Arterial Stiffening in Perspective: Advances in Physical and Physiological Science Over Centuries:

ARTERIAL STIFFENING IN PERSPECTIVE:

ADVANCES IN PHYSICAL AND PHYSIOLOGICAL SCIENCE OVER CENTURIES

Michael F. O'Rourke[a], Caroline O'Brien[a,b,c], Elazer R. Edelman[b,c]

[a] St Vincent's Clinic/ University of New South Wales/ VCCRI, Sydney, Australia

[b] Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge MA USA,

[c] Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston MA USA

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Address for correspondence:

Prof Michael F O'Rourke

Suite 810

St Vincent's Clinic

438 Victoria Street

Darlinghurst, Sydney

NSW 2010

AUSTRALIA

Phone: +61 02 8382 6874

Fax : +61 02 8382 6875

Email : m.orourke@unsw.edu.au

Dr. Kotchen's editorial [1] in the American Journal of Hypertension drew attention anew to the subject of arterial stiffening with age, and the ill effects that this has on the heart, brain and kidneys. His piece also addressed the implications that arterial stiffening has for use of new methods and concepts for measurement and interpretation of arterial pressure throughout the arterial tree. This is timely, and follows a Scientific Statement on Arterial Stiffness by the American Heart Association on the subject [2], and anticipates the American Medical Associations' recognition of pulse waveform analysis and central aortic pressure as warranting reimbursement, as a complement to the measurement of systolic and diastolic pressure by brachial cuff sphygmomanometry [3].

Clinicians rightly perceive the major advance in this field over the last century, as being the cuff sphygmomanometer, since this provides numbers for systolic and diastolic pressure which predict risk of cardiovascular events and death in persons who are apparently well [4]. But high blood pressure had been recognised clinically almost 100 years beforehand by William Bright [5] in 1827 on the basis of "hardness of the pulse", typically as palpated at the radial artery. Subsequent graphic registration of radial pulse contour improved clinical interpretation of the pulse. In 1863, Etienne Marey, the French genius of motion in all its forms, whose study of birds [6] inspired the Wright brothers approach to powered flight [7], was the first to describe changes in the radial arterial pulse in humans with aging [8]; Frederick Mahomed in 1872 [9] went further to show how the radial pulse can also be used to identify high blood pressure, then described the difference between essential hypertension and primarily renal hypertension, and then the natural history of essential hypertension:-

"These persons appear to pass on through life pretty much as others do and generally do not suffer from their high blood pressures, except in their petty ailments upon which it imprints

itself ... As age advances the enemy gains accession of strength ... the individual has now passed forty years, perhaps fifty years of age, his lungs begin to degenerate, he has a cough in the winter time, *but by his pulse you will know him* ... Alternatively headache, vertigo, epistaxis, a passing paralysis, a more severe apoplectic seizure, and then the final blow." [10]

The sphygmograph was progressively refined, with the zenith reached by the Dudgeon device [4] which attracted the attention of general and specialised physicians, and was widely used in journal articles and textbooks of the early 20th century, including those of Sir James Mackenzie (regarded as the Father of Cardiology in the English speaking world) in 1902 [11]. These devices were compact, and beautifully made, but were all mechanical and difficult to use. Their value was eclipsed by the cuff sphygmomanometer which could be used quickly (perhaps too quickly) and which provided (using Korotkov sounds) [4], numbers to quantify systolic and diastolic pressure. The numbers provided a veneer of science that the pulse waveform could not. Sphygmography lapsed, and disappeared from the mainstream of clinical medicine in the wake of World War I.

