Mechanisms of post-intervention arterial remodelling

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Abstract

It has been appreciated over the past two decades that arterial remodelling, in addition to intimal hyperplasia, contributes significantly to the degree of restenosis that develops following revascularization procedures. Remodelling appears to be an adventitia-based process that is contributed to by multiple factors including cytokines and growth factors that regulate extracellular matrix or phenotypic transformation of vascular cells including myofibroblasts. In this review, we summarize the currently available information from animal models as well as clinical investigations regarding arterial remodelling. The factors that contribute to this process are presented with an emphasis on potential therapeutic methods to enhance favourable remodelling and prevent restenosis.

Keywords

Restenosis • Constrictive remodelling • Adaptive remodelling • ECM • EEL

1. Introduction

Atherosclerosis is pervasive and if untreated can lead to stroke, myocardial infarction, dialysis, or amputation. A frequent treatment of atherosclerosis is angioplasty; over two million percutaneous transluminal coronary angioplasties (PTCAs) are performed each year, representing one of the most common procedures in hospitals around the world. However, recurrent lumen narrowing (or restenosis) occurs in 30–50% of patients depending upon the artery treated, imposing a major limitation to the long-term success of these interventions.1,2 Restenosis post-vascular intervention is the sum of two processes: intimal hyperplasia, which is thickening of the tunica intima, and arterial remodelling, which results in a change in the size of the vessel. Arterial remodelling, which is the subject of this review, refers to a permanent change in artery diameter (as opposed to vasospasm or dilatation which produces a temporary change in artery size).

Innumerable studies have focused on the pathophysiology of intimal hyperplasia (see reviews).3–7 However, studies specifically dedicated to understanding the factors that produce arterial remodelling are less prevalent. Thus, the causes and pathophysiology of arterial remodelling have not been well delineated.8 In this review, we attempt to report and reconcile currently available information on the molecular factors and possible pathways that lead to vessel remodelling. In the past, the term ‘remodelling’ has been used casually, in some cases referring to lumen narrowing caused by neointimal growth. In the current review, we have strictly defined arterial remodelling as a permanent (rather than reversible) geometric change in the vessel wall unrelated to the thickness of the neointima. Specifically, remodelling has been assessed by measuring the cross-sectional area within the external elastic lamina (EEL) or the EEL circumference (Figure 1).

Vascular remodelling may occur with de novo atherosclerosis or following vascular interventions such as angioplasty or bypass, or with transplant vasculopathy, or following the creation of an arteriovenous fistula. The underlying cause of remodelling following each of these interventions may be different.9 However, many of the causative factors may be similar. Therefore, while this review focuses primarily on post-angioplasty remodelling, pertinent evidence obtained from remodelling from other pathological processes will also be discussed.

Following arterial interventions, remodelling of the vessel wall can be either constrictive or adaptive. Constrictive, inward, or negative remodelling often accompanies intimal hyperplasia in patients treated with angioplasty. Both constrictive remodelling and intimal hyperplasia lead to luminal narrowing and the two together can greatly enhance the development of restenosis. Growing evidence indicates that constrictive remodelling may be as important or even a more important contributor to restenosis than intimal hyperplasia.10–14 Post et al.15 found that in both the rabbit and the hypercholesterolaemic Yucatan micropig, constrictive remodelling was the most important

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determinant of the late lumen loss. In the clinical setting, this finding has been reinforced by studies employing intracoronary ultrasound\(^{16,17}\) as well as histopathological analysis of specimens removed from patients treated with angioplasty.\(^{18}\)

