Overview of Coronary Flow Phenomenon in Patients with Acute Coronary Syndrome

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ABSTRACT

Acute coronary syndrome (ACS) comprises a spectrum of clinical conditions which initiated by rupture of an atherosclerotic coronary plaque with overlying acute thrombosis.Recent research in the last decade has changed our view ACS from a mere lipid deposition to an inflammatory disease; from ACS exclusively due to plaque rupture to the novel definitions of plaque erosion or calcified nodule; from the notion of a superimposed thrombus with necessary lethal consequences to the concept of healed plaques and thrombus contributing to plaque progression. The coronary thrombus may be completely occlusive, as is frequently seen in ST-segment elevation myocardial infarction (STEMI), or non-occlusive, as can be observed in unstable angina or non-ST-elevation myocardial infarction (UA/NSTEMI). Thrombus on preexisting plaque, dynamic obstruction from coronary spasm or Prinzmetal's angina, progressive mechanical obstruction, inflammation and/or infection, and secondary unstable angina due to global myocardial oxygen supply and demand mismatch. Slow coronary flow (SCF) phenomenon is a coronary microvascular disease diagnosed by detection of delayed dyeopacification in coronary arteries during an angiography in the lack of obstructive coronary artery disease. The incidence of SCF has been reported to be approximately 1-7% in patients who undergo a diagnostic coronary angiography due to suspected coronary artery disease.In the absence of substantial epicardial coronary stenosis, the coronary slow flow phenomenon (CSFP) is an angiographic clinical entity defined by delayed distal artery opacification. The extensive usage of ECG markers in numerous therapeutic contexts may be influenced by P-wave inscriptions.Thus, the aim of the present study to review coronary flow phenomenon in patients with acute coronary syndrome.

Keywords: Plaque Progression; Slow Coronary Flow Phenomenon; Acute Coronary Syndrome.

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INTRODUCTION

Plaque rupture (or fissure) caused most fatal myocardial infarctions. These findings led to the notion of the vulnerable or high-risk plaque characterized by a large central lipid core, an abundance of inflammatory cells, a paucity of smooth muscle cells (SMCs), and a thin fibrous cap. These observations spawned the widely accepted concept that instability of coronary atheromata resulted from fissuring of a thin-capped fibroatheroma caused by a weakening of its collagen structure wrought by inflammatory mechanisms. About half of ACS occurred in the presence of normal levels of C-reactive protein (CRP), a marker of inflammation **(1)**.

This concept stimulated manifold attempts to develop methods to detect the vulnerable plaque, a quest predicated on the postulate that local interventions could preclude plaque thrombosis and possibly prevent ACS. However, attempts

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to identify vulnerable plaques proved disappointing because of their low predictive value **(2)**.

Pathological studies of human coronary arteries show that plaque rupture occurs commonly in individuals without symptomatic ACS. Moreover, <5% of plaques with the features of thin-capped fibroatheroma as determined by intravascular ultrasound interrogation actually cause clinical events during over 3 years of follow-up **(3)**.

Thus, most thin-capped fibroatheroma are clinically quite stable, a realization that renders vulnerable plaque a misnomer. Indeed, plaques with thin-capped fibroatheroma morphology as assessed by radiofrequency backscatter data from intravascular ultrasound (virtual histology) commonly convert to an apparently more stable character during a 1-year follow- up period. Such evolution in plaques may reflect mutability during the natural history of human atherosclerosis but could also reflect adherence of many of these patients to a contemporary secondary prevention regimen, including smoking cessation, statins, and agents that target the renin-angiotensin axis **(4)**.

About half of ACS occurred in the presence of normal levels of CRP, a marker of inflammation **(5)**. Another study using optical coherence tomography (OCT) demonstrated that among patients with ACS and plaque rupture, two thirds of patients had imaging evidence of inflammatory cell infiltration in the region of the ruptured fibrous cap but one third did not and the latter had lower levels of CRP.In addition, plaque erosion causes up to a third of ACS in the current era**(Figure 1)**. Finally, about one fifth of ACS occur in the apparent absence of coronary thrombosis, suggesting that functional alterations beyond thrombus formation can contribute to ACS pathogenesis **(6)**.

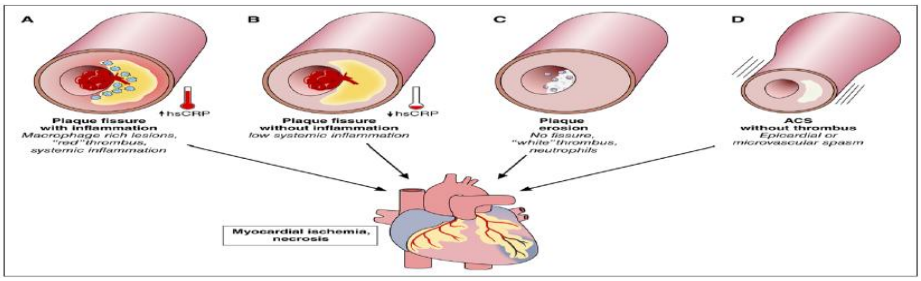

Figure (1): Four diverse mechanisms cause acute coronary syndromes (ACS).

