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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
**ΥΠΕΡΗΧΟΓΡΑΦΙΚΗ ΛΕΙΤΟΥΡΓΙΚΗ ΑΠΕΙΚΟΝΙΣΗ ΓΙΑ ΤΗΝ ΠΡΟΛΗΨΗ ΚΑΙ ΔΙΑΓΝΩΣΗ ΤΩΝ ΑΓΓΕΙΑΚΩΝ ΠΑΘΗΣΕΩΝ**

***Μεταπτυχιακή Διπλωματική Εργασία***

# *"ΜΙΑ ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΓΙΑ ΤΗΝ ΠΡΟΣΑΡΜΟΣΤΙΚΗ ΑΡΤΗΡΙΟΔΙΑΣΤΟΛΗ: Ο ΡΟΛΟΣ ΤΟΥ ΕΝΔΑΓΓΕΙΑΚΟΥ ΥΠΕΡΗΧΟΥ"*

υπό

**ΓΕΩΡΓΙΟΥ Ν. ΚΟΥΔΟΥΝΑ**

Ειδικευόμενου Αγγειοχειρουργικής

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
Διπλώματος Μεταπτυχιακών Σπουδών
*«Υπερηχογραφική λειτουργική απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων»*

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**Τίτλος εργασίας στα αγγλικά: "A SYSTEMATIC REVIEW ON ARTERIAL COMPENSATORY ENLARGEMENT: THE ROLE OF INTRAVASCULAR ULTRASOUND"**

**Πίνακας Περιεχομένων**

Στην αγαπημένη μου βαφτιστικιά, Μελίνα

ΕΥΧΑΡΙΣΤΙΕΣ

Ευχαριστώ θερμά τον Καθηγητή Αγγειοχειρουργικής κύριο Αθανάσιο Γιαννούκα που με συμπεριέλαβε στο παρόν μεταπτυχιακό πρόγραμμα σπουδών και μου έδωσε τη δυνατότητα να διδαχθώ σε βάθος επιστημονικά αντικείμενα σχετικά με την υπερηχογραφική απεικόνιση των αγγειακών παθήσεων.

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**Περίληψη**

**Αντικείμενο:** Στόχος αυτής της μελέτης ήταν να προκύψει μία συστηματική ανασκόπηση της προσαρμοστικής αρτηριοδιαστολής (ΠΑ) των στεφανιαίων, καρωτίδων και περιφερικών αρτηριών.

**Μέθοδοι:** Η μελέτη εκπονήθηκε με βάση τις PRISMA οδηγίες. Μελέτες που ερευνούσαν την ΠΑ σε στεφανιαίες, καρωτίδες και περιφερικές αρτηρίες, σχετικά με το μηχανισμό και τις επιδράσεις της, αξιολογήθηκαν ώστε να συμπεριληφθούν στην παρούσα μελέτη.

**Αποτελέσματα:** Συνολικά συμπεριλήφθηκαν 117 μελέτες, από τις οποίες 92 ερευνούσαν την ΠΑ στις στεφανιαίες αρτηρίες, 23 στις καρωτίδες και 8 στις υπόλοιπες περιφερικές αρτηρίες. Η αναδιαμόρφωση των στεφανιαίων αρτηριών εκτιμήθηκε κυρίως από ενδαγγειακή υπερηχογραφία (IVUS), ιστολογική ανάλυση, στεφανιαία αγγειογραφία, αξονική αγγειογραφία (CTA), μαγνητική τομογραφία (MRI), MDCT και υπερηχογραφία (U/S) σε 66, 11, 8, 8, 4, 2, και 2 μελέτες, αντίστοιχα. Οι καρωτίδες αρτηρίες αξιολογήθηκαν κυρίως από U/S (10 μελέτες), MRI (9 μελέτες) και ιστολογική ανάλυση (3 μελέτες). Η ΠΑ στις υπόλοιπες περιφερικές αρτηρίες αξιολογήθηκε με IVUS σε 3, ιστολογική ανάλυση σε 2, U/S σε 2 και MRI σε 1 μελέτες, αντίστοιχα.

**Συμπεράσματα:** Η ΠΑ αποτελεί μία κοινή παθοφυσιολογική απόκριση του αρτηριακού συστήματος. Ο βαθμός της προσαρμογής ποικίλει κατά μήκος του αρτηριακού δένδρου και επηρεάζεται από συννοσηρότητες, όπως ο σακχαρώδης διαβήτης. Οι μελλοντικές μελέτες στις περιφερικές αρτηρίες απαιτείται να καθορίσουν τη συμπεριφορά των αγγείων στο χρόνο, ιδιαίτερα όταν συνυπάρχει διαβήτης, και να αξιολογήσουν την επίδραση των επεμβάσεων.

**Λέξεις-κλειδιά:** προσαρμοστική αρτηριοδιαστολή, στεφανιαία αρτηρία, καρωτίδα αρτηρία, περιφερική αρτηρία, ενδαγγειακός υπέρηχος

**Abstract**

**Objective:** The purpose of this study was to provide a systematic review on the arterial compensatory enlargement (ACE) of the coronary, carotid and peripheral arteries.

**Methods:** This systematic review was performed in accordance with the PRISMA guidelines. Studies assessing the ACE phenomenon in the native coronary, carotid, and peripheral arteries and evaluating its mechanism, capabilities, or impact were examined for inclusion.

**Results:** A total of 117 articles were ultimately included. 92 studies assessed the ACE phenomenon in coronary arteries, 23 articles reported on arterial remodeling at the carotid level, and 8 studies evaluated the ACE in the rest peripheral arteries. Arterial remodeling of the coronary arteries was observed primarily by intravascular ultrasound (IVUS), pathology, coronary angiography, computed tomography angiography (CTA), magnetic resonance imaging (MRI), multidetector computed tomography (MDCT), and ultrasound (U/S) in 66, 11, 8, 8, 4, 2, and 2 studies respectively. Carotid arteries were assessed mainly by U/S (10 studies), MRI (9 studies), and pathology (3 studies). ACE in the rest peripheral arteries was assessed by IVUS in 3, pathology in 2, U/S in 2, and MRI in 1 studies, respectively.

**Conclusions:** ACE is a common pathophysiologic response of the arterial system. The degree of compensation varies along the arterial tree and with the presence or not of comorbidities such as diabetes. Prospective studies of the peripheral arteries are necessary to determine the behavior of these vessels over time, especially in the presence of diabetes and also assess the effects of intervention.

**Key words:** arterial compensatory enlargement, coronary, carotid, peripheral, intravascular ultrasound

## Introduction

Endothelial dysfunction, wall thickening, and plaque development are progressive manifestations of atherosclerotic disease. Arterial remodeling, defined as change in structural properties of the vessel through time, occurs in response to these atherosclerotic and hemodynamic alterations. There is extensive evidence of vascular enlargement compensating for atherosclerotic plaque development[1]. Glagov et al in 1987 established a theoretical threshold at which arterial compensatory enlargement (ACE) could no longer accommodate plaque build-up[2]. Remodeling delayed the development of significant coronary artery stenoses until plaque occupied, on average, 40% of the arterial area (40% plaque burden).