Alternatively, vessel enlargement, often denoted as adaptive, expansive, positive, or outward remodelling (Figure 1), has been observed in humans as a compensatory response to progressive growth of atherosclerotic plaques. This so-called Glagov phenomenon\(^{19}\) has stimulated widespread interest, since it is believed to postpone the development of a flow-limiting stenosis, although it is often inadequate to preserve luminal size. This same phenomenon is found in the setting of restenosis, as evidenced by an early study of an atherosclerotic rabbit model where vessel enlargement compensated for intimal formation following angioplasty.\(^{20}\) Prevention of lumen loss or even luminal enlargement after coronary balloon angioplasty has been achieved in animals by manipulating multiple factors including transforming growth factor beta (TGF-\(\beta_{1}\)),\(^{21-25}\) matrix metalloproteinases (MMPs),\(^{26-28}\) oxidative stress,\(^{29,30}\) smad3,\(^8\) or VEGF.\(^{31}\) These discoveries have raised the prospect that manipulating these factors might lead in the clinical setting to outward arterial remodelling resulting in effective therapeutic methods to ameliorate restenosis.

In this review, we will describe current understanding of the factors and mechanisms that produce remodelling and the switch that influences whether this process is constrictive or adaptive. We hope to provide a useful guide for future investigations into this process with the goal of identifying techniques that can harness remodelling and provide more effective methods of treating restenosis in patients following vascular interventions. We apologize for the inability to reference all the relevant publications due to limited space.\(^{32-34}\)

### 2. Current hypotheses regarding the pathophysiology of arterial remodelling

The events that control vascular remodelling remain poorly understood. While potentially all three layers of the vessel wall are involved, recent reports have suggested that remodelling is largely an adventitia-based process. The essential major players in arterial remodelling appear to be adventitial myofibroblasts as well as extracellular matrix (ECM).

The phenotypic conversion of fibroblasts to myofibroblasts is thought to be critical to this process and is considered by many as a hallmark of arterial remodelling following revascularization procedures.\(^{33-35}\) Myofibroblasts in turn produce and modify adventitial extracellular matrix. They also secrete pro-inflammatory factors, and alter tensile force. All of these are characteristic remodelling events.\(^{34}\) One hypothesis is that myofibroblasts interconnect by binding or ‘anchoring’ to ECM proteins such as collagen through integrins on the cell surface; thus, contraction of the myofibroblasts creates a constrictive band via their collagen interconnections that narrows the artery and the arterial lumen.\(^{33}\) Indeed, modulation of integrin expression has been reported to be associated with changes in vessel size.\(^{27}\) More investigations into the role of the myofibroblasts–ECM interaction in arterial remodelling are needed.

Because remodelling occurs well after the proliferation of myofibroblasts, it has been proposed that modification of the ECM plays an important role in injury-induced remodelling.\(^{14,32,34}\) The adventitial ECM is a reinforced composite of collagen and elastin fibres embedded in a viscoelastic gel of proteoglycans, hyaluronan, and water.
together with a wide assortment of glycoproteins. These structurally varied components interact by entanglement and cross-linkages to form a bioactive polymer which, in part, regulates the biomechanical properties of the arterial wall. It is thus conceivable that changes either in the abundance, interaction, or organization of these ECM components may contribute to vascular remodelling.

Collagen is a major ECM protein, which normally comprises 20–30% of the vascular protein content. Although both fibroblasts and smooth muscle cells (SMCs) produce collagen, fibroblasts, especially myofibroblasts, have been found to produce greater quantities of collagen than SMCs in balloon-injured arteries. Many studies have suggested that collagen plays an important role in arterial wall remodelling (see reviews). Alterations in adventitial collagen content have been observed after angioplasty, which may result from both changes in synthesis as well as degradation.

It has been hypothesized that excess collagen may form a constrictive band that shrinks the arterial wall. Indeed, in some studies, it has been observed that collagen is up-regulated in vessels affected by constrictive remodelling. In support of this hypothesis, several investigators have shown that down-regulation of collagen in vessels treated with angioplasty results in adaptive remodelling. However, the opposite finding has also been reported; that is, increased collagen levels in the vessel wall have been associated with adaptive remodelling after balloon injury. The concordant hypothesis is that collagen deposition in the ECM produces a scaffold holding the artery wall in place, thus preventing it from shrinking. Adding to the controversy are reports showing no change in collagen content associated with adaptive or constrictive remodelling. Finally, there are examples of adventitial accumulation of collagen after vascular injury with no effect on vessel remodelling. In a study using a MMP-9 knockout mouse, elevated adventitial collagen content in the ligated carotid artery was associated with no change in the vessel EEL. These conflicting reports highlight the fact that the effect of collagen content on arterial remodelling remains undefined.

