Curr Atheroscler Rep (2017) 19: 57
https://doi.org/10.1007/s11883-017-0696-4

Atherosclerosis, Periodontal Disease, and Treatment with Resolvins

James A. Hamilton[1] · **Hatice Hasturk**[2] · **Alpdogan Kantarci**[2] · **Charles N. Serhan**[3] · **Thomas Van Dyke**[2]

Published online: 6 November 2017

Abstract
Purpose of Review This review aims to discuss the existing evidence on the link between atherosclerosis and periodontitis by particularly presenting new findings that link the pathology and therapy of these diseases. Acute vascular ischemic events that can lead to stroke or myocardial infarction are initiated by inflammatory processes leading to rupture or erosion of plaques susceptible to thrombosis ("high risk" or "vulnerable"). These are highly inflamed plaques residing in the media and adventitia that may not be detected by angiography measurments of luminal narrowing. Statistically significant excess risk for atherosclerotic cardiovascular disease has been reported in persons with periodontitis independent of established risk factors. We hypothesized that the systemic pathologic links also represent potential therapeutic links.
Recent Findings We recently demonstrated that periodontal inflammation promotes atherosclerotic plaque inflammation and destabilization. As discrete pathological regions, these plaques with a high susceptibility to rupture can be imaged and differentiated from lower risk plaques. In cholesterol-fed rabbits with periodontal disease, circulating inflammatory mediators were also significantly elevated thereby contributing to "vulnerable blood," a systemic characteristic of high risk for cardiovascular events. New studies show that certain lipid mediators, including lipoxins and resolvins, are potent in preventing and possibly treating a number of inflammation-associated diseases, including periodontitis and vascular inflammation.
Summary The concept of the vulnerable patient and the pro-resolving approach open new terrain for discovery of paradigm-changing therapies for the prevention and treatment of two of the most common diseases of man. Importantly, lipoxins and resolvins are natural receptor agonists that do not exhibit the same pro-atherogenic side effects attributed to anti-inflammatory medications (e.g., NSAIDs) but rather coordinate resolution of inflammation and a return to homeostasis.

Keywords Atherosclerosis · Periodontal disease · Inflammation · Thrombosis · Plaque rupture

This article is part of the Topical Collection on *Vascular Biology*

✉ James A. Hamilton
jhamilt@bu.edu

[1] Department of Physiology and Biophysics, Boston University School of Medicine, 700 Albany Street, W302, Boston, MA 02118-2526, USA

[2] Department of Applied Oral Sciences, The Forsyth Institute, 245 First Street, Cambridge, MA 02142, USA

[3] Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

Introduction

Atherosclerosis and Thrombosis

Cardiovascular disease (CVD) and subsequent ischemic complications, including myocardial infarction and stroke, are the most common causes of morbidity and mortality in the USA [1]. The underlying cause of most vascular disease is atherosclerosis, a chronic progressive inflammatory condition characterized by vascular inflammation and sub-intimal lipid accumulation that can progress for years without symptoms [2•]. Atherosclerotic plaques may appear early in life and advance to severe ("high risk") plaques. An acute ischemic event (heart attack or stroke) can occur when an atheromatous plaque disrupts (thrombosis) [3, 4].

A very different response to thrombosis can also occur by the body's natural healing processes that stimulate "wound healing," in which the thrombus can be covered under a new collagenous fibrous cap [5, 6]. This healing mechanism may be life-saving; however, these plaques still remain at high risk for future rupture. Carotid endarterectomy specimens patients with luminal narrowing often show evidence of previous rupture and thrombosis, even in asymptomatic persons [6]. Although thin-cap fibrous atheromas have been identified as a risk factor, the incidence of major cardiovascular events associated with a thin cap fibroatheromas identified by intravascular ultrasound–virtual histology is < 10% over ~ 3 years of follow-up [7, 8], suggesting that other factors are important in determining plaque rupture. In this review, we present evidence that periodontal infection promotes systemic and arterial inflammation, which may promote atherothrombotic cardiovascular events such as myocardial infaction and stroke. Our hypothesis is that treatment of oral inflammation with resolvins can decrease vessel wall inflammation, mitigate atherosclerosis, and promote healing mechanisms to limit thrombus growth and vulnerability.

Periodontitis and Cardiovascular Disease

Periodontitis is a chronic oral inflammatory disease that is caused by bacteria that accumulate on teeth. The incidence of severe periodontal disease in the USA is substantial (20%) [9]. Patients with periodontal disease share many of the same risk characteristics as patients with CVD; they are older, predominantly male, and exhibit similar stress and smoking behaviors [10]. Periodontitis clearly imparts excess risk for CVD [11] and enhances CVD in animal models [12, 13, 14••] . However, the determinants of plaque instability, the major cause of atherothrombotic event, in individuals with periodontitis are poorly understood. Previous studies have suggested positive associations between periodontal infection and cardiovascular disease [12]. The keystone periodontopathogen, *Porphyromonas gingivalis*, and several other oral pathogens were shown to have the ability to invade aortic tissues [15]; however, serum antibodies against these periodontopathogens were not associated with the extent of coronary atherosclerosis nor with coronary plaque vulnerability in human subjects [16]. The results of antibiotics in clinical trials were negative in protection against CVD events undermining the impact of infectious agents [17]. Still today, the role of bacterial infection and direct impact of bacteria in the course of CVD remains controversial, and this controversy also minimizes the role of infection-inflammation-mediated mechanisms as a determinant of plaque instability and thrombosis. We have shown that periodontal inflammation complicates the early atherosclerotic processes and advances the atherosclerotic plaque development and the risk for plaque instability (vulnerable to rupture) [14••] supporting the hypothesis that inflammation initiated by microbial infections is a major determinant of plaque rupture in atherosclerosis [18, 19].

Resolvins and Resolution of Inflammation

To highlight the pro-resolving actions of resolvins that have a different mechanism of action than conventional anti-inflammatory drugs, we present detailed background below that justifies our focus on resolution, rather than inhibition, of inflammation. Resolvins belong to a genus of endogenous anti-inflammatory and pro-resolving mediators called specialized pro-resolving mediators of inflammation, SPMs. SPMs are potent therapeutics in inflammatory diseases, including periodontitis, and vascular inflammation [14••, 20–23]. In cardiovascular disease, the use of statins and antihypertensives aims to control risk factors, but there are currently no available therapies that effectively stabilize or reverse established plaques [24•].

SPMs coordinate resolution of inflammation and return to function without the pro-atherogenic side effects attributed to NSAIDs [25–27]. Decreased levels of SPMs may predispose progression of chronic vascular inflammation and vulnerability to coronary atherosclerosis and thrombosis [28]. Studies summarized in this review probe the hypothesis that the systemic impact of bacterially induced inflammatory periodontal disease contributes to atherosclerotic plaque vulnerability and thrombosis. Recent evidence [14••, 29, 30] and preliminary data suggest that local inflammation increases atherosclerosis and the risk for thrombosis in a model of atherosclerosis and periodontitis in rabbits, and resolvin E1 (RvE1) diminishes this risk and advanced atherosclerotic changes. Although resolvins are receiving increased research attention and have demonstrated remarkable clinical effects in animal models [20, 31, 32, 33••], the primary action of these molecules is often mistakenly considered anti-inflammatory alone.

