Vascular consequences of inflammation

Vascular consequences of inflammation: a position statement from the ESH Working Group on Vascular Structure and Function and the ARTERY Society

Brief title: Inflammation and large arteries

Luca ZANOLI[a], Marie BRIET[b], Jean Philippe EMPANA[c,d], Pedro Guimarães CUNHA[e,f], Kaisa M MÄKI-PETÄJÄ[g], Athanase D PROTOGEROU[h], Alain TEDGUI[i], Rhian M TOUYZ[j], Ernesto SCHIFFRIN[k], Bart SPRONCK[l], Philippe BOUCHARD[m], Charalambos VLACHOPOULOS[n], Rosa Maria BRUNO[c,i,o], Pierre BOUTOUYRIE[c,i,o]; on behalf of the Association for Research into Arterial Structure and Physiology (ARTERY) Society and the European Society of Hypertension (ESH) Working Group on Vascular Structure and Function and the European Network for Noninvasive Investigation of Large Arteries.

[a] Nephrology, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy.

[b] INSERM U1083, CNRS UMR 6214, Centre Hospitalo-Universitaire d'Angers, Université d'Angers, Angers , France.

[c] Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Paris, France.

[d] INSERM U970, Cardiovascular Epidemiology and Sudden cardiac death, Paris, France.

[e] Center for the Research and Treatment of Arterial Hypertension and Cardiovascular Risk, Internal Medicine Department, Hospital Senhora da Oliveira, Guimarães; Life and Health Science Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal.

[f] ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal.

[g] Division of Experimental Medicine and Immunotherapeutics, University of Cambridge, Cambridge, United Kingdom.

[h] Cardiovascular Prevention & Research Unit, Department of Pathophysiology Medical School, National and Kapodistrian University of Athens, Greece.

[i] INSERM U970, Paris, France.

[j] Institute of Cardiovascular & Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, United Kingdom.

[k] Lady Davis Institute for Medical Research, and [d]Department of Medicine, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, 3755 Côte-Ste-Catherine Rd., Montreal, Quebec, Canada H3T 1E2.

[l] Department of Biomedical Engineering, School of Engineering & Applied Science, Yale University, New Haven, CT, United States.

[m] U.F.R. d'odontologie, Université Paris Diderot, Hôpital Rothschild AP-HP, Paris, France.

[n] University of Athens Medical School, Athens, Greece.

[o] Department of Pharmacology, HEGP, AP-HP, Paris, France.

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Correspondence to:

Luca Zanoli, MD, PhD, FASN. Department of Clinical and Experimental Medicine, Policlinico Universitario di Catania, University of Catania, Via Santa Sofia 78, 95123 Catania, Italy.

Tel +39 3474574122 ; FAX +39 0953782376; Email: luca.zanoli@unict.it

Bart Spronck. Department of Biomedical Engineering, School of Engineering & Applied Science, Yale University, New Haven, CT, United States.

Tel: +1 203 432 6678; FAX: +1 203 432 6678; Email: bart.spronck@yale.edu

Abstract

Inflammation is a physiological response to aggression of pathogenic agents aimed at eliminating the aggressor agent and promoting healing. Excessive inflammation, however, may contribute to tissue damage and an alteration of arterial structure and function. Increased arterial stiffness is a well-recognized cardiovascular risk factor independent of blood pressure levels and an intermediate endpoint for cardiovascular events. In the present review we discuss immune mediated mechanisms by which inflammation can influence arterial physiology and lead to vascular dysfunction such as atherosclerosis and arterial stiffening. We also show that acute inflammation predisposes the vasculature to arterial dysfunction and stiffening, and alteration of endothelial function and that chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease and psoriasis are accompanied by profound arterial dysfunction which is proportional to the severity of inflammation. Current findings suggest that treatment of inflammation by targeted drugs leads to regression of arterial dysfunction. There is hope that these treatments will improve outcomes for patients.

Condensed abstract

Inflammation is a physiological response to aggression of pathogenic agents aimed at eliminating the aggressor agent and promoting healing. Excessive inflammation, however, may contribute to tissue damage and an alteration of arterial structure and function. Increased arterial stiffness is a well-recognized cardiovascular risk factor independent of blood pressure levels. In the present review we discuss (i) mechanisms by which inflammation can influence arterial physiology and lead to vascular dysfunction such as atherosclerosis and arterial stiffening, (ii) clinical models of vascular inflammation, and (iii) current evidence on anti-inflammatory therapy and regression of arterial dysfunction.

Keywords: Arterial stiffness; inflammation; pulse wave velocity; large arteries; cardiovascular disease.

Introduction

Inflammation is a ubiquitous, integrated and complex response to insults by pathogens, immunologically-mediated stimuli, irritants or chemicals. Inflammation, however, may also contribute to tissue damage if excessive or chronic. The vascular system is key to the inflammatory response since most components of the inflammatory response transit through the blood and vessels. In the vascular system, acute and chronic inflammation lead to endothelial dysfunction and arterial remodelling, which underlie many cardiovascular diseases. Vascular inflammation is a common response to injury and involves many cell types (immune cells, vascular smooth muscle cells (VSMC), perivascular adipocytes and fibroblasts), numerous mediators (cytokines, chemokines and reactive oxygen species (ROS)), multiple receptors (toll-like receptors, receptor for advanced glycation end-products, tumour necrosis factor (TNF)α receptor-associated factors, NOD-like receptors, transforming growth factor-β-(TGF-β) activated kinase 1, cytokine and chemokine receptors) and complex pro-inflammatory signalling pathways (e.g., nuclear factor κB, mitogen-activated protein kinases, canonical wingless-related integration site (WNT)/β-catenin and Signal transducer and activator of transcription 3, STAT3). Prolonged inflammation causes DNA damage, first step to vascular injury. At the core of many of these processes is an increased production of ROS, especially superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) and activation of injurious redox-sensitive signalling pathways [1]. In the present review, we propose a general overview of the basic mechanisms by which inflammation can alter arterial physiology and lead to vascular complications such as atherosclerosis and arterial stiffening. We further aim to demonstrate the bidirectional association between inflammation and vascular diseases, i.e. vascular consequences of primarily inflammatory diseases, and systemic disease caused primarily by inflammatory vascular disease. Finally, we review the epidemiological evidence of the association between low-grade chronic inflammation and vascular diseases and we will also expose to what extent anti-inflammatory drugs can reverse the effects of inflammation on large vessels.

Biological basis and redox biology of inflammation in arterial disease

The inflammatory response in arteries is triggered by humoral, physical and mechanical factors including vasoactive hormones (angiotensin II (AII), endothelin-1, aldosterone), mechanical factors (vascular stretch, pressure), ischaemic insults (ischemia-reperfusion, hypoxia), metabolic factors (hyperglycaemia, oxidized low density lipoproteins, LDL), cytokines and chemokines [2], as well as by clonal haematopoiesis of indeterminate potential and epigenetic dysregulation [3]. The autonomic nervous system has also been implicated in the acute phases of inflammation through the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis since increased catecholamine levels and glucocorticoids may stimulate innate immune cells, such as neutrophils, macrophages and lymphocytes [4-6]. These factors play a role in vascular damage associated with cardiovascular diseases.

Innate immunity in arterial disease

One of the earliest events in the inflammatory response is the activation of the innate immunity [7,8]. Endothelial adhesion molecules interact with glycoproteins on the neutrophil surface promoting interactions with the vessel wall [9]. E-selectin facilitates neutrophil tethering, rolling and adhesion through binding with P-selectin glycoprotein ligand 1, CD44 and E-selectin ligand I [2,10]. This interaction triggers integrin activation through tyrosine kinases, which induces platelet adhesion, further contributing to endothelial injury and dysfunction [10]. Following neutrophil adhesion, the cytoskeleton undergoes reorganization to establish cell polarity, which facilitates transmigration of cells into the vascular media, where resident macrophages are present. Activated neutrophils may also migrate to the perivascular adventitial tissue. Within the vascular wall and perivascular tissue, neutrophils and macrophages further drive inflammation causing vascular damage. Infiltration of innate and adaptive immune cells in perivascular fat, kidneys and myocardium is found to different degrees in experimental and human hypertension [8,11,12]. Innate

immune cells sense pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) from injured tissue via toll-like receptors (TLRs) [13]. Proinflammatory macrophages and dendritic cells (DCs) release interleukin (IL)-1β, IL-6, IL-12, IL-23, TNFα and ROS; anti-inflammatory macrophages and DCs produce IL-10. Natural Killer (NK) cells produce pro- or anti-inflammatory cytokines (interferon γ (IFNγ) or IL-10). Myeloid-derived suppressor cells are increased in blood, spleen and kidneys of AII-infused mice. Their depletion induces an exaggerated BP elevation to AII.

