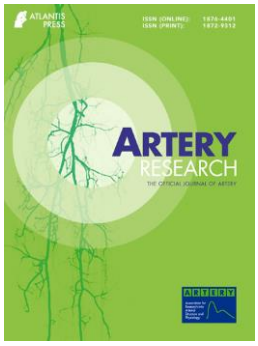

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# Arterial stiffness and inflammation – A potential target for a drug therapy

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## Introduction

Inflammation is a key element in atheroma formation, playing a pivotal role in the initiation, progression and propagation of the disease.[1] Circulating levels of several cytokines including IL-6 and TNF-$\alpha$ are elevated in subjects with atherosclerosis, and correlate with disease burden. Levels of the acute phase reactant C-reactive protein (CRP) also predict the risk of future cardiovascular events both in subjects with known cardiovascular disease (CVD),[2] and in apparently healthy individuals.[3] Moreover, the incidence of CVD is increased in patients with chronic systemic inflammatory diseases such as rheumatoid arthritis (RA),[4–7] and the inflammatory process of RA resembles the one seen in atherosclerosis. Both diseases involve activation of macrophages, T-cells, especially CD4+CD28- and B-cells as well as increased expression of adhesion molecules and increased circulating levels of TNF-$\alpha$ and CRP.[8] These facts make RA a useful "model" to investigate the relationship between systemic inflammation and CVD. The mechanism by which inflammation leads to increased CV risk remains unknown. Inflammation could lead to an increase of cardiovascular risk directly, by accelerating the atherosclerosis process or destabilizing plaques, or indirectly, via endothelial dysfunction, and a premature stiffening of the large arteries.

This review aims to explore the relationship between inflammation and arterial stiffness and to explain possible mechanisms by which inflammation could lead to arterial stiffening. Also, the recent studies, which have investigated the effect of anti-inflammatory drugs and statins for arterial stiffness reduction, will be discussed.

## Arterial stiffness

The importance of arterial stiffness has been recognized for many centuries, and recent outcome data from various patient groups demonstrate that arterial stiffness is a powerful, independent predictor of cardiovascular disease.[9–12] Aortic stiffening leads to increase in systolic blood pressure (BP) and a fall in diastolic BP and, therefore, to a widening of pulse pressure. This increases left ventricular after load and oxygen demand, whilst decreasing coronary blood flow. Increased pulse pressure

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also raises the risk of stroke and damages capillaries e.g. in renal circulation. Arterial stiffening may also directly accelerate the atherosclerotic process due to changes in shear stress and vascular remodelling.[13]

Arterial stiffness is regulated by numerous factors. Traditionally, mean arterial pressure and structural changes in the components of arterial wall were thought to be main determinants of arterial stiffness. With ageing, the neat arrangement of the elastin fibers within the media is lost and the elastin fibers become thinner and fragmented, and the stiffer collagen fibers become the load bearing ones.[14,15] Additionally, the loss of elastin fibers is associated with an increase in stiffer collagen fibers within the media, and arterial calcification. Moreover, the balance between the elastin synthesis and breakdown, by the matrix metalloproteinases contributes towards the arterial stiffening.[13] It is now recognized that arterial stiffness is also regulated by the smooth muscle tone, and that endothelium derived mediators, such as NO and endothelin-1, contribute to the functional regulation of arterial stiffness.[16,17] It has also become apparent that inflammation has an important role in the stiffening of the large arteries,[18] possibly via changes in the composition of the arterial wall due to inflammatory cell infiltration or via endothelial dysfunction.[19,20]

## Clinical evidence for inflammation-induced arterial stiffening

Epidemiological data from numerous outcome studies demonstrate the importance of inflammation in CVD.[21,22] Also, recent studies in healthy individuals and in patients with isolated systolic hypertension indicated an association between arterial stiffness and serum levels of CRP.[23,24] Aortic and brachial PWV[24] and AIx[23] are independently related to the levels of inflammation, suggesting that inflammation plays a role in the regulation of arterial stiffening. Most recently, data from the Caerphilly Prospective Study showed that both current CRP and CRP at the beginning of the 20-year follow-up were strongly associated with aortic pulse wave velocity (aPWV).[18] However, study by Schumacher et al. looking three single nucleotide polymorphisms in the CRP gene found no relationship between any of the CRP genotypes and aortic pulse wave velocity, suggesting CRP is a simply a marker of vascular damage/inflammation, not the causal molecule.[25] Furthermore, a large genome-wide association study by Elliott et al. concluded that the lack of concordance between the effect on coronary heart disease risk of CRP genotypes and CRP levels argues against a causal association of CRP with coronary heart disease.[26]

Further information about the causality between inflammation and arterial stiffness can be gained by adapting Koch's "Postulates" by answering the following questions; 1) does inflammation cause arterial stiffening? 2) does a reduction in inflammation improve arterial stiffness?

