Chapter

Role of Arterial Pressure, Wall Stiffness, Pulse Pressure and Waveform in Arterial Wall Stress/Strain and Its Clinical Implications

Thomas K. Day

Abstract

Biomechanical stress applied to the intima of arteries has long been suspected as a factor in the initiation and localisation of atherosclerotic plaque, and it is implicated in the separation of plaque from the underlying arterial wall giving rise to the acute clinical consequences of thrombosis, dissection and embolism. The factors underlying transmural stress were investigated *in-vitro* using fresh porcine abdominal aortas on an experimental rig in which pulse pressure, pulse waveform, fluid viscosity, pulse rate, vessel wall compliance and systolic and diastolic blood pressure could be varied at will. Vessel wall compliance was progressively reduced by exposure of the artery to formaldehyde vapour for increased periods of time, a saline-treated artery being used as control. Centripetal transmural stress (CTS) and strain were studied by direct observation of the displacement of a compliant false intima (FI) using real-time B and M mode ultrasound, and by measuring the differential pressure between the space beneath the FI and the adjacent vessel lumen. CTS was found to be directly related to pulse pressure ($r = 0.907$, $p < 0.001$) and inversely related to vessel wall compliance. It was independently affected by ranked peak pressure waveform ($R = 0.93$, $p < 0.01$) being higher with sharp peak pressure and lower when the waveform was rounded, and it peaked in early diastole in untreated vessels, and both in diastole and peak systole in ones stiffened by formaldehyde vapour. Mean arterial pressure exerted a profound effect via its effect on vessel wall stiffness, which was found to rise 7-fold across the mean arterial pressure range 50-130 mmHg and continued to increase in a logarithmic fashion as the upper physiological range of mean arterial pressure was exceeded. There are two potential clinical implications: in mitigating the postulated biomechanical aspects atherogenesis and atherosclerotic plaque detachment, maintaining large vessel wall compliance is important, and the main factor determining this in a healthy artery is mean arterial pressure; if the arterial wall has already become stiffened as a result of disease, and in the absence of critical stenosis, the findings suggest that the appropriate therapeutic targets are modification of pulse pressure and pulse waveform profile. Simply reducing the diastolic pressure in elderly patients may be unwise if the result is a widened pulse pressure and increased transmural strain. The distribution of atheroma at points of focal mechanical strain in the vessel wall may be explicable if the stress induced by an excessive pulse pressure provokes

the inflammatory changes seen in repetitive strain injury. Investigation of inflammatory signalling in the vessel wall provoked by repeated mechanical stress may represent a productive area for future research.

Keywords: atherosclerosis, hypertension, arterial wall elasticity, pulse waveform, mechano-sensitivity

1. Introduction

The central role of biomechanics in the pathogenesis of atheroma is supported by a body of circumstantial evidence [1]: atherosclerotic plaque is not laid down uniformly on the inner lining of arteries but at the junctions of branch vessels, at points where the external wall of the artery is fixed to surrounding structures and at kinks and bends where mechanical strain and flow turbulence occur. It is susceptible to the effects of blood pressure [2]. It is not seen in veins except when these are used as arterial grafts [3]. Blood pressure is a well-established risk factor for coronary artery disease [4]. Atherosclerosis occurs prematurely in situations where arterial wall stiffness is increased such as diabetes, pseudoxanthoma elasticum and progeria syndromes [5–7]. Blood viscosity, which contributes to the transmission of shear strain to the endothelium, is an independent risk factor for ischaemic heart disease [8]. Lastly, experimental and computer modelling studies have demonstrated an association between atherosclerosis-prone areas of the arterial tree and conditions of local blood flow characterised by high strain-low shear, and oscillatory reverse flow [9, 10].

There are two postulated mechanisms whereby such mechanical strain acting on the inner arterial wall might give rise to the development of atherosclerosis and explain its focal localisation within the arterial tree: firstly, the endothelium might be damaged directly by forces stripping it from the underlying intima or causing ultrastructural changes to the intercellular junctions thus exposing the underlying collagen network of the intima to blood components giving rise to collagen-platelet and collagen-fibrin interactions and the development of plaque according to the incrustation theory of atherogenesis. Such endothelial damage has been shown to give rise to atheroma-like lesions in experimental animals [11], and the attachment of the endothelium to underlying collagen is less strong in animals that are atheroma-prone compared to those that are resistant [12]. Direct mechanical damage to the endothelium would tend to occur at sites where there was maximum lifting and shear stress and this might explain its focal distribution. Secondly, endothelial cells are highly mechano-sensitive and certain conditions of shear stress and pulse waveform have been shown to provoke a stress response in endothelial cells favouring platelet and white cell adherence, translocation of white cells and expression of inflammatory mediators, processes that have been linked to the development of atherosclerosis [10, 13–16].

Experiments related to this latter mechanism have hitherto concentrated on the effect of shear stress, which may be likened to the aerodynamic equivalent of drag acting on the endothelial surface. Little work by contrast has been done on the inward "lift" effect in inducing stress acting at right angles to the endothelial surface, tending to lift the endothelium off the underlying substrate, and inducing conformational change on the inner wall of the artery. Conformational change in the inner arterial wall resulting from this lifting effect would tend to give rise to the boundary layer separation and local oscillatory flow reversal at low flow rate that appear to induce a pro-atherogenic endothelial cell phenotype in the tissue culture experiments [10, 15, 16].

The study of the factors affecting the inward stress/strain relationship to the arterial wall is consequently of interest both in relation to the initial development of atherosclerosis but also in relation to the stresses causing the developed atherosclerotic plaque to separate and thus cause clinical harm.

The aim of the present work was to examine directly the factors giving rise to transmural stress/strain and to their possible interactions. A bench-based test rig was employed similar to that described by Giussaniani et al. [17] modified to provide continuous pulsatile flow within fresh pig arteries.

2. Materials, methods

2.1 Arteries

Abdominal aortas from freshly slaughtered young white pigs were obtained from an abbattoir conforming to European animal welfare standards (EC Regulation 1099/2009) and were transported at 4°C Ringer's lactate solution. The average length of the test segment was 120 mm (SD 5 mm), the internal diameter of the proximal end 18.1 mm (SD+/− 0.54) and that of the distal end 13.8 mm (SD+/−2.7).

In each artery adherent loose areolar-lymphatic tissue was removed whist preserving the adventitia and all side branches were ligated at their origins with 2/0 silk whilst keeping the artery moist and cool in Ringers-lactate solution. The segments of artery used extended from the coeliac trunk to the aortic bifurcation.

For studies on the stress strain relationship across the intima in pulsatile flow conditions a fluid-filled 0.9 mm polythene saline-filled catheter was introduced through a side branch and secured by a ligature. The tip of the catheter was positioned near the midpoint of the test artery, this point being marked on the exterior wall of the artery using Gentian Violet to facilitate the subsequent positioning of the ultrasound probe. During each test run this catheter was perfused at 0.1 ml/hr. with saline using a syringe pump. Once the catheter was in position a thin deformable latex membrane (Préservatif classique, PHR Lab, Boulogne Billancourt, Fr) was introduced along the full length of the arterial lumen. The membrane overlapped the ends and was smoothed against the internal wall of the artery by filling the lumen with saline. This membrane was intended to take the role of a deformable FI. **Figure 1** shows the appearance of the lined artery and the movement of the FI in relation to the wall on B-mode ultrasound when the artery is subjected to pulsatile flow under test conditions. The presence of this lining membrane also had the advantage of preventing minor leaks. The specimen, consisting of the artery and the FI, was then mounted in the test bath illustrated in **Figure 2**, being secured over the tube at either end by sliding it over two O- rings positioned on the mounting tube and holding it between the rings with a double turn of a 4 mm Silastic sling.

