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A chemomechanobiological model of the long-term healing response of arterial tissue to a clamping injury

Lauranne Maes¹, Julie Vastmans¹, Stéphane Avril² and Nele Famaey^{1,*}

¹Biomechanics Section, Department of Mechanical Engineering, KU Leuven, Leuven, Belgium

²Mines Saint-Etienne, Université de Lyon, Université Jean Monnet, INSERM, U 1059 SAINBIOSE, F-42023 Saint-Etienne, France

Correspondence*:

Nele Famaey

nele.famaey@kuleuven.be

2 ABSTRACT

3 Vascular clamping often causes injury to arterial tissue, leading to a cascade of cellular and
4 extracellular events. A reliable *in silico* prediction of these processes following vascular injury
5 could help us to increase our understanding thereof, and eventually optimize surgical techniques
6 or drug delivery to minimize the amount of long-term damage. However, the complexity and
7 interdependency of these events make translation into constitutive laws and their numerical
8 implementation particularly challenging.

9 We introduce a finite element simulation of arterial clamping taking into account acute endothelial
10 denudation, damage to extracellular matrix and smooth muscle cell loss. The model captures
11 how this causes tissue inflammation and deviation from mechanical homeostasis, both triggering
12 vascular remodeling. A number of cellular processes are modelled, aiming at restoring this
13 homeostasis, *i.e.* smooth muscle cell phenotype switching, proliferation, migration and the
14 production of extracellular matrix. We calibrated these damage and remodeling laws by comparing
15 our numerical results to *in vivo* experimental data of clamping and healing experiments. In these
16 same experiments, the functional integrity of the tissue was assessed through myograph tests,
17 which were also reproduced in the present study through a novel model for vasodilator and
18 -constrictor dependent smooth muscle contraction.

19 The simulation results show a good agreement with the *in vivo* experiments. The computational
20 model was then also used to simulate healing beyond the duration of the experiments in order
21 to exploit the benefits of computational model predictions. These results showed a significant
22 sensitivity to model parameters related to smooth muscle cell phenotypes, highlighting the
23 pressing need to further elucidate the biological processes of smooth muscle cell phenotypic
24 switching in the future.

25 **Keywords:** Smooth muscle cells (SMC), Phenotype switch, Vascular remodeling, Vascular clamping, Myograph, Finite elements

1 INTRODUCTION

26 Multiple studies indicate that arterial occlusion by almost any type of clamp systematically leads to intimal
27 injury at the site of application. For example, endothelial denudation is a widely known effect of clamping
28 (Geenens et al., 2016a; Slayback et al., 1976; Barone et al., 1989; Margovsky et al., 1997, 1999; Hangler
29 et al., 2008; Vural et al., 2008; Famaey et al., 2010; Geenens et al., 2016b). Several studies also report
30 damage to the extracellular matrix (ECM) in the media with flattened elastic lamellae (Geenens et al.,
31 2016a; Barone et al., 1989; Margovsky et al., 1999; Famaey et al., 2010). Moreover, healing after arterial
32 clamping usually implies some degree of inflammation and subsequent tissue remodeling (Geenens et al.,
33 2016a).

34 The tonicity of vascular smooth muscle cells (SMC) after clamping was also studied extensively (Barone
35 et al., 1989; Famaey et al., 2010; Geenens et al., 2016b). Experimental data on the effects of arterial
36 clamping were collected in mice (Geenens et al., 2016a,b). In this study, descending thoracic aortas were
37 clamped at different levels of loading. Then, the aorta was either excised immediately or excised after
38 a fixed duration of healing. After excision, rings were cut and tested with a myograph to measure the
39 vascular tone under vasoconstriction and vasodilatation stimulations, followed by histological analyses. An
40 acute decline of endothelium-dependent vasodilatation was observed just after clamping, but the functional
41 response was restored after one month (Geenens et al., 2016b). Arterial clamping was also followed by an
42 inflammatory response leading to some degree of fibrosis.

43 The role of mechanobiology in the response to arterial clamping is not clearly understood. It is known that
44 in many conditions, vascular remodeling is mediated by the mechanical stimuli sensed by vascular SMCs,
45 permitting to maintain wall stresses at homeostasis (Humphrey, 2002). SMCs modulate their phenotype in
46 response to changing local environmental cues (Epstein et al., 1994), possibly performing biosynthetic,
47 proliferative, and contractile roles in the vessel wall (Thyberg et al., 1995). Contractile SMCs react to
48 environmental changes on the short term by contracting and relaxing to restore a homeostatic state. On
49 the longer term, biosynthetic vascular SMC produce and degrade the extracellular matrix, thus enabling
50 growth and remodeling (Owens et al., 2004).

51 In order to decipher the role of mechanobiology in the response to arterial clamping, *in silico* predictive
52 models can be helpful. A number of computational models for damage through overloading of soft
53 tissues have been developed and tested by Balzani et al. (2006); Rodríguez et al. (2006); Peña (2011);
54 Gasser (2011); Balzani et al. (2012); Sáez et al. (2012); Forsell et al. (2013); Famaey et al. (2013);
55 Peña (2014); Schmidt and Balzani (2016); Li and Holzapfel (2019). Most of these models are based on
56 continuum damage mechanics (Kachanov, 1986; Simo and Ju, 1987), where the amount of damaged tissue
57 is determined by a damage parameter. These models were successfully applied to predict acute damage
58 after arterial clamping. However, most of them focused on short term fiber damage and modeled neither
59 the active behavior of vascular SMCs nor the healing process occurring on the longer term.

60 Modeling the active behavior of vascular SMCs has been a topic of extensive investigation (Murtada
61 et al., 2017), combining continuum mechanics (Murtada et al., 2010, 2012) and the kinetics of pathways
62 involved in the active behavior (Hai and Murphy, 1988; Schmitz and Böl, 2011; Bouklas et al., 2018; Böl
63 et al., 2012; Liu, 2014; Adachi and Kida, 2014; Ferreira et al., 2018), including phosphorylation of myosin
64 light chain, variations of intracellular calcium concentration and membrane depolarisation (Sharifimajd
65 and Stålhand, 2014). However, to our best knowledge, none of these models depend on the concentration
66 of specific vasoreactive agents used in myograph testing: phenylephrine (PE), acetylcholine (ACh) and
67 sodium nitroprusside (SNP) as nitric oxide (NO) donor.

68 Modeling vascular healing is also rather recent. Comellas et al. (2016) presented a computational model
69 of tissue healing after mechanical overload, in which temporal evolutions of damage are homeostasis-driven.
70 However, no discrimination was made between the different tissue constituents (elastin, collagen, cells) in
71 terms of damage and mechanical behavior. This can be addressed by microstructurally-motivated growth
72 and remodeling models based on the constrained mixture model introduced by Humphrey and Rajagopal
73 (2002). In the constrained mixture theory, the different constituents of the tissue are constrained to move
74 together in a mixture but all have different biologically relevant stress-free states. Tissue remodeling is
75 governed by laws of production and degradation for each constituent based on stress states. This type
76 of model has been used to predict different tissue adaptations such as aneurysm growth for instance by
77 Mousavi et al. (2019); Latorre and Humphrey (2018b); Famaey et al. (2018); Braeu et al. (2017); Cyron
78 et al. (2016); Watton and Hill (2009); Zeinali-Davarani and Baek (2012); Baek et al. (2006); Valentín et al.
79 (2013); Alberto Figueroa et al. (2009) or wound healing by Zuo et al. (2020). However, to the best of our
80 knowledge, the constrained mixture theory has never been used to model healing after arterial clamping.

81 In the present work, we aim to computationally capture the mechanobiological effects of arterial clamping.
82 Therefore, we introduce a chemomechanical model in a constrained mixture framework, considering
83 inflammation, collagen deposition, SMC proliferation, SMC active response as well as SMC switch from
84 contractile to synthetic phenotype, all depending on the mechanical and chemical environment. After
85 introducing the details of the model, we simulate the response to arterial clamping after one and two months
86 of healing and compare the results to experimental data.

2 MATERIALS AND METHODS

87 2.1 Mouse experiments

88 As reported by Geenens et al. (2016a), 108 wildtype mice were subjected to a surgical procedure, in
89 which the descending thoracic aorta was isolated and clamped *in vivo* with a non-serrated, 2 mm wide
90 clamp at either a loading level of 0.0 N (control group), 0.6 N or 1.27 N. The clamped tissue was then either
91 immediately excised, or *in vivo* healing was allowed for 6 hours, 2 weeks or 1 month. After these four
92 time points, histological analyses were carried out to assess the structural integrity of the tissue through
93 CD105, CD45, Verhoeff's-Van Gieson and osteopontin - α -SMA stainings. After the immediate excision
94 or after 1 month, myograph tests were carried out to assess the functional integrity of the tissue. The aorta
95 segment was mounted onto two rods in an organ bath and, upon stretching of the tissue, a stable preload
96 of 20 mN was reached. Afterwards, the vasoactive substances PE, ACh and SNP were subsequently
97 added to the solution to assess endothelium dependent and independent vasodilation. In total, all mice that
98 underwent surgery were divided into eighteen groups corresponding to a particular condition, depending
99 on the clamping force and the healing time, and on the type of assessment, *i.e.* histology or myograph.
100 More details on these animal experiments are given in Geenens et al. (2016a).

