Development of Anatomophysiologic Knowledge Regarding the Cardiovascular System: From Egyptians to Harvey

Reinaldo Bulgarelli Bestetti, Carolina Baraldi A. Restini, Lucélio B. Couto
Universidade de Ribeirão Preto – UNAERP, Ribeirão Preto, SP - Brazil

Abstract

Our knowledge regarding the anatomophysiology of the cardiovascular system (CVS) has progressed since the fourth millennium BC. In Egypt (3500 BC), it was believed that a set of channels are interconnected to the heart, transporting air, urine, air, blood, and the soul. One thousand years later, the heart was established as the center of the CVS by the Hippocratic Corpus in the medical school of Kos, and some of the CVS anatomical characteristics were defined. The CVS was known to transport blood via the right ventricle through veins and the pneuma via the left ventricle through arteries. Two hundred years later, in Alexandria, following the development of human anatomical dissection, Herophilus discovered that arteries were 6 times thicker than veins, and Erasistratus described the semilunar valves, emphasizing that arteries were filled with blood when ventricles were empty. Further, 200 years later, Galen demonstrated that arteries contained blood and not air. With the decline of the Roman Empire, Greco-Roman medical knowledge about the CVS was preserved in Persia, and later in Islam where, Ibn Nafis inaccurately described pulmonary circulation. The resurgence of dissection of the human body in Europe in the 14th century was associated with the revival of the knowledge pertaining to the CVS. The main findings were the description of pulmonary circulation by Servetus, the anatomical discoveries of Vesalius, the demonstration of pulmonary circulation by Colombo, and the discovery of valves in veins by Fabricius. Following these developments, Harvey described blood circulation.

Introduction

Knowledge about the cardiovascular system (CVS), which led Harvey to the discovery of blood circulation, was achieved only gradually through the ages. It started in Egypt around 3500 BC, was elaborated by ancient Greeks, was better defined in Alexandria, and, in the West, ceased after the fall of the Roman Empire. This knowledge was preserved in the Islamic world and in European monasteries, and it later advanced with the revival of the anatomical dissection in European universities, paving the way to Harvey's discovery. This review provides an overview about how knowledge about the CVS developed through the ages.

Keywords

Cardiovascular System; Knowledge; Civilization / history; Egypt; Greek World / history; Anthropology, Cultural / trends.

Mailing Address: Reinaldo B. Bestetti •
Jeronimo Panazollo, 434, Ribeirânia, Postal Code 14096-430, Ribeirão Preto, SP - Brazil
E-mail: rbestetti44@gmail.com; rbestetti@cardiol.br
Manuscript received May 30, 2014; revised manuscript July 23, 2014; accepted July 24, 2014.

DOI: 10.5935/abc.20140148

Egypt

In ancient Egypt (3500 BC), the heart was considered the central element of a system of channels distributed throughout the body, transporting blood, feces, semen, benign and malignant spirits, and even the soul: the *metw*[1]. Erroneously, the Egyptians believed that such elements flowed within a vessel linked to the heart (receptor vessel), probably the aorta, coming from the brain. A second collector vessel, they believed, was located in the anal region[2].

There was a clear notion that the peripheral pulse originated from the heartbeat, as it can be noted in the Edwin Smith papyrus (1700 BC), and that pulse measurement could be performed using a clepsydra. The doctor perhaps compared the patient's pulse with his own. Therefore, only marked increases or decreases in the heartbeat as well as pulse irregularities could be detected[3].

The Edwin Smith papyrus stated that abnormalities in the peripheral pulse could be the reflex of an underlying cardiac disease[4]. In the Ebers papyrus (1500 BC), the central relationship between the heart and the channels system had also been emphasized in addition to peripheral pulse measurement. Furthermore, the Ebers papyrus also emphasized the presence of heart disease diagnosed by abnormalities in peripheral pulse palpation: "when the heart is diseased...its vessels become inactive so that you cannot feel them"[5].

Despite Egyptians' knowledge about the relationship between the heartbeat and the peripheral pulse, the manner in which the elements of the *metw* were distributed throughout the body was not ascribed to the heart's force. Indeed, the palpation of the pulse was believed to be the consequence of the air present in the channels[1]. In addition, it was believed that the elements of the *metw* ebbed and flowed throughout the body.

The Egyptians did not routinely perform autopsy and did not use dissection as a form of medical teaching, so they did not further advance their understanding of the anatomophysiologic properties of the CVS[1]. Nevertheless, the Egyptians were the first to associate the heartbeat with peripheral pulse as well as to establish an association between the air and the CVS[6].

Greece

Pre-aristotelian Period

The emergence of philosophers in Greece around the 7th century BC, for example, Thales from Miletus, paved the way for questions regarding the human anatomy. Medical schools came into existence along with philosophers in the 5th century BC. Alcmaeon from the medical school of Croton (520–450 BC) was the first to produce anatomical knowledge from experimental observations. He believed that the brain was the center of emotions, knowledge, mind, and the soul. Further, he associated the functions of the sense organs with the brain[7].