An alternative hypothesis is that not collagen content, but rather collagen cross-linking or the manner in which collagen molecules are compacted may be the determinant of arterial remodelling. In support of this hypothesis, administration of an inhibitor of collagen cross-linking (b-amino propionitrile) resulted in significant adaptive remodelling in the balloon-injured rabbit femoral vessel. Moreover, cystamine, an inhibitor of tissue transglutaminases (TTGs) which catalyze the crosslink of ECM proteins (including collagen), also produced enlargement of the EEL.

There are multiple subtypes of collagen and thus collagen type may be another important factor influencing the effect of collagen on arterial remodelling. Among the collagen subtypes, collagen type 1 (CN1) and type 3 (CN3) are generally considered to be most relevant to arterial remodelling. Whereas CN1 is rigid in nature, CN3 is more elastic. Whether differential production of CN1 vs. CN3 plays an important role in this process remains to be elucidated. However, based on the aforementioned published data, it is reasonable to propose that the gross amount of collagen in the arterial wall is not the sole determinant of remodelling. Possibly following arterial injury, collective changes in collagen content, cross-linking, compaction of collagen fibrils, or also the distribution of collagen type may determine the final vessel geometry.

In addition to collagen, other ECM components, including fibronectin and elastin, have also been implicated as contributors to arterial remodelling. Application of an inhibitor of fibronectin polymerization to the ligated mouse carotid artery resulted in a significant diminution in the EEL. In a pig model of PTCA, VEGF165 gene transfer was associated with an increase in adventitial elastin and vessel enlargement.

It has been well documented that the injury that follows vascular intervention such as angioplasty initiates an inflammatory response that constitutes an integral part of the remodelling processes. Also an important consequence of arterial injury is the production or activation of growth factors, cytokines, and a number of intracellular signalling pathways in both SMCs as well as fibroblasts. The consequence of at least some of these events may be the modification of adventitial ECM and stimulation of myofibroblasts leading to vessel remodelling (Figure 2). In the following section, we summarize the effects of various growth factors, proteolytic enzymes, and signalling molecules on injury-initiated arterial remodelling based on a broad range of published data. We have attempted to extract common themes about various factors that are particularly relevant to the remodelling process. Meanwhile, we also highlight areas of controversy that require additional study. It is clear from our analysis of the literature that the pathophysiology of arterial remodelling is far from completely defined.

3. Major factors participating in arterial remodelling

3.1 TGF-β1

It is generally accepted that the TGF-β family, especially TGF-β1, plays a pivotal role in arterial remodelling. TGF-β1 is a potent multifunctional regulator of a variety of vascular cellular activities, including SMC proliferation, ECM production, phenotypic conversion of adventitial fibroblasts to myofibroblasts, as well as others. Active TGF-β1 initiates cell signalling by binding to the TGF-β1 receptor type II (TβR-II), which then recruits TGF-β1 receptor type I (TβR-I). This heterotetrameric receptor complex results in activation of intracellular serine-threonine kinases on TβR-II and TβR-I, and in turn facilitates phosphorylation of Smad proteins, which represent the principal TGF-β1 signalling pathway. Phosphorylated Smad2 and Smad3 form a complex with Smad4, and this complex translocates to the nucleus regulating gene expression by interacting with transcription factors or binding directly to DNA. Alternatively, TGF-β1 may signal through Smad-independent pathways involving p38 MAPK, JNK, and protein kinase C.