Here, we present a detailed background to the discovery, chemistry, and mechanism of actions of resolvins on cellular functions. The structural elucidation of RvE1 was first reported in 2000 [34, 35]. Each enzyme in the synthetic pathway and the complete stereochemistry as well as biosynthesis have been elucidated in the biosynthesis of RvE1 (5,12,18*R*-triEPE), a potent bioactive mediator in many disease models [36]. Aspirin enhanced the production of this pro-resolving mediator that was found to be produced from a novel precursor released during hypoxia by human vascular endothelial cells that release both 18R-hydroxyeicosapentaenoic acid (18R-HEPE) and 15*R*-HEPE. Human neutrophils activated with serum-treated zymosan convert these intermediates to potent bioactive products via transcellular processing [37]. The complete stereochemistry and double-bond geometry of RvE1 were established and its production identified in human plasma using LC-MS-MS and MS^3 [38].

RvE1 biosynthesis involves an 18-hydroperoxide intermediate that is rapidly converted to 5,6-epoxy-18*R*-EPE by 5-

lipoxygenase (see Fig. 1). This led to the discovery of RvE2, which also proved to be bioactive [39, 40], and to the demonstration that its actions are mediated by specific binding to human leukocytes [36]. Once formed, the 5,6-epoxide 18*R*-hydroxyeicosapentaenoic acid is converted by the human LTA_4 hydrolase to produce RvE1 (see Fig. 1). RvE1 acts at two separate GPCR, both the ChemR23 receptor and the BLT1 receptor, altering BLT1 signaling to evoke its proresolving actions [41]. In addition to limiting or stopping neutrophilic infiltration, RvE1 also stimulates macrophage uptake of both apoptotic neutrophils and microbial debris [42]. This provides RvE1 as well as the other specialized proresolving mediators [43, 44] and D-series resolvins [37] the special ability to clean up an inflammatory site and prepare for the return to homeostasis.

RvE1, given this unique ability to regulate neutrophilic infiltration, downregulates cytokines and prostaglandins, stimulates macrophage-mediated phagocytosis of cellular debris and microbes [20, 45], and displays potent action in disease models when added back as a potential therapeutic. The ability of RvE1 to promote phagocytosis has an impact in pulmonary disease models [44, 46] and improves local inflammation in models of periodontal disease stimulating inflammatory resolution, bone protection, and tissue regeneration [20, 47]. Airway protection is a potent action of RvE1, where it has a unique ability to stimulate other proresolving mediators such as lipoxin A_4 in in vivo models of allergic airway inflammation [46].

Additional actions of RvE1 include topical clearance of inflammation on mucosal surfaces [48], and its potential ability led to clear and control of *Herpes simplex* virus-induced ocular inflammation [49]. RvE1 has been used in clinical trials for ocular inflammation. Success was reported in the treatment of dry eye in a phase II clinical trial in humans. The results from this study were further substantiated using animal models, where RvE1 improved tear production and decreased inflammation [50]. As a novel pro-resolving mediator [51], it also prevents organ fibrosis and exerts antifibrotic actions [52]. RvE1 has protective actions in reperfusion injury and protects from reflow injury in the rat heart [53] and is protective in allograft rejection [54]. In recent studies, the precursor for RvE1, 18-HEPE (Fig. 1), which is produced by human vascular endothelial cells in a hypoxic environment [55], was found to be bioactive when released by macrophages and is protective in cardiac remodeling [56]. Together, these studies of RvE1 have shown its proresolving actions on the innate immune response, counter-regulation of cytokines, and have opened up a new appreciation of the role of resolution in stimulating the clearance and killing of microbes [57, 58].

Cholesterol-Fed Rabbit

Rabbits have served as models of atherosclerosis for more than 100 years [59]. Cholesterol feeding was first shown to cause atherosclerotic plaque in 1913, and since then, rabbit studies have been used to discover and characterize many aspects of cardiovascular disease relevant to humans, including the discovery of the role of nitric oxide, which led to a Nobel Prize in 1998 and the role of vascular inflammation [59].

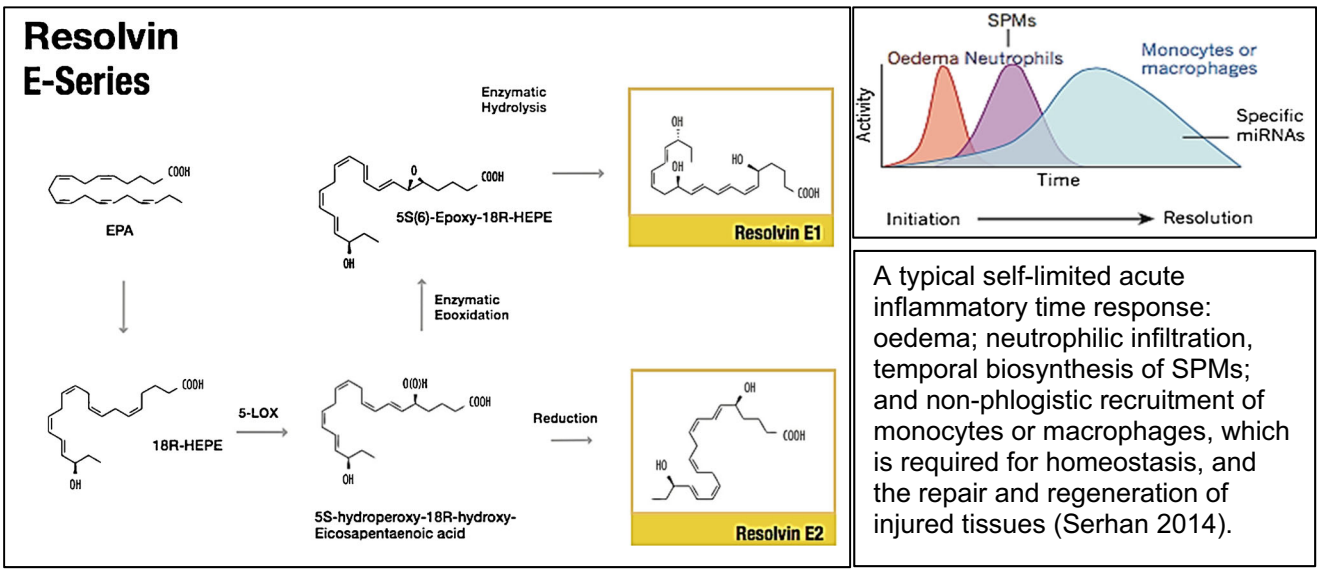

Fig. 1 Biosynthesis of resolvin E1. The complete stereochemistry of RvE1 is assigned as shown, as well as the total organic synthesis confirming the potent pro-resolving biological actions [37], which limit PMN infiltration, regulate dendritic cell migration, counter regulate cytokine and pro-inflammatory lipid mediators, and stimulate enhanced macrophage uptake of apoptotic cells, cellular debris, and microbes. These actions, regulated by RvE1 in resolution, have a diverse impact in disease models (text). The enzymes involved in RvE1 biosynthesis in human leukocytes are established [36]. The structural elucidation, biosynthesis, and actions of resolvin E1 led to the discovery of resolvin E2, related D-series resolvins, and specialized proresolving mediators (SPM) including the protectins and maresins [42]

The New Zealand White (NZW) rabbit presents a highly valuable model for inflammatory diseases, including cardiovascular diseases and periodontal disease, and does not require any genetic modification in order to compensate for atherosclerosis development (a limitation of atherothrombotic phenotype in mice) [60]. Periodontitis and atherosclerosis can be simultaneously assessed in the rabbit to test the hypothesis that the impact of local infection and inflammation on systemic inflammation is a determinant of cardiovascular plaque vulnerability and rupture.

