Vascular Smooth Muscle Function in Hypertension

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Vascular Smooth Muscle Function in Hypertension

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ABSTRACT

Hypertension is defined by an increase in systemic blood pressure above limits considered normal, currently set at 140 mmHg for systolic and 90 mmHg for diastolic pressure [1]. Assuming central venous pressure to be near zero, mean arterial pressure is determined by the product of total peripheral resistance and cardiac output. In most cases of essential hypertension, as well as in animal models of hypertension, cardiac output and its main determinants, stroke volume and heart rate, are normal, whereas total peripheral resistance is increased. Total peripheral resistance is influenced by a number of factors described by the Poiseuille's law, the most significant of which by far is the diameter of blood vessels of the arterial tree. Since blood vessel diameter is a reflection of both vascular structure and active regulation of vascular tone through mechanisms of vasoconstriction and vasodilatation, it is generally considered that alterations in total peripheral resistance are directly determined by alterations in vascular smooth muscle structure and/or function. Thus, complex blood pressure regulation systems, including renal, nervous, endocrine, immune, and others, in their turn influenced by genetic or environmental factors, converge upon the same molecular mechanisms that control the structure and function of vascular smooth muscle. In this work, rather than providing the exhaustive list of modifications in the blood pressure regulating systems that ultimately affect the vasculature in hypertension, we will focus on the structural and functional alterations of vascular smooth muscle *per se* during hypertension.

KEY WORDS

vascular smooth muscle, blood pressure, hypertension, functional and structural vascular abnormalities

Contents

CHAPTER 1

Historical Considerations on Early Physiological Studies of the Cardiovascular System

Although the earliest descriptions of the circulatory system are attributed to the Arab physician Ibn al-Nafis in The Commentary on Anatomy in Avicenna's Canon [2], it is accepted that William Harvey conclusively described the circulatory system through clever experimental approaches [3]. Many other scholars have made key contributions on the function of the cardiovascular system, but in addition to Ibn al-Nafis and William Harvey, only Galen and other few scholars will be briefly mentioned in this section.

Prior to Ibn al-Nafis, the teachings of Galen (129–207), at the time of the Roman Empire, stated that food was ultimately transformed into blood, and blood in turn was somehow transformed into the flesh of tissues [2, 3]. Galen's work was based on knowledge provided by the Ancient Greeks (around 400 B.C.) that believed that all animals, including humans, must be nourished, and that the nourishment must somehow be distributed from the intestines to all parts of the body. During this process humors were formed. Health was associated with a balance of the humors, and disease with an imbalance. The Greeks believed that the heart was the center of the physiological mechanism, the seat of the soul and the source of all blood vessels. Arteries began in the heart and carried pneuma, while veins originated in the liver and carried blood. (Figure 1.1)

> According to Galen, "*food in the gut underwent "concoction" and was transported to the liver where the blood was formed and imbued with "natural spirit." The blood then flowed to the right ventricle where some entered the lungs via the pulmonary artery to nourish them, but the remainder of the blood reached the left ventricle through "invisible pores" in the interventricular septum. In the left ventricle, the blood was mixed with "pneuma" from the air that was inhaled, and the result was the formation of "vital spirit," which was distributed throughout the body by the arterial blood. Some reached the brain where it received "animal spirit," which was then distributed via the nerves, which were thought to be hollow. The formation of "vital spirit" in the left ventricle led to the generation of fuliginous (sooty) waste products that traveled back to the lung*

through the pulmonary vein and then were exhaled with the breath." (Text retrieved with permission from West [2]).