Furthermore, Alcmaeon believed that the venous system was distinct from the arterial system, although he did not make an anatomical distinction between them. The function of the vessels was associated with wakefulness: withdrawal of blood from veins induced sleeping, but arteries, which brought blood to the brain, promoted wakefulness[8]. According to him, all vessels originated in the head, and their function was to distribute the pneuma (spirit) to the brain[9]. Nevertheless, other individuals believed that the pneuma was distributed to the brain directly via nasal breathing[10]. Alcmaeon ascribed no role of the heart in the CVS.

Empedocles from Agrigento (492–432 BC) had a different view. For him, the heart was the seat of the soul and the center of the CVS; blood vessels distributed the pneuma, which was internalized by pulmonary respiration[9]. Nonetheless, Empedocles also believed in the existence of fleshy tubes that contained blood and the terminal portions of which externalized in the skin, absorbing and expelling air[10]. Empedocles did not provide anatomical details of the heart.

The school of Kos, the main exponent of which was Hippocrates (460–375 BC), contributed in a decisive way to the rationalization of medicine. With regard to the CVS, the book *On the Heart*, which was attributed to the members of the school of Kos, reported for the first time the anatomical details of the heart, ascribing to the CVS the transportation of life throughout the body. According to the authors of such books, the lungs surrounded the heart, in the thorax, in order to cool the excess heat produced by incessant cardiac activity. The heart had a pyramidal shape, red color, and intrinsic electric activity. In contrast to the rest of the body, which was nourished with blood delivered through veins, the heart nourished itself from the pure substance created during blood dialysis[8].

According to the school of Kos, two ventricles existed and were united by the interventricular septum. The right ventricle was larger than the left ventricle, although the latter was thicker than the former because it had to tolerate the excessive heat produced by this chamber. The right ventricle communicated with the left one through a pore in the interventricular septum. The left ventricle, in contrast to the right ventricle, had no blood, but only yellow bile and membranes. It housed the mind and the spirit, which predominated over the rest of the soul[8].

All vessels of the CVS originated in the heart, connecting to it through membranes extending from the cardiac wall. Vessels were recognized (pulmonary veins) and were believed to transport air to the left ventricle; another great vessel—the pulmonary artery—transported air to the right ventricle, and at the same time, it transported blood to the lungs. Two cardiac valves were described, each one containing three leaflets; however, the anatomic structure of the aorta was not mentioned. These authors described two structures similar to the structure of the cardiac ear (atrium), which had the objective of capturing air, but they believed such structures did not belong to the heart[8]. The pericardium also was described: by absorbing water from the epiglottis, it was believed to cool the heart[11]. There was no mention of the vena cava.

In another book from the Hippocratic Corpus, *The Sacred Disease*, the CVS was described with only a few details, and there was little reference to the heart. According to this author, a pair of vessels originated in the liver and spleen and led to the brain and lower limbs. Branches of these vessels joined the heart in the thorax[10].

The Sicilian branch of the school of Cnidus, probably with works by Philistion of Locri around 370 BC, also contributed to the anatomical knowledge about the CVS: the presence of two ventricles was well known, the left being more hypertrophied than the right; the presence of two atria, whose beats were discordant in time with those of the ventricles, was also observed; moreover, the author noted the presence of a vessel connected to one ventricle only, along with semilunar valves[11]. Apparently, nothing was known about the anatomy of atrioventricular valves[10]. Figure 1 illustrates these findings.

Aristotelian Period

Aristotle (384–322 BC) believed that the heart was the most important organ of the body and was the seat of the soul. He did not believe that the pneuma was inspired by the body; the pneuma was a part of the soul, but the breath contained only air, the main function of which was to cool the heart[11]. In the same manner, he conceived the brain as a mechanism for cardiac cooling[12]. He performed hundreds of animal dissections[8], but apparently, he did not have an opportunity to dissect the human body. Therefore, he supported animal experimentation as a method to gain knowledge[11].

The great innovation—although erroneous—introduced by Aristotle in the anatomy of the CVS was the description of three cardiac ventricles, in descending order of volume from the right to the left part of the body, but all connected to the lungs. He also described the presence of vessels connecting both ventricles to the lungs, which transported air to the heart. Aristotle believed that the pulmonary artery and superior vena cava were subdivisions of another great vessel, which he called the “great vein.” In addition, he described another vessel connected to the medial ventricle, which he named the aorta. Further, he believed that the heart was the origin of all nerves and vessels[8].

