In: Angina Pectoris: Etiology, Pathogenesis and Treatment ISBN: 978-1-60456-674-1
Editors: A. P. Gallo, M. L. Jones © 2008 Nova Science Publishers, Inc.

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Chapter III

Kounis Syndrome (Allergic Angina and Allergic Myocardial Infarction)

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Summary

Background

The concurrence of acute coronary syndromes with hypersensitivity reactions as well as anaphylactic or anaphylactoid insults is increasingly in clinical practice and there are several reports associating mast cell activation with acute cardiovascular events.

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Definition

Kounis syndrome is the coincidental occurrence of acute coronary syndromes with hypersensitivity reactions involving activation of interrelated and interacting inflammatory cells and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet activating factor and a variety of cytokines and chemokines released during the hypersensitivity insult. All these inflammatory cells participate in a vicious inflammatory cycle and via multidirectional signals mast cells can enhance T cell activation, T cells can mediate mast cell proliferation and activation, inducible macrophage protein-1α can activate mast cells, mast cells can activate macrophages, and T cells can regulate macrophage activity.Clinical and experimental findings show that there is a common pathway between allergic and non allergic coronary events, because the same mediators from the same cells are present in both hypersensitivity episodes and acute coronary syndromes.

Variants

Type I variant: includes patients with normal coronary arteries without predisposing factors for coronary artery disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins

Type II variant: includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as acute myocardial infarction.

Cardiac Actions of Main Mediators

Tryptase and chymase actions: Activate the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin and can promote plaque disruption or rupture.

Furthermore, chymase converts angiotensin I to angiotensin II and angiotensin II receptors are found in the medial muscle cells of human coronary arteries. Thus, angiotensin II generated by chymase could act synergistically with histamine and aggravate the local spasm of the infarcted coronary artery.

Leukotrienes are powerful arterial vasoconstrictors and their biosynthesis is enhanced in the acute phase of unstable angina. Thromboxane is a potent mediator of platelet aggregation with vasoconstricting properties. Platelet activating factor: In myocardial ischemia acts as proadhesive signalling molecule or via activation of leucocytes and platelets to release other mediators. In experimental anaphylaxis reproduces the electrical and mechanical effects observed in allergic reactions such as ST changes and arrhythmias acting either through the release of leukotrienes or as a direct vasoconstrictor.

Histamine can induce: coronary vasoconstriction, intimal thickening, inflammatory cell modulation, platelet activation, proinflammatory cytokine production, p-selectine upregulation, sensitization of nerve ending in coronary plaques, tissue factor expression.

Clinical and Therapeutic Implications

Today, concern has been raised that intracoronary stents could be associated with in stent thrombosis, paradoxical coronary vasoconstriction and hypersensitivity reactions. Components of currently used DES have been reported to induce either separately or synergistically hypersensitivity reactions and in some occasions hypersensitivity cardiac events. Stent-activated intracoronary mast cells could release histamine, arachidonic acid metabolites, proteolytic enzymes such as tryptase and chymase, as well as a variety of cytokines -chemokines and platelet activating factor leading to local inflammation and thrombosis. These events may be more common than suspected because it is hard to document them, unless they become systemic, in which case they manifest as the Kounis syndrome. Recognition of this problem may lead to better vigilance, as well as new stent with mast cell blocking molecules that may also be disease modifying.

So far, attempts have been made to counteract the actions of the inflammatory mediators by using mediator antagonists, inhibitors of mediator biosynthesis and mediator receptor blockers. However, in the medical armamentarium there are drugs and natural molecules that are capable to stabilize and protect mast cell surface which could prevent also acute thrombotic events , at least in some instances. This has already been achieved experimentally.

Abreviations

CRH = corticotropin-releasing hormone
CSF = colony stimulating factor
CGRP = calcitonin gene related peptide
CTMC = connective tissue mast cells
EGF = endothelial growth factor
b-FGF = fibroblast growth factor
GM-CSF = granulocyte monocyte-colony
INFγ = Interferon-γ
MCP = monocyte chemotactic protein
MIF = macrophage inflammatory factor
MIP = monocyte inflammatory peptide
NGF = nerve growth factor
PACAP = Pituitary adenylate cyclase activating peptide
PAR = Protease activated receptor
SCF = Stem cell factor
TGF-β = transforming growth factor-β
TNF-α = tumor necrosis factor-α
VEGF = vascular endothelial growth factor

1. Definition

Kounis syndrome is the concurrence of acute coronary syndromes with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet activating factor and a variety of cytokines and chemokines released during the activation process.

Mast cells enter the circulation from bone marrow as mononuclear cell precursors that both express messenger ribonucleic acid (mRNA) for stem cell factor and have SCF receptors on their cell membrane. They migrate into the tissues, including the brain which does not

suffer from allergic reactions because IgE does not cross the blood-brain barrier, where the differentiate and mature. This takes several days to weeks.

On the other hand, basophils developing in bone marrow from granulocyte precursors and entering the circulation only when fully mature. They are not normally found in extravascular tissues compartments, only migrating there during late-phase allergic responses.

2. Historical Background

Although, the coincidental occurrence of acute coronary syndromes with allergic or hypersensitivity as well as with anaphylactic or anaphylactoid reactions is increasingly encountered in clinical practice it was only until 1950 when several reports associating mast cell activation with acute cardiovascular events started to appear in the medical literature (Table 1).

Table 1. Historical background of Kounis syndrome

1950	Pfister CW, et al.	Acute myocardial infarction during a prolonged allergic reaction to penicillin. Am Heart J 1950; 40: 945
1965	Zosin P, et al.	Allergic myocardial infarction. Romanian Medical Review 1965;19: 26
1991	Kounis NG, et al.	Histamine-induced coronary artery spasm: the syndrome of allergic angina. Br J Clin Pract 1991; 45: 121
1995	Constantinides P.	"Allergic reactions can promote plaque disruption" Circulation 1995; 92: 1083
1996	Kounis NG, et al.	Allergic angina and allergic myocardial infarction. Circulation 1996; 94: 1789
1998	Braunwald E.	"Allergic reactions with mediators such as histamine or leukotrienes acting on coronary smooth muscle can induce vasospastic angina" Circulation 1998;98: 2219
2003	Zavras GM, et al.	Kounis syndrome secondary to allergic reaction. Int J Clin Pract 2003; 57: 62
2006	Kounis NG.	Kounis syndrome. Int J Cardiol 2006; 119: 7
2006	Kounis NG, et al.	Hypersensitivity to DES: a manifestation of Kounis syndrome? J Am Coll Cardiol 2006; 48: 592
2007	Kounis NG, et al.	Coronary stents, Hypersensitivity and the Kounis Syndrome. J Interv Cardiol 2007; 20: 314
2008	Tavil Y, et al.	Kounis syndrome secondary to amoxicillin/clavulanic acid use. Int J Cardiol 2008 Feb 20; 124: e4

In 1991, Kounis and Zavras [1] described the "syndrome of allergic angina" as the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released

during the allergic insult Allergic angina can progress to acute myocardial infarction which was named "allergic myocardial infarction" [2-4]. Following this clinical description, Constantinides [5], in 1995, raised the possibility that "even ordinary allergic reactions could promote plaque disruption". In 1998, Braunwald [6], in an editorial, noted that vasospastic angina can be induced by "allergic reactions with mediators such as histamine or leukotrienes acting on coronary vascular smooth muscle".

Today, allergic angina and allergic myocardial infarction are referred as "Kounis syndrome" [7-13] and are cited in major cardiovascular textbooks [14], as a new cause of coronary artery spasm.

3. Kounis Syndrome Variants

There are two variants of this syndrome that have been described recently [15]. Type I variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease in whom the acute allergic insult induces either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. This variant might represent a manifestation of endothelial dysfunction or microvascular angina. Type II variant includes patients with culprit but quiescent pre-existing atheromatous disease in whom acute allergic episode can induce plaque erosion or rupture manifesting as an acute myocardial infarction. Kounis syndrome is regarded as magnificent natural paradigm and nature's own experiment [7-13] which may shed light on potential therapeutic strategies that may apply to the area of interference with plaque erosion or rupture and primary as well as secondary prevention of acute coronary and cerebrovascular events.

4. Mast Cell Activation-Degranulation

Mast cells are derived from a distinct precursor in the bone marrow and mature under local tissue micro environmental factors [16, 17]. These cells are found in most parts of the human body, including heart and vessels, and are involved in allergic and anaphylactic reactions through activation-degranulation. This activation-degranulation is taking place via the following mechanisms:

1) lgE mediated cross linking of Fce receptor I (i.e. the high affinity IgE receptors) [18],
2) by histamine-releasing factors secreted by neighbouring macrophages [19] or T-lymphocytes [20] and
3) by anaphylatoxin components of the complement system (C3a, C5a) [21], by many neuropeptides and bacterial products through Toll-like receptors [22] and by drugs such as opioids [23] or analgesics such as high doses of acetylsalicylic acid [24]. Endothelin also activates cardiac mast cells and this is regarded as a potential mechanism responsible for myocardial remodeling [25].

Upon their activation, mast cells release the contents of their granules by two separate mechanisms which may operate individually or in parallel:

1) a rapid process of anaphylactic degranulation [26],
2) a slow process of piecemeal degranulation or intra-granular activation or differential or selective release [27]. During the latter, mast cells appear to undergo ultra structural alterations of their electron dense granules indicative of secretion but without overt degranulation. Such subtle mast cell activation may be associated with the ability of mast cells to release some mediators selectively such us eicosanoids [28] and interleukin-6 [29]. In fact, it has been shown that interleukin-1 can stimulate human mast cells to release interleukin-6, without degranulation, through unique process utilizing 40-80 nm vesicles unrelated to secretory granules [30].

Mast cells are an additional source of renin and constitute a unique extrarenal renin-angiotensin system [31]. Furthermore, preformed angiotensin II and gene expression of the renin-angiotensin system have been detected in human mast cells [32].

In anaphylaetic degranulation several vasoconstricting and collagen degrading compounds are released locally and in the peripheral circulation. These compounds include preformed mediators such as, histamine, neutral proteases (tryptase, chymase, cathepsin-D), platelet activating factor and newly synthesized mediators such us an array of cytokines and chemokines and others by the metabolism of arachidonic acid through activation of a phospholipase. The latter include leukotrienes by the lipoxygenase pathway and prostaglandins such as thromboxane by cycloxygenase pathway. These mediators have been incriminated, in many clinical and experimental studies to induce, coronary artery spasm and/or acute myocardial infarction.

Cardiac mast cell-derived histamine can (Table 2 and Table 3) constrict the coronary arteries [33] and sensitize nerve endings [34] localized close to adventitial mast cells in atherosclerotic coronary arteries [35]. Apart from being powerful coronary vasoconstrictor, histamine can activate platelets and potentiates the aggregatory response of other agonists including adrenaline, 5-hydroxytryptamine, and thrombin [36-38]; it modulates the activity of inflammatory cells such as neutrophils [39], monocytes [40], and eosinophils [41]. Moreover, histamine induces proinflammatory cytokine production from endothelial cells [42], upregulates P-selectin on the endothelial cell surface [43, 44], and induces intimal thickening in a mouse model of thrombosis [45]. Cardiac histamine and interleukin-6 can be released by acute stress and this may help explain stress-related coronary inflammation [46, 47]. Stress and corticotropin-releasing hormone activate human mast cells to release vascular endothelial growth factor selectively [48, 49].

