mmHg). The injection rate is represented by the input u. The time delays for the angiotensin II to reach the venous circulation and the arterial circulation and the time delay for blood pressure to respond are, respectively, τ_1, τ_2 and τ_3, with values of 0.4,

0.312 and 0.375 min. The circulatory gains are K_1 and K_2 with values of 0.25 and 0.828, respectively. System parameters α and β are 55.2 mmHg and 167 $pg.mL^{-1}$, respectively.

A compartmental model was developed by White [5] to describe the regulatory effect of angiotensin II on arterial pressure during an infusion experiment. In this experiment humans or animals received a large amount of angiotensin II ranging between 0.01 and 0.1$\mu g.\ kg^{-1}.min^{-1}$. The system was considered to consist of two compartments (see figure 4 for details).

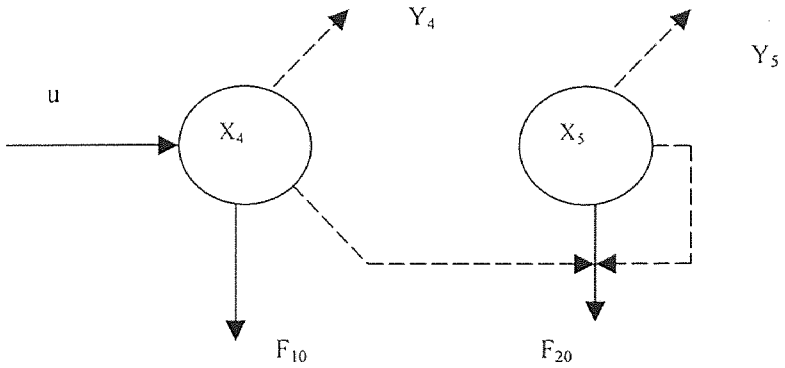


Figure 4: Two compartment angiotensin infusion model.

The state variables x_4 and x_5 are angiotensin II concentration in $pg.\ mL^{-1}$, and mean arterial blood pressure in mmHg, respectively. Experimental measurements of angiotensin II (AII) and arterial pressure are given by Y_4 ($pg.\ mL^{-1}$) and Y_5 (mmHg), respectively. The function $F_{10}(x_4,u)$ represents the total influx rate of AII, including both endogenous production and experimental infusion. The function F_{20} represents the mechanisms which affect blood pressure (BP), as mediated by both BP and AII.

In the Preston model the system was divided into two subsystems: the AII subsystem and BP subsystem. A mathematical model was developed for each subsystem as follows.

AII subsystem: A few assumptions are made to simplify the model, such as the absence of feedback from the BP subsystem to the AII subsystem, and dependence of the steady state levels of AII depend on the rate of infusion and the rate at which infused AII can be cleared. The AII subsystem can be expressed by the following mathematical equation:

$$\frac{dx_4}{dt} = -p_{202}x_4 + u \tag{1}$$

BP subsystem: The BP compartment is a first order system responding to the plasma AII stimulus. The dynamics of BP response are described by the sensitivity of the BP to plasma AII levels and the rate at which the BP tries to correct the abnormality of high pressure. The sensitivity of BP to AII levels and the rate of BP self regulation are given by the following equations:

$$F_{201}(x_4) = \frac{\alpha x_4}{\beta + x_4} \tag{2}$$

$$F_{202}(x_5) = -p_{202}x_5 \tag{3}$$

By combining the two subsystems the overall model will be expressed as follows

$$\frac{dx_4}{dt} = -p_{202}x_1 + u \tag{4}$$

$$\frac{dx_5}{dt} = p_{202}\left(\frac{Ax_4}{\beta + x_4} - x_5\right) \tag{5}$$

In addition to the renin angiotensin mechanism, there are at least eight other systems participating in arterial pressure regulation. These systems are as follows:

1- The Baroreceptor Mechanism. The baroreceptors are located in the carotid sinuses and in the arch of the aorta. When the arterial pressure increase it stimulates the baroreceptors which send signals to the vasomotor center in the lower regions of the brain (the medulla). The brain sends a signal to the autonomic nervous system to relax the heart and dilate the peripheral blood vessels, which leads to decreases in arterial pressure. [7,8,9,10,12]

2- The Chemoreceptor system: The Chemoreceptors are located in the carotid and aortic bodies. They become stimulated due to a poor delivery of oxygen, especially when the arterial pressure falls below 80 mmHg. [7,8,12]

3- The Central Nervous Ischemic response: When the arterial pressure falls to 40 mmHg, Ischemia of the vasomotor center in the medulla oblongata sends signals to the sympathetic nervous system which cause the peripheral arterioles to constrict. [7,8,10]

4- The capillary fluid shift mechanism. Capillary pressure increases as a result of elevation in arterial pressure. This forces fluid to go out of the circulation (blood compartment) into the tissue space, which helps the arterial pressure to return toward normal. [7,8,10]

5- The renal body fluid mechanism. The arterial pressure has a direct effect on kidney function. When the arterial pressure falls below normal, the kidney reduces the output of salt and water. As a result of this mechanism the volume of fluid will increase and cause the pressure to return to its normal value. [7,8,10]

6- The stress relaxation mechanism. Blood vessels slowly begin to stretch as a result of increases in arterial blood pressure. This increases the diameter of resistance vessels reducing peripheral resistance and helping the pressure to return to normal. [7,8,10]

7- The Aldosterone mechanism. Aldosterone acts on the kidney tubules so that less sodium is excreted in the urine, which leads to water retention and an increase in blood volume.

8- Antidiuretic Hormone ADH. Antidiuretic hormone ADH plays an important role in water reabsoption by increasing the water permeability of the collecting ducts leading to increased water conservation, and increased blood volume.

Arkhipova represented the cardiovascular system as two compartments, venous (V) and arterial (A), which are interconnected [9]. The flow of the fluid Q from the arterial to the venous compartment is regulated by a throttle which simulates the peripheral resistance R. A pump was placed between the two compartments to simulate the heart and the cardiac output Q_h. Fluid from other organs Q_{in} is considered as constant input to the venous compartment and fluid is removed from the arterial compartment by the kidney Q_{out} (see figure 5 for details).

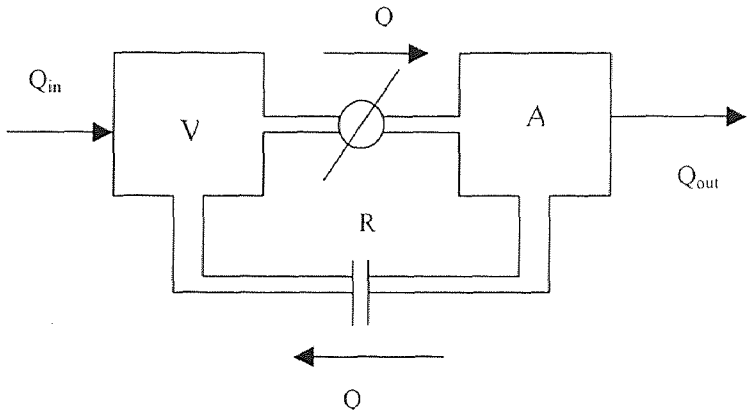


Figure 5. Diagram of the cardiovascular system.

The mathematical model showed that the average arterial pressure varied from 100 to 150 mmHg. Some mechanisms were ignored such as the Chemoreceptors, the

Ischemic response of the central nervous system, and the renin angiotensin system. Meanwhile, other mechanisms were included in the stiffness coefficients for the arterial and venous compartment, such as relaxation of stress vessels and capillary fluid shift.

This model showed that the average arterial pressure $P_a(t)$ and the venous pressure $P_V(t)$ are given in the following equations:

$$P_a(t) = K_a V_a(t) \tag{6}$$

$$P_V(t) = K_V V_V(t) \tag{7}$$

Where: K_a and K_V are the stiffness of the arterial and the venous compartments.

The cardiac output is determined by the venous pressure in accordance with the Frank-Starling law.

$$Q_h(t) = k_1 P_v(t) \tag{8}$$

The continuity equations can be written in the following form:

$$\frac{dV_a}{dt} = Q_h(t) - Q_{out}(t) - Q(t) \tag{9}$$

$$\frac{dV_V}{dt} = Q_{in}(t) - Q(t) - Q_h(t) \tag{10}$$

Arkhipova proposed a mathematical model of arterial blood pressure regulation [9]. This model studied the effect of different controls such as the baroreceptors, the renal mechanism for maintaining water-salt balance, and the aldosterone mechanism. The Baroreceptors mechanism is associated with controlling the peripheral resistance with a time delay of 5-7 seconds as given in the following equation:

$$R(t) = k_2 - k_3 V_a(t-\tau) \tag{11}$$

The venous return is given by the following equation:

$$Q(t) = \frac{P_a(t) - P_v(t)}{R(t)} \tag{12}$$

The renal mechanism for maintaining the water salt balance is linearly related to arterial blood pressure. Any increase in arterial pressure causes the separation of water and salt by the kidney to increase, which leads to reduction of extracellular fluid and eventually to a reduction of arterial pressure. In general, the renal mechanism controls the flow of the outgoing fluids $Q_{out,}$. The first major component of the renal mechanism is the glomerular filtration rate (GFR). The glomerular filtration rate takes place at Boman's Capsule under the influence of arterial pressure.

Lawrence [14] introduced the glomerular filtration rate as a function of arterial pressure, as is given by the following equation:

$$GFR = 4.50 - 1.62P_a + 0.1P_a^2 - 1.2\times10^{-3}P_a^3 + 5.73\times10^{-6}P_a^4 - 9.89\times10^{-9}P_a^5 \tag{13}$$

The second component is tubular reabsorption. Uttamsingh studied the tubular reabsorption in more detail in his model [13]. Most of the glomerular filtration is reabsorbed as it passes through the tubular system of the kidney from the glomerulus to the urethra. Tubular reaborption is divided into three parts: proximal, distal, and collecting duct [1]. Uttamsingh's model represented the renal output (U/O) as follows:

$$U/O = EFDT - EDTR \tag{14}$$

Where: EFDT= rate of flow of water into the distal tubule; and EDTR = rate of reabsorption of water in the distal nephron segments.

$$EFDT = EFLH - ELHR \tag{15}$$

Where: EFLH = rate of flow of water into the loop of Henle, ELHR = rate of reabsorption of water in the loop of Henle.

$$ELHR = EBLH \, x \, EFLH \tag{16}$$

Where: EBLH = fraction of water load reabsorbed in the loop of Henle.

$$EBLH = - \, 0.01 \, x \, EFLH + 0.65 \tag{17}$$

$$EFLH = GFR - EPTR \tag{18}$$

Where: EPTR = rate of reabsorption of water in proximal tubule and is expressed by the following equation:

$$EPTR = GTB \, x \, GFR \tag{19}$$

Where GTB = fraction of filtered load of Sodium reabsorbed in the proximal tubule.

$$GTB = 5.815 - 0.0357 \, x \, [Na^{+}] \tag{20}$$

By combining equations (15) through (20), we obtain the following equations:

$$EFLH = GFR - \{5.815 - 0.0357 \, x \, [Na^{+}]\} \, GFR \tag{21}$$

$$ELHR = -0.01 \, EFLH^{2} + 0.65 \, EFLH \tag{22}$$

By substituting equation (22) into equation (15) we get:

$$EFDT = 0.01 \, EFLH^{2} + 0.35 \, EFLH \tag{23}$$

Also;

$$EDTR = EBDT \, x \, EFDT \tag{24}$$

Where EBDT = fraction of water load reabsorbed in the distal tubule ,a function of the antidiuretic hormone concentration.

$$EBDT = 4.17x10^{-2} - 0.824.[ADH] + 0.637.[ADH]^{2} - 0.222.[ADH]^{3} + 3.45x10^{-2}[ADH]^{4} - 2.5x10^{-3}[ADH]^{5} + 7.25x10^{-5}[ADH]^{6} \tag{25}$$

$$d[ADH]/dt = \{0.25(0.73[Na^+] - 101.72) - 0.206\ ADH\}/V \quad (26)$$

Uttamsingh studied the effect of Aldosterone concentration on sodium reabsorption. Increasing aldoterone concentration leads to increased sodium reabsorption from the distal tubule (SDTR/SFDT).

$$SDTR/SFDT = 0.002\ [ald] + 0.833 \quad (27)$$

Aldosterone is the final component of the renin/angiotensin/aldosterone system. Sodium entering the distal tubule SFDT stimulates renin release RS.

$$RS = 0.0163 - 0.0093\ SFDT \quad (28)$$

$$SFDT = 0.2\{GFR.[Na^+]/1000\}\{-4.815 + 0.0357[Na^+]\} \quad (29)$$

Renin is removed from the circulation on passage through the liver. Therefore, the rate of clearance of renin is assumed to be constant with a value of 0.2 liter/min. Renin regulation ,dR/dt, is given by the following equation.

$$dR/dt = (RS - 0.2\ R)/V \quad (30)$$

Renin acts on its substrate to produce angiotensin I, which is converted to angiotensin II. The rate of angiotensin II formation is given by this equation:

$$AS = 583.3\ R.V \quad (31)$$

The rate of angiotensin clearance from plasma is considered constant with a value of 6.06 liter/min. Therefore, the balance equation for angiotensin II regulation is :

$$dA/dt = (AS - 6.06\ A)/V \quad (32)$$

The rate of aldosterone secretion is affected by angiotensin II concentration in the plasma and by Potassium PK:

$$d(ALD)/dt = \{0.25[3(4.43A-67.7)+21.64PK-55.5]-0.62ALD\}/V \quad (33)$$

By examining equations (11), (21), (19), and (23), we conclude that urine output is a function of glomerular filtration rate (GFR), Sodium concentration [Na^+], and antidiuretic hormone concentration [ADH].

Arkhipova modeled the aldosterone mechanism with a time delay τ_1 using the following equation:

$$Q_r(t) = k_6 V_a(t-\tau_1) \tag{34}$$

So as a result, the renal output Q_{out} will be :

$$Q_{out}(t) = U/O + k_6 V_a(t-\tau_1) \tag{35}$$

By substituting equations (6),(7), (9), (12), (13), and (24) into equations (6) and (7) we get the following:

$$\frac{dV_a(t)}{dt} = k_1 k_v V_v(t) - U/O - k_6 V_a(t-\tau_1) - \frac{\left[k_a V_a(t) - k_v V_v(t)\right]}{\left[k_2 - k_3 V_a(t-\tau)\right]} \tag{36}$$

$$\frac{dV_v(t)}{dt} = Q_{in} - k_1 k_v V_v(t) + \frac{\left[k_a V_a(t) - k_v V_v(t)\right]}{\left[k_2 - k_3 V_a(t-\tau)\right]} \tag{37}$$

CHAPTER 3

MATHEMATICAL MODEL

The proposed model in this study is an integration of three different models: Arkhipova's model [9], Uttamisingh's model [13], and Lawrence's model [14]. Lawrence's model showed the effect of the arterial pressure on the glomerular filtration rate. Uttamsingh's model showed the effect of antidiuretic hormone [ADH] and Sodium concentration [Na^+] on the renal mechanism for controlling water and salt balance. Arkhipova's model studied the regulation of arterial pressure and the effect of certain control loops. The combined mathematical model is given by the following equations:

$$GFR = 4.5 - 1.62P_a + 0.1\,P_a^2 - 1.2\times10^{-3}\,P_a^3 + 5.73\times10^{-6}\,P_a^4 - 9.89\times10^{-9}\,P_a^5 \quad (13)$$

$$EBDT = 4.17\times10^{-2} - 0.428.[ADH] + 0.637.[ADH]^2 - 0.222.[ADH]^3 + 3.45\times10^{-2}[ADH]^4 - 2.5\times10^{-3}[ADH]^5 + 7.25\times10^{-5}[ADH]^6 \quad (25)$$

$$d[ADH]/dt = \{0.25(0.73[Na^+] - 101.72) - 0.206\,ADH\}/V \quad (26)$$

$$U/O = EFDT(1-EBDT) \quad (38)$$

$$EFDT = 0.01\,EFLH^2 + 0.35\,EFLH \quad (23)$$

$$\frac{dV_a(t)}{dt} = k_1 k_v V_v(t) - U/O - k_6 V_a(t-\tau_1) - \frac{[k_a V_a(t) - k_v V_v(t)]}{[k_2 - k_3 V_a(t-\tau)]} \quad (36)$$

$$\frac{dV_v(t)}{dt} = Q_{in} - k_1 k_v V_v(t) + \frac{[k_a V_a(t) - k_v V_v(t)]}{[k_2 - k_3 V_a(t-\tau)]} \quad (37)$$

$$EFLH = GFR - \{5.815 - 0.0357\,x\,[Na^+]\}\,GFR \quad (21)$$

$$dR/dt = (RS - 0.2\,R)/V \quad (30)$$

$$dA/dt = (AS - 6.06\,A)/V \quad (32)$$

$$d(ALD)/dt = \{0.25[3(4.43A-67.7)+21.64PK-55.5]-0.62ALD\}/V \quad (33)$$

MODEL PARAMETERS

Arterial compartment stiffness coefficient k_a = 2.0 mmHg/mL.