Several studies have attempted to reveal the underlying mechanism of ACE to better understand its progression. To that end, one proposed mechanism is that ACE is induced by wall stress resulting from stimulation of the endothelium by the development of atherosclerotic plaque, although it may also be driven by plaque disruption of the media and the adventitia[3, 4]. Despite convincing evidence has emerged supporting compensatory enlargement after the initial publications, there has been considerable heterogeneity in the methods and metrics used, which makes it difficult to formulate a consensus in the literature[5]. Arterial compensatory mechanism can be described as positive or negative remodeling to define changes in vessel area. These terms are often misapplied in segments with a negative change in lumen area, even in the presence of increasing vessel area, which would be better defined as inadequate ACE. Various assessment modalities have been proposed to visualize the remodeling process. Among them, intravascular ultrasound (IVUS) has significantly increased the scientific interest regarding geometrical remodeling in early signs of atherosclerosis[4].

## Aim

We aimed to systematically review the existing literature in an attempt to present the current understanding of the ACE phenomenon, explore the role of IVUS in visualizing arterial remodeling, and identify areas of interest that should be addressed.

## Methods

*Study design, eligibility criteria, and patient inclusion*

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[6]. Studies assessing the ACE phenomenon in the native coronary, carotid, and peripheral arteries and evaluating its mechanism, capabilities, or impact, irrespective of study design or imaging modality, were examined for inclusion. Exclusion criteria were defined as follows: (i) studies reporting on <5 patients, (ii) experimental animal studies, (iii) studies referring to arterial remodeling due to causes other than atherosclerotic disease, (iv) studies reporting on arterial remodeling following intervention (e.g. balloon angioplasty, stenting), (v) meta-analyses, systematic reviews, editorials, letters to the editor, comments, and (vi) studies with poor quality. No institutional review board approval was required. This systematic review utilized study level data.

*Information sources and search strategy*

Two authors blind to each other conducted the database search using the MEDLINE (PubMed), Scopus, and Cochrane Library databases (last search: November 19th, 2024) applying relevant keywords. No time restrictions or geographic limitations were used. Titles and abstracts of the articles were initially screened, and relevant studies were selected for full-text screening. When studies from the same center were identified, the most recent or the most relevant publication was examined for inclusion. Any discrepancy was resolved via consensus with a third senior researcher. The researchers also hand-searched for potentially eligible studies using the snowball methodology.

*Data extraction and definitions*

Data collected from the primary sources were entered into a spreadsheet. One author extracted the data from the included studies, and a second checked the extracted information. The extracted information contained the author, year of study, type of study, number of patients, arterial segment examined, imaging technique utilized, and main findings. Erroneous statements in studies under investigation were evaluated by at least two investigators to confirm. Data was analyzed by vascular territory.

Three different definitions were applied to define arterial remodeling among the included studies. By definition 1, the remodeling index (RI) was calculated as [external elastic membrane (EEM) cross-sectional area (CSA) at the lesion site]/(EEM CSA at either the proximal or distal reference site with the least amount of plaque). Values indicated positive remodeling when RI>1.05, intermediate remodeling when RI:0.95-1.05, and negative remodeling when RI<0.95. By definition 2, positive remodeling was defined when EEM CSA at the lesion site>EEM CSA at the proximal and distal reference site, while negative remodeling was present when EEM CSA at the lesion site<EEM CSA at the proximal and distal reference site. If EEM CSA at the lesion site was intermediate between the EEM CSA at the proximal and distal reference site, this resulted in intermediate remodeling. By definition 3, RI was calculated by dividing the EEM CSA at the lesion site by the mean CSA of proximal and distal reference sites. Positive remodeling was present when RI>1 whereas RI≤1 resulted in intermediate/negative remodeling[7].

*Assessment of study quality and risk of bias*

The risk of bias for the included articles was evaluated by two investigators applying the Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool[8].

## Results

*Characteristics of the eligible studies*

The PRISMA flow diagram is presented in **Figure 1**. 117 articles were ultimately considered eligible for inclusion in this systematic review. More specifically, 92 studies[2, 7, 9-98] assessed the ACE phenomenon in coronary arteries **(Table 1)** and 23 articles[20, 79, 99-119] reported on arterial remodeling at the carotid level **(Table 2)**. ACE in peripheral arteries was assessed in 8 studies[19, 20, 79, 101, 120-123]. **(Table 3)** Arterial remodeling of the coronary arteries was observed primarily by IVUS, pathology, coronary angiography, computed tomography angiography (CTA), magnetic resonance imaging (MRI), multidetector computed tomography (MDCT), and ultrasound (U/S) in 66, 11, 8, 8, 4, 2, and 2 studies respectively. Carotid arteries were assessed mainly by U/S (10 studies), MRI (9 studies), and pathology

(3 studies). ACE in the rest peripheral arteries was assessed by IVUS in 3, pathology in 2, U/S in 2, and MRI in 1 studies, respectively.

*Risk of bias*

The assessment of risk of bias across the included articles revealed that 75 studies exhibited a moderate risk of bias, with 42 studies displaying low risk of bias. **(Supplementary Table 1)**