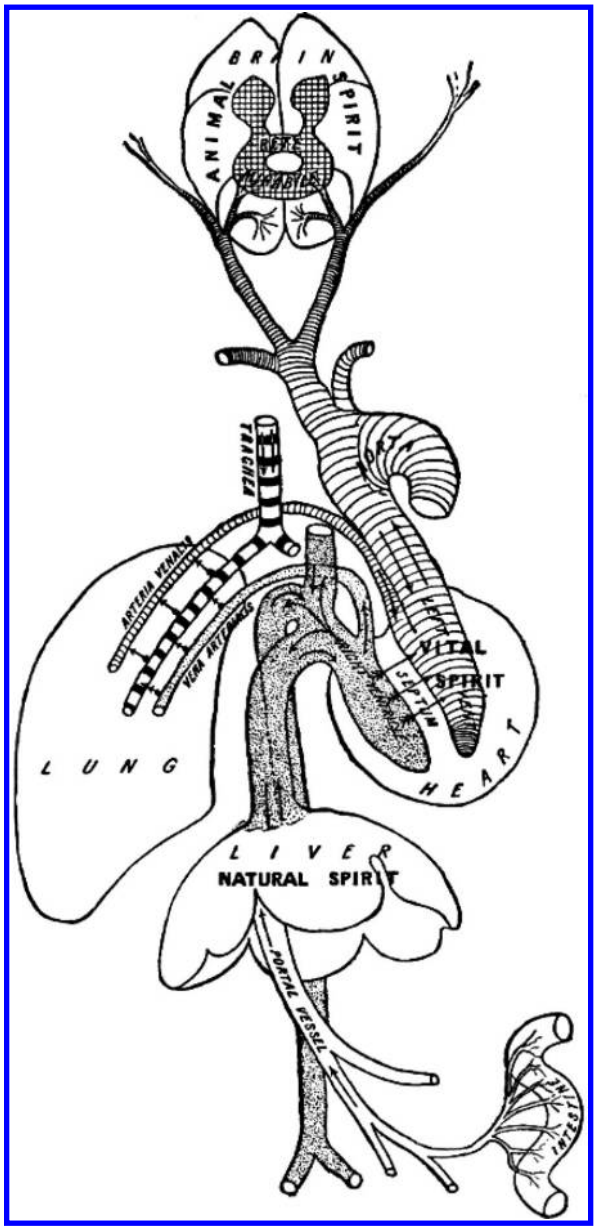

FIGURE 1.1: Scheme of the circulation of the blood according to the school of Galen. Image obtained from West [236]. Used with permission.

Galen knew that the heart moved and fluttered against the chest wall, that breathing was essential to life, that heat was extinguished in death, that the valves of the heart opened and closed, that arteries and veins were connected with the heart, that these two blood vessel were structurally different and contained blood of different color, and that blood normally passes from veins to arteries via anastomoses in the lung and periphery.

After the fall of the Roman Empire, in the period referred to as the Dark Ages (500–1400), there was no copious interest in acquiring new knowledge and scholarly activities were closely under the control of the Church. The ancient Greek teachings had to reconcile with theology and Galen's teleological inclinations matched the Christian doctrine. Apart from the Ibn al-Nafis studies, no significant contributions on the functioning of the cardiovascular system were registered at that time.

Ala al-Din Abu al-Hassan Ali Ibn Abi-Hazm al-Qarshi al-Dimashqi, or simply Ibn al-Nafis, (1213-1288), was an Arab physician who advanced the early knowledge of the pulmonary circulation. In The Commentary on Anatomy in Avicenna's Canon (1242), Ibn Nafis wrote his views on the pulmonary circulation and heart. He was the first to describe how the blood is directed to the left ventricle, from the right ventricle and through the pulmonary artery, lungs, and the pulmonary vein (and not directly from the right to the left ventricle, as described by Galen). He also first described the presence and function of the coronary circulation. His findings were confirmed, 300 years later, by Michael Servetus (1511–1553) who wrote:

> "*However, this communication is made not through the middle wall of the heart, as is commonly believed, but by a very ingenious arrangement where the refined blood is urged forward from the right ventricle of the heart over a long course through the lungs; it is treated by the lungs, becomes reddish-yellow and is poured from the pulmonary artery into the pulmonary vein.*"

Michael Servetus was a Spanish theologian, physician and cartographer burned at the stake in Geneva because his theological treatise—*Christianismi Restitutio* (*The Restoration of Christianity*)—was considered heretical by the Church [2].

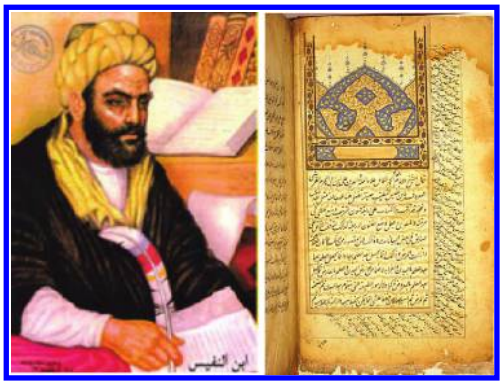

FIGURE 1.2: Ibn al-Nafis (1213–1288) made significant contributions to the early knowledge of the pulmonary circulation. Image courtesy of Wikimedia Commons.