According to Aristotle, in comparison with the left ventricle, which had air and more pure blood, the right ventricle contained blood that was warmer and more abundant. This observation was probably related to the mechanism of animal death (strangulation) before dissection. In contrast to other contributors to the Hippocratic Corpus, he did not mention cardiac valves

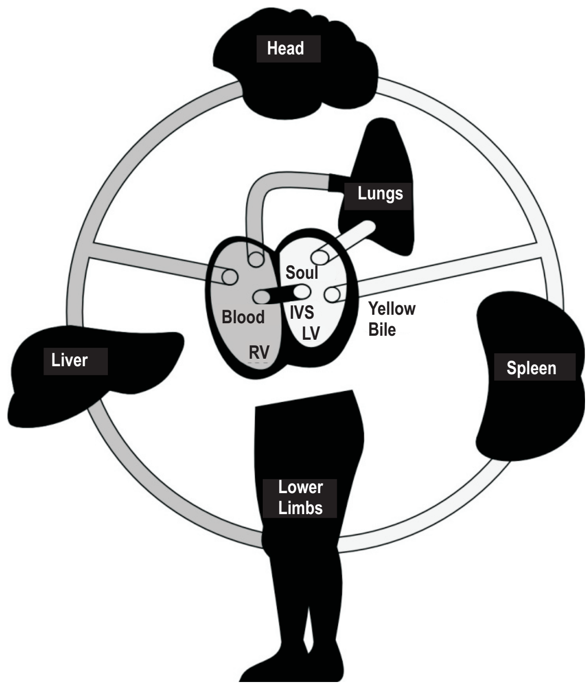

Figure 1 – *Scheme of the cardiovascular system according to the ancient Greeks. Note the presence of two parallel vessels originating in the liver and spleen, connected to the heart in the thorax and to the lower limbs and to the head. Observe the heart with a pore in the interventricular septum connecting the right ventricle to the left ventricle, two vessels connected to the right ventricle, and one vessel to the left ventricle coming from the lungs. The right ventricle is larger than the left, and the latter is thicker than the former. The right ventricle contains blood, whereas the left ventricle is filled with air and yellow bile, according to the Hippocratic Corpus (5th century BC).*

and the cardiac atria. Thus, there were two great vessels in Aristotle's cardiac model: the great vessel (vena cava and pulmonary artery) and the aorta (aorta and pulmonary veins)[12]. Today, it is believed that the medial ventricle was indeed the aorta, whereas the left ventricle corresponded to the left atrium, which Aristotle did not differentiate[13].

Praxagoras of Kos (340 BC) advanced the anatomic knowledge about the CVS in differentiating, although without anatomical support, between veins and arteries, which were simply called blood vessels (*phlebes*). Indeed, he differentiated between veins and arteries on the basis of the erroneous assumption that veins transported blood and that arteries transported the pneuma[14]. Furthermore, he stated that only arteries were associated with cardiac pulse, contrary to what was previously believed, and, for the first time, he emphasized the diagnostic value of the pulse[14]. Nevertheless, he made an important mistake in stating that veins transported blood, whereas arteries transported the pneuma[15].

Alexandrian Period

Better anatomical knowledge about the CVS appeared later in the works of Herophilus of Chalcedon (325–255 BC) and Erasistratus of Chios (310–250 BC) in the school of Alexandria in Egypt. Before this, dissections of corpses were not performed; almost all anatomical knowledge came from the dissection of animals. On the contrary, in the famous school of Alexandria, dissections of the human body were routinely performed, probably stimulated by support from the Ptolemaic pharaohs[16].

Herophilus's main contribution to the knowledge about the CVS was his differentiation of the thickness of arteries relative to veins, suggesting that the former were 6 times thicker than the latter. He termed the vessel connected to the right ventricle "the arterial vein," and he observed that arteries were less thicker than veins in the lungs[17]. He also believed that only arteries were associated with the heartbeat because the contraction and relaxation movements depended on the heart[12].

Furthermore, Herophilus recognized that nerves originated in the brain and spinal cord and not in the heart; he denied the participation of the heart in the process of breath[8]. Importantly, he included the atria as a part of the heart's anatomy[8,13]. He was probably the first to publicly perform anatomical dissections[12]. He described the carotid arteries, subclavian vein, splanchnic vessels, genital apparatus vessels, and lymphatic vessels. In addition, he differentiated the nerve endings of small vessels and observed blood in arteries[14]. He believed that arteries originated in the heart, but he did not specify where they originated[18].

Erasistratus recognized the heart's activity as an impeller pump that contracted due to its so-called intrinsic force. To the contrary to what Herophilus believed, Erasistratus emphasized that arteries did not have active movements of contraction and relaxation, but they were passively filled due to heart contraction. Erasistratus described the atrioventricular valves: those on the right side were named tricuspid and those on the left side were named bicuspid. In addition, he discovered the progressive subdivision of veins and arteries to the point that, due to their extremely small caliber, it was no longer possible to make anatomical distinction between them, but he emphasized that those vessels were always filled with blood. He named such small vessels synanastomoses, which were later denominated capillaries[19]. Some authors believe that Erasistratus was the first to describe the valves in veins[14].

Erasistratus, however, believed that arteries also transported the pneuma. For this reason, although he had described the arterial endings and the beginnings of vein structures, he did not identify the functional continuity between them. The blood was formed in the liver and transported to the right ventricle and thence throughout the body via veins. The air (pneuma) was inspired by the lungs and reached the left part of the heart via pulmonary veins. In the left ventricle, the vital spirit was formed and was distributed throughout the body by hollow nerves (arteries, which did not contain blood). In synanastomoses, the pneuma and blood were used for the body's nutrition, whereas the products of metabolism were excreted. Therefore, nothing returned to the left ventricle[12]. Unlike Herophilus, Erasistratus believed that blood vessels originated in the heart[18].

