

Commentary

QJM

Pulse pressure and arterial elasticity

S.E. GREENWALD

From the Department of Histopathology and Morbid Anatomy, Barts and The London Queen Mary's School of Medicine and Dentistry, Royal London Hospital, London, UK

The last decade has seen increased interest in the mechanical interaction between the heart and the arterial system. In particular, it has been suggested that increased arterial stiffness is associated with the development of cardiovascular disease and may even predict its development at an early stage before vascular lesions or external symptoms become evident (reviewed in references 1 and 2). The reasons for this association are not fully understood, although we have known for almost 200 years that pulse pressure is affected by the distensibility of the arterial system, its dimensions and the presence of wave reflections.³ Accordingly, renewed attention has been directed at methods of measuring arterial elasticity, either directly or by way of 'surrogates'.

The review in this issue by Mackenzie and colleagues discusses the clinical value of such measurements. They reiterate the argument outlined by O'Rourke:⁴ that after the introduction of the sphygmomanometer, the shape of the pressure wave was neglected in favour of a simple numerical representation (i.e. pulse pressure), and that with the development of improved methods, analysis of the pulse wave is back in fashion. Whatever the reasons, it is clear that the long-term performance of the heart, like that of all machines, depends not only on the average load to which it is exposed, but at least as much on time-varying and peak loads. It is surprising, at least with the benefit of hindsight, that more attention has not been given to this aspect of the circulation.

To explain the relationship between forces generated within the myocardium, pressure within

the ventricles, and changes in the shape and height of the pressure pulse as it travels away from the heart, requires a model of the circulation which, constrained by the observed anatomy and mechanical properties of the circulation, is able to predict the pressure and flow waveforms at any point, given these variables at any other upstream or downstream point. In practice, such models are most frequently used to derive estimates of central aortic pulse pressure and stiffness, using measurements at distal sites more easily accessible to non-invasive techniques. They form the basis of many of the methods often grouped under the heading of *pulse wave analysis*. Without an understanding of the limitations of such models and their underlying assumptions, the quality of the results produced by the 'algorithms' cannot be properly assessed, and there is a danger that the pronouncements of machines based on these approaches will acquire a spurious authority.

As a starting point, it is worth describing the physical properties of the arterial wall on which some of the indices of arterial elasticity described by Mackenzie *et al.* are based. A complete and rigorous description of the elastic properties of the arterial wall must obviously take into account all its observed properties. These include anisotropy, viscoelasticity, a non-linear stress-strain relationship (manifested as an increase in stiffness as a blood vessel is distended or stretched longitudinally), and the presence of residual stresses. This last property refers to the forces that remain within the vessel wall when all external loads have been removed. They are revealed by the tendency of a ring-shaped

Address correspondence to Professor S.E. Greenwald, Department of Histopathology and Morbid Anatomy, Barts and The London Queen Mary's School of Medicine and Dentistry, Royal London Hospital, Whitechapel Road, London E1 1BB. e-mail: s.e.greenwald@qmul.ac.uk

vessel segment to spring open into a horseshoe shape when cut along a line parallel to its long axis, and are thought to have evolved to minimize the stress gradients that inevitably arise across the wall of a pressurised tube. Residual stresses have been known to structural engineers for many years (and are often introduced by design into gun barrels to counteract high internal gas pressures⁵), although they were not described in the biomedical literature until 1983.^{6,7}

In principle a *constitutive equation* can be formulated which can account for all the observed properties,⁸ although some of them are difficult or currently impossible to measure *in vivo*. For the vascular physiologist, pathologist or clinician, a description in which blood vessel stiffness may be related to haemodynamic and structural factors is required, so that useful diagnostic and predictive measurements can be made non-invasively and routinely. A simplified model of arterial elasticity has been used in many studies in which measurements are confined to the circumferential direction, and elastic non-linearity is treated by defining *incremental* elastic properties over a limited region of the stress strain curve that is taken to be linear (for instance, that corresponding to the part between diastolic and systolic pressure). To calculate this quantity, which is equivalent to 'Young's modulus' as defined in Table 1 of the Mackenzie review, one must determine pressure, diameter and wall thickness over the chosen range of pressures. It may be regarded as a measure of the stiffness of the vessel wall material. The *functional* stiffness of a blood vessel, that is a measure of the relative change in its diameter in response to a known change in pressure, defined by Mackenzie *et al.* as the 'elastic modulus' (although more often known in the literature as 'elastance', 'pressure-strain' or 'Peterson' modulus⁹) is of more concern to the clinician for two reasons. Firstly, it is easier to measure, because it does not require knowledge of vessel wall thickness; secondly, it is an important determinant of the reservoir function of the large arteries (see below). Functional stiffness (E_p) is related to structural stiffness (Y) by the approximation:

$$E_p \approx Y \times h/r$$

where h is the thickness of the vessel wall and r its midwall radius. Distensibility as defined by Mackenzie *et al.* is simply the reciprocal of E_p . Thus for a vessel of given material properties, its distensibility (and hence effectiveness as an elastic reservoir) will increase as the relative thickness of its wall decreases. Conversely, medial hypertrophy leads to decreased distensibility even if the wall material remains the same.

When the left ventricle contracts, it generates a pulse wave which travels along the great arteries at a velocity proportional to the square root of E_p . This 'pulse wave velocity' (PWV) therefore depends on the combined effect of material stiffness and relative wall thickness as shown by the equation above. It is worth emphasizing that the pulse wave velocity differs from the velocity of the blood in much the same way that the speed of a breaker approaching a beach differs from that of the much slower moving tide.

The relationship between pulse pressure, the resultant pulsatile flow, arterial elasticity and dimensions is encapsulated in the concept of *impedance*. This may be described as a combination of all the factors which limit the pulsatile flow across a pulsatile pressure gradient. In addition to functional stiffness and lumen diameter, they include the timing and magnitude of wave reflection, and to a lesser extent, the inertia of the blood and viscous losses in the vessel wall. For a given cardiac output, impedance determines pulse pressure and therefore the peak load on the heart, just as resistance defines the relationship between the steady components of pressure and flow, and therefore the mean load on the heart (Figure 1).

The concept of impedance is useful in explaining the link between mean and pulse pressure. Referring to Figure 1, it is apparent that an acute increase in mean pressure will lead to increased impedance in two ways. Firstly, the material stiffness of the vessel increases because it is stretched more. Secondly, the increased pulse wave velocity results in an earlier return of the reflected wave and augmentation of the pulse pressure,^{10,11} although in the aged there is evidence that the strength of the reflection from some sites is reduced.¹² If the increase in mean pressure becomes chronic, two more factors will contribute to increased impedance. Firstly, increased collagen synthesis will lead to stiffer wall material and hence functional stiffness, and secondly, medial hypertrophy will increase the ratio of wall thickness to midwall radius (h/r) and further raise functional stiffness, regardless of any change in material properties. It is perhaps not so widely appreciated that the connection between mean and pulse pressure may be a two-way process. Not only does raised mean pressure lead to raised pulse pressure, but there is experimental evidence that an increase in pulse pressure, induced by banding the ascending thoracic aorta in pigs, can lead to an increase in mean pressure which is maintained for at least 2 months (N. Stergiopoulos, personal communication). Reduced aortic baroreceptor activity, a possible although speculative mechanism for this process, is supported by the