A wealth of information is available regarding the mechanisms by which TGF-β1 regulates neo-intimal formation (see reviews). In contrast, much less is known about the precise role of TGF-β1 signalling in post-angioplasty/injury arterial remodelling. TGF-β1 expression has been shown to be up-regulated in balloon catheter-injured carotid or coronary arteries in both animal models as well as in human restenotic vessels (see review). Consequently, considerable effort has been invested in exploring the relationship between TGF-β1 and intimal hyperplasia (or vessel remodelling) by employing agonists or antagonists of TGF-β1 in experimental models of angioplasty. As summarized in Table 1, inhibition of TGF-β1 activity using a soluble form of TβR-I, or expression of TGF-β3 or Smad7, all antagonists of TGF-β1 signalling, has been found to attenuate constrictive remodelling. Consistent with these findings, overexpression of TGF-β1 resulted in a reduction in EEL in a porcine angioplasty model. These
data strongly suggest that TGF-β1 is a potent contributor to constrictive remodelling.

Conversely, overexpression of Smad3, the primary signalling mediator for TGF-β1, in a rat carotid balloon injury model, resulted in arterial expansion rather than constriction.8 The authors postulated that this effect of Smad3 on adaptive remodelling may be mediated by connective tissue growth factor (CTGF), production of which is enhanced in response to TGF-β1/Smad3 signalling. In line with this hypothesis, periadventitial application of CTGF mimicked the effect of TGF-β1/Smad3 on adaptive remodelling.8 However, in a study where Smad3 knockout mice were used, arterial injury resulted in adaptive rather than constrictive remodelling.41 Of note in this model, Smad3 was universally deficient in all cells, whereas in the overexpression studies, Smad3 was manipulated in the arterial wall only. Nevertheless, the precise effect of Smad3 on remodelling remains unclear.

In sum, there is substantial evidence that the cytokine, TGF-β1, plays an active role in producing constrictive remodelling. However, in the presence of elevated levels of Smad3, this effect may be reversed. TGF-β1 has many downstream effects that have the potential to affect arterial remodelling (Figure 2). MMPs appear to be integral to remodelling, and accumulating evidence suggests that MMPs are downstream targets of the TGF-β1 signalling.2 However, very little information is currently available regarding the molecular details of the TGF-β1/MMP axis in arterial remodelling.
3.2 MMPs and TTGs

It is clear that adventitial extracellular matrix, particularly collagen, plays an important role in vascular remodelling. The family of MMPs is capable of degrading all components of the ECM, suggesting a potentially important role for MMPs in the remodelling process. The activity of MMPs is controlled at different levels, including transcription, activation of zymogens, and interaction with specific inhibitors, such as tissue inhibitor of metalloproteinases. Within the MMP family, MMP-2 and MMP-9 have attracted particular interest in relation to vascular remodelling, due to their expression by SMCs and their ability to breakdown components of the basement membrane and collagen. While expression of MMP-2 can be detected in the normal media, MMP-9 expression becomes apparent only after injury or an inflammatory stimulus.38

In a rat carotid balloon angioplasty model, MMP-9 overexpression was found to reduce lumen loss by promoting adaptive remodelling (Table 2).39 Consistent with this result, in a carotid ligation mouse model, in ApoE knockout mice vs. wild type, there was an increase in macrophage foam cells, enhanced MMP-9 activity, and also enhanced adaptive remodelling.40 These studies have led to the hypothesis that enhancement of MMPs accelerates breakdown of adventitial ECM, thus relieving the constraint provided by extracellular matrix on vessel enlargement. However, the reports have not been consistent. In a model of balloon angioplasty in the Yucatan micropig iliac artery,41 or in a rat carotid artery injury model,42 administration of an MMP inhibitor, Batimastat, promoted adaptive rather than constrictive remodelling of these injured vessels. In a porcine femoral balloon injury model, a different MMP inhibitor (Marimastat) also promoted adaptive remodelling.28 Moreover, in a recent study in the balloon-injured rabbit iliac artery, suppression of MMP-2 activity by low-dose bacterial endotoxin resulted in adaptive remodelling.43 Specifically evaluating MMP-9, Galis et al.44 compared arterial remodelling in a rat carotid ligation model in MMP-9 knockout vs. wild-type mice. There was increased accumulation of adventitial collagen in knockout mice; however, arterial remodelling was unchanged in knockout vs. wild type. Thus, the question still remains as to whether MMPs through their effects on ECM lead to adaptive or constrictive remodelling. The discrepancy between these studies highlights the complexity of the relationship between the ECM and arterial remodelling, which defies an oversimplified theory.

