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Following a BA in Natural Science (Chemistry) at Hertford College Oxford (1971) and a PhD in Medicine (Pathology) from Guy’s Hospital Medical School (1975), Steve Greenwald obtained a British Heart Foundation Junior Research Fellowship working on arterial elasticity in children. This was followed by a position as research assistant in the Pathology Department of The London Hospital Medical College investigating the relationship between arterial structure and mechanical properties and how this relationship is modified by vascular disease. He has been on the academic staff of The Medical College since 1980 and obtained a chair in Cardiovascular Mechanics in 2001. Since 2002 he has been head of intercalated degrees and an Associate Director of The Interdisciplinary Research Centre in Biomedical Materials at Queen Mary University of London. He was elected as the Vice President of the International Society of Pathophysiology in 2006.

His current research interests include a search for mechanical factors in the genesis of arterial disease, with emphasis on the role of fatigue failure in arterial elastin, foetal programming of essential hypertension and wave propagation in arteries. The link between the elastic properties of arteries, pulse pressure and the mechanical load on the heart is now thought to be the explanation, at least in part, for the widely recognised association between raised vascular stiffness and an increased risk of cardiovascular morbidity and mortality. On the applied side, the interest in arterial mechanical properties has lead to studies evaluating the efficacy of compliant intravascular stents and the development of a novel optical method for the non-invasive measurement of arterial compliance. The possibility of applying similar optical techniques to the measurement of cardiac output and the assessment of endothelial function is now under active investigation.
Cardiovascular biomechanics: from physical theory through engineering practice, to patient diagnosis

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Abstract

Cardiovascular biomechanics can be defined as the study of the interaction between the physical properties of the heart and the arteries; and the physical laws which govern the time-varying pressure and flow of the blood flowing through them. Its aim is to answer at least two related questions. Firstly, if the physical properties of arteries change due to ageing and or disease, how will this affect blood flow through them? Secondly, do these changes in pressure and flow lead to remodelling of the heart and arteries and what are the mechanisms underlying the remodelling. This article briefly describes a biomechanical approach to understanding the pathogenesis of vascular disease and outlines the way in which simple physical theory has been used to inform the development of a novel method for the measurement of arterial function, suitable for use in the developing and developed worlds.

Introduction

What is cardiovascular mechanics?

If nature had perfected the wheel, age-related isolated systolic hypertension and arteriosclerosis would not be a problem. The heart could have evolved as a rotary pump (or, more probably, as two rotary pumps in series, separated by the lungs) and the vascular system would function perfectly well, even if blood vessels were rigid. In reality, of course, the heart consists of two compound reciprocating pumps in series, each of which ejects an equal volume of blood, either into the pulmonary artery from the right heart or the aorta from the left. In order to accommodate this volume of blood without requiring an excessively high pressure, the aorta and pulmonary arteries must be able to expand and to store this volume for long enough to allow it to drain into the distal parts of the circulation and be ready to receive the volume ejected from the ventricles during the following heart beat. Most cardiovascular diseases (CVD) are associated with changes in the stiffness and dimensions of blood vessels and with the complex flow of blood within them and there is increasing evidence that mechanical factors are of major importance in the pathogenesis of these diseases, as well as during the ‘normal’ process of aging. Given the high incidence of CVD and the resulting expense, it is therefore of interest and importance to the physiologist, the physician and the surgeon to understand the contribution of these factors.

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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. During the last two decades there has been a steady increase in reports of an association between changes in arterial stiffness/raised pulse pressure and the development of CVD. Indeed there is now good evidence that increased stiffness and or pulse pressure may predict the onset and development of CVD at a stage before vascular lesions or external symptoms become evident. Aortic stiffness is now used in estimating CV risk scores and the prognostic value of such measurements is widely accepted. Therefore, there has been renewed interest amongst clinicians, engineers and materials scientists in existing and novel methods of measuring arterial elasticity and in developing new ways of diagnosing and treating CVD. An example from our own work on the application of physical principles governing blood flow and arterial stiffness will be outlined below.

Physical theory

Elasticity. The heart and arteries are complex multi-component structures undergoing complex bending and twisting motion. To describe their behaviour fully and rigorously requires a theory that takes into account all the observed properties. These include:

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- Anisotropy, (different properties in different directions)
- Nonlinearity, (material gets stiffer as it is stretched more)
- Viscoelasticity, (material gets stiffer the faster it is stretched)

Inelasticity, (material has different properties when stretched and when relaxed)
For the vascular physiologist, pathologist or clinician, a description in which blood vessel stiffness may be related to 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 (that is the force required to increase the diameter or circumference, elastic non-linearity is treated by confining measurements to a relatively small pressure range, for instance between diastolic and systolic pressures; viscoelasticity is dealt with by assuming a constant heart rate during a relatively short measurement period and inelasticity is averaged out over the cardiac cycle. In this way a single number can be used to define how much force (or pressure) is required to increase the diameter of a blood vessel by a known amount and therefore this single number provides an index of functional stiffness. This functional stiffness depends on the stiffness of the materials which make up the arterial wall (its material stiffness) together with the thickness of the wall as a fraction of the vessel’s radius. Thus, of two vessels made of the same material and having the same lumen radius, but different wall thickness, the one with the thicker wall will be functionally stiffer.