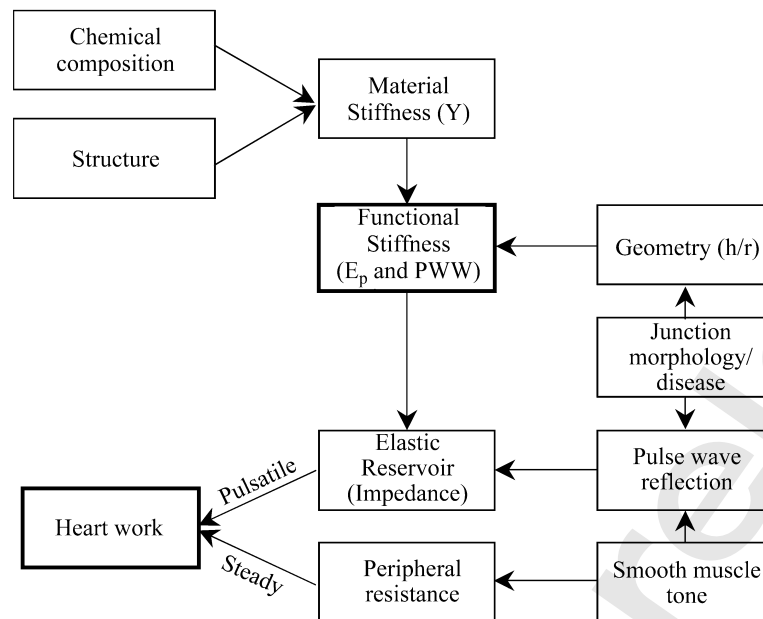


Figure 1. Relationship between structure composition and function in conduit arteries.

observation that administering the lathyrogen beta-amino propionitrile (which prevents collagen cross-linking and leads to excessively compliant arteries) reduces mean blood pressure and aortic stiffness in hypertensive rats.^{13,14} This synergy between the mean and pulsatile components of blood pressure suggests that they should always be considered together when studying the causes and consequences of vascular disease.

As explained above, increased arterial stiffness implies increased pulse pressure, and the epidemiological evidence cited by Mackenzie *et al.*, as well as that from more recent studies,^{1,2} shows that the latter is linked to increased mortality from cardiovascular disease. Suggested mechanisms for the connection have been lucidly reviewed by Dart,¹⁵ who also cites evidence that changes in stiffness *per se* may contribute directly to the progression of hypertension.¹⁶ Similar findings have been reported in patients with end-stage renal disease^{17,18} and diabetes.¹⁹ It has also been found that increased vascular stiffness may precede the development of isolated systolic hypertension.²⁰

The techniques for measuring arterial elasticity reviewed by Mackenzie *et al.* may be classified into direct and indirect methods. Direct measurement of arterial elasticity, which requires measurement of the pressure/diameter/wall thickness relationship, is feasible, although obtaining accurate non-invasive measurements of these variables remains technically challenging. Direct methods provide information about the arterial wall at a single location, and are useful for assessing changes in elasticity due to localized lesions.

For a more general assessment of vascular health, pulse wave velocity (PWV) measurements may be the preferred method, because it is possible to measure average stiffness at various locations in arterial segments hundreds of millimetres in length. When measuring PWV to determine arterial elasticity, information about the shape of the pulse wave is, perforce, discarded. If this is not done the 'true' wave velocity cannot be derived, and false values of elasticity will result. However, as is shown in the Mackenzie review, much general information about arterial elasticity and wave reflection distal to the measurement site and pulse pressure proximal to it, can be derived by analysing the shape of the pulse wave. This approach, often referred to as pulse wave analysis (PWA), forms the basis of the commercial systems described in the review. There has been some contention recently about the relative merits of PWV and PWA as a means of assessing large-artery stiffness,^{21–23} and their review provides a balanced view of these two related techniques. The two approaches (both of which, in fact, involve analysis of the pulse wave) are complementary. PWV as a means of estimating arterial elasticity is based on a clearly-understood and well-tested theoretical model (see, for example, references 24–26) that relates wave propagation to functional stiffness but tells us nothing about pulse pressure. PWA on the other hand, does not permit quantification of functional stiffness *per se*, but provides information about wave reflection and pulse pressure, and in the hands of those who favour the Windkessel model of the circulation, a means of estimating the *lumped* parameters which

