Hypertension, arterial haemodynamics and left ventricular disease: historical observations

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Introduction

The importance of arterial stiffening in the pathogenesis of cardiovascular disease has been gaining acceptance in recent years but is still widely overlooked, with the present preoccupation being atherothrombosis.¹² Arteriosclerosis is a result of a combination of endothelial dysfunction and structural abnormalities of the media of conduit arteries (in contrast to atherosclerosis which is an intimal disease) including increased collagen content, calcification and hypertrophy of vascular smooth muscle cells.³⁴ Chronic kidney disease (CKD) is known to confer an elevated risk of cardiovascular disease with an inverse graded relationship with glomerular filtration rates (GFR) independent of other risk factors.³ It is now widely accepted that the major driver of premature cardiovascular death and disease in CKD is left ventricular hypertrophy (LVH) and fibrosis rather than occlusive arterial disease.⁴

Arterial stiffening is best understood as a disturbance of one of the major functions of the arterial system, namely buffering of oscillatory changes in blood pressure that result from intermittent ventricular ejection. The highly distensible arterial system ensures that most tissues receive near steady flow with no exposure to peak systolic pressures. This mechanism is so efficient that there is almost no drop in diastolic pressure from ascending aorta to peripheral arteries.⁵ Loss of arterial distensibility results in a more rigid aorta that is less able to accommodate the volume of blood ejected by the left ventricle, resulting in greater pressure augmentation in systole and higher pulse pressures.⁶ As arterial stiffness increases, the myocardium, brain and kidneys are exposed to higher systolic pressures and greater pressure fluctuations resulting in microvascular damage.⁷ The increased impedance results in LVH. Furthermore, the effects on the left ventricle are exacerbated by lower diastolic pressure which reduces diastolic coronary perfusion, promoting subendocardial ischaemia and myocardial fibrosis.⁸ Greater reliance is placed upon systolic coronary perfusion, conferring heightened vulnerability of the myocardium to any decline in systolic function.⁹

Increased arterial stiffness, and systolic and pulse pressures are characteristic features of ageing in Western populations¹⁰ and are independent risk factors for mortality and development of heart failure.¹¹ Aortic pulse wave velocity, a widely used measure of arterial stiffness, is a powerful independent predictor of all-cause mortality and cardiovascular events in CKD, hypertensives, the elderly, diabetics and the general population.¹² Increasing research time and resources are being deployed in an effort to understand the mechanisms underlying increased arterial stiffness in a number of conditions, including essential hypertension, ageing and CKD, and thereby devise effective strategies to prevent or reverse this pathophysiology.⁴

Historical perspectives

Although the above description of the inter-relation between arterial and left ventricular disease is based
on numerous publications using modern investigative techniques, examination of medical literature over the last two centuries reveals a surprising appreciation by early investigators of the nature of this relationship.

The discovery of the links between kidney disease, arterial disease, left ventricular hypertrophy and heart failure

In 1827 Richard Bright (1789–1858; Figure 1), generally regarded as the ‘father of nephrology’, described Case VIII, William Bonham, a 55-year-old cheesemonger who had enjoyed good health but who had experienced pain in the back and loins and had been ‘subject to complaints including passing his water frequently and in deficient quantities’.13 For a year prior to his admission to Guy’s Hospital, London he had suffered from gout and great shortness of breath. At the time of admission he had significant oedema of his thighs and scrotum. His urine was ‘a deep yellow colour, clear, and coagulating in a very marked manner by heat, assuming a white curdled form’. The patient deteriorated over the next few days with decreasing urine output and died 6 days after admission. At post-mortem examination Bright wrote:

The heart remarkably enlarged; on the left side it was very thick and strong. The kidneys were very small, and hard in consistence, feeling almost cartilaginous; their prevailing colour was purplish; on their external surface they were distinctly granulated in texture...

He went on to conclude:

In this case we again distinctly trace the existence of a highly diseased condition of the kidney, coupled with the excretion of albuminous urine. The enlarged state of the heart would seem to bespeak some cause of obstruction to the circulation through the system beyond what we discovered, nor will I venture to say what share this might have had in giving rise to the dropsy.

