Constitutive interpretation of arterial stiffness in clinical studies: a methodological review

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Reesink KD, Spronck B. Constitutive interpretation of arterial stiffness in clinical studies: a methodological review. Am J Physiol Heart Circ Physiol 316: H693–H709, 2019. First published December 7, 2018; doi:10.1152/ajpheart.00388.2018.— Clinical assessment of arterial stiffness relies on noninvasive measurements of regional pulse wave velocity or local distensibility. However, arterial stiffness measures do not discriminate underlying changes in arterial wall constituent properties (e.g., in collagen, elastin, or smooth muscle), which is highly relevant for development and monitoring of treatment. In arterial stiffness in recent clinical-epidemiological studies, we systematically review clinical-epidemiological studies (2012–) that interpreted arterial stiffness changes in terms of changes in arterial wall constituent properties (63 studies included of 514 studies found). Most studies that did so were association studies (52 of 63 studies) providing limited causal evidence. Intervention studies (11 of 63 studies) addressed changes in arterial stiffness through the modulation of extracellular matrix integrity (5 of 11 studies) or smooth muscle tone (6 of 11 studies). A handful of studies (3 of 63 studies) used mathematical modeling to discriminate between extracellular matrix components. Overall, there exists a notable gap in the mechanistic interpretation of stiffness findings. In constitutive model-based interpretation, we first introduce constitutive-based modeling and use it to illustrate the relationship between constituent properties and stiffness measurements (“forward” approach). We then review all literature on modeling approaches for the constitutive interpretation of clinical arterial stiffness data (“inverse” approach), which are aimed at estimation of constitutive properties from arterial stiffness measurements to benefit treatment development and monitoring. Importantly, any modeling approach requires a tradeoff between model complexity and measurable data. Therefore, the feasibility of changing in vivo the biaxial mechanics and/or vascular smooth muscle tone should be explored. The effectiveness of modeling approaches should be confirmed using uncertainty quantification and sensitivity analysis. Taken together, constitutive modeling can significantly improve clinical interpretation of arterial stiffness findings.

PRINCIPAL FINDINGS

1. Constitutive interpretations of arterial stiffness were rare in clinical studies (0.3% of studies). Most studies that did so were association studies, providing limited causal evidence.

2. Intervention studies addressed changes in arterial stiffness through the modulation of extracellular matrix integrity or smooth muscle tone.

3. Mathematical modeling was used in a handful of studies to discriminate between extracellular matrix components.

CONCLUSION

Constitutive modeling can significantly improve clinical interpretation of arterial stiffness findings.

distensibility; extracellular matrix; pulse wave velocity; smooth muscle cell; vascular remodeling

INTRODUCTION

The interpretation of arterial stiffness findings in clinical studies is not without pitfalls and caveats. The present review is focused on the methodological aspects that need attention.

The measurement of arterial stiffness has been established as a key methodology to assess large artery function and changes thereof since the late 1990s (50, 78, 97, 145). The methods available in humans involve noninvasive vascular imaging (mainly ultrasound and magnetic resonance imaging (MRI)) and high-fidelity recording of the pulse wave (mainly by tonometry or ultrasound Doppler). The functional measure obtained from the physical measurement is either a regionally determined pulse wave velocity (PWV; in m/s) or a locally determined distensibility coefficient (DC; in 1/MPa), the latter of which decreases with increasing stiffness (16). From these primary measurements and concepts, measures are derived to harmonize units and interpretation (e.g., a PWV can be derived from a DC to interpret absolute values and changes) (16, 147) and/or correct for the (confounding) influence of actual blood pressure on the arterial stiffness observed (117, 126).

In the clinical context, arterial stiffness is mostly considered in cardiovascular risk management, where a carotid-femoral
PWV value of >10 m/s adds to existing risk scores (86, 145). For other measures, e.g., carotid DC, the cardio-ankle vascular index, and brachial-ankle PWV, no risk score thresholds have been established or recommended yet. In contrast, arterial stiffness measurements in an (interventional) study context invariably evoke mechanistic interpretation, where measured changes are considered in relation to the existing knowledge and insights at the level of the extracellular matrix (ECM) and smooth muscle cells (27, 46, 73, 77). In the last decade, a vast knowledge base has been developing from the molecular scale and genetic level toward the mechanobiological and biomechanical interactions between cells and the ECM (31, 58, 66).

Considering the practical and physical limitations of measurements and the caveats and pitfalls inherent in interpreting data across scales and levels of biological organization, we considered it timely to critically review the state of the art and identify key (methodological) aspects that deserve attention.

Our review is organized in two main sections. In ARTERIAL STIFFNESS IN RECENT CLINICAL-EPIDEMILOGICAL STUDIES, we will systematically review clinical-epidemiological studies with a focus on the constitutive (i.e., ECM and smooth muscle related) interpretation of arterial stiffness measurements published in the last 5 yr. In CONSTITUTIVE MODEL-BASED INTERPRETATION, we focused our review on the utility of constituent-based mathematical models to 1) comprehensively understand arterial wall elastic behavior and 2) support correct interpretation of arterial stiffness measurements in the clinical epidemiological setting.

ARterial Stiffness in recent Clinical-Epidemiological Studies

The aim of this section is to provide a state-of-the-art overview of recent clinical-epidemiological papers with arterial stiffness as the outcome variable. Our focus in reading these papers was on whether a constitutive interpretation was given.

Literature Search and Selection of Papers

To limit our bias toward our own research network and field, we structured our search and review as described below. We conducted a PubMed search for papers published since January 1, 2012. We used multiple terms related to arterial stiffness to ensure good coverage and used “collagen,” “elastin,” “smooth muscle,” and “extracellular matrix” as broad terms to identify content in the published title and/or abstract related to arterial ultrastructure (see syntax1).

The primary search was performed on April 10, 2018, and resulted in 514 papers (Fig. 1).

Subsequently, we made a first selection based on titles only and the following exclusion criteria: 1) experimental/non-human/ex vivo study, 2) review, 3) non-English full text, and 4) nonsystemic arterial domain (e.g., coronary, pulmonary, and uterine). Reviews did not enter the detailed content analysis (below), but those relevant to the specific topic discussed are cited where appropriate. After this first selection step, 215 papers were retained for the second selection step (Fig. 1).

In the second selection, we read title and full abstract to 1) exclude any leftover noneligible papers based on the above exclusion criteria (through explicit searches for “mice” and “rats” in the abstracts and 2) identify specifically the arterial stiffness measure(s) used in the study and the ultrastructural component(s) explicitly mentioned in the (quantitative/mechanistic) interpretation of the data in the results/discussion/conclusion section of the abstract. After the second selection, 63 papers were retained for detailed content analysis (Fig. 1).

Content Analysis of Selected Papers

For the content analysis of the selected 63 papers, we will describe 1) differences or changes in arterial stiffness measures used in the studies and 2) the corresponding quantitative and/or mechanistic interpretation in terms of constitutive changes (i.e., content and/or properties) of the ECM and/or smooth muscle. To get a structured overview, we assigned papers to four categories with primary focuses being 1) collagen, 2) elastin, 3) smooth muscle, or 4) ECM. The focus category of ECM was used to contain 1) papers with a focus on the ECM as a whole and 2) papers targeting ultrastructural components of the vascular wall other than elastin, collagen, and smooth muscle (Fig. 1).

Arterial stiffness measurement methods and measures with consideration of pressure dependence. There are important differences between methods of arterial stiffness measurement,
which are often not taken into (correct) consideration. Therefore, we focused here on the methods used in the included papers. In 50 of 63 studies, arterial stiffness was assessed as pulse wave velocity (PWV) based on pulse transit time. In contrast to the common carotid-femoral PWV (used in 42 studies), which is considered the gold standard for arterial stiffness assessment (145), 6 (of 50) studies considered PWV over the brachial-ankle trajectory (4, 43, 61, 67, 68, 158).