In contrast to the activity of MMPs, which enhance ECM degradation, TTGs catalyze protein cross-linking and ECM protein binding, Bakker et al.45 have shown that treatment with cystamine, a TTG blocker, resulted in increased EEL perimeter of the mesenteric artery in a rat ligation model. An interesting question that remains unsolved is whether TTG’s effect on vascular remodelling in this model is through regulation of collagen cross-linking and organization.

The aforementioned studies suggest that both MMPs and TTGs play an important role in the composition and organization of vascular ECM and thus both have the potential to influence vascular remodelling. It is also known that growth factors such as TGF-β1 and PDGF modulate the activities of both of these proteins (see review).46 Although the intermediates between growth factors and the ECM are not well understood, some signalling molecules, in particular nitric oxide (NO), are believed to play an important role.47 For example, NO has been shown to modulate the process of vessel remodelling by altering the production of both TTGs and MMP.48,49

3.3 Nitric oxide

The role of NO in arterial remodelling has been evaluated using balloon angioplasty, fistula as well as ligation models. These studies collectively suggest that NO promotes arterial remodelling in the form of vessel expansion. In a rabbit carotid balloon injury model, Bosmans et al.45 have shown that perivascular application of L-arginine, which generates NO, results in an increase in EEL while also suppressing neointimal growth (Table 3). Moreover, an inhibitor of NO synthesis, nitroarginine methyl ester (NAME), has been reported to produce constrictive remodelling in a rabbit fistula model connecting the common carotid artery and the jugular vein.50 Reinforcing these findings and supporting a role for NO in vessel adaptive remodelling, studies conducted with either nNOS knockout51 or n/i/eNOS triple knockout mice52 revealed a decrease in the EEL area following carotid artery ligation. Moreover, a study has been carried out to compare differential roles of iNOS and eNOS in protection against restenosis using the carotid ligation model.53 Interestingly, in iNOS knockout mice, constrictive remodelling but not intimal hyperplasia was exacerbated when compared with the wild type, whereas in the eNOS knockout, intima thickening rather than constrictive remodelling was increased. The findings are not all consistent; in a rat carotid balloon injury model, an nNOS inhibitor, 7-nitroindazole, accentuated arterial remodelling, while also promoting adaptive remodelling.54 The majority of studies have shown NO to be effective at suppressing intimal thickening while also promoting adaptive arterial remodelling.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Model</th>
<th>Injury site</th>
<th>Method</th>
<th>Neo-intima</th>
<th>EEL/IEL</th>
<th>Lumen loss</th>
<th>CN</th>
<th>Remodelling</th>
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<td>Balloon</td>
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<td>↑IEL</td>
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<td>↑CSA</td>
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<td>↓, Cystamine (TTG inhibitor)</td>
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<td>Mesentric</td>
<td>Ligation</td>
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<td>↑EEL</td>
<td>Adaptive</td>
<td>43</td>
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↑ and ↓, up and down regulation of the activity or expression of MMPs. A Elevated MMP-9 activity due to the increase of macrophages. B MMP inhibitors. C Low dose of bacterial endotoxin suppressed the MMP-2 activity.
There is a great deal known about the mechanism behind NO’s role as a vasodilator. In contrast, very little is known about the biological interplay of NO with the factors that lead to adaptive remodelling. It is conceivable that NO contributes to arterial remodelling through activation of MMPs, inhibition of TTG activity, or reaction with superoxide.