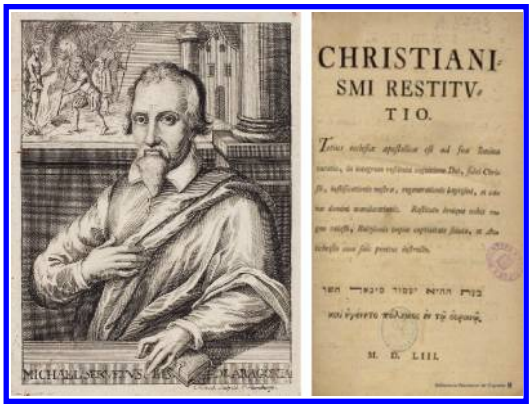

FIGURE 1.3: Michael Servetus (1511–1553) and his theological treatise— "Christianismi Restituio" (The Restoration of Christianity). Photo of Servetus courtesy of Wikimedia Commons. Photo of manuscript from Miguel Servet [237].

With the Renaissance, and the rising of art and science, Leonardo da Vinci (1452–1519) was the first to make accurate drawings of the heart, including its valves. Leonardo da Vinci also identified the atria as heart chambers, and provided a description of atherosclerotic coronary arteries. Leonardo da Vinci, in discrete opposition to Galen's propositions—that the heart was not a muscle—wrote that "*the heart is a vessel made of thick muscle, vivified and nourished by artery and vein as are other muscles*" [255].

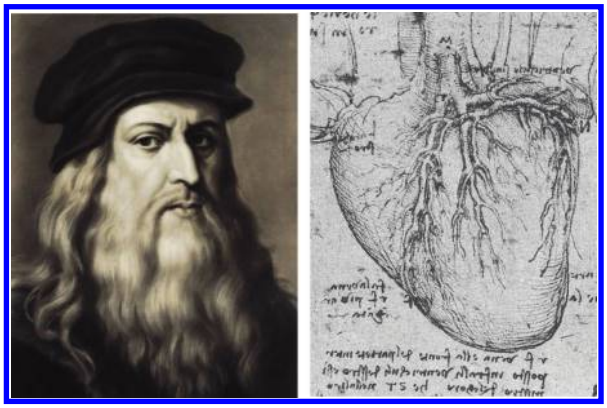

FIGURE 1.4: Leonardo da Vinci (1452–1519) made many accurate drawings of the heart. Images from: Da Vinci and the Heart: Anatomical Exploration through the Eyes of Leonardo. http://leonardodavinci.stanform.edu/projects/heart/indes.htm.

Giovanni di Paolo (1398–1482), around 1455–60, by illustrating the beheading of St. John the Baptist, provided the first artistic reference on pressure differences between the arterial and the venous systems. Although some new discoveries on the cardiovascular system were timidly registered with the revival of experimental investigation in the Renaissance, Galen's physiology and anatomy of the circulatory system persisted.

FIGURE 1.5: The Beheading of St. John the Baptist by Giovanni di Paolo. Photographic reproduction of the work via Google Art Project. http://tinyurl.com/za3nkop.

William Harvey was the physician of King James I and King Charles I (King James' son) and this helped him to further his research. Charles King's hunting expeditions gave William Harvey access to many deer carcasses and through the dissection of all sorts of animals (fish, frogs, snakes, birds, dogs, and pigs), Harvey made many observations and registered his theories. Harvey accompanied King Charles I through the English Civil War. He not only helped the wounded on several occasions, but also made crucial observations using human corpses. By ligating various vessels in the cadaver of a throttled man, Harvey showed how water passed freely through the lungs from the pulmonary artery to the left ventricle.

In 1628 William Harvey published his theories in a book entitled *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (*An Anatomical Study of the Motion of the Heart and of the Blood in Animals*).

William Harvey (1578-1657) was an English physician who was the first to describe accurately how the heart propelled the blood in a circular course through the body. He described that blood circulates not only in the lung, but also around the whole body and that the system is driven by the mechanics of the heart. By using a series of ligature experiments, he also clarified the role of valves in the veins and proved that the venous valves prevent retrograde flow of blood in the veins. William Harvey described that contraction of the ventricles occurs at the same time as the arteries are distended; that when the heart stops beating, the arteries lose pulsation; that when an artery is cut, blood spurts out and escapes with force; and that blood spurts from a severed artery at the same time that the heart contracts.