## Does inflammation cause arterial stiffening?

One approach to answer this question is to take a cohort of healthy individuals and induce an inflammatory response and observe the changes in arterial stiffness parameters. In such experimental model of acute inflammation, Vlachopoulos et al. demonstrated that *Salmonella typhi* vaccination lead to an increase in aPWV 8 h post-vaccination, furthermore this increase was preventable with aspirin pre-treatment.[27] However, the effect was very modest and maybe a better way to study the role of inflammation in arterial stiffening is to study patients with an existing inflammatory condition, such as rheumatoid arthritis (RA).

RA and other chronic inflammatory diseases are interesting and ideal model to study effect of inflammation on arterial stiffness as they are associated with increased CV mortality,[4,7,28,29] independently of traditional CV risk factors,[6] suggesting that additional, novel risk factors, such as increased arterial stiffness could be involved. Numerous studies have demonstrated that RA[30–37] and other inflammatory conditions,[34,38–40] are associated with aortic stiffening. Aortic stiffness is greatest in patients with active disease (CRP $\geq$ 10 mg/L) compared to those with quiescent disease (CRP $<$ 10 mg/L), and that CRP independently predicts aortic stiffness.[31] These findings suggest that arterial stiffness correlates with the degree of active inflammation and therefore, that inflammation could be a potential target for drug therapy for arterial stiffness reduction.

## Does a reduction in inflammation improve arterial stiffness?

### Anti-inflammatory drugs

Only a few, relatively small studies have investigated the effect of traditional anti-inflammatory drugs for arterial stiffness reduction. To complicate matters, some drugs conventionally used to treat inflammation may in fact increase CV risk. Corticosteroid use is associated with dyslipidaemia, hypertension, impaired glucose tolerance, and imbalances in thrombosis and fibrinolysis.[41] Methotrexate use can lead to hyperhomocysteinaemia, which is an independent predictor of CV events, although this problem can be overcome by concomitant supplementation of folic acid.[42] Selective COX-2 inhibitors and also non-selective NSAIDs increase mortality and CV events in numerous patients groups.[43–45] However, these drugs also have an ameliorating effect on the vasculature by the reduction of inflammation and hence oxidative stress.

Vlachopoulos et al. used *S. typhi* vaccination to induce acute inflammation in healthy subjects. Interestingly, they demonstrated that there was no change in PWV following the vaccination in those subjects that were randomised to receive aspirin pre-treatment 1200 mg (PWV +0.11 m/s; $P > 0.05$), whereas PWV significantly increased in the placebo group (+0.43 m/s; $P < 0.01$). This demonstrates that a pre-treatment with aspirin ameliorates the effect of the vaccination-induced arterial stiffening.[27]

The other studies investigating the effect of anti-inflammatory drugs for arterial stiffness reduction come from studies in patients with chronic inflammatory diseases. A cross-sectional study in patients with Adamantiades–Behcet's disease (ABD) measured arterial stiffness in those patients taking corticosteroids and in those who do not.[46] Protogerou et al. demonstrated that the AIx was lower in those patients taking corticosteroids

compared to those who do not ($12 \pm 14$ *versus* $21 \pm 14\%$, $P < 0.05$). Corticosteroids have also been shown to reduce AIx (from $28 \pm 9$ to $25 \pm 10\%$, $P = 0.006$) in an intervention study by Pieringer et al., where they treated patients with polymyalgia rheumatica for 4 weeks with prednisolone 25 mg OD.[47] Unfortunately, PWV was not assessed in either of these studies. The results of these studies are contradicted by a recent study by Wong et al. in which they demonstrated that anti-inflammatory therapy with COX inhibitors, indomethacin and rofecoxib, did not improve endothelial function or reduce arterial stiffening.[48] However, this could be explained by the reduction of prostacyclin production, a powerful vasodilator, by COX inhibitors.

Our group demonstrated in patients with RA, that aortic PWV was reduced (from $8.82 \pm 2.04$ to $7.68 \pm 1.56$, $P < 0.001$) and, concomitantly, endothelial function was normalised with anti-TNF-$\alpha$ therapy, etanercept.[31] More recently, these findings have been confirmed in a larger cohort of patients with inflammatory arthropathies. Angel et al. demonstrated that aPWV was reduced in the group of patients receiving anti-TNF-$\alpha$ therapy, but not in a control group ($-0.50 \pm 0.78$ *versus* $0.05 \pm 0.54$ m/s; $P = 0.002$).[49] Cypiene et al.[50] and Galarraga et al.[51] also confirmed these findings in RA patients receiving anti-TNF-$\alpha$ therapy.