Although the brachial-ankle and carotid-femoral trajectories are different, both measures appear to correlate reasonably well (24). One study used a PWV measured locally at the carotid artery by high-speed ultrasound (92), and one study considered PWV in the forearm (41).

In 10 studies (10 of 63 studies), stiffness was assessed locally (termed “single-point” onward) by measuring local vessel diameter and distension by ultrasound or MRI and estimating the corresponding local pulse pressure driving the cyclic distension (9, 28, 64, 80, 81, 87, 113, 125, 138, 143). Conventionally, pressure-diameter or pressure-area data are used to calculate local distensibility (DC) or compliance (CC) coefficients, which are linear approximations over the observed diastolic/systolic range. About half of the studies used the Bramwell-Hill relationship between (transverse) distensibility and (local) PWV to express measured pressure-area data in terms of PWV (16, 34, 50, 97, 126). One study (of 63 studies) used a PWV estimate obtained by the oscillometric method, which is a more indirect measure, because it invokes assumptions about (an effective) pulse wave reflection site (3). Study results with such methodology cannot be interpreted interchangeably with those of the above-described studies.

Transit time PWV and single-point measures (DC, CC, and single-point PWV) are all well known to show pressure dependence, requiring adjustment for blood pressure (123, 126). Statistical adjustments are a valid and powerful approach when groups or populations are considered but lack applicability in the setting of individual patient management (121, 124). Two of the selected studies (2 of 63 studies) used the caroid-ankle vascular index (CAVI) obtained by measuring transit time over the heart-to-ankle trajectory (116, 136) to account for pressure dependence by approximating the pressure-area relationship by a single exponential (akin to stiffness index $\beta$; see Ref. 122). A dedicated review on the methodological background in relation to the practical utility of CAVI is provided by Shirai et al. (117). We have recently introduced stiffness indexes $\beta_0$ and $\text{CAVI}_0$ (also see constitutive model-based interpretation), which in practical situations are theoretically even more resilient to the confounding effect of (operating) pressure (122, 127).

Taken together, most studies use PWV as an arterial stiffness measure and correct for blood pressure dependence by statistically adjusting for mean arterial pressure. By using, rather than correcting for it, three studies explicitly addressed the pressure dependence to assess underlying ultrastructural changes at the ECM level (42, 64, 125). Because these studies had a focus on the constitution of the ECM, these three papers are further discussed below.

_Elastin-related processes of arterial stiffening._ The elastin substructure in the arterial wall bears most of the mechanical load for pressures within the normotensive range (Fig. 2, A and B). A decrease in the stiffness of the elastin substructure leads to a shift in load bearing toward the stiffer collagen substructure in the arterial wall (Fig. 2C). The associated processes of elastin substructure fragmentation, degradation, and fiber loss were studied in 15 papers (15 of 63 papers, assigned to the focus category of “elastin”). Table 1 shows an overview of these studies, which focused mainly on gene, protein, and fiber levels of pathological characterization. Although these elastin-related processes influence collagen load bearing (as illustrated by the line color in Fig. 2C), the above studies reportedly did not assess underlying changes in collagen substructure. An extensive topical review on elastin in the context of arterial mechanics and cardiovascular disease has been published recently by Cocciolone et al. (27). Focused reviews on medial calcification/elasticxcalcinoxsis are given by Atkinson (6) and Lanzer et al. (75).

_Collagen-related processes of arterial stiffening._ The collagen substructure in the arterial wall bears the mechanical load for elevated blood pressures (Fig. 2B). An increase in the stiffness of the collagen substructure leads to a proportional increase in wall stiffness (Fig. 2D). Collagen deposition, cross-linking, turnover, and degradation were investigated in 17 studies (17 of 63 studies; assigned to the focus category of “collagen”). Table 2 shows an overview of these studies, which focused mainly on gene, protein, and fiber levels of pathological characterization. Whereas glycation-induced cross-linking is often associated with increased collagen substructure stiffness, it may directly or indirectly involve the elastin substructure as well (134). Recent reviews with sections dedicated to vascular fibrosis and collagen-related glycation processes have been published by Harvey et al. (46) and Sell and Monnier (114).

_Smooth muscle-related mechanisms of arterial stiffening._ Vascular smooth muscle can be regarded as a “variable” ECM component, partially offloading or loading the elastin and collagen substructures by increasing or decreasing tone. In vivo, the functional contribution of vascular smooth muscle to arterial stiffness can be acutely varied by relaxant or constrictive agents. Thirteen papers (13 of 63 papers) were categorized under “smooth muscle,” as shown in Table 3. The majority of these studies directly targeted contractile function of vascular smooth muscle and, hence, considered pathological description at the cell level (Table 3). In the long term, the phenotype of vascular smooth muscle cells, ranging between contractile and synthetic, may have an impact on measured arterial stiffness. Noncontractile properties were considered in three studies (43, 80, 91). Up-to-date reviews on the role of smooth muscle cells in arterial stiffening are provided by Sehgel et al. (112), Lacolley et al. (73), and Durham et al. (36). Although experimental data are rapidly developing, patient-based studies are not yet considering smooth muscle cell-centered approaches to treat stiffened arteries.

_ECMArelated processes of arterial stiffening._ The focus category of the ECM was used to contain 1) papers with a focus on the ECM as a whole and 2) papers targeting ultrastructural components of the vascular wall other than elastin, collagen, and smooth muscle. Eighteen papers (18 of 63 papers) were assigned to this category. As shown in Table 4, levels of pathological characterization were more varied (also due to classification used as such). Four papers focused explicitly on the fiber network level. You et al. (157) measured PWV...
in patients with coronary artery disease, in whom they also obtained aortic tissue specimens for quantitative histological analyses. Increased PWV was associated with an increased collagen-to-elastin content ratio, as identified both between hypertensive and normotensive groups as well as within these groups (157). Khamdaeng et al. (64) considered the difference in stiffness at diastolic and systolic pressure and used a two-dimensional, nonlinear, hyperelastic model to infer differences in elastin and collagen elastic moduli from pressure-area data, as obtained in young healthy volunteers. This approach was pioneered by our laboratory at carotid level (47, 48, 147) and recently extended to the proximal aorta (56). In their elegant study, Gaddum et al. (42) actively modified transmural pressure over a considerable range (by Valsalva and Mueller maneuvers in patients with hypertension and matched controls) to quantify the pressure dependence of PWV (measured over the arch-diaphragm trajectory by Doppler transit time). They found pressure dependence to be markedly greater in the

\[ \text{distensibility} = \frac{\Delta d}{\Delta P} \times \frac{1}{d_0} \]

where \( \Delta d \) is the diastolic-systolic diameter difference, \( \Delta P \) is the pulse pressure, and \( d_0 \) is diastolic diameter. PWV \(_{\text{dist}} \) was subsequently calculated as follows:

\[ \text{PWV}_{\text{dist}} = \sqrt{\frac{1}{2P \times \text{distensibility}}} = \sqrt{\frac{\Delta P d_0}{\Delta d 2P}} \]

Foot-to-foot (“transit time”) PWV is known to depend on diastolic blood pressure (16, 95, 96) and on diastolic (not diastolic-to-systolic) compliance. Hence, we defined PWV \(_{\text{dist}} \) as follows:

\[ \text{PWV}_{\text{dist}} = \sqrt{\frac{\Delta P}{\partial d \mid_{\text{P=DBP}}}} \]

\( d_0 \) is the derivative of pressure to diameter at diastolic blood pressure (DBP).