**Figure 1:** PRISMA flowchart (last search: November 19th, 2024)

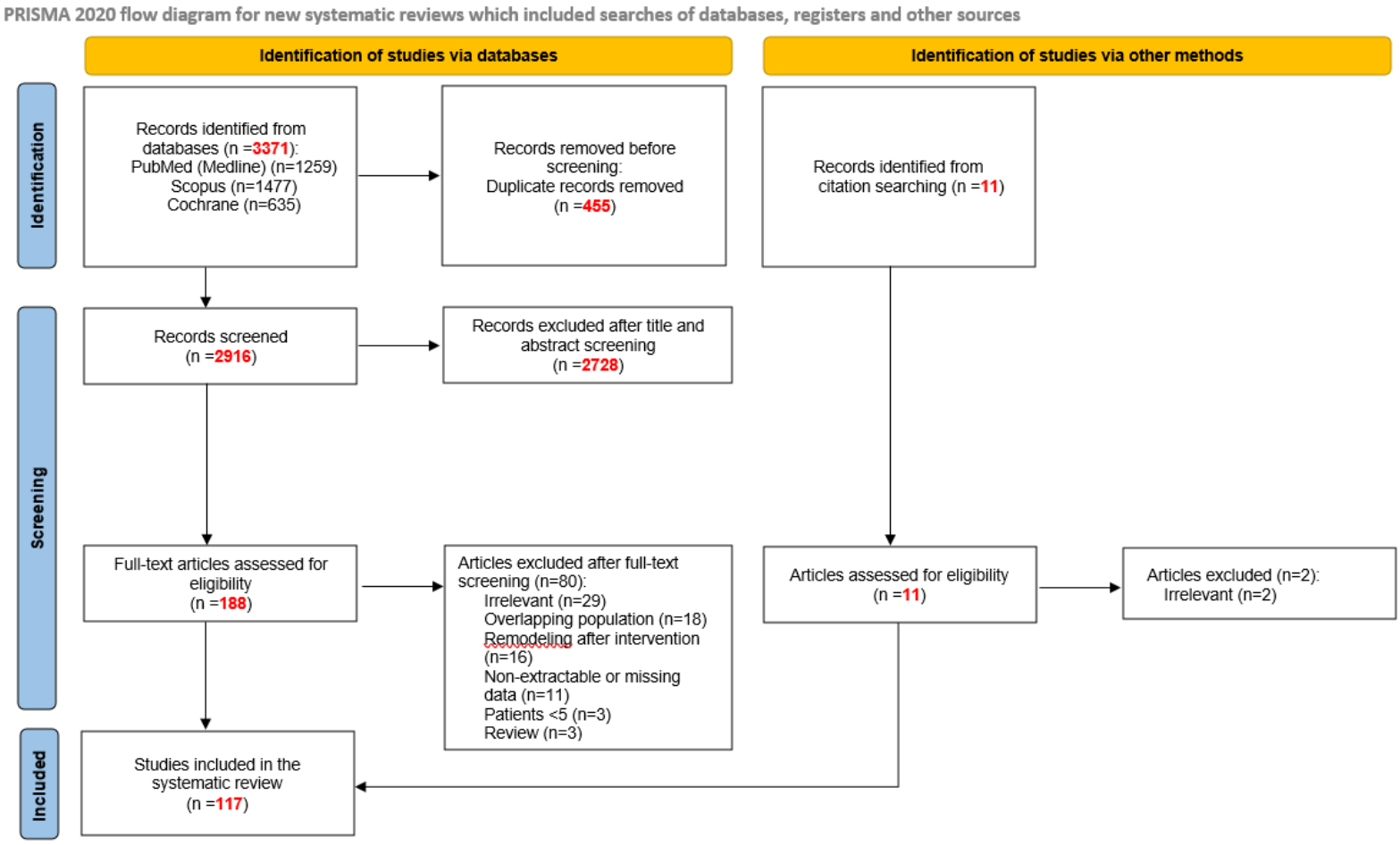

**Table 1:** Studies of arterial compensatory enlargement in coronary arteries

| Study | Design | Assessment modality | Population | Main results |
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| Glagov et al, 1987 | Cadaveric | Pathology | 136 cadaveric hearts | Coronary arteries enlarge in relation to plaque area and lumen stenosis may be prevented until the lesion occupies 40% of the internal elastic lamina area |
| Stiel et al, 1989 | Cadaveric | Pathology | 30 cadaveric hearts | Arteries may enlarge as lesion area increases |
| McPherson et al, 1991 | Cross-Sectional | U/S | 33 pts | Arterial remodeling is an important compensatory mechanism in obstructive coronary artery disease |
| Ge et al, 1993 | Prospective | IVUS | 46 pts, 92 segments | Coronary angiography cannot be used to detect the early signs of atherosclerosis due to compensatory enlargement |
| Hermiller et al, 1993 | Cross-Sectional | IVUS | 44 pts, 80 segments | Increasing plaque area increases vessel area to maintain lumen area up to 30% stenosis |
| Gerber et al, 1994 | Cross-Sectional | IVUS and Coronary angiography | 69 pts | IVUS was more reliable for delineating plaques than angiography |
| Shircore et al, 1995 | Prospective | Coronary angiography | 78 pts (MARS) | Lesion progression in one segment may lead to compensatory enlargement of remote parts of the coronary tree |
| Litovsky et al, 1996 | Cadaveric | Pathology | 137 cadaveric hearts | Arterial compensatory enlargement was observed in all arteries and luminal narrowing did not develop until plaques occupied 30% of the internal elastic lamina area |
| Nakamura et al, 1996 | Cross-Sectional | IVUS | 12 pts, 60 segments | Arterial compensatory enlargement precedes development of angiographically detectable atherosclerosis |
| Nishioka et al, 1996 | Cross-Sectional | IVUS | 30 pts, 35 lesions | Compensatory enlargement was detected in 54% of lesions whereas inadequate compensatory enlargement was present in 26% of lesions |
| Berglund et al, 1997 | Cross-Sectional | IVUS | 65 pts, 104 arterial segments | A circular lumen was maintained in 66% of all atherosclerotic lesions |
| Clarijs et al, 1997 | Cadaveric | Pathology | 32 coronary arteries | Arterial remodeling was not related to the extent of the non-diseased part of the vessel wall or lesion eccentricity |
| Pasterkamp et al, | Cadaveric | Pathology | 58 coronary arteries | Arterial compensatory enlargement was more evident in coronary, |

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| 1997 | | | | common carotid and renal arteries compared to the arteries obtained from the lower limbs |
| Tauth et al, 1997 | Cross-Sectional | IVUS | 67 pts, 71 segments | Smoking and fibrocalcific plaques were associated with constrictive remodeling whereas small vessels and hypercholesterolemia were associated with adaptive remodeling |
| Schmermund et al, 1998 | Retrospective | Electron-beam CT | 49 pts | Spotty coronary calcium may indicate early signs of atherosclerosis and compensatory arterial remodeling |
| Dangas et al, 1999 | Retrospective | IVUS | 715 pts, 777 lesions | Positive remodeling is associated with a higher long-term TLR after a nonstent interventional procedure |
| Sabate et al, 1999 | Cross-Sectional | IVUS | 80 pts, 89 lesions | Arc of calcium and plaque location at distal segments were associated with compensatory enlargement, while hard plaques were related to shrinkage |
| Shiran et al, 1999 | Retrospective | IVUS | 31 pts | Both positive and negative remodeling may occur in the left main coronary artery |
| Smits et al, 1999 | Cross-Sectional | IVUS | 69 pts | Arterial compensatory enlargement was associated with acute coronary events whereas shrinkage was related to stable angina |
| Taylor et al, 1999 | Cadaveric | Pathology | 97 cadaveric hearts | High HDL levels may be associated with positive remodeling |
| Kaji et al, 2000 | Cross-Sectional | IVUS | 56 pts, 56 lesions | Arterial compensatory enlargement may be associated with plaque rupture and acute myocardial infarction |
| Klingensmith et al, 2000 | Cadaveric | IVUS and Pathology | 7 cadavers, 7 arteries | Focal compensatory enlargement was detected in all arteries |
| Schoenhagen et al, 2000 | Cross-Sectional | IVUS | 131 pts | Positive remodeling was associated with unstable clinical presentation whereas negative remodeling was related to stable clinical presentation |
| Bezerra et al, 2001 | Cadaveric | Pathology | 36 pts | Atherosclerotic plaques causing fatal thrombosis are more often positively remodeled |
| Endo et al, 2001 | Retrospective | Coronary angiography and IVUS | 113 pts | Preinterventional arterial remodeling influenced the development of intimal hyperplasia after stenting |
| Hassan et al, 2001 | Prospective | IVUS and Pathology | 34 pts | Negative remodeling is related to increased apoptosis of intimal cells |
| Isoda et al, 2001 | Cross- | IVUS | 62 pts | Hypertension and decreased HDL levels may be associated with |