On the contrary, van Doornum et al. and more recently, Pieringer et al., reported that anti-TNF-$\alpha$ therapy did not reduce arterial stiffness.[52,53] However, they assessed arterial stiffness by measuring AIx rather than aortic PWV. AIx may not be the most appropriate parameter to measure arterial stiffness in this particular cohort, since AIx is a composite measure, which depends on wave velocity, the site of reflection and the amplitude of the reflected wave. In patients with a high baseline inflammation, a reduction in inflammation could lead to a subsequent peripheral vasoconstriction, which would lead to increased impedance mis-match at the point of reflection and therefore the net effect on AIx would remain unchanged, despite a reduction in a wave speed (PWV). This notion was confirmed in the study by Vlachopoulos et al. where the experimentally induced inflammation led to an increase of aortic PWV, but a reduction of wave reflections (AIx).[27]

### Anti-lipideamic drugs

Recently, numerous studies have reported so called "pleiotropic effects" of HMG-CoA reductase inhibitors (statins) use. These include improvement of endothelial function,[54] increased nitric oxide bioavailability,[55,56] antioxidant[57] and anti-inflammatory[58] effects as well a proposed role as an immunomodulator.[59] Therefore it comes as no surprise that numerous studies have investigated statins as a means to reduce arterial stiffness.

Tomochika et al. was the first to show in late 1990s that arterial stiffness can be reduced with a strict cholesterol-lowering therapy with pravastatin and probucol and diet.[60] A year later, Muramatsu et al. demonstrated in 59 patients with hypercholesterolemia, that those patients who had 15% or more reduction in total cholesterol following the pravastatin therapy also had a significant decrease in pulse wave velocity, total peripheral resistance, and an increase in cardiac.[61] Since these first two studies in the 1990s, numerous groups have studied the effect of different statins in various patient groups. Most studies have been conducted in patients hypercholesterolemia ($n = 17$), other patient groups include: hypertension ($n = 3$), CVD ($n = 4$), chronic kidney disease ($n = 4$), diabetes ($n = 3$), RA ($n = 2$) and obese ($n = 1$). See the Table 1 for the summary of all studies investigating the effect of statins or anti-inflammatory drugs on arterial stiffness.

## How does inflammation lead to arterial stiffening — potential mechanisms?

As discussed earlier an association between increased arterial stiffness and inflammation has been demonstrated by numerous studies, yet the mechanism is poorly understood. Direct vascular inflammation is a potential mechanism behind the increased arterial stiffness seen in patients with chronic inflammatory diseases. Large vessel vasculitis is associated with an increase in aortic stiffness.[39,62–64] This is often reversible, but in Kawasaki disease, it appears to be party irreversible.[63] Vasculitis in RA is rare, being present in only 1–3% of RA patients.[65,66] Furthermore the incidence of rheumatoid vasculitis has dramatically declined since 1980s, possibly due to the better control of inflammation.[67] Vasculitis in RA usually affects small or medium arteries and involvement of the large vessels is very rare indeed.[68] However, this does not rule out the possibility of sub-clinical vasculitis and indeed, Hollan et al. have demonstrated in patients undergoing bypass graft surgery that those patients with inflammatory rheumatic disease (IRD) ($n = 65$) had greater occurrence of mononuclear cell infiltrates within their aortic media or adventitia than those patients without IRD ($n = 51$); odds ratio (OR = 3.6, 95% CI: 1.6–8.5; $P = 0.002$).[69] Potentially, inflammatory cell infiltration within the aortic media may lead arterial stiffening by a number of different mechanisms, including changes in the amount and nature of ground substance, irreversible damage to elastic fibres and changes in smooth muscle tone. However, to date there are no data available on the relationship between aortic stiffness and degree of aortic inflammation.