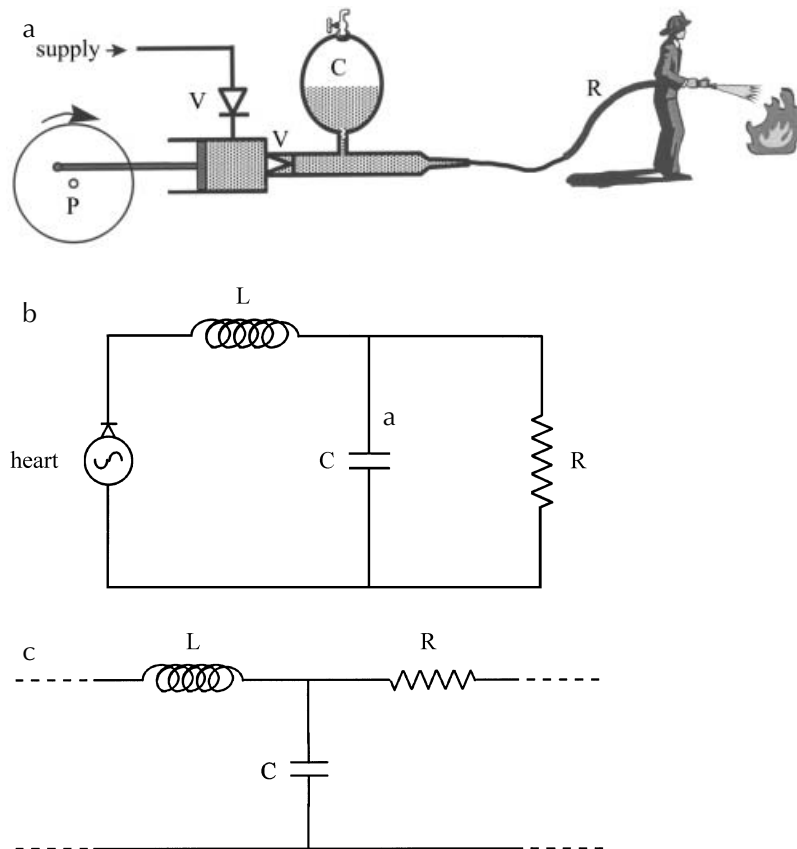


Figure 2. **a** A pulsatile pump (P) equipped with two one-way valves (V) pumping into a two-element Windkessel consisting of a pressure vessel partially filled with air, which acts as a capacitor (C) and a tube terminating in a high resistance pipe and nozzle (R). The combined effect of the capacitor and the resistor is to maintain a nearly constant outflow from the hose in spite of the variable flow produced by the pump. **b** Electrical analogue of the vascular system consisting of a capacitance (C) and a resistance (R) (the two-element Windkessel model). The addition of third and fourth elements, impedance and inductance (L) (representing the combined effects of the distal circulation and the inertia of the blood) improve the agreement between measured and predicted aortic pressure and flow in the aorta. Distributed model of the vascular system in which many individual Windkessel-like elements are arranged in series and or parallel.

define the arterial system as a whole (see Figures 2a and b). In the Windkessel model, as originally conceived by Hales²⁷ and further developed by Frank,²⁸ the systemic arterial system is characterized by a total peripheral resistance (TPR) associated primarily with the arterioles and a total arterial compliance (TAC) (the sum of individual local arterial compliances), more than half of which is due to the large elastic arteries.²⁹ This two-element model helps to elucidate the relationship between aortic pressure and flow. As the left ventricle contracts, the compliant arteries near the heart become distended and at the end of systole, when the aortic valve has closed, the blood is discharged towards the periphery at a rate which is determined by the product of the TPR and TAC. Refinements of the model which account for impedance³⁰ and the inertial effects of blood movement^{31,32} give a more precise description of the time-varying relationship between aortic pressure and flow. The usefulness and limitations

of these models have recently been reviewed.^{15,29} Despite the lack of an obvious correspondence between the lumped parameters and any discrete anatomical features, and its neglect of wave propagation, the Windkessel model provides clearly defined and measurable variables which may be measured *in vivo*. In its simplest two-element form, it is possible, given mean pressure (obtained by sphygmomanometry), and mean and pulsatile aortic flow (measured non-invasively by Doppler ultrasound, for instance) to estimate aortic pulse pressure non-invasively and with a high degree of accuracy.^{33,34}