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| | Sectional | | | negative remodeling |
| Jeremias et al, 2001 | Prospective | IVUS | 58 pts | Coronary artery distensibility may be a predictor for positive remodeling |
| Okura et al, 2001 | Prospective | IVUS | 108 pts, 108 lesions (CRUISE Study) | Lesions with preinterventional positive remodeling may have worse clinical outcome after stenting |
| Takano et al, 2001 | Cross-Sectional | IVUS and Coronary angioscopy | 38 pts, 38 lesions | Yellow plaques were associated with compensatory enlargement, while white plaques were associated with paradoxical shrinkage |
| Burke et al, 2002 | Cadaveric | Pathology | 36 cadaveric hearts | Inflammation, calcification, and medial thinning are primary determinants of positive remodeling, which appears to be a feature of plaque instability |
| Ito et al, 2002 | Cross-Sectional | IVUS | 80 pts, 90 segments | Arterial compensatory enlargement is more common in eccentric lesions with significant stenosis (>50%) compared to concentric ones |
| Kim et al, 2002 | Cross-Sectional | Black-Blood MRI | 12 pts | Outward arterial remodeling was detected in patients with nonsignificant coronary artery disease |
| Iwami et al, 2003 | Cross-Sectional | IVUS and Coronary angiography | 100 pts | Positive remodeling is more frequent in patients with new onset of angina pectoris |
| Boyajian et al, 2003 | Prospective | U/S | 61 pts | Dilatation versus shrinkage in the remodeling response to expanding lesions appears related to lumen size |
| Britten et al, 2003 | Prospective | IVUS | 25 pts, 49 segments | Cardiovascular risk factors impair compensatory arterial enlargement and even predispose to negative remodeling |
| Hirose et al, 2003 | Retrospective | IVUS and Coronary angiography | 99 pts, 104 lesions | Negative remodeling is commonly observed in lesions with intermediate stenosis |
| Hong et al, 2003 | Cross-Sectional | IVUS | 274 pts | Negative remodeling is usually present in lesions with minimal reference segment disease |
| Ishida et al, 2003 | Prospective | IVUS | 26 pts | Arterial compensatory enlargement is impaired with advancing age |
| McLeod et al, 2003 | Prospective | IVUS | 25 pts, 56 segments | Both structural and functional abnormalities are associated with negative remodeling |
| Mintz et al, 2003 | Prospective | IVUS | 39 pts (ASPECT) | Preinterventional arterial remodeling, especially negative remodeling, affects neointimal hyperplasia suppression after stenting |
| Sahara et al, 2003 | Retrospective | IVUS | 48 pts, 52 lesions | Preinterventional positive remodeling was an important predictor of |

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| | | | | diffuse in-stent restenosis |
| Tamada et al, 2003 | Cross-Sectional | IVUS | 95 pts (33 diabetic pts, 62 non-diabetic pts) | DM may result in impaired compensatory enlargement |
| Gyongyosi et al, 2004 | Prospective | IVUS and Coronary angiography | 52 pts | Expansive remodeling was associated with higher plasma levels of plasminogen activator inhibitor-1and urokinase-type plasminogen activator |
| Reddy et al, 2004 | Cross-Sectional | IVUS | 26 pts (12 diabetic, 14 non-diabetic) | Both diabetic and non-diabetic patients demonstrated positive remodeling in response to atherosclerotic plaque formation |
| Bertini et al, 2005 | Cross-Sectional | MRI | 26 pts | Positive remodeling was present in all patients with CAD, as indicated by larger vessel wall area |
| Fujii et al, 2005 | Prospective | IVUS | 50 pts, 77 lesions | Positive remodeling occurs in lesions with more fibrofatty plaque |
| Hibi et al, 2005 | Cross-Sectional | IVUS | 493 pts, 514 lesions | The variability of arterial remodeling definitions affects the incidence and determinants of remodeling patterns |
| Hong et al, 2005 | Prospective | IVUS | 85 pts | Preinterventional arterial remodeling pattern affects the development of neointimal hyperplasia and in-stent restenosis after stenting |
| Nicholls et al, 2005 | Prospective | IVUS | 122 pts (REVERSAL Study) | Arterial remodeling in response to plaque changes is a heterogenous process |
| Fernandes et al, 2006 | Prospective | MRI | 22 pts, 42 segments | Outward remodeling in patients with ACS may regress with optimization of medical treatment |
| Hartmann et al, 2006 | Retrospective | IVUS | 46 pts | Arterial compensatory enlargement is not associated with the baseline plaque burden |
| Sipahi et al, 2006 (a) | Prospective | IVUS | 210 pts, 210 lesions (REVERSAL Study) | Static and serial assessments of arterial remodeling are discordant |
| Sipahi et al, 2006 (b) | Prospective | IVUS | 128 pts, 128 lesions (REVERSAL Study) | Arterial compensatory enlargement is not limited by atheroma burden |
| Tardif et al, 2006 | Prospective | IVUS | 432 pts (A-PLUS Study) | Weak correlation between plaque area and lumen area |
| Ehara et al, 2007 | Prospective | IVUS | 96 pts | Younger patients have a tendency towards constrictive remodeling whereas expansive remodeling is more common in older patients |
| Kang et al, 2007 | Retrospective | IVUS and Coronary | 55 pts, 61 lesions | Intimal hyperplasia development after stenting is influenced by the |

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| | | angiography | | preinterventional arterial remodeling pattern |
| Kitagawa et al, 2007 | Cross-Sectional | CTA | 97 pts, 202 lesions | Lower CT density, positive remodeling, and adherent spotty calcium are related to each other and may indicate plaque vulnerability |
| Schukro et al, 2007 | Prospective | IVUS | 88 diabetic pts, 104 lesions | Constrictive remodeling was more common among insulin-treated diabetic patients |
| Iwata et al, 2008 | Cross-Sectional | IVUS | 100 pts | Arterial remodeling may be associated with plasma adiponectin levels |
| Kume et al, 2008 | Cadaveric | IVUS and Pathology | 34 cadavers, 98 segments | The fibrofatty plaque area was larger in lesions with expansive remodeling than in lesions with intermediate/constrictive remodeling |
| Manfrini et al, 2008 | Prospective | IVUS | 42 pts | Expansive arterial remodeling is strictly related to autonomic nervous system dysfunction |
| Kashiwagi et al, 2009 | Cross-Sectional | IVUS | 47 pts | Arterial remodeling pattern, fibrous cap thickness, and high-sensitivity C-reactive protein level in patients with ACS are associated with each other |
| Miao et al, 2009 | Prospective | Black-Blood MRI | 179 pts | Arterial compensatory enlargement was confirmed in a subclinical population |
| Okura et al, 2009 | Prospective | IVUS | 94 pts | Positive remodeling was associated with lower MACE-free survival |
| Kang et al, 2010 | Prospective | IVUS | 176 pts | Drug-eluting stents may have a different impact on reducing intimal hyperplasia accumulation in lesions with preinterventional positive remodeling patterns |
| Kato et al, 2010 | Prospective | IVUS | 110 pts | Arterial compensatory enlargement was associated with vulnerable plaque rupture in ACS patients |
| Hussein et al, 2011 | Prospective | IVUS | 3479 pts | Patients with concomitant peripheral artery disease experienced impaired and more constrictive coronary arterial remodeling |
| Rinehart et al, 2011 | Prospective | CTA | 25 pts, 375 segments | There was thickening of arterial wall without lumen constriction |
| Samady et al, 2011 | Prospective | IVUS | 20 pts | Low WSS segments develop constrictive remodeling whereas high WSS segments develop expansive remodeling |
| Eshtehardi et al, 2012 | Prospective | IVUS | 20 pts | Remodeling analysis indicated 40% constrictive, 24% incomplete, and 36% expansive patterns, likely reflecting plaque stabilization following |