Adaptive immunity in arterial disease

Adaptive immunity is involved in response to combined stimulation by antigen, co-stimulators, and specific cytokines [8]. Naïve $CD4^+$ T_h cells differentiate into T helper (T_h)1, T_h2, T_h17 effector (all proinflammatory), or T_{reg} cells (anti-inflammatory). T_h1 cells produce IFNγ, IL-2 and TNFα, T_h2 cells produce IL-4, IL-5, IL-9 and IL-13; T_h17 cells secrete IL-17, IL-21 and IL-22. Upon activation with MHC I-restricted antigens, naïve $CD8^+$ T cells mature into cytotoxic (T_c) cells that secrete IFNγ and TNFα, perforin and granzyme B. Perforin creates pores within the target cell membranes, through which granzymes enter cells and induce apoptosis. T-regulatory (T_{reg}) cells express the IL-2 receptor α-subunit (CD25), and the transcription factor forkhead box P3 (Foxp3). The suppressive actions of T_{reg} cells are mediated by cell-cell contact mechanisms and/or via the release of anti-inflammatory IL-10, IL-35 and TGF-β [14].

Immunological memory plays a role in hypertension. Central memory T (T_{CM}) cells are found in lymphoid organs, whereas effector memory T (T_{EM}) cells recirculate between lymphoid tissues, blood and peripheral organs and produce proinflammatory IFNγ and IL-17A. AII infusion caused T_{EM} cell accumulation in the aorta, kidney and lymph nodes of humanized mice [15]. Hypertensive patients have increased frequency of circulating senescent ($CD28^-CD57^+$) $CD8^+$, $CD8^+$ T cells expressing IFγ, TNFα, perforin and granzyme B, $CD4^+$ T_h1 and T_h17 cells [16,17]. A subpopulation

of $CD4^+$ T_{EM} cells that expresses choline acetyltransferase (ChAT) is activated via β_2-adrenergic receptors and releases acetylcholine, which binds to α7 nicotinic acetylcholine receptors on macrophages and suppresses lipopolysaccharide-induced TNFα release [18]. BP is higher in mice lacking ChAT in $CD4^+$ T cells than in control mice, and infusion of Jurkat T cells overexpressing ChAT decreases BP [19].

Decreased immune T_{reg} ($CD4^+CD25^+$ T cells) activity could counteract hypertension and cardiovascular injury. Adoptive transfer of T_{reg} reduced AII- or aldosterone/salt-induced BP elevation, together with vascular and cardiac injury [20-23]. AII decreased T_{reg} function via the binding of complement components C3a and C5a to their cognate receptor, which decreases Foxp3 expression [24]. Finally, there is an inverse correlation between circulating $CD4^+CD25^{High}CD127^{Low}$ T_{reg} and media/lumen ratio of subcutaneous resistance arteries and retinal arterioles in human essential hypertension [25].

γδ T cells represent ~0.5-10% of circulating lymphocytes in humans. They belong to $CD4^-CD8^-$ populations, tend to reside in non-lymphoid tissues and have a faster response after activation and after a recall response to antigens than MHC-restricted T cells. They produce IL-17 in response to the pro-inflammatory cytokines IL-1β and IL-23 like T_h17 cells. AII caused an increase in number and activation of γδ T cells [26]. Deficiency in γδ T cells prevented AII-induced hypertension, endothelial dysfunction and spleen and mesenteric artery perivascular adipose tissue $CD4^+$ and $CD8^+$ T cell activation [26].

The vascular inflammatory cascade

How and when the immune system is activated in hypertension remains unclear. We propose the following cascade (Figure 1). Initial blood pressure (BP) elevation and/or pro-hypertensive stimuli could induce cardiovascular injury leading to development of DAMPs or of neoantigens. In a hypertensive mice models, angiotensin II causes ROS generation in DCs that could result in production of γ-ketoaldehydes or isoketals, which react with protein lysine residues of injured

tissues to form isoketal protein adducts that function as neoantigens [27]. These activate DCs, and stimulate release of IL-6, IL-1β and IL-23, which in turn stimulate innate immunity via toll-like receptors on proinflammatory macrophages, DCs, and NK cells, as well as innate-like γδ T cells. The latter may prime both innate and adaptive immune cells. Innate immune cells and γδ T lymphocytes contribute to inflammation, both directly or by activation of adaptive immunity, inducing proinflammatory cytokines like IL-17 and IFNγ, and autoantibody production leading to vascular and kidney injury, thus contributing to progressive BP elevation. T_{EM} cells generated during this process accumulate in lymphoid organs including the bone marrow. Upon a second hit such as high-salt intake, T_{EM} cells are activated and contribute to hypertension. Throughout, anti-inflammatory cells such as T_{reg}, myeloid-derived suppressor cell and M2 macrophages may limit this response and help fine-tune vascular and kidney inflammation [28].

Reactive oxygen species, oxidative stress and vascular inflammation

The generation of ROS is central to the effects of pro-inflammatory cells because, in phagocytic cells, it is responsible for host-defence responses. In the vascular system, VSMCs, endothelial cells, fibroblasts, perivascular adipocytes, macrophages and immune cells produce ROS [29]. The major source of ROS in vascular cells is nicotinamide adenine dinucleotide phosphate oxidase (Nox), although other enzymatic sources may also contribute, such as xanthine oxidase, mitochondrial electron transport chain, uncoupled endothelial nitric oxide (NO) synthases, cyclooxygenase, lipoxygenase and cytochrome P450 oxidases [29]. Of the seven Nox isoforms identified, Nox1,2,4 and 5 are present in human arteries [30]. Nox1,2 and 5 produce O_2^- while Nox4 activation leads to increased H_2O_2 production. Vascular Nox activity is increased in cardiovascular disease leading to dysregulated ROS production, oxidative stress, activation of pro-inflammatory transcription factors and activation of redox-sensitive signalling pathways [29,30]. Increased endothelial cell O_2^- limits bioavailability of nitric oxide and also increases formation of $ONOO^-$, which is highly unstable

causing vascular inflammation, fibrosis, hypertrophy and endothelial dysfunction. Oxidative stress is counterbalanced by numerous antioxidant systems, including superoxide dismutase, catalase, peroxidases, glutathione, thioredoxin and nuclear factor erythroid 2 (Nrf-2), the master regulator of antioxidant genes [31]. In cardiovascular disease, many of these antioxidant systems are downregulated, thereby further contributing to excessive ROS accumulation.

In addition to the inactivation of NO, ROS influence vascular cell function by altering protein activity through post-translational oxidative modifications [29,30]. In vascular cells, proteins that are redox-sensitive include receptors, kinases, phosphatases, transcription factors, ion channels, cytoskeletal proteins and matrix metalloproteases (MMPs), all of which play a role in regulating endothelial and VSMC function. In addition, ROS stimulate production of vasoactive agents, such as AII, endothelin-1 and cyclooxygenase-2 and they influence intracellular calcium concentration, important in regulating vasoconstriction. In the endothelium, H_2O_2 acts as a vasodilator and is considered as an endothelium-derived relaxing factor, acting through activation of protein kinase G alpha (PKG1α) [30]. ROS in return stimulate activation of transcription factors and pro-inflammatory genes, chemokine and cytokine production and recruitment and activation of inflammatory and immune cells in a positive feedback for vascular inflammation.

Mitochondrial ROS production and DNA damage are another important sources of oxidative stress in cardiovascular disease [32]. Physiologically, mitochondrial ROS act as signalling molecules and modulate vasomotion and myogenic tone (i.e. the interaction between vasomotor tone and mechanical stimuli). In several pathological conditions, mitochondria produce excessive ROS that activate proinflammatory pathways in the vascular endothelial cells and result in vasoconstriction, inflammation and thrombosis [32]. Moreover, mitochondrial ROS, through the triggering of NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome formation and activation, lead to IL-1β activation [33].