With the conquest of Egypt by the Roman Empire, the scientific activity in Alexandria progressively declined, and dissection of human bodies was no longer performed.

Roman Period

Rufus of Ephesus, a contemporary of Jesus Christ, believed that the atria were part of the heart because they pulsed together. In the 2nd century AD, Galen (130–200 AD), a gladiators' physician in the temple of Asclepius in Pergamun, demonstrated that arteries contained blood, not air, as was the belief until that time. Further, Galen stated that the heart was a muscle with different orientation planes, which permitted its strong and incessant activity.

Galen recognized that the left ventricle was more hypertrophied than the right ventricle; he attributed these differences to the presence of air in the left ventricle, and he emphasized the function of the right ventricle in handling blood.

Two vessels originated in the right ventricle; one transported blood to the lungs (pulmonary artery), whereas the other transported peripheral blood back to the heart (vena cava). The left ventricle was the source of the great artery (aorta) as well as of other venous structures (pulmonary veins) that transported blood from the lungs to the heart[8].

Galen however made several mistakes related to the anatomy of the CVS, mainly because his dissections were performed on animals and not on humans. He stated that pores in the interventricular septum of the heart permitted blood flow from the right to the left ventricle[20]. Furthermore, he did not consider the atria as a part of the heart. He also believed in the existence of several types of pneuma (spirits). The digested food was distributed to the liver, where it was transformed into blood, which mingled with the animal spirit. This, in turn, flowed and ebbed through the vena cava system (a mechanism that he compared to the activities of tides) to nourish the body[12].

The blood that reached the right ventricle was transported to the lungs, where the impurities were vented; subsequently, the cleansed blood flowed to the heart and thence throughout the body. Part of the blood that entered the right ventricle via the interventricular septum pores reached the left ventricle. There, the blood mingled with the air coming from the trachea and pulmonary veins, thus forming the vital spirit, which ebbed and flowed via arteries throughout the body[12]. In addition, the mixture of the vital spirit with blood in contact with the heat of gaseous impurities produced by the heart flowed back to the lungs through the bicuspid atrioventricular valve[20]. The blood that reached the brain found the third type of pneuma (the animal spirit), which was then distributed to the body through hollow nerves. Finally, Galen believed that blood vessels actively dilated when the heart contracted, in opposition to the belief of Erasistratus[12].

Following Galen's period, dissections were performed less often, and anatomic studies were left behind. Galen considered the human body to be the temple of the soul, and his teleological explanations for all phenomena were in concert with the dominant force that had settled in Rome in the 4th century AD. Because knowledge was supposed to be derived from faith, anatomical knowledge was not considered important. This explains why Galen's erroneous beliefs lasted until the Renaissance, and the functioning of the CVS was understood only in the 17th century.

Medieval Period

Byzantine Period

With the progressive decline of the Occidental Roman Empire, there were essentially no further advances in medical knowledge. One exception was Oribasius' work (325–403 AD) in Byzantium (Oriental Roman Empire). Working with magnifying lenses, this author confirmed Erasistratus' description of the anastomosis between veins and arteries, mainly in the kidneys. Oribasius renamed such anastomoses as *capillaries*. Furthermore, he correctly described renal circulation: perfusion through the renal artery branch of the aorta and venous return through the renal vein branch of the inferior vena cava[21].

In 431 AD, the Nestorians, followers of Nestorius, the patriarch of Constantinople, were accused of heresy and were expelled from Constantinople. They immigrated to Edessa, in the north of Assyria (Mesopotamia), where a school of medicine had been founded in 363 AD and a hospital had been built by St. Ephraim[22]. In this school, the Assyrians were involved in close study of Greek medical literature[22,23].

When the school of Edessa was closed in 489 AD, the Nestorians took refuge in the city of Gondishapur (also transliterated as Gundishapur) in Persia, founded in 271 AD[24], taking with them the works by Hippocrates, Aristotle, and Galen translated to Syriac. Greek doctors experienced a similar displacement after the school of Athens was closed in 529 AD. These intellectuals became part of the school of Gondishapur, created in 555 AD, which served as a model for subsequent Persian medical schools. A teaching hospital was constructed and inspired the creation of other hospitals not only in the Islamic world but also in Europe[25].

The Arabs who won Persia and Mesopotamia in the 7th century incorporated this model for their schools of medicine, including Spain and Portugal, where the Arabs ruled for centuries. In this manner, medical knowledge acquired in the previous centuries, but forgotten in the Middle Ages in Europe, was preserved in the schools of the Islamic world. When important medical works were translated into Latin, from the 11th century onward, medical knowledge finally returned to Europe.