Venous compartment stiffness coefficient k_v = 0.3 mmHg/mL.

Model constant k_1 = 8.3 mL/(sec.mmHg).

Model constant k_2 = 1.895 (sec.mmHg)/mL.

Model constant k_3 = 0.0224 (sec.mmHg)/mL^2.

Model constant k_4 = 0.0076 mL/(sec.mmHg).

Model constant k_6 = 0.25 1/sec.

Constant describing the inotropic state of the heart k_I = 8.125 mL/(sec.mmHg)

Fluid flow from organs Q_{in} = 0.023mL/sec

Time delay for the baroreceptors mechanism τ_1 = 5 sec.

Time delay for the Aldosterone mechanism τ_2 = 2 hours.

Model constant A = 5305 mmHg

Model constant B = 117 $pg.mL^{-1}$

Constant associated with the speed of BP response p_{202} = 2.67 min^{-1}.

Infusion rates u = 0.01, 0.025, 0.05, and 0.1 pg. $mL^{-1}.min^{-1}$.

Plasma volume V = 4.8 liters.

Potassium concentration PK = 5 ng/liter.

CHAPTER 4

RESULTS AND DISCUSSIONS

The mathematical model described in this paper has been developed for the primary purpose of helping to understand the dynamics and control of the human renal system. The model studies the role of the renal system in arterial pressure regulation. The model equations were coded in Vissim 1.2 student version. The differential equations were integrated numerically by a fourth order variable-step Runge-Kutta routine adopting a nominal step size of 0.05 sec. The representational validity of the study was examined by comparison of the model responses to physiological responses reported in the literature.

The presence of angiotensin II in the blood leads to increased arterial blood pressure. Angiotensin II can increase the arterial pressure in two ways: 1) by constricting the arterioles throughout the body, thereby increasing the peripheral resistance and leading to increased arterial pressure, and 2) by causing the kidney to retain water and salt, over a period of days through Aldosterone secretion [3]. White developed a mathematical equation that relates Angiotensin II concentration in the blood to the arterial blood pressure [5]. He used four different infusion rates 0.01, 0.025, 0.05,and 0.1 $\mu g.kg^{-1}.min^{-1}$ of angiotensin II in the blood stream. As a result the arterial blood pressure showed a deviation from it's steady state value by 15, 23, 27,and 30 mm Hg respectively at each infusion rate (see figures 6 & 7).

The model simulates the renin/Angiotensin/Aldosterone system using equation (30), (32), and (33). Figures 14, 15, and 16 are numerical translations of equations 30, 32, and 33, respectively. As mentioned earlier, renin release is a function of sodium

concentration, especially in the distal tubule. Literature review showed that low glomerular filtration (due to low pressure) causes low concentration of ions. Low concentration of ions causes juxtaglomerular cells to release renin, so that the pressure is inversely related to renin concentration.

The model investigated renin behavior as a function of arterial pressure. Figure 14 shows renin regulation as arterial pressure ranged between 60 to 155 mm Hg. Renin was given an initial value of 0.06 GU/liter. The model behaved in agreement with the literature. Renin concentration decreased as the arterial pressure increased. At higher values of arterial pressure, renin reached a minimum value of 0.056 GU/min. (see figure 14 for details).

Renin acts as an enzyme to produce Angiotensin I. The Angiotensin I is converted to Angiotensin II. Regulation of Angiotensin II is simulated by equation (32). However, Angiotensin II is very sensitive to blood pressure. Increasing the concentration of Angiotensin II in the blood leads to increased arterial pressure (discussed earlier). Figure 15 shows the behavior of Angiotensin II concentration in the blood as a function of arterial pressure. Arterial pressure was varied from 60 to 155 mm Hg. When arterial pressure increases from 65 to 78 mm Hg, the Angiotensin II concentration stays at a constant value of 28 mg/liter. As the arterial pressure exceeds the value of 78 mmHg, Angiotensin concentration decreases to a minimum value of 25 ng/liter at P=155 mm Hg. (see figure 15). The concentration of Angiotensin II under normal physiological conditions is 27 ng/liter.

The presence of Angiotensin II in the plasma leads to increased Aldosterone secretion. Equation 33 is the mathematical simulation of Aldosterone regulation.

Aldosterone concentration is given as a function of Angiotensin II concentration. Therefore, increasing the arterial pressure leads to increased Aldosterone concentration. When the arterial pressure is varied from 60 to 110 mm Hg, Aldosterone concentration reaches a maximum value of 88 ng/liter. Then, at higher values of pressure, Aldosterone starts to decrease, reaching a minimum value of 83 ng/liter. The concentration of Aldosterone under normal physiological conditions at P =100 mm Hg is 85 ng/liter (see figure 16 for details). Potassium concentration was assumed to be constant at a value of PK=5 ng/liter.

One of the most important components of renal output is the glomerular filtration rate, GFR. Published data shows that GFR is directly related to arterial blood pressure. Increasing the arterial blood pressure leads to increasing GFR. Meanwhile, decreasing the arterial pressure causes GFR to decrease. In this study the GFR was simulated by equation (13). Figure 8 shows the behavior of the glomerular filtration rate as a function of arterial pressure. The arterial pressure ranged between 50 and 140 mmHg, as a result, the GFR increased from 56 to 120 mL/min. The obtained result behaved in agreement with the published data.

Renal output is divided into glomerular filtration and channel reabsorption. Channel reabsorption is affected by the presence of antidiuretic hormone (ADH). ADH increases water permeability in the distal tubule. The fraction of water reabsorbed in the distal tubule (EBDT) is simulated using equation (25). The graphical interpretation of equation (25) is given by figure 9. In figure 9, ADH concentration was varied from 1 to 5 mU/litre. Also, the water fraction (EBDT) was calculated. It was found that increasing ADH concentration caused EBDT to increase from 0.05 to 0.96.

There are different factors that lead to changes in renal output such as glomerular filtration, antidiuretic hormone ADH, sodium concentration, and arterial blood pressure. The proposed model simulates the real effect of each of these factors on renal output. As mentioned earlier, increasing the ADH concentration in the plasma leads to increased water reabsorption and causes the urine output to decrease. To study the effect of these factors on the urine output, first, the ADH concentration was varied from 1 to 5 Munit/Liter. Meanwhile, the glomerular filtration rate GFR and sodium concentration were given constant values of 120 mL/min and 140 meq/liter respectively. The simulation results show that urine output decreases from 4.5 mL/min to 0.25 mL/min as ADH concentration increases (see figure 12).

In addition, another trial was performed to investigate the relationship between renal pressure and urine output. Literature data shows that increasing the renal pressure leads to increased GFR and, as a result, urine output will increase. The model investigated this relationship by setting up the ADH concentration and the sodium concentration at constant values of 4 mu/lit and 140 meq/liter, respectively. Meanwhile, the renal pressure varied between 60 and 140 mm Hg. It was found that the urine output showed good agreement with the literature, increasing from about 0.28 mL/min to 0.52 mL/min as the renal pressure increased (see figure 11).

Finally, the relationship between the urine output and the sodium concentration was determined. The glomerular filtration rate and the ADH concentration were given constant values of 120 mL/min and 4 mu/liter, respectively. Also, the sodium concentration was varied from 140 meg/liter to 180 meq/liter. The graphical display of the relationship between urine output and sodium concentration is given in figure 13.

Figure 13 shows that increasing sodium concentration from 140 to 180 mEg/liter leads to increase in urine output from 0.6 mL/min to 40.0 mL/min.

Arterial pressure regulation is a very complex system. There are eight different controls that participate in arterial pressure regulation. These eight controls are divided into two groups: short-term regulation and long-term regulation. Short-term regulation depends upon the strength of the heart, the capacity of the blood vessels, and the total peripheral resistance [7,8,12]. Meanwhile, the long-term control system controls blood volume and extracellular fluid volume at the same time that pressure is controlled.

The mathematical model attempts to study the effect of the short-term and the long-term controls in arterial pressure regulation. The short-term controls include the baroreceptors mechanisms, the chemoreceptor system, the central nervous system chemical response, the stress relaxation mechanism, the capillary fluid shift mechanism and the renin-angiotensin vasoconstrictor mechanism [7,8,12]. The mathematical model ignores the chemoreceptor and the central nervous system chemical response mechanism.

The model includes the stress relaxation mechanism and the capillary fluid shift mechanism in the stiffness coefficients for the arterial and venous compartments. Also, the model included on the effects of the baroreceptor mechanism by controlling the peripheral resistance with a time delay of 5-7 seconds.

Long-term control includes two major mechanisms: the renal-body fluid mechanism and the Aldosterone mechanism. The renal-body fluid mechanism was introduced in the model as urine output. In addition, the Aldosterone mechanism was included in the model with a time delay of 1-2 hours.

Theory indicates that these controls work together to compensate for any deviation of arterial pressure from its normal value of 100 mm Hg. If the arterial pressure increases due to excess water intake or due to large quantities of salt intake, these controls bring the arterial pressure back toward the normal value. Also, theory indicates that the short-term controls try to reduce the arterial pressure deviation' to the extent possible, within a few seconds. Then, the long-term controls are activated to further regulate the arterial pressure.

In this study the arterial pressure was increased from 100 mmHg to 126 mm Hg and the venous pressure was given an initial value of 10 mmHg. The arterial pressure stayed at the new value (126 mmHg) until the short-term control (Barorceptor mechanism) was activated within 5 seconds. Activation of the Barorceptors caused the arterial pressure to drop from 120 mm Hg to 110 mm Hg.

Decreasing the arterial pressure increased the venous pressure from 10 mm Hg to 18.0 mm Hg (see figure 17 for details). The effect of long-term control (Aldosterone and Renal output) is later activated to reduce arterial pressure from 110 mm Hg to 103 mm Hg. Figure 17 shows that the Aldosterone mechanism is activated at t=15 second, but, in the human body, the Aldosterone mechanism takes effect after approximately 2 hours. The reason for this inconsistency in delay time is the limitation of the software, which shows both Baroreceptors and Aldosterone on the same graph.

Blood flow through blood vessels is driven by pressure differences throughout the vascular system. Blood vessels limit blood flow through resistance. Theory indicates that any increase in pressure decreases resistance. The model expresses the vessel resistance in equation (11). A graphical presentation of equation (11) is given in figure 18. The

resistance at P =100 mmHg is equal to 0.7 sec mm Hg/mL. To accommodate the pressure increase, the resistance drops from 1.9 to 0.45 sec.mmHg/mL. In order to decrease the arterial pressure from 126 to 110 mm Hg, the resistance increases from 0.45 to 0.7 sec.mmHg/mL. Also, the resistance is increased from 0.7 to 0.8 sec.mmHg/mL to decrease arterial pressure from 110 to 103 at t = 15sec. (See figure 18).

The Cardiac output Q_h is given in equation (8). According to the Frank Starling mechanism, Q_h is a function of venous pressure. As a result, any deviation in venous pressure will cause Q_h to change. Figure 19 is a representation of equation (8). The initial value of Q_h is given as 85 mL/sec. Decreasing venous pressure from 10 mm Hg to 8.0 mmHg causes Q_h to drop from 90 to 63 mL/sec. When the Baroreceptors are activated, venous pressure increases. As a result Q_h increases from 63 to 130 mL/sec. However, activation of the Aldosterone mechanism, causes Q_h to decrease from 130 mL/sec to about 108 mL/sec.

Venous return is simulated by equation 12. Venous return is a function of pressure difference and peripheral resistance. Venous return starts at 50 mL/sec. When the pressure difference increases, venous return jumps dramatically from 50 mL/sec to 127 mL/sec. After t=5 sec, venous return decreases from 127 mL/sec to 118 mL/sec. Meanwhile, activation of the Aldosterone mechanism helps to bring down the value from 118 to 110 mL/sec. (see figure 19).

Glomerular filtration rate plays an important role in urine output regulation. The glomerular filtration rate was given an initial value of 1.94 mL/sec. Increasing the pressure causes GFR to increase to a new value of 1.96 mL/sec. At t = 5 sec, GFR

increases to 1.978 mL/sec. Then, GFR decreases to a value of 1.955 mL/sec due to reduction in the arterial pressure (see figure 21).

The renal output adopted the same behavior as the GFR. First, the renal output increased from 0.00963 mL/sec to 0.00973 mL/sec. Then, at t = 5 sec the renal output increased to a new value of 0.00984 mL/sec. But at t = 15 sec, the renal output dropped to 0.00968 mL/sec (see figure 20).

Studying diseases such as hypertension is an important aspect of this model, when a person is said to be hypertensive, it means that his or her blood pressure is greater than normal. Angiotensin II and Aldosterone are considered to be major contributors to the elevated blood pressure seen in hypertension. Angiotensin II increases arterial pressure in tow ways: 1)- by constricting the arterioles and increasing the peripheral resistance, 2)- by increasing salt and water reabsorption.

This model shows that increasing Angiotensin II concentration leads to increase arterial pressure (See figure15),and also leads to increased Aldosterone secretion. Figure 13 shows that increasing Aldosterone secretion leads to increased sodium reabsorption. As a result, renal output decreases and causes blood volume to increase.

One of the clinical treatments for hypertension is to disable the renin-angiotensin system. Disabling the renin-angiotensin system is achieved by treating patients with ACE inhibitors. An ACE inhibitor blocks, such as captopril, ACE the enzyme used to convert Angiotensin I to Angiotensin II [6].

CHAPTER 5

RECOMMENDATION

The model simulated the effects of glomerular filtration rate, Aldosterone concentration, antidiuertic hormone (ADH), and blood pressure on renal output. Potassium concentration was considered to be constant. Potassium concentration plays a major role in Aldosterone formation (see equation 33). In addition, total Blood volume was considered to be constant at 4.8 liter. Under normal physiological conditions, blood volume varies due to many effects such as water intake or sodium intake. In order to obtain more accurate results, Potassium concentration and blood volume changes should be considered in future studies

.