IL-1β inflammation pathway

Dissecting the inflammatory cascade shows a tight link between its components; the upstream cytokine IL-1β affects IL6 levels that in turn control the secretion of a downstream mediator C-reactive protein (CRP) (Figure 2). IL-1β and IL-6 inhibition is now an important target for some inflammatory diseases (see infra). In the plasma of patients with myocardial infarction, an IL-1β peak preceded the IL-6 peak, strengthening the upstream position of IL-1β [34]. In vitro, IL-1β strongly stimulates IL-6 synthesis by various types of cells including vascular cells. IL-1β induces a proinflammatory phenotype of endothelial cells and increases the expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule-1. IL-1β also alters cardiomyocyte functions. Chronic administration of IL-1β induced coronary intimal lesions and vasospastic responses in pigs while IL-1 receptor antagonist infusion decreased neointima area [35].

IL-6 is a soluble cytokine with pleiotropic effect on inflammation and immune responses. The synthesis of IL-6 is driven, among others, by toll like receptors activation, TNFα and IL-1 signalling activation. In patients with myocardial infarction, direct measurements of IL-6 concentration at the site of plaque rupture and in the general circulation indicate a local production of IL-6 [36]. In addition to its position in the inflammatory cascade, IL-6 has been involved in the loss of endothelial barrier function [37], extracellular matrix remodelling and atherosclerotic plaque progression in mice [38].

IL-18 and IL-1β are major proinflammatory cytokines with pleiotropic activities. These cytokines are synthesized as inactive precursors requiring cleavage by caspase-1, within the complex NLRP3 inflammasome, to become biologically active molecules in inflammatory cells and also in endothelial and vascular smooth muscle cells. IL-18, produced by endothelial cells, cardiomyocytes, and by infiltrating macrophages [39], is expressed in human failing myocardium and in human carotid atherosclerotic plaques in presence of plaque instability [40]. Experimentally,

IL-18 administration in apoE$^{-/-}$ mice increased plaque size and progression, and altered plaque stability by decreasing intimal collagen content and plaque thickness [39].

CRP is synthetized by hepatocytes in response to IL-6 exposure. CRP deposition or expression in atherosclerotic lesions of human coronary arteries and in human infarcted heart tissues raises the question of a direct pathogenic role of CRP in cardiovascular diseases. Recombinant CRP administration has been associated with prothrombotic and proinflammatory effects in vitro in endothelial cells [41], in cardiomyocytes, and in vivo in human healthy subjects [42]. Despite data from transgenic mice overexpressing CRP could suggest an implication of CRP in thrombosis after arterial injury and in cardiac remodelling in the context of myocardial infarction [41], epidemiological and Mendelian randomization studies refute the causal role of CRP in the risk of cardiovascular events (see below).

Box 1. Chronic low-grade sub-clinical inflammation plays an important role in vascular dysfunction and damage in cardiovascular diseases. The inflammatory response is mediated in large part through ROS. Many pro- or anti-inflammatory immune cells and cytokines are involved in the inflammatory response and mechanisms of hypertension.

Inflammation and atherosclerosis

Atherosclerotic plaques develop in predisposed areas of the arterial tree where blood flow is either slow or oscillatory and endothelium displays increased susceptibility to activation, as well as greater permeability to LDL and remnant cholesterol, favouring subendothelial retention. One of the triggering events in the initiation of atherosclerotic process is the oxidation of LDL (although other targets are involved such as high density lipoproteins, HDL), the consequent release of bioactive (phospho)lipids in the arterial intima and production of proinflammatory and chemotactic factors for lymphocytes and monocytes [43]. Infiltrated monocytes differentiate into macrophages or DCs, that internalize oxidized LDL (oxLDL) and become foam cells. Surprisingly, early uptake of cholesterol by macrophages suppresses inflammatory responses, and promotes a reparative M2 phenotype [44]. Yet, continued cholesterol accumulation leads to predominant M1 populations. Recruited immune cells accumulate under hypoxic conditions and undergo apoptosis and necrosis, leading to the formation of the necrotic core and contributing to destabilisation of plaque. Advanced, rupture-prone lesions that are associated with clinical events are rich in M and T cells exhibit large necrotic cores with thinned fibrous caps, rarefaction of SMCs and reduced collagen content. Finally, inflammation can hamper the protective effects of HDL on endothelium. In presence of inflammation, HDL fails to prevent LDL oxidation, exhibits reduced reverse cholesterol transport function and induces endothelial dysfunction [45].

Innate immunity in atherosclerosis

The chronic inflammatory disease of atherosclerosis is promoted by both innate and adaptive immunity [7]. The innate response is instigated by the activation of vascular cells and monocytes/macrophages. Subsequently, an adaptive immune response develops against an array of potential antigens presented to effector T lymphocytes by antigen-presenting cells. In the early stages of atherosclerosis, proinflammatory cytokines can alter endothelial functions. TNFα, for example, increases cytosolic Ca^{2+} and regulates myosin light chain kinase and RhoA [46], which

disrupts endothelial junctions [47], leading to loss of barrier function and facilitation of leukocyte transmigration. Cytokines also induce the expression of chemokines and adhesion molecules in endothelial cells, favouring the recruitment, adhesion and migration of lymphocytes and monocytes into the inflammatory vessel wall. Once in the intima, leukocytes can be permanently activated by locally generated cytokines, which can accelerate the transformation of macrophages into foam cells by stimulating the expression of scavenger receptors and enhancing cell-mediated oxidation. Cholesterol crystals act as metabolic triggers of the NLRP3 inflammasome, which promotes the maturation of IL-1β and IL-18 [48]. At an advanced stage of the disease, proinflammatory cytokines (IL-1β, TNFα and IFNγ) destabilize atherosclerotic plaques by promoting cell apoptosis and matrix degradation. Macrophage apoptosis results in the formation of cell debris with toxic components, which contributes to the enlargement of the lipid core; plaque SMC apoptosis leads to thinning of the fibrous cap, favouring its rupture. Proinflammatory cytokines significantly affect the expression of MMPs and their inhibitors, TIMPs, inducing substantial remodeling of many components of the extracellular matrix of the arterial wall. For example, IFNγ inhibits collagen synthesis whereas IL-1 and TNFα induce a broad range of MMPs in vascular cells, including MMP-1, -3, -8, and -9. Finally, the antithrombotic properties of endothelial cells are deeply altered by cytokines, in addition to profoundly altered shear stress conditions. Proinflammatory cytokines also modify the fibrinolytic properties of endothelial cells, precipitating thrombus formation and promoting the development of acute ischemic syndromes.

Adaptive immunity in atherosclerosis

T cell responses are initiated when specific molecular epitopes on antigens, including oxLDL and heat shock proteins, are presented by antigen-presenting cells and recognized by T cell antigen receptors. DCs are the main cell type responsible for the activation of naïve T cells and play a crucial role in triggering adaptive immunity. In atherosclerotic plaques, DCs co-localize with T cells, suggesting that they are involved in T cell activation within the plaque. However,

sensitization of naïve T cells most likely occurs in the regional lymph nodes [7]. A number of experimental studies have clearly shown a critical pathogenic role for the T_h1 response, associated with the production of IFNγ [7].

Atherosclerosis is also associated with B cells activation. IgG antibody production by B2 cells requires T cell co-stimulation, whereas innate production of natural IgM antibodies by B1 cells does not require co-activation of T cells. Both IgG and IgM antibodies against oxLDL have been described. Studies in mouse models provided evidence for a proatherogenic role of B2 cells [49]. Natural T_{reg} cells are detected in much lower amounts in atherosclerotic plaques than in other chronically inflamed tissues, suggesting an impairment of local tolerance against potential antigens in atherosclerotic lesions [50]. T_{reg} cells exert a protective role in atherosclerosis and are reduced in patients with acute coronary syndromes.

From acute to chronic inflammation in atherosclerosis

Physiologically, most inflammatory processes are self-limiting and controlled by endogenous pro-resolutions pathways. Whether acute inflammation is needed or not to induce chronic inflammation is unknown. The general view is that defective acute inflammation resolution, caused by the imbalance between proinflammatory and specialized pro-resolving mediators (SPMs) such as thromboxane A_2/prostacyclin ratio, proinflammatory leukotrienes/lipoxins, leads to the defective efferocytosis and chronic inflammatory state observed in atherosclerosis [51]. In early and stable plaques there is an high SPMs/proinflammatory mediator ratio. High SPMs levels reduce lesion necrosis, enhance efferocytosis and have a protective role in several factors that exacerbate atherosclerosis. In advanced/vulnerable plaques, levels of proinflammatory mediators increase and the imbalance between SPMs and proinflammatory mediators lead to plaque progression.