The artery was rotated until the catheter tip lay inferiorly, directly opposite the ultrasound probe. The tubes upon which the artery was mounted were then slid far enough apart for the artery to be lie in a relaxed straight line, not under tension. The bath was filled with oxygenated Ringer's lactate at 37°C, up to but not over the top of the uppermost wall of the artery. Contact jelly was applied and the ultrasound probe set up over the tip of the catheter so as to give a view of the artery an the membrane in transverse section. The probe was held in a clamp in contact with the superior wall of the artery but not pressing sufficiently to deform it.

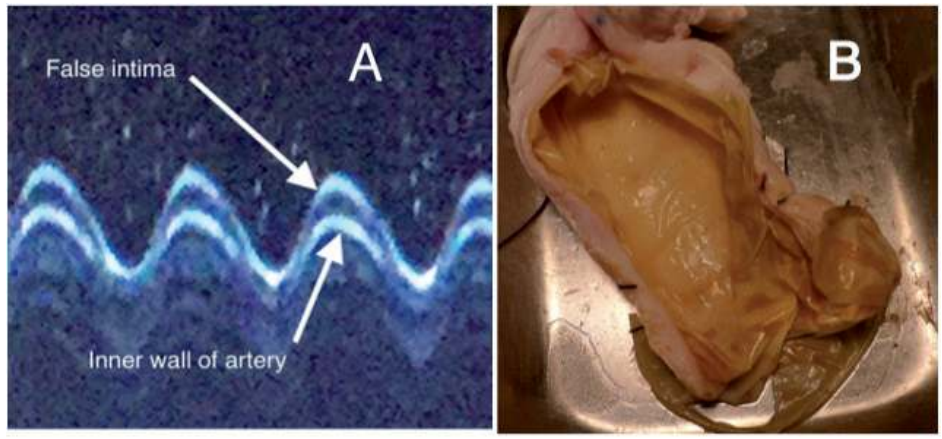

Figure 1.
A. The movement in B-mode ultrasound of the posterior wall of the artery and the false intima (FI) subjected to a pulse pressure of 60 mmHg and a peak pressure wave of an intermediate level of sharpness. B. The thin latex false intima lining the opened test artery; the perfused catheter is placed between the FI and the inner arterial wall to measure the differential pressure between this space and the adjacent arterial lumen.

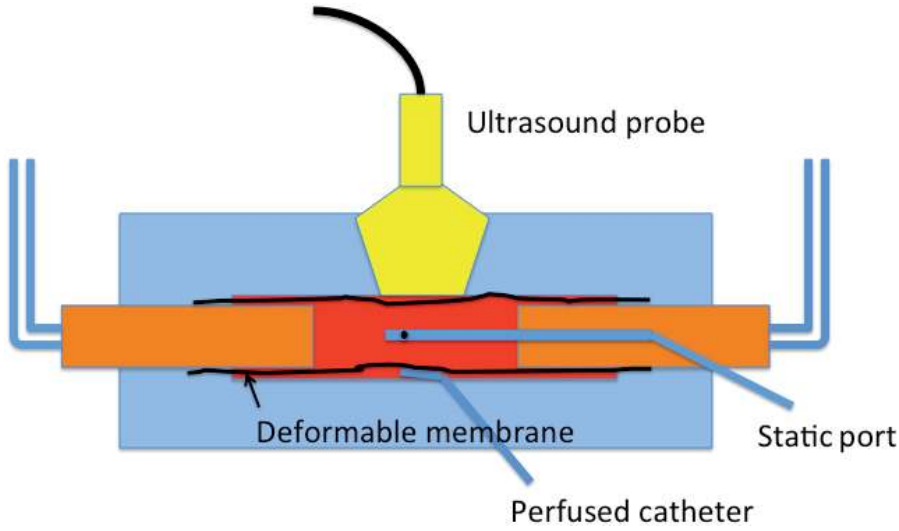

Figure 2.
The artery in its test bath. The stress imposed on the FI throughout the pressure cycle is observed by recording the differential pressure between the perfused catheter and the adjacent lumen, whilst the strain response of the FI to the passage of the pulse wave is observed using M-mode ultrasound.

2.2 Perfusion apparatus

The arteries were perfused with isotonic saline or sucrose/saline solutions with sucrose concentration adjusted to provide a range of viscosities using the apparatus shown in **Figure 3**. The perfusate was circulated from a 1 L reservoir by a centrifugal pump, forming a primary circuit by which an adjustable head of pressure could be obtained through adjustment of the return circuit valve. This circuit was tapped through a side branch to form a secondary circuit by means of which the test artery was perfused. This circuit circulated fluid at the established head of pressure through the test artery then back to the reservoir via a barostatic valve and flow meter. Pulsatile flow was imposed on the fluid by a 60 ml glass syringe pump which was operated by means of a series of cams of different profiles turned by a geared and governed slow speed electric motor. These cams were designed to reduplicate a variety of human aortic waveforms [18]. Eight cams were manufactured to deliver stroke volumes between 8 and 32mls.

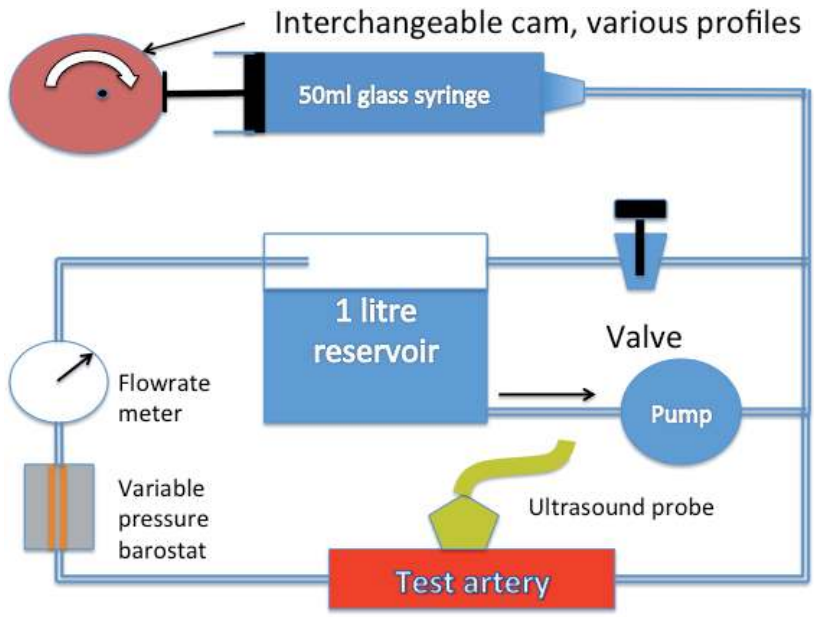

Figure 3.
Perfusion apparatus.