Plaque rupture with systemic inflammation:

Liuzzo et al. (7) have implicated systemic inflammation in ACS as assessed by the biomarker CRP. Laboratory studies and observations on human plaques point to inflammatory mechanisms as key regulators of the fragility of the fibrous cap and of the thrombogenic potential of the lipid core **(Figure 2)**. Macrophages likely pave the way for the rupture of the fibrous cap of the plaque: When activated, these cells elaborate enzymes that degrade all components of the arterial extracellular matrix. These enzymes include matrix metalloproteinases and certain cathepsins. Multiple mechanisms regulate these matrix-degrading proteinases: transcription, translation, activation of zymogen precursors, and balance with endogenous inhibitors such as the tissue inhibitors of matrix metalloproteinases or the cystatins. Thus, increased amounts of activated proteinases or reduced levels of their corresponding inhibitors can enhance breakdown of the extracellular matrix of plaque **(8)**.

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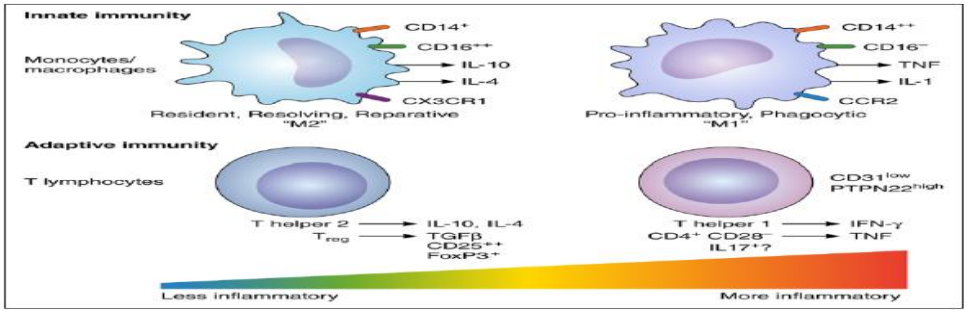

Figure (2): Imbalance in adaptive immune pathways can modulate atherosclerotic plaque activity.

Plaque rupture without systemic inflammation:

When plaque rupture occurs in the absence of systemic inflammatory activation, other mechanisms may contribute to pathogenesis, including extreme emotional disturbance ranging from external events of short duration such as earthquakes and a beloved team's loss of a football (soccer) match to acute manifestations of more long-term emotional disturbances. Intense physical exertion and local mechanical stress at the level of the artery wall, either increased circumferential stress or reduced shear stress, may also predispose to plaque rupture **(9)**.In addition, subclinical inflammation in the microenvironment of the culprit stenosis might compound the chain of events leading to coronary instability, although the triggers for and effectors of such local inflammation may differ from those that operate in patients with systemic inflammation **(10)**.

Local changes in the equilibrium between esterified and free cholesterol might promote plaque rupture **(Figure 3)**. Cholesterol crystal formation in the lipid core could heighten the risk of plaque rupture and thrombosis and can coactivate the inflammasome, an intracellular multimeric complex that generates active IL-1βand IL-18 **(11)**.

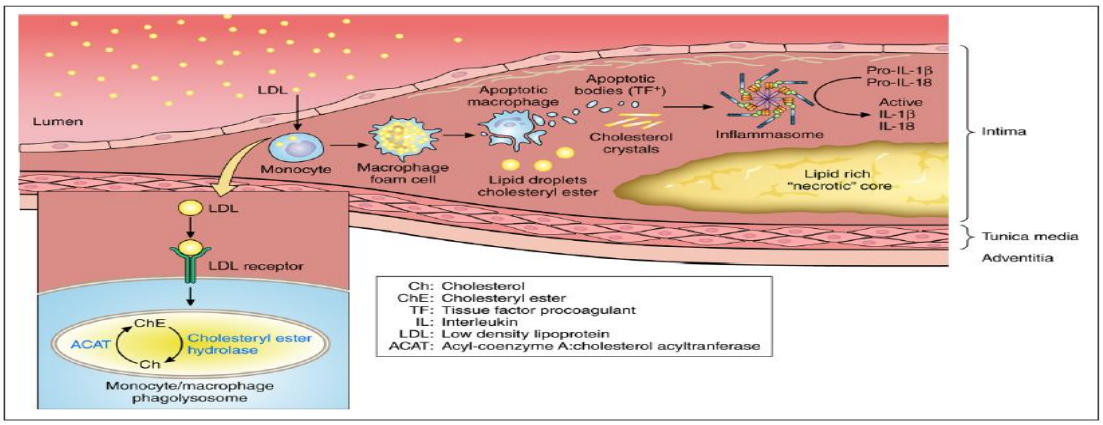

Figure (3): Cholesterol crystals activate local innate immune pathways in the atherosclerotic plaque.