An alternative approach, based on the concept of an electrical transmission line divides the vascular tree into small sections, each of which may be regarded as individual Windkessel systems with their own compliance, resistance and inductance (a measure of the inertia of the blood in the section) (Figure 2c). It has the advantage of direct correspondence between the model transmission

line and the anatomy of the vascular tree, and takes into account the propagation and reflection of pressure and flow waves from one segment to the next (see references 29 and 35 for reviews). Given the appropriate values of all these local variables and the flow wave produced by the left ventricle, it is possible to predict the shape size and timing of the pressure and flow waves at any point in the vascular system. The computational procedure used to accomplish this is known as a transfer function. Of greater interest to the clinician is the inverse problem: estimation of pulse pressure in the aorta given its value at distal sites, such as the radial, brachial or carotid arteries, where it can be measured non-invasively. As O'Rourke and his colleagues have shown (summarized and reviewed in references 4 and 36), by applying the *inverse* transfer function to a distal pressure wave, the proximal pressure wave may be derived. (The inverse transfer function is related to the original in the same way that the operation of taking a square root of a number is related to the process of squaring it.) In their commercially-available system, described by Mackenzie *et al.*, O'Rourke and colleagues describe a 'generalized' inverse transfer function which is an average of individual functions obtained empirically from a large number of subjects by direct measurement. This is used to derive the central pressure waveform and therefore pulse pressure from that measured peripherally. The procedure has been validated by comparing the calculated aortic pressure wave derived from the brachial or carotid pressure wave measured tonometrically to that obtained in the ascending aorta with a high-fidelity pressure transducer. Given the wide age range of the subjects measured, the agreement between the measured and calculated waves is impressive.⁴ Efforts are still in progress to validate the technique further^{4,37} and some doubt remains about its ability to derive accurate estimates of central pressure in diseased subjects.³⁸

The value of the pulse pressure and the factors which determine its magnitude (i.e. wave reflection and arterial stiffness), as a means of describing the general health of the cardiovascular system and predicting mortality from cardiovascular disease is now almost beyond doubt. Of the available methods for measuring these factors, some (pulse wave velocity, for example) are founded on well-understood physical principles, whereas others (such as oscillometry and pulse wave analysis) rest on a more empirical foundations. In the absence of any single approach which is clearly superior to the others, the choice of technique will, as usual, rest on a balance between ease of use, cost, and other

more intangible and perhaps less rationally chosen qualities.

References

1. Van Bortel LM, Struijker-Boudier HA, Safar ME. Pulse pressure, arterial stiffness and drug treatment of hypertension. *Hypertension* 2001; **38**:914–21.
2. Domanski M, Norman J, Wolz M, Mitchell G, Pfeffer M. Cardiovascular risk assessment using pulse pressure in the first national health and nutrition examination survey (NHANES I). *Hypertension* 2001; **38**:793–7.
3. Young T. On the functions of the heart and arteries. *Philos Trans* 1809; **99**:1–31.
4. O'Rourke MF, Pauca A, Jiang XJ. Pulse wave analysis. *Br J Clin Pharmacol* 2001; **51**:507–22.
5. Timoshenko S. *Strength of Materials, Part II*, 3rd edn. New York, Van Nostrand, 1956.
6. Chuong CJ, Fung YC. Three-dimensional stress distribution in arteries. *J Biomech Eng* 1983; **105**:268–74.
7. Vaishnav RN, Vossoughi J. Estimation of residual strains in aortic segments. In: Hall CW, ed. *Biomedical Engineering II, Recent Developments*. New York, Pergamon Press, 1983:330–3.
8. Fung YC. *Biomechanics: Mechanical Properties of Living Tissues*. New York, Springer Verlag, 1993:22–65.
9. Peterson LH, Jensen RE, Parnell J. Mechanical properties of arteries in vivo. *Circulation Research* 1960; **8**:622–39.
10. O'Rourke MF, Yaginuma T. Wave reflections and the arterial pulse. *Arch Int Med* 1984; **144**:366–71.
11. O'Rourke M. Arterial stiffness, systolic blood pressure and logical treatment of arterial hypertension. *Hypertension* 1990; **15**:339–47.
12. Greenwald SE, Carter AC, Berry CL. The effect of age on the reflection coefficient of the aorto-iliac junction in man. *Circulation* 1990; **82**:114–23.
13. Iwatsuki K, Cardinale GJ, Spector S, Udenfriend S. Reduction of blood pressure and vascular collagen in hypertensive rats by B-aminopropionitrile. *Proc Natl Acad Sci USA* 1977; **74**:360–2.
14. Berry CL, Greenwald SE, Menahem N. Effect of beta-aminopropionitrile on the static elastic properties and blood pressure of spontaneously hypertensive rats. *Cardiovasc Res* 1981; **15**:373–81.
15. Dart AM, Kingwell BA. Pulse pressure: a review of mechanisms and clinical relevance. *J Am Coll Cardiol* 2001; **37**(4):975–84.
16. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**:1236–41.
17. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**:2434–9.
18. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001; **103**:987–92.