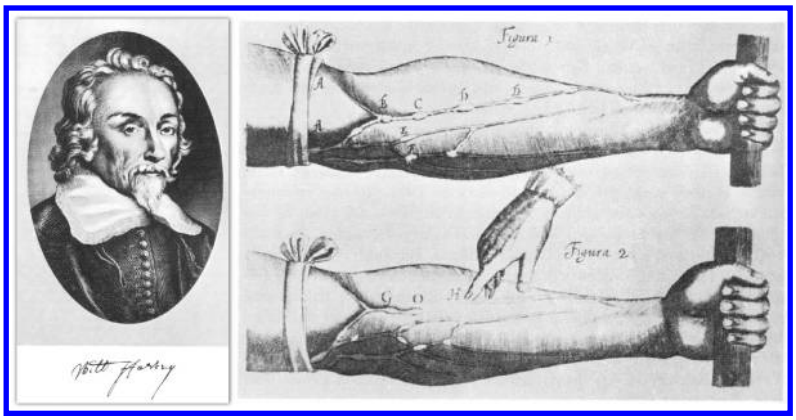

FIGURE 1.6: William Harvey (1578–1657) first accurately described how the heart propelled the blood in a circular course through the body. Picture of William Harvey and drawing from his book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, both in the public domain. https://commons.wikimedia.org/wiki/File:William_Harvey_(_1578-1657).jpg.

Measurements of blood pressure were successfully performed in several animal species by the Reverend Stephen Hales (1677–1761). Stephen Hales inserted fine tubes into arteries and measured the height to which the column of blood rose. In addition, Reverend Hales took wax casts of the ventricle of the heart and estimated how much blood the heart pumped. He correctly described the roles of the mitral valve and aortic valve during systole and diastole; explained the pulsations of arteries in terms of their elasticity and attributed the resistance to blood flow to friction due to the passage of blood through small blood vessels [4].

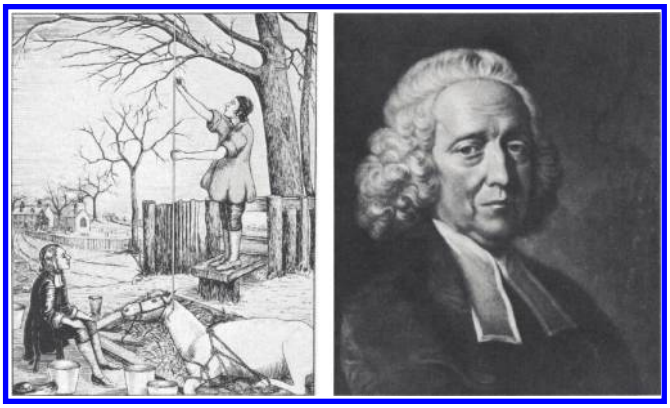

FIGURE 1.7: Reverend Stephen Hales (1677–1761) first performed measurements of blood pressure in several animal species. Images used with permission from the Royal Society of Medicine [247].

The French scientist Jean Léonard Marie Poiseuille (1797–1869) investigated the factors that affect resistance to flow or the rate of fluid flow. Poiseuille's work was published in main papers in 1840 and 1841 and summarized in a memoir ("*Le mouvement des liquides dans les tubes de petits diamètres*") in 1846 [5].

Poiseuille showed that pressure difference causes fluid flow—in the direction from high to low pressure and the greater the pressure differential between two points, the greater the flow rate (Equation 1). Poiseuille also determined the factors responsible for the resistance to flow (Equation 2): the length of the tube—with a long tube imposing a greater resistance than a short one; the viscosity of the fluid—the greater the viscosity, the greater the value of resistance; the radius of the tube—the greater the radius, the greater the flow (all other factors remaining the same). Of importance, the radius is raised to the fourth power in Poiseuille's equation, meaning that any change in the radius has a very large effect on resistance.

The first derivation of the equation (Equation 3) known as the Poiseuille's law for laminar flow, or simply Poiseuille's law, is attributed to the physicist Eduard Hagenbach (1833–1910). The name Poiseuille's law was generously suggested by Hagenbach (1860), although others prefer Hagen-Poiseuille's law in view of Hagenbach's contributions.