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**Fig. 2. Effects of elastin and collagen on arterial mechanics.**

A: typical arterial pressure-radius relationship illustrating the increase in pressure load bearing by collagen with increasing pressure (line color). B: pressure dependence of distensibility (dist), distensibility-based PWV (PWV \(_{\text{dist}} \)), “diastolic foot” PWV (PWV \(_{\text{dia}} \)), and stiffness index \( \beta_0 \) (122). Indexes are calculated for normotensive (NT; 120/80 mmHg) and hypertensive (HT; 160/100 mmHg) pressure ranges. C and D: influence of elastin stiffness (C) and collagen stiffness (D) on the pressure-radius relationship and stiffness measures as determined over the NT range. All graphs were generated using constitutive modeling, specifically a thin-walled four-fiber collagen constitutive model (Eq. 4) with neo-Hookean elastin behavior (Eq. 2) and no smooth muscle (8), parameterized with \( c_1 = 80 \) kPa, \( c_1 = c_1 = c_1 = 40 \) kPa, \( c_1 = c_1 = c_1 = c_1 = 2 \), and \( \beta_1 = 0 \), \( \beta_2 = 90 \), \( \beta_3 = 45 \), and \( \beta_4 = -45 \), an unloaded radius and thickness of 10 and 2 mm, respectively, and an axial stretch of 1.25. In C, the \( c_1 \) values used were 40, 80, and 120 kPa. In D, \( c_1 = c_1 = c_1 = c_1 \) values of 20, 40, and 60 kPa were used; \( c_1 = c_1 = c_1 = c_1 \) were kept unchanged.

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2 Distensibility was calculated as follows: distensibility = \( \frac{\Delta d}{\Delta P} \times \frac{1}{d_0} \), where \( \Delta d \) is the systolic-diastolic diameter difference, \( \Delta P \) is the pulse pressure, and \( d_0 \) is diastolic diameter. PWV \(_{\text{dist}} \) was subsequently calculated as follows:

\[ \text{PWV}_{\text{dist}} = \sqrt{\frac{1}{2P \times \text{distensibility}}} = \sqrt{\frac{\Delta P d_0}{\Delta d 2P}} \]

Foot-to-foot (“transit time”) PWV is known to depend on diastolic blood pressure (16, 95, 96) and on diastolic (not diastolic-to-systolic) compliance. Hence, we defined PWV \(_{\text{dist}} \) as follows:

\[ \text{PWV}_{\text{dist}} = \sqrt{\frac{\Delta P}{\partial d \mid_{\text{P=DBP}}}} \]

\( d_0 \) is the derivative of pressure to diameter at diastolic blood pressure (DBP).
Table 1. Level of pathological characterization in clinical-epidemiological studies focusing on elastin-related arterial stiffening

| Reference            | Year    | Context          | Arterial Stiffness Measure | Focus                  | Gene | Protein | Fiber | Cell | Fiber | Network | Vessel | Wall |
|----------------------|---------|------------------|----------------------------|-------------------------|------|---------|-------|------|-------|----------|--------|------|
| Lee et al. (79)      | 2015    | Coronary disease | cPWV                       | Anti-elastin antibody titer |     |         |       |      |       |          |        |      |
| Maclay et al. (84)   | 2012    | COPD             | cPWV                       | Proteolytic degradation  |     |         |       |      |       |          |        |      |
| Smith et al. (119)   | 2012    | Predialysis CKD  | cPWV                       | Matrix metalloprotease-2, |     |         |       |      |       |          |        |      |
| Rabinovich et al. (103) | 2015  | COPD             | cPWV                       | Plasma desmosine         |     |         |       |      |       |          |        |      |
| Maloberti et al. (85) | 2015  | Williams-Beuren  | cPWV                       | Deleted gene             |     |         |       |      |       |          |        |      |
| Longobardo et al. (81) | 2017  | Bicuspid valve   | aoDC                       | Elastin single nucleotide |     |         |       |      |       |          |        |      |
| Hansen and Rasmussen (45) | 2015  | Diabetes         | cPWV                       | Fibulin-1                |     |         |       |      |       |          |        |      |
| Kruger et al. (70)   | 2012    | Heart failure    | cPWV                       | Fibulin-1                |     |         |       |      |       |          |        |      |
| Laugesen et al. (76) | 2013    | Diabetes         | cPWV                       | Fibulin-1                |     |         |       |      |       |          |        |      |
| Mayer et al. (90)    | 2016    | General population | cPWV      | MGP                      |     |         |       |      |       |          |        |      |
| Pivin et al. (101)   | 2015    | Family population | cPWV                  | MGP                      |     |         |       |      |       |          |        |      |
| Sardana et al. (107) | 2017    | Diabetes         | cPWV                       | MGP                      |     |         |       |      |       |          |        |      |
| Thamratnopkoon et al. (139) | 2017 | CKD               | cPWV, CAVI                   | MGP                      |     |         |       |      |       |          |        |      |
| Albu et al. (3)      | 2013    | Postmenopause    | oscPWV, CAVI                | MGP, osteoprotegerin,   |     |         |       |      |       |          |        |      |
|                       |         |                  |                            | osteocalcin              |     |         |       |      |       |          |        |      |
| Namba et al. (94)*   | 2017    | Anticoagulants   | cPWV                       | MGP, osteocalcin         |     |         |       |      |       |          |        |      |

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; cPWV, carotid-femoral pulse wave velocity (PWV); aoDC, aortic distensibility coefficient; CAVI, cardio-ankle vascular index; oscPWV, PWV estimate from the oscillometry signal; MGP, matrix Gla protein. ● Level(s) at which a study assessed arterial stiffening. *Intervention study.

normotensive group compared with the hypertensive group. Furthermore, they showed (isobaric) PWV to be equal between both groups at 8 m/s and a transmural pressure of ~95 mmHg. Using a nonlinear two-constituent model, Gaddum et al. (42) tentatively interpreted their measured findings as resulting from changes in elastin/collagen content in combination with a decrease in elastin elastic modulus. Justifiably, the investigators evaluated the validity of their modeling approach by observing that the data in the hypertensive group was well represented by a simpler model (i.e., with fewer parameters; also see Local minima and overfitting). The model complexity/overfitting consideration was a major aspect of our study that

Table 2. Level of pathological characterization in clinical-epidemiological studies focusing on collagen-related arterial stiffening

| Study            | Year    | Context          | Arterial stiffness measure | Focus                  | Gene | Protein | Fiber | Cell | Fiber | Network | Vessel | Wall |
|------------------|---------|------------------|----------------------------|-------------------------|------|---------|-------|------|-------|----------|--------|------|
| Rosa et al. (105) | 2012    | Aldosteronism    | cPWV                       | Collagen fiber accumulation |     |         |       |      |       |          |        |      |
| Bai et al. (9)   | 2015    | Renal disease    | β-PWV                      | COL1A1 expression       |     |         |       |      |       |          |        |      |
| Adi et al. (2)   | 2015    | Polymorphisms    | cPWV                       | COL4A1 polymorphism     |     |         |       |      |       |          |        |      |
| Mirault et al. (92) | 2015 | Vascular Ehlers-Danlos syndrome | cPWV          | COL3A1 gene defect      |     |         |       |      |       |          |        |      |
| Lyck Hansen et al. (82) | 2015 | Proteome         | cPWV                       | Collagen types           |     |         |       |      |       |          |        |      |
| Cecelja et al. (21) | 2016 | Twins cohort     | cPWV, cDC                  | Collagen type IV        |     |         |       |      |       |          |        |      |
| Sven et al. (135) | 2015   | Diabetes         | cPWV                       | Collagen cross-linker    |     |         |       |      |       |          |        |      |
| Hofmann et al. (51) | 2013 | AGEs             | cPWV                       | Collagenase digestive collagen |     |         |       |      |       |          |        |      |
| Mac-way et al. (83) | 2014 | Peritoneal dialysis | cPWV          | Cross-linking            |     |         |       |      |       |          |        |      |
| Semba et al. (115) | 2015   | AGEs             | cPWV                       | Cross-linking by carboxymethyl-lysine |     |         |       |      |       |          |        |      |
| Hampson et al. (44) | 2015 | Postmenopause    | cPWV                       | Pro-collagen type I C-peptide, telopeptide of collagen type I |     |         |       |      |       |          |        |      |
| Cotie et al. (28) | 2016    | Coronary disease | cDC                        | Pro-collagen type I C-peptide, telopeptide of collagen type I |     |         |       |      |       |          |        |      |
| Stakos et al. (128) | 2013 | Exercise-induced chest pain | cPWV          | Telopeptide of collagen type I, matrix metalloprotease-1, tissue inhibitor of metalloproteinase 1 |     |         |       |      |       |          |        |      |
| Kondo et al. (67) | 2016    | Risk factors     | baPWV                      | Telopeptide of collagen type I |     |         |       |      |       |          |        |      |
| Yun et al. (158)  | 2016    | Hospital cohort  | baPWV                      | Telopeptide of collagen type I |     |         |       |      |       |          |        |      |
| Kouguchi et al. (68)* | 2013 | Collagenase      | baPWV                      | Chicken collagen hydrolysate |     |         |       |      |       |          |        |      |
| Igase et al. (61)* | 2018    | Collagenase randomized control trial | baPWV          | Pork collagen peptide    |     |         |       |      |       |          |        |      |