Periodontitis with similar characteristics to human periodontal disease can be established within 6 weeks with a ligature and *P. gingivalis* challenge. After 6 weeks, the disease progresses without further application of *P. gingivalis*, and the infection persists in the periodontal pockets [47]. Unlike other animal models, rabbits do not develop periodontitis when only ligatures are introduced; *P. gingivalis* is required to induce dysbiosis, initiating an inflammatory cascade and periodontitis. In the rabbit model of periodontitis, topical lipoxins and resolvins prevent and reverse periodontitis [20, 47].

The NZW rabbit fed a 0.5% cholesterol-supplemented diet (Western diet) has permitted demonstration of the relationship between periodontitis and large vessel atheroma formation in vivo and showed that periodontitis increases large vessel atherogenesis [13, 14••]. Figure 2a, b depicts the changes, especially the dramatic synergistic effects on pathology, in the gingiva of rabbits fed a 0.5% cholesterol diet with or without periodontal disease induced by topical *P.gingivalis* application. Dramatic effects were also seen in the aorta (Fig. 2c, e). The animals without periodontitis developed atherogenic changes, characterized by fatty streak lesions at the aortic arch and patchy lesions along the thoracic aorta as a result of the cholesterol diet. In the rabbits with *P. gingivalis*-induced periodontal disease, atherosclerotic lesions were robustly increased and extended to the thoracic and abdominal aorta regions occupying up to 80% of the lumen area from aortic sinus to the femoral bifurcation (Fig. 2c) [14••].

Histological assessments of the aorta confirmed that animals with periodontitis (Fig. 2a) had typical characteristics of advanced atherosclerosis, including thickening intima along with a medial atrophy and fibrous cap formation (Fig. 2a–d). The quantification of plaque-covered area and intima/media ratio clearly shows the impact of periodontitis on atherosclerotic changes (Fig. 2e). Cholesterol diet resulted in a thickened tunica intima, and this thickening was much greater with periodontitis. We have also demonstrated a dose/response

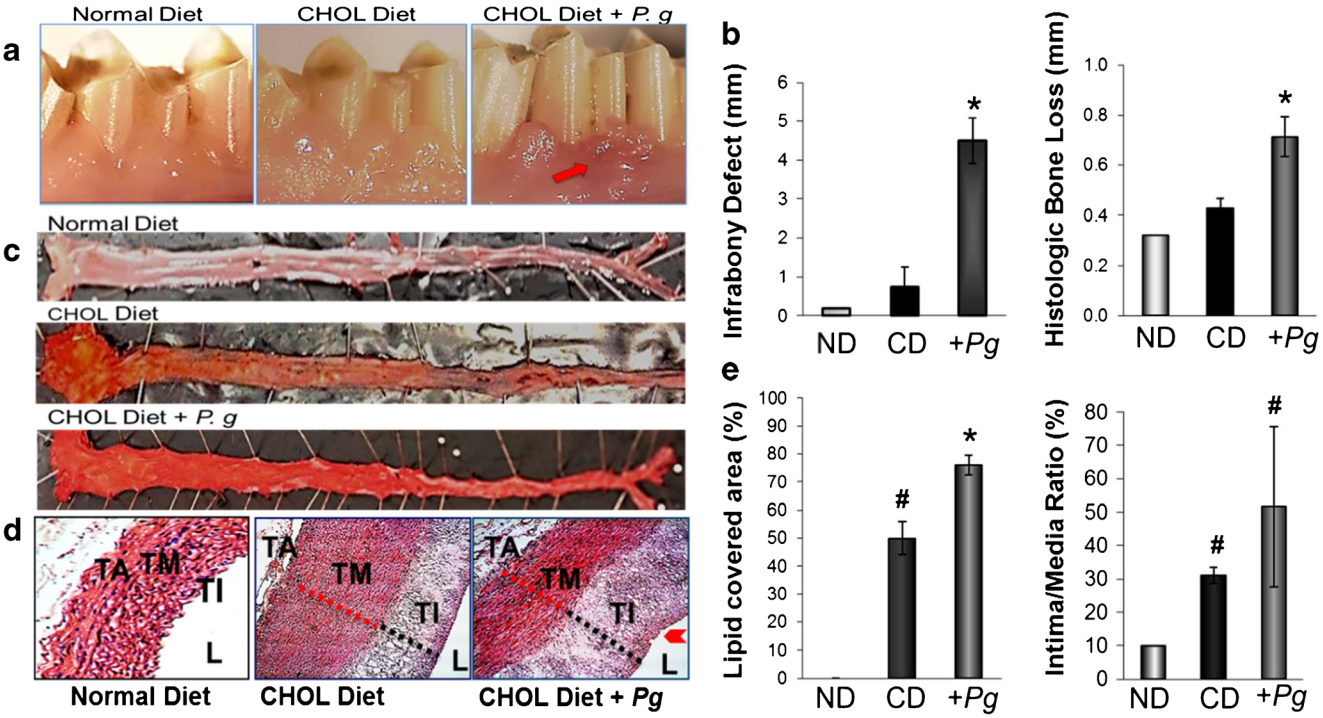

Fig. 2 Periodontal disease enhances diet-induced early atherogenesis in rabbits. **a** Periodontitis was induced in 0.5% cholesterol-fed NZW Rabbits. At 13 weeks, the disease was obvious with all characteristics of human periodontitis (red arrow). **b** Direct quantitative measurements and quantitative histological sections demonstrated bone loss. **c** Aortic fatty streaks were significantly increased in animals with periodontal disease as shown in Sudan IV-stained en face aorta images. **d** Periodontitis enhanced the development of atherosclerosis. The TI and TM increased significantly beyond the increase with cholesterol feeding alone, and a thin fibrous cap is visible (red arrow). The *Tunica intima* in animals on normal diet showed is a normal thin layer consisting of endothelial cells, subendothelial connective tissue, and a thin elastic membrane connecting the *tunica media*. **e** Quantification of lipid covered area revealed significant increases with periodontitis and a higher intima/media ratio. ND: normal diet; CD: cholesterol diet; Pg: P. gingivalis; TM: tunica media; TI: tunica intima; TA: tunica adventitia; L: lumen

inhibition of periodontal destruction and great reductions in the atheromatous changes enhanced by periodontitis when topical RvE1 (not shown) is applied preventively. Furthermore, we observed that, in the absence of periodontal disease, locally applied oral-topical RvE1 significantly prevented vascular inflammation to an even greater extent [14••], supporting the hypothesis that periodontal inflammation accelerates atherosclerosis and complicates the response to treatment.