### 3.4 Oxidative stress

Oxidative stress is a general term used to describe the steady-state level of oxidative damage in a cell, tissue, or organ, caused by reactive oxygen species (ROS). ROS levels in the adventitia of the porcine coronary artery increase substantially following balloon injury. Moreover, increased oxidative stress has correlated positively with the development of restenosis. Antioxidants have been shown to reduce restenosis; it has been demonstrated that the beneficial effects of antioxidants on restenosis are at least in part attributable to adaptive remodelling of the vessel wall. For example, Nunes et al. found that the combined use of vitamins C and E reduced the lumen loss without modifying the degree of intimal hyperplasia after balloon injury in a porcine model (Table 4). Using a rabbit angioplasty model, Durand et al. have shown that local expression of antioxidant enzymes, superoxide dismutase (SOD) and catalase, reduced ROS production and constrictive remodelling of the iliac artery. Importantly, based upon the data from patients treated with coronary balloon angioplasty, Probucol, a strong antioxidant agent which was given preoperatively, reduced restenosis by preventing constrictive remodelling. These studies together suggest a beneficial effect of antioxidants in that they promote adaptive remodelling or at minimum they prevent constrictive remodelling. Another interesting example is haem oxygenase-1 (HO-1), a vascular protective enzyme with potent anti-inflammatory and anti-oxidant effects. A recent study revealed a strong association between HO-1 promoter polymorphism and restenosis in patients undergoing femoropopliteal balloon angioplasty. This association was absent in the patients with stent implantation. Because restenosis after stenting is mainly due to in-stent neointimal hyperplasia, the authors speculated that the beneficial effects of HO-1 after balloon angioplasty were mainly due to an attenuation of constrictive remodelling.

### 3.5 Other factors

Multiple factors have been evaluated with regard to their ability to affect restenosis. Most often, the primary outcome measured has been intimal thickness or intimal hyperplasia. Vessel size or arterial remodelling are less frequently assessed. We have, however, searched for additional factors beyond those already discussed, effects of which on arterial remodelling have been assessed (Table 5). In a pig PTCA model, VEGF gene transfer to the adventitia prevented the lumen loss by inducing adaptive remodelling. In another study in pigs, HO-1 gene transfer into the injured femoral artery effectively reduced intimal hyperplasia, but did not alter the EEL area when compared with control. Thus, more thorough investigations are needed to further elucidate the role of HO-1 in remodelling. Nevertheless, the role of antioxidants in the treatment of vascular disease remains controversial without a solidly demonstrable benefit. In terms of mechanism, it is worth noting that simultaneous production of superoxide and NO generates peroxynitrite that activates latent MMPs, suggesting a relationship between three of the factors that have been shown to regulate arterial remodelling.

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**Table 3 Effects of NO on remodelling**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Model</th>
<th>Injury site</th>
<th>Method</th>
<th>Neo-intima</th>
<th>EEL/IEL</th>
<th>Lumen loss</th>
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<td>↔</td>
<td></td>
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</table>

↑ and ↓, up and down regulation of NO production. L-NAME, nitro-L-arginine methyl ester, an inhibitor for NO synthesis. †7-nitroindazole.

**Table 4 Effects of oxidative stress on remodelling**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Model</th>
<th>Injury site</th>
<th>Method</th>
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<th>Lumen loss</th>
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<td>↑ EEMa</td>
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<td>↑ EEL</td>
<td>↓b</td>
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</tbody>
</table>

↓, reduction of oxidative stresses. *EEM, external elastic membrane, a parameter used in ultrasound studies that equates EEL. †Decrease of collagen density.
change in EEL.\(^{67}\) It will be worthwhile in the future to address whether ADAMTS subtypes have differential effects on remodelling. Two physiologically important plasminogen activators, the tissue type (tPA) and the urokinase type (uPA), have been identified, both up-regulated following balloon injury of the rat carotid artery. Interestingly, while perivascular administration of recombinant tPA to the injured vessel produced adaptive remodelling, recombinant uPA had an opposite effect.\(^{68}\)