Box 2. The atherosclerotic process is promoted by both innate and adaptive immunity.

Low-grade inflammation and cardiovascular diseases

Although inflammation is a key factor in vascular disease, most of the time it remains low-grade and subclinical. Clinical studies performed in several groups of patients have shown consistent associations between inflammatory molecules and subclinical markers of arterial diseases such as endothelial dysfunction and arterial stiffness. In this section we will discuss on the evidences originated from event data.

Association between inflammatory markers and cardiovascular diseases (CVD)

Subjects with high baseline levels of CRP (independently of previous CVD) have an increased risk of developing future myocardial infarction independently of established risk factors. Several meta-analyses on individual data have now reported an association between single measurements of CRP or IL-6 and incident CVD [52,53]. Moreover, circulating CRP and/or IL-6 significantly improve CVD risk prediction beyond the effect of traditional risk factors, especially for those at intermediate risk.

Studies based on repeated assessments of CRP provide contrasted results. In the ARIC study, subjects with sustained elevated CRP (≥3mg/dL) or with increased CRP (from <3mg/dL to ≥3mg/dL) over 6 years had a significantly increased risk of coronary heart disease (CHD) and mortality in the subsequent 14 years of follow-up compared with subjects having a constant low/moderate CRP level (<3mg/dL) [54]. Interestingly, the risk of CHD did not decrease in subjects with decreased CRP compared to those with constantly low/moderate CRP. In the Whitehall II study, while the concentrations of CRP over 15 years prior to fatal CHD were systematically higher as compared to controls, the slope of the CRP trajectories between the two groups did not differ [55]. Given these evidences, the question of the causality between CRP and incident CVD has been raised. In addition to biological plausibility, Mendelian randomisation studies suggest that the association between IL-6 Receptor (IL-6R) pathway but not CRP and CHD could be causal [56-58]. In particular, a single nucleotide polymorphisms in the gene IL-6R rs7529229 was used to evaluate

the efficacy and safety of IL-6R inhibition for primary prevention of coronary heart disease. The IL-6R rs7529229 SNP was associated with a decreased odds of CHD events [58]. This Mendelian randomisation approach is consistent with the cardiovascular protection induced by IL-6R blockade from infusion of Tocilizumab in patients with rheumatoid arthritis in randomised trials [59] and provides a much higher level of evidence on causal pathways than observational associations. This makes IL6 appear as a potential therapeutic target while CRP is more a marker of inflammation. These Mendelian randomization studies have also limitations; among them, they do not take into account interactions between the genome and environment (epigenetics), they might be confounded by the presence of other interacting genes [60], and only explain a very small risk (here 5%).

IL-1ß inflammation pathway as a target for CVD prevention?

Canakinumab is a specific antibody blocking the IL-1ß receptor and thus the inflammation pathway. CANTOS is the first randomized controlled trial that tested whether canakinumab anti IL-1ß could reduce the risk of recurrent CVD events in patients with prior myocardial infarction on optimal secondary prevention [61]. CANTOS demonstrated a 14-15% reduction in the combined primary end-point (nonfatal myocardial infarction, any nonfatal stroke, or cardiovascular death) in the canakinumab 150-300 mg groups. Interestingly, the treatment did not modify the risk of diabetes. The median concentration of CRP, but not of lipids, decreased significantly between 26% and 41% at 48 months according to the Canakinumab dose when compared to baseline value, with similar effects on IL-6 level. This indicates that this treatment may specifically impact the inflammation pathway in atherosclerosis with beneficial effect. The CIRT trial [62], tested whether low-dose methotrexate, a non-specific modulator of inflammation as compared to placebo reduced major vascular events among a group of post-myocardial infarction patients with either diabetes or metabolic syndrome. This trial was based on observational evidence of reduced cardiovascular events among patients with rheumatoid arthritis and psoriatic arthritis on treatment with methotrexate and on the ability of methotrexate to reduce TNFα, IL-6 and CRP levels. The CIRT

trial failed to demonstrate a benefit with low-dose methotrexate compared to placebo. The CANTOS trial is the first proof of concept that targeting inflammation through IL leads to improvement of cardiovascular outcome while CRP is a marker of the efficacy of the anti-inflammatory treatment.

Box 3. At the population level, IL-6 is the inflammatory biomarker demonstrating the most robust and independent association with incident CVD events. More data are needed to confirm that targeting inflammation pathways prevents recurrent CVD events.

Inflammation, salt, microbiota and arterial stiffness

The action of salt as a promotor of hypertension is often related to an increased stimulation of the Renin-Angiotensin-System and associated with volume expansion. Surfacing evidence attributes a vascular inflammation promotion effect for salt through IL-17 stimulation. Salt promotes dedifferentiation of $CD4^+$ cells into T_h17 cells, responsible for the production of IL-17, which in turn plays a role in the control of renal tubular sodium transport channels. This salt-induced differentiation of immune cells promotes a pro-inflammatory phenotype, ultimately leading to increased BP, target organ damage and increased arterial stiffness. In a recent meta-analysis, salt consumption reduction was associated with a decrease in pulse wave velocity (PWV), independently of BP [63].

The gut microbiome is a new dimension in cardiovascular research, with a mechanistic role being attributed to its capacity to interfere in the control of inflammation, glucose tolerance, insulin sensitivity and oxidative stress [64,65]. Recent evidence suggests a reverse association between the composition and diversity of gut microbiome and arterial stiffness in women [66]. Moreover, short-chain fatty acids, a product of gut microbial metabolism, reduce arterial stiffness and blood pressure in mice [67]. Factors such as dietary intake and promotion of biodiversity in the microbiotic component of the gut can interfere in the induction of a systemic inflammatory effect, depending on the ability of certain gut bacterial species to express pro-inflammatory metabolites [65,68]. In this regards, the gut-derived metabolite trimethylamine N-oxide has a role in the development of oxidative stress, vascular inflammation and dysfunction [65,69]. Gut microbiome may influence arterial stiffness through the metabolism of polyphenols and trimethylamine N-oxide [69], however, data from Pluznick on a mice model do not validate this concept since stiffness increase was only dependent on blood pressure changes [67]. These findings are particularly relevant considering that several strategies are proposed to modify the gut's microbiota composition.

Box 4. Increased salt intake promotes the emergence of pro-inflammatory phenotypes. Models analysing the gut microbiome should be explored to uncover new pathways leading to reduction of inflammation-induced arterial stiffness and BP.

Inflammation and vascular aging

Physiologically, the wall of large arteries lose elasticity over time. As consequence, arterial stiffening reduce the reservoir function of the conduct arteries and, through the increase of systolic and pulse pressure, has an impact on cardiac function, microcirculation and end organ functions. Inflammation can lead to an accelerated vascular aging through the alteration of the arterial wall properties and the increase of arterial stiffness [1,70]. A widely accepted mechanism by which vascular stiffness increases by aging and inflammation involves remodeling and content changes in the extracellular matrix (i.e., elastin and collagen). Current findings suggest that also the intrinsic stiffening of vascular cells and endothelial mechanisms may also contribute to the vascular aging [71,72].

Arterial inflammation and mechanical stress

The arteries are stretched under pulsatile conditions because of blood pressure and beating of the heart [73]. Stretch and resulting stresses act as major trophic factors and induce the activation of important signaling pathways [74]. Mechanical stress is also the main determinant of plaque rupture. The interaction between stress and stretch also defines arterial stiffness. The Moens-Korteweg equation shows that, conceptually,

$$\mathrm{PWV} = \sqrt{\frac{E \cdot h}{2 \cdot r \cdot \rho}}, \qquad (1)$$

with E the incremental Young's modulus (a measure of material stiffness), h the wall thickness, r the inner wall radius, and ρ the blood mass density. $E \cdot h$ defines the structural stiffness of the wall. It follows that a PWV increase can be due to 1) an increase in E, 2) an increase in h (through hypertrophy and/or hyperplasia), and/or 3) a decrease in r.