Equation 1	Equation 2	Equation 3
$Q = \frac{P_1 - P_2}{R}$	$R = \frac{8\eta L}{\pi r^4}$	$Q = \frac{(P_1 - P_2)\,\pi r^4}{8\eta L}$

Where:

Q = flow rate

$P_1 - P_2$ (or ΔP) = pressure differential (the pressure drop along two points or a circulatory bed)

R = resistance

L = the length of the tube

η = the dynamic viscosity

r = the radius

π = the mathematical constant Pi

Poiseuille's original goal was to understand the laws governing blood flow in a living circulation. However, he realized that *in vivo* studies would not permit a clear formulation of the laws and decided to undertake his studies on the flow of liquids in small diameter glass capillaries.

Jean Léonard Marie Poiseuille's studies contributed to the understanding of the properties of blood cells and the flow of blood. His observations helped to understand, e.g., that at higher shear stresses, disaggregation, and deformation of red blood cells leads to decreasing viscosity, whereas at low shear rates red blood cells aggregate, increasing viscosity; that blood cells tend to move away from blood vessel walls in small diameter vessels, which leads to a reduction in apparent viscosity (due to a reduction in hematocrit, which results from the centralization of the blood cells); that blood flow in the arterioles and venules features a plasma layer at the vessel wall in which there are few red cells; that "plasma-skimming" occurs at vessel bifurcations, and that white cells tend to adhere to the vessel wall.

Poiseuille's law applicability to the *in vivo* flow of blood was more recently demonstrated by Lipowsky et al. [248]. As predicted by Poiseuille, they showed that there is a good correlation between the resistance per unit length of vessel and the exponent of vessel radius close to 4.0.

FIGURE 1.8: Jean Léonard Marie Poiseuille (1797-1869), French scientist that investigated the factors that affect resistance to flow. Image courtesy of Wikimedia Commons.

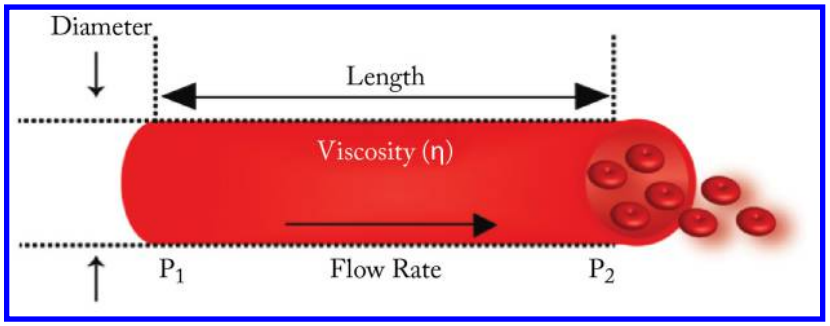

FIGURE 1.9: Flow of a fluid depends on pressure difference and on factors responsible for the resistance to flow (length of the tube, the viscosity of the fluid, and the radius of the tube).

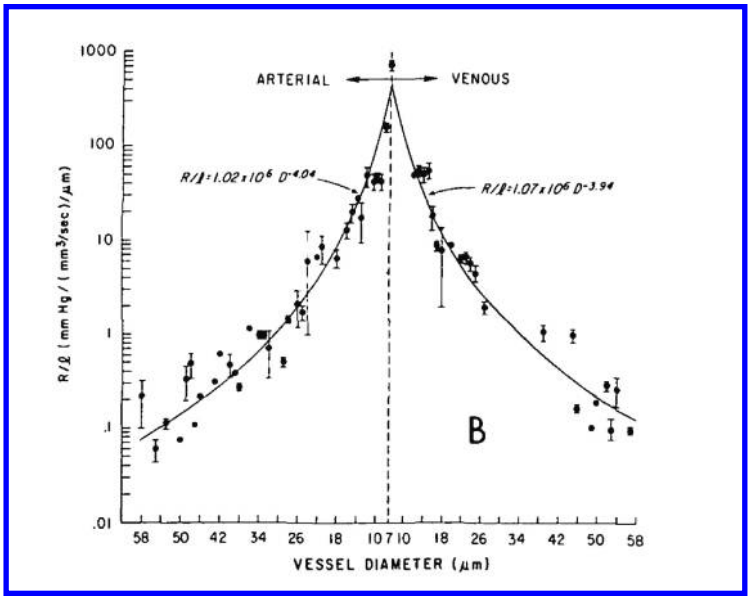

FIGURE 1.10: Resistance per unit length of vessel (R/L) where R = ΔP / Q. The resistance R to blood flow was computed from simultaneous measurements of flow Q and pressure drop ΔP, in single unbranched vessels of mesentery. The solid curves are power law regressions of the form R/L = aDm. Image from Sutera and Skalak [5], used with permission.