101 2.2 Constitutive model

102 2.2.1 Passive material behavior

103 The anisotropic and nonlinear passive mechanical behavior of arterial tissue is often represented by
104 a Gasser-Ogden-Holzapfel (Gasser et al., 2006) hyperelastic formulation. The deviatoric strain energy
105 function is decomposed in an isotropic Neo-Hookean part, representing the elastin fibers in the tissue,
106 and an exponential, anisotropic part, representing two collagen fiber families running in two symmetric
107 directions. Assuming a fully incompressible material and ignoring the volumetric contribution, the strain

108 energy function of the elastin and collagen contribution is respectively written as

$$\begin{aligned}\hat{\Psi}^{elas} &= C_{10}(\bar{I}_1^{elas} - 3), \\ \hat{\Psi}_i^{coll} &= \frac{k_1}{2k_2} \exp \left\{ k_2 [(\kappa \bar{I}_1^{coll} + (1 - 3\kappa) \bar{I}_i^{coll}) - 1]^2 \right\} - 1, \quad i = 4, 6,\end{aligned}\quad (1)$$

109 where C_{10} and k_1 represent the stiffness of elastin and collagen. k_2 determines the exponential collagen
110 behavior and κ quantifies the fiber dispersion. \bar{I}_1^{elas} and \bar{I}_1^{coll} are the first invariants or traces of the
111 deviatoric right Cauchy-Green stretch tensors $\text{tr}(\bar{\mathbf{C}}^{elas}) = \text{tr}(J^{-2/3} \mathbf{F}^{elasT} \mathbf{F}^{elas})$ and $\text{tr}(\bar{\mathbf{C}}^{coll}) =$
112 $\text{tr}(J^{-2/3} \mathbf{F}^{collT} \mathbf{F}^{coll})$, where \mathbf{F}^{elas} and \mathbf{F}^{coll} are the deformation gradients of elastin and collagen
113 respectively and J is the Jacobian of the deformation gradient \mathbf{F} . More information on these different
114 deformation gradients follows in section 2.2.4. \bar{I}_4^{coll} and \bar{I}_6^{coll} are the fourth and sixth invariants of $\bar{\mathbf{C}}^{coll}$
115 and \mathbf{M}_i , representing the stretch along the preferred fiber direction, written as

$$\bar{I}_i^{coll} = \mathbf{M}_i \cdot (\bar{\mathbf{C}}^{coll} \mathbf{M}_i), \quad i = 4, 6, \quad (2)$$

116 with \mathbf{M}_i the undeformed fiber vector defined by the fiber angle α_i with respect to the circumferential
117 direction. Therefore, $\mathbf{M}_i = [0 \cos \alpha_i \sin \alpha_i]^T$, assuming that the radial direction is the first direction, the
118 circumferential direction the second and the axial the third.

119 2.2.2 Active material behavior

120 Contractile SMCs in the media actively generate vascular tone. An active component to the strain energy
121 function, as described by Murtada et al. (2010) and used by Famaey et al. (2013) takes the form

$$\hat{\Psi}^{csmc} = \frac{\mu_{smc}}{2} (n_3 + n_4) \left(\sqrt{\bar{I}_4^{smc}} + u_{rs} - 1 \right)^2, \quad (3)$$

122 where μ_{smc} is a stiffness-like material parameter, n_3 and n_4 together are the fractions of the smooth muscle
123 filaments in the force-producing states. u_{rs} represents the normalized sliding between the filaments arising
124 from the difference between the stress in the surrounding matrix P_{mat} and the driving stresses of the cross-
125 bridges of the filaments P_{smc} . Murtada et al. (2010) give an in-depth explanation of these variables. This is
126 also further elaborated in section 2.5. \bar{I}_4^{smc} is the fourth invariant of \mathbf{M}_{smc} and $\bar{\mathbf{C}}^{smc} = J^{-2/3} \mathbf{F}^{smcT} \mathbf{F}^{smc}$,
127 the deviatoric right Cauchy-Green stretch tensor of the smooth muscle fibers associated with the smooth
128 muscle deformation gradient \mathbf{F}^{smc} . \bar{I}_4^{smc} can be written similarly to equation 2, where \mathbf{M}_{smc} represents
129 the orientation of the cells. Assuming that the cells are aligned along the circumferential direction, we
130 write $\mathbf{M}_{smc} = [0 \ 1 \ 0]^T$.

131 2.2.3 Strain energy function

132 Similarly to Famaey et al. (2018), the overall strain energy density stored in the material is calculated
133 with a mass-averaged rule as

$$\begin{aligned}\Psi &= \Psi^{elas} + \Psi^{coll} + \Psi^{csmc} \\ &= \rho^{elas}(k) \hat{\Psi}^{elas}(k) + \sum_{\tau=0}^k \rho^{coll}(k, \tau) \hat{\Psi}_i^{coll}(k, \tau) + \rho^{csmc}(k) \hat{\Psi}^{csmc}(k),\end{aligned}\quad (4)$$

134 where $\rho^{elas}(k)$ represents the elastin density at the current time step k . $\rho^{csmc}(k)$ is the density of SMCs in
135 their contractile phenotype and $\rho^{coll}(k, \tau)$ is the density of collagen cohort τ . These considered densities

136 and constituent specific strain energy densities relate to the reference configuration. The deposition of
 137 collagen is discretized, such that different collagen cohorts can be identified, depending on the time of
 138 production. We consider all the initially present collagen as one cohort deposited at $k = 0$. On top of that,
 139 at every discrete time step, one cohort per collagen family is produced. At every time step, all existing
 140 cohorts, for example previously deposited at time step τ , are degraded through a slowly decaying survival
 141 fraction. In the present study, we consider two symmetric fiber families, each divided into $k + 1$ cohorts at
 142 every time step k .

143 **2.2.4 Deformation gradient**

144 The strain energy defined in equation 4 depends on the deformation gradients of the considered
 145 constituents. According to the constrained mixture growth and remodeling theory, the total deformation
 146 gradient of elastin \mathbf{F}^{elas} is written as

$$\mathbf{F}^{elas} = \mathbf{F}\mathbf{G}^{elas}, \tag{5}$$

147 where \mathbf{G}^{elas} is a deformation gradient containing the deposition stretches of elastin in the *in vivo*
 148 homeostatic reference state of the artery and \mathbf{F} represents any deformation of the mixture as a whole with
 149 respect to this reference.

150 The total deformation gradient of a certain collagen cohort τ is

$$\mathbf{F}^{coll}(\tau) = \mathbf{F}\mathbf{F}_{dep}^{coll}(\tau)^{-1}\mathbf{G}^{coll}. \tag{6}$$

151 \mathbf{G}^{coll} represents the deformation of the collagen cohort at deposition. $\mathbf{F}_{dep}^{coll}(\tau)$ is the deformation of the
 152 mixture at the time of deposition with respect to the homeostatic reference state and \mathbf{F} is the current
 153 deformation. In a steady state regime, the deformation at deposition of all collagen still present is equal
 154 to the current deformation, such that $\mathbf{F}_{dep}^{coll} = \mathbf{F}$ and that \mathbf{F}^{coll} is simply equal to \mathbf{G}^{coll} , the collagen
 155 deposition stretch tensor. Collagen is assumed to be deposited at a constant stretch g^{coll} (Bellini et al.,
 156 2014) along the main fiber direction. Therefore, for a particular fiber direction \mathbf{M} (Cyron et al., 2016),

$$\mathbf{G}^{coll} = g^{coll}\mathbf{M} \otimes \mathbf{M} + \frac{1}{\sqrt{g^{coll}}}(\mathbf{I} - \mathbf{M} \otimes \mathbf{M}). \tag{7}$$

157 Contractile SMCs are assumed to only feel the deformation with respect to the state at which they were
 158 deposited. Therefore, their deformation gradient is

$$\mathbf{F}^{csmc}(\tau) = \mathbf{F}\mathbf{F}_{dep}^{csmc}(\tau)^{-1}, \tag{8}$$

159 where $\mathbf{F}_{dep}^{csmc}(\tau)$ is the deformation gradient of the mixture at the time of deposition τ of the considered
 160 cohort.

161 All deformations are considered fully incompressible. Moreover, volumetric changes due to mass addition
 162 or loss are neglected, such that no deformation is observed as a result of growth.

163 **2.3 Damage model**

164 Figure 1 gives an overview of the considered damage effects. A short-term damage model for contractile
 165 SMCs and collagen inspired by Famaey et al. (2013) and Balzani et al. (2006) is considered. The fraction
 166 of damaged cells is modeled as a damage parameter d^{csmc} , calculated as

$$d^{csmc} = 1 - \exp(-\beta/m^{csmc}), \tag{9}$$

167 where m^{csmc} is a damage constant and

$$\beta = \max abs(\lambda_{\theta\theta} - 1), \quad (10)$$

168 where $\lambda_{\theta\theta}$ is the local circumferential stretch with respect to the *in vivo* reference stretch, assuming that the
169 deformation gradient is known in a predefined local coordinate system whose axes are aligned with the
170 local radial, circumferential and axial directions.

171 The fraction of damaged collagen d^{coll} becomes

$$d^{coll} = 1 - \exp\left(-\Delta\zeta/m^{coll}\right), \quad (11)$$

172 where again m^{coll} is a constant. $\Delta\zeta$ is calculated as the difference between the current and homeostatic
173 fiber stresses (see also equation 13).

174 We assume that endothelium can be damaged as a result of overloading of the inner elastin of the media,
175 since the endothelium itself bears almost no load. As stated by Jufri et al. (2015), endothelial cells react
176 differently to physiological and pathological ranges of mechanical stretch, where the latter may induce
177 apoptosis (Kou et al., 2009). We therefore assume that the local endothelium dies if a certain threshold m^{ec}
178 of the local β is exceeded.

179 2.4 Remodeling model

180 A remodeling algorithm is defined considering six main components. In the following sections,
181 remodeling pathways are introduced for the two main passive load-bearing constituents elastin and collagen.
182 Two SMC phenotypes are considered, active load-bearing contractile cells and non-load-bearing synthetic
183 cells that produce extracellular matrix. We also consider the healing of the endothelium and the infiltration
184 of inflammatory agents. The scheme on figure 2 is an overview of the remodeling pathways with the
185 corresponding equations introduced in the following sections.

186 2.4.1 Elastin

187 We assume that the production or degradation of elastin is negligible over the considered time frame
188 and that new elastin cannot be produced. The elastin density at each time point is therefore equal to the
189 homeostatic density ρ_0^{elas} .

190 2.4.2 Collagen

191 The density at time step k of a collagen cohort deposited at time τ is (Famaey et al., 2018; Valentín et al.,
192 2013)

$$\rho^{coll}(k, \tau) = m^{coll}(\tau) q^{coll}(k, \tau). \quad (12)$$

193 $m^{coll}(\tau)$ represents the amount of collagen of the specified cohort at the time of deposition τ and $q^{coll}(k, \tau)$
194 is the fraction of this cohort that survives until time k .