Haemodynamics
As the left ventricle beats it ejects about a cupful of blood into the aorta at a speed between 0.5 and 1 metre per second. The patterns of flow are complex and change not only in time, during the cardiac cycle, but also in space as the blood encounters curves and junctions throughout the vascular system. Furthermore, the flow may become turbulent when it emerges from a stenosis or stagnant when passing through an aneurysm. These complex normal and pathological flows can be measured with ultrasound or MRI and they can also be simulated numerically. Both approaches are necessary to understand the interaction between the flowing blood and the vessel wall, and may help in the design of more effective devices and treatments such as vascular grafts and stents.
When the left ventricle contracts it produces a wave of pressure which causes the aorta to expand to accommodate the volume of blood ejected. At the end of systole the pressure in the ventricle falls below that of the aorta and, as blood starts to flow back into the heart, the aortic valve shuts. During systole the combined effect of the contracting ventricle causes the wave of pressure to travel down the aorta (and up the carotid arteries) towards the periphery. This wave manifests itself as a ripple in the wall of the arteries it traverses and the speed that the ripple propagates depends on the stiffness of the arteries: the greater the stiffness, the higher the speed. (During diastole the energy stored in the stretched aorta continues to drive the blood downstream.) When the pulse pressure wave encounters a change in the properties of the arterial wall such as an occlusive lesion or a junction, like all waves it undergoes a reflection and these reflections travel back towards the heart. When a reflected wave encounters the wave generated by the next heart beat, the two can add together, producing a local increase in pulse pressure. Where this occurs depends on where the reflection is located and how fast the original and reflected waves travel which, as explained above, depends on how stiff the artery is. In many cases the original and reflected waves meet in the proximal aorta during systole in which case the heart is subjected to increased afterload tending to cause ventricular hypertrophy which, in turn can predispose to angina or exacerbate pre-existing ischaemic disease due to atherosclerosis. These effects are summarised in figure 1.
The synergistic interaction between arterial stiffness, blood flow and pressure is summarised in figure 2. This approach based on simple physical principles allows one to investigate and understand the role of mechanical factors in the pathogenesis of cardiovascular disease. It also suggests new therapies based on treating the causes of vascular remodelling leading to altered stiffness. Furthermore it encourages the exploitation of simple physical principles in the development of non-invasive methods for diagnosis of arterial disease. In what follows I shall, as an example, outline the development of a novel method for the measurement of arterial stiffness and touch upon some of the problems associated with producing a device suitable for clinical use.
Figure 1. Increased aortic stiffness leads to increased cardiac load for two reasons. Firstly the myocytes must generate a greater tension to eject the required stroke volume into the aorta thus raising systolic blood pressure. This leads to cardiac remodelling dyspnoea and increased oxygen demand, as shown on the left of the diagram. Secondly the increased stiffness results in raised pulse wave velocity so that the reflected wave returns during systole thus raising systolic pressure yet further, as shown on the right. Both effects predispose towards angina. (Adapted from 1).

Figure 2. Interealationship between vessel composition, structure, elasticity, geometry, elastic reservoir function and cardiac work. Functional stiffness, which determines pulse pressure and therefore the peak load on the heart, depends on the combined effects of composition and geometry. Hypertrophic arteries which have a greater functional stiffness even if their material properties are unaltered, become stiffer and therefore increase this load as the heart attempts to maintain normal levels of flow. Age related increases in stiffness have a similar effect. The dotted line represents a feedback loop indicating that changes in pulse pressure and flow can lead to remodeling, which in turn lead to further changes in pressure and flow. For instance raised mean pressure leads to medial hypertrophy, increased functional stiffness and PWV. This results in augmented pulse pressure and further remodeling of the heart and conduit arteries. Redrawn from 16.

From theory to practice
Development and testing of a prototype measuring system
As described above, arterial stiffness may be measured by determining the speed of the pulse wave generated by the heart. To do this it is necessary to detect the pulse at two sites a known distance apart and then to measure the time it takes for the pulse to travel between them. There are several commercial methods in current use for doing this non-invasively, including tonometry for detecting the pressure
wave, duplex or echo tracking ultrasound, or MRI for detecting the resulting change in arterial diameter and Doppler ultrasound for detecting the transient flow wave as blood flows away from the centre of the vessel in response to the travelling pressure wave. These commercial systems are expensive and, in general are not suitable for routine or screening use. During the last few years we have developed a novel system for detecting the pulse based on the principle of photoplethysmography (PPG) and have shown that with the probes placed over the carotid and femoral arteries it is able to estimate aortic PWV with reasonable accuracy and repeatability.