Speed of uptake of the cuff sphygmomanometer was extremely high, and companies like Baum in New York City with its Baumanometer were very successful and still remain in business. Speed of uptake depended on an educated profession, an established need, and by 1914, the recognition that measurement of arterial pressure could detect the "silent killer" [12]. The lead was taken by medical examiners for the insurance industry such as Fisher, who established the value of the device for predicting premature invalidity and death of applicants for life insurance in a classic JAMA article [12]. The hundredth anniversary of this article has just passed. The device played its role in war and peace over the next 50 years, being used for screening of applicants for the military, initially in a limited way, then exclusively

for recognition of a condition which was described as “hypertension” [13]. Two Commanders in Chief of the USA, Presidents Woodrow Wilson (probably) and Franklin Roosevelt (definitely) [14] were disabled by this condition while still in office during the first and second World Wars respectively. Hypertension and its effects on the brain impaired US negotiations for lasting peace at the end of both World Wars.

Fisher’s initial emphasis [12] was on systolic pressure, but with passage of time, diastolic pressure was taken as the best indicator of hypertension in young subjects i.e. under age 50 [15], and this is still the case, but with risk in persons older than 60 years, now best detected on the basis of raised systolic or pulse pressure (because diastolic pressure falls as the arteries stiffen with age). This was established by the SHEP study in 1991 [16], and confirmed by the Syst-Eur [17] and Syst-China [18] studies. Early interpretation of arterial pressure numbers was originally based on the simplistic view attributed to Mackenzie, but generated by his literary executor William Orr, that diastolic pressure is a manifestation of arteriolar tone (and so the lower the better) while systolic pressure is a manifestation of cardiac strength (and so the higher the better) [19].

Hypertension, the Circulation of Blood, Physiological Principles and Physical Laws

The saga of hypertension entails the study of the circulation as a whole, and the study of the circulation is closely linked with the development of physical laws and physiological principles and laws. William Harvey [20] in 1628 published his life work (to that time) on the concept of the circulation, generated by the heart, causing passive expansion of the arteries with each beat, so that blood flowed on and into minute arterioles at high pressure. He later described the phenomenon of wave travel and reflection in arteries, as when an

artery is obstructed by a reed [21]. Harvey had many supporters, but many detractors as well. His description of the circulation and his answers to criticism are readily available in English translation (from Latin) [20]. It is surprising how few clinicians have read these brief, entertaining, (and even raunchy) tomes.

Examples of Harvey's exasperation are shown in his Second Open Letter to Jean Riolan of Paris (figure 1) [21]. As Harvey receded, Isaac Newton emerged, and soon after Harvey's demise, King Charles II founded the Royal Society of London to improve natural knowledge by enquiring into all natural phenomena including biology, human disease, physics, astronomy, navigation. The motto of the Royal Society became "Nullius in Verbo" (Talk is Cheap), and indeed the Society supported critical research like Newton's studies in Cambridge on the basis of motion, including that of blood in the circulation and his (the first), description of the viscosity of fluids (as Defectus lubricatis). Newton became President of the Royal Society and later "Warden of the Mint" whose standards for purity of precious metals were a serious national problem.

The Royal Society also published Stephen Hales' Statical Essay: Containing Haemastatics [22] in which he became the first person to measure blood pressure in an animal (and to describe the effects of haemorrhage on the pressure values themselves and on heart rate) [22]. He compared the arterial system's cushioning function in terms of the contemporary fire engines' air-filled dome, which acted to smooth pulsations of the engine's pump into steady flow at high pressure through the nozzle of the hose. The German word "Windkessel", loosely interpreted as "air chamber", is still often used to describe an elastic reservoir [19]. Hales noted that (mean) pressure in small peripheral arteries was similar to that in central arteries, consistent with the arterial system being a very efficient conduit to transmit blood

flow at high pressures over long distances to the smallest vessels which comprised the "peripheral resistance". As a young physician, J.P. Poiseuille in the early nineteenth century confirmed this view of high pressure delivery of blood to tiny vessels in the mesentery [23]. This was the reason for his later use of tiny capillary tubes to establish the fourth power of arterial calibre to describe the relationship of pressure gradient to steady flow [23]. Poiseuille's contribution to physics and viscosity was based on his interest in the physiology of the circulation. In this era, physicians and biologists sought physical laws to explain their observations. Physicists used biological materials to formulate the laws.