Calcification is another potential mechanism behind inflammation-induced arterial stiffness. Inflammatory cytokines can lead to phenotypic transformation of vascular smooth muscle cells, which increases bioapatite formation and therefore calcification.[70] Also, Fetuin-A, an endogenous inhibitor of vascular calcification, is down-regulated during inflammation and recently it has been demonstrated that Fetuin-A is an independent risk factor for progressive arterial stiffness.[71]

Another mechanism, which could be responsible for arterial stiffening during inflammation, is a change in the balance between elastin breakdown and synthesis. The release of matrix metalloproteinases (MMP) from the leukocytes can degrade elastin within the media and therefore result in arterial stiffening.[72] MMP synthesis is induced by CRP[73] and are up-regulated in patients with RA.[74–76] Moreover, Yasmin et al. demonstrated in 677 subjects, that MMP-9 levels are independently associated with aortic stiffness.[72] Results from a smaller study ($n = 213$) contradict these

**Table 1** Summary of studies investigating anti-inflammatory and cholesterol-reduction drugs for arterial stiffness reduction.

| Author | Year | Drug | Population | *n* | Effect on arterial stiffness |
|---|---|---|---|---|---|
| Tomochika[60] | 1996 | Pravastatin & Probucol | Familial hypercholesterolemia | 12 | ↓ |
| Muramatsu[61] | 1997 | Pravastatin | Hypercholesterolemia | 59 | ↓ |
| Smilde[88] | 2000 | Simvastatin & Atorvastatin | Familial hypercholesterolemia | 45 | ↓ |
| Leibovitz[89] | 2001 | Atorvastatin | Hypercholesterolemia | 17 | ↓ |
| Shige[90] | 2001 | Simvastatin | Hypercholesterolemia | 20 | ↓ |
| Ferrier[91] | 2002 | Atorvastatin | Isolated systolic hypertension | 22 | ↓ |
| Ichihara[92] | 2002 | Fluvastatin | End-stage renal disease & diabetes type 2 | 22 | ↓ |
| Raison[93] | 2002 | Atorvastatin | Hypercholesterolemia & hypertension | 23 | ↑ |
| Karter[94] | 2003 | Atorvastatin | Hypercholesterolemia | 23 | ↓ |
| Kontopoulos[95] | 2003 | Atorvastatin | Hypercholesterolemia ± coronary heart disease | 36 | ↓ |
| Kosch[96] | 2003 | Fluvastatin | Renal transplant | 26 | = |
| Leibovitz[97] | 2003 | Atorvastatin & Amlodipine | Hypercholesterolemia & hypertension | 21 | ↓ |
| Stepien[98] | 2003 | Pravastatin | Hypercholesterolemia & healthy volunteers | 29 | = |
| Saliashvili[99] | 2004 | Simvastatin | Coronary artery disease | 10 | ↓ |
| VanDoornum[100] | 2004 | Atorvastatin | Rheumatoid arthritis | 29 | ↓ |
| Ichihara[101] | 2005 | Prava-, simva- & fluvastatin | Hypercholesterolemia & hypertension | 85 | ↓ |
| Matsuo[102] | 2005 | Cerivastatin | Hypercholesterolemia | 10 | ↓ |
| Shinohara[103] | 2005 | Atorvastatin | Hypercholesterolemia & diabetes | 22 | ↓ |
| VanDoornum[52] | 2005 | Anti-TNF | Rheumatoid arthritis | 14 | = |
| Vlachopoulos[27] | 2005 | Aspirin | Healthy volunteers— typhoid vaccine | 100 | ↓ |
| Yokoyama[62] | 2005 | Fluvastatin | Hypercholesterolemia | 40 | ↓ |

Table 1 (*continued*)

| Author | Year | Drug | Population | *n* | Effect on arterial stiffness |
|---|---|---|---|---|---|
| Maki-Petaja[31] | 2006 | Anti-TNF | Rheumatoid arthritis | 9 | ↓ |
| Protogerou[46] | 2006 | Corticosteroids | Bechet's disease | 74 | ↓ |
| Dogra[104] | 2007 | Atorvastatin & Gemfibrozil | Chronic kidney disease | 90 | ↓ |
| Efrati[105] | 2007 | Simvastatin | Hypercholesterolemia | 40 | ↓ |
| Maki-Petaja[106] | 2007 | Simvastatin & ezetimibe | Rheumatoid arthritis | 20 | ↓ |
| Pirro[107] | 2007 | Rosuvastatin & Diet | Hypercholesterolemia | 71 | ↓ |
| Wong[48] | 2007 | Indomethacin & rofecoxib | Rheumatoid arthritis | 37 | = |
| Cypiene[50] | 2007 | Anti-TNF | Rheumatoid arthritis | 15 | ↓ |
| Hongo[108] | 2008 | Fluvastatin | Coronary artery disease | 93 | ↓ |
| Mizuguchi[109] | 2008 | Pitavastatin | Hypercholesterolemia | 30 | ↓ |
| Pieringer[47] | 2008 | Prednisolone | Polymyalgia rheumatica | 13 | ↓ |
| Galarraga[51] | 2009 | Anti-TNF | Rheumatoid arthritis | 26 | ↓ |
| Meng[110] | 2009 | Atorvastatin | Coronary artery disease | 63 | ↓ |
| Miyashita[111] | 2009 | Pitavastatin | Diabetes type 2 | 45 | ↓ |
| Orr[112] | 2009 | Atorvastatin | Obese | 26 | ↓ |
| Angel[49] | 2010 | Anti-TNF | Inflammatory arthropathies | 35 | ↓ |
| Fassett[113] | 2010 | Atorvastatin | Chronic kidney disease | 37 | ↓ |
| Pieringer[53] | 2010 | Anti-TNF | RA and ankylosing spondylitis | 30 | = |