Arterial pressure and pulse pressure wave profile were recorded via side tap taken off the upstream side of the inflow tube enabling differential pressure to be measured between the arterial lumen and the water bath adjacent to the artery at the same level (the arterial pressure). CTS was measured by recording the differential pressure between the perfused catheter in the sub-membrane space and a static port in the adjacent arterial lumen. These two differential pressures were measured using Honeywell 24PCBPFAD transducers calibrated using a mercury manometer, and recorded simultaneously using a dual channel Thornton 464 (Waltham, Ma) chart recorder.

The deformation of the arterial wall in response to pressure change and the displacement of the FI during pulsatile flow was observed during different phases of the pressure cycle using a linear 7.5Mhz ultrasound probe, by means of which the transverse section artery, its wall and the FI could be visualised using split B and M-mode ultrasound, **Figure 1**. Care was taken to ensure that the artery itself and the catheters and tubes connected to the differential pressure transducers were free of bubbles.

2.3 Variables

2.3.1 Static observations, non-pulsatile flow

Observations on the effects of non-pulsatile arterial pressure on arterial wall diameter and thickness were made using the experimental apparatus described above omitting the perfused cannula beneath the FI. Pressure was raised in a stepwise fashion using the barostatic valve, having closed the primary return circuit valve, and measurements of the artery made in cross section using B mode ultrasound.

2.3.2 Direct and derived variables, pulsatile flow

The perfusion apparatus allowed one group of variables to be adjusted and controlled directly whilst the other parameters were held at set levels. These direct

variables were: pulse rate, baseline ("diastolic") pressure, cam profile, outflow resistance and arterial wall stiffness. Outflow resistance was a directly set value achieved by adjusting the outflow barostat to a specific pressure in relation to flow. Fluid viscosity was adjusted by alternating saline as a perfusate with a viscosity of 1 mPa.s for sucrose/saline solutions at concentrations of 10, 20 and 30% providing a range of viscosities at 15 deg. C from 1.4 to 3.9 mPa.s [19]. Arterial wall stiffness was adjusted by exposing the test artery to formaldehyde vapour for periods up to 48 hours whilst another artery kept in Ringer's lactate for the same period acted as a control. The degree of increase in stiffness produced by formadelhyde exposure is similar in order of magnitude to that reported in post-mortem studies of atherosclerotic human aortas [20] and to the effects of hypertension in the test vessels. The effect of altering a single variable on CTS and FI could thus be studied, and this was done so within series of individual arteries where the other parameters could be maintained at set levels. In this way, for example, the effect of changing the pulse rate on NS and false intima separation under different conditions of diastolic and systolic pressure and fluid viscosity could be explored in artery with an established elastic properties.

Changing the cams for ones of different stroke volume and profile created two derived variables, waveform and pulse pressure. Pulse pressure showed a direct physical link to CTS with some variation between cam profiles which was dependent on the shape of the pressure wave. In exploring this, different cams were used to alter the shape of the pressure wave and a schedule of machine settings worked through (**Table 1**) to harvest groups of identical pulse pressure for comparison of the effects of waveform and vice versa. In comparison of the effect of pulse pressure on CTS independent of waveform, peak waveform shape was ranked according to the area under each peak within 40 mmHg of peak pressure. The total number of pressure waves of equivalent peak sharpness thus harvested was 122 and the number of identical pulse pressures (tested at different pulse rates and baseline pressures) was 186. The schedule of machine settings permitted the independent effects of baseline pressure, pulse rate and viscosity to be studied whilst the other variables were kept constant (**Table 1**).

2.3.3 Measurement of hoop stress modulus

For the direct measurement of hoop stress elastic modulus, strips 10 mm in width were cut from the proximal end of each test aorta using a guillotine-guide which compressed and held the artery between two plates of Perspex provided with cutting slots, and measurement of stress/strain relationships was undertaken at stresses of between 0 and 100mN/mm^2 at 0.2 N intervals using the tensiometer device illustrated in **Figure 4**. Either end of each hoop was firmly held between two aluminium blocks lined with fine sandpaper that were screwed together and then

Pulse rate and test intervals bpm	Baseline pressure and test intervals mmHg	Cam no.	Viscosity mPa.s	Arterial wall stiffness Kpa	Derived Peak waveform sharpness	Derived upsweep velocity	Derived pulse pressure	CTS
40–180 (20)	40–160 (20)	1–8	1–3	400-7000	Ranked according to area below peak	Ranked according to gradient	Measured directly	Measured directly

Table 1.
Range of machine settings and direct and derived variables measured.

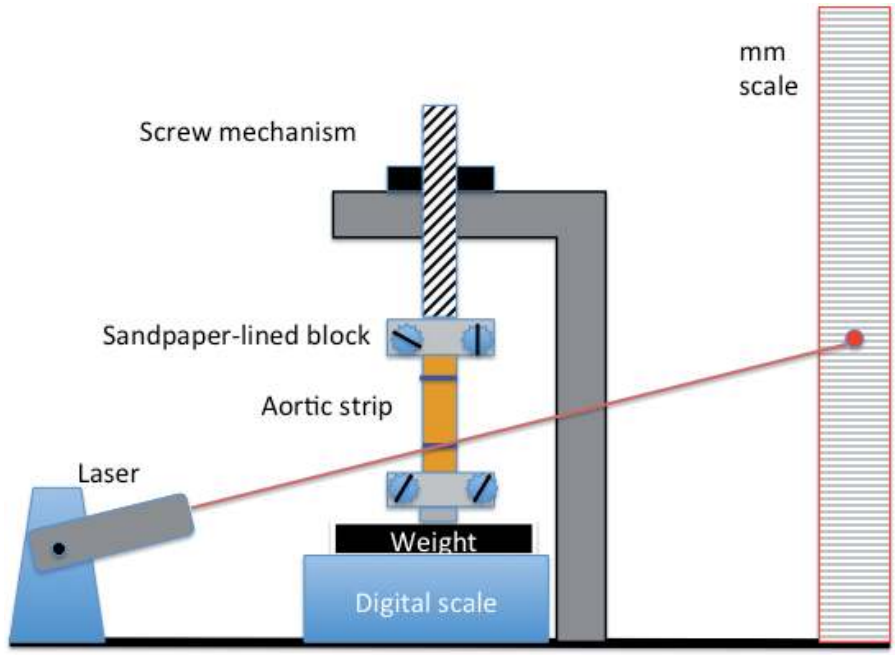

Figure 4.
Tensiometer apparatus for measurement of stress/strain relationship of aortic hoop strips.

attached with magnets to the tensiometer once the hoop strip was mounted. Two points about 4 cm apart were marked at the upper and lower extremity of each hoop with Gentian Violet and the laser was then used to project the relative position of these marks onto a scale as the progressive loads were applied. The average cross sectional area of each hoop was calculated by measuring the width and thickness of the arterial strip with a micrometer at three positions in the middle and at the junction of the central and upper and lower thirds at the beginning and end of each test, and taking the mean.

2.4 Statistics

Pearson's correlation was used for parametric variables and Spearman's ranking coefficient for the non-parametric relationship between sharpness of the peak pressure wave and DP. 95% confidence limits are shown in **Figure 4**. For the purpose of transposing hoop stress measurements into equivalent lumenal pressures the artery was treated as a thin walled cylinder and the relationship between the tension in the wall and the corresponding internal arterial pressure was derived mathematically from the formula: Pressure equivalent (mmHg) = 47 x Hoop stress (KPa) x t/d, where t/d is the thickness to diameter ratio.

