Changes in biomechanical properties of the coronary artery wall contribute to maintained contractile responses to endothelin-1 in atherosclerosis

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A B S T R A C T

Introduction

The endothelin (ET) system is up-regulated in human coronary atherosclerosis with elevated levels of ET-1 detected in plasma (Lerman et al., 1991), correlating to the extent of disease (Salomone et al., 1996) and with increased ET-1 expression within the atherosclerotic plaque (Zeiher et al., 1995; Bacon et al., 1996). Interestingly, in response to this increased synthesis of ET peptide in human atherosclerosis detected in vitro (Maguire and Davenport., 1998a; Ihling et al., 2001) and in vivo (Böhm et al., 2002) we find no corresponding increase in density of ET receptors in the medial smooth muscle layer of coronary artery and indeed there is a profound down-regulation of ET receptor expression in the non-contractile intimal smooth muscle layer (Bacon et al., 1996; Maguire and Davenport, 2000; Katugampola et al., 2002). Histological analysis of diseased coronary artery has demonstrated marked atrophy of the contractile medial smooth muscle in the remodelled arterial wall that is predicted to contribute to plaque instability (Burke et al., 2002).

The mechanical properties of atherosclerotic artery have been studied both in vitro (Beattie et al., 1998; Baldewsing et al., 2008) and in vivo (van Popele et al., 2001; Baldewsing et al., 2008; Wykretowicz et al., 2009), where the diseased artery has been shown to be stiffer than healthy artery in clinical studies. Holzapfel and Ogden (2010) have provided a review of the studies on the theoretical modelling of arterial smooth muscle function. These include the study of Yang et al. (2003) on a model integrating the electro- and mechano-chemical functions of smooth muscle cell, as well as that of Zulliger et al. (2004) on a pseudo-strain energy function describing the arterial mechanical properties with the coupling of collagen, elastin, and smooth muscle...
active properties. Despite the well-modelled smooth muscle functions in these studies, the changes of arterial active properties with atherosclerotic disease remain unclear.

Our hypothesis was that the contractile responses to ET-1 in isolated rings of human atherosclerotic coronary artery should be markedly attenuated compared to histologically normal vessels. This should be a consequence of the relative reduction in the amount of contractile smooth muscle present, compounded by a decrease in arterial distensibility resulting from gross changes in the vessel structure, particularly intimal thickening, increased fibrosis and the presence of lipid laden and calcified plaque (Stary et al., 1994, 1995). Our aim was to compare contractile responses to ET-1 in human normal and atherosclerotic coronary artery in vitro and to develop finite element (FE) models to compare the passive and active mechanical properties of these vessels in health and disease. We first performed mechanical tests and FE modelling to obtain the passive mechanical properties (stretch and distensibility in response to mechanical loading in the absence of chemically mediated smooth muscle cell activation) of both the normal and diseased arteries. We then used these determined passive properties in further FE modelling of the arterial active response to ET-1 to understand how atherosclerosis-induced changes in arterial structure and mechanical properties may affect this active response to ET-1.

Unexpectedly we find that compared to histologically normal coronary artery, in vitro contractile responses to ET-1 are well maintained in atherosclerotic vessels with FE modelling demonstrating the capacity of medial smooth muscle cells in diseased arteries to develop elevated contractile strains in response to ET-1 compared to normal arteries.

Materials

Human tissue

Anonymised human coronary artery samples were used in this study with local ethical approval (REC 05/Q0104/142). Samples were obtained from Papworth Hospital Research Tissue Bank (Cambridgeshire 1 Research Ethics Committee reference 08/H030456) and were collected with written informed patient consent. Histologically normal arteries (no visible evidence of atherosclerosis) were from 68 patients transplanted for cardiomyopathies (Dec and Fuster, 1994) and atherosclerotic artery samples with evidence of coronary artery disease (CAD, visible plaque present) were from 55 patients transplanted for ischaemic heart disease. n-Values refer to the number of patients from whom tissue was obtained. Artery samples for the contractile functional experiments were transferred to the laboratory in Krebs solution and used within 12 h of retrieval. ET-1 was purchased from Sigma-Aldrich and used within 12 h of retrieval. ET-1 was purchased contractile functional experiments were transferred to the laboratory in normal and atherosclerotic coronary artery in vitro and to develop finite element (FE) models to compare the passive and active mechanical properties of these vessels in health and disease. We first performed mechanical tests and FE modelling to obtain the passive mechanical properties (stretch and distensibility in response to mechanical loading in the absence of chemically mediated smooth muscle cell activation) of both the normal and diseased arteries. We then used these determined passive properties in further FE modelling of the arterial active response to ET-1 to understand how atherosclerosis-induced changes in arterial structure and mechanical properties may affect this active response to ET-1.