findings by reporting that there is a negative association between MMP-2 and -9 and aortic stiffness.[77] Nevertheless, Yasmin et al. demonstrated that aortic stiffness and elastase activity are influenced by MMP-9 gene polymorphisms, suggesting that the genetic variation in this protein may have a causal role in the process of large artery stiffening.[78]

Normal blood vessel walls are composed of endothelial cells, smooth muscles cells (SMC) and extracellular matrix (EMC). Healthy extracellular matrix is a complex collection of fibrous proteins and glycoproteins, which are embedded in a hydrated ground substance of glycosaminoglycans (GAG), such as hyaluronan and proteoglycans.[79] Hyaluronan

is a component of inflammatory process within the arterial wall. Tissue enriched with hyaluronan tends to trap water and swell, forming a viscous hydrate gel which allows ECM to resist compression forces.[80] These changes in hydration state can then potentially lead to stiffening of the arterial wall. Furthermore, inflammatory response initiates accumulation of monocytes and lymphocytes, followed by migration and proliferation of SMC.[81] This can lead to an increased accumulation of hyaluronan[80] and versican[79] around proliferation and migrating SMCs. Inflammation may stiffen the arterial also via smooth muscle cell proliferation directly and increased synthesis of collagen.[82]

Finally, inflammation can also stiffen arteries indirectly via endothelial dysfunction and therefore due to changes in smooth muscle tone.[82] Although the mechanism by which inflammation causes endothelial function is not completely understood, tetrahydrobiopterin ($BH_4$), a naturally occurring essential co-factor for endothelial nitric oxide synthase (eNOS)[83] is thought to play an important role. Recent, *in vitro* studies, suggest that activation of inducible NOS (iNOS) may lead to endothelial dysfunction by depleting the bioavailability of $BH_4$ from eNOS and subsequently uncouple eNOS, resulting in production of superoxide ($O_2^-$) rather than NO.[84–86] When $O_2^-$ reacts with NO *in vivo*, peroxynitrite is formed, leading to oxidation of $BH_4$ and a reduction in the allosteric stability of eNOS, further uncoupling of eNOS. *Vice versa*, arterial stiffness may induce endothelial dysfunction by reducing the pulsatile perfusion, which subsequently results in a reduced NO production by eNOS.[13] Although an association between endothelial dysfunction and arterial stiffness has been demonstrated in numerous animal[87] and human studies,[16] the role of nitric oxide in regulating aortic stiffness remains controversial.

The mechanisms by which anti-inflammatory therapies lead to reduction of arterial stiffness can only be speculation at present. Reduction of systemic inflammation could lead to changes in the arterial wall composition and therefore to ameliorate stiffness. This process could involve any of the mechanisms discussed earlier, such as reduction of inflammatory cell infiltration within the media, reduction of MMP synthesis, state of vessel wall hydration or via improvement of endothelial function. Whereas, the mechanism behind the reduction of arterial stiffness with anti-lipideamic drugs could be explained by their anti-inflammatory effects or their ability to improve endothelial function.

## Conclusion

A strong body of evidence demonstrates that inflammation plays an important role in arterial stiffening. There are number of potential mechanisms by which inflammation could lead to arterial stiffening, suggesting that inflammation could provide a novel target for drug therapies in the concept of arterial stiffness reduction. Indeed, several small-scale interventional studies have demonstrated that inflammation-reduction, either by traditional anti-inflammatory drugs or with cholesterol-reduction therapies, with anti-inflammatory properties, ameliorates arterial stiffness in various patient groups. Nevertheless, large outcome studies are needed to establish whether a reduction in arterial stiffness with anti-inflammatory or cholesterol-reduction therapies translates to an improvement of cardiovascular outcome.

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