Table 2. Histamine: Effects of H1, H2, H3 and H4 receptors

	H1-receptors	H2-receptors	H3-receptors	H4-receptors
Coronary arteries	Mediate contraction	Mediate relaxation	Inhibit endogenous norepinephrine release and enhance the degree of shock during anaphylaxis	Control chemotaxis of mast cells and eosinophils and the release of Interleukin-I6
Sinus node-Atria	Do not affect the rate. Do not affect inotropic action. Do not affect chronotropic action.	Increase sinus rate stimulation. Positive inotropic action. Positive chronotropic action.		
Ventricles	Do not affect inotropic action. Do not affect chronotropic action. Do not affect auromatically.	Positive inotropic action. Positive chronotropic action. Increase automatically.		
AV conduction	Slow AV conduction	Attenuate the response to sympathetic stimulation		

Table 3. Cardiac effects of histamine

- Coronary vasoconstriction
- Activates platelets and potentiates the aggregatory response of agonists e.g. adrenaline, 5-hydroxytryptamine, and thrombin
- Intimal thickening
- Inflammatory cell modulation
- Modulates the activity of neutrophils, monocytes, and eosinophils
- Platelet activation
- Proinflammatory cytokine production
- P-selectine upregulation
- Sensitizites nerve endings in coronary plaques
- Tissue factor expression

A novel action of histamine is the induction of tissue factor expression and activity in human aortic endothelial cells and human vascular smooth muscle cells [50]. Tissue factor is a key enzyme in the activation of coagulation. It binds activated factor VII, which in turn activates factor X leading to thrombin formation. Elevated tissue factor antigen and activity have been detected in plasma and in atherectomy specimens of patients with unstable angina

[51] denoting that tissue factor is involved in the initiation and propagation of acute coronary syndromes. This effect of histamine is completely abolished by H1 receptor antagonists [50].

Table 4. Cardiac actions of proteases, leukotrienes, thromboxane, platelet activating factor

Tryptase

1. Activates the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin and can promote plaque disruption or rupture.
2. Degrates the pericellular matrix components fibronectin and vitronectin and neuropeptides, such as vasoactive intestinal peptide (VIP) and calcitonin gene related peptide (CGRP)
3. Activates neighboring cells by cleaving and activating protease-activated receptor (PAR)-2, and thrombin receptors
4. Tryptase can degrade HDL

Chymase

1. Converts angiotensin I to angiotensin II and angiotensin II receptors are found in the medial muscle cells of human coronary arteries. Thus, angiotensin II generated by chymase could act synergistically with histamine and aggravate the local spasm of the infarcted coronary artery. Chymase also can remove cholesterol from HDL
2. Activates MMP-1,-2,-9 and plays a major role in the physiologic degradation of fibronectin and thrombin
3. Releases latent TGF-β1 from the extracellular matrix
4. Inhibits smooth muscle growth
5. Induces apoptosis of arterial smooth muscle cells and endothelial cells

Cathepsin D

1. Elastolytic, angiotensin II-forming protease
2. Degrates both fibronectin and VE-cadherin which are necessary for adhesion of endothelial cells to their basement membrane and to each other

Leukotrienes

Powerful arterial vasoconstrictors and their biosynthesis is enhanced in the acute phase of unstable angina.

Thromboxane

A potent mediator of platelet aggregetion with vasoconstricting properies.

Platelet Activating Factor

In myocardial ischemia acts as proadhesive signalling molecule or vial activation of leucocytes and platelets to release other mediators. In experimental anaphylaxix reproduces the electrical and mechanical efforts observed in allergic reactions such as ST changes and arrhythmias acting either through the release of leukotrienes or as a direct vasoconstrictor.

Tryptase and chymase (Table 4) effectively activate the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase and stromelysin found in atheromatous plaques and play an important role in atheromatous plaque erosion or rupture [52]. Chymase converts angiotensin I to angiontensin II and angiotensin II receptors are found in the medial muscle cells of human coronary arteries. Thus, the angiotensin II generated by chymase released from mast cells could act synergistically with histamine and aggravate the local spasm of the infarcted coronary artery [53]. Platelet activating factor (PAF) has been implicated in acute myocardial ischemia either as proadhesive signaling molecule or through activation of leucocytes and platelets to release other mediators [54]. Leukotrienes are powerful arterial vasoconstrictors and enhance leukotriene biosynthesis has been detected during the acute phase of unstable angina [55]. Thromboxane is a potent mediator of platelet aggregation and has vasoconstricting properties [56]. Moreover, during experimental anaphylaxis, PAF reproduces the mechanical and electrical changes observed during allergic reactions such as ischemic S-T segment changes and arrhythmias [57, 58]. During these experiments, PAF acted either through the release of leukotrienes and thromboxane [59] or directly producing vasoconstriction [60].

Mast cells are important for allergic reactions [61], but also in immunity [62-64] and inflammatory conditions [65- 67]. Mast cells develop from CD 34+,c-kit+ progenitor cells that arise from hematopoietic stem cells in the bone marrow [68]. These progenitor cells express the receptor c-kit for Stem Cell Factor (SCF), which has growth, differentiate and chemoattractant properties for mast cells. Mast cell progenitors have also been described in the peripheral blood [69, 70]. Mast cells mature in tissues depending on microenvironmental conditions. In addition to SCF, mast cell chemoattractants include, nerve growth factor (NGF) [71], RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) (CCL5) and MCP 1(Mast Cell Protein) (CCL2) [72, 73]. Several cytokines play an important role in mast cell differentiation and proliferation. IL-3 directly stimulates proliferation of uncommitted progenitors and directly promotes granule assembly [74]. IL-4 possesses mast cell growth factor activity [75], can promote phenotype switching to connective tissue-type mast cells [76], and enhances expression of neuropeptide receptors [77]. Mature mast cells vary considerably [78] in their cytokine [79] and proteolytic enzyme content. However, the phenotypic expression of mast cells does not appear to be fixed [75, 80]. In fact, brain mast cells in normal rodents lack c-kit receptor [81] and FcεRI proteins [82].

Mast cells are located perivascularly [83] in close proximity to neurons [84-90], in particular close to CRH-positive neurons in the rat median eminence [91].

5. Mast Cell Triggers

Mast cells are well known to be stimulated by IgE and antigen through aggregation of their specific receptors (FcεR1) [92, 93]. However there are numerous additional mast cell triggers (Table 5). These include immunoglobulin free light chains [94-96], anaphylatoxins, cytokines, hormones, neuropeptides, toxins and a number of drugs [67, 90, 97-102]. Neuropeptide triggers include substance P(SP) [103-105], neurotensin (NT) [106], nerve growth factor (NGF) [84, 107], which is released under stress [108], hemokinin [109], and

pituitary adenylate cyclase activating polypeptide (PACAP) [110, 111], SCF and IL-6 have been shown to induce IL-6 release without degranulation. IL-33 is a recently identified member of the IL-1 family of molecules that can induce cytokine production in human mast cells even in the absence of FceRI aggregation [112]. IL-33 induced IL-6 and IL-1b production by P815 mastocytoma and bone marrow mast cells(BMMC).Stimulation of BMMC with IL-33 for 24 h significantly increased TNF-α and MCP-1 secretion, as well as IL-2 secretion and PGD-2 [113, 114]. IL-33 induced IL-13 production by mouse mast cells independently of IgE-FcεRI signals [115]. IL-33 enhanced the survival of naive human umbilical cord blood mast cells(HUCBMC) and promoted their adhesion to fibronectin; it

Table 5. Mast cell triggers

I. Natural	
A. Immunologic	D. Hormones
Anaphylatoxins (C3a, C5a)	CRH
CGRP	Ucn
IgG 1 + IgE	
IL-1	E. Infectious
IL-33	LPS (TLR 4)
Immunoglobulin – free light chains	Peptidoglycan (TLR 2)
PAF	Viral antigens (TLR 3,5,7,9)
PGE 2	
Superallergens	F. Toxins
MCP -1,-2,-3	Fire ants
MIP-1 Table 1. Mast cell Triggers	Jelly fish
	Snake venoms
	Wasps
B. Neuropeptides /Neurotransmitters	
Acetylcholine	G. Vascular
Adrenomedullin	Adenosine
Bombesin	Endothelin
PACAP	Oxidized LDL
Somatostatin	Reactive oxygen species
S P	Thrombin
VIP	
	II. Drugs
C. Growth Factors	Adenosine
NGF	Contrast media
SCF	Curare
Lymphopoietin	Ibuprofen (high doses)
	Morphine

also induced IL-8 and IL-13 production in naïve HUCBMCs, and enhanced production of these cytokines in IgE/anti-IgE-stimulated HUCBMCs [112]. IL-33 also acts both alone and

in concert with thymic stromal lymphopoietin (TSL) to accelerate the in vitro maturation of CD34(+) mast cell precursors and induce the secretion of Th2 cytokines and Th2-attracting chemokines [116]. TSL is considered a "master switch" in allergic inflammation [117] and in airway inflammation [118, 119]. IL-33 also increased mast cell response (TSL), a recently described potent mast cell activator [120].Adrenomedullin (AM) is a peptide that has been found to be involved in carcinogenesis [121], in the regulation of macrophage [122] and mast cell activation [123], as well as in complement fixation [124]. AM induced histamine [123] or beta-hexosaminidase [65] release from rat and human mast cell through a receptor-independent pathway. In a recent study, mast cells in the vicinity of tumors were shown to produce AM [125]. In the same study, AM was found to be chemotactic for human mast cell and stimulated mRNA expression of VEGF, MCP-1, and basic fibroblast growth factor (FGF) in this cell type; differentiated, but not undifferentiated human mast cell, responded to hypoxia with elevated AM mRNA/protein expression.

OxLDL has been implicated in the pathogenesis of atherosclerosis and has been shown to induce microvascular dysfunction through degranulation of mast cells [126]. OxLDL activates mast cells by increasing mRNA and protein levels of interleukin IL-8 [127].

Superallergens are proteins of various origins able to activate FcεRI+ cells (mast cells and basophils) through interaction with membrane-bound IgE. Several superallergens have been reported. Protein Fv, a sialoprotein produced in the human liver and released in biological fluids during viral hepatitis, is the most potent IgE-mediated stimulus for the activation of human basophils, as well as lung [128] and heart [129] mast cells. Other allergens include protein L, a bacterial cell-wall component that causes release of several mediators by human heart mast cells, as well as antigens of the HIV virus and Staphylococcus aureus [130].

Mast cells have been found to synthesize and secrete endothelins (ET) and also have ET receptors, therefore suggesting an autocrine path of action [131]. ET are cytokine-like agents that can be synthesized and bound by a large number of different cell types. Their role in the immune system and in the pathophysiology of different diseases is thus complicated [132]. There are 3 different ET peptides, ET1 ET2 and ET 3, as well as two different receptors ET-A and ET-B. ET-1 caused degranulation of fetal skin mast cell (FSMC), but not BMMC through ET(A)-mediated pathways; furthermore, ET-1 induced TNF-alpha and IL-6 production by FSMC, but not by BMMC, and significantly enhanced VEGF production and TGF-beta1 mRNA expression by FSMC. Finally, ET-1 was produced by FSMC, but not by BMMC in response to Toll-like receptor ligands [133]. A recent study [134] showed that mast cells may be implicated in preventing ET-1 toxicity through ET-1 degradation by chymase.