195 The degradation of collagen depends on the current fiber stress. Upon discretization of equation 8 in
196 Famaey et al. (2018) or 53 in Valentín et al. (2013), the survival fraction of a certain collagen cohort is

$$q^{coll}(k, \tau) = \exp\left(-\sum_{\tilde{\tau}=\tau}^k K_{qh}^{coll} \Delta t \left(1 + \Delta\zeta(k, \tilde{\tau})^2\right)\right), \quad (13)$$

197 where K_{qh}^{coll} is the homeostatic decay constant and $\Delta\zeta(k, \tilde{\tau})$ represents the difference between the current
198 and homeostatic fiber stresses as defined in Famaey et al. (2018); Valentín et al. (2013).

199 The production of new collagen cohorts is proportional to the current density of synthetic cells. The rate
 200 at which they produce collagen depends on the presence of contractile cells and on the mechanical stimulus
 201 $\Delta\lambda$ felt by these latter cells. The production rate at time τ is written as

$$m^{coll}(\tau) = m_0^{coll}\Gamma(\tau), \tag{14}$$

202 where

$$\Gamma(\tau) = \left(1 + \frac{\rho^{csmc}(\tau)}{\rho_0^{csmc}} K_m^{coll} \Delta\lambda\right) \frac{\rho^{ssmc}(\tau)}{\rho_0^{ssmc}}. \tag{15}$$

203 ρ^{csmc} and ρ_0^{csmc} are the current and homeostatic densities of contractile cells and ρ^{ssmc} and ρ_0^{ssmc} are the
 204 corresponding densities of the synthetic cells. K_m^{coll} is a remodeling parameter and the mechanical criterion
 205 for remodeling is written as

$$\Delta\lambda = \lambda_{\theta\theta} - 1. \tag{16}$$

206 Note that $\Delta\lambda$ is very similar to β^{csmc} . It can however be positive or negative for circumferential stretch or
 207 compression respectively.

208 2.4.3 Contractile smooth muscle cells

209 Contractile SMCs dedifferentiate into synthetic cells upon mechanical triggering, for example as observed
 210 by Wang et al. (2018) or when losing grip to the surrounding extracellular matrix. We assume that these
 211 cells react to stretch in the circumferential direction as

$$\frac{d\rho^{csmc}}{dt} = -\Delta\lambda K_{dd}^{smc} \rho^{csmc}. \tag{17}$$

212 Through numerical integration, this becomes

$$\rho^{csmc}(k) = \rho^{csmc}(k-1) (1 - \Delta\lambda K_{dd}^{smc} \Delta t), \tag{18}$$

213 where K_{dd}^{smc} is a rate parameter for cell differentiation and Δt the considered time step. Regardless of
 214 this equation, the maximum relative amount of contractile cells $\rho^{csmc}/\rho_0^{csmc}$ is bounded by the relative
 215 amount of elastin $\rho^{elas}/\rho_0^{elas}$ since we assume that cells cannot be contractile if they are unable to grip the
 216 extracellular environment. The increase of contractile SMCs is also bounded by the available amount of
 217 synthetic cells to differentiate from.

218 2.4.4 Synthetic smooth muscle cells

219 Whereas contractile cells are quiescent in their normal state, synthetic SMCs are more proliferative (Hao
 220 et al., 2003). We therefore assume that their density can increase through dedifferentiation or proliferation
 221 based on the mechanical environment (Mantella et al., 2015). Moreover, their proliferation also increases
 222 as a reaction to inflammation (Yang et al., 2018). We write the evolution law of these cells as

$$\frac{d\rho^{ssmc}}{dt} = (\Delta\lambda K_{pl}^{smc} + K_{ic}^{smc} \phi^{ic}) \rho^{ssmc} + \Delta\lambda K_{dd}^{smc} \rho^{csmc}. \tag{19}$$

223 Therefore, in discretized form, the current synthetic cell density is

$$\rho^{ssmc}(k) = \rho^{ssmc}(k-1) (\Delta\lambda K_{pl}^{smc} \Delta t + 1 + K_{ic}^{smc} \Delta t \phi^{ic}) + \rho^{csmc}(k-1) - \rho^{csmc}(k), \tag{20}$$

224 where K_{pl}^{smc} and K_{ic}^{smc} are rate parameters related to the mechanical and inflammatory stimulus respectively
 225 and ϕ^{ic} is the current fraction of inflammation.

226 2.4.5 Endothelial cells

227 After degradation, the endothelium heals following the logistic growth law

$$\frac{d\phi^{ec}}{dt} = K^{ec} (1 - \phi^{ec}) \phi^{ec} \quad (21)$$

228 or

$$\phi^{ec}(k) = (K^{ec} \Delta t (1 - \phi^{ec}(k-1)) + 1) \phi^{ec}(k-1), \quad (22)$$

229 in which K^{ec} is a rate parameter and ϕ^{ec} is the total fraction of endothelium present. $\phi^{ec} = 1$ means that
230 the endothelium is fully recovered. If $\phi^{ec} = 0$ and no endothelial cells are present at all, no recovery is
231 possible.

232 2.4.6 Inflammation

233 We model inflammation provoked when platelets and leukocyte adhere to the de-endothelialized artery
234 and send inflammatory agents in the tissue. We therefore assume that the inflammation is directly related to
235 the fraction of intact endothelium:

$$\phi^{ic} = 1 - \phi^{ec}, \quad (23)$$

236 where ϕ^{ic} represents a relative level of inflammation with a maximum of 1.237 **2.5 Contractility model**

238 Equation 3 describes the energy generated by SMCs. As stated before, this energy depends on the muscle
239 filament sliding and on the fraction of the filaments in their force-producing states.

240 Similarly to Famaey et al. (2013); Murtada et al. (2010), the driving equation for the evolution of the
241 relative sliding of the myofilaments u_{rs} is

$$\dot{u}_{rs} = \frac{1}{\eta} (P_{smc} - P_{mat}), \quad (24)$$

242 with

$$P_{mat} = \frac{\partial \Psi^{csmc}}{\partial \lambda_\theta} = J^{-2/3} \mu^{csmc} (n_3 + n_4) \left(\sqrt{\bar{I}_4^{csmc}} + u_{rs} - 1 \right), \quad (25)$$

243 and

$$P_{smc} = \begin{cases} \kappa_c n_3, & \text{for } P_{mat} < \kappa_c n_3 \\ P_{mat}, & \text{for } \kappa_c (n_3 + n_4) \geq P_{mat} \geq \kappa_c n_3 \\ \kappa_c (n_3 + n_4), & \text{for } P_{mat} > \kappa_c (n_3 + n_4) \end{cases} \quad (26)$$

244 In a steady-state or homeostatic condition, u_{rs} is evolved to a situation where $P_{smc} = P_{mat}$.
245 Mathematically, three situations can be discerned. Potentially, the u_{rs} value from a previous state already
246 allows $\kappa_c (n_3 + n_4) \geq P_{mat} \geq \kappa_c n_3$ to be true in the new steady-state, such that $P_{smc} = P_{mat}$ already
247 holds, as can be seen from equation 26. u_{rs} then does not evolve further in the new steady-state. The
248 previous u_{rs} may also cause P_{mat} to be smaller than $\kappa_c n_3$. In that case, u_{rs} evolves until $P_{mat} = \kappa_c n_3$. At
249 the final steady-state, u_{rs} is then written as

$$u_{rs} = \frac{\kappa_c n_3}{\mu_{smc} (n_3 + n_4)} + 1 - \sqrt{\bar{I}_4^{csmc}}. \quad (27)$$

250 Alternatively, if the previous u_{rs} causes P_{mat} to be greater than $\kappa_c (n_3 + n_4)$, u_{rs} evolves to

$$u_{rs} = \frac{\kappa_c}{\mu_{smc}} + 1 - \sqrt{\bar{I}_4^{csmc}}. \quad (28)$$

251 The steady-state configuration of the muscle filaments can therefore be calculated at any level of
252 deformation, quantified by \bar{I}_4 .

253 As defined by Murtada et al. (2010); Hai and Murphy (1988), the myofilaments switch between their
254 states n_1, n_2, n_3 or n_4 by the set of differential equations

$$\begin{bmatrix} \dot{n}_1 \\ \dot{n}_2 \\ \dot{n}_3 \\ \dot{n}_4 \end{bmatrix} = \begin{bmatrix} -k_1 & k_2 & 0 & k_7 \\ k_1 & -(k_2 + k_3) & k_4 & 0 \\ 0 & k_3 & -(k_4 + k_5) & k_6 \\ 0 & 0 & k_5 & -(k_6 + k_7) \end{bmatrix} \begin{bmatrix} n_1 \\ n_2 \\ n_3 \\ n_4 \end{bmatrix}, \quad (29)$$

255 where n_1 and n_2 represent the fractions of myofilaments in their detached state, while n_4 and n_3 represent
256 the fractions of attached filaments, dephosphorylated and phosphorylated, respectively. As explained by
257 Murtada et al. (2010), the rate parameters k_1 and k_6 are dependent on the calcium concentration $[Ca^{2+}]$
258 using Michaelis-Menten kinetics as

$$k_1 = k_6 = \frac{[CaCaM]^2}{[CaCaM]^2 + K_{CaCaM}^2} s^{-1}, [CaCaM] = \alpha_{Ca}[Ca^{2+}]. \quad (30)$$

259 The second equation represents the formation of Calcium-Calmodulin complex, where α is a positive
260 constant. K_{CaCaM} in the first equation, inspired by Yang et al. (2003) is a CaCaM-dependent
261 phosphorylation rate parameter.

262 We assume that $[Ca^{2+}]$ represents the intracellular calcium contraction. This concentration can be
263 influenced by vasoactive agents, such as the vasodilator NO and the vasoconstrictor PE. The response to
264 these agents is normalized with respect to the maximal possible response by the Hill equation:

$$R_{NO} = \frac{[NO]}{[NO] + K_{NO}} \quad (31)$$

265 and

$$R_{PE} = \frac{[PE]}{[PE] + K_{PE}}, \quad (32)$$

266 where $[NO]$ and $[PE]$ are the respective extracellular concentrations of NO and PE. K_{NO} and K_{PE}
267 determine the inflection points of the Hill curves. PE causes an increase of the calcium concentration,
268 whereas NO decreases it. The current intracellular calcium concentration is determined as

$$[Ca^{2+}] = [Ca^{2+}]_{hom} + \alpha_{PE}R_{PE} - \alpha_{NO}R_{NO}, \quad (33)$$

269 where $[Ca^{2+}]_{hom}$ is the homeostatic intracellular calcium concentration and α_{PE} is the maximum extra
270 calcium concentration in response to PE. α_{PE} is the maximal calcium concentration that is removed in
271 response to NO. Plugging the resulting $[Ca^{2+}]$ back into equation 30, a NO and PE dependency of the rate
272 parameters k_1 and k_6 is observed.