Constantinides Rabbit with Atherothrombosis

Periodontitis and Atherosclerosis, Plaque Rupture, and the Impact of RvE1

The most dramatic and clinically useful development of the rabbit model was the introduction of pharmacological triggering of plaque disruption and thrombosis with Russell viper venom (RVV) and histamine after atherosclerosis is developed in the rabbit aorta. This intervention combines activation of coagulation factors Xa and Va and vasoconstriction with histamine to simulate a myocardial infarction caused by plaque rupture and formation of a luminal thrombus [61]. The lengthy time period for development of vulnerable plaques (2 years) was reduced to 6 months by the introduction of balloon de-endothelialization by Baumgartner and Abela et al. [62, 63]. The most recent modification is a 3-month protocol with 1% cholesterol diet for 2 weeks followed by balloon injury and then 6 weeks of cholesterol diet and 4 weeks of normal chow that was developed on the Hamilton lab [64]. The plaques have been well characterized by histology and shown to consist of both stable and vulnerable [early (types II and III) and advanced (types IV, Va, Vc, VI)]. Thus, the model replicates many features of human disease that take decades to develop. Furthermore, model replicates features of thrombosis seen in human coronary arteries [64–69], which have not been replicated in mice or other animal models. A major advantage of the rabbit model is that thrombosis can be experimentally controlled, which cannot be performed in humans, and permits studies of plaques in vivo by new advanced methods such as noninvasive MRI [70] and invasive procedures [71]. The newest study by Stein-Merlob et al. used a fluorescently labeled nanoparticle to demonstrate that plaque disruption occurred at regions of high endothelial inflammation [71], and an accompanying editorial described the rabbit model as a "well validated model of atherosclerosis" [72].

Vulnerable plaques in the rabbit, as in humans, are associated with an overlying thrombus [73], achieving the desired goal of identifying the plaques at highest risk for disruption. Plaque rupture is characterized by a necrotic core with an overlying highly inflamed thin fibrous cap infiltrated by macrophages. The entire vessel wall is inflamed and monocyte/macrophage infiltration correlates with large, occlusive thrombi [73, 74].

To specifically identify the role of RvE1, the histopathological characteristics of atherosclerotic plaque and thrombus in the Constantinides rabbits were compared those in untreated rabbits and cholesterol-fed rabbits with and without *P. gingivalis* (unpubished data). The total lesion area was significantly reduced in RvE1-treated animals (Fig. 3a, b); furthermore, in plaques that did develop, histological analysis demonstrated a significant reduction in foam cell formation (Fig. 3c, d), collagen deposition, and the amount of RAM11-positive cells (depicting macrophages) (Fig. 3e). Extensive collagen deposition in plaques from untreated animals were associated with significant RAM11+ staining and platelet aggregation at the fibrous cap site indicating a vulnerable phenotype (Fig. 3c, e). Collectively, histopathological and MRI analyses (Fig. 3c, e, f) indicate that RvE1 prevents the progression to a more complex lesion. These results suggest that control of systemic inflammation with a resolution agonist may offer protection from cardiovascular events.

Systemic Inflammation and the Vulnerable Patient

The studies reported in this review support the concept that systemic inflammation involving remote sites in the body and different organs has systemic vascular actions impacting atherosclerosis. This concept gives rise to the idea that excess inflammation becomes a risk factor for atherosclerosis and other diseases and supports the concept of "the vulnerable patient" presented more than a decade ago by numerous cardiologists [75, 76]. The cardiovascular vulnerable patient is susceptible to acute coronary syndrome based on plaque, blood, or myocardial vulnerability [75, 77]. This concept is further supported by our findings.

Vulnerable blood may comprise numerous atherosclerosis-promoting molecules such as cytokines and provide a stimulus from sites distant from the atherosclerotic plaque [78]. For example, C-reactive protein (CRP) is a nonspecific marker of systemic inflammation and can originate from multiple sites. With acute inflammation, CRP levels can increase by up to 2 orders of magnitude and activate endothelium and accumulate within the plaque [79, 80]. Other markers of systemic inflammation, such as soluble adhesion molecules, circulating bacterial endotoxin, soluble human heat-shock protein 60, and antibodies to mycobacterial heat-shock protein 65, may predict an increased risk of atherosclerosis [81]. Inflammation is a major determinant of plaque rupture [24•, 82]. Elevated systemic inflammation predicts CVD events and local inflammatory foci both coincide with and induce systemic inflammation [30, 83, 84]. Atherosclerosis was originally recognized as infiltration of lipids into the vessel wall, primarily from LDL in the circulation and later as a local pathology that was accelerated by local inflammation [85]. Extensive evidence from human atherosclerosis and animal models [86, 87], especially the pig model [88] and rabbit model in