19. Lehmann ED, Riley WA, Clarkson P, Gosling RG. Non-invasive assessment of cardiovascular disease in diabetes mellitus. *Lancet* 1997; **350**(Suppl. 1):S114–19.
20. Shroff SG. Pulsatile arterial load and cardiovascular function: facts, fiction and wishful thinking. *Therapeut Res* 1998; **9**:59–66.
21. Wilkinson IB, Webb DJ, Cockcroft JR. Aortic pulse-wave velocity. *Lancet* 1999; **354**:1996–7.
22. Lehmann ED. Aortic pulse-wave velocity versus pulse pressure and pulse-wave analysis. *Lancet* 2000; **355**:412.
23. Lehmann ED. Clinical value of aortic pulse-wave velocity measurement. *Lancet* 1999; **354**:528–9.
24. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries*, 3rd edn. London, Edward Arnold, 1990:85–6.
25. Greenwald SE, Newman DL, Bowden NLR. Comparison between theoretical and directly measured pulse propagation velocities in the aorta of the anaesthetized dog. *Cardiovasc Res* 1978; **112**:407–14.
26. Callaghan FJ, Geddes LA, Babbs CF, Bourland JD. Relationship between pulse-wave velocity and arterial elasticity. *Med Biol Eng Comp* 1986; **24**:248–54.
27. Hales S. *Statical Essays. Haemostatics II*. London, Inays and Manby. Reprinted by Hafner Publishing, New York, 1964:1733.
28. Frank O. Die Grundform des arteriellen pulses. *Zeitung Biologie* 1899; **37**:483–526.
29. Westerhof N, Stergiopoulos N. Models of the arterial tree. *Stud Health Technol Inform* 2000; **71**:65–77.
30. Stergiopoulos N, Meister JJ, Westerhof N. Evaluation of methods for estimation of total arterial compliance. *Am J Physiol* 1995; **268**:H1540–8.
31. Patel DJ, Defreitas FM, Fry DL. Hydraulic input impedance to the aorta and pulmonary artery in dogs. *J Appl Physiol* 1963; **18**:134–40.
32. Stergiopoulos N, Westerhof BE, Westerhof N. Total arterial inertance as the fourth element of the windkessel model. *Am J Physiol* 1999; **276**:H81–8.
33. Stergiopoulos N, Westerhof N. Role of total arterial compliance and peripheral resistance in the determination of systolic and diastolic aortic pressure. *Pathol Biol (Paris)* 1999; **47**:641–7.
34. Stergiopoulos N, Segers P, Westerhof N. Use of pulse pressure method for estimating total arterial compliance in vivo. *Am J Physiol* 1999; **276**:H424–8.
35. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries*, 3rd edn. London, Edward Arnold, 1990:288–93.
36. O'Rourke MF. Wave travel and reflection in the arterial system. *J Hypertens* 1999; **17**(Suppl. 5):S45–7.
37. Cameron JD, McGrath BP, Dart AM. Use of radial artery applanation tonometry and a generalized transfer function to determine aortic pressure augmentation in subjects with treated hypertension. *J Am Coll Cardiol* 1998; **32**:1214–20.
38. Lehmann ED. Regarding the accuracy of generalized transfer functions for estimating central aortic blood pressure. *J Hypertens* 1999; **17**:1225–7.