273 k_2 and k_5 , that define the rate of dephosphorylation, are also directly affected by the NO concentration
 274 since NO activates myosin light chain phosphatase (Carvajal et al., 2000). We write

$$k_2 = k_5 = k_{2,hom} + \alpha_2 R_{NO}, \quad (34)$$

275 where $k_{2,hom}$ is the homeostatic rate of dephosphorylation and α_2 is the maximal increase in response to
 276 NO.

277 NO is produced by a healthy endothelium in response to, for example, the vasodilating agent acetylcholine
 278 (ACh) or wall shear stress (WSS). Cohen et al. (1997) measured the NO concentration in response to ACh.
 279 Their findings are approximated with the equation

$$[NO]_{ec} = 2.8 \cdot 10^{-7} \cdot \frac{\log_{10}([ACh]/1M) + 8.2}{0.9 + \log_{10}([ACh]/1M) + 8.2} \cdot 1M, \quad (35)$$

280 where $[NO]_{ec}$ is the extracellular concentration of NO produced by the endothelium, $[ACh]$ is the
 281 extracellular concentration of ACh and $1M$ refers to a concentration of one molar.

282 In summary, the whole dependency of the contractile state of the contractile cells on the vasoactive agent
 283 PE, NO and ACh is schematically represented in figure 3.

284 2.6 Finite element model

285 The material, damage and remodeling models explained above are used for an *in silico* reproduction
 286 of the experiments carried out by Geenens et al. (2016a) *in silico*. A finite element model is set up in
 287 Abaqus/Standard 2017 to represent a mouse aorta. The diastolic geometry of the aorta is represented as a
 288 half cylinder with inner diameter 0.65 mm and thickness 0.04 mm (Bersi et al., 2016). Due to symmetry,
 289 only a length of 0.04 mm of the cylinder is modeled. The geometry consists of 12852 full integration,
 290 hexahedral, hybrid elements (C3D8H). The simulation goes through a number of steps explained below,
 291 according to the steps followed in the actual experiments. An overview is also shown in figure 4.

292 2.6.1 Homeostasis

293 In order to model the *in vivo*, mechanobiologically homeostatic condition of the mouse aorta, the
 294 prestressing algorithm explained in Mousavi and Avril (2017); Famaey et al. (2018); Maes et al. (2019) is
 295 used. This algorithm looks for a suitable deposition stretch deformation gradient for elastin G^{elas} in order
 296 to balance the diastolic *in vivo* reference geometry with the intraluminal diastolic pressure $p = 10$ kPa,
 297 while the top and bottom of the arterial section are fixed in axial direction. The collagen deposition stretch
 298 g^{coll} and the axial elastin deposition stretch g_{ax}^{elas} are fixed as prior knowledge. This simulation is shown in
 299 figure 4 as step 1.

300 2.6.2 Clamping

301 As shown in step 2 of figure 4, the clamping of the aorta is simulated using two undeformable parallel
 302 plates, similarly to Famaey et al. (2013) and as shown figure 4. Self-contact of the inner surface of the artery
 303 is defined, as well as contact between the plates and the outer surface of the artery. The plates first move
 304 towards each other until reaching the desired clamping force, while no damage to the material is allowed.
 305 Two different clamp forces are discerned: 0.6 N or 1.27 N per 2 mm length of the clamp, respectively
 306 named load 1 and load 2. In a few next steps, the clamps are held at a constant distance and the damage
 307 model explained in section 2.3 is activated. When the damage to the endothelium and contractile SMC
 308 has stabilized, the damage is held constant again, while the clamp plates are removed. During the whole
 309 process the intraluminal pressure is fixed at mouse aortic level $p = 10$ kPa.

310 2.6.3 Remodeling

311 After the releasing of the clamp, the remodeling algorithm explained in section 2.4 is activated, while
 312 keeping the pressure constant. This is shown as step 3 in figure 4. The local collagen and SMC densities
 313 are initialized based on the previously calculated local damage. The initial value of ϕ^{ec} is defined as the
 314 percentage of intact endothelial layer in the entire considered segment. Therefore, this is not a locally
 315 defined variable, and the same value is attributed to every integration point.

316 Due to the initial loss of contractile SMC and collagen, a dilatation of the artery is observed. This
 317 nonhomeostatic mechanical state drives remodeling. Every remodeling step corresponds to one day of
 318 remodeling. During this process, all nodes are constrained to only move in the radial direction in order to
 319 avoid excessive shearing between the layers and failure of the simulation.

320 2.6.4 Myograph test

321 After 31 days of remodeling (cases R1 and R2 for loads 1 and 2), immediately after clamping (cases A1
 322 and A2 for loads 1 and 2) or immediately after obtaining the homeostatic configuration (cases A0 and R0),
 323 a myograph test is simulated, as in the mouse experiments explained in section 2.1. For further reference,
 324 an overview of these six cases is given in table 1.

325 During the simulation, first, the axial boundary condition is released, as well as the intraluminal pressure
 326 to simulated excision, as shown by step 4 in figure 4. Step 5 depicts the simulation of a myograph
 327 experiment as explained in section 2.1 similarly to Famaey et al. (2013). An undeformable rod with a
 328 radius of 0.15 mm in Abaqus is pushed into the artery until the approximate required preload of 0.0133 N
 329 per mm length of the arterial segment is reached, assuming that the preload was set at 0.02 N for a length of
 330 approximately 1.5 mm in the actual experiments carried out by Geenens et al. (2016a). The rod is then fixed
 331 at this position, while 10^{-6} M PE, 10^{-5} M ACh or 10^{-6} M NO is virtually added through field variables.
 332 A contact definition is prescribed between the rod and the inner surface of the artery. Preconstriction due to
 333 PE and relaxation due to ACh or NO can then be observed according to the smooth muscle contraction
 334 model described in section 2.5.

335 2.6.5 Remodeling beyond 31 days

336 In order to further examine the behavior of the remodeling model, the finite element analysis of section
 337 2.6.3 was extended to a remodeling period of 91 days. The effect of slight adaptations to the model was
 338 investigated as well. The first adaptation is the assumption that synthetic SMCs do not redifferentiate into
 339 their contractile phenotype, such that equations 17 and 19 only hold when $\Delta\lambda$ is greater than or equal to
 340 zero. In the opposite case, only the inflammation level influences the SMC densities:

$$\begin{aligned} \frac{d\rho^{csmc}}{dt} &= 0 \\ \frac{d\rho^{ssmc}}{dt} &= K_{ic}^{smc} \phi^{ic} \rho^{ssmc}. \end{aligned} \quad (36)$$

341 The second adaptation is the assumption that collagen production is solely dependent on the amount
 342 of synthetic SMCs, while their production rate is not directly affected by the mechanical environment.
 343 Equation 15 then simplifies to

$$\Gamma(\tau) = \frac{\rho^{ssmc}(\tau)}{\rho_0^{ssmc}}. \quad (37)$$

344 2.7 Model parameters

345 An overview of all used parameter values is given in tables 2 and 3. A code number from 1 to 5 is
346 attributed to every parameter, explaining the way its value was determined. We either used an exact value
347 from the specified reference (1), or used a representative value from the reference, when for example a
348 range was given based on the results of tests on multiple samples (2). Some parameter values are estimated
349 (5), or the parameter is manually fitted to the experimental myograph data (see section 2.1), either with an
350 idea of the order of magnitude from literature (3), or without (4).

3 RESULTS

351 3.1 Damage due to clamping

352 Figure 5 shows the distribution of β (see equation 10), defining the local loss of contractile SMC due to
353 clamping. The highest damage is concentrated at the inner side of the wall at the edge of the clamp.

354 Table 4 gives an overview of the relative collagen, contractile SMC and endothelium content acutely after
355 clamping at the three different clamp loads (cases A0, A1 and A2). From this table it can be concluded
356 that the difference between clamping at 0.6 N and 1.27 N is small in terms of acute damage. There is
357 approximately 70% loss of endothelium, 9% collagen loss and 28% contractile SMC loss in both cases.
358 The small difference in damage is due to a minimal required clamp displacement to increase the reaction
359 force from 0.6 N to 1.27 N, yielding only small stretch differences.

360 3.2 Remodeling

361 Table 4 also shows the situation after the simulated *in vivo* healing period of 31 days (cases R0, R1 and
362 R2) using the presented remodeling model, taking into account cell differentiation, ECM production by
363 synthetic cells and inflammation after clamping injury.

364 Figure 6 shows the evolution of the total content of each constituent relative to its normal amount over a
365 remodeling time of 31 days after damage due to clamping at 1.27N. In other words, it shows the evolution
366 from case A2 to case R2. Due to the similar level of damage at cases A1 and A2, as is clear from table 4,
367 the evolution from cases A1 to R1 resembles the one depicted in this figure.

368 There is an initial dedifferentiation of the cells from their contractile to synthetic phenotype due to an
369 initial overstretching of the wall. Along, with the high initial inflammation level, this also causes the
370 synthetic cells to proliferate, such that the collagen content increases. At about 14 days, the initial stiffness
371 loss is compensated, and the collagen, synthetic and contractile cell contents slowly return to their normal
372 levels.

373 3.3 Myograph test

374 Figure 7 shows the normalized reaction force in the simulated rod while it moves towards the preload
375 position before the addition of vasoactive substances. It indicates the overall stiffness of each material for
376 each case. There was no discernible difference between cases A1 and A2 on the one hand and cases R1 and
377 R2 on the other hand, as can be observed in figure 7. Furthermore, the simulations do not show differences
378 between cases A0 and R0.