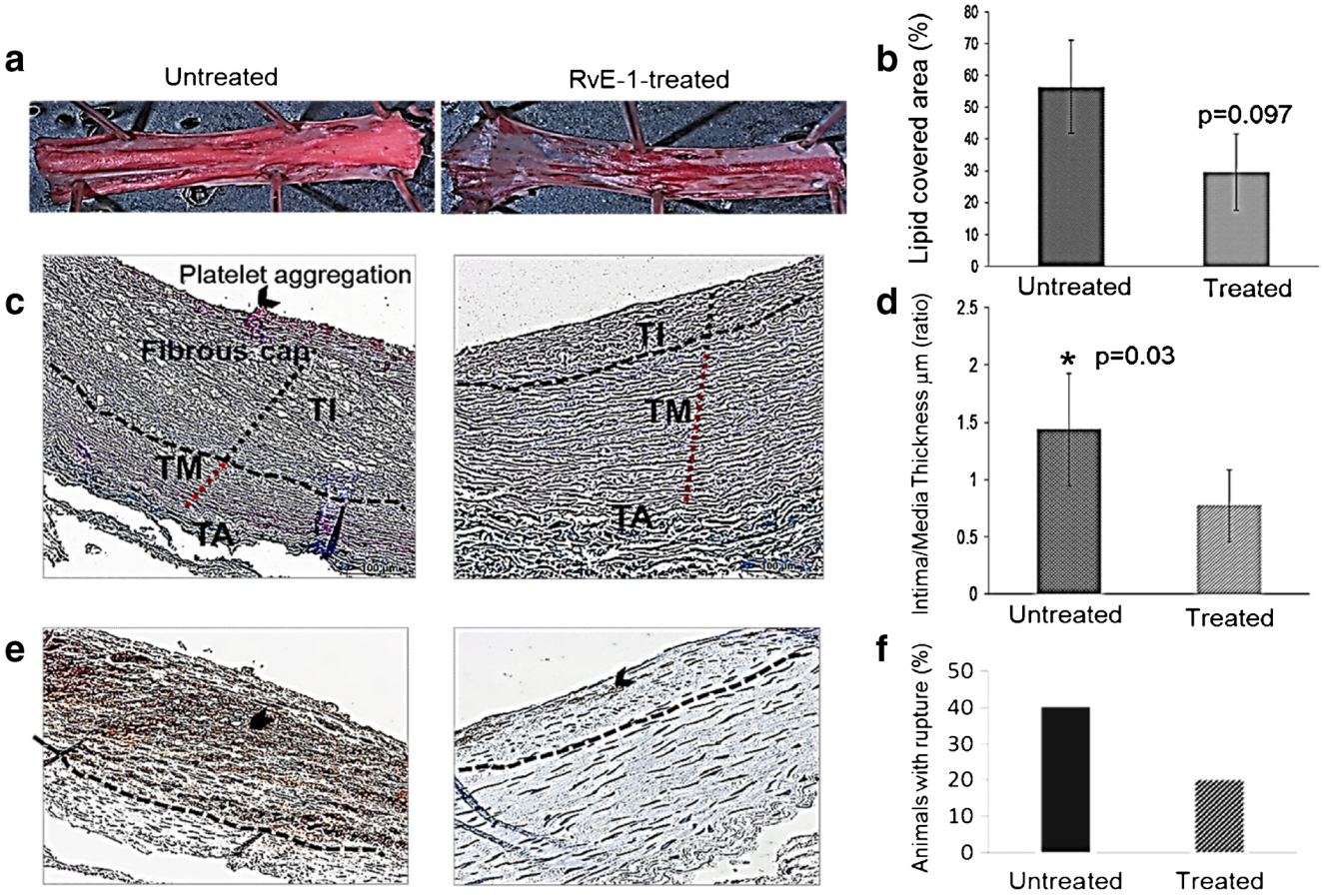

Fig. 3 RvE1 treatment in rabbits with advanced atherosclerosis and thrombosis. **a** Selected images of en face aortas stained with Su-dan IV. Rabbits fed 1.0% cholesterol (Constantinides model) and oral topical treatment applied between 2 and 3 months**. b** Mean lipid covered area (p = 0.097)**. c** Selected histological sections stained with H&E. Arrow depicts platelet aggregation at the fibrous cap indicating vulnerability of the plaque in the untreated. Dotted lines reveal that resolvin treatment has the potential to dramatically reduce the vulnerability and regresses plaque. **d** Mean intima/media ratio (*p = 0.03). **e** Selected immunohistochemical staining for macrophages in the intima using RAM11 monoclonal mouse anti-body specific to rabbit macrophages (black arrow). Resolvin treatment (1 mg/ml) reduced macrophage infiltration. **f** Percent of animals that had plaque rupture after triggering with RVV and histamine detected by MRI and confirmed by histology (n = 5/group)

our studies [64, 89], emphasizes that inflammation affects all regions of a vulnerable plaque (intima, media, and adventitia). However, for vulnerable plaque, inflammation in the endothelium is especially important as it stimulates exposure to thrombus-promoting molecules both in the blood and in the plaque [2•]. As discrete pathological regions, these high-risk plaques can be imaged and differentiated from lower risk plaques, which are considered "normal vessel wall."

Conclusion

Our new results clearly demonstrate a molecular connection between widely separated sites of vascular inflammation and oral inflammation, as well as increased generalized inflammation in the vessel wall. We propose that this leads to increased risk for thrombosis and also to growth and propagation of the thrombus. Our new studies also show that the systemic nature of these diseases presents a valuable therapeutic approach. Omega-3 polyunsaturated fatty acids (n-3 PUFA) found in marine oils (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA) in the diet are converted to resolvins to mitigate and control inflammation in localized sites (Fig. 1). The products are also transmitted through the circulation to distal sites to have beneficial effects beyond their initial cellular origin. We have shown that application of resolvin in the oral cavity effectively reduces local inflammation in the periodontal tissues and also demonstrates distal and beneficial systemic effects on atherosclerosis. Current therapies for thrombosis are inadequate and often carry high risks, and the resolvin/omega-3 fish oil therapy could provide a very effective and safe therapy that can be taken chronically, which will also serve as a preventive approach for plaque inflammation and rupture long term. Our results and ongoing work provide support for the concept of the "vulnerable" patient [75, 76] and a molecular mechanism of inflammation in

the vessel wall [90]. Uncontrolled or chronic systemic inflammation, prevalent in obesity and type 2 diabetes, sets people at high risk for cardiovascular disease.

Acknowledgements We thank Grace Yee for help in preparing the manuscript. The authors also thank Daniel Nguyen, Olivia Nguyen, and Konstantinia Almpani for their assistance in periodontitis and the CVD model in rabbits and histopathology. The preliminary studies were supported by the Forsyth Institute Pilot Grant Program.