Finite element models of the passive mechanical properties of normal and atherosclerotic coronary artery

For each normal artery sample the FE model was created using Abaqus (Dassault Systèmes, Vélizy-Villacoublay, France), comprising a single circular ring with diameter and wall thickness estimated from the vessel histology (Fig. 1A). The models were assigned with first order Ogden hyperelastic properties with shear modulus μ and hardening exponent α (Abaqus Theory Manual), assuming incompressible material. The model reaction forces were matched with those of the corresponding tensile ring tests using an error minimisation approach with MATLAB (MathWorks, Natick, USA) to determine the optimum μ and α that provide the best matching. Mean values of μ and α of the normal artery models were then calculated and expressed as mean ± sem.

A similar approach was applied to the atherosclerotic artery models, with an additional inner vessel wall layer included to represent plaque tissue (Fig. 1B). For atherosclerotic artery the wall outer layer was assigned with the same mean values of μ and α determined for normal artery and the additional inner plaque layer was assigned with different optimum values of μ and α determined by matching the modelled force–stretch results with those of the passive tensile ring tests for the diseased artery samples.

In order to compare the overall stiffness of the normal and atherosclerotic arteries, each of the FE models was loaded with internal physiological pressures of 80 mm Hg and 120 mm Hg. The distensibility D of each arterial sample was determined from the geometry changes of the model using Eq. (2):

\[
D = \frac{A_{d20} - A_{80}}{A_{80}(P_{120} - P_{80})}
\]

where \(A_{80}, A_{120}, P_{80}, \) and \(P_{120}\) are the lumen area A and pressure P at 80 mm Hg and 120 mm Hg, respectively. The stiffness of the arteries

response to 10 μM phenylephrine by 1 μM acetylcholine. After 30 minute equilibration, cumulative concentration–response curves (CRC) were then constructed to ET-1 (10^-10 - 10^-6 M) and experiments were completed by addition of 100 mM KCl to determine maximum possible contractile response for each tissue. ET-1 responses were expressed as force developed (mN) or % terminal KCl response. Data were analysed using the non-linear iterative curve-fitting programme GraphPad Prism (GraphPad Software Inc., La Jolla, USA) to determine values of pD2 (−log EC50 (the concentration of ET-1 that produces 50% of the maximum ET-1 response)) and maximum response (\(E_{MAX}\)).

Passive tensile ring tests

The passive mechanical properties of normal and atherosclerotic human coronary arteries were determined using tensile ring tests. The arterial samples were snap frozen to maintain structural integrity, stored at −70 °C and defrosted before use. The defrosted samples were expected to have negligible smooth muscle cell activation induced by stretching. The artery rings were set up as above, uniaxial loadings were applied to the rings and the reaction forces and arterial deformations in response to mechanical stretch were recorded in both normal (n = 5) and atherosclerotic (n = 6) arterial rings. The mechanical stretch λ of the ring was calculated as:

\[
λ = \frac{2L}{C}
\]

where L is the distance between the two wires that were used to stretch the arterial ring, and C is the inner circumference of the ring without loading, which was measured from the histology image of the artery.

Methods

Human coronary artery functional assay

Experiments were carried out as previously described (Maguire, 2002). Briefly, 4 mm rings of histologically normal (n = 68) or atherosclerotic (n = 55) endothelium-denuded human coronary artery were set up for isometric force recordings in 5 ml organ baths containing oxygenated Krebs solution at 37 °C. For diseased arteries all 4 mm segments contained visible atherosclerotic plaque, although plaque size was variable between samples. Following an active force normalisation procedure to determine optimum resting force, successful removal of the endothelium was confirmed by lack of reversal of the contractile response to 10 μM phenylephrine by 1 μM acetylcholine. After 30 minute equilibration, cumulative concentration–response curves (CRC) were then constructed to ET-1 (10^-10 - 10^-6 M) and experiments were completed by addition of 100 mM KCl to determine maximum possible contractile response for each tissue. ET-1 responses were expressed as force developed (mN) or % terminal KCl response. Data were analysed using the non-linear iterative curve-fitting programme GraphPad Prism (GraphPad Software Inc., La Jolla, USA) to determine values of pD2 (−log EC50 (the concentration of ET-1 that produces 50% of the maximum ET-1 response)) and maximum response (\(E_{MAX}\)).