In 1839 Bright and his junior colleague Joseph Toynbee (1815–66)14 noted thickened arteries in their microdissections of diseased kidneys, and published the observations in 1843 under Toynbee’s name alone, at Bright’s request. Successor to Bright at Guy’s Hospital, Sir Samuel Wilks (1824–1911) wrote on Bright’s disease at length in 1853 and confirmed the association between Bright’s disease and LVH.15 In 1872 Sir William Withey Gull (1816–90), also from Guy’s Hospital, and Henry Gawen Sutton (1837–91) linked the LVH found in Bright’s disease to what we now know as arteriosclerosis by describing the large arteries in CKD as ‘much thickened by the formation of “hyalin-fibroid” substance’.16 In 1850, Sir George Johnson (1818–96) from King’s College Hospital London17 wrote:

In all cases of chronic renal disease...the author had observed great hypertrophy of the arterial walls...the obstruction of the systemic capillaries would account for the hypertrophy of the left ventricle of the heart so frequently seen.

Thus, for the first time it was postulated that systemic arterial changes might be responsible for the link between diseased kidneys and LVH. It is notable that the title of this paper includes mention of the ‘pathology of the renal blood vessels in Bright’s disease’. Later Johnson emphasized the fact that the small arteries throughout the body were also diseased.18,19

An impressive and detailed understanding of the links between CKD, LVH and arterial stiffening was demonstrated in 1856 by the German physician, Ludwig Traube (1818–56). In a major work titled Ueber den Zusammenhang von Herz- und Nieren-krankheiten (The Relationship Between Cardiac and Renal Diseases) he put forward a comprehensive hypothesis that related cardiac hypertrophy to the renal disease first noted by Bright. Traube postulated a series of pathophysiological events that
have proved partially accurate. He argued that arteriosclerosis ‘was the result of long-lasting high-grade tension of the aortic system’ and that ‘...arteriosclerosis would have here the same foundation as the hypertrophy of the left ventricle’. Traube graciously acknowledges in his publications that it was a little known English physician from St Bartholomew’s Hospital London, William Senhouse Kirkes (1822–64), who first introduced the crucial idea of high intra-arterial pressure as a pathological agent.20 Kirkes had also highlighted the association between apoplexy (stroke), Bright’s disease and LVH. Unfortunately, Kirkes died at the age of 42 leaving unfinished a major book that was never published.

In Guy’s Hospital, Sir William Withy Gull (1816–90) and Henry Sutton (1836–91), examined and measured vessels taken from autopsies, and described the ‘hyaline-fibrinoid’ microscopic appearances of the vessels in what were probably hypertensive patients, placing the lesion clearly in the muscular layer of the vessels, and naming the condition ‘arteriocapillary fibrosis’.21 This general change was noted to be associated with LVH:

the hyaline-fibroid material in the walls of the arterioles must be an impediment of elasticity... the left ventricle, therefore, owing to this diminished elasticity, has of necessity to contract with greater force to carry on the circulation.

Blood pressure measurement and analysis of pulse wave forms

Thus, by the end of the 19th century, a number of London clinicians and German pathologists had established clear connections between CKD, arteriosclerosis, hypertension, LVH and heart failure. This had been done mainly through careful clinical and post-mortem examinations. To study the pulse wave more accurately, it was necessary to display and record it. In 1833, Jules Hérisson,22 introduced a ‘sphygmometer’. This apparatus compressed the radial artery with a bulb containing mercury and assessing the oscillations in the height of the column. Hérisson gave no measurements of the pressures he recorded, even though he linked a ‘hard’ pulse to LVH and apoplexy. Dr Robert Ellis Dudgeon (1820–1904)23 describes the history of the next development that of the sphygmograph, in his book published in 1882. In essence, this involved attaching a lever, usually a thin piece of wood, to an artery, magnifying the movement through systems of more levers to make it easily visible. Thus arose the ‘sphygmoscope’ of Scott-Allison, machines designed by Naumann and Butcher, Chelius’ ‘Kastenpulsmesser’ (a type of plethysmograph), Longuet’s and Baker’s ‘sphygmographs’ and Stein’s ‘sphygmophone’, which rendered the pulse wave audible by an electromagnetical induction coil. Karl Vierordt of Tubingen (1818–84)24,25 used a lever, pan weights and scales to measure pressures by compression of the artery, but his apparatus was impossibly complicated and only gave a very crude indication of the waveform. His major contribution was to cause a pen to inscribe a tracing on moving smoked paper providing a permanent record of the pulse wave. It was Etienne-Jules (1830–1904) in Paris who made proper analysis of the pulse wave possible in humans by refining Vierordt’s apparatus (Figure 2).26,27 Sir John Burdon Sanderson (1828–1905) in London and Baithasar Foster (1840–1913) in Birmingham modified Marey’s sphygmograph to allow more accurate graduation of the pressure applied to the artery.25,28,29 However, both did this with the aim of improving the shape and fidelity of the tracing, and not of measuring the arterial pressure.