APPENDIX A

NUMERICAL RESULTS

Figure 6: Change in Blood Pressure at Various Infusion Rates

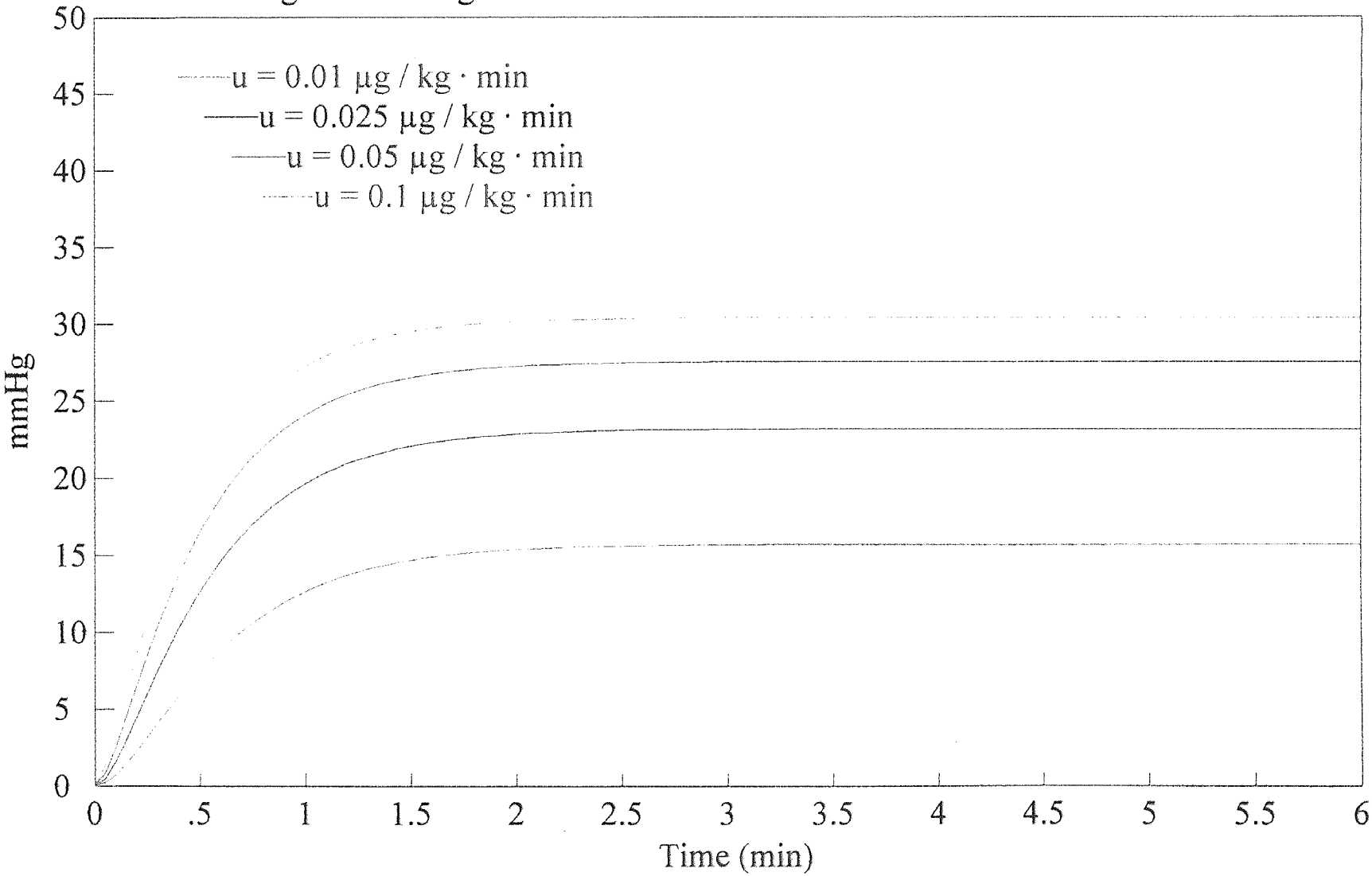


Figure 7: Change in arterial Plasma Angiotensin II at various Infusion rates

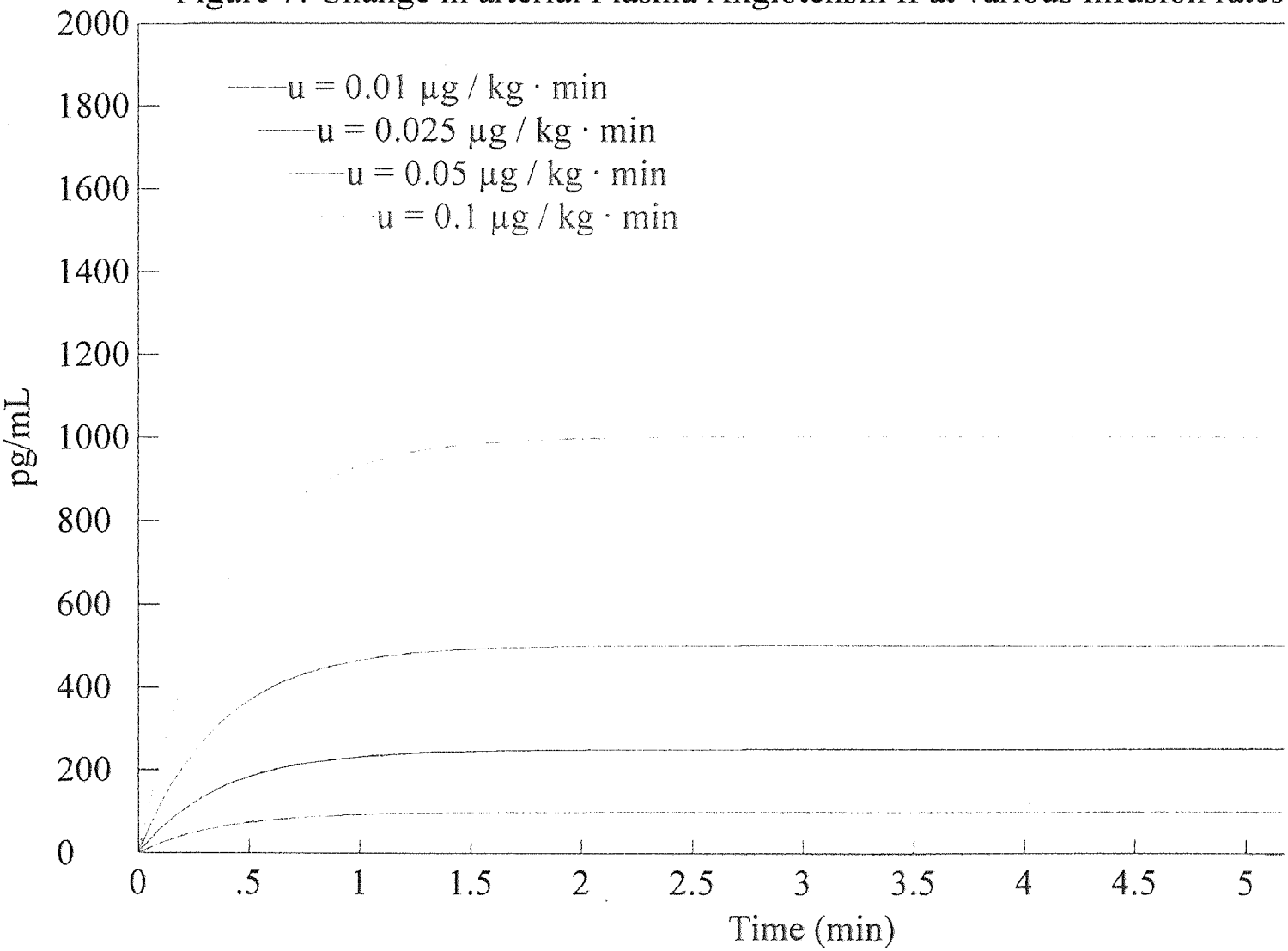


Figure 8: GFR Change as Pressure Increased from 50 to 140 mmHg

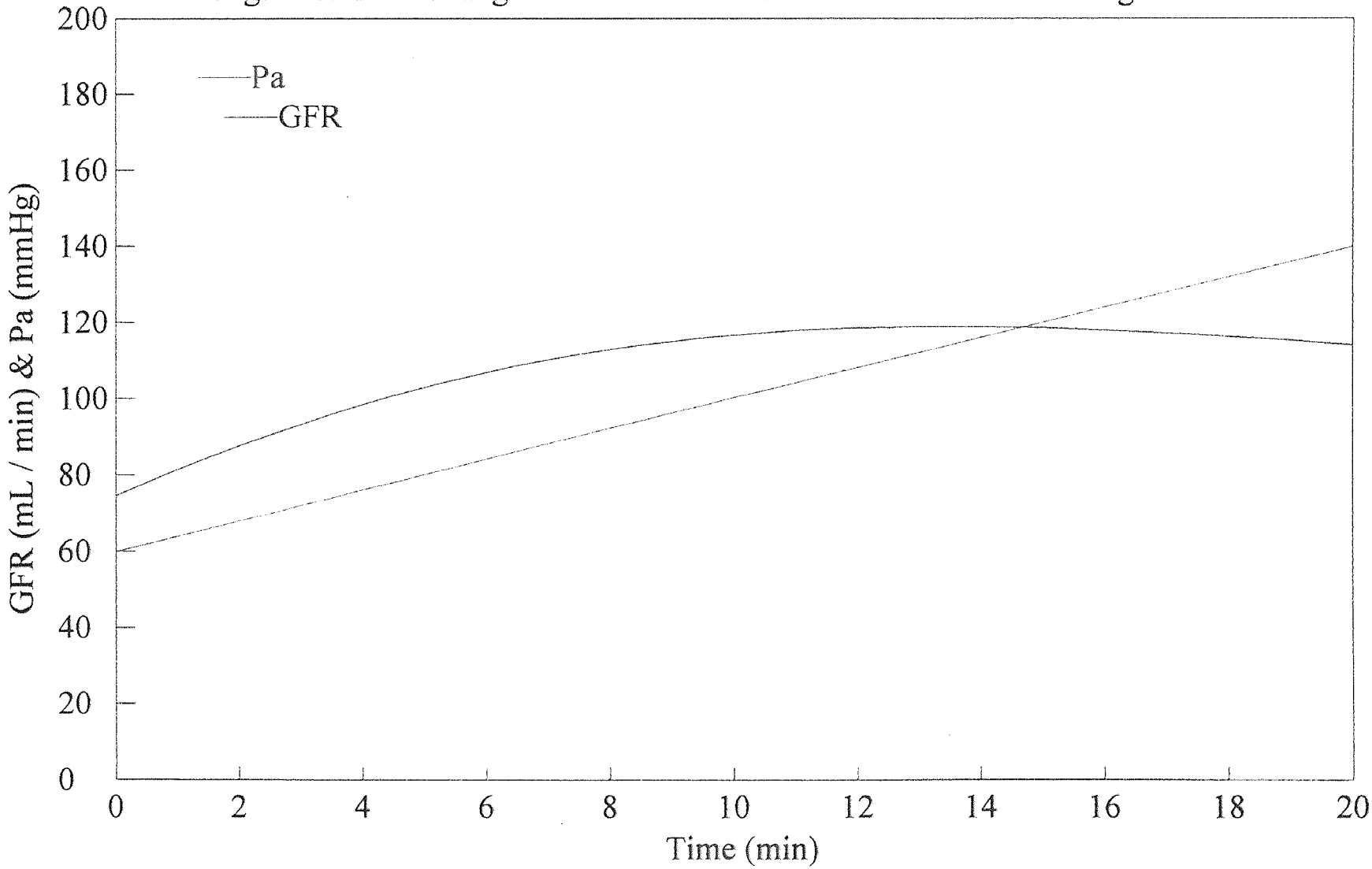


Figure 9: Water reabsorption in the Distal Nephron as ADH changes.