CHAPTER 2

An Overview of Vascular Physiology

2.1 A TELEOLOGICAL PERSPECTIVE ON CIRCULATION

According to the Celestial Committee on Design of a Mammalian Circulation (C.C.D.M.C.), "*the function of the circulation is to supply oxygen, metabolic fuels, vitamins and hormones, and heat, to every living cell of the organism, and also to remove metabolic end-products, and heat, from every cell. The amount of circulation should be in accordance with the individual needs of each cell*" [6].

According to Alan C. Burton (1904-1979), the C.C.D.M.C. is an imaginary group appointed by the Creator to explain the purpose, the priorities, mechanisms of control, and problems of the Circulation. With the help of the C.C.D.M.C., Dr. Burton used teleological thinking to explain the mechanisms of functioning and control of the circulation [6].

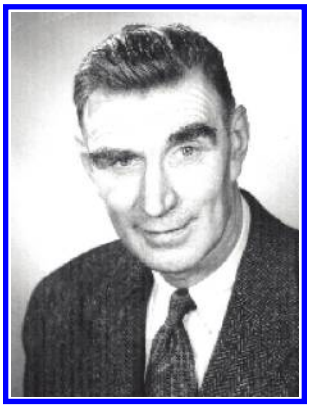

FIGURE 2.1: Alan Chadburn Burton (1904–1979), an English physicist who was attracted to physiology through his interest in skin temperature and heat exchange. Image used with permission from the APS. http://www.the-aps.org/fm/presidents/introab.html.

The metabolic needs, or energy expenditure, which can be quantified by arterio-venous difference of substrates or oxygen consumption, vary among cells, organs, and tissues of a given organism. Therefore, changes in blood flow to guarantee delivery of oxygen and nutrients to all the cells

of the body, and to collect waste materials from those cells and transport them to the liver, kidneys, and other areas where they can be selectively removed and excreted, must take place selectively.

Differences between the distribution of blood flow and energy expenditure among the organs/tissues indicate that metabolic needs is not the only factor controlling blood supply to the organs/tissues. The circulation is directly influenced by the organ's function. For example, blood flow to the skin is mainly regulated by the needs of temperature regulation of the whole organism and blood flow to the kidneys is driven to maintain electrolyte composition and fluid balance rather than by their metabolic needs. In addition, the metabolic demand of a given tissue may insignificantly change blood flow, as is the case of the brain where blood flow is mainly redistributed between different areas, whereas total blood flow may not change at all, or it may increase blood flow as much as 10 or 20 times, as is the case of skeletal muscle during exercise. Table 2.1 illustrates differences in blood flow and energy expenditure by human and mouse organs/tissues.

TABLE 2.1: Blood flow and energy expenditure of the main human and mouse organs

	Blood Flow (mL/min/100 g)		Energy expenditure (%)	
Organ/Tissue	**Mouse**	**Human**	**Mouse**	**Human**
Brain	98.15	50.34	6.42	21.35
Heart	658.82	100.0	3.69	10.23
Liver	146.77	100.0	52.17	19.53
GI tract	90.19	55.0	2.25	4.27
Skeletal Muscle	26.19	3.24	13.0	20.99
Adipose Tissue	38.39	3.27	4.98	2.6
Others	55.21	2.47	17.5	21.03
Whole body	56.47	7.86	100.0	100.0

Blood flow in mouse and human was calculated based on studies from Fenneteau et al. [253] and Kim et al. [254], respectively. Mouse was included for comparisons because they are widely used as experimental models for research in human diseases, including arterial hypertension. The respiratory quotient (RQ) of each organ and tissue in mouse was assumed to be the same as that of an overnight fasting human. The rates of organ and tissue blood flow were calculated from blood flow rates expressed as a fraction of the cardiac output and energy expenditure of brain, heart, liver was determined using allometric equations that relate organ/tissue energy expenditure to body mass. Adapted from Kummitha et al. [7].

Since the organs/tissues have particular needs and those vary from time to time depending on the organism activity (metabolic needs of the tissues), an effective distribution of circulation (blood supply) to these various organs/tissues needs to be very efficiently controlled.