Islamic Period

During the Islamic Period, dissections of human bodies were prohibited for religious reasons; only animal dissections were allowed; thus, there was no marked scientific progress regarding the CVS. Rhazis (865–925 AD) contributed importantly in disagreeing with Galen regarding the presence of bone in the cardiac base[26]. Haly Abbas (930-994 AD) advanced the morphological characterization of the pulmonary artery in two muscle layers, in describing the aorta more precisely, and in describing the coronary arteries in 965[27]. Importantly, he suggested a functional communication between the endings of veins and arteries[28]. However, it is controversial whether or not he hypothesized communication between both ventricles[27,28].

Still in the 10th century, Al-Akhawayni Bukhari (?-983 AD) made important contributions to the understanding of CVS anatomophysiology, facilitated perhaps by the fact that he was able to perform autopsies on human cadavers in ancient Persia[27]. He stated that the heart had four cavities, the pulmonary vessels, and the aorta, all of them with valves that impeded blood reflux. He described the pericardium with anatomic precision.

Although Al-Akhawayni Bukhari recognized two pores in the interventricular septum that permitted communication between both ventricles, he emphasized that most of the blood received by the right ventricle was transported to the lungs. From the lungs, blood was transported to the left ventricle, from there to the aorta, and from the aorta throughout the body. Thus, Al-Akhawayni Bukhari described a rudimentary lung circulation, emphasizing that the function of the heart was to pump blood and that blood vessels transported only blood, not the pneuma. He also described, with precision, the coronary arteries[28] in 975 AD[27], at about the same time as Hally Abbas.

It fell to Avicenna (980–1037 AD), however, to go back in time. Although he clearly recognized the cardiac systole and diastole[29], Avicenna adopted the cardiocentric model of Aristotle and accepted the presence of pores in the interventricular septum. In his view, the left ventricle was the cardiac chamber that housed the pneuma, and it was the seat of emotions[30].

In 1260, Ibn Nafis (1210–1288 AD) commented on Avicenna's works and almost described pulmonary circulation. Although it is probable that Ibn Nafis occasionally performed autopsies on humans[31], his description seems to be more theoretical rather than practical[32]. Nevertheless, the ethical conviction with which he described the anatomical characteristics of the interventricular septum proves that he really performed anatomical dissections on humans[33]. Therefore, he denied the presence of pores in the interventricular septum in such a way that there was no communication between both ventricles; he also denied the presence of three ventricles[34].

He stressed that blood was transported to the right ventricle; from this cavity, through the pulmonary artery, it reached the lungs; from these organs, through pulmonary veins, it returned to the heart, whence, via the aorta, it was distributed throughout the body. Still under Galen's influence, he believed that the transformation of the vital spirit took place in the left ventricle and was distributed along with blood. In his view, the rest of the body circulation occurred according to Galen's ideas. Ibn Nafis believed that cardiac nutrition was made possible by vessels that permeated the heart body (coronary arteries)[35].

European Period

In the 10th century, with the establishment of the medical school of Salerno, Italy, there was a revival of medical learning. The classical medical works of the Greeks, whose practical teachings guided ancient medicine, remained lost in time, but they were, however, stored in monasteries and copied by Benedictine monks. Because they were not being put into practice, they fell into disuse, and surgical procedures were abandoned. Only with the founding of the medical school of Salerno did animal dissection became routine. Furthermore, Salerno's masters translated ancient Greek works into Latin, including data related to surgical procedures. In this manner, they emphasized surgical therapeutics, which led to a revival in the need for anatomical knowledge[36].

The Catholic Church did not prohibit human anatomical dissections. On special occasions when the cause of death was unclear or in periods of epidemics, autopsies were performed for accurately diagnosing the underlying cause of death[37]. A register, dating approximately 1306, records an autopsy performed by Pietro d'Abano for medico-legal purposes[38]. The lack of bodies for dissection was another important limiting factor for anatomical knowledge[39].

In Bologna, in 1316, Mondino da Luzzi (1276–1326 AD) restarted systematic anatomical dissections of humans with the main objective of gaining knowledge about the structure of the human body[40]. However, such dissections were performed by a barber. The main consequence of this incorrect practice was the lack of progress in anatomical knowledge. Thus, Mondino da Luzzi believed in the presence of three ventricles. Even worse, along with the third ventricle, Mondino da Luzzi emphasized the presence of pores in the interventricular septum[41], and he did not identify the atria.

Berengario da Carpi (1470?–1550 AD) modified the study of anatomy by personally dissecting some corpses. For this reason, in 1521, he clearly showed the existence of only two ventricles, two atria, and semilunar and atrioventricular valves, thus recovering the knowledge acquired by the ancient Greeks and the Alexandria school and adding to that the existence of papillary muscles as components of the subvalvar apparatus[42].

Leonardo da Vinci (1452–1518 AD), who probably dissected the human body, ascribed a functional significance to the atria, showing that the atria contracted when the ventricles dilated. Moreover, he emphasized that the heart is a mere muscle, not a seat of spirits or air. In addition, he presented a detailed picture of the mitral apparatus and described the moderator band of the right ventricle. However, da Vinci still believed in the existence of pores in the interventricular septum and adopted Galen's model of blood distribution throughout the body[43].