Compliance with Ethical Standards

Conflict of Interest James A. Hamilton, Hatice Hasturk, Alpdogan Kantarci, Charles Serhan, and Thomas Van Dyke declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009;119(3):e21–181. https://doi.org/10.1161/CIRCULATIONAHA.108. 191261
2.• Hansson GK, Libby P, Tabas I. Inflammation and plaque vulnerability. J Intern Med. 2015;278(5):483–93. https://doi.org/10.1111/joim.12406. **This review highlights the importance of inflammation in atherosclerotic plaque vulnerability and addresses the need for identifying the inflammatory mechanisms, high-risk conditions and novel plaque-stabilizing therapies beyond lipid lowering in order to successfully prevent rupture-prone plaques and acute coronary syndromes.**
3. Vilahur G, Padro T, Badimon L. Atherosclerosis and thrombosis: insights from large animal models. J Biomed Biotechnol. 2011;2011:907575. https://doi.org/10.1155/2011/907575.
4. Shah PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol. 2003;41(4 Suppl S):15S–22S.
5. Davies MJ. Pathology of arterial thrombosis. Br Med Bull. 1994;50(4):789–802.
6. Qiao Y, Farber A, Semaan E, Hamilton JA. Images in cardiovascular medicine. Healing of an asymptomatic carotid plaque ulceration. Circulation. 2008;118(10):e147–8. https://doi.org/10.1161/CIRCULATIONAHA.108.764779.
7. Calvert PA, Liew TV, Gorenne I, Clarke M, Costopoulos C, Obaid DR, et al. Leukocyte telomere length is associated with high-risk plaques on virtual histology intravascular ultrasound and increased proinflammatory activity. Arterioscler Thromb Vasc Biol. 2011;31(9):2157–64. https://doi.org/10.1161/ATVBAHA.111.229237.
8. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226–35. https://doi.org/10.1056/NEJMoa1002358.
9. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ, CDC. Periodontal Disease Surveillance workgroup: James Beck GDRP. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res. 2012;91(10):914–20. https://doi.org/10.1177/0022034512457373.
10. Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. J Clin Periodontol. 2013;40(Suppl 14):S70–84. https://doi.org/10.1111/jcpe.12062.
11. Ryden L, Buhlin K, Ekstrand E, de Faire U, Gustafsson A, Holmer J, et al. Periodontitis increases the risk of a first myocardial infarction: a report from the PAROKRANK Study. Circulation. 2016;133(6):576–83. https://doi.org/10.1161/CIRCULATIONAHA.115.020324.
12. Slocum C, Kramer C, Genco CA. Immune dysregulation mediated by the oral microbiome: potential link to chronic inflammation and atherosclerosis. J Intern Med. 2016;280(1):114–28. https://doi.org/10.1111/joim.12476.
13. Jain A, Batista EL Jr, Serhan C, Stahl GL, Van Dyke TE. Role for periodontitis in the progression of lipid deposition in an animal model. Infect Immun. 2003;71(10):6012–8.
14.•• Hasturk H, Abdallah R, Kantarci A, Nguyen D, Giordano N, Hamilton J, et al. Resolvin E1 (RvE1) attenuates atherosclerotic plaque formation in diet and inflammation-induced atherogenesis. Arterioscler Thromb Vasc Biol. 2015;35(5):1123–33. https://doi.org/10.1161/ATVBAHA.115.305324. **This study demostrated that uncontrolled periodontal inflammation is capable of inducing a distal inflammatory pathology in vessel walls promoting atherosclerotic plaque to rupture-prone "high-risk" plaque characterized with large necrotic areas, this fibrous cap and dense inflammatory infiltration. Further, the study revealed that resolution of local periodontal inflammation by topical application of RvE1 averts atherosclerosis. This study is the first to demonstrate that a topical treatment for periodontal disease can have profound systemic actions.**
15. Reyes L, Herrera D, Kozarov E, Roldan S, Progulske-Fox A. Periodontal bacterial invasion and infection: contribution to atherosclerotic pathology. J Clin Periodontol. 2013;40(Suppl 14):S30–50. https://doi.org/10.1111/jcpe.12079.
16. de Boer SP, Cheng JM, Range H, Garcia-Garcia HM, Heo JH, Akkerhuis KM, et al. Antibodies to periodontal pathogens are associated with coronary plaque remodeling but not with vulnerability or burden. Atherosclerosis. 2014;237(1):84–91. https://doi.org/10.1016/j.atherosclerosis.2014.08.050.
17. Campbell LA, Rosenfeld ME. Persistent C. pneumoniae infection in atherosclerotic lesions: rethinking the clinical trials. Front Cell Infect Microbiol. 2014;4:34. https://doi.org/10.3389/fcimb.2014.00034.
18. Kebschull M, Demmer RT, Papapanou PN. "Gum bug, leave my heart alone!"—epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. J Dent Res. 2010;89(9):879–902. https://doi.org/10.1177/0022034510375281.
19. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nat Rev Immunol. 2015;15(1):30–44. https://doi.org/10.1038/nri3785.
20. Hasturk H, Kantarci A, Goguet-Surmenian E, Blackwood A, Andry C, Serhan CN, et al. Resolvin E1 regulates inflammation at the cellular and tissue level and restores tissue homeostasis in vivo. J Immunol. 2007;179(10):7021–9.
21. Fredman G, Spite M. Specialized pro-resolving mediators in cardiovascular diseases. Mol Asp Med. 2017; https://doi.org/10.1016/j.mam.2017.02.003.
22. Norling LV, Perretti M. The role of omega-3 derived resolvins in arthritis. Curr Opin Pharmacol. 2013;13(3):476–81. https://doi.org/10.1016/j.coph.2013.02.003.
23. Levy BD, Serhan CN. Resolution of acute inflammation in the lung. Annu Rev Physiol. 2014;76:467–92. https://doi.org/10.1146/annurev-physiol-021113-170408.

24.• Bertrand MJ, Tardif JC. Inflammation and beyond: new directions and emerging drugs for treating atherosclerosis. Expert Opin Emerg Drugs. 2017;22(1):1–26. https://doi.org/10.1080/14728214.2017.1269743. **This review discusses novel therapies that can address the inflammatory etiology of the atherosclerosis in the prevention of acute cardiovascular events. It highlights the urgent need in drug development aiming to target inflammatory pathways as a promising avenue for novel therapies in atherosclerosis.**

25. Elajami TK, Colas RA, Dalli J, Chiang N, Serhan CN, Welty FK. Specialized proresolving lipid mediators in patients with coronary artery disease and their potential for clot remodeling. FASEB J. 2016;30(8):2792–801. https://doi.org/10.1096/fj.201500155R.

26. Serhan CN, Chiang N. Endogenous pro-resolving and anti-inflammatory lipid mediators: a new pharmacologic genus. Br J Pharmacol. 2008;153(Suppl 1):S200–15. https://doi.org/10.1038/sj.bjp.0707489.

27. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510(7503):92–101. https://doi.org/10.1038/nature13479.

28. Fredman G, Hellmann J, Proto JD, Kuriakose G, Colas RA, Dorweiler B, et al. An imbalance between specialized pro-resolving lipid mediators and pro-inflammatory leukotrienes promotes instability of atherosclerotic plaques. Nat Commun. 2016;7:12859. https://doi.org/10.1038/ncomms12859.

29. Maekawa T, Takahashi N, Tabeta K, Aoki Y, Miyashita H, Miyauchi S, et al. Chronic oral infection with Porphyromonas gingivalis accelerates atheroma formation by shifting the lipid profile. PloS one. 2011;6(5):e20240. https://doi.org/10.1371/journal.pone.0020240.

30. Subramanian S, Emami H, Vucic E, Singh P, Vijayakumar J, Fifer KM, et al. High-dose atorvastatin reduces periodontal inflammation: a novel pleiotropic effect of statins. J Am Coll Cardiol. 2013;62(25):2382–91. https://doi.org/10.1016/j.jacc.2013.08.1627.

31. Serhan CN, Jain A, Marleau S, Clish C, Kantarci A, Behbehani B, et al. Reduced inflammation and tissue damage in transgenic rabbits overexpressing 15-lipoxygenase and endogenous anti-inflammatory lipid mediators. J Immunol. 2003;171(12):6856–65.

32. Wu B, Mottola G, Schaller M, Upchurch GR Jr, Conte MS. Resolution of vascular injury: Specialized lipid mediators and their evolving therapeutic implications. Mol Asp Med. 2017; https://doi.org/10.1016/j.mam.2017.07.005.

33.•• Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. FASEB J. 2017;31(4):1273–88. https://doi.org/10.1096/fj.201601222R. **This review is an extensive overview of a series of studies over a decade that opened a new avenue in our understanding of inflammation and resolution of inflammation by specialized proresolving mediators, endogenous mediators that include the n-3-derived families resolvins, protectins, and maresins, as well as arachidonic acid-derived (n-6) lipoxins. Identified in recent years, these mediatos promote resolution of inflammation, clearance of microbes, reduction of pain, and tissue regeneration via novel mechanisms and offer a prardign shift in the treatment of inflammatory diseases.**

34. Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med. 2000;192(8):1197–204.