TLRs were shown to be important in recognition of ligands associated with bacterial or viral infections, and play a key role in the development of adaptive immune responses [135, 136] especially in asthma [137]. Ten human TLRs have been identified so far [136, 138, 139]. Rodent mast cells express bacterial Toll-like receptors (TLR) 2 and 4 [140, 141]. Human mast cells express viral TLR-9 [82], activation of which produced IL-6 [142], while TLR-3 activation produced IFN [143]. Lipopolysaccharide (LPS) induced TNF release of through TLR-4, while peptidoglycan induced histamine release through TLR-2 from rodent mast cells. Fetal rat skin-derived mast cells express TLR 3, 7 and 9 and activation by CPG

oligodeoxynucleotide induces release of TNF and IL-6, as well as RANTES and MIP, but without degranulation [144, 145]. LPS could not induce release of GM-CSF, IL-1 or LTC_4 [81]. However, LPS did induce secretion of TH2 cytokines, IL-5, IL-10 and IL-13 and increased their production by FcεRI cross-linking [146]. Elsewhere, it was shown that TLR-2 activation produced IL-4, IL-6 and IL-13, but not IL-1 [147], while LPS produced TNF, IL-1, IL-6 and IL-13, but not IL-4 or IL-5, without degranulation [147].

CRH [148] and it structurally related peptide, urocortin (Ucn) [149] can activate skin mast cells and induce mast-cell dependent vascular permeability in rodents. CRH also increases vascular permeability in human skin [150], a process dependent on mast cells. CRH-2 receptor expression was shown to be upregulated in stress-induced alopecia in humans [151], while CRHR-1 expression was increased in chronic urticaria [152]. Acute restraint stress induces rat skin vascular permeability [153], an effect inhibited by a CRH receptor antagonist and absent in mast cell deficient mice [154]. Histamine is a major regulator of the hypothalamus [154] and can increase its CRH mRNA expression [155]. Moreover, human mast cells can synthesize and secrete large amounts of CRH [156], as well as IL-1 and IL-6 which are independent activators of the HPA axis [157].

Mast cells are frequently found in close proximity to mucosal nerves and vagal nerves have been reported to influence mast cells [158]. Very early studies have shown that vagal stimulation causes mast cells to degranulate [159, 160] in the gastrointestinal mucosa of rats and guinea pigs [161, 162]. Mediators released from mast cells such as histamine can then cause vagal stimulation [163, 164]. It has been, therefore, hypothesized that there is crosstalk between mast cells and nerves in vitro[165-166] and in the CNS [167]. A reversible increase of the surface of rat mesenteric mast cells was noted after vagal stimulation,feeding or even oldfactory stimulation of the animals [168]. Mast cell stabilizing agents reduced the bronchoconstriction caused by SP and neurokinin A and E [169]. In another study, histamine and serotonin released from the rat perfused heart by compound 48/80 or by allergen challenge increased noradrenaline or acetylcholine exocytotic release [170]. Vagal stimulation has also been found to exert a trophic effect on mast cells [171].

A number of drugs can also stimulate mast cells [Table 5], best known of which is morphine [172].

6. Mast Cell Mediators

Mast cells can secrete a multitude of biologically potent mediators (Table 6) that permit them to participate in innate or acquired immunity [64, 65, 173]. There are various vasodilatory and proinflammatory mediators, such as the preformed histamine, heparin, kinins, proteases, as well as the newly synthesized leukotrienes, prostaglandins, nitric oxide (NO) and cytokines [174-176].

A number of growth factors are also secreted such as Vascular Endothelial Growth Factor (VEGF) [65, 177, 178], which has been shown to be released selectively in response to PGE2 [179], adenosine [180] and CRH [181]. VEGF was specifically shown to induce dilation of microvessels [182].

Table 6. Mast Cell Mediators and their actions

Mediators	***Main Pathophysiologic Effects***
Prestored	
Biogenic Amines	
Histamine	Vasodilation, angiogenesis, mitogenesis,pain
5-Hydroxytryptamine (5-HT, serotonin)	Vasoconstriction, pain
Chemokines	
IL-8 (CXCL8), MCP-1 (CCL2),	
MCP-3 (CCL7), MCP-4 (CXCL13),	
RANTES (CCL5)	Chemoattraction and tissue infiltration of leukocytes
Enzymes	
Arylsulfatases	Lipid/proteoglycan hydrolysis
Carboxypeptidase A	Peptide processing
Chymase	Tissue damage, pain, angiotensin II synthesis
Kinogenases	Synthesis of vasodilatory kinins, pain
Mediators	***Main Pathophysiologic Effects***
Metalloproteinases	Tissue damage
Phospholipases	Arachidonic acid generation
Tryptase	Tissue damage, activation of PAR, inflammation,pain
Peptides/Proteins	
Corticotropin-releasing hormone (CRH)	Inflammation, vasodilation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation
Neurotensin	Inflammation, pain
Renin(CTMC only)	Vascular contriction
Somatostatin (SRIF)	Anti-inflammatory (?)
Substance P (SP)	Inflammation, pain
Vasoactive intestinal peptide (VIP)	Vasodilation
Urocortin	Inflammation, vasodilation
Vascular endothelial growth factor (VGEF)	Neovascularization, vasodilation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory
Heparin	Angiogenesis, NGF stabilization

Table 6. Mast Cell Mediators and their actions (Continued)

Mediators	***Main Pathophysiologic Effects***
Hyaluronic acid	Connective tissue
Angiogenic factors	
Adrenomedullin	
Angiogenin	
Angiopoietin	
EGF	
FGF α	
basic FGF	
IL-8	
Neuropillin	
PDGF	
TGF β	
VEGF	
De novo synthesized	
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,8,10,13,16,17,32	Inflammation, leukocyte migration, pain
IFN-γ; MIF; TNF-α,TGF-beta	Inflammation,leucocyte, proliferation, activation
Growth Factors	
SCF, GM-CSF, b-FGF, NGF, VEGF	Growth of a variety of cells
Phospholipid metabolites	
Leukotriene B_4 LTB_4	Leukocyte chemotaxis
Leukotriene C_4 (LTC_4)	Vasoconstriction, pain
Platelet activating factor (PAF)	Platelet activation, vasodilation
Prostaglandin D_2 (PGD_2)	Bronchonstriction, pain
Others	
Nitric oxide (NO)	Vasodilation
ROS	Inflammation

Proteases released from mast cells could act on plasma albumin to generate histamine releasing peptides [183, 184] that could further propagate mast cell activation and inflammation. Proteases could also stimulate protease activated receptors (PAR) inducing microleakage and widespread inflammation [185, 186]. Proteases can activate fibroblasts thereby promoting collagen deposition and fibrosis.

Reactive oxygen species (ROS) are produced in cells by a variety of enzymatic and non-enzymatic mechanisms. In a very early study, immunologic or nonimmunologic stimulation

of rat peritoneal and human lung mast cells, as well as human leukemic basophils, induced parallel release of histamine and O(-) (2) within 2 min [187].

An increase in intracellular ROS production was observed in rat peritoneal mast cells (RPMCs) following stimulation with antigen [188-190], compound 48/80 [188-190] the calcium ionophore A23187 [190], SP [188], and NGF [188]. In contrast D-mannitol increased ROS production in stimulated mast cells without a marked effect on degranulation or histamine secretion [130].

In addition, chemicals such as mercuric chloride [191], silver [192], ionophore [193], phorbol myristate acetate (PMA) [144], vitamin K [195], silica [196], as well as bacteria [197] and fungal components [198] can produce ROS in mast cells. Recently it was reported that 5-Lipoxygenase (5-LO) was the primary enzyme involved in ROS production by human mast cells and mouse BMMC following FcεRI aggregation. Cyclooxygenase was also involved in ROS production, whereas NADPH oxidase was not [199].

Several studies implicate mast cells in the induction of intestinal ischemia reperfusion (IR) injury [200-202]. It has been shown that ROS play an essential role in the activation of mast cells in IR[203, 204]. Mast cell activation is also important in IR injury of the heart. In one study, use of the mast cell stabilizer cromolyn significantly reduced, while activation by compound 48/80 increased IR-dependent histamine levels [205].

In a model of myocardial ischemia and reperfusion injury in rat heart muscle cells in vivo, a superoxide dismutase mimetic significantly reduced myocardial damage, mast cell degranulation and the incidence of ventricular arrhythmias [206].

7. Selective Release of Mast Cell Mediator

Mast cell have been reported to secrete without degranulation but through ultrastructural alterations of the cell electron dense granular core indicative of secretion. This process has been termed "activation" [62, 207, 208], "intragranular activation" [89] or "piecemeal" degranulation [209]. During this process, mast cells can release many mediators differentially or selectively (Table 7) [210-212] as originally shown for serotonin [213] and eicosanoids [214-216]. IL-6 was shown to be released in response to IL-1 through small vesicles (40-80 nm in diameter), unrelated to the secretory granules (800-1000 nm) in diamerter [217]. VEGF could also be released selectively without degranulation by CRH [218]. PGE2 also induced VEGF release from human mast cells without degranulation [169], while adenosine induced selective release of the angiogenic factors IL-8 and VEGF [180].The only way to explain these observations would be through the ability of mast cells to undergo “differential” or “selective” release of mediators [213] without degranulation[219].

Exosomes are small, 30–100 nm membrane vesicles, which are released extracellularly after fusion of multivesicular endosomes with the cell membrane. They have emerged as a novel mechanism of genetic exchange since it has been shown that they are involved in transferring mRNAs and microRNAs between cells [220].

Exosomes containing MHC II antigens have been shown to be released by mast cells during degranulation[221]. In another study, it was demonstrated that mast cell associated

exosomes induce immature dendritic cells (DCs) to up-regulate MHC class II, CD80, CD86, and CD40 molecules and to acquire potent Ag-presenting capacity to T cells [222].

Table 7. Mechanisms of mast cell secretion

Degranulation	Anaphylaxis
Selective release	Infection, Inflammation
Piecemeal degranulation	MS, scleroderma
Exosomes	Infection
Transgranulation	Brain

Exosomes have been implicated in the induction of tolerance in the gut epithelium towards food antigens [223], and in the maintenance of pregnancy [224] by several mechanisms.

8. Natural Mast Cell Secretion Inhibitors

There are no, so far, effective clinically available mast cell inhibitors (Table 8, Table 9). Disodium cromoglycate (cromolyn) is a potent inhibitor of rodent mast cell histamine secretion [225], but very weak inhibitor of human mast cells [66].

Table 8. Natural mast cell inhibitors

Chondroitin Sulfate
Flavonoids (luteolin,quercetin)
Heparin
Nitric Oxide
Somatostatin (mucosal must cells only)
Vitamin A (retinoic acid)
Vitamin E (tocopherol)

In the human mastocytoma cell line (HMC-1), vitamin E inhibits the PI3K/PKB signaling pathway with consequent inhibition of proliferation and reduced survival [226].

Vitamin E inhibits protein kinase C (PKC),which is involved in degranulation and cytokine production [227]. In many studies, vitamin E reduced mast cell degranulation by scavenging free radicals. However vitamin E also reduces the production of free radicals by NADPH-oxidase [228] or mitochondria [229], activates several drug-metabolizing enzymes (cytochrome P450 CYP3A and CYP4F2) 230], and modulates signal transduction and gene expression[171], suggesting that it may have additional modes of action.

Retinoic acid was also shown to inhibit proliferation of leukemic mast cells [232, 233].

Middleton and colleagues first showed that certain flavonoids could inhibit rodent mast cell secretion [234]. Flavonoids are polyphenolic compounds present in fruit, vegetables, nuts, seeds, wine, tea, and coffee with anti-oxidant and anti-inflammatory actions [234].