379 Figure 8 gives an overview of the results of the simulated myograph experiments upon the addition of
380 vasoactive substances, compared to the results obtained on mouse arteries, as explained in section 2.1. The
381 figure shows how the isometric force changes upon addition of PE, NO and ACh. PE drives an increased
382 phosphorylation rate $k_1 = k_6$ of the myofilaments through an increased intracellular calcium level, inducing
383 a vasoconstrictive effect. NO has the reverse effect on calcium and it also increases the dephosphorylation

384 rate $k_2 = k_5$. ACh does not act directly on the contractile SMC, but triggers the endothelium to produce
385 NO. Therefore, the vasodilating effect of ACh is smaller than that of NO.

386 **3.4 Remodeling beyond 31 days**

387 The evolution of relative collagen, synthetic cells and contractile cells density over a remodeling period
388 of 91 days is shown in figure 9, for the original remodeling model (A) and two adapted models (B and
389 C) as explained in section 2.6.5. Beyond one month, unnatural periodic behavior emerges when using the
390 original model, caused by the initial extra loss of contractile SMC upon overstretching, causing an extra
391 stiffness loss, and a delay in the increased collagen production through the proliferation of synthetic cells.

392 When synthetic cells do not redifferentiate into the contractile phenotype, a more rapid stabilization of
393 the remodeling is observed (figure 9 B). However, the loss of contractile cells due to clamping overload
394 will never be compensated in this case.

395 The results of the last variant of the remodeling model are shown in figure 9 C and show an increased
396 oscillation of the synthetic cell density. Collagen production is not dependent on a mechanical stimulus
397 anymore, such that a bigger increase in synthetic cell count is required to restore the collagen density, and
398 along with it, restore the homeostatic mechanical environment.

4 DISCUSSION

399 The aim of this study is to introduce a computational model predicting healing in arterial tissues subjected
400 to mechanical overloading and damage, for instance after clamping. Three models are introduced for the *in*
401 *silico* simulation of the experiments carried out by Geenens et al. (2016a): a damage model for clamping, a
402 remodeling model to predict healing and a contractility model to simulate myograph experiments.

403 The contractility model is original as it is the first to take the vasoactive substances PE, NO and ACh
404 into account. Their respective influence on the rate of phosphorylation and dephosphorylation of myosin
405 light chain leads to a reliable response in the simulation of a myograph experiment, as shown in figure
406 8. The model is based on signaling pathways on the cellular level, dependent as well as independent on
407 intracellular calcium, as shown in figure 3. The approach is different from the recent model presented by
408 Murtada et al. (2016), in which the smooth muscle tone prediction was based on a structurally motivated
409 model of the contractile unit. In their implementation, the response to an external factor, such as a change
410 in loading or in the concentration of a vasoactive agent, is modeled as an evolving scaling factor for
411 the myosin filament length. Before us, the continuum mechanics-based model of Murtada et al. (2017)
412 was the only one that accounted for the dependency of the phosphorylation rates on the diffusion of the
413 vasoconstrictor potassium chloride (KCl) from the adventitia, although diffusion itself is neglected in the
414 present study.

415 The remodeling model includes novel aspects of cell differentiation upon mechanical stimulus and the
416 production of extracellular matrix by synthetic SMCs. This production is also dependent on a certain
417 level of tissue inflammation, as for example done by Latorre and Humphrey (2018b). In the present
418 approach however, the inflammation level is directly related to the damage and healing of the endothelium.
419 Inflammation increases the synthetic cell proliferation, thus indirectly enhancing collagen production
420 (Davis et al., 2003), as summarized in figure 2. Hence, our remodeling model includes all the relevant
421 biological processes and pathways, in contrast to more phenomenological models, where collagen turnover
422 is directly related to a mechanical stimulus, such as in Mousavi et al. (2019); Famaey et al. (2018); Braeu
423 et al. (2017); Cyron et al. (2016); Baek et al. (2006); Valentín et al. (2013); Alberto Figueroa et al. (2009).

424 This more detailed description of SMC behavior in vascular healing and remodeling comes at an increased
425 computational cost. Moreover, figure 9 shows stability issues of the model in the form of unnatural temporal
426 oscillations of the densities at longer time scales. A solution could be to neglect the transient effects and
427 only consider the steady state, such as done by Latorre and Humphrey (2018a). Alternatively, we can
428 include damping in the model to obtain a critical or overdamped dynamic system in order to avoid unnatural
429 periodic behavior. From a mathematical point of view, the main limitation is the high number of parameters,
430 as summarized in tables 2 and 3. Some parameters are determined based on previous works or based
431 on their physical meaning, others were set in order to match experimental findings, mainly based on the
432 tissue properties at 0 and 31 days of healing, which were however not sufficient to uniquely determine the
433 parameter values.

434 Unfortunately, the currently available experimental data is not sufficient to proof its pilot application.
435 It is likely that other parameter combinations would amount to the same results as shown in figure 8.
436 Nevertheless, the phenomenological nature of this new model is strongly reduced as compared to state-
437 of-the-art models. A high number of parameters can be qualified as physics-based, such that their values
438 can be obtained through the design of dedicated biochemical experimental set-ups. This will allow these
439 parameter values to be measured with more certainty, or with smaller confidence intervals, capturing the
440 individual differences and differences between tissue types, allowing a better focus of the parameter fitting
441 process.

442 Constrained mixture models are generally computationally expensive due to its high memory use,
443 inversely related to the length of the time step. To ensure the feasibility, we chose to use a time step of one
444 day, where a time convergence study showed errors of less than five percent with respect to the situation
445 with a time step of half a day. Also in an attempt to limit the computational cost, only a very short segment
446 of artery is modeled and the defined boundary conditions cause a plane strain situation. Considering a
447 longer segment, possibly along with a more realistic patient-specific geometry, would improve the reliability
448 of the model, mainly near the edges of the clamp and near the edges of the excised sample during the
449 myograph simulation. Using this very short artery segment allows to use a non-localized variable ϕ^{ec} that
450 represents the overall intactness of the endothelium in the segment. Localizing the endothelial damage
451 would greatly affect the complexity of the model, since diffusion of inflammatory agents and NO would
452 need to be integrated. Similarly, taking into account the migration of SMC as an important mechanism in
453 vascular remodeling, would increase the complexity as the remodeling in a certain integration point would
454 be affected, not only by all variables defined in that specific location, but also by its surroundings. In a
455 similar way, one could also consider re-endothelialization as a non-localized process of proliferation and
456 migration of nearby endothelial cells. Including all these processes would increase the biofidelity of the
457 model, although it is unclear to what extent, given the already many unknowns in the present version.

458 Furthermore, to further improve the remodeling model, an improved understanding of biological and
459 biochemical phenomena is required. To this day, some unknowns, uncertainties and controversies remain.
460 For example, it is unclear to what kind of mechanical stimulus cells react. There are indications that SMCs
461 and fibroblasts have a preferred structural stiffness of the extracellular matrix and react based on deviations
462 from this ideal value (Humphrey, 2008). On the other hand, certain signaling pathways are thought to be
463 triggered by so-called baroreceptors, sensitive to mechanical stretch (Lacolley et al., 2017). Multiple studies
464 have investigated the effects of cyclic straining of arterial tissue, as reviewed by Mantella et al. (2015).
465 Some apparently contradictory results emerge. For example, Chang et al. (2003) observed an increased
466 SMC proliferation under *in vitro* cyclic strain, while Morrow et al. (2005); Guha et al. (2011) observed
467 a decreased proliferation, potentially due to a different experimental design that mimics *in vivo* loading

468 conditions better (Mantella et al., 2015). The widely accepted theory that precursor cells differentiate into
469 synthetic cells and subsequently become fully differentiated contractile cells has been challenged recently
470 as well, given that both phenotypes can be present in healthy tissues while maintaining vascular tone and
471 tissue architecture (Rensen et al., 2007).

472 In summary, the presented models provide a detailed description of vascular SMC behavior under
473 conditions of damage as well as at different concentrations of vasoactive agents. This allows us to study
474 tissue healing and the effects of, for example, vasoactive or anti-proliferative drugs. However, there are
475 still many unknowns regarding these phenomena, which is why more detailed and carefully designed
476 experiments are needed in order to fully capture SMC behavior in all its aspects.

477 To conclude, in this study, a damage model, as well as a remodeling and cell contractility model were
478 introduced, taking into account endothelial damage and healing, tissue inflammation, mechanosensing,
479 extracellular matrix production and phenotype switching of SMCs. Using these models, *in vivo* clamping
480 tests on mice aortas and subsequent healing and myograph tests, were simulated through finite element
481 modeling. The results of the simulated myograph tests showed great resemblance to the results of the actual
482 experiments. This detailed mechanobiological description of vascular SMC behavior can be clinically
483 relevant to enable *in silico* investigations of drug effects. However, the results show that there is still a need
484 for an improved biological and biochemical fundamental understanding to reliably capture vascular SMC
485 mechanobiology at all the relevant spatio-temporal scales.

CONFLICT OF INTEREST STATEMENT

486 The authors declare that the research was conducted in the absence of any commercial or financial
487 relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

488 LM, SA and NF conceived the presented ideas. LM developed and implemented the presented algorithms.
489 JV, SA and NF reviewed the computational methods. LM wrote the manuscript. JV, SA and NF reviewed
490 the manuscript. SA and NF supervised the project.

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DATA AVAILABILITY STATEMENT

497 The raw data supporting the conclusions of this article will be made available by the authors, without undue
498 reservation.

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FIGURE CAPTIONS

Table 1. Clarification of the codes of the six cases for which a myograph experiment is modeled: A0, R0, A1, R1, A2 and R2.