Michel Servetus (1511–1553 AD) (Figure 2), a theologian trained in anatomy, described pulmonary circulation in a few pages of his *Christianismi Restitutio* (1553), which led to his death at the stake in 1553. Nevertheless, Servetus believed that the blood in the right ventricle passed through the left side of the heart through the pulmonary capillaries; there were no pores in the interventricular septum. Further, blood mingled with air in the lungs, but not in the left ventricle, furthering his claim that the change in blood color occurred in the lungs and also explaining the size of the pulmonary artery, which is much larger than necessary if the function of this vessel was only pulmonary nutrition[44]. He believed that blood passed from the pulmonary artery to pulmonary veins via blood capillaries[45]. These convictions arose following the routine practice of anatomical dissection.

Andrea Vesalius (1514–1564 AD) became the most celebrated anatomist of the medieval period. After he was hired to work at the Faculty of Padua in 1537, he performed a large number of anatomical dissections. The consequence was the publication of his book *De humani corporis fabrica libri septem* in 1543 in which Vesalius corrected many mistakes made by earlier anatomists. With respect to the CVS, he showed the absence of *rede mirabilis* in human beings[37].

However, in the first edition of *Fabrica*, Vesalius did not allude to the absence of pores in the interventricular septum[37]. Only in 1559, after Matteo Realdo Colombo (1516–1559 AD) asserted the absence of pores in the septum, did Vesalius definitively correct previous mistakes related to cardiac anatomy. It was he who gave the name *mitral* to the atrioventricular valve, which separates the left atrium from the left ventricle[46].

In his book *De re anatomica libri XV* (1559), Matteo Realdo Colombo, contrary to Vesalius, correctly described the anatomical position of the kidneys and demonstrated pulmonary circulation. He stated that blood was transported from the right ventricle to the pulmonary artery and from there to the lungs, where it was attenuated; thence, it moved from the lungs, along with air, through the pulmonary vein and to the left ventricle. Further, he drew attention to the width of the pulmonary artery, as Servetus had done. Notably, Colombo never mentioned the existence of pores in the interventricular septum[47].

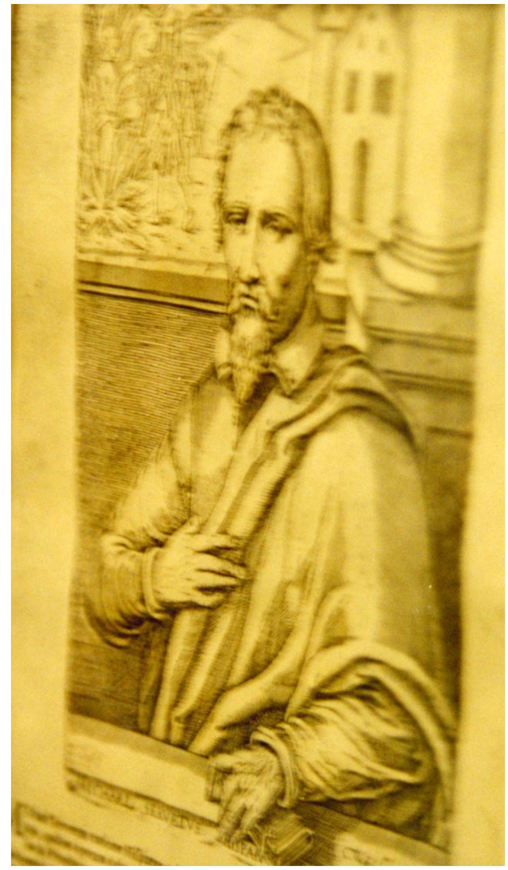

Figure 2 – *Michel Servetus, who described pulmonary circulation. Semmelweiss Medical History Museum, Budapest, Hungary. Courtesy of the author (RBB).*

It is also debatable whether Colombo, like Servetus and Ibn Nafis, was influenced by Servetus himself. Apparently, Servetus sent a draft of his book to Padua in 1546. Whether or not Colombo had access to it is still an open question[31] as is his putative contact with Ibn Nafis's work[48].

With the exception of Antonio Benivieni, in 1507, a few scientists gave enough attention to the anatomopathological abnormalities in humans. Colombo interestingly described cardiac abnormalities such as the hydrothorax probably secondary to decompensate chronic heart failure, bacterial endocarditis, myocardial infarction, and chronic pericarditis[49].

Although Amatus Lusitanus described the existence of valves in the azygos vein in 1551, he proposed an incorrect explanation about the anatomical significance of these structures. In his seminal publication of 1603, *De venarum ostiolis*, Fabricius ab Aquapendente described the presence of such valves in almost all bodies, their structures and anatomical characteristics, and the perception that they worked to contain blood reflux. Nevertheless, Fabricius saw only a partial opposition to blood reflux and suggested that part of blood was distributed via veins to tissues[50].

William Harvey was a student of Fabricius at Padua University. Taking into account Fabricius' discovery of vein valves, he perceived their correct functions, i.e., to contain blood and direct blood flow. This provides some perspective about his discovery of blood circulation in 1628.