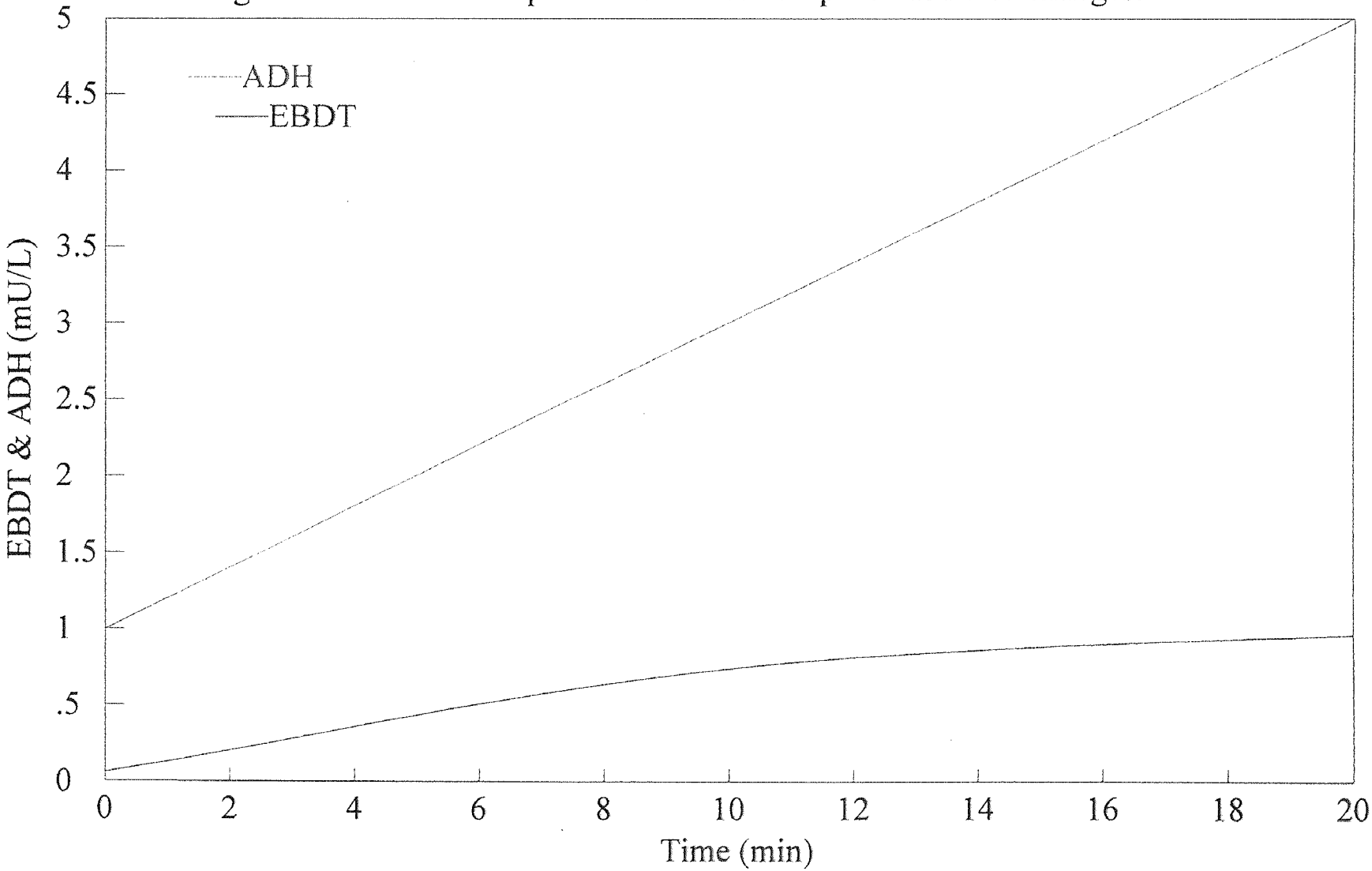


Figure 10: Sodium Reabsorption as Aldosterone ranged between 85 to 800 ng/L

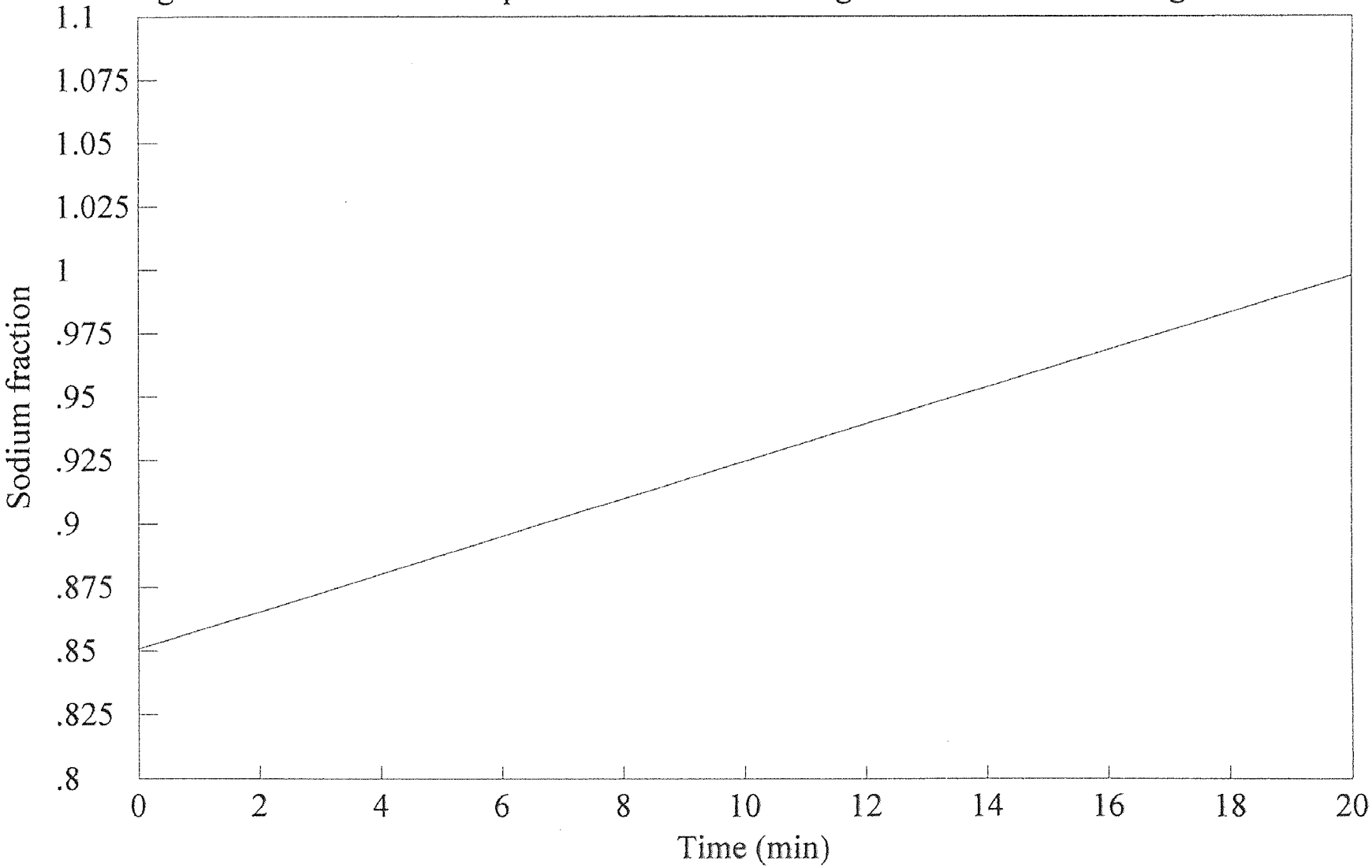


Figure 11: Urine Output as Blood Pressure Increases From 60 to 140 mmHg

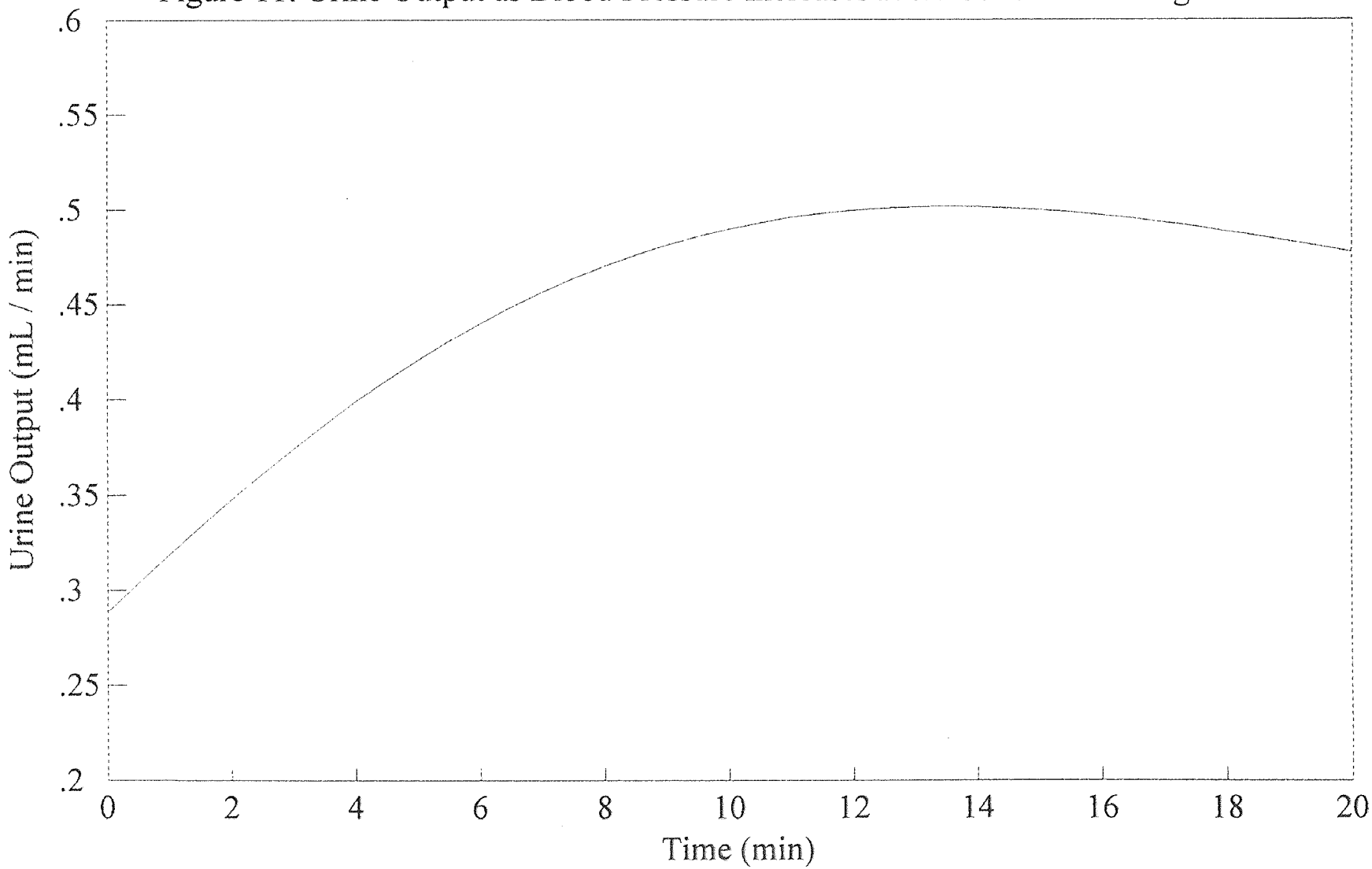


Figure 12: Urine output As ADH concentration Increases

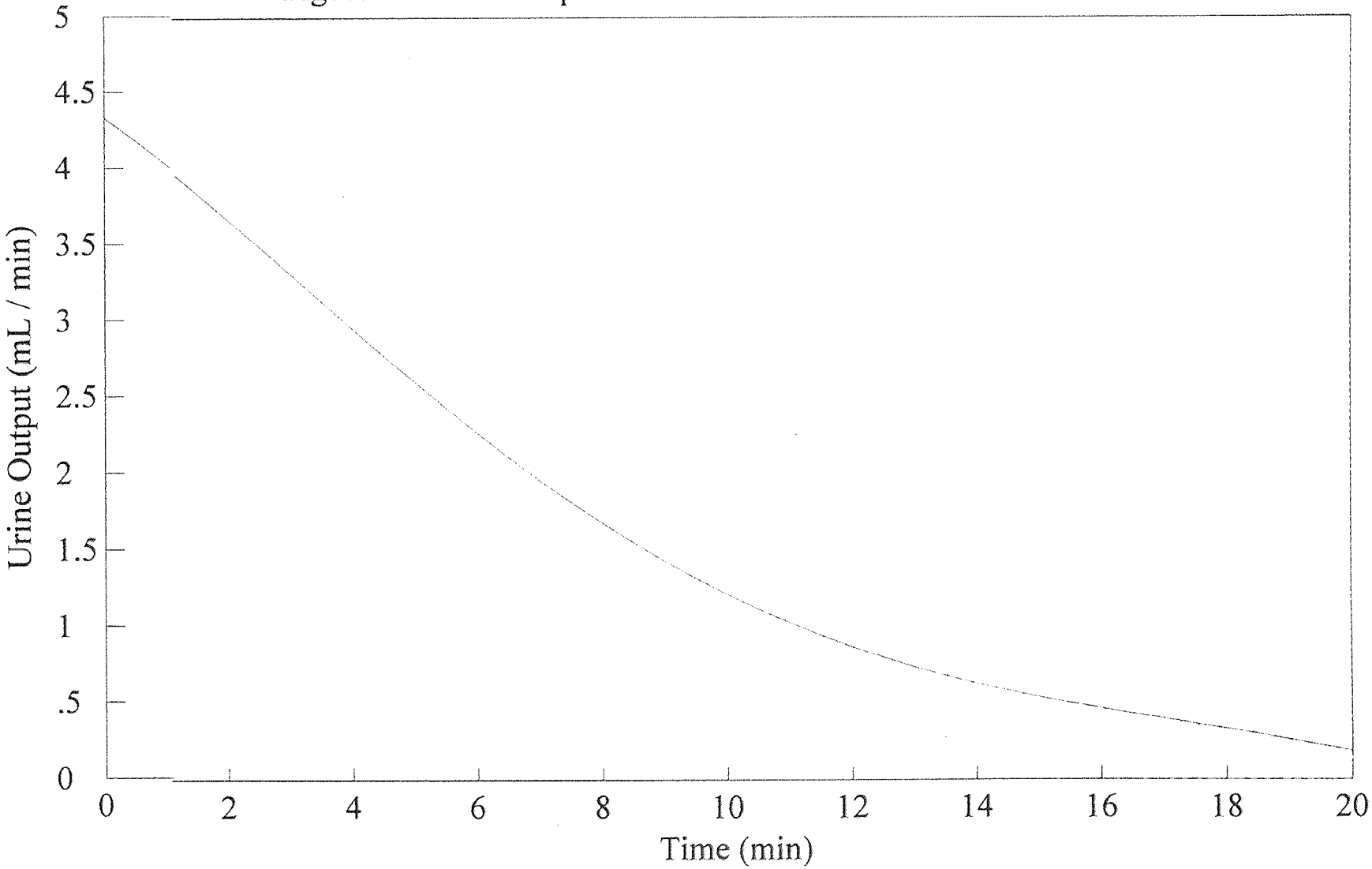


Figure 13: Urine Output as Sodium Concentration Increases From 140 to 180 meq / L