Contrary to the global variable PWV, VSMCs sense and maintain local tensile (circumferential) stress (σ):

$$\sigma = \frac{P \cdot r}{h}. \qquad (2)$$

Physiologically, in order to maintain σ, in response to a pressure (*P*) increase a VSMC will show an adaptive response and produce matrix (↑*h*) to restore σ to its homeostatic value. To maintain σ, if *P* changes by a given factor, *h* should change by the same factor (given a constant *r*) [75].

In parallel, endothelial cells sense shear stress. Mean wall shear stress is approximately proportional to blood viscosity and volume flow rate, while inversely proportional to the 3th power of radius. Any change in radius will have consequences in term of exposure of the endothelium to high/low shear stress. Concentric remodeling (↑*h* and ↓*r*) will increase wall shear stress with subsequent secretion of endothelium derived factors which will dilate (and thin) the artery. Several factors (e.g., hypertension and aging) eventually lead to a loss of this dilatory mechanism ("endothelial dysfunction"). In other words, the structure of large (and small) vessels depends on the dynamic balance between tensile stress and wall shear stress, determined by changes in wall structure. The relation between shear stress and atherosclerosis has been extensively studied [76]. Atherosclerotic lesions tend to develop in low shear/bidirectional/turbulent zones, particularly the inner curvature and bifurcations, explaining aggravating of lesions downstream of atherosclerotic stenosis. Furthermore, arterial stresses and stretches are pulsatile, significantly influencing the VSMC's biological response to these stresses/stretches [77].

Inflammation leads to mechanical over-adaptation

Hypertension lead to media thickening by matrix deposition and/or VSMC hypertrophy. AII infusion in mice leads to a BP increase, but also has an inflammatory effect causing over-adaptation: two weeks of AII infusion led to a mean blood pressure increase from 106 to 144 mmHg (a factor 1.36), but caused thoracic aortic wall thickness to increase from 39 to 102 μm (a factor 2.62) [78]. This in turn led to a decrease in σ and distensibility. Circumferential material stiffness (similar to *E*) did not change whereas structural stiffness (*E*·*h*) did increase due to the wall thickness increase, causing a sharp decrease in distensibility and a concomitant increase in PWV. The observed increase in wall thickness was partially due to medial hypertrophy (1.7-fold increase in medial cross-sectional area), but much more due to adventitial thickening (4.7-fold increase in

adventitial area) caused by collagen deposition. Additionally, AII infusion leads to IL-6 production as well as macrophage recruitment and wall thickening, all mainly in the adventitia [79].

Inflammatory over-adaptation is regionally different along the aorta

In experimental models, AII infusion revealed regionally different effects along the aorta: proximal ascending thoracic aorta is prone to aneurysm development, whereas the suprarenal abdominal aorta is prone to dissection [79,80]. In all regions, with AII infusion, σ increased with BP during the first 7 days. After that, remodeling caused σ to decrease. In the infrarenal aorta, σ returned to pre-infusion values (adaptation), whereas in the other segments of the aorta, σ dropped below baseline (over-adaptation). The observed over-adaptation and adventitial thickening directly correlated with the presence of adventitial $CD45^+$ cells, indicating the key role of inflammation in mechanical over-adaptation. In the thoracic aortic regions, the presence of $CD3^+$ cells tracked that of $CD45^+$ cells, indicating involvement of T cells. Previous studies have shown a direct role of T cells in hypertension and in adventitial thickening of the descending thoracic aorta: in male recombination activating gene 1 knock-out mice (which do not produce mature B or T cells), AII infusion did not lead to excessive adventitial thickening and led to a blunted hypertensive response [81]. Arterial thickening (as well as the hypertensive response) was restored upon adoptive transfer of T cells (but not B cells).

Box 5. Arterial inflammation co-occurring with hypertension may cause arterial stiffening through an over-adaptative VSMC response.

Acute inflammation and arterial function

While infection is not synonymous of inflammation, the majority of data on the effect of the latter on arterial function have been derived from infection/vaccination studies. Data are limited, but interestingly they are not limited to cross-sectional associations but extend to mechanistic studies that suggest cause-and-effect relationships between acute inflammation and endothelial dysfunction [86,87] whereas the link between acute inflammation and arterial stiffening is doubtful [88,89], likely because the mechanisms involved in stiffening have longer time constants. The short duration and reversibility of inflammation does not affect negatively prognosis in infection/vaccination models [84].

Prophylaxis-reversal of arterial damage caused by acute inflammation

The acute impairment of endothelium-dependent dilatation (both conduit arteries and resistance vessels), the increase of arterial stiffness and the reduction of wave reflection (augmentation index, Aix) returned to normal 32 hours after vaccination [87,89]. Based on the inflammation/vaccine model, aspirin and statins have shown a protective effect on endothelial function and aortic stiffness [89,90], whereas the impact of exercise on endothelial function and arterial stiffness/wave reflection indices is doubtful [88,91,92].

Mechanisms of acute inflammation-induced vascular dysfunction

We have several clues about the mechanisms involved in the stiffening caused by acute inflammation. Adhesion molecules and tight junctions increasing the links between VSMC and the extracellular matrix, together with intrinsic VSMC stiffness can change in the short term. Inflammatory markers/mediators, such as IL-6, as well as MMP-9, were reversibly increased 8 hours after vaccination, whereas CRP levels sloped upwards 32 hours post-vaccination [89]. Similar responses of IL-6 to the Salmonella Typhi vaccine have been repeatedly shown [87,89,90]. However, while pre-treatment with oral aspirin abrogated the effect on aortic stiffness, IL-6 still increased [89], suggesting that other cytokines, such as IL-1, could be involved. The cytokine response was neither prevented by pretreatment with statins in hypercholesterolaemic patients, while the endothelial function

deterioration was abrogated [90]. On the other hand, only in the placebo arm and not in the statin pretreatment arm, a reduction of NO metabolites and total antioxidant capacity was observed [90], implying involvement of NO bioavailability and antioxidant status.

In the salmonella vaccine model, asymmetric dimethylarginine, an endogenous L-arginine analogue that interferes with L-arginine for NO production, increased in healthy subjects, in whom a reduction in flow mediated dilatation (FMD) was observed, while it did not in coronary artery disease patients in whom FMD reduction was marginal [93]. Reduction of FMD in vaccinated healthy subjects is correlated with an increase of tetrahydrobiopterin, a cofactor necessary for the production of NO and a possible defence mechanism against inflammatory challenges.

Box 6. In infection/vaccination studies, acute inflammation leads to endothelial dysfunction.

Low-grade chronic inflammation and vascular diseases

Transplant arteriosclerosis

The immune response to endothelial and VSMCs contributes to acute and chronic graft failure of transplanted solid organs. T and B cells of the adaptive immune system, activated by graft-derived antigens, lead to the development of transplant arteriosclerosis, a vascular condition characterized by intimal hyperplasia, alteration of extracellular matrix composition, vasodilatory dysfunction, lipid deposition, and intraplaque haemorrhage [94]. Transplant arteriosclerosis is mediated by cytokines that stimulate the migration and activation of T cells into allograft arteries and promote VSMCs proliferation and endothelial dysfunction (i.e., IFNγ, IL-1, IL-17 and TNFα), and antibodies that facilitate immune cell transmigration into the arterial wall and amplify T cell responses to allograft arteries through the up-regulation of cell adhesion molecules and von Willebrand factor and the increase of the antigen-presenting capabilities of the endothelium.

Periodontitis inflammation and cardiovascular diseases

Periodontitis is a highly prevalent and multifactorial chronic low-grade inflammatory condition associated with dysbiotic plaque biofilms and destruction of the tooth-supporting apparatus. Patients with periodontitis have more coronary events and stroke compared to non-periodontal disease subjects [95,96]. Chronic low-grade inflammation can explain the increased CV risk reported in these patients through the development of endothelial dysfunction, impaired arterial stiffness and greater carotid intima-media thickness (IMT) [97,98].