AGE, advanced glycation end product; cPWV, carotid-femoral pulse wave velocity (PWV); β-PWV, PWV calculated from stiffness index β; cPWV, carotid PWV; cDC, carotid distensibility coefficient; baPWV, brachial-ankle PWV; COL1A1, collagen type I α1; COL4A1, collagen type IV α1; COL3A1, collagen type III α1. ● Level(s) at which a study assessed arterial stiffening. *Intervention study.

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Table 3. Level of pathological characterization in clinical-epidemiological studies focusing on smooth muscle-related arterial stiffening

| Study | Year | Context | Arterial Stiffness Measure | Focus | Gene | Protein | Fiber | Cell | Fiber | Network | Vessel | Wall |
|-------|------|---------|---------------------------|-------|------|--------|-------|------|-------|---------|--------|------|
| Adam et al. (1)* | 2016 | Cystic fibrosis | cfPWV | Cystic fibrosis transmembrane conductance regulator | | | |
| Shimizu et al. (116)* | 2016 | Coronary disease | CAVI | Nitroglycerin | | | |
| Fok et al. (41)* | 2012 | Nitric oxide | Forearm PWV | Smooth muscle tone | | | |
| Tanaka et al. (138) | 2017 | Aging | cCC | Smooth muscle tone | | | |
| Cicke et al. (26) | 2013 | Dipping | cfPWV | Smooth muscle tone | | | |
| Naka et al. (93) | 2012 | Diabetes | cfPWV | Vasodilation | | | |
| Liao et al. (80) | 2015 | Rho kinases | β-PWV | Rho kinase 2 single-nucleotide polymorphism | | | |
| Mels et al. (91) | 2016 | Differences in the black population | cfPWV | Creatine kinase | | | |
| Gu et al. (43) | 2015 | Memecean | baPWV | Osteoglycin = mimecan, endothenin-1 | | | |
| Amano et al. (4)* | 2018 | Prostate | baPWV | PDE5 inhibition | | | |
| Attina et al. (7)* | 2013 | Exercise capacity | cPPWV | PDE5 inhibition | | | |
| Takahashi et al. (136)* | 2012 | Healthy volunteers | CAVI, baPWV | Prostaglandin I2 analog | | | |
| Ballard et al. (10)* | 2015 | Statin myalgia | cPPWV | Simvastatin | | | |

cfPWV, carotid-femoral pulse wave velocity (PWV); CAVI, cardio-ankle vascular index; cCC, carotid compliance coefficient; β-PWV, PWV calculated from stiffness index β; baPWV, brachial-ankle PWV; PDE, phosphodiesterase. Level(s) at which a study assessed arterial stiffening. *Intervention study.

was focused on explaining the stiffness/pressure/age pattern we identified in a hypertensive outpatient sample and arterial stiffness reference population (125). The pressure-area data we obtained in younger and older patients with hypertension were fitted with a single-exponential model for interpolation purposes (126). Subsequently, we used an existing constitutive model (161) and developed a stepwise modeling scheme to quantitatively interpret the age-related (cross-sectional) differences in pressure-area data. We also found a decreased elastin elastic modulus as (partially) explaining the increased stiffness in older patients with hypertension (98, 125). The validity of our modeling approach was corroborated by the observation of 1) a similar change in simulated and measured carotid wall thickness and 2) reproducible findings using followup data of the same patients under lowered blood pressure conditions. The collagen-elastin matrix architecture (i.e., fiber network characteristics) was not quantified in the histological analyses of You et al. (157) or in the above studies using constitutive model-based interpretation of arterial stiffness findings. Although in experimental studies the biomechanical and mecha-

Table 4. Level of pathological characterization in clinical-epidemiological studies focusing on extracellular matrix-related arterial stiffening

| Study | Year | Context | Arterial stiffness measure | Focus | Gene | Protein | Fiber | Cell | Fiber | Network | Vessel | Wall |
|-------|------|---------|---------------------------|-------|------|--------|-------|------|-------|---------|--------|------|
| Wens et al. (153) | 2014 | Pompe disease | cfPWV, CDC | Glycogen accumulation | | | |
| Boardman et al. (14) | 2016 | Preterm birth | cfPWV, CAVI | Elastin and collagen development | | | |
| Kozel et al. (69) | 2014 | Williams syndrome | cfPWV | Neutrophil cytosolic factor-1 gene deletion | | | |
| de Oliveira Alvim et al. (32) | 2012 | Reactive oxygen species | cfPWV | p22hox gene polymorphisms, TNF-α | | | |
| Knoll et al. (65) | 2012 | Case report | cfPWV | Complement activation | | | |
| Cseprekal et al. (29) | 2014 | Renal transplant | cfPWV | Bone alkaline phosphatase, osteocalcin | | | |
| Kuo et al. (72) | 2018 | Hemodialysis | cfPWV | Leptin | | | |
| Tsai et al. (141) | 2015 | Renal transplant | cfPWV | Leptin | | | |
| You et al. (157) | 2012 | Coronary disease | cfPWV | Elastin-collagen content | | | |
| Gaddum et al. (42) | 2015 | p-Dependence | cfPWV | Elastin-collagen load bearing | | | |
| Khamdaeng et al. (64) | 2012 | p-Dependence | cDC | Elastin-collagen load bearing | | | |
| Sprock et al. (125) | 2015 | Hypertension | cDC | Elastin-collagen load bearing | | | |
| Mandruffino et al. (87) | 2014 | Smoking | cDC | IgG | | | |
| Valvano et al. (143)* | 2015 | Metabolic syndrome | Distensibility | Mesoglycan | | | |
| Peeters et al. (100) | 2017 | Diabetes | cfPWV | MMP-3 | | | |
| Kromidas et al. (62) | 2015 | Cardiac function | cfPWV | Transforming growth factor-β1, MMP-9, tissue inhibitor of metalloproteinase-1 | | | |
| Kuloglu et al. (71) | 2013 | Vitamin D | cfPWV | Vitamin D | | | |
| Seker et al. (113) | 2013 | Vitamin D | oscPWV | Vitamin D | | | |

p-dependence, pressure-dependent stiffness; cfPWV, carotid-femoral pulse wave velocity (PWV); cDC, carotid distensibility coefficient; CAVI, cardio-ankle vascular index; baPWV, brachial-ankle PWV; oscPWV, PWV estimate from oscillometry signal; MMP, matrix metalloproteinase. Level(s) at which a study assessed arterial stiffening. *Intervention study.
nobiological interactions between vascular cells and the
ECM are increasingly considered, we did not find patient-
based studies specifically characterizing cell-matrix interac-
tions in our search. Reviews on cell-matrix interactions have
been put forward by De Luca (31), Kohn et al. (66), and
Humphrey et al. (58).