According to the C.C.M.D.C., the general principle of control of the circulations is as follows.

Official Plan of the C.C.D.M.C. for Control of the Distribution of the Circulation

1. General Rule: Flow = Pressure Drop / Resistance
2. Priorities: Brain, heart. Control driving pressure in aorta to constancy, by special reflexes. Keep resistance to flow of brain relatively constant; change resistance of coronaries somewhat by local and nervous control
3. General Control: (a) by mass action of sympathetic nerves; (b) by circulating hormones; (c) by universal aerobic metabolite (carbon dioxide).
4. The heart shall be independently rhythmic, but controlled by nerves for general control of circulation.
5. Special Local Control: (a) different vessels can respond differently to the same circulatory hormones; (b) special (parasympathetic) nerves to special organs.
6. Local Autonomy of Control: (a) by local metabolites (carbon dioxide, lactic acid, pH) – that is reactive hyperemia; (b) Inflammatory reactions to disease and pathology.

This scheme will in general be followed in original design, and by evolutionary processes of selection.

(Signed) Gabriel, Secretary

(from the minutes of the C.C.M.D.C)

Retrieved from Burton [6], used with permission.

2.2 BLOOD FLOW REGULATION

Complex blood flow regulation systems, including renal, nervous, endocrine and immune, in their turn influenced by genetic or environmental factors, converge upon the same molecular mechanisms that control the structure and function of vascular smooth muscle. (Figure 2.2). Neurotransmitters (norepinephrine, dopamine, serotonin), hormones (angiotensin II, vasopressin), blood-borne or immune-associated factors (histamine, cytokines), endothelium- and adipose tissue-derived products (nitric oxide, endothelin-1, prostanoids, adipokines) bind to specific receptors and enzymes in vascular smooth muscle cells leading to activation of many signaling pathways and, ultimately, to changes in smooth muscle cell function.

Due to specific and individual tissue/organ demands, specific control mechanisms for some blood vessels are also in place [8] (e.g., products of local metabolism, products released by infiltrating cells, subpopulations of receptors, etc.). The local mechanisms for regulating blood flow are intrinsic to the various tissues and can function independently of neurohumoral influences. Local regulatory processes allow tissues in the body to have some autonomy to guarantee their particular requirements of blood flow [6].