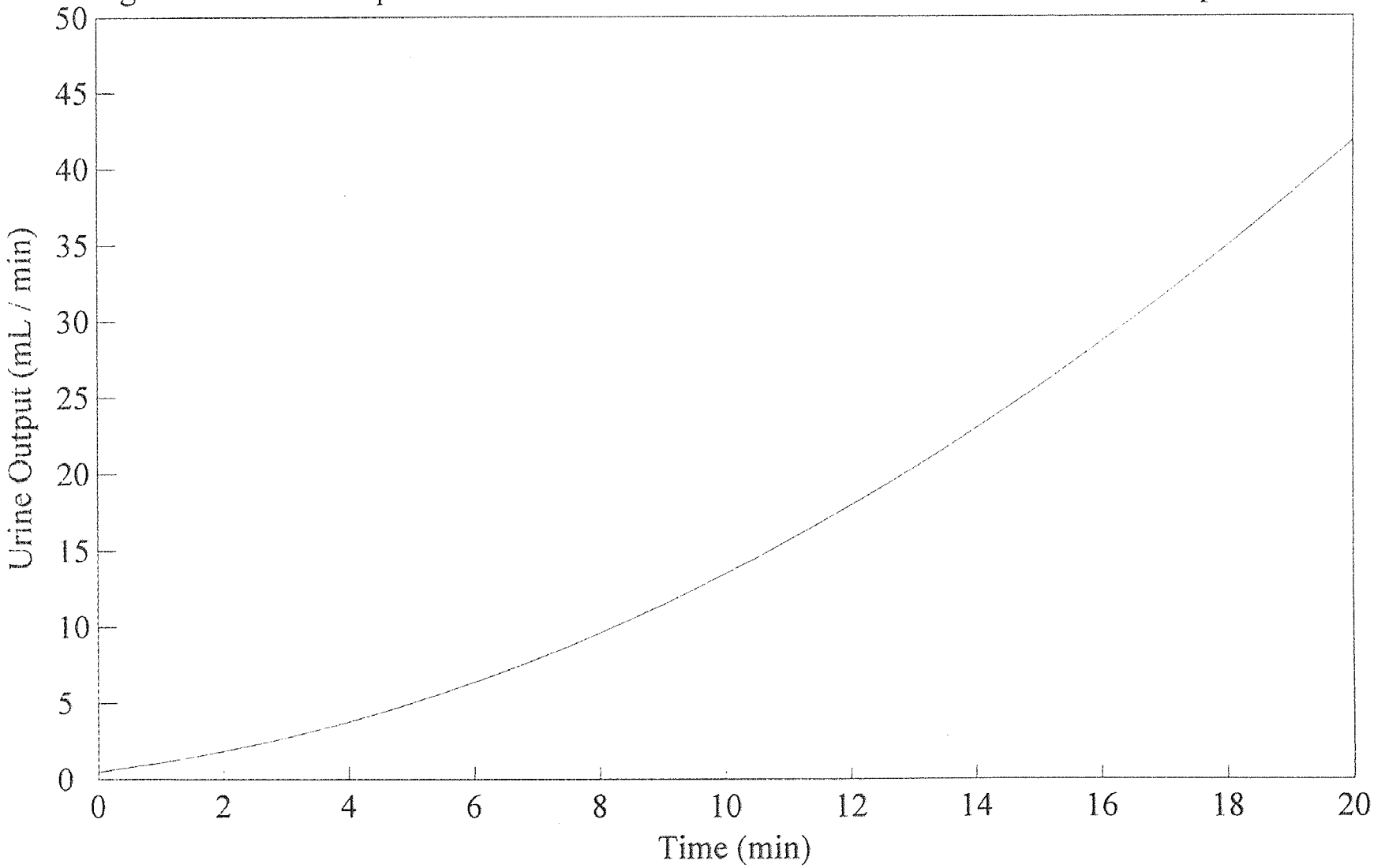


Figure 14: Renin regulation as Blood Pressure Increased From 60 to 155 mmHg

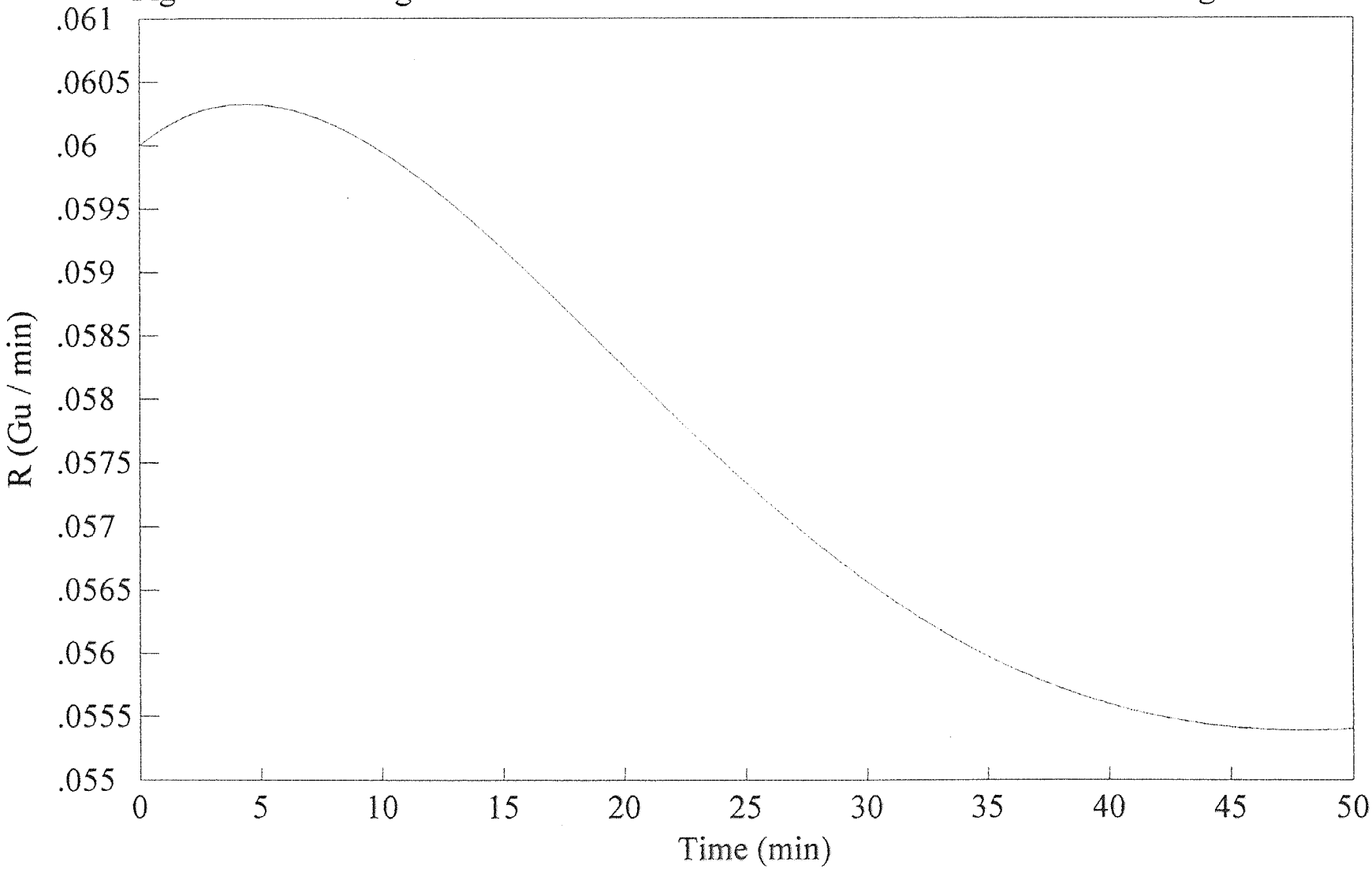


Figure 15: Angiotensin II Formation as Blood Pressure Increased From 60 to 155 mmHg