**Overall Summary of Clinical-Epidemiological Review Findings**

Taken together, 63 of 514 papers (12%) searched from
2012 explicitly addressed ultrastructural changes. Of those, the
vast majority of papers (52 of 63 papers) described cross-
sectional associations of sub-ECM level factors with PWV
(Table 1, 2, 3, and 4). A small number of intervention studies
(11 of 63 studies) addressed changes in arterial stiffness
through modulation of ECM integrity (1, 61, 68, 94, 143) or
smooth muscle tone (4, 7, 10, 41, 116, 136). Only a handful (3
of 63 studies) used a modeling approach to quantitatively
interpret these changes at the level of elastin, collagen, and
ECM (42, 64, 125).

Overall, the above illustrates that the pathological charac-
terization alongside arterial stiffness measures in clinical stud-
ies shows a gap (Tables 1, 2, 3, and 4), challenging mechanistic
interpretation. We submit that the consequent lack of quanti-
tative mechanistic insight limits the field in designing and
testing treatment approaches to target the ultrastructural basis
of arterial stiffening (15, 37, 140, 159). Motivated by previous
work of ours and others (13, 23, 39, 125, 142, 151), we
consider the skillful application of constitutive models to
clinical arterial stiffness data of great potential value to close
the mentioned gap. Therefore, in the next section, we will
discuss the applicability of constitutive modeling and provide
some guidance on releasing its potential.

**CONSTITUTIVE MODEL-BASED INTERPRETATION**

Here, first, we will give a brief introduction to constitutive-
based modeling of arterial wall mechanics (54, 57). The arterial
wall consists of three main load-bearing constituents: collagen,
elastin, and vascular smooth muscle. A constitutive model of
the arterial wall explicitly and mathematically describes the behavior of (some of) these individual constituents and pro-
vides a quantitative/mechanistic link between these constitu-
ents (contents and properties) and in vivo arterial stiffness
measurements (Fig. 3). Second, we will use model simulations
to illustrate the effects of changes in constituent properties on
arterial measures available in vivo: the “forward” approach.
The simulations will also show why most of these measures
depend significantly on blood pressure. Third, supported by a
review of the available modeling literature, we will discuss
how in vivo arterial measurements can be used to obtain
information on arterial wall constituents, i.e., the “inverse
approach.”

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Note that the definitions of “forward” and “inverse” approach as used in this article are formally different from those used in the mechanics field, where a forward approach implies finding displacements given properties and loads and an inverse approach implies finding properties given loads and displace-
ments.
Elastin models. Elastin was previously modeled either as a neo-Hookean material, for which \( W \) is defined as follows:

\[
W_{\text{elastin}} = \frac{c_1}{2}(I_C - 3)
\]  

(2)

or following Zulliger et al. (160), who defined \( W \) as follows:

\[
W_{\text{elastin}} = c_1(I_C - 3)^{3/2}
\]  

(3)

\( I_C \) is the first invariant of \( C \) (\( I_C = \lambda_1 + \lambda_2 + \lambda_3 \)). Both formulations assume bulk elastin to behave isotropically.

Collagen models. Collagen is assumed to be oriented in fiber families in the axial-circumferential plane that are symmetric about the vessel axis. “Two-fiber family” models (53) only model two diagonally oriented families, whereas “four-fiber family” models additionally model a longitudinal family and a circumferential family (8). A commonly used collagen SEF is of the following form:

\[
W_{\text{collagen}} = \sum_{k=1}^{N} \frac{c_k^2}{N \times c_3^2} \left( \exp \left[ \frac{c_k^2((\lambda_k^\text{k})^2 - 1)^2}{2} \right] - 1 \right)
\]  

(4)

where \( N \) is the number (2 or 4) of collagen families, \( c_2^k \) and \( c_3^k \) are the \( k \)th collagen family’s material parameters, and \( \lambda_k^\text{k} \) is the \( k \)th collagen family’s stretch, defined as \( \lambda_k^\text{k} = \sqrt{\lambda_\text{k}^2 \sin^2 \beta_k + \lambda_\text{k}^2 \cos^2 \beta_k} \) with \( \beta_k \) being the \( k \)th collagen fiber family’s angle relative to the axial direction in the reference configuration.

Zulliger et al. (160) proposed a different SEF, in which the engagement of individual collagen fibers is explicitly modeled by means of a log-logistic probability density function (\( p_{\text{fiber}} \)) as a function of the fiber stretch. In that case,

\[
W_{\text{collagen}} = W_{\text{fiber}} \ast p_{\text{fiber}}
\]  

(5)

where \( W_{\text{fiber}} \) is the SEF of an individual collagen fiber and “\( \ast \)” is the convolution operator.

Smooth muscle models. Not all in vivo constitutive modeling studies have incorporated smooth muscle behavior. Masson and colleagues (88, 89) modeled the Cauchy stress contribution due to smooth muscle contraction following Rachev and Hayashi (104) as follows:

\[
t_{\text{SM}} = T_m\lambda_0 \left[ 1 - \left( \frac{\lambda_m - \lambda_0}{\lambda_m - \lambda_0} \right)^2 \right] e_0 \otimes e_0
\]  

(6)

and added the \( t_{\text{SM}} \) term to the Cauchy stress from Eq. 1. \( T_m \) is a constant that denotes the level of activation (in Pa), \( \lambda_m \) is the stretch at which the contraction is maximum, and \( \lambda_0 \) is the stretch at which the active force generation ceases (89).

Zulliger et al. (161) and Spronck et al. (125) modeled the Cauchy stress contribution of smooth muscle as follows:

\[
t_{\text{SM}} = c_{\text{SM}}S_1S_2(\lambda_0\lambda_{\text{pre}} - 1)e_0 \otimes e_0
\]  

(7)

where \( c_{\text{SM}} \) is a parameter that determines maximum stress development and \( \lambda_{\text{pre}} \) is the (constant) smooth muscle “pre-stretch” (161). \( S_1 \in [0,1] \) is a function that relates the smooth muscle tone to the level of stretch in the vessel (“myogenic response”), and \( S_2 \in [0,1] \) is a function that ensures that smooth muscle develops tension only within a certain stretch range.

Modeling assumptions and choices. Hyperelasticity and incompressibility. The use of a SEF implies the assumption of hyperelasticity (“lossless deformation”). However, arterial wall tissue behaves viscoelastically to some extent and under specific conditions, causing arterial mechanics and stiffness to be strain rate dependent and, therefore, heart rate dependent (137). Because arterial tissue consists mostly of water (which behaves incompressibly, except at very high pressures or velocities; see Refs. 18 and 60), it can be assumed to be incompressible.

Cylindrical geometry. Although complex arterial geometries can be imaged using e.g., MRI and studied using fluid-solid interaction modeling (FSI), in the studies presented here, a cylindrical geometry is assumed, and the artery is assumed to be torsion free.

Thick-walled versus thin-walled geometry. Arterial models can be modeled as either a thick-walled or thin-walled tube. Thick-walled models have the advantage that the distribution of stress throughout the wall (along the radial coordinate) can be studied. However, mechanical stress in an unloaded (pressure free and axially free) artery is not zero: there is a residual stress gradient (11). Implementation of such a gradient in the unloaded state is mandatory to ensure that the stress distribution under in vivo loading conditions is realistic. The most common method of implementing residual stress in models is by means of an opening angle, which can be empirically measured by longitudinally cutting an arterial ring. However, in vivo this procedure is clearly inadmissible. To overcome this problem, one may 1) assume the artery to be thin walled, in which case there is no stress gradient that needs to be described, 2) try to estimate the opening angle by fitting it as an additional parameter, or 3) use a different reference configuration.