Several mechanisms have been proposed to explain the link between periodontitis, vascular dysfunction and CV events. Periodontal pathogens can enter the bloodstream through the abundant gingival vasculature surrounding the teeth and activate the host inflammatory response. Constant bacteraemia has been shown in everyday life events such as chewing or tooth brushing. However, the intensity and the frequency of the bacteraemia is higher in periodontitis patients than in control. Different pathophysiological mechanisms have been suggested. The direct model deals with the

invasion of the vascular endothelium by pathogenic bacteria such as *Porphyromonas gingivalis.* This interpretation is supported by an increased production of innate immune markers such as ICAM family proteins, pro-inflammatory cytokines and chemokines, leading to an immunological switch of endothelial cells from a normal anti-thrombotic to a pro-thrombotic state. Periodontal pathogens have been identified in atheromatous plaques [99], can directly invade endothelial cells leading to vascular inflammation [100], and trigger an innate [101] or auto-immune response [102]. Animal studies indicate that infection with periodontal pathogens, *Porphyromonas gingivalis* in particular, can support the formation of atheromatous plaques. The indirect model is based on the upregulation of inflammatory cascades involving TNFα, IL-1, IFs, IL-8, monocyte chemoattractant protein-1, and CRP, which are elevated in periodontitis patients. Further, there is evidence of a neutrophil hyper-responsiveness in periodontitis patients leading to an increased production/activity of ROS than in healthy controls [103]. Finally, recent studies indicates common genetic locus associated with coronary artery disease and periodontitis.

Taken together, the above data strongly suggest that periodontitis is an independent contributor to systemic inflammation, and may serve as a model to explore the biological relationship between low-grade chronic inflammation and vascular diseases.

Periodontitis is a treatable disease. The treatment is based on the reduction of the periodontal bacterial load. Intervention trials suggest that periodontal therapy improves endothelial function and intima media thickness (IMT) and reduces TNFα and CRP [104-106]. A significant decrease in fibrinogen levels and platelet activation have been also reported following periodontal therapy. Similarly, the hyper-reactivity of the peripheral blood neutrophils by periodontal bacteria is also reduced by lowering the bacterial load through periodontal therapy.

Box 7. Transplant arteriosclerosis is mediated by cytokines and antibodies that lead to VSMCs proliferation and endothelial dysfunction. There is a large body of evidence that links periodontitis

to cardiovascular diseases. Periodontal therapy reduces chronic inflammation and improves vascular function.

Chronic severe inflammation and arterial function

The risk of cardiovascular events is higher among subjects with chronic severe inflammation, such as those with inflammatory bowel disease (IBD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). However, only part of the excess in cardiovascular risk reported in these patients can be explained by classical cardiovascular risk factors, suggesting that additional mechanisms are involved.

Recently, it has been reported in several meta-analyses of cross-sectional studies that aortic PWV and AIx are significantly increased in patients with IBD [107-109], RA [110], SLE and SSc [111,112]. Few cross-sectional studies suggest that muscular artery stiffness is increased in these patients [110,113-116]. In patients with severe chronic inflammation, also other alterations of the arterial wall (reduced FMD and increased carotid IMT) are reported [109,112,117-120]. Taken together, current data suggest that chronic severe inflammation can lead to functional and structural arterial stiffening (Table 1). Moreover, as suggested by interventional longitudinal studies performed in these patients (see above), the increased arterial stiffness is, at least in part, related to TNFα processes (Figure 3).

Several markers of inflammation are associated with alterations of arterial structure and function in patients with chronic severe inflammation. In a multicentre longitudinal study, aortic PWV was increased in IBD patients with active disease and was reduced in those in remission during a follow up of 4 years [121]. Disease duration is associated negatively with FMD in patients with SLE [122], positively with IMT in patients with RA and SLE [123,124], and positively with carotid-femoral PWV in patients with IBD and SLE [108,111]. Patients with a longer disease duration are exposed to a significantly higher amount of inflammation than patients with short disease duration. Other factors associated with alterations of arterial structure and function in patients with chronic severe inflammation are erythrocyte sedimentation rate [124], CRP [110], scores of disease activity [110,124], and leucocyte count [108].

Box 8. Chronic severe inflammation is associated with increased artery stiffness. Both functional and structural arterial stiffening processes can be involved in these patients.

Primary systemic vasculitides and arterial structure and function

Arteries can be the principal target of inflammation during primary systemic (non-infectious) vasculitides (PSV). The mechanisms involved in the pathogenesis of vascular wall inflammation include endothelial dysfunction, autoantibody-mediated or -associated vascular damage, immune complex formation and complement activation [128]. The main vascular consequences involve a loss of vessel wall integrity and/or lumen compromise of the microcirculation, as well as, thrombosis and aneurysm rupture of the macrocirculation. As a result, there is an increased incidence of cardiovascular events (coronary artery disease, stroke, aneurysm rupture) and mortality in most PSV [129,130]. In each of them, intense inflammation can promote atherosclerosis and arteriosclerosis even in unaffected vessels. The arterial disease observed even in PSV patients free of overt PSV-related complications include increased IMT and arterial stiffness (Table 2) [131]. Taken together, functional and structural abnormalities of the macrocirculation can be observed in all types of PSV, independently of the size of vessel involved in the primary inflammatory process of the vasculitis. Whether similar systemic lesions exist in the microcirculation (e.g., retina) of all patients with PSV is poorly investigated. The potential mechanisms underlying this association are reported in Figure 4.

The clinical implications of accelerated atheromatosis and arteriosclerosis in PSV are poorly studied. It is likely that vascular pathologies in PSV patients contribute significantly to the increased incidence of cardiovascular morbidity and mortality. It has been also suggested that the reversibility of functional properties might be an useful marker of remission or activity in PSV [131].

Box 9. An acceleration of arteriosclerosis and atheromatosis have been reported in PSV due to the response to local vessel wall inflammation. The underlying causes of these systemic macrovascular effects and their potential clinical implications should be better investigated.

The effect of anti-inflammatory therapies on arterial stiffness in patients with chronic inflammation

Many studies have investigated the effect of anti-inflammatory drugs on arterial stiffness in a variety of chronic inflammatory conditions [121,132-142]. Classical non-steroid and steroid anti-inflammatory drugs have not shown protective effects against arterial stiffening, likely because of their mode of action leading to an adverse cardiovascular risk profile (inhibition of prostaglandin secretion, mineral-corticoid action of glucocorticoids leading to an increase in blood pressure). Recently, anti-inflammatory drugs have been developed which target more specific pathways. In a recent meta-analysis performed in patients with RA, aortic PWV and AIx improved following anti-TNFα therapy independently of age and clinical response to treatment [132]. Similarly, in 55 patients with inflammatory arthritis, a 1-year treatment with anti-TNFα therapy, but not placebo, led to a slowing of aortic stiffness and carotid IMT progression [133]. Contrary to anti-TNFα agents, the effect of IL-6R antagonist tocilizumab on aortic PWV is not clear in patients with RA [134,135].

In psoriasis patients, global longitudinal strain, left-ventricular twisting and coronary flow reserve were improved after 4 months of treatment with anti-IL-12/23 agent (ustekinumab), anti-TNFα treatment (etanercept), or cyclosporine with the greatest improvements seen in the ustekinumab group [136]. Interestingly, PWV and AIx were only improved by ustekinumab. This could potentially be explained by the fact that IL-12 signalling plays an integral part in the pathogenesis of psoriasis and hence inhibition of IL-12 would have a greater benefit in the vasculature in this particular patient cohort. In another study performed in 29 patients with moderate to severe psoriasis, 6 month-treatment with anti-TNFα monoclonal antibody adalimumab led to an improvement of FMD and a reduction of PWV [137].

In a recent multicentre longitudinal study [121], PWV increased during 4 years of follow-up in IBD patients treated with salicylates and was reduced in those treated with anti-TNFα therapy. The effect of anti-TNFα therapy was more evident in patients with a recent (<4 years) diagnosis of IBD [138].

These data are in accordance with two meta-analyses [139,140] and suggest that a better and early control of inflammation can help to slow down aortic stiffening over time together with improving the disease.

In patients with ankylosing spondylitis, despite significant improvement in markers of disease activity and inflammation, anti-TNFα therapy did not reduce arterial stiffness [141]. These somewhat unexpected results could potentially be due to a low baseline PWV in these relatively young subjects.

Finally, it has been recently shown that inhibiting IL-1B by canakinumab [61] led to reduction in cardiovascular event rate in patients with atherosclerosis (see above for details). The effect of this class of drugs on arterial stiffness (and/or IMT or endothelial function) is not reported so far, however only weak correlations between arterial stiffness and IL-1B were found in cohort studies [142].