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| | | | | statin treatment |
| Manfrini et al, 2012 | Prospective | MDCT | 102 diabetic pts | Diabetes mellitus may lead to impaired adaptive remodeling |
| Matsuo et al, 2012 | Cross-Sectional | IVUS | 68 pts | Lesions with positive remodeling exhibited more characteristics of fibroatheroma |
| Nozue et al, 2012 | Prospective | IVUS | 119 pts (50 diabetic pts, 69 non-diabetic pts) (TRUTH Study) | A significant statin-induced reduction of atheroma volume along with negative remodeling was observed in non-diabetic patients, while these changes were not observed in diabetic patients |
| Ouldzein et al, 2012 | Cross-Sectional | IVUS | 68 pts | Plaque ruptures responsible for ACS are usually positively remodeled |
| Takaoka et al, 2012 | Retrospective | CT and IVUS | 31 pts | The incidence of positive remodeling tended to be greater on CT than IVUS |
| Araki et al, 2013 | Retrospective | IVUS | 146 pts, 174 vessels | Plaques in patients with positive remodeling had increased lipidic and necrotic areas |
| Hamirani et al, 2013 | Prospective | MDCT | 140 pts (ACCURACY Trial) | There is an association between arterial remodeling and the severity of atherosclerosis |
| Puri et al, 2013 | Retrospective | IVUS | 340 pts | Patients experiencing MACE were more likely to demonstrate constrictive remodeling within the left main coronary artery |
| Inaba et al, 2014 | Prospective | IVUS | 552 pts, 552 coronary arteries (PROSPECT Study) | Glagov's remodeling concept was validated in vivo |
| Katranas et al, 2014 | Prospective | CTA | 22 pts, 28 arteries | Excessive expansive remodeling is associated with high-risk plaque features including low ESS, decreased plaque stiffness, and increased plaque volume |
| Takayama et al, 2015 | Prospective | Coronary angioscopy and IVUS | 46 pts (TOGETHAR Study) | Plaques with positive and negative remodeling were changed into those with intermediate remodeling by pitavastatin |
| Antoniadis et al, 2016 | Prospective | Coronary angiography and IVUS | 219 pts, 313 coronary arteries (PREDICTION Study) | Compensatory remodeling (78.9%), excessive expansive remodeling (10%), constrictive remodeling (11.1%) |
| Kwon et al, 2016 | Cross- | IVUS | 133 pts | Plaque rupture was associated with positive remodeling whereas plaque |

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| | Sectional | | | erosion with negative remodeling |
| Liu et al, 2017 | Retrospective | CTA | 12 pts, 365 segments | Negative remodeling was more likely to occur in low and moderate VMS segments, whereas, expansive remodeling was more likely to occur in high VMS segments |
| Du et al, 2018 | Prospective | IVUS | 136 diabetic pts, 143 lesions | Negative remodeling is associated with increased glycated albumin and decreased endogenous secretory receptor for advanced glycation end products |
| Goyal et al, 2018 | Cross-Sectional | IVUS | 245 pts | Although the plaque fissure and rupture can be interchangeable in ACS, it may be another manifestation of the plaque disruption with the limited extension to the lipid core and less positive remodeling |
| Lee et al, 2018 | Prospective | CTA | 1255 pts (PARADIGM Study) | Statins decreased the risk of positive remodeling and high-risk plaques |
| Galal et al, 2019 | Prospective | CTA | 55 pts | Different morphological characteristics of positively remodeled lesions may be good potential predictors of future cardiovascular events |
| Geng et al, 2021 | Retrospective | IVUS | 162 pts, 212 lesions | Negative remodeling of intermediate lesions is associated with adverse long-term clinical outcomes |
| Cho et al, 2022 | Retrospective | CTA | 79 ESRD pts | Positive arterial remodeling (>1.1) was present in 81.0% of patients and 53.8% of plaques |
| Kashiwagi et al, 2023 | Retrospective | CTA | 149 pts | Not positive arterial remodeling was related to ACS development |

Abbreviations: U/S, ultrasound; IVUS, intravascular ultrasound; pts, patients; MARS, Monitored Atherosclerosis Regression Study; TLR, target-lesion revascularization; HDL, high density lipoprotein; CRUISE, Can Routine Ultrasound Influence Stent Expansion; ASPECT, ASian Paclitaxel-Eluting Stent Clinical Trial; DM, diabetes mellitus; MRI, magnetic resonance imaging; CAD, coronary artery disease; REVERSAL, Reversal of Atherosclerosis with Aggressive Lipid Lowering; A-PLUS, Avasimibe and Progression of Lesions on UltraSound; ACS, acute coronary syndrome; CTA, computed tomography angiography; CT, computed tomography; MACE, major adverse cardiac events; WSS, wall shear stress; MDCT, multidetector computed tomography; TRUTH, Treatment With Statin on Atheroma Regression Evaluated by Intravascular Ultrasound With Virtual Histology; ACCURACY, Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography; PROSPECT, Providing Regional Observations to Study Predictors of Events in the Coronary Tree; ESS, endothelial shear stress; TOGETHAR, Stabilization and Regression of Coronary Plaques Treated With Pitavastatin Proven by Angioscopy and Intravascular Ultrasound; PREDICTION,

Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology; VMS, von Mises stress; PARADIGM, Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging; ESRD, end-stage renal disease

**Table 2:** Studies of arterial compensatory enlargement in carotid arteries

| Study | Design | Assessment modality | Population | Main results |
|---|---|---|---|---|
| Masawa et al, 1994 | Cadaveric | Pathology | 36 cadavers, 42 carotid bifurcations | Arterial compensatory enlargement occurs in response to intimal thickening and plaque formation |
| Steinke et al, 1994 | Prospective | U/S | 32 pts | Arterial compensatory enlargement occurs in early stages of atherosclerosis |
| Pasterkamp et al, 1997 | Cadaveric | Pathology | 57 carotid arteries | Arterial compensatory enlargement was more evident in coronary, common carotid and renal arteries compared to the arteries obtained from the lower limbs |
| Labropoulos et al, 1998 | Prospective | U/S | 39 arteries | All peripheral arteries, especially the more distal vessels, dilate in response to early signs of atherosclerosis |
| Saito et al, 2002 | Prospective | U/S | 130 pts | Hypertension and unstable shape of plaque were strongly associated with arterial compensatory enlargement |
| Kazmierski et al, 2004 | Cross-Sectional | U/S | 233 pts, 466 arteries | Arterial compensatory enlargement occurs until an increase of IMT up to the critical point of 1.2mm |
| Chironi et al, 2005 | Prospective | U/S | 373 pts (statin group:291 pts, fibrate group:82 pts) | Fibrate treatment was associated with lower compensatory enlargement compared to statin treatment |
| Iannuzzi et al, 2005 | Prospective | U/S | 310 pts (Progetto ATENA Study) | Arterial remodeling is detectable in patients with metabolic syndrome and early signs of atherosclerosis |
| Hardie et al, | Retrospective | MDCT | 108 pts | Expansive remodeling was significantly greater in patients with cerebral ischemic |