Choice of reference configuration. Traditionally, a stress-free reference configuration is chosen, which for a cylindrical arterial ring is the cut-open configuration. From this state, the vessel is computationally closed and pressurized, and the vessel wall deformation (\( F \)) is defined with respect to this stress-free reference configuration. To overcome the aforementioned problem of needing to estimate the opening angle in vivo, one can also choose the in vivo configuration (at, e.g., mean arterial pressure and in vivo axial stretch) as a reference (11). This has the advantage that naturally, stresses are homogeneous at this reference, and no opening angle is needed. Residual stress is incorporated by assigning “deposition stretches” to the individual wall components. In this case, \( F \) is defined with respect to an in vivo reference and, hence, \( F = I \) for the vessel wall at this configuration. Then, at this same configuration, the individual wall components experience a deposition stretch (e.g., the arterial elastin is at \( F = F_{\text{elastin}} = G_{\text{elastin}}^r \) where \( G_{\text{elastin}}^r \) is the elastin deposition stretch tensor).

The Forward Approach: Translating (Changes in) Constitutive Properties to (Changes in) Stiffness Measurements

Here, we will illustrate how elastin and collagen, two primary load-bearing ECM constituents, influence commonly used clinical arterial stiffness measures. Figure 2 shows arterial pressure-radius relationships computed from a constitutive model (example is of aortic size). In Fig. 2A, one can appreciate that arterial constitutive models enable, for a given...
pressure, to delineate which amount of the pressure load is borne by collagen and which by elastin. As is known from experimental physiology, with increasing pressure, an increasing amount of load is borne by the collagen fiber network that gets straightened and recruited. The crossover point, where pressure load bearing is equal between collagen and elastin, is indicated by a square (Fig. 2). From the pressure-radius curve (as measured or as computed using a constitutive model), we can directly estimate most of the clinical arterial stiffness measures. Importantly, we can evaluate those measures for any given pressure (range), whether normotensive or hypertensive. Figure 2B shows this and shows how constitutive models can be used to quantitatively evaluate the pressure dependence of distensibility, PWV, and stiffness index $\beta_0$ (122). Figure 2, C and D, shows how these whole vessel stiffness measures are affected by (isolated) changes in elastin and collagen material stiffness.

The Inverse Approach: Translating (Changes in) Stiffness Measurements to (Changes in) Constitutive Properties

This section reviews previous studies that have used constitutive modeling to solve the “inverse approach,” i.e., to derive, given one or more stiffness measurements, what the underlying constitutive properties are. Furthermore, it provides recommendations and directions for future studies using this approach.

Eleven studies have previously addressed the “inverse approach.” Table 5 shows these studies with their particular measurement techniques and modeling choices. To solve the inverse approach, a constitutive model is fitted to measurement data, which means that the model parameter values are iteratively varied to minimize the difference between model behavior and measured behavior. The objective function, which quantifies this difference, may be formulated in terms of measured-modeled pressures, axial forces, or axial and circumferential stresses (38). Four studies shown in Table 5 used a Fung constitutive model (64, 110, 130, 131) and thus could not distinguish between individual arterial wall constituents. Although such an approach is limited with regard to ultrastructural or constitutive interpretation of arterial stiffness measurement, we have included these papers because they describe important steps in the development of methods for constitutive model fitting of patient data.

Measurement data. Although the following is clearly related to the stiffness measures described in arterial stiffness in recent clinical-epidemiological studies, here the focus is on the utility of the methodologies for constitutive modeling of clinical data. A first important difference between studies is the type of measurement data used. Six studies used (invasive) catheter data for either pressure or diameter acquisition or both, which severely limits applicability and prohibits screening of large cohorts. Masson and colleagues (88, 89) and Spronck et al. (125) used fully noninvasive data acquisition by using ultrasound andplanation tonometry at the carotid artery. A drawback of studying the carotid artery is that this artery is known to show less remodeling (stiffening) with aging and may, therefore, be less appropriate to represent the whole arterial bed (99). The ascending thoracic as well as the abdominal aorta can be imaged using ultrasound (the position of the ribcage prohibits insonation of the descending thoracic aorta) (56). Arterial distensibility and PWV can also be obtained by MRI (34), but with poorer availability and accessibility than ultrasound in a clinical-epidemiological setting. For assessment of distensibility, a noninvasive measurement of the proximal aortic (pulse) pressure waveform is not feasible [although personal observations (by K. D. Reesink) of carotid tonometric and aortic arch catheter waveforms show good resemblance]. Potentially, this problem may be solved by generating a central aortic pressure waveform using a generalized transfer function (22). The relevance of inaccuracy and variability of this method in the context of constitutive parameter estimation remains to be established.

Another important measurement to calibrate constitutive models is that of arterial wall thickness. One study estimated wall thickness as a fit parameter (132). However, estimated thickness varied up to 90% between cardiac cycles, stressing the importance of using thickness data of some kind. Five studies used thickness as estimated from a population regression equation. A subset of these uses thickness as measured from autopsy samples (110, 130, 131), whereas others use intimamedia thickness (IMT) from ultrasound recordings (5, 129). As its name implies, IMT takes into account only the thickness of the intima and media (as estimated from lumen-intimal and media-adventitial echo complexes) and does not include adventitial thickness. The latter is especially relevant when considering pathology involving significant adventitial thickening (12). To account for adventitial thickness, Masson and colleagues (88, 89) and Astrand et al. (5) used a scaling factor of 1.5 to convert IMT to an approximated full wall thickness.

Because IMT can be readily obtained for superficial straight arteries, IMT measurement may be added to an ultrasound distensibility protocol to acquire patient-specific arterial wall thickness information. This approach was taken by Masson and colleagues (88, 89) and by Spronck et al. (125). Masson and colleagues (88, 89) modeled adventitial behavior together with perivascular tethering using a two-parameter exponential model. Heusinkveld et al. (49) and Spronck et al. (125) ignored adventitial thickness and, as such, likely underestimated total wall thickness. However, in the latter study specifically the (age-related) change in wall thickness was considered, with the measured increase in IMT corroborating the model-predicted wall thickness increase.

RECOMMENDATIONS. In our opinion, the invasiveness of using a catheter precludes its use in large (screening) population studies. Noninvasive measures (ultrasound or MRI) provide reliable diameter waveform estimation and, hence, are to be preferred. Carotid pressure waveforms can be noninvasively obtained using applanation tonometry. When the aortic region is of interest, the use of a generalized transfer function to obtain the central blood pressure waveform should be explored.

Wall thickness data are indispensable in determining material stiffness and wall stress. As attempts to determine thickness as a fitted parameter were shown to yield unreliable results (132), we recommend estimating in vivo wall thickness by means of ultrasound IMT tools that are available. In addition, a novel technique to assess extra-media thickness (EMT) may have great potential in combination with IMT in quantifying and discriminating both adventitial and medial wall thickness changes (118).
Table 5. *Studies characterizing arterial constituent properties based on in vivo measurements*