	Immediately after clamping	After one month healing
Clamp load of 0.0N	A0	R0
Clamp load of 0.6N	A1	R1
Clamp load of 1.27N	A2	R2

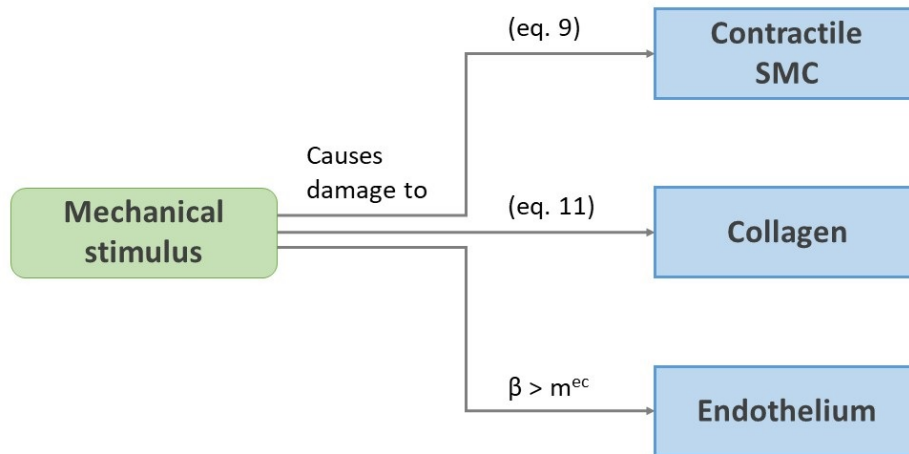


Figure 1. Schematic representation of the damage effects presented in section 2.3.

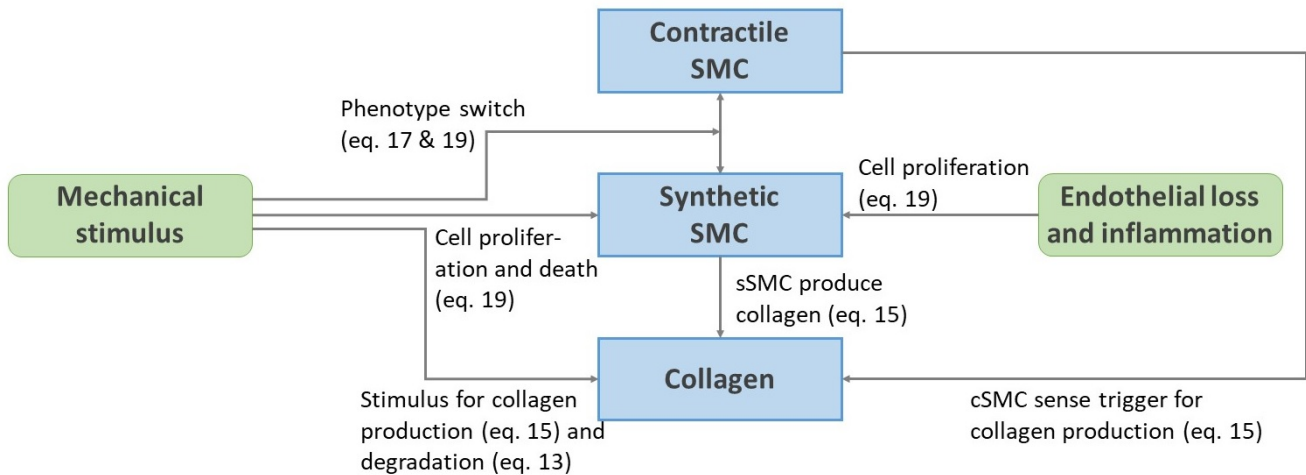


Figure 2. Schematic representation of the remodeling pathways presented from equation 13 to 22.

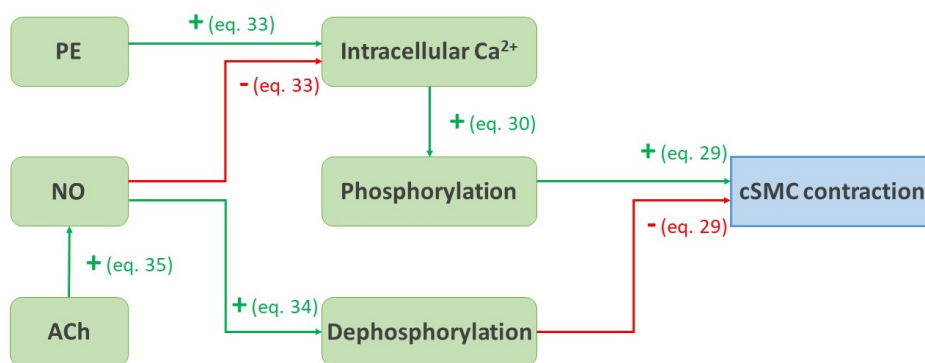


Figure 3. Schematic representation of the pathways presented from equation 29 to 35. A green arrow with a plus sign represents a positive influence, a red arrow with a minus sign represents a negative influence.

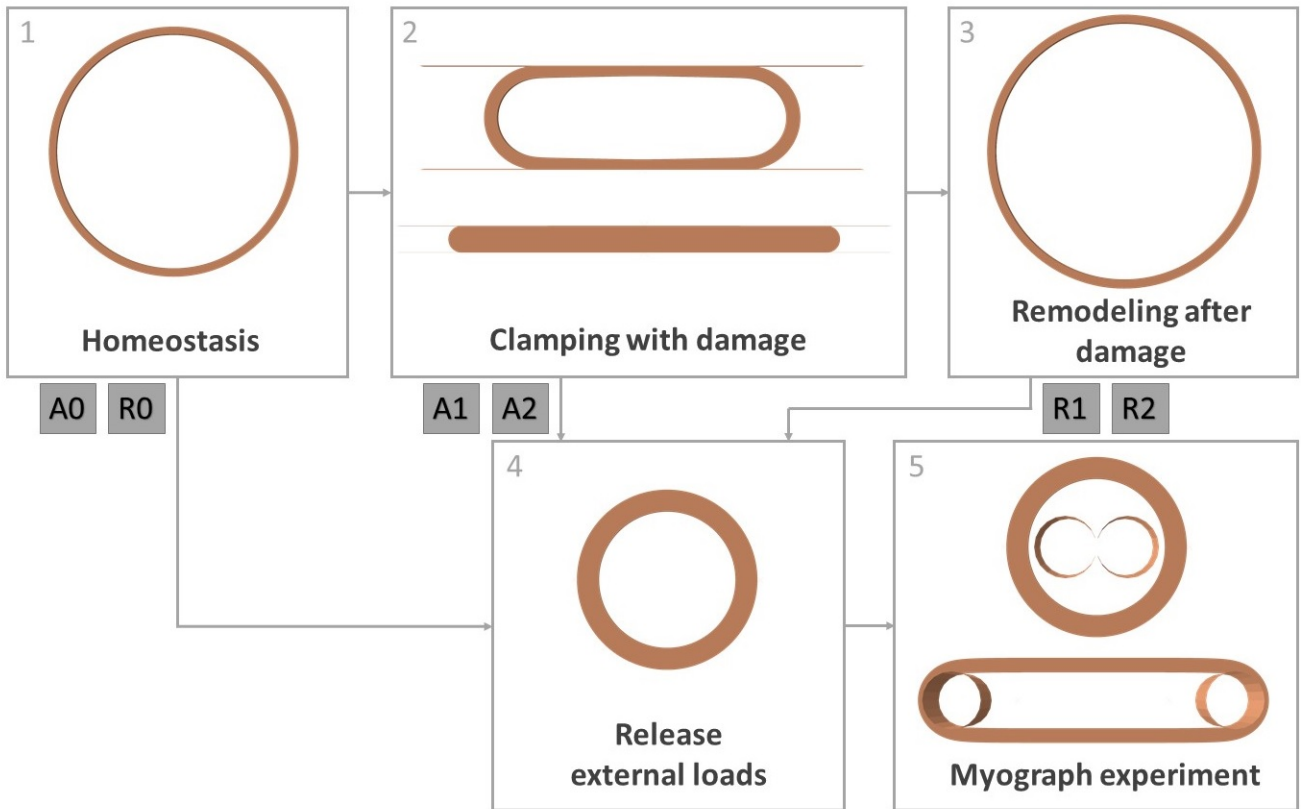


Figure 4. Overview of all simulation steps. Step 1: obtaining homeostatic configuration, step 2: clamping the artery while allowing damage to the constituents, step 3: remodeling of the tissue after damage, step 4: releasing intraluminal pressure and axial tension, step 5: simulation of a myograph experiment. Step 4 and 5 are done after step 1 (cases A0 and R0), after step 2 (cases A1 and A2) and after step 3 (cases R1 and R2).

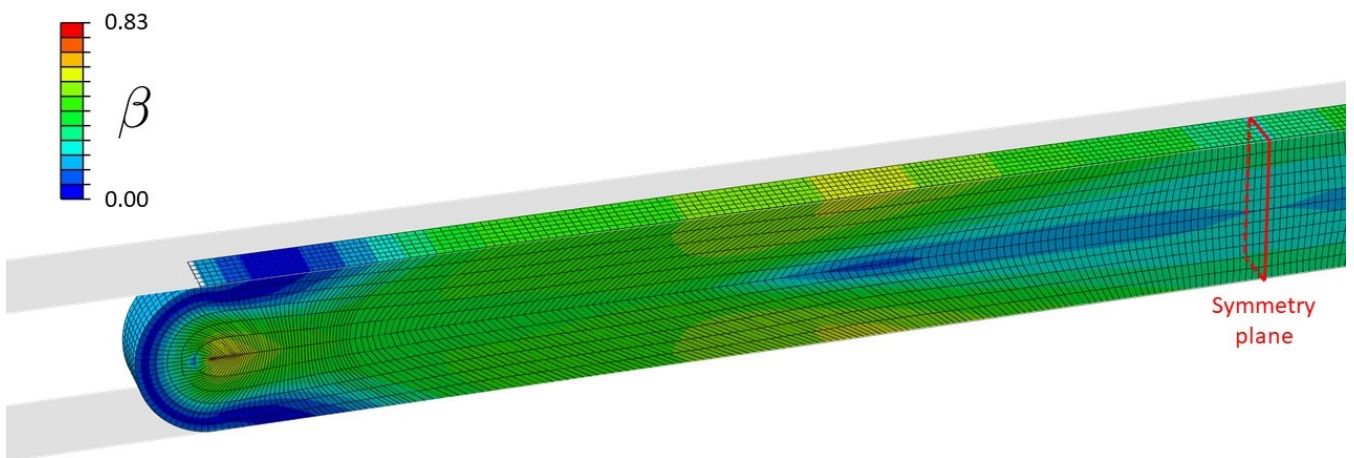


Figure 5. Distribution of β during clamping at a load level of 1.27N, causing contractile SMC and endothelial damage.