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| 2007 | | | | symptoms than in asymptomatic patients |
| Underhill et al, 2009 | Prospective | MRI | 67 pts | Intraplaque hemorrhage may indicate impending luminal compromise |
| Duivenvoorden et al, 2010 | Prospective | MRI | 15 pts | Endothelial shear stress is a critical determinant of arterial remodeling and arterial stiffness |
| Hayashi et al, 2010 | Prospective | MRI | 23 pts | Although atherosclerotic plaques progress over time, there was no change in lumen size |
| Beijers et al, 2011 | Prospective | U/S | 385 pts (Hoorn Study) | Metabolic syndrome is associated with maladaptive remodeling |
| Ferreira et al, 2012 | Prospective | U/S | 293 pts (Amsterdam Growth and Health Longitudinal Study) | Patients with persistent metabolic syndrome present maladaptive outward remodeling that may be reversed with recovery from the metabolic syndrome |
| Matsuo et al, 2012 | Cross-Sectional | IVUS | 29 pts | Lesions with positive remodeling exhibited more characteristics of fibroatheroma |
| London et al, 2013 | Cross-Sectional | U/S | 155 ESRD pts | ESRD is characterized by accelerated age-associated arterial stiffening and outward remodeling |
| Kurosaki et al, 2016 | Retrospective | MRI | 70 pts | Expansive remodeling was associated with a higher risk for ischemic events |
| Saam et al, 2016 | Prospective | Black-Blood MRI | 111 pts | Expansive arterial remodeling is not a very practical marker for plaque vulnerability |
| Kashiwazaki et al, 2017 | Retrospective | MRI | 82 pts | Expansive arterial remodeling can predict ischemic complications following CAS |
| Della-Morte et al, 2018 | Prospective | U/S | 876 pts (Northern Manhattan Study) | Increased carotid intima media thickness and plaque burden represent arterial remodeling with luminal dilatation |

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| Chen et al, 2019 | Cross-Sectional | MRI | 66 pts | The expansive remodeling ratio may be a practical marker of plaque vulnerability |
| Nagata et al, 2020 | Prospective | MRI and Pathology | 27 pts | Calcium-binding protein S100A4 demonstrated a positive correlation with the degree of expansive remodeling |
| Dilba et al, 2021 | Prospective | MRI | 164 pts (PARISK Study) | Although the remodeling ratio was similar, plaques containing intraplaque hemorrhage had smaller lumen area compared to plaques without intraplaque hemorrhage |

Abbreviations: U/S, ultrasound; pts, patients; IMT, intima-media thickness; MDCT, multidetector computed tomography; MRI, magnetic resonance imaging; ESRD, end-stage renal disease; CAS, carotid artery stenting; PARISK, Plaque At RISK

**Table 3:** Studies of arterial compensatory enlargement in peripheral arteries

| Study | Design | Assessment modality | Population | Main results |
|---|---|---|---|---|
| Losordo et al, 1994 | Cross-Sectional | IVUS | 20 pts | Focal compensatory enlargement occurs in response to progressive atherosclerosis |
| Clarijs et al, 1997 | Cadaveric | Pathology | 54 femoral arteries | Arterial remodeling was not related to the extent of the non-diseased part of the vessel wall or lesion eccentricity |
| Pasterkamp et al, 1997 | Cadaveric | Pathology | 50 renal, 54 common iliac, 56 external iliac, 54 femoral arteries | Arterial compensatory enlargement was more evident in coronary, common carotid and renal arteries compared to the arteries obtained from the lower limbs |
| Labropoulos et al, 1998 | Prospective | U/S | 19 iliac, 23 CFA, 21 SFA, 23 popliteal | All peripheral arteries, especially the more distal vessels, dilate in response to early signs of atherosclerosis |
| Gyongyosi et al, 2004 | Retrospective | IVUS | 50 pts | All patients experienced concomitant expansive and constrictive remodeling, with high C-reactive protein levels predicting expansive remodeling pattern |
| Chung et al, 2009 | Retrospective | U/S | 1583 pts | Arterial remodeling is an essential homeostatic response that is preserved in spite of the presence of risk factors and developing atherosclerosis |
| Matsuo et al, 2012 | Cross- | IVUS | 64 pts (50 renal, 14 | Lesions with positive remodeling exhibited more characteristics of |

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| | Sectional | | iliac arteries) | fibroatheroma |
| Chi et al, 2013 | Prospective | 3D-Black-Blood-MRI | 25 pts | Compensatory enlargement was limited in the adductor canal compared to the proximal bifurcation segment |

Abbreviations: IVUS, intravascular ultrasound; U/S, ultrasound; CFA, common femoral artery; SFA, superficial femoral artery; pts, patients; MRI, magnetic resonance imaging;

**Discussion**

Glagov et al[2] described ACE for the first time in humans studying 136 fixed hearts. His findings suggested that the arterial lumen was preserved up to 40% of stenosis and above this threshold the arterial lumen was being compromised. The value of this threshold is not consistent throughout the literature, ranging from as low as 30% to as high as 45%[11, 12]. This disparity may be due to differences in study design and metrics, population or arterial segment examined, but they may also reflect true variation in capacity for ACE. One significant finding in postmortem studies was the different degree of ACE in different segments of coronary arteries. Zarins et al[124] confirmed the Glagov phenomenon but also reported that the greater response was noticed on the distal segments of the coronaries. A study of 48 fixed hearts suggested that outward remodeling was significantly greater in atherosclerotic lesions of low grade stenosis[125]. Additional findings suggested that circumferential plaques were associated with impaired ACE compared to eccentric plaques (12.7% vs 20.7%). However, this study did not assess the distribution of ACE in eccentric plaques, so it is not clear if the ACE is localized to the arc of vessel covered by the plaque or through the relatively healthy tissue. Segments with higher grade of stenosis were linked with negative remodeling, however this decreased vessel diameter might be relative depicting the post-stenotic dilatation of the vessel and not a true negative remodeling of the proximal segment.

For the past 35 years, coronaries have been the main area of interest in the study of the ACE phenomenon. Aside from the postmortem studies, a lot of studies have used IVUS to improve their assessment of arterial morphology, behavior, and compensatory enlargement. IVUS increased accuracy on detecting lumen reduction makes it a better tool compared to angiography. One of the first studies which used IVUS to assess ACE, showed that the compensatory enlargement precedes the development of angiographically detectable coronary atherosclerotic lesions, which indicates that positive remodeling occurs during the early stages of atherosclerosis[16]. However, one of the technical disadvantages of IVUS is the inability to differentiate the internal elastic membrane, but it can measure the atherosclerotic plaque and the external elastic lamina. Reddy et al showed that diabetic patients had greater positive remodeling compared to the non-diabetic for low burden atherosclerotic plaque which was defined as <55%[52]. In a subsequent

study the same author attempted to identify specific factors that influence the positive remodeling of the arterial wall as well as factors which were associated with negative remodeling[126]. They reported that inflammatory lesions or unstable atherosclerotic plaques are associated with positive remodeling. Additionally, obesity, hyperlipidemia, diabetes, and hypertension are associated with negative remodeling. Percutaneous coronary intervention and post-coronary artery bypass grafting coronaries were also associated with negative remodeling.

Additional IVUS studies on coronary arteries in diabetic patients have reported smaller arterial size[50, 127]. Vavuranakis et al[128] used IVUS to evaluate the arterial response to nitroglycerin and showed that diabetic coronaries had an inadequate response to nitroglycerin injection. In another study by the same author, diabetic patients were shown to have impaired ACE response to atherosclerosis while nondiabetic patients had adequate ACE[129]. These findings were depicted on the fact that the compensatory enlargement was correlated with the percentage of stenosis only in non-diabetic patients.