Table 9. Agents capable to stabilize mast cells

1. Simultaneous inhibition of H1 and H2
2. Lodoxamide
3. Sodium nedocromil (intal)
4. Sodium cromoglycate (lomuntal)
5. Ketotifen-H1-blocker (Zaditen)
6. Flavonoid quercetin (intacellular Ca)
7. Flavone luteolin inhibits T-cells, mast cells and mast cell-dependent T-cell activation
8. Relaxin (hormone from corpus luteus and prostate, generates NO)
9. IgG1 humanized monoclonal antibodies recognizing and masking corresponding IgEs in mast cell membrane*)*
10. NO inhibits IL-6 production through TNF-α inhibition
11. Peptides from C3α, C3α+, C3α9+, inhibit FcεRI-induced degranulation and TNF-α release
12. Zaprinast (phosphodiesterase inhibitor)
13. Stem cell factor (SCF) targeting drugs, since SCF is essential for mast cell development, proliferation, survival, adhesion, and homing

Kimata et al. [235] reported that luteolin, quercetin and baicalein inhibited the release of histamine, leukotrienes and prostaglandin D2, as well as the secretion of granulocyte macrophage-colony stimulating factor by human cultured mast cells in response to cross-linkage of FcεRI and subsequently showed that these compounds also inhibited IgE-mediated TNF-α and IL-6 production by bone marrow-derived cultured murine mast cells. It was also shown quercetin and other flavonoids could inhibit histamine, IL-6, IL-8, TNF-α and tryptase from IgE-stimulated human mast cells [236]. The same flavonoids could also inhibit leukemic mast cell proliferation [237].

Chondroitin sulphate, a major natural constituent of connective tissues, especially cartilage, and of mast cell secretory granules, had a dose-dependent inhibitory effect on rat peritoneal mast cell release of histamine induced by compound 48/80; this inhibition was stronger than that of the clinically available mast cell 'stabilizer' cromolyn. Moreover, inhibition by chondroitin sulphate increased with the length of preincubation and persisted after the drug was washed off, while the effect of cromolyn was limited by rapid tachyphylaxis [238].

Chondroitin sulphate's inhibitory actions have been recently tested with a traditional Korean formulation, OK205, which includes of water-soluble chitosan, glucosamine HCl, chondroitin sulfate used to treat rheumatoid arthritis. Choi et al [239] tested the inhibitory effects of OK205 on cytokine production in a human mast cell line (HMC-1 cells) and reported a decrease in production of TNF-α and IL-6. Heparin, the structure of which is quite similar to that of chondroitin sulphate and is also stored in mast cells, had been shown to inhibit in vivo release of histamine [240].

IL-10 inhibits the release of TNF-α and of IL-8, but not of IL-5, by activated CBMC. Interestingly, IL-10 also inhibits the release of histamine by activated CBMC, contrasting with data reported for rodent mast cell. These findings suggest that IL-10 might have anti-inflammatory effects on IgE/anti-IgE-challenged human mast cell by inhibiting their release

of TNF-alpha, IL-8 and histamine [241]. However other studies have reported lack of an inhibitory action on human mast cell tryptase and IL-6 release [242], suggesting there may be species differences.

TGF-1b acts as a novel potent inhibitor and modulator of human intestinal mast cell effector functions [243]. It has also been found to downregulate FcERI expression [184] in mouse mast cells. This inhibition of mast cell function induced by TGF-1b might be of use in the control of mast cell associated disorders of the intestine such as allergic reactions, Crohn's disease, irritable bowel syndrome, and parasitic infection.

Somatostatin is an important regulator in the neuroendocrine-immune network. Several studies have shown that somatostatin inhibits mast cell activity and could prevent the intestinal responses to mast cell hyperplasia [245, 246]. In contrast, somatostatin was shown to stimulate connective tissue mast cells in vitro [214, 247].

Nitric oxide is a gas and free radical that has important physiological roles including defense against microorganisms, but also regulation of cellular activation[248] and gene expression [249]. It has been demonstrated that mast cells express NO synthases (NOS) and produce NO themselves[250]. Importantly, it has been shown that NO directly inhibits IgE depended mast cell degranulation [251, 252]. Endogenous and exogenous NO protects against IR injury in isolated guinea pig hearts; perfusion of the hearts with two inhibitors of the NOS pathway, (L-NMMA and L-NAME) significantly enhanced histamine and LDH release; these effects were attenuated by co-infusion with L-arginine. Perfusion of the heart with sodium nitroprusside (SNP), 3-morpholinosydnonimine (SIN-1), glyceryl trinitrate (GTN), reduced histamine release, effects that were amplified by concomitant perfusion with superoxide dismutase [253, 254]. Endogenous and exogenous NO inhibits mast cell degranulation and protease release [255], adherence to fibronectin [256], leukotriene [257], cytokine, and chemokine production [258, 259]. NOS-2 can be induced in response to pregnancy, IR injury, angiogenesis, antibody against CD8, and liver cirrhosis, as well as by several inflammatory stimuli such as IFN-γ, IL-1β and crosslinking of IgE on mast cell [258]. Recent data suggest that NO protects mast cells from activation-induced cell death [260]. Studies have also shown that the stabilizing effect of NO on mast cells may have a cardioprotective role [261].

9. Coronary Inflammation

The presence of mast cells has been established in human heart tissue [262, 263]. Their location and certain cytokines produced by mast cells, suggested they play an important role in cardiac diseases [264]. Mast cells are particularly prominent in coronary arteries during spasm [265] and accumulate in the shoulder region of human coronary plaque rupture [261-263].

Many mediators released from cardiac mast cells, such as TNF, basic fibroblast growth factor (bFGF or FGF-2), and transforming growth factor-β (TGF-β) could influence cardiovascular pathophysiology (Table 5). Cardiac mast cells can participate in the development of atherosclerosis, coronary inflammation and cardiac ischemia [262, 266-268]. Chymase can also induce the removal of cholesterol from HDL particles and increase uptake

by macrophages that become "foam" cells, major components of coronary atheromas [269-272]. They do this, by impairing the ability of HDL to act as a high affinity cholesterol receptor [273] and destabilizing the LDL bound to the heparin proteoglycan component of the exocytosed granules of mast cells and by this way promoting LDL retention in the arterial intima [273]. Cardiac mast cell-derived histamine [274] can constrict the coronaries [275] and can sensitize nerve endings [164].

In a systematic study of the population density of mast cell in human coronary atherosclerosis, fewer mast cells were found in normal coronary intima, than in fatty streaks [266]. Chymase may also play a role in plaque destabilizaton by inhibiting collagen synthesis. Chymase inhibitors tested in animal models of myocardial infection, cardiomyopathy and heart failure have provided us with promising results [276].

Another important action of chymase is the ACE-independent coversion of angiotensin-I (ANG I) to angiotensin-II (ANG II), after vascular injury. It has recently been reported that mast cells are a novel and previously undescribed source of renin in human and rodent myocardium [277], and immediate- type allergic reaction elicits renin release from mast cells, which activates the local renin-angiotensin system, thereby promoting norepinephrine release [278]. As renin is stored in human mast cells, allergic reactins could initiate renin release, leading to local angiotensin formation and hyperadrenergic dysfunction. ANG I and ANG II concentrations in the interstitial fluid of the canine heart have been found to be 100-fold higher than plasma levels and are not modified by intravenous ANG I infusions [279]. This result indicates that ANG I found in the heart is synthesized in situ, and most of cardiac ANG II derives from the conversion of locally produced, rather than blood-derived, ANG I. In myocardial IR, mast cells degranulate and release renin to form ANG I; this is followed by the generation of ANG II via local ACE. ANG II then activates angiotensin type 1 (AT_1) receptors located on the membrane of sympathetic nerve terminals, promoting release of norepinephrine (NE) (277). NE and ANG II are known to contribute to reperfusion arrhythmias that are prevented by pharmacological mast cell stabilization, renin inhibition, or AT_1-receptor blockade [280].

Increasing evidence implicates acute psychological stress and cardiac mast cells in coronary heart disease (CHD), especially when occurring without angina, that appears to involve a sizable portion of myocardial infarction (MI) [281-284]. Acute stress induces rat cardiac mast cells activation, an effect blocked by cromolyn [285]. Both histamine [286] and IL-6 [287] are significant independent factors of CHD morbility and mortality. Acute stress induced histamine release from mouse heart [288], as well as increase serum histamine and IL-6 [288, 289]. These effects are dependent on mast cells and are greater in apolipoprotein E (ApoE) knockout mice that develop atherosclerosis [288, 289]. Serum IL-6 elevations in patients with acute CHD were documented to derive primarily from the coronary sinus [290]. There are also reports of anaphylactic CHD that has been termed the "Kounis" syndrome [291-293].

Adrenomedullin (AM) also is a potent vasodilatory hypotensive peptide and is expressed in the heart, where it is known to play a protective role [244]. Cardiac mast cells are able to synthesize and store AM, and upon stimulation to release it near coronary arterioles and venules [295].

Adenosine and its receptors have also been shown to play an important role in cardiovascular disease. Adenosine acts on mast cells via A2a, A2b [296] receptors causing degranulation [297] and the release of IL-8 [298], as well as VEGF [299] that could participate in IR injury. Activation of A3 receptors has also been shown to cause more mast cells to degranulate [300, 301] and A3R knockout mice were tolerant to IR injury [301].

10. Common Pathway between Allergic and Non-Allergic Coronary Syndromes

Today, it is almost certain that the majority of cases of unstable angina and acute myocardial infarction are the result of combined coronary artery spasm and plaque erosion or rupture followed by thrombus formation. The following mediators, released during acute allergic episodes, have been found to be increased in blood or urine of patients suffering from acute coronary syndromes on non-allergic etiology.

Patients with acute coronary syndromes of non-allergic etiology have been found to have more than twice tile blood concentration of histamine than normal subjects [286]. Arachidonic acid metabolites such as thromboxane and leukotrienes have been found significantly higher in the systemic arterial circulation in the acute stage of non-allergic myocardial infarction than in circulation of normal controls [302]. lnterleukin-6 levels, derived from inflamed coronary plaques and areas of myocardial necrosis, have been found elevated in patients with non-allergic acute coronary syndromes [303, 304]. In a recent study [305], tryptase levels were elevated in patients with non-allergic acute coronary syndromes with higher concentration in the ST segment depression group of patients and it was postulated that tryptase may be a potential new marker characterizing the unstable plaque. Tryptase levels were found all elevated in non-allergic patients with significant coronary artery disease as a result of chronic low-grade inflammatory activity present in the atherosclerotic plaques [66]. It is proposed that tryptase measurements may emerge as a novel way of identifying asymptomatic patients with coronary artery disease and represent a new biomarker of therapeutic efficacy in these patients [306].

Therefore, the same substances from the same cells are present in both acute allergic episodes and acute coronary syndromes.

11. Mast Cell Activation Precede Acute Coronary Events

The important question which arises in acute coronary events is whether inflammatory cells including mast cells and their contents are the cause or the result of the event.