| Study                          | Year | Artery studied       | Measurement Data       | Wall thickness | Strain Energy Function                  | Number of Fitted Parameters | Axial Force Constraint | Thick Walled |
|--------------------------------|------|----------------------|------------------------|----------------|-----------------------------------------|----------------------------|------------------------|--------------|
| Schulze-Bauer and Holzapfel    | 2003 | Thoracic aorta       | Catheter (133)         | Regression equation (74, 110) | Fung (148)                       | 6                          | Axial stress in optimization | No           |
| Stålhand et al. (132)          | 2004 | Abdominal aorta      | Echotracking (120)     | Regression equation (74, 110) | N-H + 2-fiber (53)              | 7/10\(^a\)                  | none                    | Yes          |
| Stålhand et al. (130)          | 2005 | Abdominal aorta      | Echotracking (120)     | Fit result                 | N-H + 2-fiber (53)              | 8                          | Penalized in optimization | Yes          |
| Stålhand et al. (131)          | 2006 | Abdominal aorta      | Echotracking (120)     | Regression equation (74, 110) | Fung (148)                       | 8                          | Penalized in optimization | Yes          |
| Stålhand et al. (129)          | 2009 | Abdominal aorta      | Echotracking (120)     | Regression equation (74, 110) | Fung (148)                       | 8                          | Penalized in optimization | Yes          |
| Åstrand et al. (5)             | 2011 | Abdominal aorta      | Echotracking\(^c\)     | Scaled IMT regression equation\(^b\) (5, 53) | N-H + 2-fiber (53)             | 6                          | Axial stress in optimization | No           |
| Masson et al. (89)             | 2008 | Carotid              | Echotracking\(^c\)     | Scaled IMT regression equation\(^b\) (5, 53) | N-H + 2-fiber (53)             | 6                          | Axial stress in optimization | No           |
| Masson et al. (88)             | 2011 | Carotid              | Echotracking\(^c\)     | Scaled IMT regression equation\(^b\) (5, 53) | N-H + 2-fiber (53)             | 6                          | Axial stress in optimization | No           |
| Khamdaeng et al. (64)          | 2012 | Carotid              | Echotracking\(^c\)     | Scaled IMT regression equation\(^b\) (5, 53) | N-H + 2-fiber (53)             | 6                          | Axial stress in optimization | No           |
| Spronck et al. (125)           | 2015 | Carotid              | Echotracking (126)     | Zulliger (isotropic + 2-fiber, probability density function engaged + active) (161) | N-H + 2-fiber (53)             | 8/6\(^e\)                  | Penalized in optimization | Yes          |
| Heusinkveld et al. (49)        | 2018 | Carotid              | Echotracking (52)      | IMT\(^f\) (52)            | N-H + 2-fiber (53)             | 4                          | Penalized in optimization | Yes          |

IMT, intima-media thickness; N-H, neo-Hookean. \(^7\) in case only the systolic or diastolic portion is used for fitting, 10 if both are fitted simultaneously and described using different constitutive parameters; \(^8\) equation based on IMT data, the output of which is subsequently scaled by a factor of 1.5 to convert IMT to full wall thickness; \(^9\) data not previously reported; \(^b\) constitutive model focused on media, and adventitial + tethering pressure is modeled using a lumped parameter exponential form (60); \(^c\) manually determined from the ultrasound B-mode image; \(^d\) IMT is used as an approximation of the full wall thickness, neglecting adventitial thickness; \(^e\) 8 parameters were used to fit the "young" data set, after which 6 parameters were used to fit the (aging) transition from "young" to "old." Blank lines separate groups of related studies.
Choice of constitutive model. As outlined above, many different constitutive models have been used. Elastin is most often (6 studies) modeled as neo-Hookean (Eq. 2) but sometimes using a slightly modified formulation (Eq. 3; 1 study). Both formulations use only one parameter that needs to be estimated, which makes them equally favorable in the light of parameter (over)fitting. Furthermore, both elastin models, when combined with a collagen model, capture basic arterial mechanics well. Watton et al. (150) posed, “Accurately modeling the mechanical response of elastin is a particularly important issue, if a constitutive model is required to explicitly represent the mechanical response of each constituent of arterial tissue as opposed to the overall phenomenological mechanical response [i.e., measured stiffness behavior—Ed.] of the artery.” Watton et al. (150) studied the behavior of both formulations and concluded that the neo-Hookean formulation appears most appropriate and accurate.

Seven studies modeled the collagen fiber network as a two- or four-fiber family structure. “Fiber family” is used to express the underlying distributive behavior of fibers in the orientations considered. Holzapfel et al. (53) proposed the two-fiber form in 2000. In 2007, Hu et al. (55) showed that adding longitudinal and circumferential collagen fiber families improves fitting, also when taking into account the additional parameters required using the Akaike information criterion. Schroeder et al. (109) recently compared several constitutive models and concluded that the four-fiber family model best predicted biaxial arterial behavior from uniaxial testing data. Zulliger et al. (160) proposed the use of a two-fiber family collagen model but formulated the mechanical behavior of the individual families differently by explicitly modeling engagement. This approach was also taken by Spronck et al. (125) and has the advantage of more realistically describing collagen engagement, with the drawback that the parameters describing its behavior are highly correlated.

Although it is known that arterial smooth muscle in human large arteries does regulate arterial stiffness to some extent (see ARTERIAL STIFFNESS IN RECENT CLINICAL-EPIDEMIOLOGICAL STUDIES), only three “clinical” constitutive modeling studies have taken smooth muscle tone into account (88, 89, 125). The main disadvantage of adding a smooth muscle stress component is the risk of overfitting, which is further elaborated below. The studies that did incorporate smooth muscle tone used either a formulation as proposed by Rachev and Hayashi (104) or by Zulliger et al. (161). Ideally, to estimate the contractile contribution of smooth muscle to arterial tone, a patient is given a transient dose of a vasoactive drug (15) or physiological intervention (106) while arterial pressure and diameter signals are captured. Addition of such data balances model complexity and thus would allow separation of the load-bearing contribution of smooth muscle from that of collagen and elastin.

Recommendations. Elastin is best modeled using a neo-Hookean model (Eq. 2) (150). Although a four-fiber family description of collagen has been shown to be superior over a two-fiber using laboratory ex vivo data (55, 109), it does require more parameters to be estimated. Therefore, we recommend starting using a two-fiber collagen description and ideally compare it in the in vivo setting to the four-fiber description. For collagen, the SEF in Eq. 4 is more widely used and more conveniently implemented than a convolution-based SEF (Eq. 5). Although the latter is “elegant” in that it explicitly models engagement, several (nonpatient-specific) fixed parameters underlie this model, the fixing of which potentially introduces additional modeling artifacts. Modeling smooth muscle does carry a risk of overfitting and in our opinion should be performed only when measurements are taken at multiple levels of arterial tone.

Axial force. Constitutive models of the arterial wall may describe behavior not only in the circumferential direction (shown in Fig. 2) but also in the axial direction. There is a direct coupling between axial and circumferential behavior, implying that nonphysiological axial behavior will also affect circumferential behavior and thus the overall modeling outcome (59). This coupling was illustrated by Holtackers et al. (52), who showed that in vivo in volunteers, a change in carotid axial stretch induced by rotation of the head is detectible in the circumferential pressure-diameter relationship. From ex vivo biomechanical experiments, we know that axial force remains approximately constant over a wide range of transmural pressures (17, 146, 152). Such constant axial force constraint can be implemented in models by adding an additional term to the fitting routine. Two techniques have been proposed. In thin-walled models, axial and circumferential stress can be directly calculated from measured pressure and diameter data. Assuming that axial force is constant with pressure, “measured” axial stress can be computed and used in the fitting routine to compare with model axial stress (5, 110, 129). Axial and circumferential stresses can be added (because they have the same units) to obtain the objective function, whereas no scaling factors are required. The alternative method is to penalize the deviation of axial force (not stress) with pressure (125, 130, 131). The penalty may then be weighted and combined with a pressure objective function. The advantage of this weighting is that one may influence the trade off between satisfying the pressure behavior versus satisfying the axial force constraint.

Recommendations. In all cases, an axial stress constraint should be used. Because axial force is known to remain approximately (not analytically) constant with varying pressure, an absolute constraint should be avoided. Using a penalization involving a weighting factor is desirable in this case, which allows the researcher to put more emphasis on fitting circumferential (pressure-diameter) data. We have previously successfully used a circumferential-to-axial weighting factor ratio of 10:1 (49, 125).