35. Serhan CN, Clish CB, Brannon J, Colgan SP, Gronert K, Chiang N. Anti-microinflammatory lipid signals generated from dietary N-3 fatty acids via cyclooxygenase-2 and transcellular processing: a novel mechanism for NSAID and N-3 PUFA therapeutic actions. J Physiol Pharmacol : Off J Pol Physiol Soc. 2000;51(4 Pt 1):643–54.

36. Oh SF, Pillai PS, Recchiuti A, Yang R, Serhan CN. Pro-resolving actions and stereoselective biosynthesis of 18S E-series resolvins in human leukocytes and murine inflammation. J Clin Invest. 2011;121(2):569–81. https://doi.org/10.1172/JCI42545.

37. Serhan CN, Hong S, Gronert K, Colgan SP, Devchand PR, Mirick G, et al. Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med. 2002;196(8):1025–37.

38. Arita M, Bianchini F, Aliberti J, Sher A, Chiang N, Hong S, et al. Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. J Exp Med. 2005;201(5):713–22. https://doi.org/10.1084/jem.20042031.

39. Oh SF, Dona M, Fredman G, Krishnamoorthy S, Irimia D, Serhan CN. Resolvin E2 formation and impact in inflammation resolution. J Immunol. 2012;188(9):4527–34. https://doi.org/10.4049/jimmunol.1103652.

40. Tjonahen E, Oh SF, Siegelman J, Elangovan S, Percarpio KB, Hong S, et al. Resolvin E2: identification and anti-inflammatory actions: pivotal role of human 5-lipoxygenase in resolvin E series biosynthesis. Chem Biol. 2006;13(11):1193–202. https://doi.org/10.1016/j.chembiol.2006.09.011.

41. Arita M, Ohira T, Sun YP, Elangovan S, Chiang N, Serhan CN. Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. J Immunol. 2007;178(6):3912–7.

42. Schwab JM, Chiang N, Arita M, Serhan CN. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. Nature. 2007;447(7146):869–74. https://doi.org/10.1038/nature05877.

43. Spite M, Claria J, Serhan CN. Resolvins, specialized proresolving lipid mediators, and their potential roles in metabolic diseases. Cell metabolism. 2014;19(1):21–36. https://doi.org/10.1016/j.cmet.2013.10.006.

44. El Kebir D, Gjorstrup P, Filep JG. Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. Proc Natl Acad Sci U S A. 2012;109(37):14983–8. https://doi.org/10.1073/pnas.1206641109.

45. Ohira T, Arita M, Omori K, Recchiuti A, Van Dyke TE, Serhan CN. Resolvin E1 receptor activation signals phosphorylation and phagocytosis. J Biol Chem. 2010;285(5):3451–61. https://doi.org/10.1074/jbc.M109.044131.

46. Haworth O, Cernadas M, Yang R, Serhan CN, Levy BD. Resolvin E1 regulates interleukin 23, interferon-gamma and lipoxin A4 to promote the resolution of allergic airway inflammation. Nat Immunol. 2008;9(8):873–9. https://doi.org/10.1038/ni.1627.

47. Hasturk H, Kantarci A, Ohira T, Arita M, Ebrahimi N, Chiang N, et al. RvE1 protects from local inflammation and osteoclast- mediated bone destruction in periodontitis. FASEB J. 2006;20(2):401–3. https://doi.org/10.1096/fj.05-4724fje.

48. Campbell EL, MacManus CF, Kominsky DJ, Keely S, Glover LE, Bowers BE, et al. Resolvin E1-induced intestinal alkaline phosphatase promotes resolution of inflammation through LPS detoxification. Proc Natl Acad Sci U S A. 2010;107(32):14298–303. https://doi.org/10.1073/pnas.0914730107.

49. Rajasagi NK, Reddy PB, Suryawanshi A, Mulik S, Gjorstrup P, Rouse BT. Controlling Herpes simplex virus-induced ocular inflammatory lesions with the lipid-derived mediator resolvin E1. J Immunol. 2011;186(3):1735–46. https://doi.org/10.4049/jimmunol.1003456.

50. Li N, He J, Schwartz CE, Gjorstrup P, Bazan HE. Resolvin E1 improves tear production and decreases inflammation in a dry eye mouse model. J Ocul Pharmacol Ther : Off J Assoc Ocul Pharmacol Ther. 2010;26(5):431–9. https://doi.org/10.1089/jop.2010.0019.

51. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nature immunology. 2005;6(12):1191–7. https://doi.org/10.1038/ni1276.

