

Available online on 15.05.2022 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Historical Archive of Blood Pressure and Evolution of Hypertension

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Article Info:

Abstract



Article History:

Received 21 March 2022
Reviewed 26 April 2022
Accepted 03 May 2022
Published 15 May 2022

Cite this article as:

Tengiz I, Fici F, Ercan E, Grassi G, Robles NR, Faikoglu G, Historical Archive of Blood Pressure and Evolution of Hypertension, Journal of Drug Delivery and Therapeutics. 2022; 12(3):215-219

DOI: <http://dx.doi.org/10.22270/jddt.v12i3.5333>

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Blood pressure is the pressure of the blood within the arteries of the circulatory system. The pulse is the feeling of the heartbeat in some arteries. Hypertension also known as high blood pressure, is the name given to a common medical condition in which the force exerted by the blood carried from the heart to the body against the walls of the arteries is high enough to cause health problems such as heart disease. Hypertension has been known since antiquity. Descriptions have been found in the Egyptian papyri, in ancient Chinese and Indian medical literature, as well as, in the work of ancient Greek physicians such as Galen and Hippocrates and Muslim scientists into Latin in Andalusia and Sicily. When we come to the 17th century, we see that blood circulation was experimentally proven by William Harvey. The important work of the 18th century, blood pressure was first recognized and first attempts were made to measure this pressure. The clinical sphygmomanometer that could measure systolic pressure over the radial artery is defined by Samuel von Basch in 1880. 20th century has witnessed changes in terminology, discovery of the measurement method that is recently used and emergence of pathogenetic definitions and by the middle of the twentieth century, checking BP by sphygmomanometer became part of the routine physical examination in hospitals and clinics. It was considered necessary to treat hypertension after the detrimental effects of high blood pressure on the body were noticed. So reserpine, hydralazine, ganglion blocking agents, peripheral adrenergic inhibitor, oral diuretics, beta blocker, ACE inhibitors, calcium channel blockers drugs such as were synthesized. While the use of some drugs is limited due to their side effects, some are still used in the treatment of hypertension today. Additionally the potential for gene therapy in hypertension is one that will be watched with interest. The search for new antihypertensive drugs are still ongoing. The potential for gene therapy in hypertension is one that will be watched with interest.

Keywords: History of blood pressure, pulse, hypertension, antihypertensive drugs

Have you ever wondered about how blood pressure (BP) was recognized? Is it a disease or a physical adaptation? Is palpable pulse a sign of viability? Or on the contrary, it is an indicator of mortality? Most importantly, how did the history archive these concepts?



Because; answers to these questions might have been hidden in this archive. On the contrary to common belief, history of hypertension dates back to ancient times rather than 17th century. Edwin Smith Surgical Papyrus that was believed to be authored by Imhotep, the God of Medicine in ancient Egypt, in B.C. 3000s is the most scientific one of known medical papyri. The statement *'Pulse is an index of the heart and of the condition of the patient'* is written in the papyrus.



The Yellow Emperor's Classic of Internal Medicine

Following wording is written in The Yellow Emperor's Classic of Internal Medicine that is believed to be written by legendary Chinese Emperor Huangdi around 2,600 B.C.; *'The blood current flows continuously in a circle and never stops', 'When the heart pulse beats vigorously and the strokes are markedly prolonged, the corresponding illness...makes the patient unable to speak' and 'If too much salt is used in foods, the pulse hardens...'*. It was recognized 4000 years before William Harvey evidenced the blood circulation that hypertension causes intracranial hemorrhage and aphasia, while salt is a contributing factor in hypertension. The historical link between hypertension and kidneys was

probably started, when a Chinese physician, Choun-You-J, said *'When the pulse upon depressing, is very firm and upon superficial palpation tight, then the disease has its seat in the kidney'* around 200 B.C. ¹. The quality of a person's pulse is considered a condition that is both palpable by the trained physician and indicates cardiovascular status in Indian Ayurvedic medicine. Presumably, the term "hard pulse" is the modern medicine equivalent of hypertension. ².