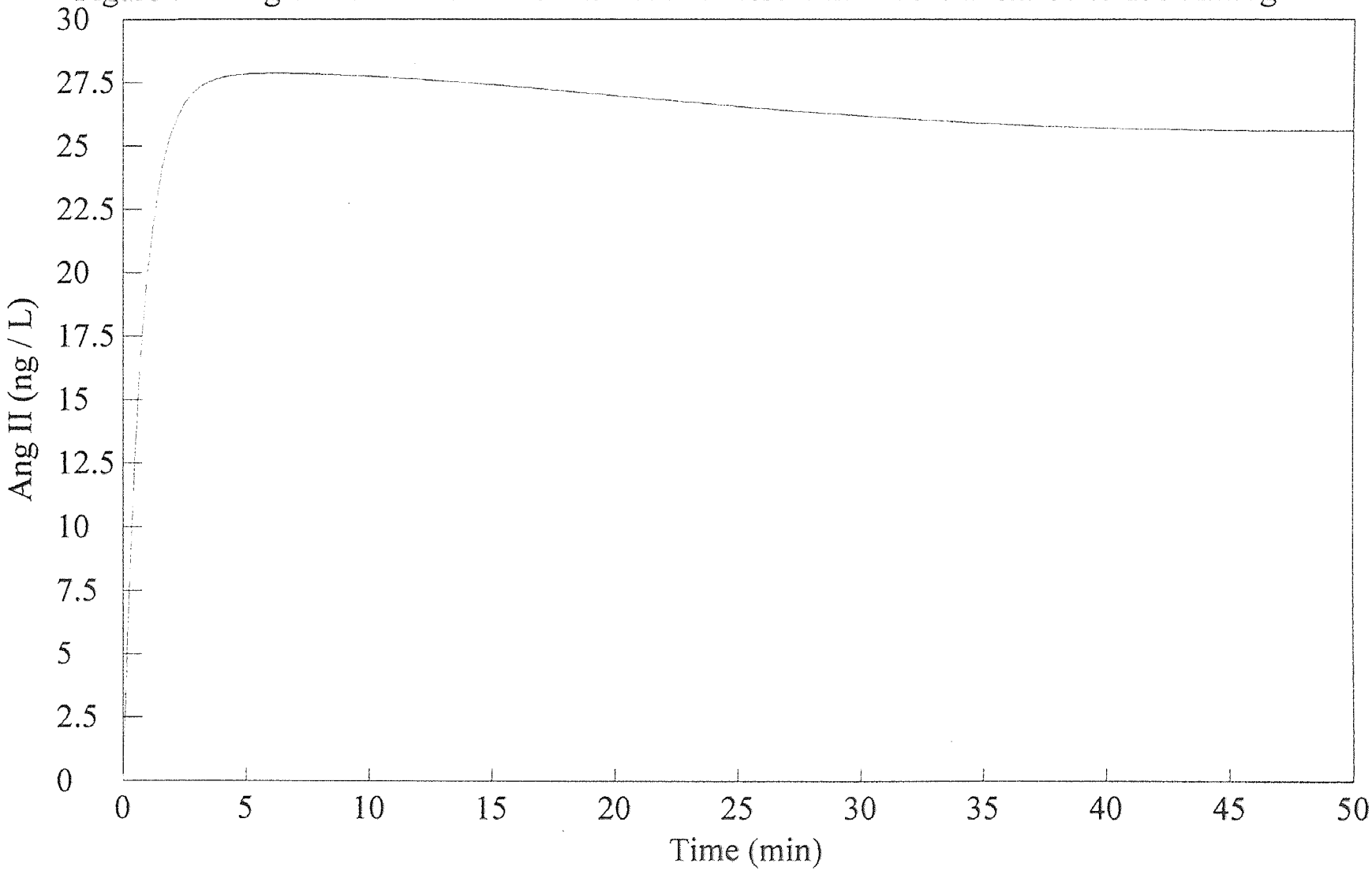


Figure 16: Aldosterone Formation as Blood Pressure Increased From 60 to 155 mmHg

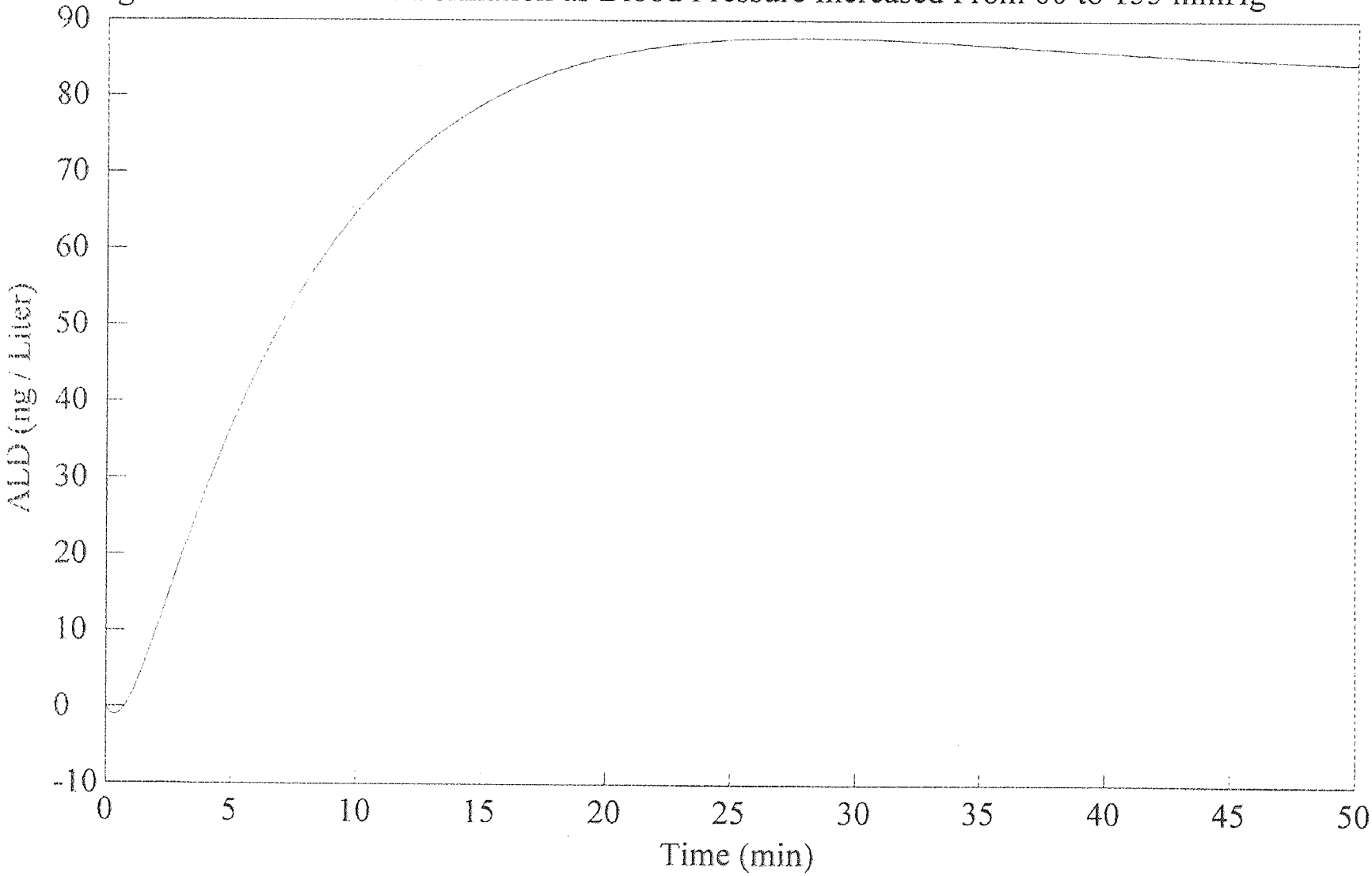


Figure 17: Arterial Pressure and Venous Pressure

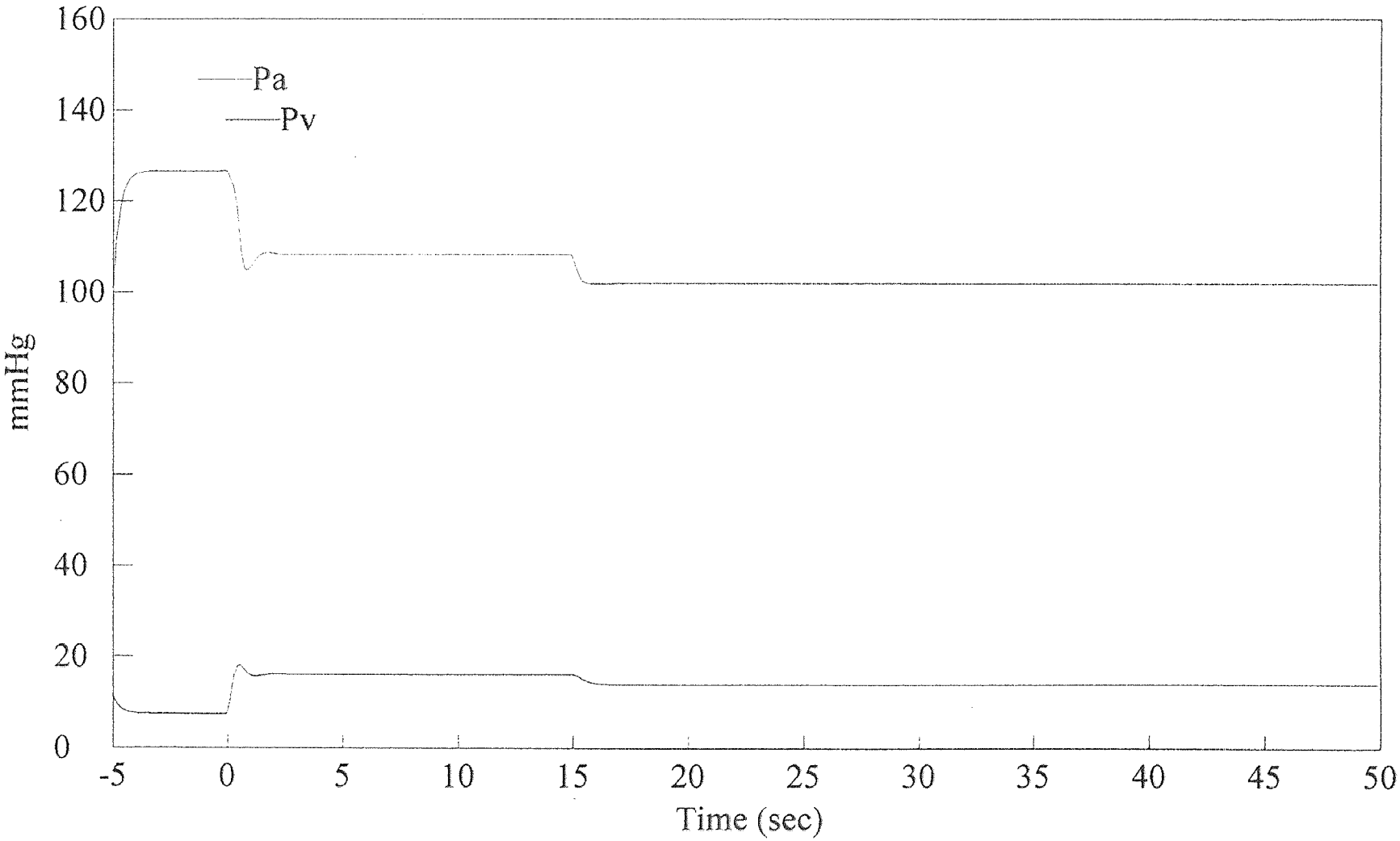


Figure18: The Peripherial Resistance

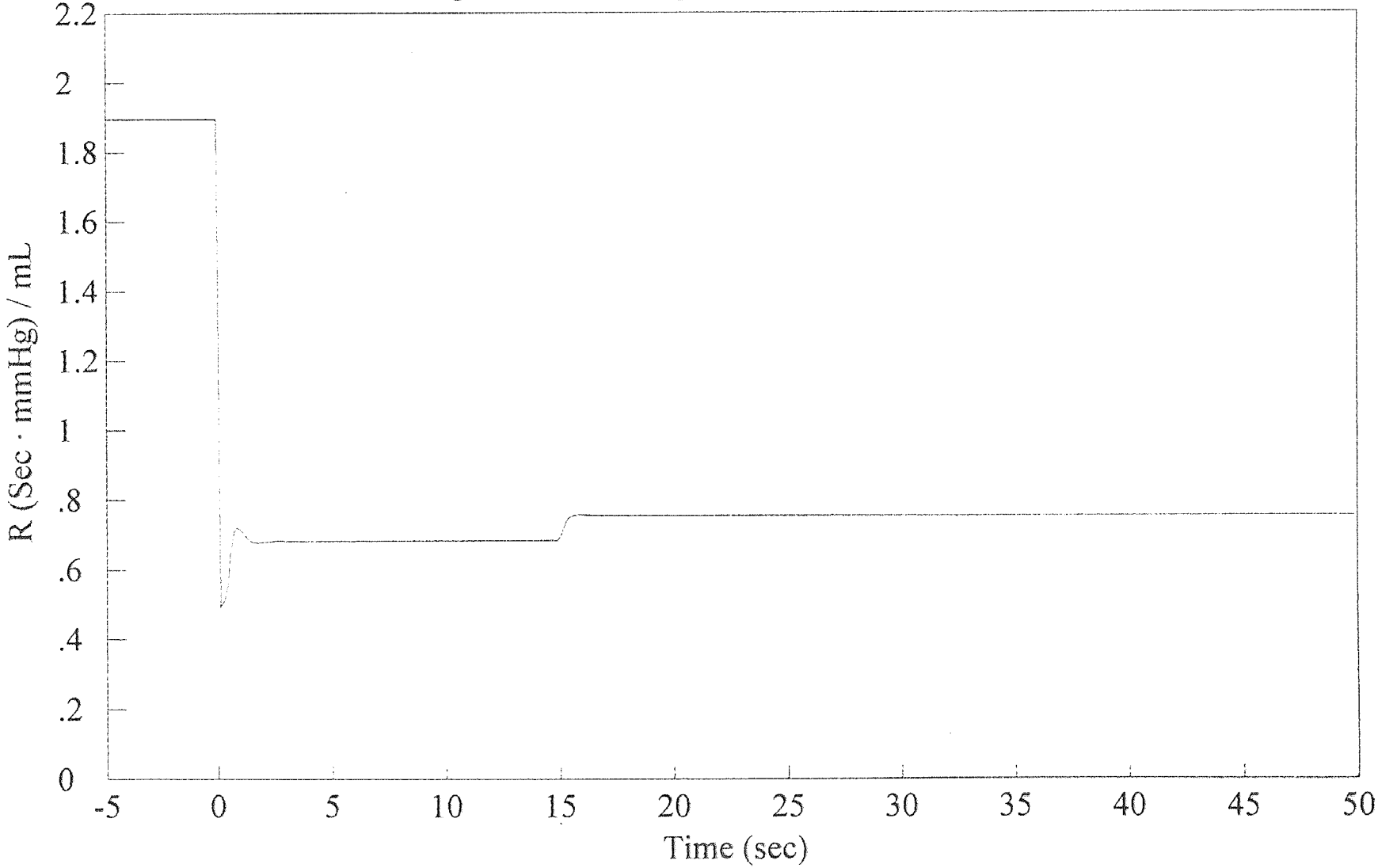


Figure 19:Cardaic Output and Venous Return

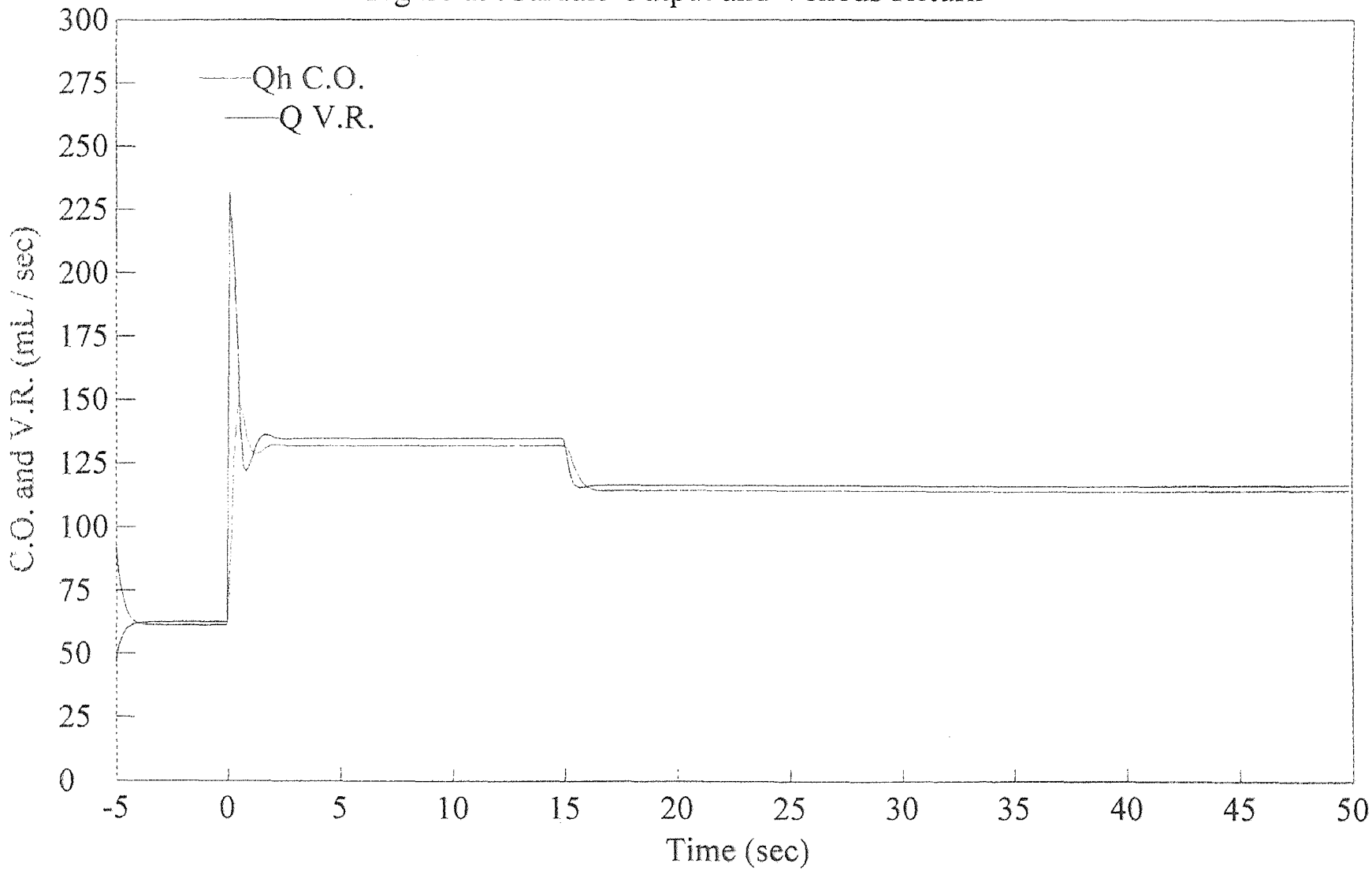


Figure 20: Glomerular Filtration Rate

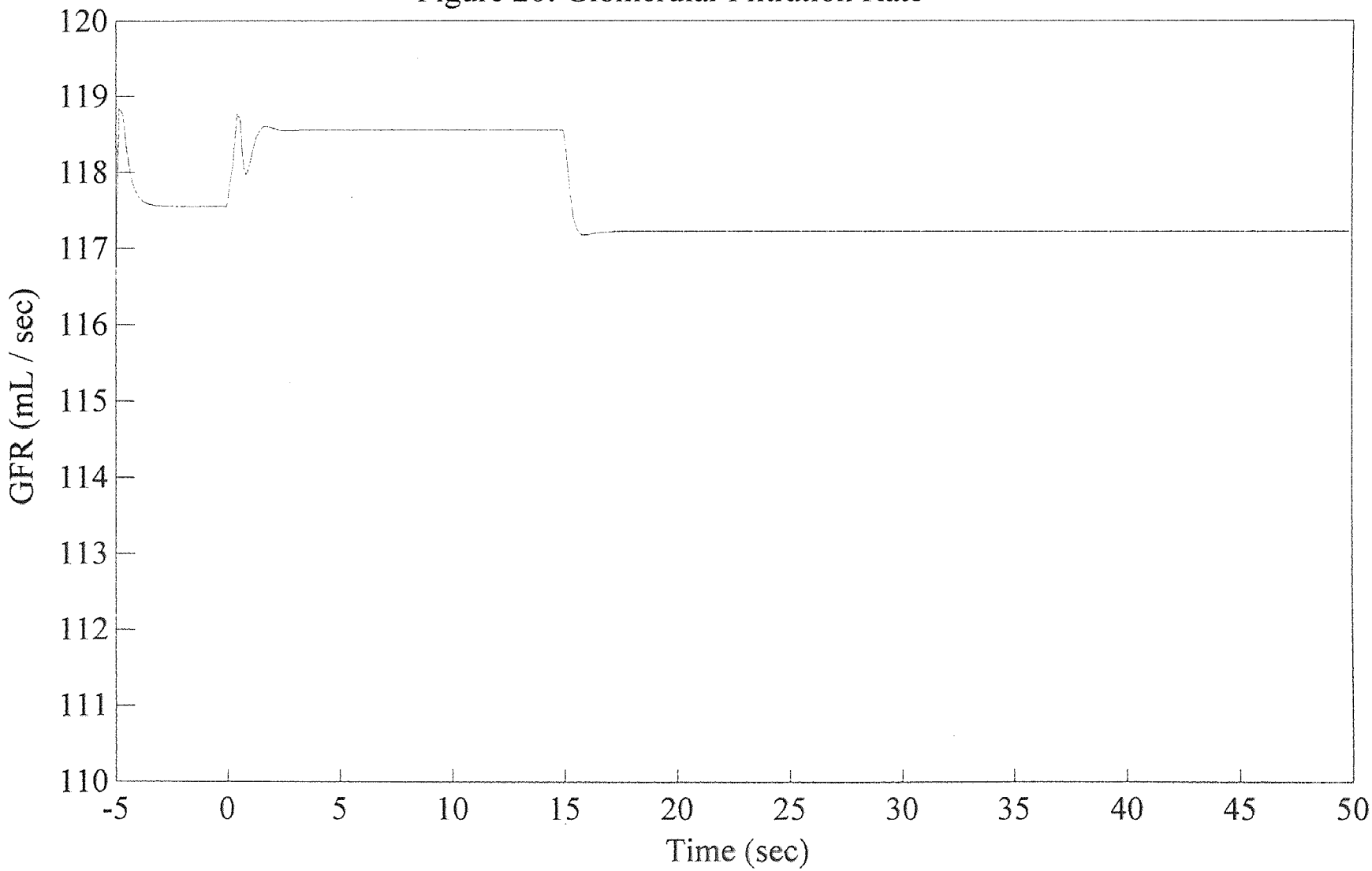


Figure 21: Urine Output

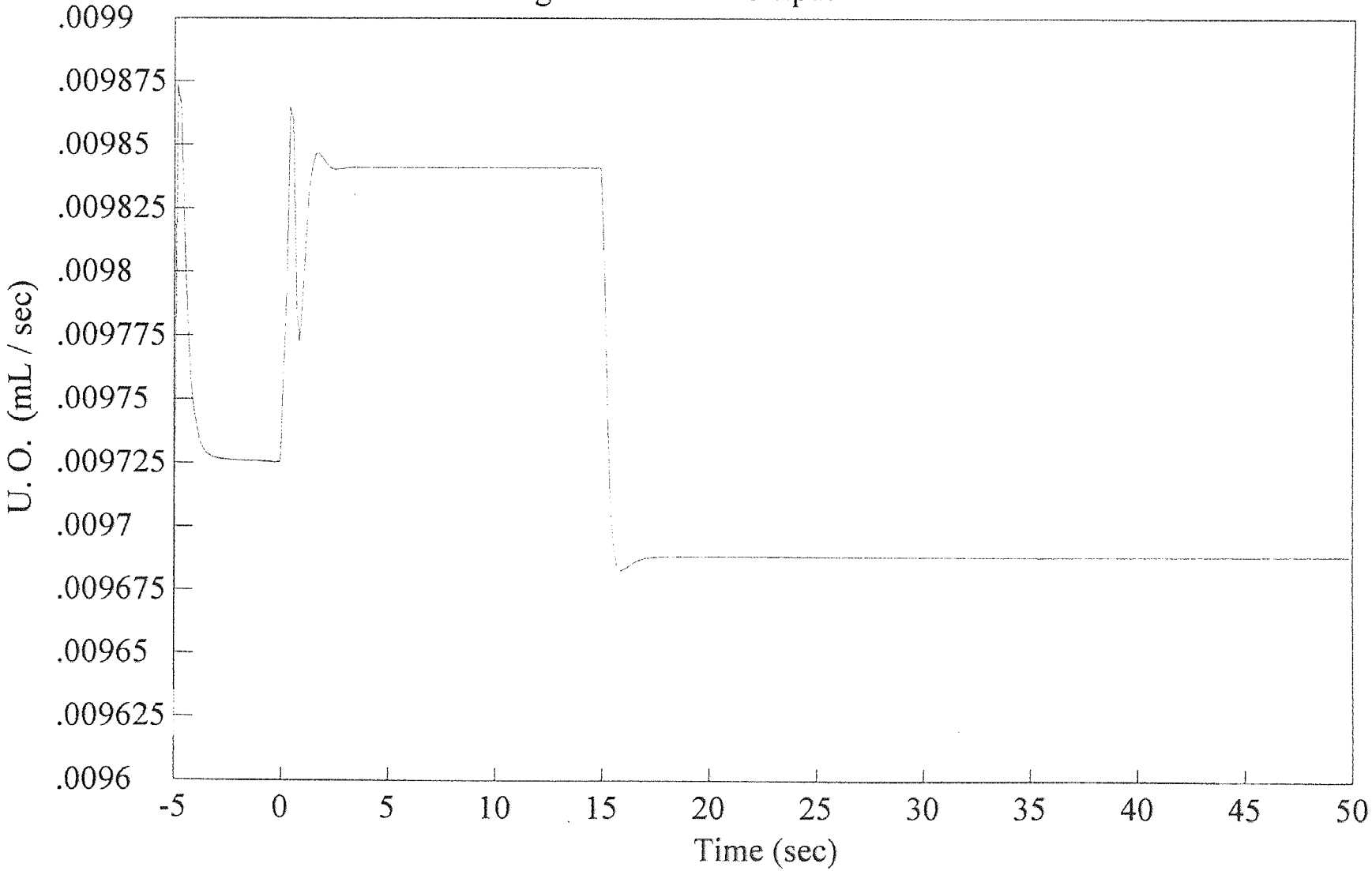


Figure 1 shows the basic anatomy of human kidney.