Around Poiseuille's time, another physician and polymath in England, Thomas Young [24] was utilising biological material (readily available from abattoirs; there were no synthetics), and arteries to establish the theory of elasticity including the modulus which now bears his name. Moens [25] and Korteweg [26] established the relationship between elasticity of a vessel's wall and density of fluid within to the speed of transmission of the pulse wave in the vessel. This work settled the question raised by Harvey (figure 2) as to whether a wave of pressure passed along the vessel wall or a wave of flow passed through the arterial lumen, by creating a hybrid view subsequently confirmed theoretically [13] as a wave of pressure passing along the wall of the artery with a speed which depends on relative artery dimension [wall thickness ÷ diameter], Young's modulus of wall elasticity, and density of blood within. With constant relative dimension (wall thickness ÷ diameter) and constant density, pulse wave velocity is a measure of arterial stiffness (i.e. of Young's modulus). Pulse wave velocity in human arteries is in the range of 4-16 metres/ second, and much faster than the velocity of blood within the artery (peak of around 1 metre/ second). These findings also explained Harvey's description of wave reflection at a ligature occluding an artery (figure 2), and John Hunter's subsequent use of multiple ligatures in the femoral artery proximal to

popliteal aneurysm so as to reduce risk of rupture immediately proximal to the first (i.e. most distal) ligature [27].

Wave travel and reflection are not possible if the circulation is seen only as the elastic reservoir or Windkessel (i.e. Hales' model of the arterial tree). Pulse wave velocity is at present the best measure or aortic stiffness. Stiffness can also be measured as elasticity (Ep) from the relationship between stress (ΔP) and strain (ΔD) [24]. In practice, elasticity indices are hard to measure reliably, since change in pressure needs be measured at the same site as change in diameter. Further, for measurement of Young's modulus, wall thickness must be determined as well. Conventional measures include the intima (which is not load-bearing), and the media which is load-bearing but in-homogeneous. PWV remains the presently approved best measure of stiffness, but input impedance and characteristic impedance may replace this [28,29]. The work of cardiovascular physiologists Starling, Frank, Wiggers and many others [30-33] in the early 20th century was based on studies of blood viscosity and arterial elasticity (figure 3). Newton's laws of motion were applied to fluids by physicists Navier and Stokes [13]. The phenomenon of wave travel in arteries led to the need for consideration of wave reflection, since wave travel was so fast (4-16 metres/ second) as to traverse and re-traverse the arterial tree within the course of one heart beat. Secondary fluctuations of pressure and flow during systole and diastole were described as caused by wave reflection [30-33].

Prior to the Second World War, Hamilton and Dow [30] had described "standing waves" of pressure along the aorta of dogs indicating that wave reflection in the arterial tree was extremely high, approximating 100%. This work was subsequently expanded after the Second World War, with the major Handbooks of Circulation [31] for the American

Physiological Society (circa 1963) emphasising views on pressure wave reflection, and supplemented with corresponding data on effects of reflection on flow waves [32]. Carl Wiggers (author of "Pressure Pulses in the Arterial System" [33]) was appointed Founding Editor of the journal "Circulation Research" for the American Heart Association in1953. His tome [33] had embraced and emphasised wave reflection and had described use of Fourier analysis for interpretation of pulse waveforms in the frequency as well as the time domain. Views on wave reflection in the recent literature are very confused, with many new contributors not citing, and apparently being unaware of previous perspectives. Different views are set out in the McDonald's textbook (5^{th} ed) (figure 3).