None of these methods can detect the pulse in the aorta itself, relying on pulse detection in the carotid and femoral arteries, with possible uncertainty in the distance measurements and timing. All these methods require skilled operators and a high level of expertise to hold the probes and get adequate signals. Furthermore, the femoral approach, requiring exposure of the skin near the groin, is not patient friendly. We have adapted a method described in a US patent based on the idea of aortic pulse detection via the intercostal arteries, which solves many of the aforementioned difficulties. However there appear to be no literature reports of its development. The principle, as realised in our approach, is to detect the pulse in the skin of the back fed by the intercostal arteries which, being close to the skin can be easily visualised by PPG. It is assumed that because the intercostal arteries are close to the aorta, the arrival of the pulse accurately reflects the timing of the aortic pulse wave. Figure 3 shows how this is realised.

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Before developing this idea, it is necessary to provide good evidence that the timing assumption is justified. In other words the physical/mechanical principles behind the device’s mode of operation must be understood. To do this we are investigating the propagation of light in a physical model of the chest in which the optical properties of the aorta, the intercostal arteries, the muscles of the back the sub-dermal capillaries and the skin are simulated. At the same time we are carrying out a computer simulation of these processes. At each stage the experimental and computer modelling results will compared and differences used to fine-tune both models in such a way as to minimise the differences between them.

Is there a need?

However strong the scientific evidence behind a new diagnostic device, before it can be accepted by the medical profession (which is, rightly, conservative) it must be thoroughly validated to show that the results it produces compare closely to an accepted gold standard. Typically a preliminary validation study on a small number of healthy subjects is performed in which the results obtained with the new device are compared to a device or technique which is widely accepted and has been assessed in many independent studies. For pulse wave velocity measurements the gold standard is intra-arterial measurement of pressure at two sites, which being invasive and requiring angiography to position the pressure measuring device(s) is ethically unacceptable in healthy subjects. In the development of our PPG system we have therefore approached the validation in two stages. Firstly on healthy volunteers we have compared PWV measurements obtained with Doppler ultrasound in which the pulse is detected in the carotid and femoral arteries, with our PPG method in which the probes are positioned over the intercostal spaces. Doppler ultrasound is a well established technique although, as mentioned above, it does not allow direct measurement of aortic pulse wave velocity. Nevertheless the agreement in PWV between the two approaches was satisfactory. The second step in the validation process is currently in progress. It involves PWV measurements obtained as in step 1, from the intercostal spaces and comparison with intra-arterial PWV values from patients undergoing elective coronary angiography in whom the pressure measuring catheters are already in place. Ethical permission must, of course, be obtained for measurements on all subjects whether healthy or hospital in-patients. For these experiments this has been relatively straightforward because our new device is non-invasive and the invasive catheter measurements are part of the routine diagnostic procedure undertaken by our patient group.

Our device, in common with many others resulting from investigations based on biomechanical principles, may be suitable for development into a system suitable for routine clinical use. Before investing time, energy and money in this development it is necessary to consider the following questions:

- Is there a clinical need?
  - Do the clinician perceive the need or is it likely they can be convinced of it?
  - Do the healthcare planners perceive the need or can they too be convinced?
- Is the technology feasible?
  - What alternatives already exist and how does the new device improve on these?
  - Will it be cost effective?
These questions are not always easily answerable and can not necessarily be answered until large scale (and therefore expensive) validation studies are carried out. It is therefore necessary, having achieved a successful proof of principle, to seek more substantial funding, either from a government agency or from industry or from a combination of the two. In the UK and Europe such sources of combined funding are accessible, but further discussion of funding is beyond the scope of this brief account. An equally serious hurdle to investigating the effectiveness of a device which may have commercial potential, is approval from the Medical and Healthcare Products Regulatory Agency. This is a governmental organisation, similar to the FDA in the USA, whose function is to ensure that all medical devices or drugs meet stringent safety standards as laid down by the European Union. To gain this approval it is necessary to demonstrate in the laboratory that the device is electrically safe, poses no radiation hazard (whether electromagnetic or ionising), will not interfere with the proper functioning of other devices in the vicinity and can be sterilised if necessary. Furthermore a detailed risk analysis must be performed to assess the likelihood and consequences of any part of the system’s failing. This includes the effects of errors in any computer software on which its proper functioning depends. Although these requirements can appear daunting and the testing can add significantly to the development costs, they ensure that the design of the device and the way it is used clinically is properly scrutinised at an early stage before it is too late to modify.

Finally, if the device has been validated, if it has been shown to be safe and to produce reliable and useful clinical data, it must then be transformed into a user friendly system, “packaged” and marketed. If they have not already gained funding from a commercial company many practicing scientists with entrepreneurial skills choose to establish their own spin out companies, often with the support of their university to produce a commercial prototype. For those who may not wish to follow this path, there is the possibility of selling or licensing their technology to a medical device or pharmaceutical company.

To conclude, cardiovascular biomechanics is a subject that has, in the past, drawn together mathematicians, physicists, physiologists and engineers, motivated by the wish to understand that most fascinating of nature’s machines – the human organism. Today, as in all other types of biomedical research, the scientist has joined forces with the technologist and entrepreneur. This combination of skills is essential not just for ‘high-tech high cost’ medical innovations, affordable only in the developed world but also for simpler solutions for use in developing countries as well, such as the device described here. Cardiovascular Biomechanics has helped and will help realise the theme of this conference, “Building a Healthy Future”.

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References