Figure 2 shows the basic anatomy of the nephron. Each nephron has glomerulus, loop of henle, and collecting duct.

Figure 3 shows a summary of the renin-angiotensin system. Low blood flow in the afferent simulate the juxtaglomerular to secret renin which acts on angiotensinogen to produce Angiotensin I. Angiotensin I is converted by ACE to angiotensin II.

Figure 4 shows Preston (3) infusion model where x_4 and x_5 are angiotensin II concentration and blood pressure. Also Y_4 and Y_5 are experimental measurements of angiotensin II and blood pressure.

Figure 5 shows the cardiovascular system. Compartment A simulates arterial volume and compartment V simulates venous volume. R simulates the peripheral resistance and Q_h is cardiac output.

Figure 6 shows the change in blood pressure at various infusion rate of 0.01, 0.05, 0.025' and 0.1 $\mu g. Kg^{-1}.min^{-1}$.Also, this figure is numerical simulation of equation (4).

Figure 7 simulate the change in arterial plasma Angiotensin II concentration at various infusion rate of 0.01, 0.05, 0.025' and 0.1 $\mu g. Kg^{-1}.min^{-1}$.Also, this figure is numerical simulation of equation (5).

Figure 8 simulates glomerular filtration rate (GFR) as the arterial pressure (Pa) ranges between 50 and 140 mmHg. Also, this figure is numerical simulation of equation (13).

Figure 9 simulates water reabsorption (EBDT) in the distal nephron as the antidiuretic hormone concentration (ADH) ranges between 1 and 5 (mU/liter). Also, this figure is numerical simulation of equation (25).

Figure 10 simulates sodium reabsorption in the distal nephron as the Aldosterone concentration ranges between 85 and 800 (ng/liter). Also, this figure is numerical simulation of equation (27).

Figure 11 simulates urine output as blood pressure in creases from 60 to 140 mmHg. Where the ADH concentration = 4 mU/liter and sodium concentration is 140 ng/liter Also, this figure is numerical simulation of equation (38).

Figure 12 simulates urine output the antidiuretic hormone concentration (ADH) increases. Sodium concentration is 140 ng/liter and glomerular filtration rate (GFR) = 120 mL/min. Also, this figure is numerical simulation of equation (38).

Figure 13 simulates urine output sodium concentration varies from 140 to 180 meq/liter. The glomerular filtration rate (GFR) = 120 mL/min and ADH = 4 mU/liter. Also, this figure is numerical simulation of equation (38).

Figure 14 simulates renin regulation in the blood as blood pressure increased from 60 to 155 mmHg. Pressure increases causes the renin to decrease. This figure is numerical simulation of equation (30).

Figure 15 simulates angiotensin II formation in the blood as blood pressure increased from 60 to 155 mmHg. Pressure increases causes the renin to decrease which leads to decrease angiotensin II formation This figure is numerical simulation of equation (32).

Figure 16 simulates Aldosterone formation in the blood as blood pressure increased from 60 to 155 mmHg. Pressure increases causes the renin to decrease which leads to decrease angiotensin II formation as a result Aldosterone formation will drop. This figure is numerical simulation of equation (33).

Figure 17 simulates the arterial pressure and venous pressure regulation. Baroreceptor mechanisms and Aldosterone mechanism take effect at 5 and 15 second. This figure is numerical simulation of equations (36) and (37).

Figure 18 simulates the peripheral resistance. The baroreceptors are responsible for controlling the peripheral resistance. This figure is numerical simulation of equation (11).

Figure 19 simulate the cardiac output Q_h and the venous return Q. Increasing the pressure leads to increase both Q_h and Q. This figure is numerical simulation of equations (8) and (12).

Figure 20 simulates the role of glomerular filtration rate (GFR) in arterial blood pressure regulation. Increasing blood pressure leads to increase GFR. This figure is numerical simulation of equation (13).

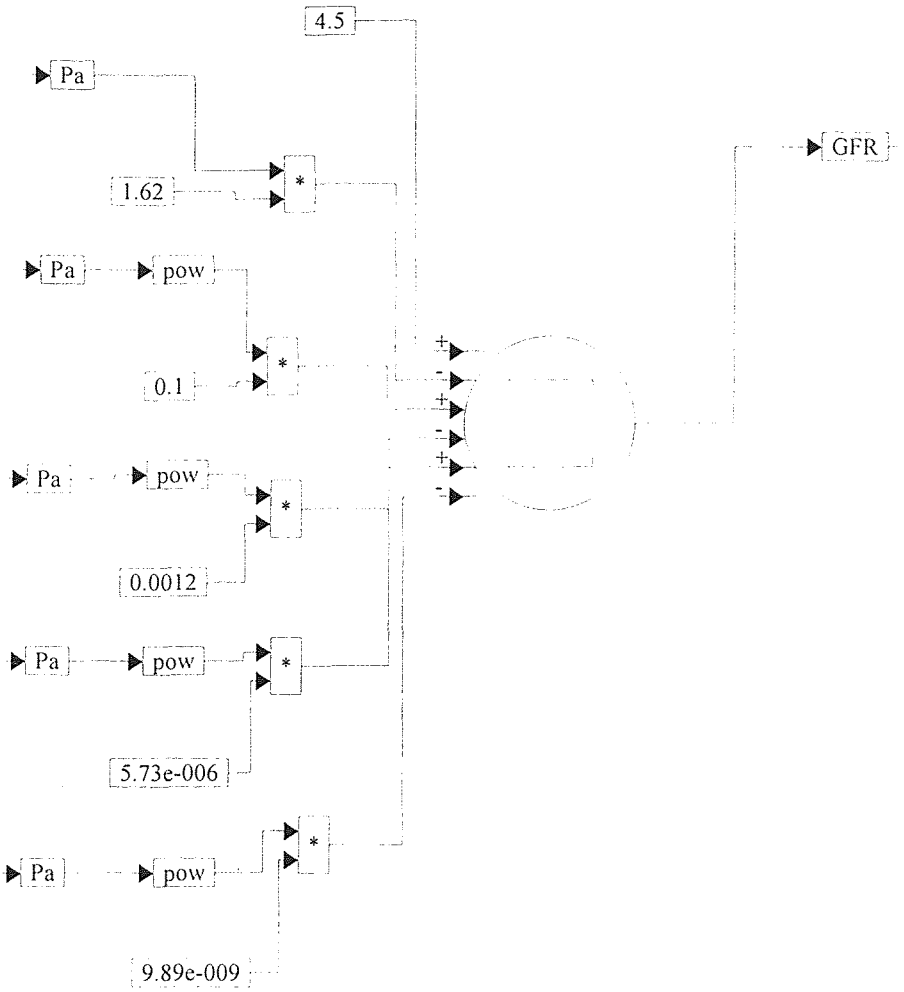
Figure 21 simulates the role of urine output in arterial blood pressure regulation. Increasing the pressure leads to increase the urine output which aids to reduce blood volume and leads to reduce blood pressure. This figure is numerical simulation of equation (38).

APPENDIX B

VISSIM CODE

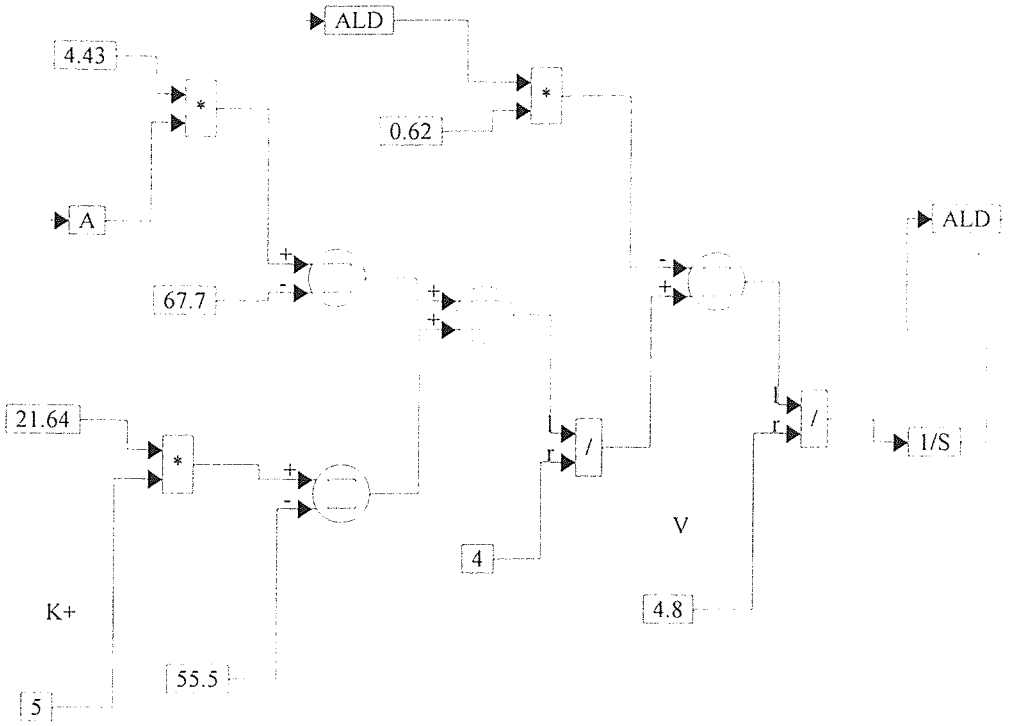
VisSim-gfr.vsm

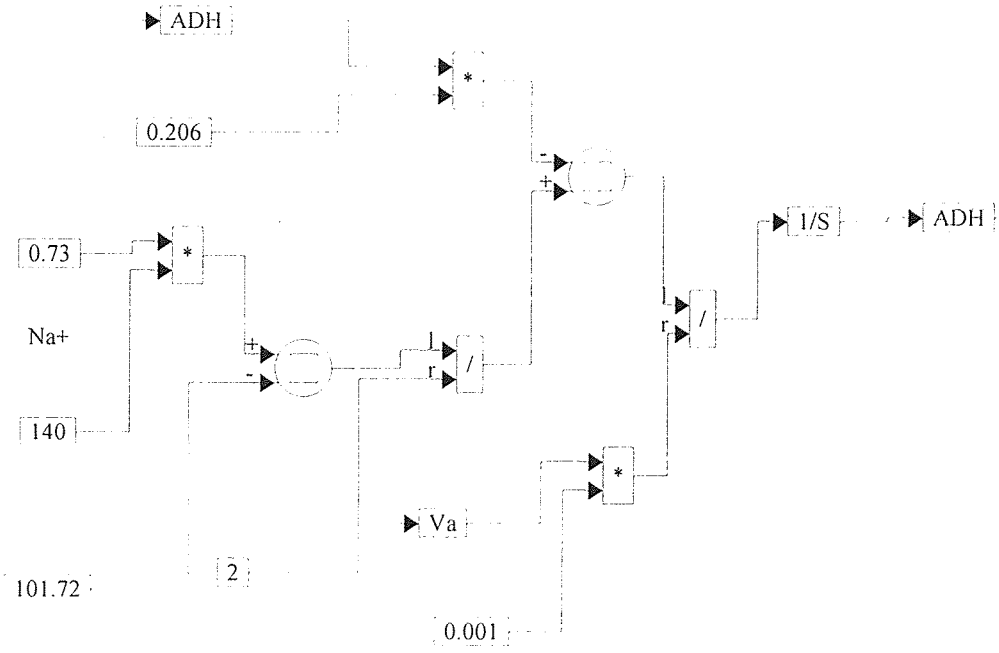
Glomerular Filtration Rate (GFR).
This is vissim code for equation (13).



VisSim-adh.vsm

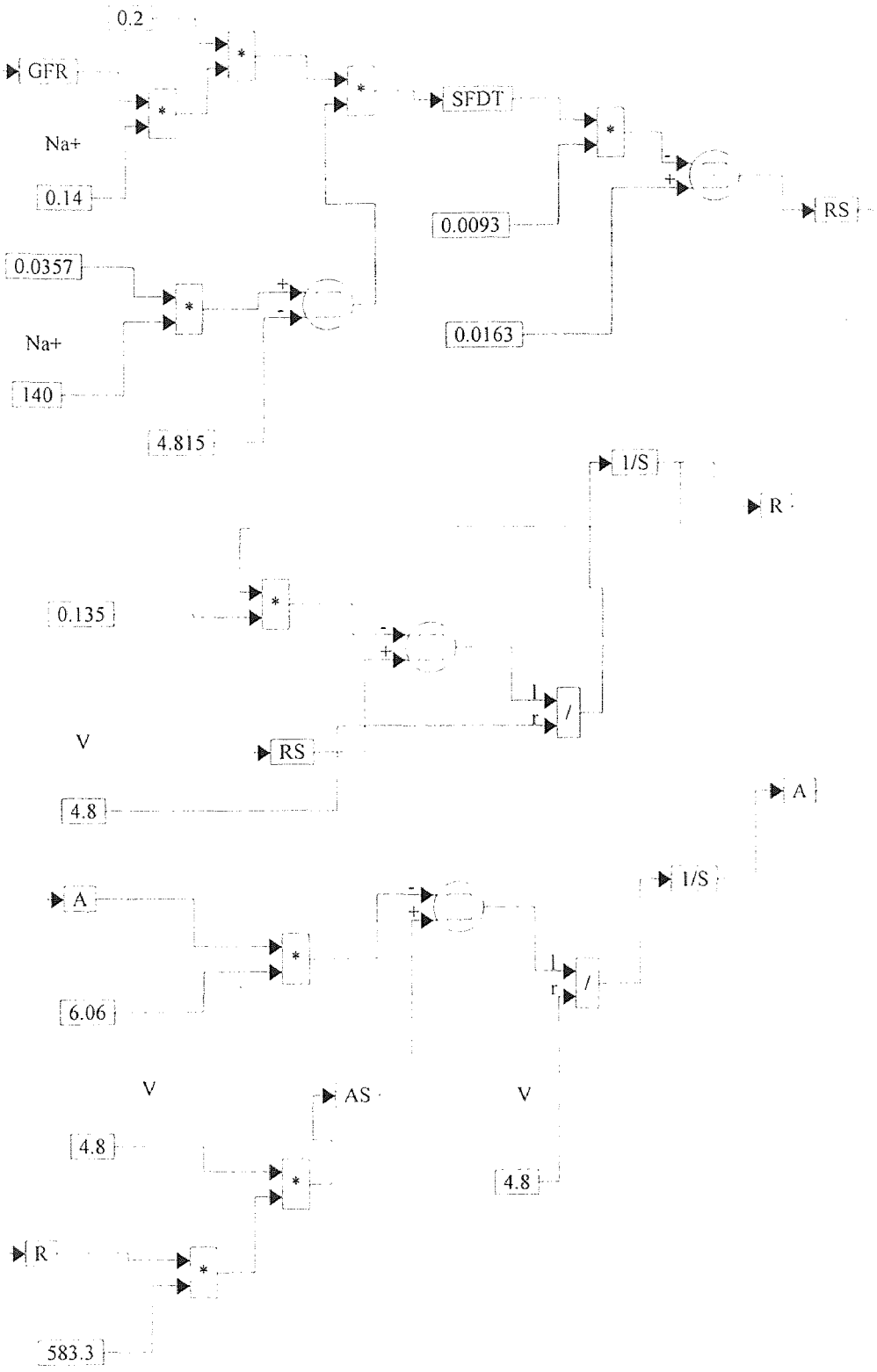
Aldosterone Formation (ALD) and ADH formation.
This is vissim code for equations (26) and (33).