3. Results

3.1 Elastic response of the arterial wall to changes in arterial pressure

In both pulsatile and non-pulsatile flow the arterial wall showed a 3-phase elastic response to rising arterial pressure (see figures below). In the first phase, corresponding to sub-physiological pressure, the artery is relatively flaccid and distends easily with no thinning. In the second phase, corresponding to the normal physiological range of pressure, the stress/strain relationship is almost linear and over this linear

segment Young's modulus can be calculate at about 400–600 KPa and the wall begins to thin. As the pressure increases beyond the physiological range there is a marked loss of compliance with an 8 to 10 fold increase in Young's modulus. In this last phase the arterial wall thins to its minimum. **Figure 5** shows the proportional change in inner wall diameter and wall thickness of pig abdominal aortas (n = 5) subjected to stepwise changes in static (non-pulsatile) pressure over the range 0 – 250 mmHg.

The character of this 3-phase response to rises and fall in intralumenal pressure was explored using arterial hoop strips cut from the proximal end of the abdominal aortic segment.

Figure 6 illustrates how Young's modulus measured in this way rises steeply once the upper limit of the physiological range of pressure is exceeded. The implications of this loss of wall compliance with rising arterial pressure are seen once pulsatile flow is introduced (**Figure 7**).

In the studies using pulsatile flow over a range of arterial diastolic and systolic pressures induced by varying the stroke volume load and the baseline diastolic pressure at a constant outflow resistance, a similar negative correlation was observed between the mean arterial pressure (MAP) and arterial wall compliance expressed as the proportional increase in cross-section per mm Hg pressure change (Spearman's $R = -0.74$, $p < 0.001$). **Figure 7** is a semi-log plot of the compliance versus MAP using 11 runs at different pressure settings in a single fresh pig abdominal aorta. The fall in arterial wall compliance with increased MAP follows the same three-phase response as that shown in **Figures 5** and **6**. As MAP approaches the upper limit of the physiological range there is a logarithmic reduction in compliance as the artery enters the third phase of stress/strain relationship and this is associated with corresponding rise in the pulse pressure, CTS, FI separation and the sharpness of the pressure peak.

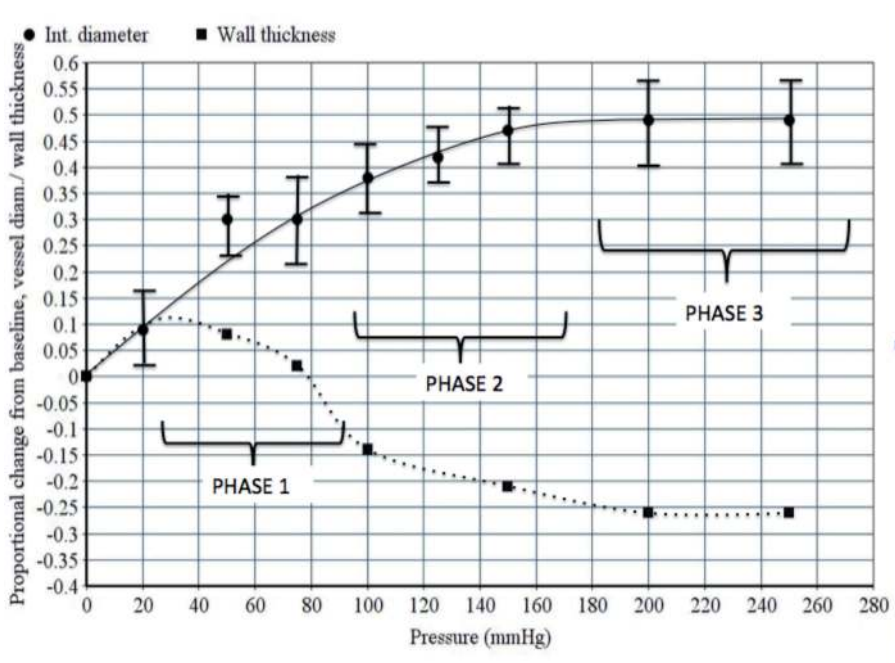

Figure 5.
*3-phase elastic response of the arterial wall to rising static pressure (non-pulsatile flow), n = 5 +/– SEM. Throughout the physiological range of pressure the arterial diameter increases in response to rising pressure and the wall thins; at the upper limit of pressure the arterial diameter reaches an elastic limit and the wall its minimum thickness. A similar 3-phase stiffening of the arterial wall in response to mean arterial pressure is seen under conditions of pulsatile flow (**Figure 7**) and as the wall stiffens pulse pressure increases and the strain across the inner arterial wall rises proportionately.*

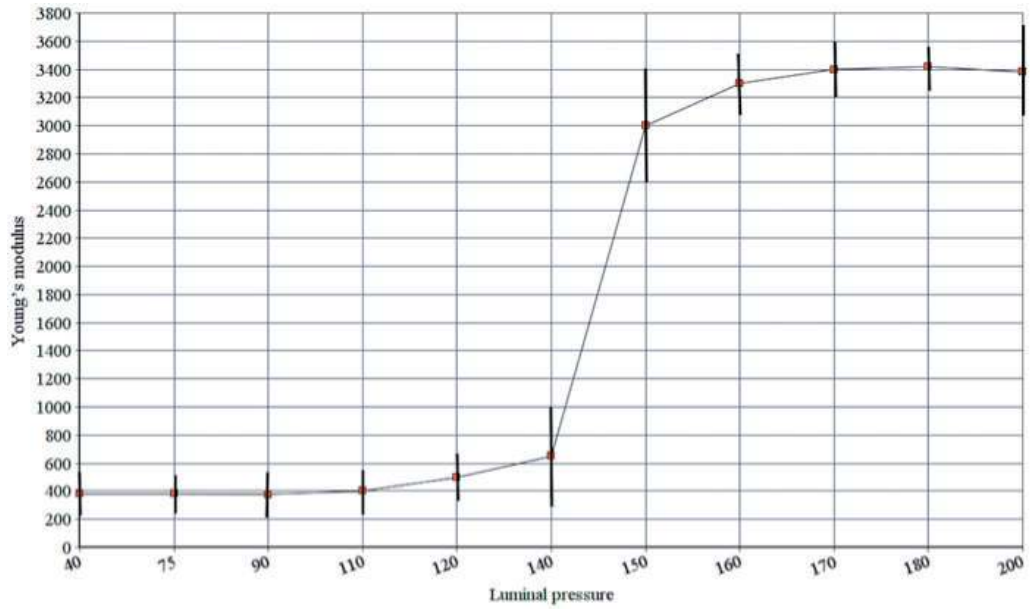

Figure 6.
Changes of Young's modulus (Kpa) in hoops trips of arterial wall subjected to increasing tension. Equivalent lumenal pressure derived from the Young-Laplace formula is shown on the X axis. N = 5, runs 20.