Frederick Akbar Mahomed (1849–84; Figure 3) from Guy’s Hospital was the first to attempt clinical measurement of high blood pressure conceptualized as a primary event incorporating the morbid changes already recognized in the post-mortem room by Wilks,30 Johnson31,32 and Gull and Sutton.33 Mahomed was the first to correctly describe ‘high arterial tension’ as one of the most common medical scourges of humankind. He built on Sanderson’s modifications of Marey’s sphygmograph of 186334 by making it lighter so that the pressure it exerted was much lower. Therefore it was more responsive, and capable of being strapped to the forearm so that the ivory pad could rest lightly on the radial artery. However, the major modification, with the assistance of a jeweller, was to introduce a screw, so that measurements of the pressure required to occlude the arterial wave could be made quite simply in ounces of troy weight, the measure still used to weigh gold.

Mahomed used his modified sphygmograph to study the form and pressure of the pulse in hundreds
of patients with a wide variety of diseases. There is mention in his papers of checking blood pressure by using the screw that he had added, and a pressure of ‘between one and six ounces’ is mentioned as one of the characteristics of ‘high arterial tension’. Probably in the majority of cases the ‘high’ arterial tension was implied by the waveforms, which were extensively studied and discussed in the literature of the period. He fully appreciated the importance of pulse character. In the first paragraph of his first paper written as a medical student he wrote with extraordinary maturity:

The pulse ranks first amongst our guides; no surgeon can despise its counsel, no physician shut his ears to its appeal... Our sense of touch however highly educated, is manifestly liable to error and... it is by the aid of this more accurate sense (i.e. sight) we should study the pulse in its marvelous changes of character and form, as recorded by the sphygmograph.

Mahomed went onto study pulse and blood pressure in Bright’s disease in which he described high tension in the arterial system. Both Mohamed and Sir James Mackenzie (1853–1925), widely acclaimed as the founder of 20th-century UK cardiology, gauged arterial stiffness from the character of the pulse waveform, and this also was used in contemporary life insurance examinations to decline applicants with ‘anticipated senility’. Thus, by the end of the 19th century, the links between arterial stiffening and survival had become well established. In his historic textbook, William Osler stated, Longevity is a vascular question, which has been well expressed in the axiom that a man is only as old as his arteries. To a majority of men death comes primarily or secondarily through this portal. The onset of what may be called physiological arterio-sclerosis depends in the first place, upon the quality of arterial tissue (vital rubber) which the individual has inherited and secondly upon the amount of wear and tear to which he has subjected it.

This description of the ‘quality of arterial tissue’ or ‘vital rubber’ was perhaps the first appreciation of the importance of arterial distensibility to health and therefore of the potential pathophysiological importance of arterial stiffening. In his seminal book The Study of the Pulse published in 1902, MacKenzie also appreciated the importance of reduced arterial distensibility and described the association between arterial stiffening and what is now recognized as diastolic left ventricular dysfunction.

The progress of... degeneration in the arteries is practically the physical history of the individual after the zenith of his strength has been reached, accompanied by an imperceptible but progressive limitation of the field of his heart’s response to effort. Although for long he may lead a vigorous life within this limitation, with no evident discomfort, yet during the fourth decade of life the ease with which violent efforts are made is gradually lessening, and violent exertions are as a rule carefully avoided. Running after trains is not to be done in comfort, and the ascent of hills is undertaken with more deliberation. All this proceeds pari passu with diminished resiliency of the arterial wall.