The mechanisms by which anti-inflammatory therapies lead to a reduction of arterial stiffness (Figure 3) derive from what we know through animal models. Potentially, treatment with anti-inflammatory drugs (i.e., anti-TNFα), leading to reduced release of cytokines, could lead to beneficial changes in the arterial wall composition via improvement of endothelial function, reducing direct vascular inflammation and hence reducing the number of inflammatory cells present within the aortic wall, or via changes in the arterial wall properties, such as inhibition of smooth muscle cell proliferation, changes in glycosaminoglycan content of the extracellular matrix, reduction of calcification and inhibition of elastin degrading matrix metalloproteinase synthesis [143]. What is missing here is the time constant of these phenomena, compared with the very long time constant of arterial remodelling [144]. Despite the crucial role of oxidation in the pathophysiology of vascular lesions due to inflammation, attempts at enhancing endogenous antioxidant substances or supplementation with antioxidants have not shown positive effects on cardiovascular events despite demonstrated short term effects [145].

Together with the potential benefits on vascular dysfunction and cardiovascular events, also the potential side effects of drugs affecting the immune processes should be considered. In this regards, several immunosuppressive drugs, including anti-TNFα, anti-IL-12/23, anti-IL-1B and anti-IL-6R, reducing the activity of the immune system may lead to an increased risk for opportunistic infections; most of these drugs (with the exception of anti-IL-1B) have been also associated with an increased risk for cancer. Moreover, the IL-6R antagonist tocilizumab lead also to a reduction of lipoprotein(a), increase in LDL and reduction in HDL, as well as modification of inflammatory and thrombotic markers. Therefore, the net effect of cardiovascular benefits and/or risks of tocilizumab remains unclear.

Box 10. Numerous anti-inflammatory treatments have been shown to be beneficial in reducing arterial stiffness in patients with chronic inflammatory conditions. The mechanism by which these drugs lead to a reduction of arterial stiffness may include: improvement of endothelial function, beneficial changes in the arterial wall components, inhibition of matrix metalloproteinases and reduction of arterial wall inflammation.

Conclusion

Inflammatory processes profoundly disrupt arterial physiology and promote both arteriosclerosis and atherosclerosis. The inflammatory process induces most of its adverse effects through oxidative stress and production of ROS. With aging and progression of vascular disease, production of ROS increases and protection mechanisms are altered. Innate and adaptive immunity plays a prominent role in the pathophysiology of hypertension and mediates at least part of the adverse effect of renin-angiotensin system activation on arteries and CV system. Inflammation may result from unsuccessful adaptation of the human body to its environment, and particularly to the microbiota, both in gut and in the mouth. The dietary changes (sodium load and protein intake) on microbiota may induce systemic low-grade inflammation and promote vascular damage. Atherosclerosis is now considered as a predominantly inflammatory disease involving innate and adaptive immunity. Most of the inflammatory cascades are activated in atherosclerosis primarily for clear oxidized LDL from the arterial wall. A positive feedback links excessive transfer of cholesterol via LDL, insufficient clearance of ox-LDL and focal deposition of cholesterol with subsequent inflammation and immune activation. Major cytokines are elevated in atherosclerosis and arteriosclerosis. Great effort has been made toward identifying key cytokines as therapeutic targets, with IL-1β being the most promising. Certain components of the inflammatory response may have cytotoxic effects, such as CRP. The role of mechanical factors by themselves has been largely overlooked. Mechanical factors such as pressure, heart rate and blood flow are strong determinants of the trophic response of the arterial wall, and promote transfer of macromolecules and cells to the wall. On the other hand, inflammatory remodelling directly alters these factors. As such, they may (partially) explain the relation between microvascular and macrovascular aspects of arterial lesions.

Epidemiological and clinical evidence of the link between inflammation, either low grade, acute, chronic, focal or systemic, and arterial lesions is overwhelming. We have only presented some aspects of the many links, several others could have been included in this review. Considering that aortic PWV is a vascular biomarker and a CV risk factor [146,147], increased aortic stiffness could be used

to pinpoint subjects with low grade or severe inflammation who are at increased cardiovascular risk. We have already reported that low-grade and severe inflammation lead to vascular disease. Therefore, considering that the risk of CVD in subjects with chronic inflammation is increased, their management should not be limited to control the inflammatory manifestations of disease, but rather, in a preventative and proactive action, also aimed at identifying subjects with a higher risk of developing CVD, such as those with hypertension and increased aortic stiffness. Currently, there are no specific indications for the management of the CVD risk in patients with inflammation. Therefore, these subjects should be treated according to the grade of arterial hypertension and the presence of further risk factors.

Further studies could be needed to test whether inflammation can be implemented in algorithms for CVD risk prediction. Many links, however, are still indirect and need to be further validated. One of the methodological difficulty is that proxies are used both for inflammation and cardiovascular lesions. Biological biomarkers only represent a snapshot of selected inflammatory markers. When linking inflammatory biomarkers with cardiovascular events, one should keep in mind that those remain proxies for complex and pleiotropic inflammatory processes, that are highly variable between and within persons. Similarly, biomarkers of arterial lesions such as endothelial dysfunction or arterial stiffening are less variable in time, but are influenced by many factors, such as blood pressure, aging and neuroendocrine status, which have been shown to influence the effect of acute inflammation on the vasculature. Even evidence from interventional trials do not provide a definitive proof of a causal relationship between inflammation and arterial lesions. For instance, microorganisms are known to cause severe arterial lesions (streptococcus, treponema pallidum, mycotic aneurysms, tuberculosis, etc.). However, the mechanisms by which infection can lead to arterial lesions are complex, as for periodontitis (immunologic, circulating microorganisms?). Whether less severe infections and bacteraemia can lead to arterial lesions (microorganisms can be present in the arterial wall) remains an open question. Finally, fluoroquinolones increase the risk of aortic dissection and rupture by activating MMP expression in fibrous tissues [148]. Other anti-inflammatory drugs such as anti-IL-6

tocilizumab have an unfavourable metabolic profile that could counteract their positive anti-inflammatory effects. This further illustrates the complex relationship between inflammation, infection and some anti-infectious agents.

A clear benefit is added when the evaluation of CVD risk is done through an objective measurement of intermediate end points associated to arterial function, such as arterial stiffness (PWV) and others (FMD, carotid IMT). An added and very important argument for this strategy is that patients may have their manifestations of inflammation controlled, maintaining a persistent low-grade inflammatory activity (with no clinical indication for any added medical intervention), that will keep fuelling vascular structural modifications. This can be followed and evaluated with consecutive measures of arterial function indexes (namely PWV), identifying patients that have increasing cardiovascular risk despite apparently controlled inflammation [149].

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Conflict of Interest

None declared.

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Figure Legend

Figure 1. Proposed mechanisms by which the immune system is activated in hypertension. IL, interleukin; ROS, reactive oxygen species; T_h, T helper cell; TNFα, tumor necrosis factor-alpha.

Figure 2. Biological effects of inflammatory biomarkers on the cardiovascular system. CRP, C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; MCP, monocyte chemoattractant protein; NO, nitric oxide; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

Figure 3. Potential mechanisms by which inflammation could induce functional and structural arterial stiffening and how this process could be reverted by anti-TNFα drugs. eNOS, endothelial nitric oxide synthase; H_2O_2, hydrogen peroxide; IL-1, interleukin-1; MMPs, matrix metalloproteinases; NO, nitric oxide; O2-, superoxide; ROS, reactive oxygen species; SMC, smooth muscle cell; TIMP, tissue inhibitor of matrix metalloproteinases; TNFα: tumour necrosis factor alpha. Adapted from Zanoli L et al. [150].

Figure 4. Potential mechanisms leading to the acceleration of atheromatosis and arteriosclerosis in primary systemic vasculitidies (PSV). Adapted from Argyropoulou OD et al.[131].

Table 1. Available evidence on arterial damage in subjects with chronic severe inflammation [96-108].

Disease	Endothelial dysfunction	Accelerated atheromatosis	Accelerated arterial stiffening	
			Elastic arteries (aorta)	Muscular arteries (brachial artery)
IBD	+++ [109]	+++ [109]	+++ [108]	+ [113,114]
RA	+++ [117]	+++ [118]	+++ [110]	+ [110]
SLE	+++ [120]	+++ [119]	+++ [111]	+ [115]
SSc	+++ [112]	+++ [112]	+++ [112]	+ [116]

IBD, inflammatory bowel disease; RA. Rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; +, data derived from few single centre cohorts; +++, evidence based on meta-analyses.