Thick versus thin-walled models and choice of reference configuration. Thick-walled models enable study (or consideration) of the stress distribution within the arterial wall. As described in the introduction to CONSTITUTIVE MODEL-BASED INTERPRETATION, residual stress must be taken into account for the results to be meaningful (11). Five thick-walled model studies did take residual stress into account by defining an opening angle (88, 89, 130–132) but did not constrain the stress distribution within the arterial wall. It is known, however, that blood vessels adapt toward a homogeneous distribution of wall stress across the wall (25). Spronck et al. (125) enforced this condition by posing a constraint to penalize a nonhomogeneous transmural stress distribution, i.e., in addition to assuming average wall stress to remain constant with age-related dilatation. All previous clinical constitutive-based modeling studies to date have used a stress-free reference configuration.
**RECOMMENDATIONS.** When the stress distribution within the arterial wall is not of particular interest to the researcher, it is most straightforward to use thin-walled models. When this distribution is of interest, think-walled models with an in vivo reference configuration (11) appear promising and should be explored. In case separate medial and adventitial thickness measurements are available (e.g., carotid IMT/EMT), a bilayered model can be used to explicitly model these separate layers (11), allowing study of (changes in) stress distribution between these layers.

**Local minima and overfitting.** Fitting is an iterative process, where generally 1) the objective function is evaluated for an initial set of parameter values, 2) the derivatives of the objective function with respect to the parameter values are estimated, 3) using these derivatives, parameter values are updated (a “step” is taken in the direction where the objective function is lower), and 4) the objective function is evaluated for the updated set of parameters. This four-step process is repeated until a minimum in the objective function is found (a locus in the parameter landscape where all local derivatives are positive, i.e., where each step taken would lead to an increase in the objective function).

Two potential problems may arise when fitting a model to data. The first problem is that multiple (i.e., local) minima may be present in the objective function, which represent suboptimal solutions to the optimization problem. To overcome this problem and obtain the global minimum, the fitting procedure is typically started several times from multiple start points, and, subsequently, the minimum with the smallest objective function value is accepted as the global minimum.

The second problem, overfitting, is more difficult to solve. Overfitting implies that multiple combinations of parameters exist that yield a (nearly) identical objective function value. In other words, multiple parameter combinations make the model describe the data equally well; there is no reason for choosing one over the other (40, 49). The problem of overfitting can be reduced by 1) reducing the number of model parameters that need to be fitted (“simplifying the model”) and/or 2) increasing the amount of information on which the objective function is based. In laboratory tests, the latter can be accomplished by performing both inflation and extension tests and performing those at different axial stretches and transmural pressures, respectively (33). In vivo, this is generally not feasible, although head rotation (52) and a cold pressor test (106) may be useful to inform and improve parameterization by adding data on biaxial mechanics and smooth muscle tone, respectively. In addition, parameter identification is aided by assuming the artery axial force and vascular tone to remain constant over the cardiac cycle (see “choice of model” and “axial force”). Rather than trying to capture mechanics/behavior under one condition, both research and clinical settings are often well served by determining a difference or change in arterial mechanics/behavior. Therefore, in our own previous constitutive modeling approach, we focused on quantifying the (cross-sectional, age-related) difference in pressure-area curves, which allowed for a reduction in the number of parameters considered (125).

**RECOMMENDATIONS.** To ensure that a fitting solution represents a global minimum, the fitting routine should be started from multiple start points, and the lowest minimum should be taken. Overfitting should be checked for by inspecting the parameter landscape and/or by performing a sensitivity analysis. In case overfitting is recognized, 1) the constitutive model should be simplified, 2) model parameters should be fixed, or 3) more measurement data should be acquired, e.g., by varying axial stretch or smooth muscle tone or even by repeating the same experiment to reduce effective measurement noise (49).

**Outlook**

Constitutive modeling of patient data is still in its infancy. Despite the challenges presented, we strongly believe that personalized constitutive modeling, especially using noninvasively obtained data, will greatly advance the arterial stiffness field.

**Illustrative patient case.** The methodology presented could provide valuable insights into several diseases that involve arterial stiffening. We will illustrate this through a patient case. The patient, 65 yr old, has a blood pressure of 160/90 mmHg (i.e., the patient is hypertensive) and has been diagnosed with type 2 diabetes. The patient also shows increased arterial stiffness, as assessed by a high (>10 m/s) carotid-femoral PWV.

The following question remains: Why is this patient’s arterial stiffness (PWV) increased? Is it a sign of structural damage? If so, at what level? What would then be a therapeutic target? Several scenarios are possible. Hypertension is associated with arterial stiffening, which may involve medial thickening (smooth muscle hypertrophy and/or matrix deposition) as well as adventitial thickening through inflammation and collagen deposition (12, 20, 155). Furthermore, the mechanical competency of this patient’s elastin is likely influenced by the patient’s age through mechanical fatigue, calcification, and proteolytic damage (27, 35). Additionally, diabetes is associated with increased collagen cross-linking through an increase in advanced glycation end products (108). Finally, PWV itself directly depends on blood pressure at the time of measurement (126).

Patient-specific constitutive-based modeling could, in this case, provide insights into the cause of the stiffening; it can distinguish between elastin and collagen, potentially between media and adventitia, and between blood pressure and intrinsic effects. Particularly, this is useful in developing drugs that specifically aim at arterial destiffening (15). These include cross-link breakers (154), drugs that prevent elastin degradation (19, 35, 149), and drugs that block or prevent medial calcification (111) but also antihypertensive drugs that may have a destiffening effect (102).

**Summary of recommendations.** Implementation of patient-specific, constitutive-based modeling in a research setting can be relatively straightforward. We suggest starting examination of the carotid artery by means of ultrasound wall tracking (diameter waveform and IMT/EMT) and planation tonometry (pressure waveform) scaled using brachial blood pressure (144). An SEF consisting of a neo-Hookean part plus a two-fiber family part (Eqs. 2 and 4) provides a good starting point. A bilayered model configuration (especially when an EMT measurement is available) with an in vivo reference configuration is optimal (11). Models should be fitted to the data using an axial force constraint while carefully monitoring the fitting process to avoid overfitting.

**Suggestions for further methodological improvements.** To date, bilayered models with an in vivo instead of a stress-free.
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reference configuration have not been fitted to patient data. Such studies would enable layer-specific constitutive modeling without the need to estimate residual stress-related parameters such as axial stretch and opening angle. Omission of these fitting parameters will improve robustness of fitting results and may even allow the user to add more detail to constitutive models, e.g., an explicit formulation for collagen cross-linking. In addition, physical (head rotation and Valsalva/Mueller maneuvers) or physiological (cold pressor test) options for modulating in vivo measured arterial properties could enable even more detailed in vivo mechanical phenotyping. Finally, further exploration should also include quantitative studies into viscous arterial wall behavior, which may help explain the heart rate dependence of arterial stiffness measurements as well as the propensity of aortic aneurysm development (30, 137, 156).

CONCLUSIONS

The present review charts the recent (5 yr) advance in constitutive interpretation of arterial stiffness measurements in the clinical-epidemiological setting. Most studies assess correlations between sub-ECM level factors and pathways on the one hand and arterial pulse wave velocity or distensibility on the other hand, which limits the quantitative and causal interpretation across these scales. Constitutive modeling approaches to close this gap in the vascular mechanics fields are emergent. With proper consideration of model assumptions and limitations in relation to measurement data and uncertainty, i.e., supported by comprehensive sensitivity analyses and evaluation of alternatives, constitutive modeling should in the future significantly add to the clinical interpretation of arterial stiffness findings.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.D.R. conceived and designed research; K.D.R. analyzed data; K.D.R. and B.S. drafted manuscript; K.D.R. and B.S. edited and revised manuscript; K.D.R. and B.S. approved final version of manuscript; B.S. performed computational experiments; B.S. interpreted results of experiments; B.S. prepared figures.

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