Clinical Implications of Arterial Stiffening

Throughout the late nineteenth century and beginning of the twentieth, arterial stiffness was recognised as comprising a major component of left ventricular load. Roy [34] stressed the aging effects on human arteries from childhood. Sir James Mackenzie, the first cardiac specialist in the English-speaking world, described the effects of arterial stiffening with age as impairing cardiac function and causing breathlessness from the fourth decade of life [11]. Creighton Bramwell and Nobel laureate A.V.Hill measured arterial stiffness as Pulse Wave Velocity (PWV) in humans and confirmed increase in PWV with age [35]. Clinicians, however, had not been taught about arterial elasticity in medical school, and were all too comfortable with the simplistic view that Orr wrongly attributed to Mackenzie, of systolic pressure being a measure of cardiac strength (the higher the better), and diastolic pressure being a measure of peripheral resistance, and the lower the better [13]. It was only the

Systolic Hypertension in the Elderly Project (SHEP) study (first published in 1991) [16] which established the risk posed by elevated systolic pressure in persons over age 60 years.

Following the end of the Second World War, there was strong stimulus to understand the circulation better. President Roosevelt's sudden death [14] had established the relationship between cerebral hemorrhage and elevated blood pressure, and reawakened concerns about Woodrow Wilson's illness at a critical time after World War I. Cardiac surgery was thriving and was extended further with development of cardio-pulmonary bypass. The American Physiological Society had reached the zenith of its influence with publication of its handbooks in 1962-1965, and celebration of its Centenary in 1987.

In the late 1940s at St. Bartholomew's Hospital in London – the hospital where Harvey had practiced three centuries earlier, Donald McDonald, Physiologist, and Mathematician John Womersley, released from service after World War II, began their collaboration on pulsatile arterial hemodynamics based on theory and relatively primitive experiments [13,36,37]. They showed that the relationship between pulsatile pressure gradient and flow could be regarded as linear, since non-linear terms were sufficiently small to be neglected to a first approximation [36,37]. Michael Taylor's frequency domain studies built on these concepts [38-40] in the same laboratory at "Barts", and subsequently in Sydney, on impedance and transfer functions to describe relationships between pressure and flow pulsations (as impedance) at the same site in the arterial tree and between pressure pulsations at different sites. Similar work followed from Donald Fry and colleagues at the National Institutes of Health in Bethesda [41-44], headed by Eugene Braunwald in the 1960s [45]. Experimental work applied to humans, studied at cardiac catheterisation and cardiac surgery, led on to

present quantitative developments on effects of aging and arterial stiffening in humans, and the ill-effects of large artery changes on delicate cerebral and renal microvasculature [46].

The most recent advances in this field have followed embrace of arterial hemodynamics into clinical practice, beginning with management of hypertension with drugs which were far more effective and better tolerated than those available up to 1970. These now include calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, vasodilating beta blockers, nitrates, and drugs which delay breakdown of nitric oxide by inhibiting vasopeptidase. These new drugs alter arterial stiffness and wave reflection [47, 48]. The most prolific, logical, and consistent group in this field has been led from Paris by Michel Safar, with influential protégés very active in Europe but spread around the world to include the USA, Japan, China and Australia. With help from pharmaceutical companies, particularly Servier in Paris, Safar and colleagues have arranged a series of 10 conferences on Structure and Function in Arteries over the past 25 years. With the support of the American Heart Association, papers from the meetings, reviewed independently have been features in regular editions of Hypertension or the American Journal of Hypertension. Major statements from the European Society of Hypertension and European Society of Cardiology [28] have now been followed by a Scientific Statement on Arterial Stiffness from the American Heart Association [29].