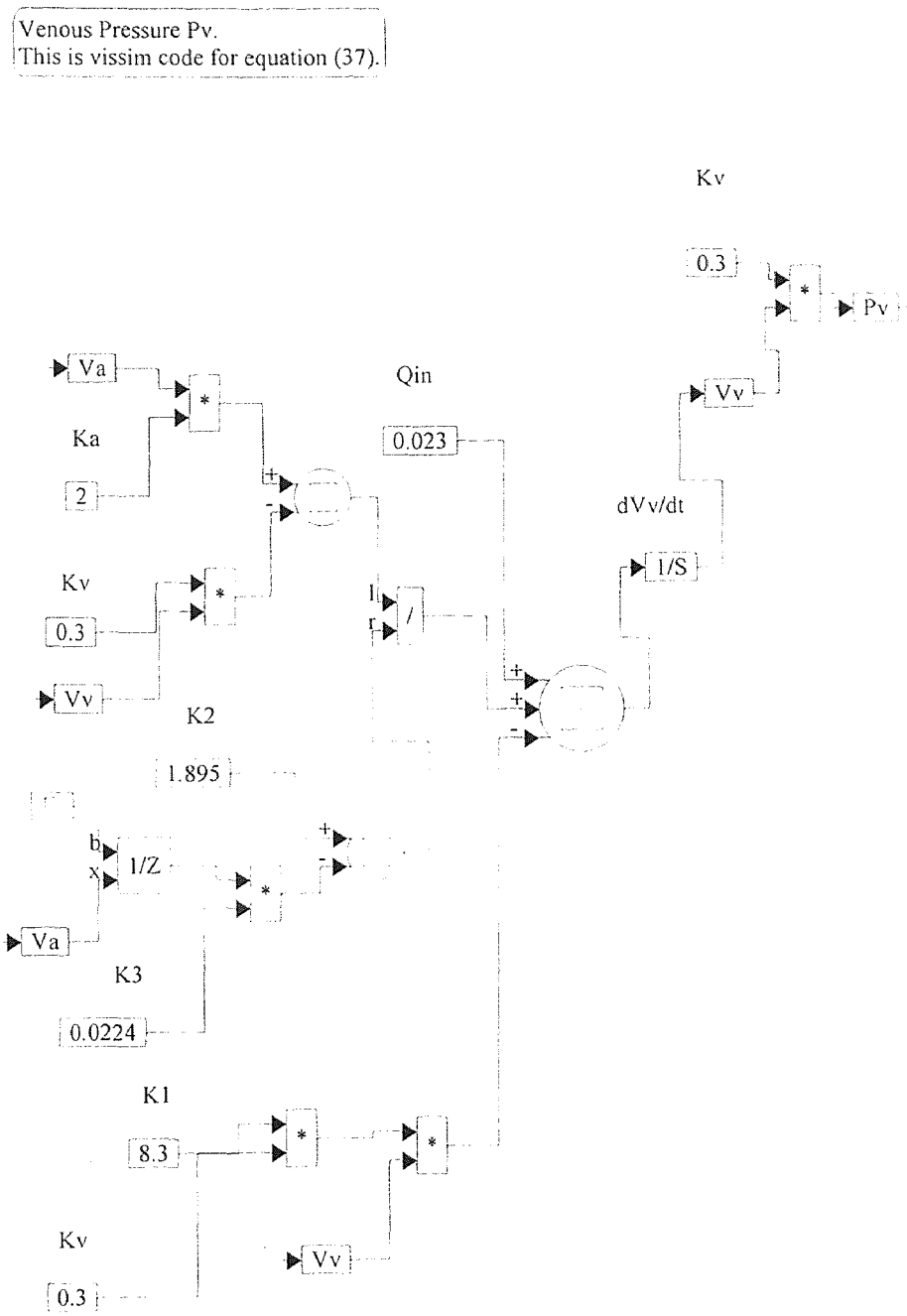


VisSim-angii.vsm

Renin Release (RS), Reninr formation (R), and Angiotensin II formation (A).
This is vissim code for equations (28), (30), and (32).

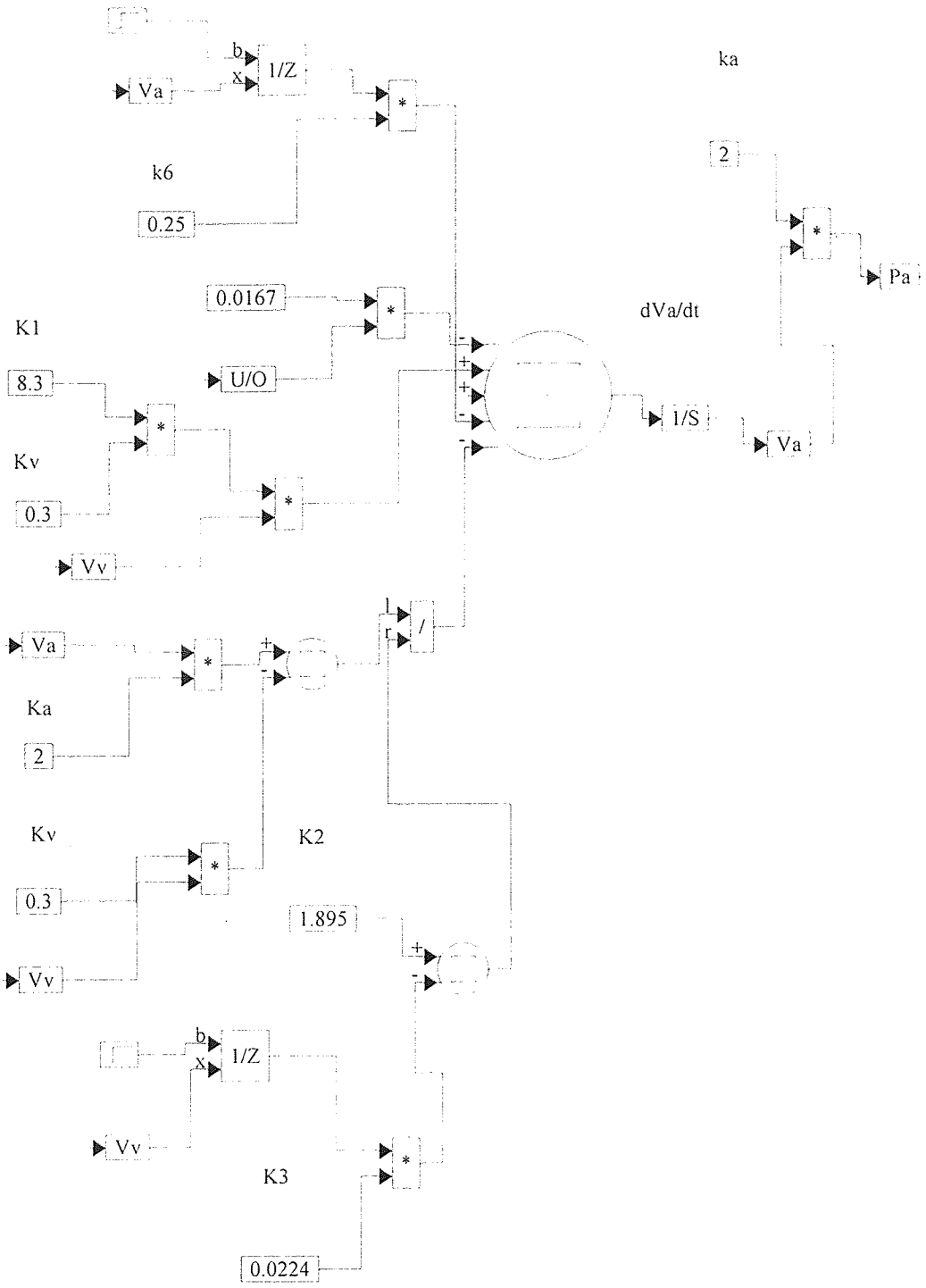


VisSim-pv.vsm



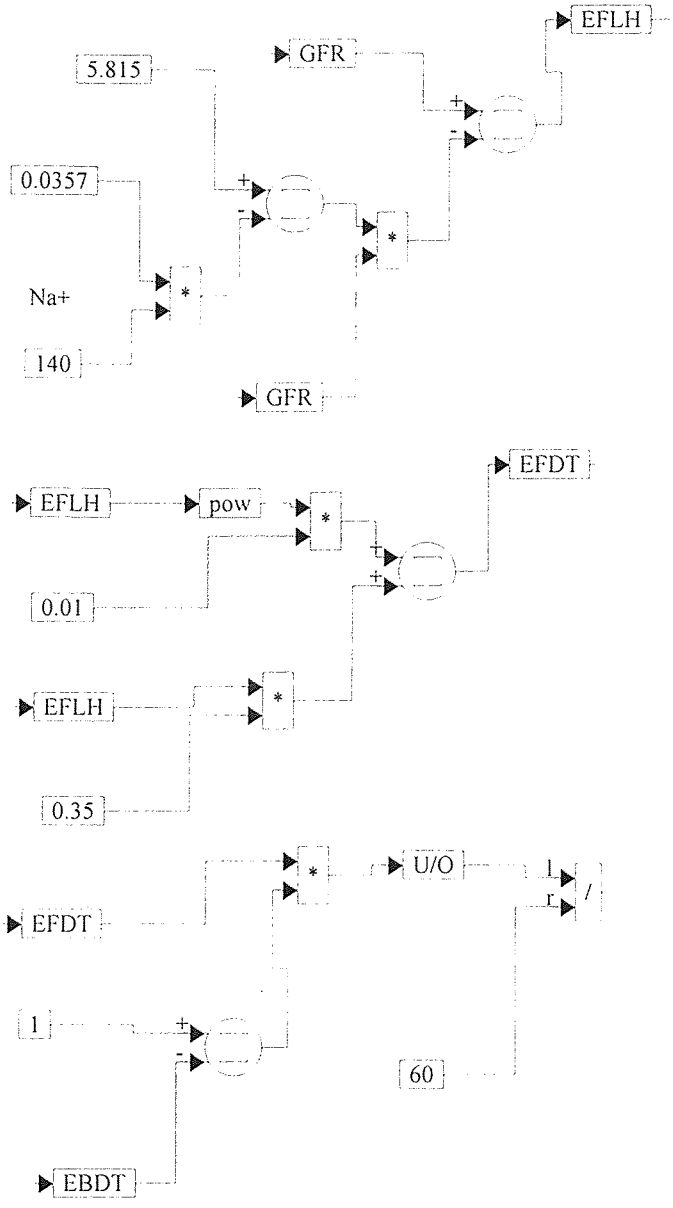
VisSim-pa.vsm

Arterial Pressure Pa.
This is vissim code for equation (36)



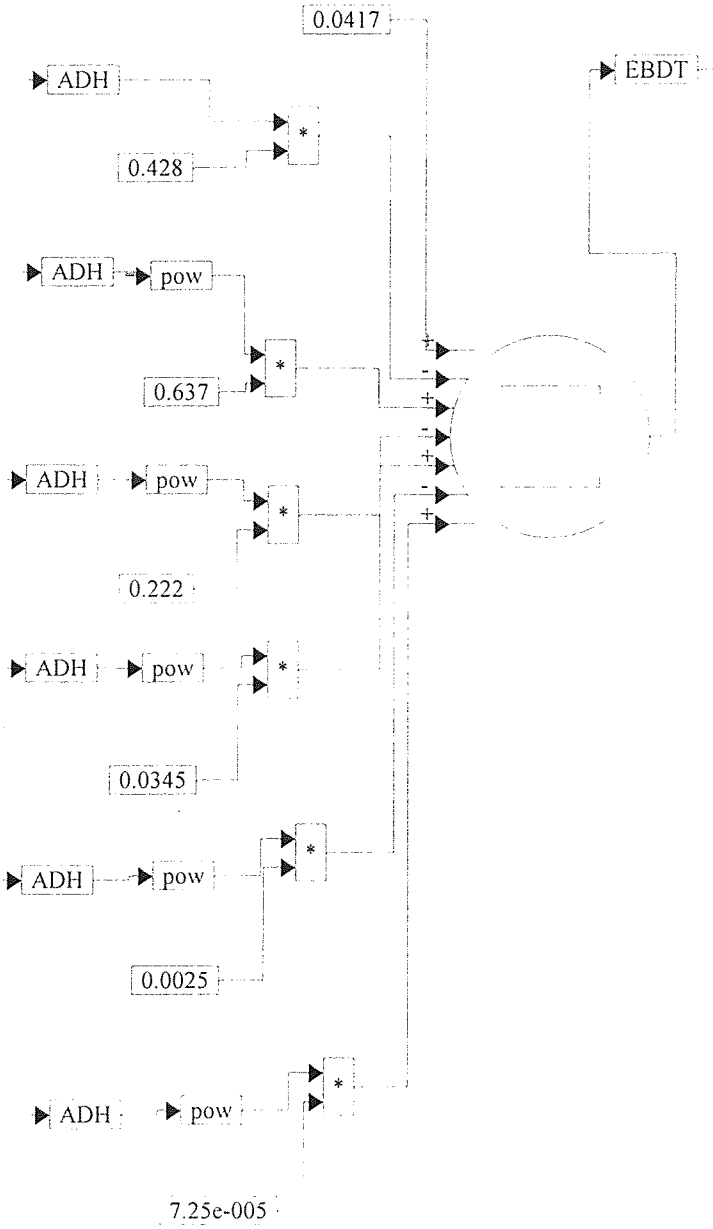
VisSim-uo.vsm

Urine Output U/O.
This is vissm code for equations (21), (23), and (28).



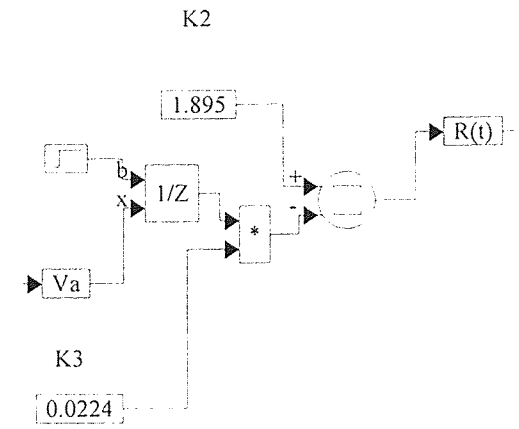
VisSim-adh3.vsm

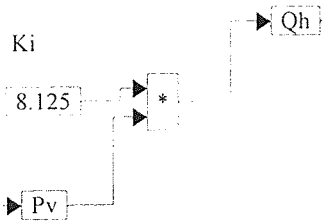
ADH Regulation
This is vissim code for equation (25).

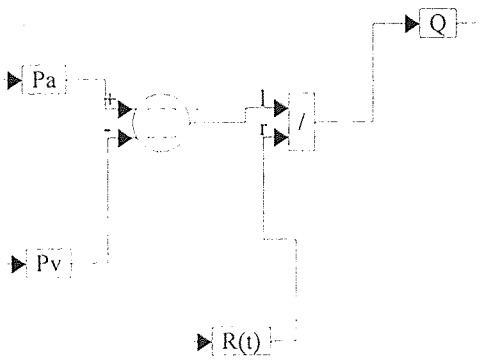


VisSim-randq.vsm

Peripherial Resistance (R), Cardaic output (Qh), and Venous Return (Q).
This is vissm code for equations (11), (8), and (12).







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