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D = \frac{A_{d20} - A_{80}}{A_{80}(P_{120} - P_{80})}
\]

where \(A_{80}, A_{120}, P_{80}, \) and \(P_{120}\) are the lumen area A and pressure P at 80 mm Hg and 120 mm Hg, respectively. The stiffness of the arteries
was examined by this normalised $D$ (i.e. change of lumen area normalised by the initial area) rather than the non-normalised $D$ to prevent the influence of the significant geometry differences between the normal and diseased groups.

**Finite element modelling of artery ET-1 responses**

Two-dimensional FE models that had the geometries of idealised normal and atherosclerotic artery rings were created. The normal artery model contained two separated regions of adventitia and media (Fig. 1C), with diameter and wall thickness estimated from the arterial rings used in the tensile ring experiments. Both of these regions were assigned with the previously derived mean values of hyperelastic $\mu$ and $\alpha$ determined for normal artery wall. The medial layer was assigned with an additional thermal expansion property to model the muscle force generation in response to addition of ET-1 under isometric conditions, where applied temperature in the model represents the applied concentration of ET-1 used in the contraction experiments. The thermal expansion property was modelled with an error function (erf) (Eq. (3)) using a user subroutine to generate the reaction forces that match the ET-1 contraction experiments:

$$\varepsilon = P_1 \text{erf}(P_2 T)$$

$\varepsilon$ and $T$ are the strain and applied temperature, respectively, and $P_1$, $P_2$, and $P_3$ are three parameters that were modified to generate the forces that match the ET-1 contraction experiments.

The idea of this modelling approach is to use the thermal modelling capability within the Abaqus FE software to represent directly the contractile effect of ET-1. The relationship between thermal strain and temperature represented in Eq. (3) should be interpreted directly as the effect of ET-1 concentration $T$ on the muscle contraction strain $\varepsilon$. The value of $P_1$ governs the maximum contractile response in the muscle, while $P_2$ and $P_3$ control the shape of the curve representing the relationship between contractile strain and ET-1 concentration. $P_2$ determines the shift of the curve to left or right and $P_3$ determines the slope of the curve.

The model was first applied with a pre-stretch load (25 mN) that corresponded to the mean basal force determined by the normalisation procedure in the contraction studies in normal arteries. Thermal loadings of the same magnitudes of the administered ET-1 concentrations were then applied. The results of the model were compared to those of the ET-1 contraction experiment and an error minimisation approach was performed using MATLAB to change the three parameters of Eq. (3) with multiple iterations until a minimum average difference was achieved.

The model of the atherosclerotic artery ring was then created, which contained an additional layer of plaque (Fig. 1D), the size of which was estimated from the atherosclerotic samples used in the tensile ring experiments. The adventitia and media were again modelled with the same properties as those of the normal artery model. The plaque region was assigned with hyperelastic $\mu$ and $\alpha$ determined from the atherosclerotic artery tensile tests. A pre-stretch load (36 mN) was applied, derived from the normalised basal force determined in the contraction study in diseased arteries, and the same thermal loadings were applied to the diseased artery model. The reaction forces were then matched with the contractile responses to ET-1 using a MATLAB error minimisation approach by modifying the $P_1$, $P_2$, and $P_3$ thermal parameters of the atherosclerotic model.

The atherosclerosis-induced changes of arterial contraction under physiological condition were then examined by applying internal pressures of 80 mm Hg and 120 mm Hg to both normal and atherosclerotic models, along with a thermal loading of $3 \times 10^{-7}$ K (equivalent to $3 \times 10^{-7}$ M ET-1). The distensibility $D$ of each model was then calculated using Eq. (2), and comparisons were made between the cases of without applying muscle contraction (passive), applying the determined normal muscle tone to both models, and applying diseased muscle tone to the diseased model.
ET-1 mediated contractile responses in normal and atherosclerotic human coronary artery

Optimised basal forces were significantly different in normal (25 ± 2 mN) and diseased (36 ± 3 mN) coronary artery. ET-1 contracted normal (pD2 = 8.03 ± 0.06, n = 68) and diseased (pD2 = 7.98 ± 0.06, n = 55) coronary artery with comparable potency. Absolute maximum responses to ET-1 were significantly greater in normal (EMAX 38 ± 2 mN) than in diseased (27 ± 3 mN) artery (Fig. 2A) but when normalised to the terminal KCl response no difference in maximum response to ET-1 in the two groups was obtained (normal, EMAX 78 ± 2% KCl; CAD, EMAX 76 ± 2% KCl) (Fig. 2B), indicating that the reduced response to ET-1 most likely reflected a generalised decrease in contractility of the atherosclerotic tissue rather than an ET-1 specific effect.