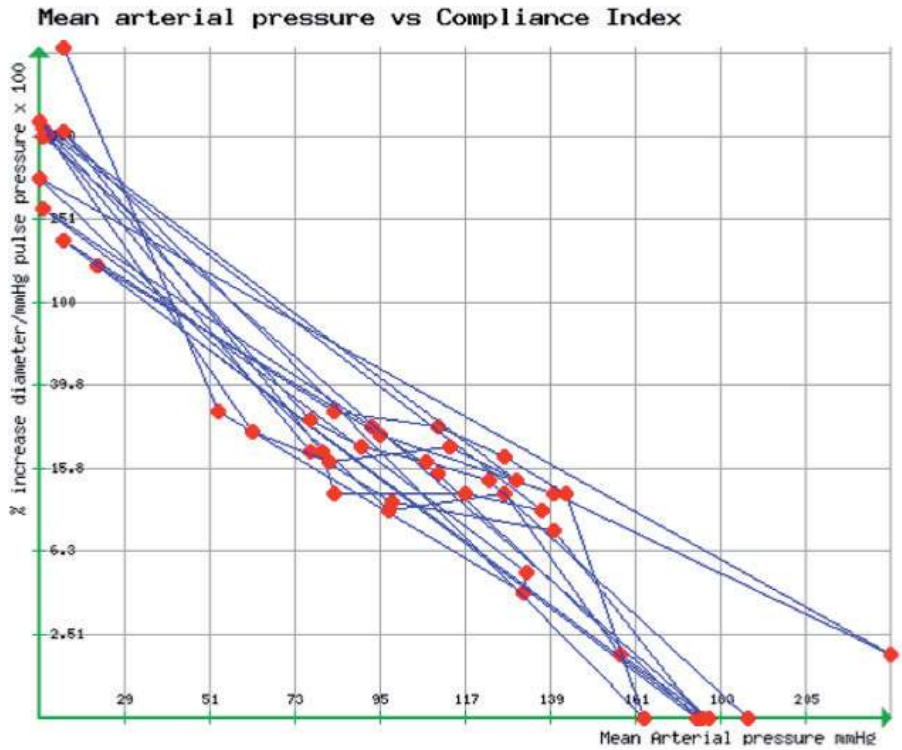

Figure 7.
Under pulsatile flow conditions a rise in mean arterial pressure just above the normal range for the pig [21] gives rise to an exponential loss of wall compliance which is correlated with a corresponding increase in transmural strain. 11 runs in a single artery.

3.2 Arterial wall compliance under pulsatile flow conditions

As arterial wall compliance drops, pulse pressure increases and the systolic peaks of the pressure wave sharpen. **Figure 8** compares the pressure traces where

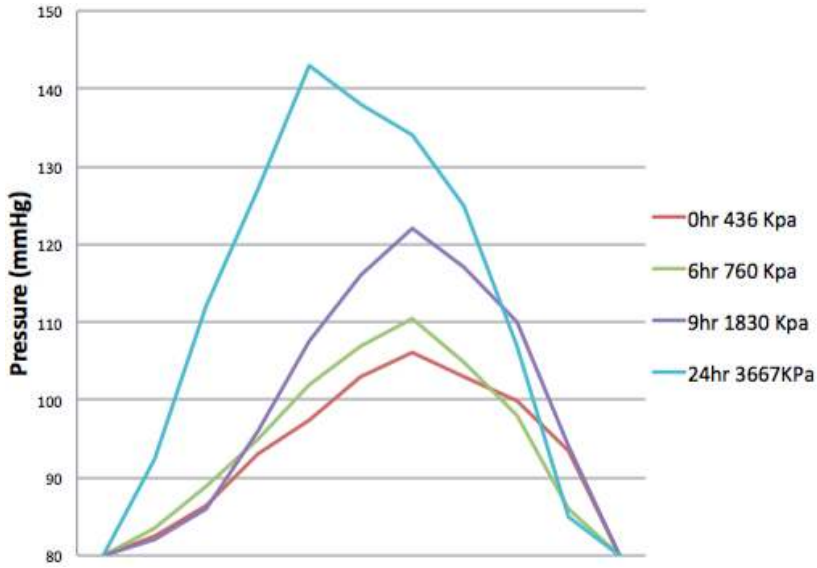

Figure 8.
Mean changes in pulse pressure and waveform profile with progressive loss of arterial wall compliance over a one-second pressure cycle. The key shows the period of exposure to formaldehyde vapour and resulting mean Young's modulus (Kpa) in relation to hoop strips cut from the proximal end of the test vessel after 6,9 and 24 hours of exposure. The volume load, cam profile and volume cycle and outflow resistance are held constant. n = 5, runs 20.

the arterial wall compliance alone has been changed by progressive formaldehyde exposure, the volume load, baseline pressure, pulse rate and outflow resistance being held constant. The corresponding Young's modulus for each period of formalin exposure measured at the equivalent of 100 mmHg pressure load using hoop strips cut from the proximal end of the test artery is shown in the key.

As arterial wall compliance decreases under pulsatile flow conditions the separation of the FI during passage of the pressure wave increases and reaches its maximum during the transition from systole to diastole and vice-versa. **Figure 9** shows the timing of the mean separation of the FI from the underlying vessel wall observed using B/M mode ultrasound throughout the phases of the pulse pressure wave cycle measured in five representative arteries as the wall is progressively stiffened. When the arterial wall is relatively compliant little separation of the FI occurs: as it stiffens increasing "lifting" separation of the FI is seen during passage of the pressure wave and occurs out of phase with the pressure wave itself, initially only in systolic/diastolic transitions but as the vessel stiffens further both in systolic and diastolic transitions.

3.3 Pulse pressure, centripetal strain and separation of the FI

The pulse pressure is very closely directly correlated to the CTS ($r = 0.907$, $p < 0.001$) and to the internal displacement of the FI when controlled for peak pressure waveform. **Figure 10** shows the relationship controlled for slightly blunted peaks characterised by an area under peak pressure 3.5 mm^2 (where each square represents 12 mmHg pressure over a period of 40 msec). Maximum proportional internal displacement of the FI is seen to occur as the peak pressure declines at the start of diastole (**Figure 9**) and is greatest when the pressure change is abrupt.

3.4 Waveform profile, viscosity, pulse rate, and diastolic pressure

No effect of pulse rate, or perfusate viscosity over the range 1 to 3.9 mPa.s on CTS or FI strain was observed independent of the effect of pulse pressure. This

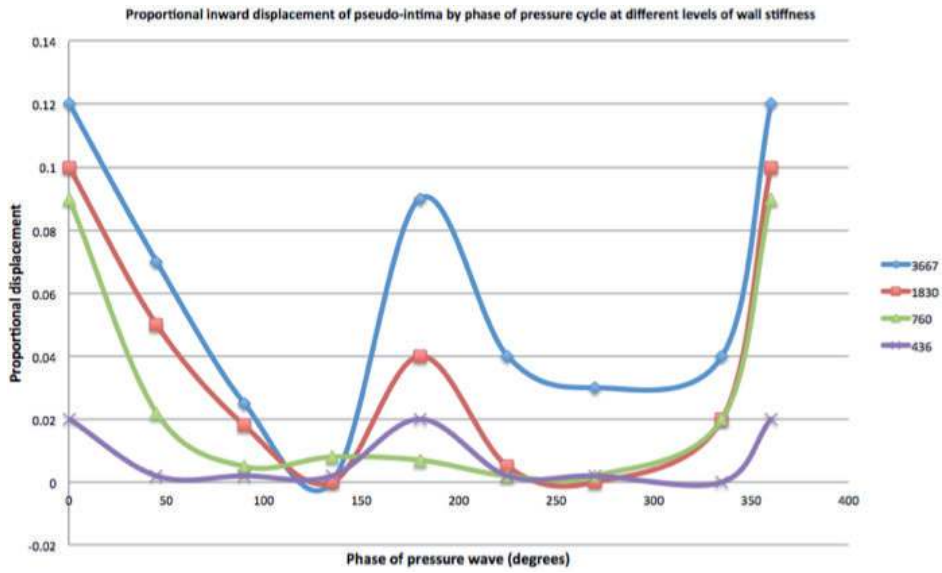

Figure 9.
Timing of strain response of the FI throughout the pressure cycle as the vessel wall is stiffened by progressive exposure to formaldehyde vapour. Figures in the key refer to corresponding mean Young's modulus derived from hoop strip tensiometry of the exposed formaldehyde vessels.