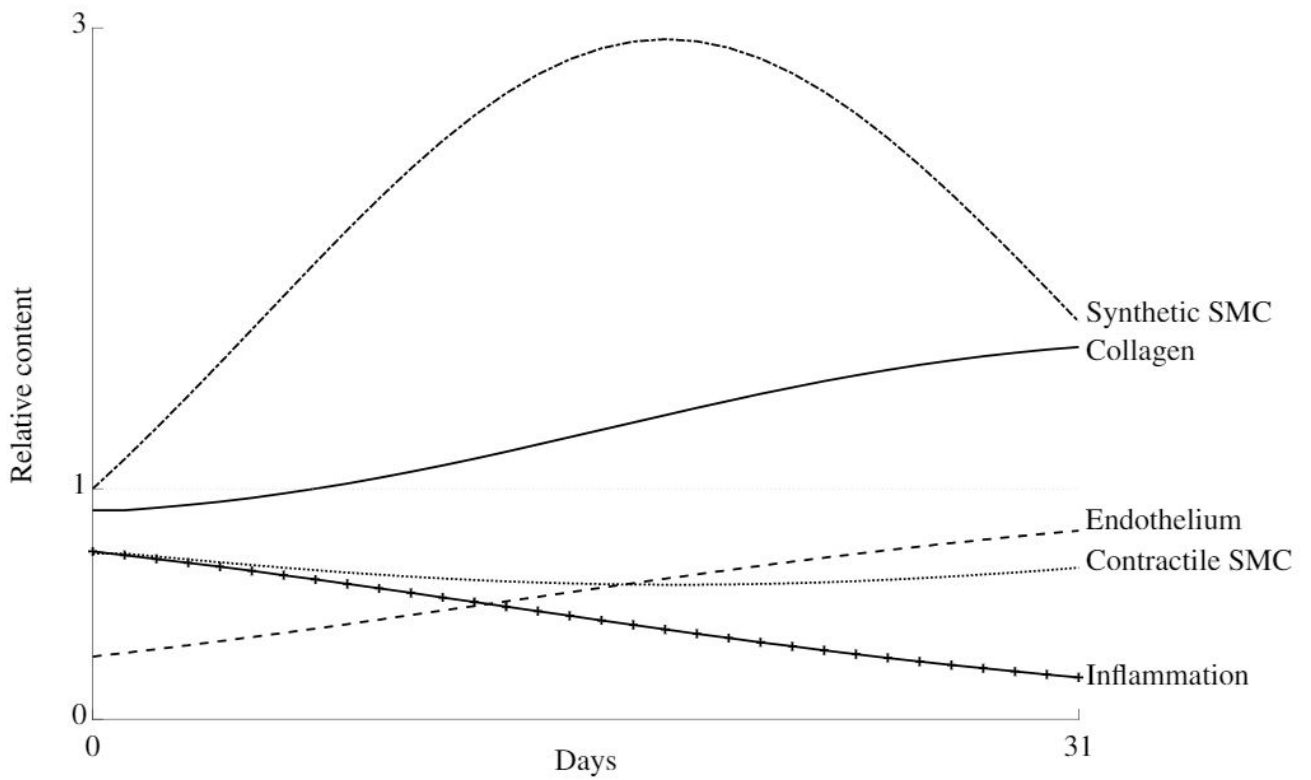


Figure 6. 31 days evolution of the relative content of all considered constituents in the arterial wall during healing after damage due to clamping at load level 2.

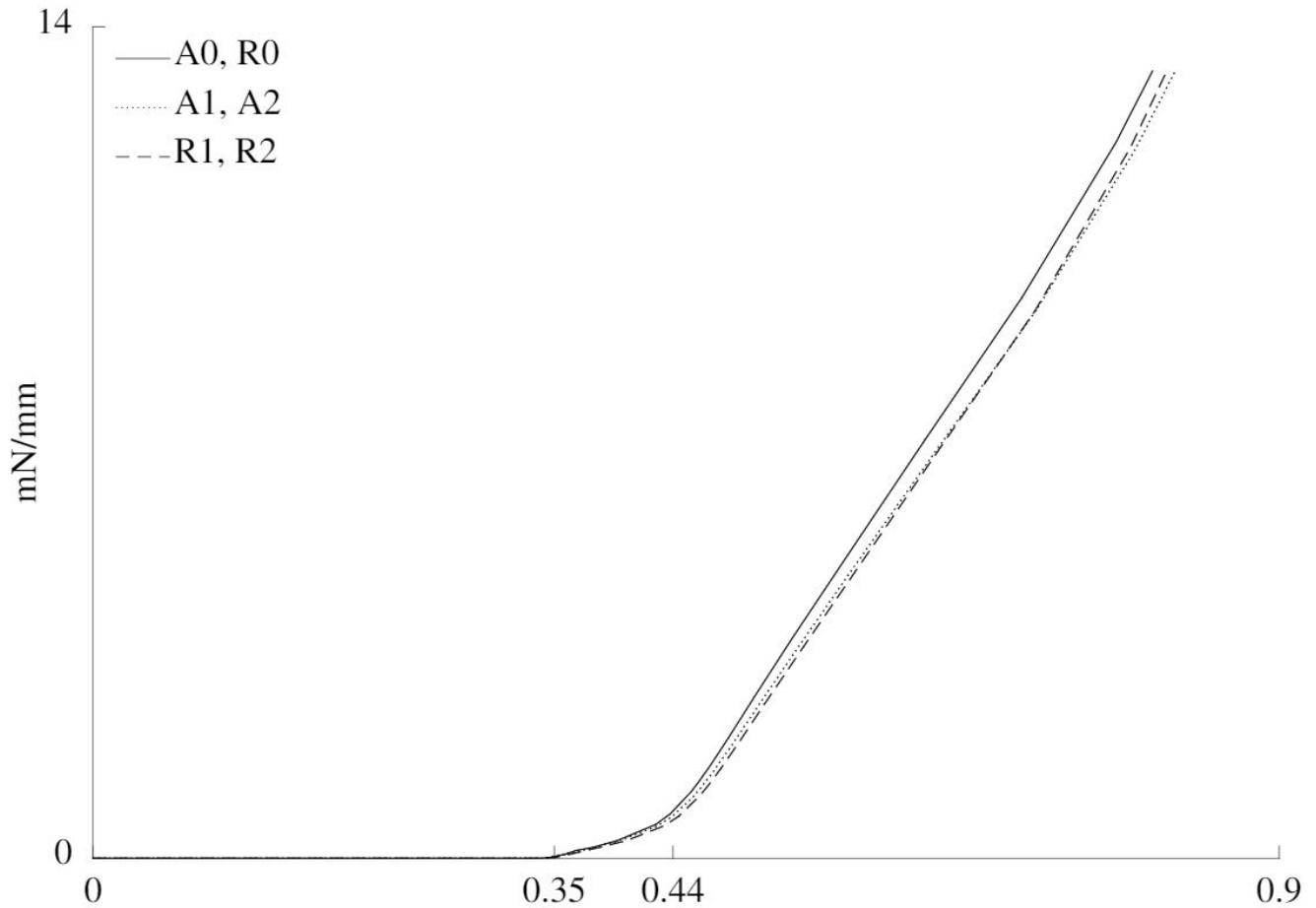


Figure 7. Normalized force versus rod displacement for the six cases. Three different zones are discerned. From 0 to approximately 0.35 mm of displacement, the rod does not touch the sample yet, such that the force is zero. From approximately 0.35 to 0.44 mm, the cylindrical shape of the sample is straightened out. Finally, after approximately 0.44 mm, the sample is further stretched.