Table 2. Available evidence on arterial damage in primary systemic vasculitides (PSV) (table modified by Argyropoulou OD et al. [131]).

Disease	Accelerated atheromatosis	Accelerated arterial stiffening
Large vessel PSV		
Takayasu arteritis	++	+
Giant cell arteritis	++	+
Medium vessel PSV		
Polyarteritis nodosa	º	º
Kawasaki disease	++	++
Small vessel PSV		
ANCA-associated*	++	+
IgA (Henoch Schonlein)	º	º
Cryoglobulinemia	º	º
Variable size PSV		
Behcet's disease	+++	+++
Cogan's syndrome	º	º

ANCA, anti-neutrophil cytoplasmic antibodies; PSV, primary systemic vasculitides; º, lack or scarce data; +, data derived from few single center cohorts; ++, large number of evidence derived from multiple single center cohorts; +++, evidence based on meta-analysis; *, the evidence concern granulomatosis with polyangiitis vasculitis (previously known as Wegener's).

List of abbreviations

AII	**Angiotensin 2**
AIX	augmentation index
BP	Blood pressure
ChAT	choline acetyltransferase
CHD	coronary heart disease
CRP	mediator C-reactive protein
CVD	cardiovascular diseases
DAMPS	Damage-associated molecular patterns
DC	dendritic cells
FMD	flow mediated dilatation
Foxp3	forkhead box P3
HDL	high density lipoprotein
IBD	inflammatory bowel disease
ICAM	intercellular adhesion molecule
IF	interferon
IL	Interleukin
IMT	intima media thickness
LDL	Low density lipoproteins
MMP	Matrix metalloproteinases
NLRP3	NOD-like receptor family, pyrin domain containing 3
NO	nitric oxide
NOX	adenine dinucleotide phosphate oxidase
Nrf-2	Nuclear factor erythroid 2-related factor 2
PAMPS	pathogen-associated molecular patterns
PKG1a	protein kinase G alpha
PSV	primary systemic vasculitides
PWV	pulse wave velocity
RA	rhumatoid arthritis
RhoA	Ras homolog family member A
ROS	Radical oxygen species
SLE	systemic lupus erythematosus
SPMs	specialized pro-resolving mediators
SS	systemic sclerosis
STAT3	Signal transducer and activator of transcription 3
T_{CM}	Central memory cells
T_{EM}	effector memory cells
TGF	transforming growth factor
TLR	toll like receptor
TNF	tumour necrosis factor
VSMC	vascular smooth muscle cells
WNT	wingless-related integration site

Figure 1.

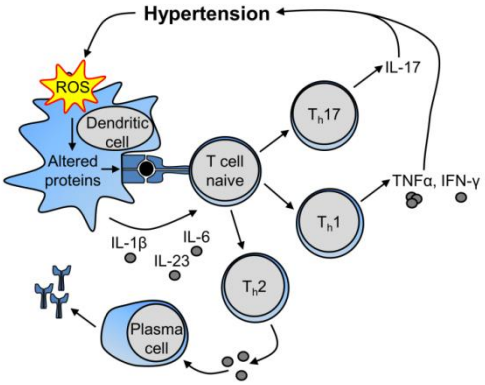

Hypertension
ROS
Dendritic cell
Altered proteins
T cell naive
IL-17
T_h17
TNFα, IFN-γ
T_h1
IL-1β
IL-6
IL-23
T_h2
Plasma cell

Figure 2.

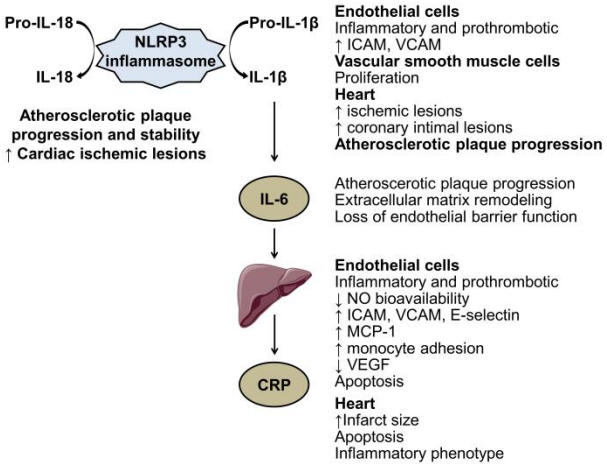

Pro-IL-18
NLRP3 inflammasome
IL-18
Pro-IL-1β
IL-1β
Atherosclerotic plaque progression and stability
↑ Cardiac ischemic lesions
Endothelial cells
Inflammatory and prothrombotic
↑ ICAM, VCAM
Vascular smooth muscle cells
Proliferation
Heart
↑ ischemic lesions
↑ coronary intimal lesions
Atherosclerotic plaque progression
IL-6
Atheroscerotic plaque progression
Extracellular matrix remodeling
Loss of endothelial barrier function
Endothelial cells
Inflammatory and prothrombotic
↓ NO bioavailability
↑ ICAM, VCAM, E-selectin
↑ MCP-1
↑ monocyte adhesion
↓ VEGF
Apoptosis
CRP
Heart
↑Infarct size
Apoptosis
Inflammatory phenotype

Figure 3.

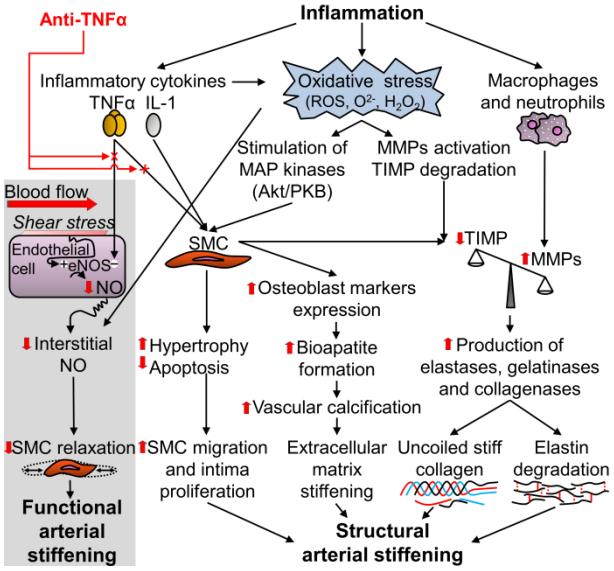
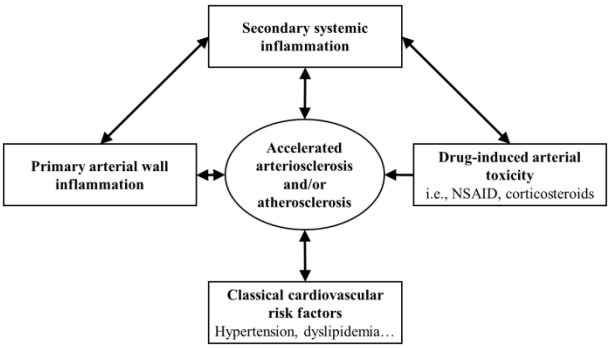

Anti-TNFα
Inflammation
Inflammatory cytokines
TNFα IL-1
Oxidative stress
(ROS, O^{2-}, H_2O_2)
Macrophages
and neutrophils
Stimulation of
MAP kinases
(Akt/PKB)
MMPs activation
TIMP degradation
Blood flow
Shear stress
Endothelial
cell
eNOS
NO
SMC
TIMP
MMPs
Osteoblast markers
expression
Interstitial
NO
Hypertrophy
Apoptosis
Bioapatite
formation
Production of
elastases, gelatinases
and collagenases
Vascular calcification
SMC relaxation
SMC migration
and intima
proliferation
Extracellular
matrix
stiffening
Uncoiled stiff
collagen
Elastin
degradation
Functional
arterial
stiffening
Structural
arterial stiffening

Figure 4.


Secondary systemic inflammation
Primary arterial wall inflammation
Accelerated arteriosclerosis and/or atherosclerosis
Drug-induced arterial toxicity
i.e., NSAID, corticosteroids
Classical cardiovascular risk factors
Hypertension, dyslipidemia…