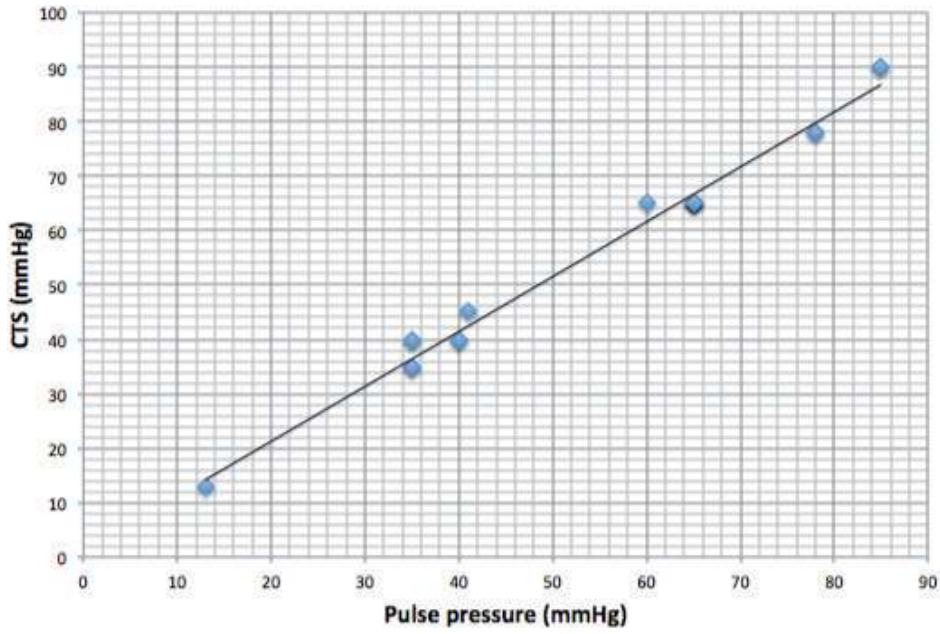

Figure 10.
Close relationship between pulse pressure and CTS controlled for the same waveform, area under peak (AUP) = 3.5 mm, n = 6 runs = 18.

does not exclude the possibility that viscosity may affect *shear strain* acting on the endothelium in pulsatile flow conditions which was not measured. Increased vessel wall stiffness is reflected in sharpening of the peak pressure wave and increased pulse pressure and both are associated with increased CTS. A close correlation was found between pulse pressure, CTS and FI separation irrespective of pulse rate, baseline ("diastolic") pressure, waveform or fluid viscosity. However this correlation depended on comparing like waveform profiles. When waveform profiles alone were altered by changing the cam profiles and selecting identical pulse pressures

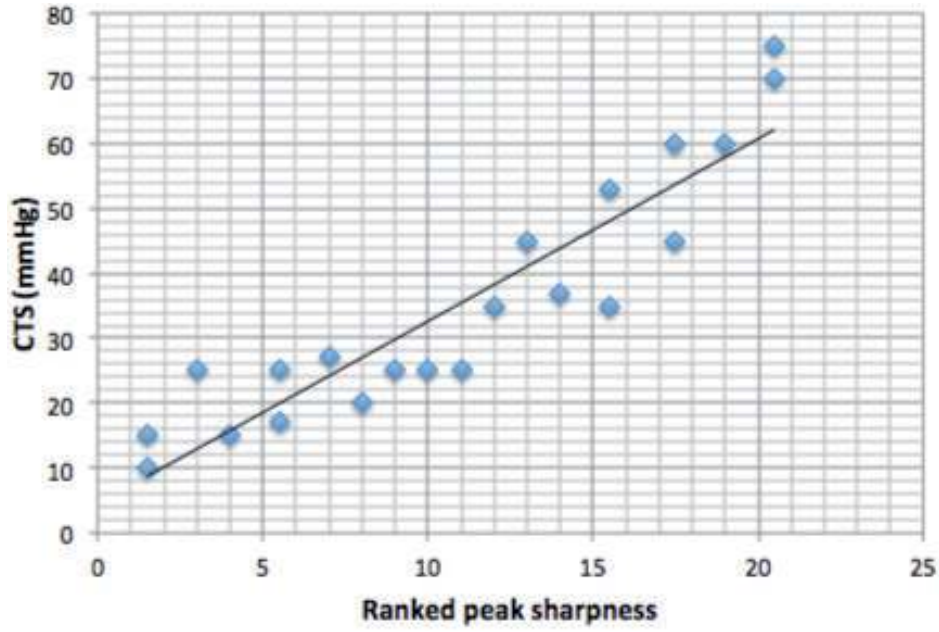

Figure 11.
Relationship between peak waveform profile and CTS when the pulse pressure remains the same, MAP in range 75-100 mmHg. Sharper peaks give rise to a greater CTS in pulsatile flow, whilst with blunted ones the CTS is reduced.

for analysis, the sharper the pressure transition the greater the CTS and false intima separation, (Spearman's R 0.93, $p < 0.001$), **Figure 11**).

4. Discussion

Blood pressure along with age, smoking habits and serum low-density lipoprotein cholesterol concentration (LDL-C) is a risk factor in the development of ischaemic heart disease and the risk of atherosclerotic large and middle-sized arterial disease throughout the body [22]. Much attention has been paid to the clinical management of blood pressure and LDL-C. By comparison relatively little attention has been given to the haemodynamic inter-relationships whereby blood pressure and other variables such as blood viscosity, vessel wall stiffness and pulse pressure waveform may interact to stress the arterial wall and influence the development of vascular disease. The presence of cholesterol in atherosclerotic plaques, the results of experimental animal studies and the clinical effectiveness of statins have tended to concentrate attention on the cholesterol accumulation theory of atherogenesis perhaps to the detriment of the study of these biomechanical factors. Although LDL-C undoubtedly plays a part in the atherogenic process in relation to atherogenic inflammatory changes in the vessel wall, the clinical relevance of targeting blood cholesterol in itself remains unclear especially in the elderly [23–25]. Recent studies suggest that non-statin lowering LDL-C in itself is not necessarily useful [26] and that statins exert their effect via an anti-inflammatory rather than cholesterol-lowering pathway, a pathway in which mechanical stress is also implicated [27–29]. It follows that pursuing blood cholesterol targets in a patient already on an appropriate does of statins may be less productive than pursuing blood pressure and lifestyle targets. Bearing in mind the focal distribution of atheroma in the vascular tree at points of mechanical strain alluded to in the introduction, and the established role of inflammatory signalling in atherogenesis, it may also be appropriate now to reappraise atherosclerosis in terms

of a biomechanical-inflammatory disease akin to a repetition strain injury where similar inflammatory mediators and histological changes are involved [30, 31] rather than regarding it as a disease of principally metabolic origin.