In order to assess ACE, several studies employed less invasive imaging techniques like CTA and MRI. Two of the studies that used Black-Blood MRI in healthy populations with nonsignificant coronary atherosclerosis showed increase in total vessel size without compromising the lumen, suggesting adequate ACE[40, 70]. Finally, in one early published study, McPherson et al used high frequency epicardial ultrasound during open heart surgeries suggesting that the total arterial area in segments with atherosclerotic lesion was increased relative to healthy segments[10].

While most studies examining ACE focused on coronaries, some authors describe it in the peripheral vasculature. Losordo et al used IVUS to assess 62 paired superficial femoral arteries in patients who were undergoing endovascular intervention[120]. In the diseased segments the total arterial area was increased compared to the normal paired site which suggest a focal compensatory mechanism. Labropoulos et al studied multiple arterial sites including the carotids, abdominal aorta, iliacs, common femoral artery, superficial femoral artery and popliteal artery using duplex ultrasound[101]. The findings were significant for peripheral artery dilation in response to intima-media thickening and early atherosclerotic plaque formation. Interestingly, the greater degree of ACE was noticed in the popliteal artery which corroborates previous findings that indicate

greater percent ACE in distal arterial segments than proximal[124]. In a prospective study of patients with low grade stenosis (<30%) of the internal carotid arteries Steinke et al[100] found that 41% of patients had increase in arterial diameter compensating for the degree of the stenosis. These findings are contradicted by Pasterkamp et al[130], who were unable to confirm the ACE phenomenon in a series of patients who underwent IVUS of the femoral arteries as well as in postmortem femoral artery segments. In a subsequent postmortem study, the same author showed that the degree of remodeling varies within the arterial system[20]. More specifically, common carotid, coronary, and renal arteries underwent greater ACE compared to iliac and femoral arteries. The author suggests that this variety within the arterial tree might be a result of an autoregulatory mechanism where the threshold for the ACE in response to an increased shear stress maybe lower for the arteries supplying the organs compared to the lower extremities. Moreover, even in the same arterial tree such as the superficial femoral artery, distal segments were at greatest risk of stenosis, which may be explained by the external compression of the vasculature at the adductor hiatus and impaired ACE as demonstrated by both cadaveric and Black-Blood MRI assessments of the region[123, 131].

Atheroma deposition is extensive in the thoracic and abdominal aorta in addition to its development in the smaller peripheral vessels. While the presence of aortic atherosclerosis is well documented, few studies evaluate the potential relationship between plaque formation and ACE. A cadaveric study of the abdominal aorta reported that atherosclerotic plaque formation is associated with aortic enlargement and decreased media thickness[132]. Benvenuti et al[133], suggested that the mechanism or arterial remodeling is not the same in all segments of the aorta. The thoracic aorta was more likely to undergo ACE than the abdominal aorta, where the plaque formation was associated with obstructive disease rather than dilation. Finally, Mohiaddin et al[134], supported the Glagov hypothesis using MRI and identified patients with asymptomatic abdominal atherosclerosis where the increase in aortic plaque burden had a corresponding increase in total vessel volume and preservation of the arterial lumen.

*Future perspectives*

There is significant evidence for arterial compensatory enlargement following development of atherosclerosis. This evidence is confounded by the absence of a

standardized metric to describe the phenomenon. Furthermore, the bulk of the literature on this topic examines the role of compensatory enlargement in attenuating the adverse effects of coronary atherosclerosis. While this region is of vital importance for its clinical relevance for potentially fatal cardiovascular disease, the focus on coronaries is a detriment to the study of peripheral vasculature. These studies also exclude comorbid conditions despite their common cooccurrence with atherosclerosis. The literature assessing the capacity for arterial compensatory enlargement in a diabetic population is particularly sparse, especially in light of the fact that diabetes has known effects on the elasticity of arteries and a strong association with hypercholesterolemia which can lead to atherosclerosis. Moving forward, understanding the behavior of these lesions after angioplasty, will assist the interventionalist in decision making for the best treatment. Coronaries data showed similar luminal gain after balloon angioplasty regardless positive or negative remodeling. However, the mechanism of luminal gain was different. In the positive remodeling group, the plaque was compressed during the angioplasty, while in the negative remodeling group the vessel exhibited a degree of stretching[135]. Pasterkamp et al[136] evaluated femoral arteries after balloon angioplasty suggesting that the luminal gain was not related to the mode of the arterial remodeling but the remodeling affected the dilation mechanism. As a result, and with the ongoing expansion of the infrainguinal angioplasty armamentarium with drug coated balloons, drug eluting stents and atherectomy devices, femoral and popliteal remodeling signifies the need of understanding the pathophysiology in order to choose the appropriate treatment.

*Limitations*

All the preceding studies sought to evaluate the extent of atheroma burden and the corresponding ACE, but there is no standardization of metrics, which confounds comparisons among them. Some of the differences in terminology can be explained by the variable capacity of diverse imaging modalities. It is only possible to evaluate internal elastic lamina area in cadaveric studies, so investigations with other imaging modalities approximate plaque area and describe wall area in its place. The use of cadaveric studies along-side in vivo investigations assumes that fixatives perfectly capture the natural shape of the vasculature, which is particularly troublesome for studies in which deformation is the primary outcome

measure. The literature is also inconsistent in its use of areas or diameters to describe the size of vessels, with these terms being used interchangeably in published descriptions of ACE. Finally, of the studies examined in this review, none assess the clinical implications of ACE on the arterial capacity to accommodate stenting or catheterization, nor do they address the impact of ACE on patient care.

## Conclusion

ACE is a common pathophysiologic response that is evident in the arterial system. The extent of compensation varies along the arterial tree and with the presence or not of comorbidities such as diabetes. Prospective studies are necessary to determine the behavior of the vessels over time. Future studies should also examine the efficacy of medications and procedures on arterial segments with atherosclerotic lesions both with and without ACE.


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**Supplementary Table 1** Risk of bias assessment for observational studies (ROBINS-E tool)