Passive mechanical properties of normal and atherosclerotic coronary artery

Passive tensile ring test data showing the force–stretch relationship for normal and diseased artery samples are shown in Fig. 2C. Matching the force–stretch results of the normal artery FE models with those of the tensile ring tests resulted in mean hyperelastic shear modulus μ = 2004 ± 410 Pa and hardening exponent α = 22.8 ± 2.2 for the vessel wall of normal artery. These values were applied to the wall regions of the atherosclerotic FE models, resulting in values for the plaque region of μ = 2464 ± 1075 Pa and α = 38.3 ± 6.7. The mean distensibility D of the normal and diseased artery samples derived from the FE models were 1.12 ± 0.11 × 10^{-3} mm Hg^{-1} and 0.87 ± 0.18 × 10^{-3} mm Hg^{-1} respectively, indicating a trend for the normal artery wall to exhibit greater distensibility than the diseased vessels.

Finite element modelling of the ET-1 response in normal and atherosclerotic coronary artery

The FE models of the normal and atherosclerotic arteries applied with pre-stretch forces and thermal loadings are shown in Fig. 3A and B. The optimum matching of the reaction forces between the ET-1 experiments and the normal (Fig. 3A) and diseased (Fig. 3B) FE models resulted in parameters of the thermal property of the normal artery model of P1 = −0.086, P2 = 2.6 × 10^{-7} K^{-1}, and P3 = 0.34, whereas those of the atherosclerotic artery model were P1 = −0.273, P2 = 3.6 × 10^{-7} K^{-1}, and P3 = 0.20. The negative values of P1 for both models resulted in the contraction of artery rings in response to ET-1. The higher magnitude of P1 required for the atherosclerotic artery model indicated that the maximum strain associated with the drug response was greater in the diseased than in the normal arteries. This suggests that smooth muscle cells of the diseased arteries generate more force per cell to ET-1 than those of the normal arteries.

The distensibility D of these two models under the physiological condition without applying contractile muscle tone (passive) and applying healthy or diseased muscle tones was determined from the modelling of the ET-1 response (Table 1). The diseased model had a lower D than the normal model in the passive condition, as previously obtained in the modelling of the tensile ring tests. Applying the diseased muscle tone significantly increased D for the diseased model, which achieved a similar level as that of the normal model with normal muscle tone.

Discussion

Medial contractile smooth muscle atrophy and proliferation of non-contractile intimal smooth muscle are hallmarks of human atherosclerosis. We hypothesised that these changes would contribute to a marked loss of contractile response to ET-1 in isolated rings of human diseased coronary artery compared to histologically normal artery. However, although we found a significant reduction in the maximum response to ET-1 in diseased artery, the response was still over 70% of that in control arteries. The consequence of this maintained constrictor response for patients may be that in vivo ET-1 produced locally in the diseased vessel wall would produce focal vasospasm resulting in profound reduction in coronary blood flow owing to the already compromised lumen. Variant angina, coronary vasospasm frequently associated with atherosclerosis, can be life threatening but in a recent case has been treated with bosentan implying that ET-mediated vasconstriction is a likely cause at least in some individuals (Krishnan et al., 2010).

In human normal and atherosclerotic coronary artery in vitro we have previously demonstrated that contractile responses to ET-1 are mediated via the ETₐ receptor (Maguire and Davenport, 1998b, 2000). We find no increase in ET receptor density and no up-regulation of ETₐ receptors in human atherosclerosis (Bacon et al., 1996) to explain this maintained contractile response to ET-1 in disease and therefore we investigated the passive mechanical properties of normal and atherosclerotic coronary arteries using tensile ring tests and FE analysis. Our data indicated that the diseased arteries were stiffer (i.e. exhibited lower distensibility) than normal arteries, in agreement with previous in vivo observations (van Popele et al., 2001; Wykretowicz et al., 2009). Distensibility was chosen as the indicator of arterial stiffness owing to its direct representation of the overall arterial compliance and close correlation with the volume of blood flow through the artery. Elastic modulus, which is commonly used as a representation of stiffness, varies across the plaque and arterial wall of the thickened walled atherosclerotic artery (Beattie et al., 1998; Baldewsing et al., 2008) and is therefore not an appropriate indicator of overall arterial compliance. The distensibility in the passive condition is determined