In this context the study of haemodynamic variables in relation as to how they may interact to cause mechanical stress becomes relevant.

The weaknesses in the present model are that it is an in vitro study involving fresh specimens maintained as far as possible in physiological conditions. The haemodynamic parameters and dimensions of porcine vessels are similar but not identical to those of their human equivalents [21]. The model examines pulsatile flow in a moving column of fluid but the nature of the pulsatility and the flow may be different from that encountered in vivo. In terms of the broad principles the experimental set-up nevertheless provides a thought-provoking model of the stress/strain response of a major artery similar to the human equivalent. With this caveat in mind the principle mechanical findings, namely: (a) a rise in mean arterial pressure above the physiological range results in a precipitate increase in transmural strain consequent upon the vessel wall stiffening in response to pressure and (b) that this increased strain is proportional to pulse pressure and is affected by the shape of the pulse pressure peak and vessel wall compliance provide theoretical support for concentrating on blood pressure management and in particular on management of pulse pressure in the reduction of clinical risk both from atherogenesis and from plaque detachment. Artificially increasing vessel wall stiffness to the extent seen in hypertension also increases transmural strain and emphasises the central role of loss of large vessel compliance, whether caused by hypertension or disease, in the physical strain across the vessel wall under pulsatile flow conditions. Measures to preserve large vessel compliance such as regular exercise, blood pressure and diabetic control thus logically becomes a key element in the management of cardiovascular risk [32, 33] and in the reduction of the risk associated with onward transmission of damaging pressure waves to vulnerable distal vessels [34]. The possible role of heat therapy and garlic extracts in this respect requires further confirmation [35, 36]. In summary the parameters showing an effect in regard to CTS are: mean arterial pressure, pulse pressure, wall compliance and pressure waveform.

There is an interplay between these factors; this interplay with some postulated clinical correlations is illustrated in **Figure 12**.

With regard to further study it would be interesting to look into the effect of changing the characteristics of pulsatile flow in respect to pulse pressure and waveform on the expression of adhesion molecules, oxygen free radicals and nitric oxide by the endothelium, and to investigate further the possible repetitive strain nature of hypertensive atherogenesis. This experimental set-up may also prove useful in investigating the role of biomechanical variables in atheromatous plaque detachment and in helping to develop newer more compliant materials for arterial grafts and stents.

The postulated role of pulse pressure and pulse waveform in atherogenesis would be further supported if it could be shown in clinical studies that subjects with relatively low pulse pressure and rounded pulse pressure waveforms, such as those with untreated mild congenital aortic stenosis, had a lower burden of atheroma in distal vessels than in comparable controls. The role of blood pressure in the initiation of inflammatory changes in the vessel wall might be further explored by examining whether good blood pressure control reduces the expression of inflammatory mediators associated with cardiovascular risk such as CRP.

4.1 Clinical implications

The conclusion of the present study is a hypothesis based on observational evidence and *in-vitro* experimentation. Should the hypothesis be confirmed by

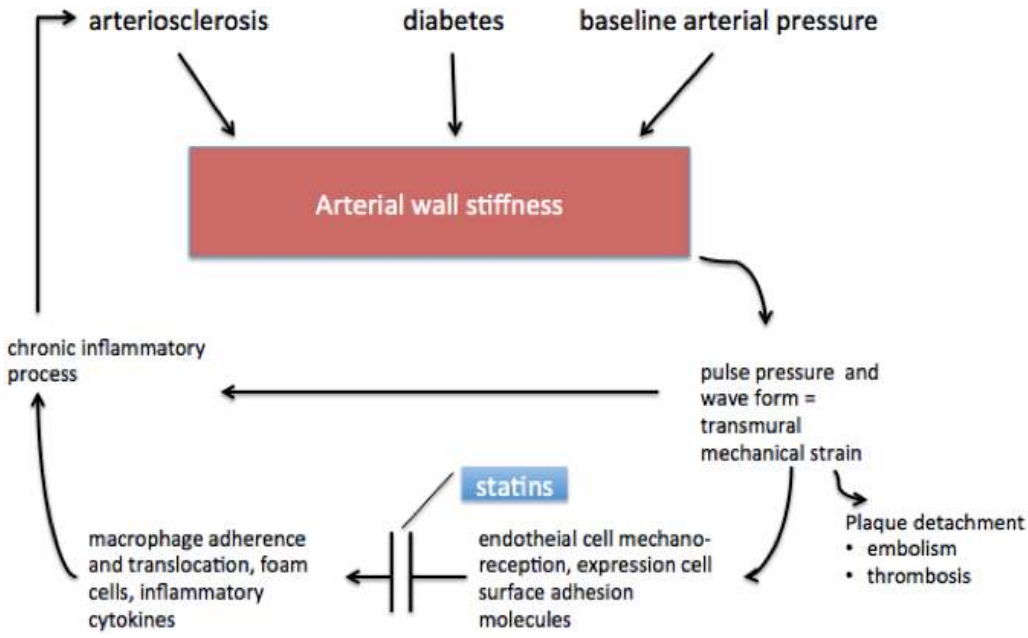

Figure 12.
Postulated relationship between vessel wall stiffness, blood pressure and mechanisms involved in the pathophysiology of atherosclerosis and cardiovascular risk.

clinical studies these findings provide theoretical support for the following clinical measures: control of mean arterial pressure and pulse pressure are particularly appropriate targets for prevention; large vessel wall compliance is important, and in a vessel already stiff, the transmural strain and hence the mechanical contribution to the risk of plaque separation is determined by pulse pressure and the sharpness of the systolic peak. The choice of treatment should be determined accordingly, and efforts to reduce the diastolic pressure in elderly hypertensive patients may be misplaced: the rational targets should be mean arterial pressure, pulse pressure and waveform. A key element is the role of arterial wall compliance in large vessels.

In brief it may be helpful to consider atherosclerosis as a disease of mechanical-inflammatory origin to which metabolic elements contribute a part rather than concentrating on the contribution of metabolic elements alone.

5. Conclusions

Pulse pressure, mean arterial pressure, pulse pressure waveform and arterial wall elasticity were found to affect transmural stress and strain in pig aortas subjected to a variety of haemodynamic stresses *in vitro*. Moderate rises in mean arterial pressure across and above the physiological range gave rise to exponential increases in wall stiffness and transmural stress. Transmural stress is implicated in both atherogenesis and plaque separation. It is proposed that atherosclerosis should be seen as a disease of mechanical-inflammatory origin whereby repeated excess mechanical stress gives rise to a state of sustained inflammatory healing in the vessel wall akin to a repetition strain injury. The way in which statins impair this inflammatory response is discussed. These studies suggest that preventative and therapeutic measures should target mean arterial pressure, pulse pressure, arterial pressure waveform and emphasises the importance of maintaining arterial wall elasticity in capacitance vessels. The

possible link between mechanical transmural stress and inflammatory signalling in the vessel wall requires further evaluation. This study provides theoretical support for the central role of blood pressure management in the control of cardiovascular risk.