Figure 3 presents a schematic timeline of the main discoveries discussed in the text.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Bestetti RB, Restini CBA; Acquisition of data: Bestetti RB; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Bestetti RB, Restini CBA, Couto LB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

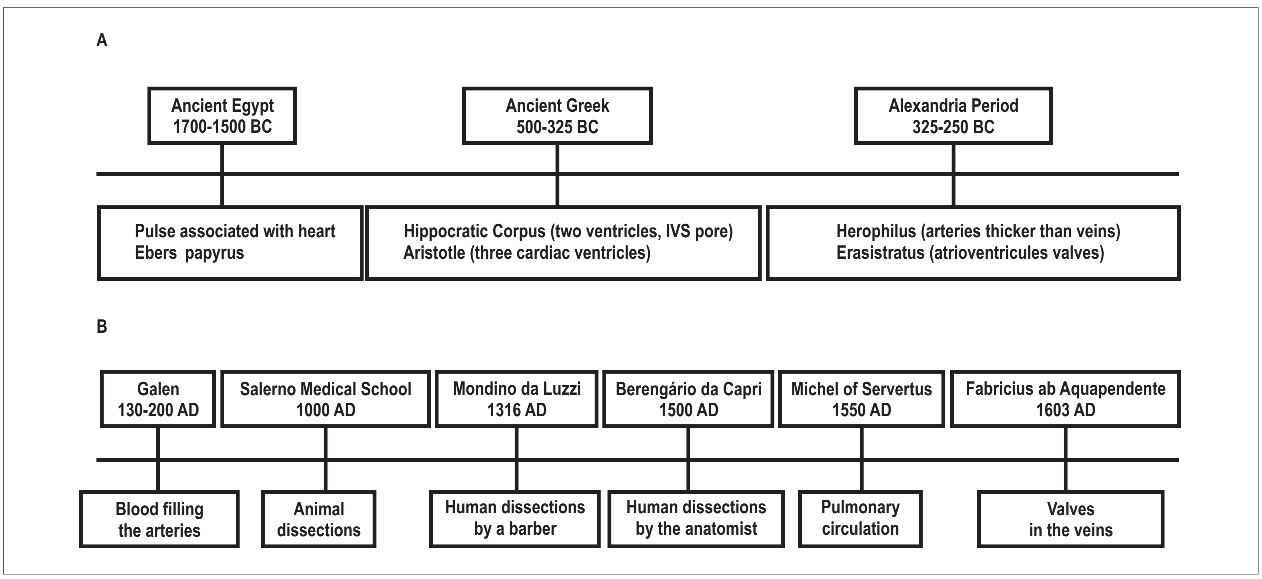

Figure 3 – *Development of knowledge about the cardiovascular system through the ages: Panel A, events before Christ (BC); Panel B, events following Christ (Anno Domini, AD); IVS: intraventricular septum.*