However, it was quickly followed by the dark era of the Medieval Age that lasted for thousands of years and was characterized by very scarce gain in terms of knowledge about heart and circulation. Reasoning, criticism and discussion, knowledge, science and earth life were replaced by belief, blind confidence, scholastic philosophy, religion and eternal life, respectively, in the dark era of the Medieval age. The dark Medieval Europe could see the daylight through translation of Muslim scientists into Latin in Andalusia and Sicily only in 11th to 12th centuries; it could reveal out the Renaissance one of the historic moments in European history, in 14th to 15th centuries.



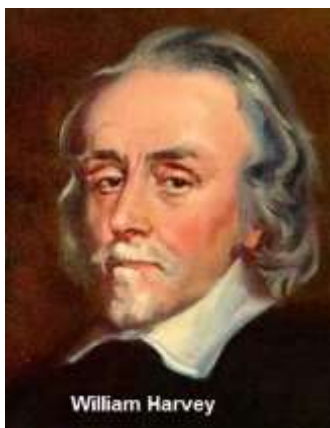
Al-Akhawayni Bukhari

Another name for Al-Akhawayni Bukhari, a famous Persian practitioner of the 10th century, is Joveini³. There is an important medical book named *Hidāyat al-Muta'allimin fi al-Tibb* by Joveini. In the chapter of this book titled "Fi al-Imtala", a disease resembling hypertension is mentioned. This scientist thought that the cause of hypertension was an excess of blood in the blood vessels. According to Al-Akhawayni, *al-Imtela'* patients had abnormal blood volume and symptoms such as sleepiness, dyspnea, pulsus magnus, weakness. He also talks about "severe flushing of the face, swelling of the veins, rupture of a vessel and risk of death" in relation to hypertension crisis and associated hemorrhagic stroke.^{4,5}

Since the sphygmomanometer had not yet been discovered in the Middle Ages, the physical basis of the concept of hypertension had not yet been formed. However, the information we have reached about "*al-Imtela'*" shows that it is a disease very similar to hypertension³.

Also, Greek physicians such as Galen and Hippocrates mentioned the disease "*al-Imtela'*" before Akhawayni. However, unlike Akhawayni, they claimed that this disease existed because harmful substances could not be removed from the body and did not mention its symptoms.

Details on circulation could sprout in early 17th century. William Harvey could experimentally prove the blood circulation in 1616. Approximately 80 years later (1694), Giorgio Baglivi reported that apoplexy is caused by cerebral hemorrhage probably secondary to renal hypertension in his necropsy studies¹.



William Harvey



Stephen Hales

In the 18th century, we see that blood pressure was first defined and tried to be measured. In 1733, scientist Stephen Hales discovered that blood puts pressure on blood vessels. In addition to systolic arterial pressure, Hales has worked on pulmonary and venous pressure, measuring blood volume, and calculating the flow velocity in the arteries¹.

19th century witnessed the efforts to develop methods for measuring the BP and subsequent theories on its link to diseases. Jean Poiseuille, a senior medical student, invented the mercury manometer to measure BP in 1828 and he demonstrated the respiratory BP waves. Jules Hérisson modified Poiseuille's mercury manometer using glass and a thin membrane in 1833. However, palpation of pulse had been used for a long time to estimate the BP despite all efforts to improve measurement methods¹. Carl Ludwig achieved to record blood pressure with a kymograph in 1847. This

method had been used in experimental studies approximately for 100 years and regarded as classical method. In 1880, Samuel von Basch defined a clinical sphygmomanometer that could measure systolic pressure over the radial artery¹.

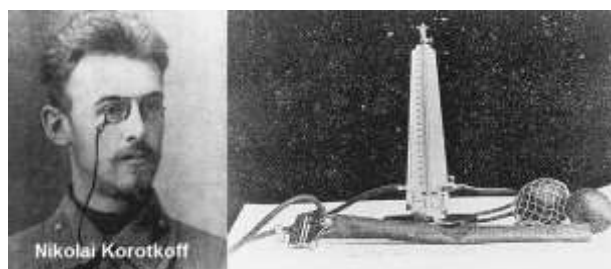


Richard Bright

However, Scipione Riva-Rocci designed the first clinically acceptable sphygmomanometer in 1896. This measured systolic pressure by obliterating the brachial artery with an inflatable rubber cuff⁶. Improvement of measurement methods in 19th century paved the way for an evident advancement in knowledge about regulation of BP and diseases secondary to blood pressure changes.