There is now evidence that mast cells not only enter the culprit lesion before plaque erosion or rupture but also release their contents before an actual coronary event. Kaartinen et al. [307] showed that mast cells infiltrate not only the sites of coronary arteries at which plaque rupture or erosion has occurred but also sites of coronary plaques susceptible to

erosion or rupture which means they invade before an actual initial event. The same applies also for other inflammatory cells such as macrophages and T lymphocytes. Therefore, there is much evidence to suggest that inflammatory cells infiltrate the lesions before erosion or rupture and they are not part of inflammatory response to rupture initiated by other processes. In another report, concerning patients who had died within 2 days after the acute coronary event [308], infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture were found in a ratio of 200 to 1 compared with normal endothelial segments. It is known mat circulating blood contains only mast cell precursors and these precursors take several days to weeks to differentiate into morphologically identifiable mast cells filled with cytoplasmic secretory granules [309, 310]. Therefore, the mast cells must already have been present at the erosion or rupture sites before the episode in the above patients. In fact, the number of mast cells was highest in one of the above patients who had the shortest interval between the onset of symptoms and death.

Histamine concentration was found to be elevated in the great cardiac vein in 8 of 11 patients suffering from attacks of variant angina [311] and in none of 8 control patients. In the same patients, the authors did not observe any histamine elevation during or after acetylocholine-induced coronary artery spasm. In contrast, elevation of plasma histamine levels was antecedent to angina attacks in 3 patients. In addition high levels of histamine were observed even in the absence of ST segment elevation in the same group of patients.

Tryptase levels were found elevated during spontaneous ischemic episodes in 8 patients suffering from unstable angina [312], but not after ergonovine-provoked ischemia in patients suffering from variant angina, suggesting that a primary yet unknown stimulus activates mast cells in patients suffering from episodes of unstable angina. In a recent report [313] it was found that arachidonic acid products such as leukotrienes and thromboxane were significantly higher in non-allergic patients with unstable angina than in patients with stable angina and in patients with nonischemic chest pain. In the same report it was shown that myocardial ischemia elicited by stress test in the stable angina patients was not accompanied by any change in leukotriene and thromboxane up to 6 days after positive exercise test. The authors of this study concluded that this can rule out a role of ischemia per se in the induction of increased eicosanoid products.

12. Ischemic Myocardial Damage seems to be the Primary Event during Allergic Episodes

It is generally believed, that during an allergic episode, systemic vasodilation, reduced venous return, leakage of plasma and volume loss due to increased vascular permeability and the ensuing depression of cardiac output contribute to coronary hypoperfusion with subsequent myocardial damage. Indeed, during severe acute allergic episodes circulating blood volume may decrease by as much as 35% within 10 min due to transfer of intravascular fluid to extravascular space and severe vasodilation resistant to epinephrine and responding only to other potent vasoconstrictors has been reported [314-316]. This effective shift of fluid volume is countered by compensatory vasopressor mechanisms involving the release of epinephrine and norepinephrine [317] as well as the activation of angiotensin system [318,

319]. The ensuing increase in catecholamines mighty produce varied effects. Some patients during acute allergic episodes experience maximum peripheral vaso-constriction [320] whereas others have decrease systemic vascular resistance [317]. These variable effects of internal compensatory mechanisms might explain why epinephrine injections sometimes fail to help acute and severe allergy. Furthermore, the endogenous catecholamine/release which can be enhanced by therapeutic administration can have an adverse effect in myocardium, including ischemic chest pain and electrocardiographic changes in the absence of diseased coronary arteries [321, 322].

However, experimental and clinical evidence indicates that the human heart can be the site and the primary target of anaphylaxis. In experimental anaphylaxis with ovalvumin sensitized guinea pigs [323] it was shown that within 3 min after the antigen administration the cardiac output decreased by 90%, the arterial blood pressure rose significantly by 35% as did the left ventricular end diastolic pressure indicating pump failure. In the same time range, electrocardiographic recordings uniformly showed signs of acute myocardial ischemia.

The blood pressure started declining steadily after 4 min. The authors of this paper concluded that "the idea that the registered anaphylactic damage might be due to peripheral vasodilation can be definitely excluded. In addition, the rapid increase in left ventricular end diastolic pressure suggests that decreased venous return and volume loss due to an increase of vascular permeability are unlikely to be the primary causes of the documented depression of cardiac output and blood pressure". In this study, it must be pointed out that, coronary vascular resistance and vasoconstriction of epicardial coronary arteries were not assessed.

However, in another study [324] with isolated guinea pig hearts undergoing anaphylaxis following intra-aortic injection of antigen, an abrupt heart rate increase reaching the peak within 2 min, a transient increase in ventricular contractile force followed by prolonged decrease, and a prompt and prolonged decrease in coronary blood flow were observed. Actually, the above reports were not the only ones, but they corroborated the findings of previous report [325] according to which the anaphylactic cardiac damage can be dissociated temporarily into two sets of events: an initial primary cardiac reaction caused by intracardiac release of histamine and a subsequent cardiovascular reaction secondary to systemic release of mediators.

In a group of patients with spontaneous angina [326], after infusion of histamine, with pre-treatment with cimetidine to antagonize H2 receptors, 40% of the patients developed angina with ST elevation, decrease coronary blood flow, increase coronary vascular resistance but with no significant changes in the mean arterial blood pressure.

Today, it is known that histamine acts via four different histamine receptors all of which contribute to the severity of the allergic myocardial damage. H1-histamine receptors mediate coronary vasoconstriction and increase vascular perneabilty. H2-histamine receptors mediate a minor degree of relaxation of the coronary arteries and increase atrial rate and atrial and ventricular contractility. The interaction of H1- and H2-receptor stimulation mediate decreased diastolic pressure and increased pulse pressure [327]. Histamine binding to H1-receptors during anaphylaxis stimulates endothelial cells to convert the amino acid L-arginine into nitric oxide (NO), a potent autocoid vasodilator [328, 329]. Enhanced NO production decreases venous return, thus contributing to the vasodilation that occurs during anaphylaxis [330]. H3-histamine receptors have been identified [331] on presynaptic terminals of the

sympathetic effector nerves that innervate the heart ant the systemic vasculature. These receptors have been found to inhibit endogenous norepinephrine release which would be expected to enhance the degree of shock during anaphylactic events. The recently identified H4-histamine receptors control chemotaxis of murine mast cells [332] and human eosinophils [333, 334] and the release of interleukin -16 from human lymphocytes [335]. The recruitment of these specific inflammatory cells at the sites of me allergic response correlate with the severity of the allergic reaction [336, 337].

13. Frequency of Kounis Syndrome and Clinical Relevance

Acute coronary syndromes associated with acute allergic reactions are increasingly encountered in clinical practice, but it has been difficult to determine their true frequency because adequate reporting mechanisms do not exist. Indeed, unlike many disorders, mere is no requirement to report such reactions to any national registry [338]. For similar reasons, determining the incidence and prevalence of Kounis syndrome has been challenging. However, in a recent study [339] by pushing a single ant against the ventral forearm of 21 healthy volunteers, allowing it to sting for 60s, two of the subjects (9.5%) developed chest pain with electrocardiographic changes suggesting acute myocardial ischemia. In another survey concerning anaphylaxis during anesthesia, it was shown that cardiovascular symptoms were the most common (73.6%) clinical features [340]. In the canton Bern, Switzerland, during a 3-year period 226 individuals were diagnosed as having presented generalized anaphylaxis with circulatory problems [341].

There are several causes that have been reported as capable of inducing Kounis syndrome. These include a number of conditions, several drugs and a variety of environmental exposures (Table 9). Although many cases of Kounis syndrome might go unreported, searching the world literature shows that the reports concerning Kounis syndrome are increasing. Between them, there are reports of hymenoptera sting-induced Kounis syndrome and cases of drug-induced Kounis syndrome. A detailed list of drugs capable of inducing Kounis syndrome (Table 10) has been published recently [12]. The first report of acute myocardial infarction during a prolonged allergic reaction to penicillin was published in the American Heart journal in 1950 [342]. In the majority of cases of Kounis syndrome hypotension and increased oxygen demand were the consequence of the allergic coronary artery spasm and/or acute myocardial infarction. Adrenaline administration which can induce acute myocardial infarction [343] and venom hemorrhagins or endothelins [344] which can also induce coronary artery spasm have been definitely excluded. However, in patients with overt or quiescent pre-existing coronary artery disease or endothelial dysfunction, acute allergic episodes can induce plaque damage or artery spasm manifesting as type II or type I variant of Kounis syndrome, respectively.

Table 9. Causes capable of inducing Kounis syndrome

Conditions	Drugs	Environmental exposures
Angio-edema	Antibiotics	Ant stings
Bronchial asthma	Analgesics	Bee stings
Exercise induced anaphylaxis	Antineoplastics	Wasp stings
Food allergy	Contrast Media	Jellyfish sting
Idiopathic anaphylaxis	Corticosteroids	Grass cutting
Mastocytosis	Intravenous anaesthetics	Poison ivy
Serum sickness	Non steroidal	Latex contact
Urticaria	Anti-inflammatory	Limpet ingestion (the kiss of death)
Churg-Strauss syndrome	Drugs (NSAIDs)	Millet allergy
	Skin disinfectants	Shellfish eating
	Thrombolytics	Viper venom poisoning
	Anticoagulants	
	Others	

Table 10. Drugs that have been reported to induce Kounis syndrome

Antibiotics

Ampicillin
Ambicillin/sulfactam
Amoxicillin
Amikacin
Cafazolin
Cefoxitin
Cerufoxime
Cephradine
Cinoxacin
Lincomycin
Penicillin
Sulbactam/cefoperazone
Sulperazon
Trimethropin/sulfamethoxazol
Vancomycin

Contrast Media

Iohexone
Loxagate
Meglumine diatrizoate
Sodium indigotindisulfonate
Analgesics
Dipyrone

Antineoplasics

5-fluoroucacil
Capecitabine
Carboplatin
Denileukin
Interferons
Paclitaxel
Vinca alkaloids

Intravenous Anaesthetics

Etomidate
Rocuronium bromide
Suxamethonium
Trimethaphan

NSAIDs

Diclofenac
Naproxen

Thrombolytics and Anticoagulants

Heparin
Lepirudin
Streptokinase
Urokinase

Skin Disinfectants

Chlorhexidine
Povidone-iodine

Others

Allopurinol
Enalapril
Esmolol
Dextran 40
Fructose
Insulin
Iodine
Lanzoprasol
Protamine
Tetanus antitoxin
Glaphenine

It seems likely that atopic individuals are at higher risk of acute coronary syndromes than normal people. In a population based study [345] men with increased levels of IgE had significantly increased incidence of myocardial infarction, stroke and peripheral arterial disease. In the same study women had both significantly lower IgE levels and lower rates of cardiovascular disease. The authors of this study concluded that a causal role of IgE in the development of cardiovascular disease should not be excluded. It has been shown that in platelets isolated from atopic patients, the immunological stimulation with anti-lgE antibodies produced platelet aggregation and release of histamine [346]. The exposure of platelets from healthy donors to increasing concentrations of thrombin produced a progressive aggregation of platelets which was parallel to the release of histamine. Both effects were significantly enhanced in platelets isolated from atopic donors [347].

Table 11. Clinical and Electrocardiographic Features of Kounis Syndrome

Clinical Symptoms

- Chest discomfort
- Acute chest pain
- Dyspnea
- Faintness
- Nausea
- Vomiting
- Syncope
- Pruritus
- Urticaria
- Hypotention
- Diaphoresis
- Pallor
- Palpitations
- Bradycardia
- Tachycardia

Electrocardiographic Symptoms

- T-wave flattering
- T-wave inversion
- ST segment depression
- ST segment elevation
- QRS complex prolongation
- QT segment prolongation
- Sinus tachycardia
- Sinus bradycardia
- Nodal rhythm
- Atrial fibrillation
- Ventricular ectopics
- Bigeminal rhythm

Several reports have shown that type I variant of Kounis syndrome has better prognosis than type II variant [348]. However, in both types the prognosis depends on the magnitude of the initial allergic response, the patient's sensitivity, the patient's comorbidity, the site of antibody-antigen reaction, the allergen concentration and the route of allergen entrance. Patients who present with any grading [349] of systemic allergic reactions associated with clinical, laboratory and electrocardiographic findings of acute myocardial ischemia should be diagnosed as having Kounis syndrome (Table 11). Chest pain, during an allergic insult, with electrocardiographic ischemic changes but with normal cardiac enzymes, negative toponins, normal sestamibi scan, normal coronary angiogram and positive ergonovine or histamine test [350] are in favour of type I variant of the syndrome. Acute allergic reactions associated with acute myocardial infarction with angiographic evidence of coronary artery disease constitute type II variant of Kounis syndrome.