Author details

Thomas K. Day
Independent Researcher, London, UK

*Address all correspondence to: thomasday3@me.com

References

[1] Texon M. The hemodynamic concept of atherosclerosis. Bul NY Acad Med. 1960;36(4):263-274.

[2] MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamier J. Blood pressure, stroke and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regeression dilutaion bias. *Lancet* 1990;335:765-774.

[3] Walton KW, Slaney G, Ashton F. Atherosclerosis in vascular grafts for peripheral vascular disease. Atherosclerosis 1985;54:49-64.

[4] Stokes J III, Kannel WB, Wpolf PA, D'Agostino RB, Cupples LA. Blood pressure as a risk factor for cardiovascular disease. The Framingham study – 30 years of follow-up. *Hypertesnion* 1989;13 (suppl I):I-13-I-18.

[5] Christensen T, Neubauer B. Arterial wall stiffness in insulin-dependant diabetes mellitus. Acta Radiol. 1988;29(3):299-302.

[6] Campens L, Vanakkar OM, Trachet B, Segers P, Leroy BP, De Zaeytijd J, Voet D, De Paepe A, De Backer T, De Bakkar J. Characterisation of cardiovascular involvement in pseudoxanthoma elasticum families. Arteriosclerosis, Thrombosis and Vasc Biol. 2013;33:2646-2652.

[7] Gerhard-Herman H, Smoot LB, Wake N. Mechanisms of premature vascular aging in children with Hutchinson-Gilford progeria syndrome. Hypertension. 2012;59(1):92-97.

[8] Low GD, Lee AJ, Rumey A, Price JF, Fowkes FG. Blood viscosity and the risk of cardiovascular events: the Edinburgh Artery Study. Brit J. Haematol. 1997;96(1):168-173.

[9] Dai G, Kaazempur-Morfrad MR, Natarajan S, Zhang Y, Vaughn S, Blackman BR, Kamm RD, Garcia-Cardeña G, Gimbrone MA. Distinct endothelial phenotypes evoked by arterial waveforms derived from atherosclerosis-susceptible and resistant regions of human vasculature. Proc Natl Acad Sci USA. 2004;101:14871-14876.

[10] Kwak BR, Bäck M, Bochaton-Piallat M-L, Caligiuri G, Daemen MJAP, Davies PF, Hoefer IE, Holvoet P, Jo H, Krams R, Lehoux S, Monaco C, Steffens S, Virmani R, Weber C, Wentzel JJ, Evans PC. Biomechanical factors in atherosclerosis: mechanisms and clinical implications. Eur Heart J. 2014:35;3013-3020.

[11] Moore S. Endothelial injury and atherosclerosis. Exp Mol Biol. 1979;31(1):182-190.

[12] Merrilees MJ, Scott L. Culture of rat and pig aortic endothelial cells. Difference in their growth rate and glycosaminoglycan synthesis. Atherosclerosis. 1981;38(1-2)19-26.

[13] Hansson G. Inflammation, atherosclerosis and coronary artery disease. N Engl J Med. 2005;16: 1685-1695.

[14] Fels B, Kuschen-Vihrag K. It takes more than two to tango: mechanosignaling of the endothelial surface. Pflugers Arch. 2020;472(4): 419-433.

[15] Davies PF. Flow-mediated mechanical transduction. Physiol Rev. 1995;75(3):519-560

[16] Nagel T, Resnick N, Atkinson WJ, Dewey CF, Gimbrone MA. Shear stress selectively upregulates adhesion

molecule-1 expression in cultured human vascular endothelial cells. J Clin Invest. 1994;94(2):885-891.

[17] Giussani DA, Moore PJ, Spencer JAD, Hanson MA. Changes in frequency and in complaince affect the pulsatility index of the Doppler flow velocity waveform at constant flow in an in vutre pulsatile flow model. J Matern Fetal Invest. 1995:5;78-82.

[18] Smulyan H, Safar ME. Systolic blood pressure revisited. J Amer Coll Cardiol. 1997;29:1407-1413.

[19] Telis VRN, Telis-Romero J, Mazzotti HB, Gabas AL. Viscosity of aqueous carbohydrate solutions at different temperatures and concentrations. J Food Prop. 2007:10(1);185-195.

[20] He C and Roach MR. The composition and mechanical properties of abdominal aortic aneurysms. *J Vasc Surg.* 1993:20 (1);6-13).

[21] Hannon JP, Bossone CA, Wade CE. *Normal Physiological Variables for Conscious Pigs used in Biomedical Research (1989)*. Letterman Army Institute of Research. Institute Report 379.

[22] Alexander WR. Hypertension and the pathogenesis of atherosclerosis. Hypertension 1995;25(2):155-161.

[23] Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med. 1979;90:85-91.

[24] Ravnskov U, Diamond D, Hama R, Hamazaki T, Hammarskjöld B, Hynes N, Kendrick M, Langsjoen PH, Malhotra H, Mascitelli L, McCully KS, Ogushi Y, Okuyama H, Rosch PJ, Schersten T, Sultan S, Sunberg R. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systemic review. Brit Med J. 2016; 6:e010401.

[25] Wong AP, Mohamed AL, Niedzwiecki A. Atherosclerosis and Cholesterol Theory: a Reappraisal. World J Cardiovascular. Res. 2016; 6:391-409.

[26] Lincoff AM, Nicholls SJ, Riesmeyer JS for the ACCELERATE Investigators. Evacetrarib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med. 2017;376:1933-1942.

[27] Teupser D, Bruegel M, Stein O, Stein Y, Thiery J. HMG-CoA reductase inhibitors reduce adhesion of human monocytes to endothelial cells. Biochem Biophys Res Commun. 2001; 289(4):838-844.

[28] Greenwood J Mason JC. Statins and the vascular endothelial inflammatory response. Trends Immunol. 2007; 28(2):88-98.

[29] Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation 2004; 109(23i):1227-1132.

[30] Exposure-dependent increases in IL-1beta, substance P, CTGF and tendinosis in flexor digitorum tendons with upper extremity repetitive strain injury. Fedorczyk JM, Barr AE, Rani S, Gao HG, Amin M Amin S, Litvin J, Barbe MF. *J Orth Res*. 2010:28(3)298-307.

[31] Landén NX, Dongqing L, Stähle M. Transition from inflammation to proliferation: a critical step during wound healing. Cell Mol Life Sci. 2016:73(20);3861-3885.

[32] Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61

prospective studies. Lancet. 2002;360:1903-1913.

[33] Steppan J, Barodka V, Berkowitz DE, Nyhan D. Vascular stiffness and increased pulse pressure in the aging cardiovascular system. Cardiol Res Pract. 2011; 2011:263-585. doi 10.4061/2011/263585.

[34] O'Rourke MF, Safar ME. Relationship between aortic stiffeniong and microvascular disease in the brain and kidney. Hypertesnion 2005;46:200-204.

[35] Breithaupt-Grögler K, Ling M, Boudoulas H, Belz GG. Protective effect of garlic intake on the elastic properties of the aorta in the elderly. Circulation 1997;96(8):2649-2655.

[36] Brunt VE, Howard MJ, Francisco MA, Ely BR, Minson CT. Passive heat therapy improves endothelial cell function, arterial stiffness and blood pressure in sedentary humans. J. Physiol. 2016:594(18);5329-5342.