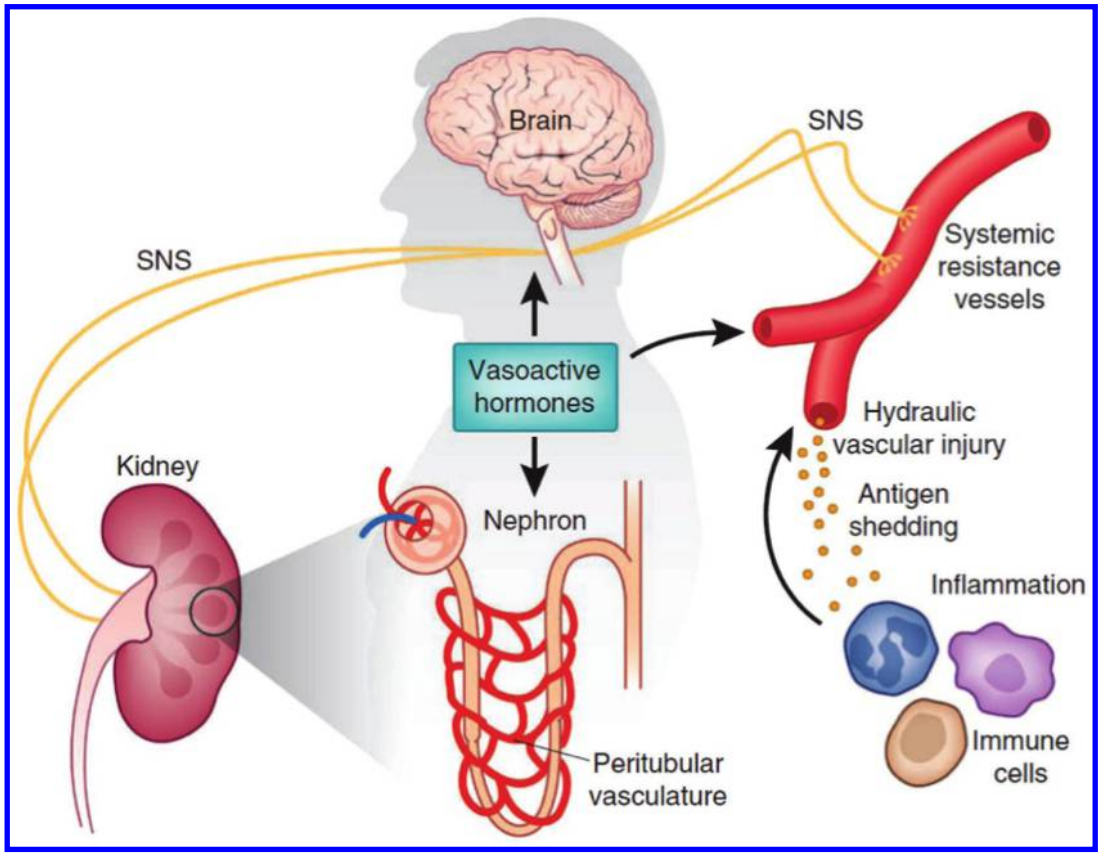

FIGURE 2.2: Complex blood flow regulation systems, including renal, nervous, endocrine, and immune, in their turn influenced by genetic or environmental factors, converge upon the same molecular mechanisms that control the structure and function of vascular smooth muscle. Image obtained from Coffman [8], used with permission from Nature Publishing Group.

Considering that the smaller vessels provide most of the resistance to flow, the arterioles are a major controlling influence on the volume flow rate and on the tissues demands for oxygen and

nutrients. Arterioles can constrict flow to one part of the body (by decreasing the radius), while enhancing flow to another part of the body (by increasing the radius).

As mentioned in Chapter 1, Poiseuille's law clearly shows that blood flow can be regulated by changes in vessel diameter and blood pressure. As stated in Poiseuille's law, blood flow can be increased by increasing the pressure or by increasing the vessel diameter/radius. Since the resistance is so sensitive to the radius, adjustments to blood flow are primarily made by varying the diameter of blood vessels. For example, during physical exercise, vasodilation allows increases in blood flow to important muscles and organs. Conversely, a decrease in blood vessel radius, due to an atherosclerotic plaque, greatly reduces blood flow. Increases in blood pressure can compensate decreases in flow, but this implies in increased cardiac work and increased pressure in the arterial walls.

Since vascular smooth muscle contraction and relaxation determine blood flow to the various territories, the processes that control vascular contraction and relaxation in physiological conditions will be briefly reviewed. These processes have been extensively reviewed elsewhere [9], including in these series [10]. Briefly, vascular smooth muscle contraction is produced by crossbridge cycling of myosin and actin filaments, the main determinant of which is phosphorylation of the 20 KDa myosin light chain (MLC_{20}). This event produces a conformational change of the myosin head allowing for interaction with actin and ATP hydrolysis and resulting in sliding of myosin and actin filaments with subsequent contraction. Thus, the contractile state of vascular smooth muscle is a function of the level of phosphorylation of MLC_{20}, which in turn depends on the activity of MLC kinase (MLCK), enzyme that phosphorylates MLC_{20}, and myosin light chain phosphatase (MLCP), enzyme that dephosphorlylates MLC_{20}. MLCK is activated upon binding to the calcium-calmodulin ($Ca^{2+}-CAM$) complex, and since formation of this complex depends on the availability of Ca^{2+}, the intracellular free Ca^{2+} concentration is the main determinant of smooth muscle contraction. Therefore mechanisms that directly or indirectly regulate Ca^{2+} homeostasis via entry from the extracellular environment or release from intracellular stores have all been intensively studied as mediators of vascular smooth muscle contraction. Additionally, Ca^{2+}-independent mechanisms, such as inhibition of MLCP following its phosphorylation by Rho kinase, mediate Ca^{2+} sensitization and also contribute to vascular smooth muscle contraction.

Vascular smooth muscle relaxation occurs when the intracellular free Ca^{2+} concentration or the sensitivity to Ca^{2+} decrease. This can occur if MLPC is activated, in the absence of mechanisms that stimulate MLCK, or as an "active relaxation" mechanism involving a combination of decreased free Ca^{2+} and decreased Ca^{2+} sensitivity [11], such as seen in response to nitric oxide (via guanylate cyclase-produced cGMP) or prostacyclin (via adenylate cyclase-produced cAMP).