There are a number of cytokines, growth factors, and enzymes that have the potential to alter the levels of MMPs, NO, and ROS, and theoretically any of these could affect arterial remodelling. For example, treatment of the injured rat carotid artery with IGF-1 has been found to stimulate eNOS expression.\(^{69}\) Thus, it is not unreasonable to speculate that IGF-1 may modulate arterial remodelling via the NO pathway. As more studies are performed to elucidate the specific contribution of the individual factors to arterial remodelling, additional targets are expected to emerge which will potentially afford new therapeutic solutions.

### 4. Potential opportunities and challenges in therapeutic targeting of arterial remodelling

Currently, the only clinically available effective treatments of restenosis are rapamycin- and paclitaxel-coated stents. However, when stents are used, arterial remodelling becomes irrelevant, since the stent fixes and prevents modification of the absolute vessel diameter.\(^{62}\) Other methods of drug delivery are rapidly coming to fruition including drug-coated balloons where adaptive remodelling could play an important role in the eventual outcome of these interventions. Moreover, external or perivascular application of drugs following surgical bypass or endarterectomy is an additional approach, through which the treatments that effect adaptive remodelling could be beneficial. Interestingly with this approach, drug is delivered directly to the vessel adventitia with the potential of having a profound effect on adaptive remodelling. Combination drug therapy as a treatment of restenosis is appealing, if two drugs with different and potentially synergistic effects can be combined. One could imagine a drug that inhibits intimal hyperplasia and a second that stimulates adaptive remodelling would have a powerful combined effect on restenosis.

It is worth noting that most of the therapeutic trials thus far have had the degree of intimal thickening as their primary target. Measures of adaptive or constrictive remodelling from the clinical setting are largely lacking. However, as the importance of remodelling in cardiovascular diseases is increasingly recognized, there is likely to be growing interest in targeting the regulatory factors to either reduce constrictive or promote adaptive remodelling. Locally modifying factors such as TGF-\(\beta\), MMPs, NO, or ROS may represent useful strategies to treat restenosis through attenuation of vessel constriction. Although currently there are no drugs that are clinically used to specifically target the remodelling process, encouraging studies have emerged, such as a report on Probuloc, an antioxidant, that has been shown to reduce constrictive remodelling following angioplasty when taken pre-operatively by patients.\(^{50}\) In addition, based upon animal studies, some TGF-\(\beta\)-inhibiting agents and MMP-9 inhibitors, NO donors, and antioxidants should be considered possible therapeutics targeting arterial remodelling. In the future, more clinical trials are warranted to identify drugs that can positively and effectively influence the remodelling process.

In spite of the positive remodelling effects of treatments targeting the molecular factors listed in Tables 1–5, great challenges exist in translating positive pre-clinical results into clinically successful therapies.

For example, there is likely a strong relationship between intimal hyperplasia and vessel remodelling. In fact, vessel enlargement may be an adaptive response to intimal hyperplasia (i.e. the vessel’s way of compensating for the luminal narrowing produced by intimal thickening). It may well be that adaptive remodelling occurs only after signals are released from the intimal plaque. Inevitably, the two processes are closely tied together; e.g. up-regulation of the TGF-\(\beta\) signalling protein, Smad3, has been shown to produce adaptive remodelling while also inducing intimal growth.\(^{68}\) It should also be appreciated that the molecular factors involved in arterial remodelling are often multifunctional and exert differential actions on many cell types throughout the arterial wall. Thus, either precisely controlled local drug delivery to the adventitia or drugs that discriminate vascular cell types may be critical in selective modification of vessel wall geometry. Lastly, crosstalk among pathways may play an important role in the remodelling process; manipulation of one portion of the process may affect another. For example, drugs that produce collagen breakdown have been shown to be favourable for adaptive remodelling in some angioplasty models.\(^{69}\) However, collagen degradation products are potent stimuli for monocytes and myofibroblasts, both of which contribute to constrictive remodelling.\(^{32}\) There is little doubt that arterial remodelling is a very complex process, the mechanism of