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Fig. 2. (A) Contractile responses to ET-1 in histologically normal (●) and diseased (■ CAD) coronary artery expressed in mN force. (B) The same data normalised to the response of 100 mM KCl in each vessel ring. (C) Passive tensile ring test data showing the force–stretch relationship for normal (●) and diseased (■ CAD) coronary artery samples.
by the material properties of the arterial wall, and future studies to
determine how changes in distensibility correlate to alterations in
the expression of, for example extracellular matrix proteins, would be
informative. Indeed, recently the first layer-specific comparative proteomic
analyses of human atherosclerotic coronary intima and media have
been reported, which indicated changes in the intimal expression of
extracellular matrix proteins collagen α-1 (IV) and microfibril-associated
glycoprotein 4 and in the markers of contractile phenotype, SM22α
and myosin regulatory light 2 (de la Cuesta et al., 2011). Whereas in
the media there was evidence for dysregulation of cytoskeleton proteins
consistent with the switch of medial smooth muscle cells from contrac-
tile to synthetic phenotype, which may also explain the compression
and thinning of the medial layer in response to intimal thickening (de
la Cuesta et al., 2013).

The mechanisms of the arterial responses to ET-1 were demonstrat-
ed using FE models, where the diseased artery had similar, or slightly
lower, reaction forces when compared with the normal artery. The
maintained ability of diseased arteries to contract to ET-1 to a similar
extent as normal arteries, despite loss of smooth muscle, may result
from an increase of the reactivity of the remaining smooth muscle
cells to ET-1, as indicated in the FE modelling where the $P_1$ parameter
(thermal reactivity) was higher in the atherosclerotic compared to
normal artery model. There may be an underestimate of the diseased
model $P_1$ as medial thickness was kept the same in the FE normal and
diseased models for ease of comparison rather than reduced in the dis-
eased model to reflect medial atrophy. A limitation of this study is that
contractile responses have not been normalised to medial thickness;
however, this avoids any ambiguity in identifying the active medial
layer in the diseased artery that would introduce uncertainty into the
analysis. Therefore we predict that the magnitude of the contractile
response $P_1$ for the diseased artery would be even higher if the medial
thickness of the atherosclerotic artery model were reduced, while the
force response was maintained.

Finally the physiological distensibility results of the normal and
atherosclerotic models with muscle tones suggest that the diseased
artery has an adaptation response which changes muscle reactivity to
increase the arterial contraction to applied ET-1, resulting in a distensi-
bility that is closer to that of the normal artery. The mechanisms
underlying this observation require further investigation.

### Table 1

<table>
<thead>
<tr>
<th>Artery</th>
<th>D (mm Hg$^{-1}$)</th>
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<tbody>
<tr>
<td></td>
<td>Passive</td>
</tr>
<tr>
<td>Normal</td>
<td>$1.10 \times 10^{-2}$</td>
</tr>
<tr>
<td>CAD</td>
<td>$0.67 \times 10^{-2}$</td>
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**Fig. 3.** Finite element models of (A) normal and (B) atherosclerotic arteries loaded with pre-stretch forces and thermal contractions, with adjacent graphs showing the matching of reaction forces from the ET-1 contractile experiments by the FE models.

**Conclusion**

This study has identified a maintained active response of human
atherosclerotic artery to ET-1 in vitro despite extensive thinning of the
media smooth muscle layer. As well as providing comparisons of the
mechanical properties of the normal and diseased arteries, the tensile
tests and FE modelling demonstrated the potential elevated contractile
strains developed by diseased smooth muscle cells in response to ET-1.
These results suggest that adaptation mechanisms occur with the path-
ogenesis of atherosclerosis to maintain the distensibility of the diseased
vessel wall in response to vasoconstrictor such as ET-1. If ET-1 produc-
tion is increased in the atherosclerotic artery then the maintained ability
of the diseased artery wall to respond to this peptide may contribute to
local vasospasm that is associated with this disease.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

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