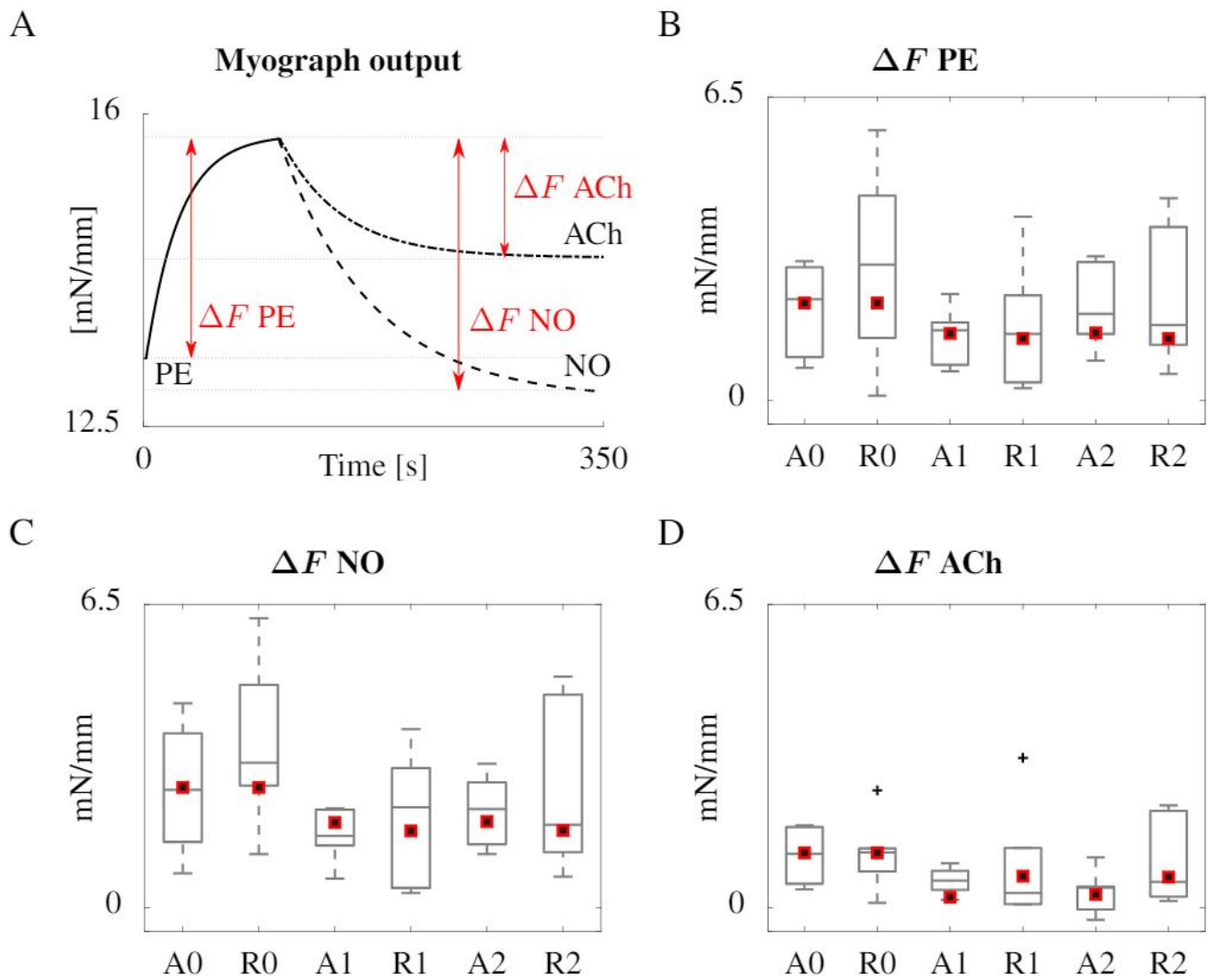


Figure 8. Overview of the results of the simulated (red squares) and experimental (boxplot) myograph results. (A) representative scheme of the isometric force measured in the simulated myograph upon addition of vasoactive substances, (B) force increase due to PE addition, (C) and (D) subsequent force decrease after addition of NO and ACh respectively. All forces are normalized with the axial length of the sample. The boxplots show the median values, the 25th and 75th percentiles, the total extent of the measurements without outliers (whiskers) and the outliers (crosses).

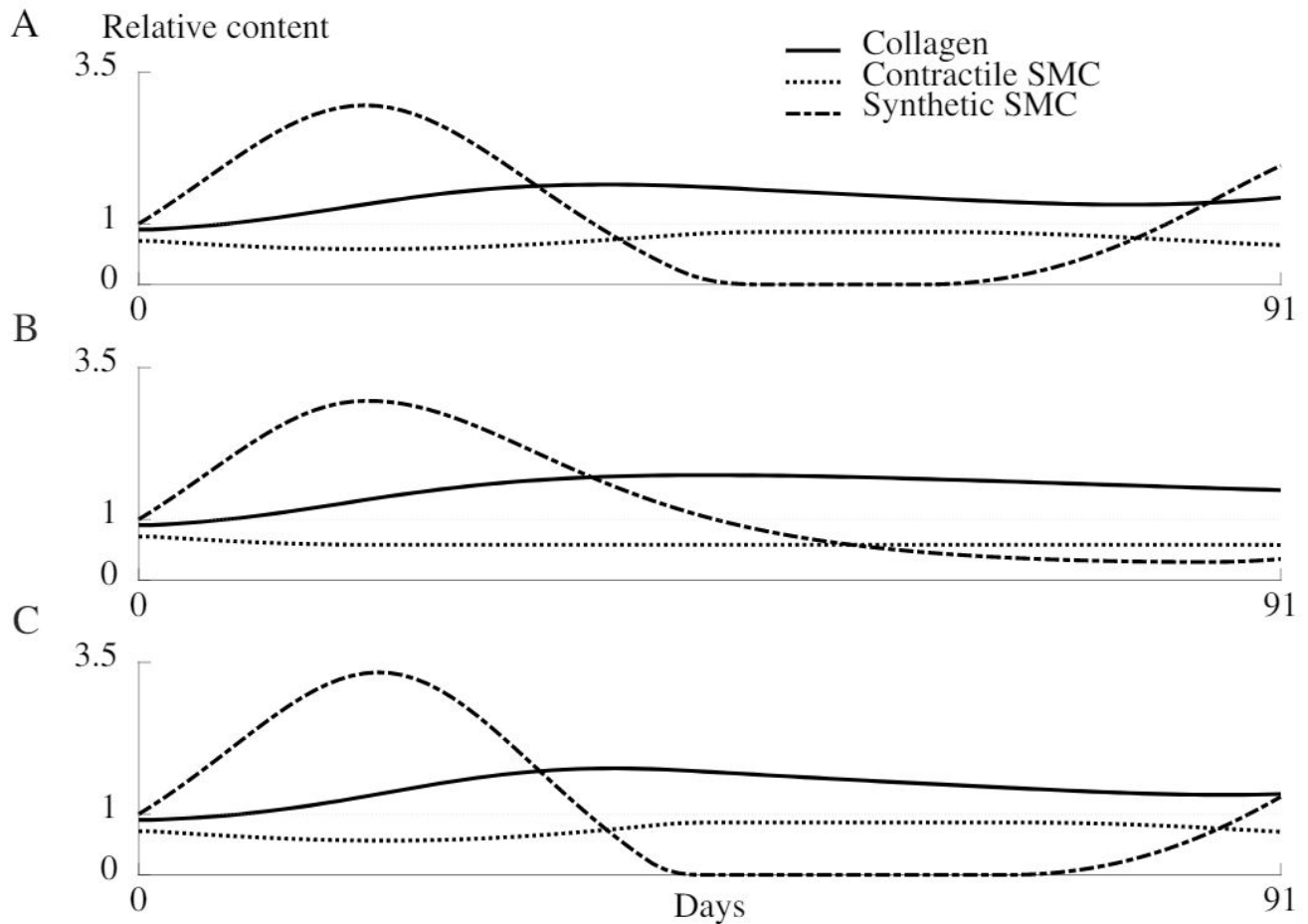


Figure 9. Evolution of the relative density of collagen, synthetic SMC and contractile SMC during 91 days of healing for the original remodeling model (A) and two adapted versions (B and C). (A) Original model as described in section 2.4. (B) The mechanical trigger that regulates the number of synthetic cells can only act by increasing the number of cells, and is otherwise deactivated. (C) The production of collagen is only related to the number of synthetic cells, not to the mechanical environment.

Table 2. Overview of parameter values for constituent densities, passive and material properties, prestretch values, damage parameters and remodeling parameters. (1) The exact value from the reference is used. (2) A representative value from the reference is used. (3) The parameter is manually fitted in the same order of magnitude as the reference. (4) The parameter is manually fitted. (5) The parameter is estimated.

Parameter	Value	Source
Initial densities		
ρ_0^{elas}	0.35	Bersi et al. (2016) (2)
ρ_0^{coll}	0.30	Bersi et al. (2016) (2)
ρ_0^{smc}	0.30	Bersi et al. (2016) (2)
ρ_0^{ssmc}	0.05	Bersi et al. (2016) (2)
Passive material parameters		
C_{10}	0.04 MPa	Bersi et al. (2016) (2)
k_1	1.0 MPa	Bersi et al. (2016) (2)
k_2	1.5	Bersi et al. (2016) (2)
κ	0.1	(5)
α	$\pi/8$ rad	(5)
SMC parameters		
μ^{smc}	0.42 MPa	Murtada et al. (2010) (3)
κ_c	1.55 MPa	Murtada et al. (2010) (3)
Prestretches		
g_{ax}	1.67	Bersi et al. (2016) (1)
g_c	1.1	Bellini et al. (2014) (2)
Damage parameters		
m^{smc}	1.0	(4)
m^{coll}	20.0	(4)
m^{ec}	0.38	(4)
Remodeling parameters		
K_{qh}^{coll}	$\log(2.0)/100 \text{ day}^{-1}$	(4)
K_m^{coll}	26.64	(4)
K_{pl}^{smc}	4.0 day^{-1}	(4)
K^{ec}	0.08 day^{-1}	(4)
K_{dd}^{smc}	1.6 day^{-1}	(4)
K_{ic}^{smc}	0.01 day^{-1}	(4)

Table 3. Overview of parameter values for the SMC contractility model. (1) The exact value from the reference is used. (2) A representative value from the reference is used. (3) The parameter is manually fitted in the same order of magnitude as the reference. (4) The parameter is manually fitted. (5) The parameter is estimated.

Parameter	Value	Source
SMC contractility parameters		
k_3	0.4 s^{-1}	Hai and Murphy (1988) (1)
k_4	0.1 s^{-1}	Hai and Murphy (1988) (1)
k_7	0.01 s^{-1}	Hai and Murphy (1988) (1)
η	$60.0 \text{ MPa}\cdot\text{s}$	Murtada et al. (2010) (1)
K_{NO}	$8.0\text{e-}8 \text{ M}$	(4)
K_{PE}	$2.0\text{e-}7 \text{ M}$	(4)
$[Ca^{2+}]_{hom}$	$2.7\text{e-}7 \text{ M}$	Utz et al. (1999) (2)
α_{NO}	$1.4\text{e-}7 \text{ M}$	(4)
α_{PE}	$1.28\text{e-}7 \text{ M}$	(4)
α_{Ca}	0.24	(4)
K_{CaCaM}	$1.78\text{e-}7 \text{ M}$	Murtada et al. (2010) (1)
$k_{2,hom}$	0.5 s^{-1}	Hai and Murphy (1988) (1)
α_2	0.1 s^{-1}	(4)

Table 4. The fraction of overall elastin, collagen, contractile SMC (cSMC), synthetic SMC (sSMC) and endothelium content with respect to their normal content. Note that the level of inflammation is zero in the normal artery wall state, and has a maximal value of 1. Cases A0, A1 and A2 refer to the acute situation after clamping at three load levels (0.0N, 0.6N and 1.27N). R0, R1 and R2 correspond to the respective cases after 31 healing days.

Case	A0	R0	A1	R1	A2	R2
Elastin	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Collagen	1.0000	1.0000	0.9076	1.6123	0.9071	1.6157
cSMC	1.0000	1.0000	0.7170	0.6539	0.7190	0.6575
sSMC	1.0000	1.0000	1.0000	1.7225	1.0000	1.7253
Endothelium	1.0000	1.0000	0.3113	0.8463	0.2719	0.8184
Inflammation	0.0000	0.0000	0.6887	0.1537	0.7281	0.1816