We present this perspective to balance those who come to see this subject only in reference to the times of their own careers. Increasingly, in an era dominated by electronic searches that focus on only the most recent literature, emerging publications concentrate on recent events, failing to recognise and cite facts, principles and laws, set out by others in the near and distant past, and failing to reconcile their findings with their predecessors. Examples in this

field include the phenomenon of wave reflection, which is attributed solely to properties of large arteries [49], discounting the work over centuries by luminaries of physiology and physics, who attribute the major part of wave reflection as emanating from the multiple junctions of low resistance arteries with high resistance arterioles throughout the body (figure 3). Recent concepts such as "wave intensity analysis" lead to inconsistencies including "Reservoir Wave Concept" and "Instantaneous Wave-free Ratio" of aortic pressure and flow. Experienced European physiologists, Westerhof and Segers [50], reject these terms as "misconceptions that violate physical principles". Science ultimately calls for explanation of phenomena on the basis of known laws. This brief review is offered in the spirit of Harvey's reproach to Riolan (figure 2), and Newton's strong defence of scientific method as President of the Royal Society, and Warden of the Mint, as described in a biography by Gleick [51] (figure 4). Harvey and Newton acknowledged their struggles and attributed their achievements to giants of the past on whose shoulders they stood [51]. In the same spirit, we too must not forget the past especially as it defines the present and drives the future.

What does the future hold?

Modern clinicians associate blood pressure with the brachial cuff sphygmomanometer. This device has served us well, but it is not out of place to suggest that in the near future this instrument will disappear from the physicians' desk. It is no longer used routinely by anaesthetists in operating theatres where finger plethysmographs provide more important information as pulse waveforms and arterial oxygen saturation. It is no longer used in major trauma units where the finger sphygmographs is used initially, followed by intra-arterial pressure and monitoring from a radial, brachial, femoral or aortic site – with the last two preferred in shocked patients or those undergoing intra-aortic balloon counterpulsation.

For routine evaluation, will the systolic and diastolic cuff pressures be considered appropriate, when importance of one (SP) over the other (DP) has been misunderstood over the past century, and continuing? The modern oscillometric devices all have proprietary algorithms to provide systolic and diastolic pressure comparable to SP and DP determined by K sounds (but with extremely wide limits of mean =< 5 mmHg and SD =< 8 mmHg, as described by the AAMI and FDA [13]. But most and possibly all of the oscillometric devices determine mean pressure primarily, then SP by reaching up to a higher value detected from cuff pulsations, and DP similarly by reaching down and using proprietary algorithms. Will the BP of the future be expressed as mean pressure and pulse pressure? [14] Or will the cuff be used at all, with non-invasively recorded BP replaced by non-invasive measurement of PWV in conjunction with contour of the arterial pulse? MRI measurements of vascular impedance are approaching financial practicability, and presently only add 3 minutes or so to an examination required for another purpose.

In the future, we would like to see resolution of findings from modern CMR techniques including the lesions of "pulse wave encephalopathy" [52,53] with the older findings of arterial damage in humans and experimental animals with acute and chronic hypertension [54,55]. We would like to extend the seminal work of Harvey Cushing [56] on cerebral blood flow, and hypertension as induced by elevated intracranial pressure, and the possibility that secondary stroke induced by trauma can be prevented or minimised by reduction of wave reflection through use of nitrates or similar drugs [14,57,58].

The future is bright, and will be seen in a new world of sensors and data manipulation as available now on consumers' health devices, and "apps" on mobile phones. It is likely to be far different to the present brachial cuff.

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ABSTRACT

Arterial stiffening is not a new issue in medicine or research, but was the prime concern of Richard Bright in the early 19th century, and of the prominent London physicians and pathologists who tried to unscramble the relationship between kidney, heart, cerebrovascular disease and hardness of the pulse in the late 19th century. It was of major concern to medical educators including Osler and Mackenzie who were still active in practice 100 years ago.

It is all too easy (when dependent on the internet) to consider arterial stiffness to be a new issue. The terms arterial stiffness, aortic stiffness, or wave reflection do not appear as categories for articles such as this in respectable journals, nor in categories for meetings of specialised physicians. Yet as described in this article, the subject was of interest to clinicians, investigators such as Harvey in the 17th century, and to physicists who developed laws and principles of elasticity from study of biological materials including ligaments and arteries.

This paper provides a perspective on arterial stiffness from the time of William Harvey and Isaac Newton to the present, with a glance into the future.