Since life threatening allergic reactions with circulatory compromise can occur at an annual rate of 7.9 - 9.1 per 100.000 populations with 10% of these due to food, 18% due to drugs, and 59% due to venoms [341] knowledge of individual hypersensitivity is crucial. Ischemic heart disease patients with history indicative of hypersensitivity must undergo a reliable diagnostic procedure including skin testing and antibody testing. Cases of Kounis syndrome are more often encountered in clinical practice than anticipated and we believe that many more causative factors will be incriminated in the future. Careful patient interrogation may reveal a mechanism involving mast cell activation to preceed acute coronary events. In patients with any grading of systemic allergic reactions routine evaluation of myocardial injury markers such as cardiac enzymes and troponins together with histamine and tryptase levels should be undertaken. Although allergic episodes are common in everyday practice only few patients develop chest pain with/or electrocardiographic changes during these episodes. We believe that there is a threshold level of mast cell content (histamine, tryptase, chymase, leukotriene, thromboxane, PAF and chemokines) above which it can provoke coronary artery spasm and/or plaque erosion or rupture.

14. An Emerging Clinical Problem: Kounis Syndrome and Coronary Stent Thrombosis

Stent thrombosis is an emerging serious clinical problem in patients treated with Drug Eluting Stents [351]. Recent data [352] have shown that a small but increasing number of patients develop stent thrombosis after insertion of drug eluting stents (DES). Stent thrombosis may lead to catastrophic consequences [353] including myocardial infarction with estimated 30-day mortality ranging from 20 to 48%. Several meta-analyses of large trials, have shown that the overall mortality from DES was increased by 2, 3, and 4 years in comparison with the bare metal stents [354]. Another study[355] showed that the rate of cardiac death and non fatal myocardial infarction between 7-18 months after DES insertion was 4.9% and additional up to 3 years data[356] showed that the rate of mortality and myocardial infarction after sirolimus eluting stent insertion raised to 6.3%. These studies have prompted a statement from Food and Drug Administration (FDA) warning about the small but significant increase in the rate of death and myocardial infarction from possible

stent thrombosis followed 18 months to 3 years after stent implantation [357]. However, these rates have been challenged and three recent reports [358-360], showed no significant differences in the rates of death, myocardial infarction and stent thrombosis between DES and bare metal stents. It has been suggested that large randomized trials are necessary[361,362] in order to ascertain the long-term safety of DES.

Stent thrombosis has been classified as acute, occurring within 48 hours, subacute, occurring between the 2nd and the 30th day, late, occurring after the first 30 days to one year and very late occurring after one year of the implantation. This was followed by the "Academic Research Consortium " definitions which defines stent thrombosis as definite stent thrombosis which means acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion, probable stent thrombosis which means either unexplained death within 30 days following stent insertion or acute myocardial infarction involving the target-vessel territory without angiographic confirmation and possible stent thrombosis which means unexplained death occurring at least 30 days following stent insertion[363].

Potential causes of stent thrombosis (Table 12) include delayed endothelialization, stent length, complex lesions, suboptimal stent insertion, flow disturbances and changes in shear stress, withdrawal of clopidogrel and/or aspirin, brachytherapy for in-stent restenosis, patient characteristics and hypersensitivity to stent components [364]. The concurrence of acute coronary syndromes with hypersensitivity reactions has been long ago established [1} and the question which arises is whether hypersensitivity to DES components could be associated with acute coronary events [365,366].

Table 12. procedural, clinical and angiographic variables of stent thrombosis

1.	Supoptimal stent insertion
2.	Stent length
3.	Vessel calcification
4.	Multivessel disease
5.	Totally occluded lesion at baseline
6.	Post-procedural TIMI flow <3
7.	Insulin dependent diabetes
8.	Advanced age
9.	Low ejection fraction
10.	Flow disturbances
11.	Changes in shear stress
12.	Withdrawal of clopidogrel and/or aspirin
13.	Clopidogrel resistance
14.	Brachytherapy
15.	Delayed endothelialization
16.	Hypersensitivity to stent components

Since it is not known if stent thrombosis is a time limited event, this might become a major clinical concern in patients who have been already treated with DES. Therefore, the search for causation and application of prophylactic and therapeutic measures for stent-

associated coronary events must be of paramount importance for both patients and physicians.

15. Kounis Syndrome: Hypersensitivity to DES Components

Data deriving from FDA`s Manufacturer and User Device Experience Center (MAUDE)[367] and the Research on Adverse Drug/Device events And Reports (RADAR)[368] project have shown that 262 cases of Drug-Eluding Stent implantation were associated with hypersensitivity reactions. RADAR project reviews in detail adverse event reports gathered from different sources and evaluates causal associations between drugs and potentially fatal adverse events. Although only 17 cases were classified as probably or certainly caused by the stent insertion, 4 of them developed fatal in-stent thrombosis and died at 4, 5, 18, and 18 months after implantation respectively[369]. These reactions included rash, itching, hives, dyspnea, fever, atypical chest pain, high or low blood pressure, joint pain, joint swelling, and anaphylaxis. The cutaneous rash was associated with hives, desquamation or blisters and covered the entire body in the 21% of the cases. Based on MAUDE seriousness codes, 95% of these reactions were classified as serious requiring hospitalizations, emergency interventions, intravenous steroids, cardiac catheterizations, or resulted in permanent disability and even death. Laboratory findings associated with the above reactions included eosinophilia and elevated IgE titers. Clinical or laboratory findings did not abate with discontinuation of the concurrent antiplatelet medications. MAUDE and RADAR project data may be biased because there are underreported events, lack of information for causality attribution and inclusion of reports deriving from concomitant medications. However, allergy to DES is regarded real clinical entity today[370] and there is obvious risk for serious complications. It has been proposed that health professionals should be vigilant and should submit detailed adverse event reports to the manufacturer of DES or to the FDA[369]. The proportion of 262 cases with allergic reactions in over six million DES implantation seems to be well below the 4% expected for allergy from drugs alone. However, new cases on serum sickness-like reactions after placement of sirolimus-eluting stents have been recently reported [371]. Apart from the risk of thrombosis, physicians should be aware also of the reports of life threatening paradoxical coronary vasoconstriction associated with DES implantation [372-375]. A series of 13 patients who developed severe life threatening coronary artery spasm after DES implantation has been recently published [376]. Two patients did not respond to vasodilators and died. The post mortem examination in one patient showed scattered mast cells infiltrating the adventitia of the left anterior coronary artery suggesting a hypersensitivity reaction to the stent [377]. Simultaneous multivessel acute drug-eluting stent thrombosis has been recently reported suggesting hypersensitivity reaction involving multiple vessels as a possible cause [378].

Coronary events associated with hypersensitivity reactions are not common and are dependent on allergen concentration, number of insulting allergens, route and rate of allergen entrance in the circulation, magnitude of the initial allergic response, area and localization of antibody-antigen reaction, patient`s sensitivity and patient`s comorbidity[379] . A threshold

level of inflammatory cell content, closely associated with the above conditions, has been suggested, above which this can provoke smooth muscle contraction and plaque erosion or rupture [380].

16. Stent Components: Potential Allergens

DES components include the metal stent itself, the polymer coating and the impregmated drugs which for today are: the antimicrotubule antineoplastic agent paclitaxel for TAXUS brand and the anti-inflammatory, immunosuppressive and antiproliferative agent rapamycin for CYPHER brand. Other investigative agents such as zotarolimus, everolimus, biolimus, tacrolimus, pimecrolimus etc. are currently undergoing safety and efficacy trials either impregnated in metal stents or used in transplant recipients in order to prevent rejection. All DES components either separately or synergistically seem to be able to induce hypersensitivity reactions and hypersensitivity coronary events (Table 13). Allergic inflammation is initiated by allergens cross-bridging their corresponding, receptor-bound, immunoglobin IgE antibodies on the mast cell or basophil cell surface. These cells degranulate and release their mediators when the critical number of bridged IgE antibodies reaches the order of 2000 out of maximal number of some 500 000-1000 000 IgE antibodies on the cell surface [381]. However, recent findings indicate that mast cells can be activated by non allergic triggers often without degranulation, but with selective release of potent and vasoactive compounds [382, 383]. Clinical studies indicate that allergic patients simultaneously exposed to several allergens have more symptoms than mono-sensitized individuals [384]. A recent study showed that IgE antibodies with different specificities can have an additive effects and even small amounts of corresponding allergens can trigger mediator release when the patient is simultaneously exposed to them [385]. This data suggest that a possible sensitization to DES should not be clinically evaluated as a consequence of exposure to a single component but rather viewed in the context of potential sensitization to multiple DES compounds. In addition, recent in vitro studies [386] have shown that paclitaxel enhances tissue factor expression and activity in endothelial cells in concentrations comparable with those achieved locally after paclitaxel stent insertion [387]. Rapamycin also increases thrombin and tumor necrosis factor-α-induced endothelial tissue factor expression and activity at concentrations that are encountered in vivo [388]. Furthermore, histamine, the main amine released during hypersensitivity reactions, can also induce tissue factor expression and activity in human vascular smooth muscle cell and aortic endothelial cell [389]. Therefore, paclitaxel, rapamycin and the released histamine may contribute to a prothrombotic environment after insertion of DES.

Table 13. Hypersensitivity reactions to DES components

1. Sirolimus

- acrocyanosis
- angioedema
- flushing
- pruritus
- interstitial pneumonitis
- Schonlein-Henoch purpura
- localized eczematiform eruption
- palpable purpura due to leucocytoplastic vasculitis
- paradoxic coronary vasoconstriction

2. Paclitaxel

- angioedema
- atrioventricular block
- bronchospasm
- cutaneous flushing
- diaphoresis
- Kounis syndrome
- left bundle branch block
- ventricular tachycardia
- urticaria

3. Polymers and Latex

- allergic conjunctivitis
- allergic rhinitis
- allergic allergic stomatitis
- facial angioedema
- generalized anaphylactic reaction
- generalized urticaria
- interstitial asthma
- neurodermatitis
- stomatitis venenada

4. Nickel

- allergic contact dermatitis
- baboon syndrome
- bronchial asthma
- dependent edema
- diffuse exanthema
- fever
- flexural dermatitis
- itching erythema
- pericarditis
- pompholyx formation
- rosacea
- sarcoid granuloma (delayed hypersensitivity)

17. Paclitaxel and Sirolimus Induced Allergic Reations and Kounis Syndrome

Paclitaxel together with docetaxel belong to a dinstict type of antineoplastic drugs which in micromolar concentrations, easily achieved in patients, inhibit microtubule assembly (M-phase of the cell cycle) resulting in dissolution of the mitotic spindle structure, thereby inhibiting proliferation of cells[390]. They also promote microtubule resistance to depolymerization which results in the production of nonfunctional microtubules [391]. Morphological features and a DNA fragmentation pattern such as of programmed cell death indicate that paclitaxel may trigger cell apoptosis [392].