Richard Bright, another scientist with studies of blood pressure, in 1827 associated the pathological finding of sclerosing, contracted kidneys with hardness and fullness of the pulse, edema, albuminuria, hypertrophy of the left ventricle. He also highlighted the difference between cardiac and renal edema, helping us to understand kidney diseases especially nephritis. Vasoconstrictor and vasodilator nerve fibers were discovered in 1852 and 1858, respectively.

Essential hypertension was described by Frederick Mahomed in 1874. In addition, Mahomed suggested that high blood pressure is more common in the elderly population and that organs such as the brain, heart and kidney may be negatively affected^{7,8}.



Nikolai Korotkoff

20th century has witnessed changes in terminology, discovery of the measurement method that is recently used and emergence of pathogenetic definitions. Theodore Janeway used the terms 'essential hypertension' and 'hypertensive vascular disease' for the first time in 1904 and demonstrated the diurnal pattern of BP⁹. Two French interns, Leo Ambard and Eugene Beaujard, conducted an experiment in the same year and reported that essential hypertension is secondary to retention of sodium chloride¹. In 1905, Nikolai Korotkoff defined measurement of systolic and diastolic BP that is based on auscultation method, which is currently regarded as standardized method. When

the mercury sphygmomanometers were used in the early twentieth century and defining of the systolic and diastolic BP by appearance/disappearance of Korotkoff sounds as heard via the stethoscope, the modern quantitative concept of hypertension came into existence. In the middle of the twentieth century, measuring blood pressure with a sphygmomanometer, which was revolutionary in the diagnosis of hypertension, became routine ¹⁰.



In 1934, Harry Goldblatt induced experimental hypertension by occluding renal arteries of dogs and reported that critical vasoconstriction of renal arteries may lead to malignant hypertension in humans ¹¹. Irvine Page and Eduardo Braun-Menendez concomitantly defined a molecule, called Renin, in 1940 ^{12,13}.

Looking at the historical findings, it seems that hypertension is not a condition or disease that needs to be treated. Below photograph was shot in Yalta on February 1945. Being leader of a superpower in that period was not the only common characteristics of those three leaders. They were all hypertensive and Roosevelt, Stalin and Churchill died due to cerebrovascular accident in 1945, 1953 and 1965, respectively. Was it a coincidence that all of them were treatment-free? Or did medicine of that era adopt another approach for hypertension? The necessity to treat hypertension was acknowledged far after measurement of blood pressure could be achieved and hazardous effects of high blood pressure on the body were determined.



In 1931, Paul Dudley White linked high blood pressure to a compensatory mechanism and stated *'Hypertension may be an important compensatory mechanism which should not be tampered with, even when it is certain that we could control it'*. Similarly, John Hay supported this approach in the same year through his statement: *'There is some truth in the saying that the greatest danger to a man with a high blood pressure lies in its discovery, because then some fool is certain to try and reduce it'*. The condition was not really different in 1940s. In 1946, R.D. Scott made this statement: *'Many cases of essential hypertension not only do not need any treatment but are better off without it. Generally, the less said about the blood pressure is such people, the better'*.

However, scientists had started to recognize, in 1950s, that hypertension is not a physiological compensatory mechanism of aging and that it is a predictor of morbidity and mortality by damaging target organs following an approximately 15- to 20-year complication-free period.

Such as reserpine, thiocyanates and veratrum derivatives, hydralazine, ganglion blocking agents (hexamethonium, pentolinium, mecamlamine) and peripheral adrenergic inhibitor (guanethidine) more specific, potent and highly effective drugs were discovered in the 1940s-50s. However, these caused significant side effects when administered as injections ^{14,15}.



Sir James W. Black

Moyer reported that it is difficult to regulate kidney functions even with antihypertensive drugs. Even in *Circulation* magazine, Sjoerdsma commented, *"I look on the work of physicians who pursued the drug approach in hypertension as being well nigh heroic"* ¹⁷.

Later, a new group of drugs with natriuretic properties, which have natriuretic properties and can be tolerated, was developed: thiazides. Following this development, oral diuretics were discovered and hypertension became easier to manage. β -blockers with less side effects. The application of some medicinal chemistry by John Stephenson resulted in prazosin and pronethanol, the first β -blockers ¹⁸. But, later withdrawn because of oculomucocutaneous syndrome, sclerosing serositis and carcinogenicity. At the beginning of the 1960s, James Black developed the drug propranolol, which is safer, more potent and still considered the prototypical β -adrenoceptor antagonist ²¹.