| Study | Confounding | Selection | Classification of exposures | Deviations from intended exposures | Missing data | Measurement of outcomes | Selection of the reported result |
|---|---|---|---|---|---|---|---|
| Glagov 1987 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Stiel 1989 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| McPherson 1991 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Ge 1993 | Moderate | Moderate | Low | Low | High | Low | Low |
| Hermiller 1993 | Moderate | High | Low | Low | Moderate | Low | Low |
| Gerber 1994 | Moderate | Moderate | Low | Low | High | Low | Low |
| Losordo 1994 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Masawa 1994 | Moderate | Low | Low | Low | Low | Low | Low |
| Steinke 1994 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Shircore 1995 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Litovsky 1996 | Low | Low | Low | Low | Moderate | Low | Low |
| Nakamura 1996 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Nishioka 1996 | Moderate | Moderate | Low | Low | High | Low | Low |
| Berglund 1997 | Low | Low | Low | Low | Low | Low | Low |
| Clarijs 1997 | Moderate | High | Moderate | Low | High | Low | Low |
| Pasterkamp 1997 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Tauth 1997 | Moderate | Low | Low | Low | Low | Low | Low |
| Labropoulos 1998 | Low | Low | Low | Low | Low | Low | Low |
| Schmermund 1998 | Moderate | Moderate | Low | Low | Low | Moderate | Low |
| Dangas 1999 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Sabate 1999 | Low | Low | Low | Low | Low | Low | Low |
| Shiran 1999 | Low | Low | Low | Low | High | Low | Low |
| Smits 1999 | Moderate | Low | Low | Low | Low | Low | Low |
| Taylor 1999 | Moderate | Low | Low | Low | Low | Low | Low |
| Kaji 2000 | Moderate | Low | Low | Low | Low | Low | Low |
| Klingensmith 2000 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Schoenhagen 2000 | Low | Low | Low | Low | Low | Low | Low |
| Bezerra 2001 | Moderate | Moderate | Low | Low | Low | Moderate | Low |
| Endo 2001 | Moderate | Low | Low | Low | Low | Low | Low |
| Hassan 2001 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Isoda 2001 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Jeremias 2001 | Moderate | Low | Low | Low | Low | Low | Low |
| Okura 2001 | Low | Low | Low | Low | Low | Low | Low |
| Takano 2001 | Moderate | Low | Low | Low | Low | Low | Low |
| Burke 2002 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Ito 2002 | Moderate | Moderate | Low | Low | Moderate | Low | Low |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kim 2002 | Moderate | Moderate | Low | Low | High | Low | Low |
| Saito 2002 | Low | Low | Low | Low | Low | Low | Low |
| Boyajian 2003 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Britten 2003 | Low | Low | Low | Low | Low | Low | Low |
| Hirose 2003 | Moderate | Low | Low | Low | Low | Low | Low |
| Hong 2003 | Low | Low | Low | Low | Low | Low | Low |
| Ishida 2003 | Moderate | Moderate | Low | Low | Moderate | Low | Low |
| Iwami 2003 | Moderate | Low | Low | Low | Low | Low | Low |
| McLeod 2003 | Moderate | Low | Low | Low | Low | Low | Low |
| Mintz 2003 | Low | Low | Low | Low | Low | Low | Low |
| Sahara 2003 | Moderate | Low | Low | Low | Low | Low | Low |
| Tamada 2003 | Low | Low | Low | Low | Low | Low | Low |
| Gyongyosi 2004 (peripheral) | Low | Low | Low | Low | Low | Low | Low |
| Gyongyosi 2004 (coronary) | Moderate | Low | Low | Low | Low | Low | Low |
| Kazmierski 2004 | Low | Low | Low | Low | Low | Low | Low |
| Reddy 2004 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Bertini 2005 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Chironi 2005 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Fujii 2005 | Moderate | Low | Low | Low | Low | Low | Low |
| Hibi 2005 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Hong 2005 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Iannuzzi 2005 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Nicholls 2005 | Low | Low | Low | Low | Low | Low | Low |
| Fernandes 2006 | Moderate | Low | Low | Low | Low | Low | Low |
| Hartmann 2006 | Low | Moderate | Low | Low | Low | Low | Low |
| Sipahi 2006 (a) | Low | Low | Low | Low | Low | Low | Low |
| Sipahi 2006 (b) | Low | Low | Low | Low | Low | Low | Low |
| Ehara 2007 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Hardie 2007 | Low | Moderate | Low | Low | Low | Moderate | Low |
| Kang 2007 | Moderate | Low | Low | Low | Low | Low | Low |
| Kitagawa 2007 | Low | Low | Low | Low | Moderate | Low | Low |
| Schukro 2007 | Low | Low | Low | Low | Low | Low | Low |
| Iwata 2008 | Moderate | Low | Low | Low | Low | Low | Low |
| Kume 2008 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Manfrini 2008 | Moderate | Low | Low | Low | Low | Low | Low |
| Chung 2009 | Moderate | Low | Low | Low | Low | Moderate | Low |
| Kashiwagi 2009 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Miao 2009 | Low | Low | Low | Low | Low | Low | Low |
| Okura 2009 | Low | Low | Low | Low | Low | Low | Low |
| Underhill 2009 | Moderate | Low | Low | Low | Low | Low | Low |
| Duivenvoorden | Moderate | Moderate | Moderate | Low | Low | Low | Low |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2010 | | | | | | | |
| Hayashi 2010 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Kang 2010 | Low | Low | Low | Low | Low | Low | Low |
| Kato 2010 | Low | Low | Low | Low | Low | Low | Low |
| Beijers 2011 | Moderate | Low | Low | Low | Low | Low | Low |
| Hussein 2011 | Low | Low | Low | Low | Low | Low | Low |
| Rinehart 2011 | Moderate | Low | Low | Low | Low | Low | Low |
| Samady 2011 | Low | Low | Low | Low | Low | Low | Low |
| Eshtehardi 2012 | Moderate | Low | Low | Low | Low | Low | Low |
| Ferreira 2012 | Low | Low | Low | Low | Low | Low | Low |
| Manfrini 2012 | Low | Low | Low | Low | Low | Low | Low |
| Matsuo 2012 | Low | Low | Low | Low | Low | Low | Low |
| Nozue 2012 | Low | Low | Low | Low | Low | Low | Low |
| Ouldzein 2012 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Takaoka 2012 | Low | Low | Low | Low | Low | Low | Low |
| Araki 2013 | Low | Low | Low | Low | Low | Low | Low |
| Chi 2013 | Low | Moderate | Low | Low | Moderate | Low | Low |
| Hamirani 2013 | Low | Low | Low | Low | Low | Low | Low |
| London 2013 | Moderate | Low | Low | Low | Low | Low | Low |
| Puri 2013 | Low | Low | Low | Low | Low | Low | Low |
| Inaba 2014 | Low | Low | Low | Low | Low | Low | Low |
| Katranas 2014 | Low | Low | Low | Low | Low | Low | Low |
| Takayama 2015 | Low | Low | Low | Low | Low | Low | Low |
| Antoniadis 2016 | Moderate | Low | Low | Low | Moderate | Low | Low |
| Kurosaki 2016 | Low | Low | Low | Low | Low | Low | Low |
| Kwon 2016 | Low | Low | Low | Low | Low | Low | Low |
| Saam 2016 | Low | Low | Low | Low | Low | Low | Low |
| Kashiwazaki 2017 | Low | Low | Low | Low | Low | Low | Low |
| Liu 2017 | Low | Low | Low | Low | Low | Low | Low |
| Della-Morte 2018 | Moderate | Low | Low | Low | Low | Low | Low |
| Du 2018 | Moderate | Low | Low | Low | Low | Low | Low |
| Goyal 2018 | Low | Low | Low | Low | Low | Low | Low |
| Lee 2018 | Low | Low | Low | Low | Low | Low | Low |
| Chen 2019 | Moderate | Moderate | Low | Low | Low | Low | Low |
| Galal 2019 | Low | Low | Low | Low | Low | Low | Low |
| Nagata 2020 | Low | Moderate | Low | Low | Moderate | Low | Low |
| Dilba 2021 | Moderate | Low | Low | Low | Low | Low | Low |
| Geng 2021 | Moderate | Low | Low | Low | Low | Low | Low |
| Cho 2022 | Low | Low | Low | Low | Low | Low | Low |
| Kashiwagi 2023 | Moderate | Low | Low | Low | Low | Low | Low |