Most cytostatic drugs have reported to induce allergic reactions [393]. There are several reported instances of hypersensitivity reactions, mainly of anaphylactic type (type I) but also types II, III, and IV [394] . Severe and leathal reactions have also occurred [395,396]. Antineoplastics capable to induce acute coronary syndromes include [397] the antimicrotubule paclitaxel (Taxol), the antimetabolite 5-fluoruracil (Adrucil), its prodrug capecitabine (Xeloda), the alkaloids cisplatin (Platinol), the interleukin-2 agent denileukin diftitox (Ontak), the vinca alkaloids and interferons.

Apart from, neutropenia, thrombocytopenia, paralytic ileus, alopecia, gastrointestinal upset and peripheral neuropathy, hypersensitivity reactions are quite common with the use of paclitaxel with 90% of these occurring after the first or second dose [398].

According to a recent report [399] up to 42% of patients, receiving systemic paclitaxel for treatment of various types of cancer, experience some kind of hypersensitivity reactions and up to 2% of the patients developed serious allergic reactions. So far, there are several reports associating type I and type II variants of Kounis syndrome with paclitaxel systemic administration [400-411]. In another report [412], a patient experienced anaphylactic reaction during a Taxus stent implantation. This patient developed erythematous rash and hypotension immediately after the stent insertion. The case complicated with coronary spasm and thrombus formation. This reaction was successfully treated with steroids, antihistamines, epinephrine, dopamine and intraaortic balloon counterpulsation. Delayed severe multivessel coronary artery spasm and aborted sudden death has also been observed after systemic Taxus stent implantation [372]. Paclitaxel-induced hypersensitivity reactions can be decreased considerabley if a test dose of paclitaxel is implemented before the initiation of therapy [413]. In another study [414], involving 23 patients with recurred ovarian cancer, combination chemotherapy with carboplatin and paclitaxel induced hypersensitivity reactions in 5 patients. One of these patients exhibited severe allergic reaction compatible with Kounis syndrome. The rest of the patients developed eruptions, hypotension and tachycardia. It must be pointed out that all hypersensitivity reactions occurred immediately after carboplatin administration and not during paclitaxel administration. Perhaps, in this occasion, paclitaxel has acted as hapten. Low molecular weight antineoplastics have been proposed that have haptenic properties [13].

Sirolimus (rapamycin, Rapamune^{R}) is a macrolide antibiotic derived from actinomycete streptomyces hygroscopius which for many years has been used as an immunosuppressive and antiproliferative agent in the treatment of organ rejection in transplant recipients. Unlike cyclosporine and tacrolimus, sirolimus does not inhibit the calcineurin pathway, but inhibits

the mammalian target of rapamycin (mTOR), a multifunctional serine-threonine kinase that acts on IL-2-mediated signal transduction pathways, which is central regulator of cell growth proliferation and apoptosis [415]. Sirolimus prevents DNA and protein synthesis by regulation of p70S6 kinase phosphatase which leads in arrest of cell cycle [416]. These properties have been utilized also in coronary stents in order to reduce neointimal formation and restenosis.

Apart from the well known adverse effects associated with sirolimus use such as hyperlipidemia, hypercholesterolemia and thrombocytopenia some serious hypersensitivity reactions have been observed with its use.

Generalized, pruritic, ulcerating maculopapular rash necessitating cessation of sirolimus have been observed in a liver transplant patient [417]. A variety of cutaneous effects have been also reported in renal transplantation patients [418]. Sirolimus can induce allergic angioedema with diffuse swelling of eyelids, epiglottid edema, edema of floor of the mouth, tongue and soft Palate [419]. Despite vigorous therapy of these patients with angioedema complete resolution of this effect may occur only after withdrawal of sirolimus.

Furthermore, sirolimus-induced pulmonary hypersensitivity have been reported [420,421]. Acneiform eruption [422], leucocytoclastic vasculitis [423,424], even cardiac tamponade [425] are some additional but rare side effects.

In an experimental study [426] the side effects of rapamycin on treated rats were evaluated by histopathological examination of heart, kidney and eyes. Rapamycin administration at doses of 1.5 and 1.0 mg/kg/day resulted in focal myocardial infarction in 60% and 9% of rats respectively. In one animal a small area of focal retina ischemic necrosis was evident at the higher dose while no rat nephrotoxicity found in any rapamycin dose. In addition, animal experiments indicate a propensity for thombus formation in a rat model with synthetic vascular grafts treated by systemic or local administration of rapamycin [427]. Although no evidence of hypersensitivity was noted in this experiment, thrombus formation was largest in animals that received high dose of rapamycin either orally or intraperitoneally, when compared with the control group [428].

In humans, paradoxical coronary vasoconstriction[373] and life threatening coronary spasm[374] followed sirolimus eluting stent deployment has been also reported and was attributed to severe endothelial dysfunction[375] as in type I variant of Kounis syndrome. For example, localized hypersensitivity and late coronary thrombosis secondary to a sirolimus eluting stent has been reported in a 58-year old man who died 18 months later after stent implantation [429,430]. The inflammatory cells found at autopsy to infiltrate the intima, the media and the adventitia were the same namely macrophages, eosinophils, lymphocytes, and plasma cells with those participating in the process of Kounis syndrome.

18. Investigative Agents: Everolimus, Zotarolimus, Biolimus Induced Allergic Reactions

Several efficacy and safety trials are currently under way in order to evaluate the ability of some new sirolimus analogues for better inhibition of neointimal proliferation, even more reduction of the stenotic area, further increase of the lumen area and to avoid local

inflammation and late thrombosis. Some of these analogues have developed specifically for elution from intravascular stents but some others have been already used in transplant recipients and have been associated with rare but severe hypersensitivity reactions.

Everolimus, like sirolimus does not inhibit the calcineurin pathway but inhibits mTOR, has been recently received approval for immunosuppressive therapy in heart transplant patients in Austria and Germany [431]. In one report [432] among 114 patients treated with everolimus, 6(5.3%) developed lingual angioedema in a period between 2 to 41 days after initiation of therapy. In one of these patients two severe episodes of lingual angioedema necessitated the discontinuation of everolimus. However, trials involving everolimus –coated stents have yielded satisfactory results in restenosis reduction and extend of late loss [433-435].

Biolimus and zotarolimus, two newly synthesized sirolimus analogues inhibiting mTOR, have been developed specifically for elution from intravascular stents. First studies in humans and in animals has rendered satisfactory results in reducing restenosis [436-439].

However, these agents have not been used, so far, for treatment of transplant organ rejection and long term results and side effects from their use have not been established.

19. Calcineurin Pathway Inhibitors: Tacrolimus and Pimecrolimus Induced Allergic Reactions

Tacrolimus and pimecrolimus like cyclosporine do not inhibit mTOR but inhibit calcineurin pathway. Calcineurin is a ubiquitously expressed serine-threonine phosphate and is activated by sustained elevations of intracellular calcium. Activated calcineurin facilitates dephosphorylation of nuclear factor of activated T cells which is the primary downstream of transcriptional effector of calcineurin. Calcineurin inhibition by tacrolimus and pimecrolimus maintains immunosupression through prevention of IL-2 production [440]. Allergic reactions related to tacrolimus have been reported in children after liver transplantation [441-444]. In a recent report [445] of 121 children treated with tacrolimus after liver transplantation, 12(10%) experienced angioedema with peripheral eosinophilia and elevated levels of IgE. In another report [446] multiple food allergies were developed in children taking tacrolimus after heart and liver transplantation. Life threatening food allergy in a child treated with tacrolimus has been also described [441]. It has been suggested that tacrolimus, as a potent IL-2 inhibitor, may cause a shift towards the subset of lymphocytes called Th2 lymphocytes with the development of atopic allergy [441,446]. However, in a recent in vivo study, with tacrolimus-eluting stents, medial necrosis, adventitial inflammation and local arterial toxic effects were absent [447].

Pimecrolimus differs tacrolimus in inhibition of lymphocyte activation during the sensitization phase of contact hypersensitivity. Pimecrolimus only weakly interferes with lymphocyte activation and does not affect hyperplasia of draining lymph nodes during sensitization [448]. Pimecrolimus has not been used so far in drug-eluting stents. However, rare cases of cancer have been reported in people who have been using pimecrolimus cream and tacrolimus ointment for various dermatological diseases [449].

20. Methylprednisolone, Dexamethasone, Cytochalasin D, Vascular Endothelial Growth Factor and DNA-Eluting Stents

Corticosteroids are the treatment of choice for both systemic and local hypersensitivity reactions. Although their mechanism of action is not yet totally clear, corticosteroids can suppress the release of arachidonic acid from cell membrane and inhibit eicosanoid biosynthesis. The suppression of arachidonic acid release, especially from mast cells, is mediated through the inhibition of phospholipase A2. Corticosteroids, through reduction of the transcription of several proinflammatory cytokines, including C-reactive protein, could reduce the risk of myocardial infarction by 50% and can successfully treat vasospastic angina [450,451]. In patients with persistently elevated C-reactive protein, after successful coronary stent implantation, immunosuppressive therapy with high dose [452], but not low dose, oral prednisone for 45 days has resulted in a striking reduction in the clinical events and angiographic restenosis rate. Therefore, in an effort to reduce peri-strut inflammation after implantation of drug-eluting stents, corticosteroid-eluting stents have been developed.

Experiments in pigs with methylprednisolone-eluting stents have shown that both vascular macrophage infiltration and in-stent neointimal hyperplasia could effectively be decreased [453]. Other experiments with phosphorylcholine-coated stents eluting methylprednisolone have shown that inflammatory response and thrombus formation could effectively be decreased [454].

Dexamethasone eluting stents have exhibited an improvement in the clinical and angiographic outcomes as compared with the control stents [452] and are associated with reduced plasma concentration of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)[455] and lower adverse events during follow-up[456]. High doses of dexamethasone-loaded stents do not significantly reduce neointimal hyperplasia [457] and can induce morphological changes pointing to a loss of vascular integrity [458]. Other studies, with dexamethasone-eluting stents,including patients with diabetes mellitus, have shown that the restenosis rate is higher, suggesting that stent restenosis is unlikely to be related to decreased acute systemic inflammation but to an increased local resistance to inflammatory mediators[452}. However, it should be mentioned that corticosteroids have been implicated as causative agents for hypersensitivity reactions and anaphylaxis in some occasions and should be avoided in sensitized individuals [459-462].

The impact of vascular endothelial growth factor (VEGF) as an endothelial cell-specific mitogen after stenting has been experimentally investigated. Stent deployment results in endothelial denudation which is followed by smooth muscle cell proliferation, neo-intimal hyperplasia and restenosis. However, VEGF-eluting stents do not accelerate re-endothelialization and do not inhibit restenosis in rabbits [463]. An alternative, more effective approach with gene-eluting stents [464] may be considered for enhancement of re-endothelialization, by virtue of local delivery of naked plasmid DNA encoding for human VEGF-2.

Cytochalasin D-eluting stents are promising in reducing in stent hyperplasia [465]. Cytochalasins are lipophilic fungal metabolites that prevent actin monomer addition at the

rapidly growing end of actin filaments. Actin filaments are components of cytoskeleton. They are required for intracellular signaling, cell migration, replication and protein synthesis [466].