References

1. Nunn JF. Ancient Egyptian medicine. Concepts of anatomy, physiology and pathology. British Museum Press, London; 1996.
2. Boisaubin EV. Cardiology in ancient Egypt. Tex Heart Inst J. 1988;15(2):80-5.
3. Wilson JA. Medicine in ancient Egypt. Bull Hist Med. 1962;36(2):114-23.
4. Hamburger WW. The earliest known reference to the heart and circulation. Am Heart J. 1939;17:259-74.
5. Willerson JT, Teaff R. Egyptian contributions to cardiovascular medicine. Tex Heart Inst J. 1996;23(3):191-200.
6. Loukas M, Hanna M, Alsaiegh N, Shoja MM, Tubbs RS. Clinical anatomy as practiced by ancient Egyptians. Clin Anat. 2011;24(14):409-15.
7. Celesia GG. Alcmaeon of Croton's observations on health, brain, mind, and soul. J Hist Neurosci. 2012;21(4):409-26.
8. Mavrodi A, Paskevas G. Morphology of the heart associated with its function as conceived by ancient Greeks. Int J Cardiol. 2014;172(1):23-8.
9. Loukas M, Tubbs RS, Louis-Jr RG, Pinyard J, Vais S, Curry B. The cardiovascular system in the pre-Hippocratic era. Int J Cardiol. 2007;120(2):145-9.
10. French RK. The thorax in history 1. From ancient times to Aristotle. Thorax. 1978;33(1):10-8.
11. Hurlbutt-Jr FR. Peri kardies. A treatise on the heart from Hyppocratic Corpus. Bull Hist Med. 1939;7:1104-13.
12. Atkinson MH. Man's changing concepts of the heart and circulation. Can Med Ass J. 1964;91:596-601.
13. Van Praagh R, Van Praagh S. Aristotles triventricular heart and the relevant early history of the cardiovascular system. Chest. 1983;84(4):462-8.
14. Androutsos G, Karamanou M, Stefanadis C. The contribution of Alexandrian physicians to cardiology. Helenic J Cardiol. 2013;54(1):15-7.
15. Wilson LG. Erasistratus, Galen, and the pneuma. Bull Hist Med. 1959;33:293-314.
16. Wiltse LL, Pait GT. Herophilus of Alexandria (325-255 B.C.): The father of anatomy. Spine. 1998;23(17):1904-14.
17. Dobson JF. Herophilus of Alexandria. Proc R Soc Med. 1925;18:19-32.
18. French RK. The thorax in history 2. Hellenistic experiment and human dissection. Thorax. 1978;33(2):153-66.
19. Dobson JF. Erasistratus. Proc R Soc Med. 1927;20(6):825-32.
20. Pasipoularides A. Galen, father of systematic medicine. An essay on the evolution of modern medicine and cardiology. Int J Cardiol. 2014;172(1):47-58.
21. Eftychiadis AC. Renal and glomerular circulation according to Oribasius (4th century). Am J Nephrol. 2002;22(2-3):136-8.
22. Whipple AO. Role of nestorians. Ann Med Hist (New Ser). 1936;2:313-23.
23. Johna S. From warriors to guardians: the Assyrians and their role in the history of medicine. Am Surg. 2002;68(10):927-9.
24. Miller AC. Jundi-shapur, bimaristans, and the rise of academic medical centres. J R Soc Med. 2006;99(12):615-7.
25. Zargaran A. Ancient Persian medical views on the heart and blood in the Sassanid era (224-637 DC). Int J Cardiol. 2014;172(2):307-12.
26. Shoja MM, Tubbs RS. The history of anatomy in Persia. J Anat. 2007; 210(4):359-78.
27. Dalfardi B, Nezhad GS, Mehdizadeh A. How did Hally Abas look at the cardiovascular system? Int J Cardiol. 2014;172(1):36-9.
28. Yarmohammadi H, Dalfardi B, Rezaian J, Ghanizadeh A. Al-Akhawayni's description of pulmonary circulation. Int J Cardiol. 2013;168(3):1819-21.
29. Dalfardi B, Yarmohammadi H. The heart under the lens of Avicenna. Int J Cardiol. 2014;173(1):e1-2.
30. Khan MS. Ibn Sina's treatise on drugs for the treatment of cardiac diseases. Islam Quar. 1983;27(1):49-56.
31. Loukas M, Lam R, Tubbs S, Shoja MM, Apaydin N. Ibn al-Nafis (1210-1288); the first description of the pulmonary circulation. Am Surg. 2008:74(5):440-2.
32. Meyhorf M. Ibn an-Nafis (XIIIth cent) and his theory of the lesser circulation. Isis. 1935;23:100-20.
33. Wilson LG. The problem of discovery of the pulmonary circulation. J Hist Med All Sci. 1962;17(4):229-44.
34. Bittar EE. A study of Ibn Nafis. Bull Hist Med. 1955;29(5):429-47.
35. Haddad SI, Khairallah A. A forgotten chapter in the history of the circulation of the blood. Ann Surg. 1936;104:1-8.
36. Lyons AS. Medical sects and the center at Alexandria. In: Lyons AS, Petrucelli RJ. (eds.). Medicine: an illustrated history. New York: Abradale Press; 1978.
37. Andrioli G, Trincia G. Padua: the renaissance of human anatomy and medicine. Neurosurgery. 2004;55(4):746-54.
38. Del Nero P. L'Università di Padova. Otto secoli di storia. Signun Padova Editrice: Padova; 2002
39. Alston MN. The attitude of the church towards dissection before 1500. Bull Hist Med. 1944;16:221-38.
40. Crivellato E, Ribatti D. Mondino de Liuzzi and his Anathomia. Cl Anat 2006;19(7):581-7.
41. Infusino MH, Win D, O'Neil YV. Mondino's book and the human body. Vesalius. 1995;1(2):71-6.
42. Fontanini F, Signorelli S. Berengário da Carpi: ci mostrò muscoli papillari, corde tendinae e valvole del cuore. G Ital Cardiol. 1997;27(6):621-3.
43. Shoja MM, Agutter OS, Loukas M, Benninger B, Shokouhi G, Namdar H, et al. Leonardo da Vinci's studies of the heart. Int J Cardiol. 2013;167(4):1126-38.
44. Cattermole GN. Michael Servetus: physician, Socinian and victm. J R Soc Med. 1997;90(11):640-4.
45. Temkin O. Was Servetus influenced by Ibn An-Nafis? Bull Hist Med. 1940;8:731-4.
46. Silverman ME. Andreas Vesalius and De Humani Corporis Fabrica. Clin Cardiol. 1991;14(3):276-9.
47. Eknoyan G, De Santo NG. Realdo Colombo (1516-1559). Am J Nephrol. 1997;17(3-4):261-8.
48. Coppola ED. The Discovery of the pulmonary circulation: a new approach. Bull Hist Med. 1957;31:44-77.
49. Moes RJ, O'Malley CD. Realdo Colombo: "On those things rarely found in anatomy". Bull Hist Med. 1960;34:508-28.
50. Franklin KJ. Valves in the veins: an historical survey. Proc R Soc Med. 1927;21(1):1-33.