In 1967, the first multicenter study of hypertension was performed and published in *JAMA*. The results of the study were quite remarkable because drug treatment of hypertension showed morbidity and mortality benefits.



It was first speculated after 1970s that hypertension is a prognostic factor. In 1972, Thomas G Pickering said: *'There is no certain cut-off for high blood pressure. The relation between the arterial pressure and the mortality is quantitative; as the pressure increases, prognosis gets worse'*. These claims were repeated through stronger evidences in 1980s and 1990s. Modern medicine's hypertension perspective was dictated by G. Rose's statement *'hypertension occurs when the benefits arising out of reduction of blood pressure outweighs the benefits of not reducing it'* in 1981 and W.B. Kannel's statement *'The objective of antihypertensive treatment should not solely be reducing the blood pressure; it should be also improve the cardiovascular outcomes'* in 1992²³. Non-pharmacological approaches were also included in the treatment of hypertension, but the pharmaceutical industry continued to search for new molecules, as it was clear that pharmacological treatment was very successful.

In 1956, Leonard T. Skeggs and his colleagues discovered ACE. This was followed by the work of scientists such as Sérgio Henrique Ferreira, Kevin K. F. Ng, John R. Vane, David Cushman, Miguel Ondetti. Finally, captopril, the first oral ACE inhibitor, was developed in 1975 and approved by the FDA in 1981.

Calcium channel blockers, one of the most commonly used agents in the treatment of cardiovascular diseases and hypertension today, were investigated in the 1960s during experimental studies on molecules under coronary dilatation screening, discovered in 1964 by the German pharmacologist Albrecht Fleckenstein, and used in the 1980s^{26,27}.

Scientists sought to develop Angiotensin II receptor antagonists after realizing that Angiotensin II damages the heart and kidneys, increasing the risk of myocardial infarction and stroke. However, since these drugs do not have oral bioavailability, structural modifications were made and losartan was approved by the FDA in 1995^{28,29}.

All these pharmacological developments; created easier, more effective and less side-effect treatment options. Even lower-dose treatment regimens have been created with combinations of different drug classes.

List of Available Antihypertensive Drugs From the 1930s to the Present

1930s	Veratrum alkaloids
1940s	Thiocyanates, Ganglion blocking agents, Catecholamine depletors (Rauwolfia derivatives)
1950s	Hydralazine, Peripheral sympathetic inhibitors (Guanethidine), Monoamine oxidase inhibitors, Diuretics
1960s	Central α_2 -agonists, β -Adrenergic inhibitors
1970s	α -Adrenergic inhibitors, α - β -Blockers, Converting enzyme inhibitors
1980s	Calcium channel blockers
1990s	Angiotensin II receptor antagonists

In 2000s, hypertension is deemed an independent risk factor for cardiovascular diseases, a notion far beyond the definition of hypertension as high blood pressure. Therefore, a treatment discipline is adopted that also reduces the cardiovascular risk of the patient rather than a decrease in numeric values alone.

Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in 2002, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT BPLA) in 2005, and Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension in 2008 (ACCOMPLISH) studies were conducted and various drugs and their effects were investigated, and similar studies continue^{30,31,32}.

Conclusion

Hypertension is the most common disease among all non-communicable chronic diseases worldwide. Moreover, our understanding of the pathophysiology of essential hypertension is still incomplete in many ways. There are a few new developments such as extra-renal deposition of excess sodium in the skin, central indispensable role of T-cell infiltration in the kidney for Angiotensin II-mediated hypertension and the role of gut microbiota in broadening our understanding of the pathophysiology of hypertension (33-37). The search for new antihypertensive drugs is still ongoing. So far, many drugs have been discovered in the treatment of hypertension. Some of these could not be tolerated due to their side effects, and some are still used frequently today. In addition to pharmacological treatment, some studies suggest that several genes may play a role in hypertension, so gene therapy may also be beneficial. The challenge remains for the next generation of researchers for further advancement as we had better understand human biology. The history of hypertension and the discovery of antihypertensive drugs are fascinating because save the lives of millions.

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