52. Qu X, Zhang X, Yao J, Song J, Nikolic-Paterson DJ, Li J. Resolvins E1 and D1 inhibit interstitial fibrosis in the obstructed kidney via inhibition of local fibroblast proliferation. J Pathol. 2012;228(4):506–19. https://doi.org/10.1002/path.4050.
53. Keyes KT, Ye Y, Lin Y, Zhang C, Perez-Polo JR, Gjorstrup P, et al. Resolvin E1 protects the rat heart against reperfusion injury. Am J Physiol Heart Circ Physiol. 2010;299(1):H153–64. https://doi.org/10.1152/ajpheart.01057.2009.
54. Levy BD, Zhang QY, Bonnans C, Primo V, Reilly JJ, Perkins DL, et al. The endogenous pro-resolving mediators lipoxin A4 and resolvin E1 preserve organ function in allograft rejection. Prostaglandins Leukot Essent Fat Acids. 2011;84(1–2):43–50. https://doi.org/10.1016/j.plefa.2010.09.002.
55. Dalli J, Serhan CN. Specific lipid mediator signatures of human phagocytes: microparticles stimulate macrophage efferocytosis and pro-resolving mediators. Blood. 2012;120(15):e60–72. https://doi.org/10.1182/blood-2012-04-423525.
56. Endo J, Sano M, Isobe Y, Fukuda K, Kang JX, Arai H, et al. 18-HEPE, an n-3 fatty acid metabolite released by macrophages, prevents pressure overload-induced maladaptive cardiac remodeling. J Exp Med. 2014;211(8):1673–87. https://doi.org/10.1084/jem.20132011.
57. Chiang N, Fredman G, Backhed F, Oh SF, Vickery T, Schmidt BA, et al. Infection regulates pro-resolving mediators that lower antibiotic requirements. Nature. 2012;484(7395):524–8. https://doi.org/10.1038/nature11042.
58. Ishida T, Yoshida M, Arita M, Nishitani Y, Nishiumi S, Masuda A, et al. Resolvin E1, an endogenous lipid mediator derived from eicosapentaenoic acid, prevents dextran sulfate sodium-induced colitis. Inflamm Bowel Dis. 2010;16(1):87–95. https://doi.org/10.1002/ibd.21029.
59. Abela OG, Ahsan CH, Alreefi F, Salehi N, Baig I, Janoudi A, et al. Plaque rupture and thrombosis: the value of the atherosclerotic rabbit model in defining the mechanism. Curr Atheroscler Rep. 2016;18(6):29. https://doi.org/10.1007/s11883-016-0587-0.
60. Bodary PF, Eitzman DT. Animal models of thrombosis. Curr Opin Hematol. 2009;16(5):342–6. https://doi.org/10.1097/MOH.0b013e32832e9ddd.
61. Constantinides P, Chakravarti RN. Rabbit arterial thrombosis production by systemic procedures. Arch Pathol. 1961;72:197–208.
62. Baumgartner HRSA. Folgen des gefa¨sskatheterismus am normo- und hypercholesterinaemischen kaninchen. Path Microbiol. 1966;29:393–405.
63. Abela GS, Picon PD, Friedl SE, Gebara OC, Miyamoto A, Federman M, et al. Triggering Of plaque disruption and arterial thrombosis in an atherosclerotic rabbit model. Circulation. 1995;91(3):776–84.
64. Phinikaridou A, Hallock KJ, Qiao Y, Hamilton JA. A robust rabbit model of human atherosclerosis and atherothrombosis. J Lipid Res. 2009;50(5):787–97.
65. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation. 2011;124(4):489–532. https://doi.org/10.1161/CIR.0b013e31820d8d78.
66. Crignon C. The discovery of blood circulation: revolution or revision? Gesnerus. 2011;68(1):5–25.
67. Kalani MY, Martirosyan NL, Eschbacher JM, Nakaji P, Albuquerque FC, Spetzler RF. Large hemangiopericytoma associated with arteriovenous malformations and dural arteriovenous fistulae. World Neurosurg. 2011;76(6):592 e7–10. https://doi.org/10.1016/j.wneu.2011.05.023.
68. Kaltman JR, Thompson PD, Lantos J, Berul CI, Botkin J, Cohen JT, et al. Screening for sudden cardiac death in the young: report from a national heart, lung, and blood institute working group. Circulation. 2011;123(17):1911–8. https://doi.org/10.1161/CIRCULATIONAHA.110.017228.
69. Polkinghorne BG, Muscatello DJ, Macintyre CR, Lawrence GL, Middleton PM, Torvaldsen S. Relationship between the population incidence of febrile convulsions in young children in Sydney, Australia and seasonal epidemics of influenza and respiratory syncytial virus, 2003–2010: a time series analysis. BMC Infect Dis. 2011;11:291. https://doi.org/10.1186/1471-2334-11-291.
70. Hua N, Baik F, Pham T, Phinikaridou A, Giordano N, Friedman B, et al. Identification of high-risk plaques by MRI and fluorescence imaging in a rabbit model of atherothrombosis. PloS one. 2015;10(10):e0139833. https://doi.org/10.1371/journal.pone.0139833.
71. Stein-Merlob AF, Hara T, McCarthy JR, Mauskapf A, Hamilton JA, Ntziachristos V et al. Atheroma susceptible to thrombosis exhibit impaired endothelial permeability in vivo as assessed by nanoparticle-based fluorescence molecular imaging. Circ Cardiovasc Imaging. 2017;10(5). doi:https://doi.org/10.1161/CIRCIMAGING.116.005813.
72. Calcagno C, Fayad ZA. Intraplaque and cellular distribution of dextran-coated iron oxide fluorescently labeled nanoparticles: insights into atherothrombosis and plaque rupture. Circ Cardiovasc Imaging. 2017;10(5). doi:https://doi.org/10.1161/CIRCIMAGING.117.006533.
73. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol. 2006;47(8_Suppl_C):C13–8. https://doi.org/10.1016/j.jacc.2005.10.065.
74. Hao H, Gabbiani G, Camenzind E, Bacchetta M, Virmani R, Bochaton-Piallat ML. Phenotypic modulation of intima and media smooth muscle cells in fatal cases of coronary artery lesion. Arterioscler Thromb Vasc Biol. 2006;26(2):326–32. https://doi.org/10.1161/01.ATV.0000199393.74656.4c.
75. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. Circulation. 2003;108(14):1664–72. https://doi.org/10.1161/01.CIR.0000087480.94275.97.
76. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part II. Circulation. 2003;108(15):1772–8. https://doi.org/10.1161/01.CIR.0000087481.55887.C9.
77. Myerburg RJ, Interian A Jr, Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. Am J Cardiol. 1997;80(5B):10F–9F.
78. de Gaetano M, Crean D, Barry M, Belton O. M1- and M2-type macrophage responses are predictive of adverse outcomes in human atherosclerosis. Front Immunol. 2016;7:275. https://doi.org/10.3389/fimmu.2016.00275.
79. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation. 2000;102(18):2165–8.
80. Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation. 2002;105(16):1890–6.

81. Kiechl S, Egger G, Mayr M, Wiedermann CJ, Bonora E, Oberhollenzer F, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. Circulation. 2001;103(8):1064–70.
82. Cimmino G, Loffredo FS, Morello A, S DE, De Palma R, Cirillo P et al. Immune-inflammatory activation in acute coronary syndromes: a look into the heart of unstable coronary plaque. Curr Cardiol Rev. 2016. https://doi.org/10.2174/1573403X12666161014093812.
83. Lindy O, Suomalainen K, Makela M, Lindy S. Statin use is associated with fewer periodontal lesions: a retrospective study. BMC Oral Health. 2008;8:16. https://doi.org/10.1186/1472-6831-8-16.
84. Hayashi C, Viereck J, Hua N, Phinikaridou A, Madrigal AG, Gibson FC 3rd, et al. Porphyromonas gingivalis accelerates inflammatory atherosclerosis in the innominate artery of ApoE deficient mice. Atherosclerosis. 2011;215(1):52–9. https://doi.org/10.1016/j.atherosclerosis. 2010.12. 009.
85. Zaromytidou M, Antoniadis AP, Siasos G, Coskun AU, Andreou I, Papafaklis MI, et al. Heterogeneity of coronary plaque morphology and natural history: current understanding and clinical significance. Curr Atheroscler Rep. 2016;18(12):80. https://doi.org/10.1007/s11883-016-0626-x.
86. Westrick R, Fredman G, Early CC. Platelets: context-dependent vascular protectors or mediators of disease. Arterioscler Thromb Vasc Biol. 2015;35(7):e25–9. https://doi.org/10.1161/ATVBAHA.115.305898.
87. Daugherty A, Tall AR, Daemen M, Falk E, Fisher EA, Garcia-Cardena G, et al. Recommendation on design, execution, and reporting of animal atherosclerosis studies: a scientific statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2017;37(9):e131–e57. https://doi.org/10.1161/ATV.0000000000000062.
88. Granada JF, Kaluza GL, Wilensky RL, Biedermann BC, Schwartz RS, Falk E. Porcine models of coronary atherosclerosis and vulnerable plaque for imaging and interventional research. EuroIntervention: J EuroPCR Collab Work Group Interventional Cardiol Eur Soc Cardiol. 2009;5(1):140–8.
89. Phinikaridou A, Ruberg FL, Hallock KJ, Qiao Y, Hua N, Viereck J, et al. In vivo detection of vulnerable atherosclerotic plaque by MRI in a rabbit model. Circ Cardiovasc Imaging. 2010;3(3):323–32. https://doi.org/10.1161/CIRCIMAGING.109.918524.
90. Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. Nat Rev Immunol. 2010;10(1):36–46. https://doi.org/10.1038/nri2675.