### Table 5 Miscellaneous factors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Model</th>
<th>Injury site</th>
<th>Method</th>
<th>Neo-intima</th>
<th>EEL/IEL</th>
<th>Lumen loss</th>
<th>CN</th>
<th>Remodelling</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑:VEGF</td>
<td>Pig</td>
<td>Coronary</td>
<td>Balloon</td>
<td></td>
<td>↑ EEL</td>
<td>↓</td>
<td>↑</td>
<td>Adaptive</td>
<td>(^{31})</td>
</tr>
<tr>
<td>↓:Eplerenone(^a)</td>
<td>Micro-pig</td>
<td>Coronary</td>
<td>Balloon</td>
<td>≪</td>
<td>↑ EEL</td>
<td>↓</td>
<td>↓</td>
<td>Adaptive</td>
<td>(^{40})</td>
</tr>
<tr>
<td>↓: (β-APN)(^b)</td>
<td>Micro-pig</td>
<td>Coronary</td>
<td>Balloon</td>
<td>↓</td>
<td>↓ EEL</td>
<td>↑</td>
<td>↓</td>
<td>Constrictive</td>
<td>(^{39})</td>
</tr>
<tr>
<td>↓:tPA(^c)</td>
<td>Rat</td>
<td>Carotid</td>
<td>Ligation</td>
<td></td>
<td>↑ EEL</td>
<td>↑</td>
<td>↓</td>
<td>Adaptive</td>
<td>(^{68})</td>
</tr>
<tr>
<td>↑:tPA(^d)</td>
<td>Rat</td>
<td>Carotid</td>
<td>Balloon</td>
<td>↑</td>
<td>↑ EEL</td>
<td>↑</td>
<td>↑</td>
<td>Adaptive</td>
<td>(^{68})</td>
</tr>
<tr>
<td>↑:ADAMTS-1</td>
<td>Mouse</td>
<td>Carotid</td>
<td>Ligation</td>
<td></td>
<td>↑ CSA</td>
<td>≪</td>
<td>↑</td>
<td>Adaptive</td>
<td>(^{66})</td>
</tr>
</tbody>
</table>

\(^a\)Eplerenone reduces collagen content by inhibiting mineralocorticoid receptors. \(^b\)β-APN, β-aminopropionitrile (inhibitor of collagen crosslinking). \(^c\)pUR4, inhibitor of fibronectin polymerization. \(^d\)Tissue-type plasminogen activator. \(^e\)Urokinase plasminogen activator.
which is far from defined. Consequently, we remain a distance away from translational therapies attaining beneficial vessel enlargement.

5. Conclusion

Growing evidence suggests that constrictive remodelling may be as much a culprit as intimal hyperplasia in producing permanent lumen loss after vascular interventions.10-11 In stark contrast to the weight of information that is available regarding intimal hyperplasia, the data on remodelling are limited and often can only be extracted from studies of restenosis with a focus on intimal hyperplasia. Nevertheless, in studies where arterial modelling has been assessed, several factors have been identified that have the potential to regulate this process. There is a growing appreciation that arterial remodelling is an adventitial process that is affected by both myofibroblasts as well as a host of ECM proteins, including collagen.34 Current evidence indicates that multiple factors are involved in post-intervention arterial remodelling. Rather than acting independently, these factors are likely to be interlinked through crosstalk between different pathways. Still, a great deal of controversy remains and there are many conflicting studies. Thus, there is great need and opportunity for future research in this interesting and important pathophysiological process that contributes to recurrent vascular disease.

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References