21. Hypersensitivity to Polymers and Latex

Synthetic biodegradable polymers are commonly used in drug eluting stents as a vehicle for local drug delivery and as a solution to improve their quality. The impregnated drugs are released by diffusion through and/or breakdown of the base polymer. Cypher stents are coated with a thin layer of poly-n-butyl methacrylate and polyethylene-vinyl acetate copolymer. In sirolimus eluting stens, about 80% of the rapamycin is eluted by 30 days, leaving a polymer-coated metal stent with small drug amounts. In Taxus stents, about 10% of paclitaxel is eluted by 10 days and the rest remains in the polymer for long period [467].

Hypersensitivity reactions have been reported with the use of polymers (Table 4) like those in latex and vinyl gloves as well as with polyurethane and methyl-methacrylate in dentistry[468,469[. The latter has induced labial edema and allergic stomatitis confirmed by patch tests in orthodontic patients [470,471]. Chronic urticaria [472], stomatitis venenata [473] and allergic erythema of the hard palate [474] have been also reported to auto-polymerized acrylic resin. These allergic reactions are usually type IV reactions caused by compounds of low molecular weight that are acting as haptens. They can initiate an allergic reaction when they carried by a protein. For acrylic resins these would be formaldehyde, benzyl peroxide, methyl-methacrylate, and plasticizers such as dibutyl phthalate [475].

Nonbioerodable polymers such as polyurethane polydimethyl siloxane (silicone) and polyethylene terephthalate (Dacron) can promote inflammation when implanted in swine coronary arteries [476-478]. Macrophages, giant cells, tissue damage and fibrosis are seen during subcutaneous implantation of poly-n-butylmethacrylate which is a component of bone cement and the polymer coating of cypher stents [479]. Furthermore, the polyethylene-vinyl acetate compound of the cypher copolymer induces inflammatory reaction in 25% of rabbits when used as an antigen delivery matrix [480]. Cases of immediate and delayed allergic reactions to anionic cellulose polymers carboxymethylcellulose and methyl hydroxyethylcellulose have been reported recently [481].

It should be emphasized that the allergic reactions to latex components can be exacerbated when a variety of foods are ingested. Latex can cross react with the hevemine in fruits and cause an immediate hypersensitivity reaction [482]. The inflammatory and allergic properties of polymers have made their use problematic in gene delivery[483], although polymer-coated gene-delivery stents have been shown in animal studies to be effective for both reporter[484] and therapeutic[485] vector delivery. However, encouraging results have been achieved recently through gene vector delivery from the direct metal alloy surfaces of stents which had been pretreated with polyallylamine bisphosphonate [486].

22. Hypersensitivity to Metals

The majority of intracoronary stents are made from 316L stainless steel which contains nickel, chromium, and molybdenum. Ions from the above metals are eluted through the action of blood, saline, proteins, and mechanical stress.

It has been already known that allergy and inflammatory reactions have occurred in patients with prosthetic valves and other endovascular prostheses [487]. Allergic reactions to metallic implants have been incriminated for postoperative complications such as loosening or formation of new tissue around the metals [488,489]. In a patient with aseptic loosening of an orthopaedic chromium/cobalt alloy and positive patch tests to potassium dichromate, peri-inplantar tissue examination showed oligoclonal T-cell infiltration and Th1-type cytokine expression [490].

Hypersensitivity reactions to nickel occur in up to 17.2% of the population and are the most frequent cause of allergic contact dermatitis [491]. In patients undergoing percutaneous atrial septal defect and patent foramen ovale closure, nickel allergy can be the cause of systemic effects such as chest discomfort, palpitation, and migraine headache with or without aura [492]. It is postulated that local allergic reaction to the implanted device could result in formation of platelet adhesions which could embolize in heart and brain causing chest discomfort and headache [492]. Local nickel allergy from intracardiac devices and subsequent systemic allergic reactions confirmed by patch tests as an allergy to nitinol (nickel-titanium alloy) have necessitated the removal of these devices[493-495].

Reports concerning hypersensitivity reactions to various metals used in orthodontics have been also published [496]. Nickel is the metal which can provoke the most severe responses [497]. Delayed hypersensitivity reactions to nickel and molybdenum might be part of inflammatory process and one of the triggering factors for development of in-stent restenosis [498]. The rate of nickel allergy following initial stent implantation has been estimated [499] to be 9.2%.

Skin clips containing nickel, chromium, molybdenum, cobalt, and titanium can induce allergic reactions and may be the cause of delayed wound healing [500]. Hypersensitivity to molybdenum has been incriminated to induce a syndrome resembling systemic lupus erythematosus [501].

Contact allergy to gold has been associated with increase incidence of restenosis when patients are stented with gold-plated stents and these stents have been abandoned [502]. On the other hand, the titan stent which is a stainless steel stent coated with titanium-nitride oxide (TINOX) can prevent discharge of nickel, chromium and molybdenum and it seems promising in eliminating local allergy and inflammation[503].

23. Delayed Hypersensitivity to DES and Late Coronary Events

Release kinetics of drugs from DES polymers is a complex phenomenon depending on multiple factors. The release varies with the type of polymer, layering, drug to polymer formulation ratio, overcoat, dose density and total amount loaded [504]. Important

determinants for tissue drug accumulation include drug physicochemical properties, distribution of drug in the arterial wall, rate and duration of release, endothelial function and arterial wall condition [505]. Drug release from stents is characterized by an initial fast release followed by sustained slow release [506]. Lipophilic drugs are released slowly allowing. Hydrophilic drugs tend to elute faster into the blood and need higher amounts and shorter duration of delivery in order to achieve optimum local levels [507]. However, in human atherosclerotic intimas, drug release kinetics seems to differ considerably and might be prolonged.

The time of appearance of hypersensitivity events depend on these kinetics and can include immediate reactions (type I), antibody mediated cytotoxic reactions (type II), immune complex mediated reactions (type III), and delayed hypersensitivity reactions (type IV). When hypersensitivity is considered as the cause of DES thrombosis, the time of appearance of hypersensitivity events depends on allergen release kinetics, number and level of the insulting allergens and existence of drug-reactive lymphocytes [508]. Atopic patients with increased propensity to hypersensitivity reactions possess long lasting reactivity due to high frequency of drug-specific lymphocytes, thus potentially making them prone to react again even years after drug avoidance [509].

24. Future Directions Concerning DES

At the present, as it was stated by the FDA, coronary DES remain safe and effective when used in patients according to approved by the agency indications. However, it seems likely that, with these sophisticated devices, cases of mild hypersensitivity reactions to DES might go unreported; thus it is anticipated that many more cases will be encountered in the coming years.

Therefore, in atopic patients, in patients with food allergy and who have already experienced a first Kounis syndrome and are going to have DES implantation, and until further studies characterizing the incidence, the course, the risk of occurrence in a given patient, the circumstances and the definite cause of coronary stent thrombosis will be undertaken, one can make a good case for:

- detailed history taking regarding allergies and drug hypersensitivity reactions, patch-testing,
- antibody testing, macrophage and T-cell activation studies, and desensitization strategies when and where applicable, monitoring the levels of inflammatory mediators after implantation, and considering the use of corticosteroids and mast cell stabilizers since the latter have abrogated late thrombotic events experimentally[510].

Thousands of patients worldwide every year are benefited with DES treatment because it reduces significantly the need of second procedures to treat restenosis. New DES development targeting to prevention of stent thrombosis are under evaluation. Eptifibatite-eluting stents are currently being evaluated in vitro as antiproliferative and antithrombotic

devices [511]. The proposed dimethyl sulfoxide eluting stent which suppresses tissue factor expression and activity, as well as thrombus formation seems to be a novel strategy [512]. Accelerated endothelialization could be achieved with stents loaded with an integrin-binding cyclic Arg-Gly-Asp peptide attracting endothelial progenitor cells [513]. Again, stents coated with CD34 antibodies can attract endothelial progenitor cells and accelerate endothelialization5 [514]. An interesting new approach for DES is the use of peroxisome proliferator-activated receptor-γ agonists which diminish inflammation and enhance endothelialization [515]. Hypersensitivity to DES components and the Kounis syndrome should be always considered as a possibility. New DES combining drugs with anti-inflammatory, antiallergic, and/or antithrombotic agents might be the solution of the problem.

25. Management of Kounis Syndrome

Treatment of Kounis syndrome is directed firstly towards the alleviation of the acute allergic insult and secondly the therapy of the acute coronary event. The first is achieved by administration of H1 and H2 blockers together with the administration of corticosteroids. This treatment alone can be successful in cases of type I Kounis syndrome without any additional effort. Administration of corticosteroids is mandatory because these drugs:

- Suppress the release of arachidonic acid from cell membrane and inhibit eicosanoid biosynthesis (via phospholipase A2 inhibition)
- Induce cell apoptosis and reduce inflammation via up-regulation of death receptor CD95 and its ligand CD95L
- Induce synthesis of proteins called annexins (lipocortins) which modulate inflammatory cell activation, adhesion molecule expression and transmigratory and phagocytic functions.

In the cases where type I Kounis syndrome progresses to acute myocardial infarction with increased cardiac enzymes and troponins and in the cases where the acute allergic episode induces type II Kounis syndrome with plaque erosion or rupture manifesting as an acute myocardial infarction then, antiallergic treatment is combined with classical treatment of acute myocardial infarction.

26. Conclusion

So far, attempts have been made to counteract the actions of inflammatory mediators by using, experimentally, mediator antagonists, inhibitors of mediator biosynthesis and mediator receptor blockers [516]. However, in the medical armamentarium drugs such as sodium nedocromil, sodium cromoglycate, ketotifen, lodoxamide and others which are currently used experimentally that are interfering with mast cell stabilization (Table 8, Table 9) might be useful tools in the future. There is also considerable evidence today that the polyphenolic plant compounds such as flavonoids that block basophils and mast cells and inhibit mediator

release [517] may be used. In a recent study [518], anti-lgE therapy with humanized lgG1 nonoclonal antibodies was recognized and masked the region of mast cell surface responsible for IgE binding thus offering protection against mast cell degranulation. Following this study, it has been suggested [519] that in atopic patients, who produce large amounts of interleukin-4 and interleukin-13, treatment with anti-lL-4Rα antibodies might inhibit acute and severe allergic episodes. All these agents and natural molecules capable to stabilize and protect mast cell membrane could prevent also acute thrombotic events, at least in some instances. It has been stated [307] that "a new possibility emerges for the prevention of the progression of coronary plaques to unstable lesions, and that is; inhibition of mast cell degranulation". This has already been achieved experimentally by Nemmar et al. [510]. These investigators managed to abrogate late thrombotic events by stabilizing mast cell membrane with sodium cromoglycate and reducing inflammation with dexamethasone. Clinical reports have also showed that corticosteroids can reduce the risk of myocardial infarction. For example, in patients with no indication of severe asthma , the risk of myocardial infarction was 22% lower with the use of inhaled corticosteroids and in patients with severe asthma the risk of myocardial infarction was 81% lower with the use of inhaled corticosteroids [520]. Corticosteroids may be considered as a treatment of choise for patients with refractory vasospastic angina, particularly when the patient has an allergic tendency, such as bronchial asthma [521].

Does, therefore, Kounis syndrome represent a magnificent natural paradigm and nature's own experiment in a final trigger pathway implicated in cases of coronary artery spasm and plaque rupture?

Whether this question will be answered in future clinical trials is unknown. If so, case selective mast cell surface membrane protection and stabilization should be considered a potential therapeutic strategy for patients prone to food-induced allergy, for allergic patients to stent components, for atopic patients in general and for patients who have already experienced a first Kounis syndrome.

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