The first clinician to actually to measure the arterial pressure in a systematic way, and express it in millimeters of mercury was the Austrian Samuel Siegrfried Ritter von Basch (1837–1905) using an apparatus that employed external pressure. Scipione Riva Rocci (1863–1937) introduced the occlusive cuff method of measurement. We use his sphygmomanometer method today, illuminated by the observations of the Russian surgeon, Nicolai Sergeivich Korotkov in 1905.
The domination of blood pressure measurements in the 20th century

Practitioners of the sphygmomanometer favoured the use of diastolic rather than systolic pressure in the early 20th century. Diastolic blood pressure was considered more reliable because its value was closer to mean pressure than systolic and therefore, thought to be a better guide to elevated peripheral resistance. Thus, the view became entrenched that systolic blood pressure was good, because it represented the maximum force generated by the heart, whereas diastolic blood pressure was bad, because it represented the resistance the heart had to overcome.43 Such a view was widely held until questioned by the Framingham results published in 1981,44 and then contradicted by the US National Institutes of Health’s Systolic Hypertension in the Elderly Project (SHEP).45 Until 1991, studies on arterial pressure had consistently reported a positive relationship between cardiovascular events and diastolic pressure.46–51

As elevated systolic arterial pressure was recognized more frequently before organ damage was evident, the emphasis changed from diastolic to systolic pressure, with the recognition that systolic pressure more accurately predicted adverse outcome in the middle aged and elderly.52 The detection and treatment of systolic hypertension now dominates clinical practice and isolated systolic hypertension is a well-recognized entity.53 Furthermore, for any given systolic pressure, events are inversely related to diastolic pressure indicating that increased pulse pressure is an important independent risk factor for cardiovascular disease in older age groups.45,54–62 Although these findings have been questioned,63 they can potentially be explained by arterial stiffening becoming the dominant cause of elevated blood pressure and cardiovascular disease with age and in pathological conditions such as CKD.63,64

The impact of arterial stiffness and systolic hypertension may have influenced world events in many ways (Figure 4). Franklin Roosevelt was one notable victim with a pre-stroke blood pressure of 250/160.65 Winston Churchill was also known to be hypertensive. He also almost certainly had minor strokes as well as angina through the Second World War with a major stroke while Prime Minister in 1953 before finally dying from another stroke in 1965.66 To complete the trio, Josef Stalin also suffered from uncontrolled hypertension with multiple strokes before succumbing to an intracranial haemorrhage.67 Thus, the world leaders who shaped geopolitics at the end of the Second World War, probably had their abilities and behaviour

influenced by arterial stiffening and systolic hypertension.

The wheel appears to have turned near full circle with the re-realization that it is indeed arterial stiffening that reduces arterial ‘cushioning’ so that the phasic ejection of the left ventricle causes greater fluctuations in pressure and greater peak systolic pressure. A number of office-based devices that measure arterial stiffness are now commercially available.66 Ironically the most useful methods, pulse wave analysis and pulse wave velocity measurements, are based on pathophysiological and clinical studies on arterial elasticity that were commenced in the 19th century.43

Conclusions

The ‘modern’ paradigm of arterial stiffness providing the link between CKD and cardiovascular disease would not be a surprise to Richard Bright if he were alive today. Difficulties in measuring arterial stiffness meant that blood pressure measurement using a sphygmomanometer became the focus of research and treatment throughout most of the 20th century. It is not in doubt that blood pressure control has saved countless lives through the years but the limitations of blood pressure measurements are increasingly recognized. Measuring arterial stiffness is now simple and reliable (Figure 5). Consensus groups have been set up producing guidelines on measurement,12 reference ranges69 and meta-analyses on the predictive value of
different parameters of arterial stiffness on cardiovascular outcomes.69,70 The time is now ripe for testing these parameters as means of reducing the cardiovascular risk in the large and expanding CKD population. Several agents are worthy of consideration. Some are relatively novel such as endothelin receptor antagonists. Others, cheap ‘orphan’ drugs long used for other indications such as allopurinol and spironolactone. Interventions might also involve targeting environmental factors such as high levels of bioavailable phosphate in a ‘western’ diet.4 With hindsight, much time has been lost since the early 19th century when the concept of arterial stiffening and its relationship to CKD and left ventricular disease was already recognized. Richard Bright may have been amused, if not pleased, that the area of cardio-renal research has never looked so ‘bright’.

Conflict of interest: None declared.

References

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