Plasma low-density lipoprotein can enter the arterial wall and accumulate in mononuclear phagocytes via scavenger receptors. Lipid-laden macrophage foam cells can die, contributing to the accumulation of extracellular cholesteryl ester and cholesterol monohydrate crystals in the lipid-rich necrotic core of the plaque. The dying macrophages can also release apoptotic bodies and microparticles that contain the potent procoagulant tissue factor (TF+). The

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cholesterol crystals can coactivate the inflammasome, an intracellular supramolecular structure that generates the biologically active forms of the proinflammatory cytokines interleukin (IL)-1βand IL-18. Large crystals might also cause mechanical disruption of the fibrous cap.

OCT has colocalized cholesterol crystals in human coronary arteries with thin-capped plaques.The development of micro-OCT with a 2-µm resolution may shed new light on this potential mechanism of instability by assessing its occurrence in vivo.Cholesterol crystals might also theoretically resist plaque rupture by increasing the stiffness of the lipid pool, although this mechanism probably contributes little to plaque stability **(12)**.The role of calcium mineral as a causal factor in ACS remains controversial. Large collections of calcified tissue do not augment the biomechanical instability of plaques or associate with lesions that provoke ACS.Small foci of calcification within the atherosclerotic intima, some causing spotty calcification visible on computed tomography, can also introduce biomechanical inhomogeneities that can favor plaque destabilization **(13)**.

Plaque erosion:

Lüscher (14) suggested that mechanisms of plaque disruption distinct from macrophage-driven rupture of the fibrous cap of plaque can commonly cause ACS. The mechanism of plaque thrombosis described by pathologists as superficial erosion appears not to involve inflammation mediated by macrophages, as in the case of fibrous cap fracture. Superficial erosion complicates lesions with a distinct epidemiology and morphology and involves pathophysiological mechanisms that differ from rupture of the fibrous cap. Indeed, neutrophil activation seems to play a pivotal role in thrombosis due to plaque erosion**(Figure 4)**. In postmortem coronary artery specimens, luminal thrombi superimposed on eroded plaques contain many more myeloperoxidase-positive cells than thrombi associated with ruptured plaques**(14)**.

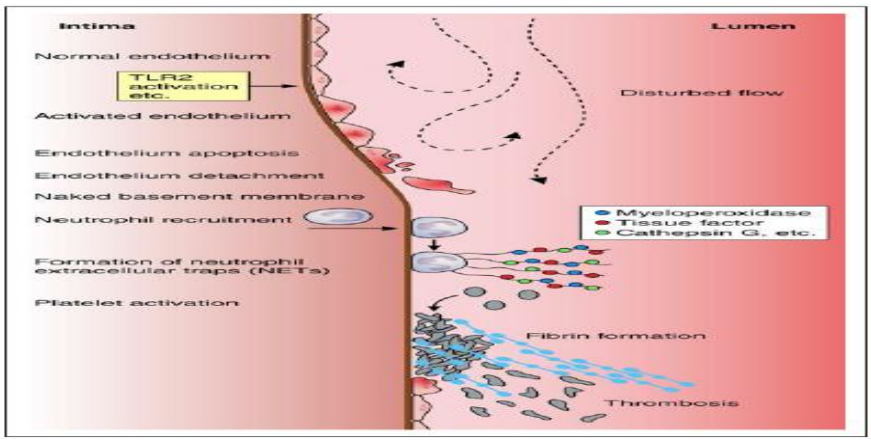

Figure (4):Pathways implicated in arterial thrombosis caused by superficial erosion. Stimuli such as disturbed flow or engagement of innate immune receptors such as Toll-like receptor-2 (TLR2) can activate the endothelial cells that line the arterial intima. These cells can undergo cell death, eg, by apoptosis, depicted by the cell with the interrupted membrane and pyknotic nucleus. Injured or dying endothelial cells can desquamate, uncovering the basement membrane. Neutrophils attracted by chemokines produced by activated endothelial cells can congregate on the denuded intima and can in turn degranulate and die, releasing neutrophil extracellular traps (NETs). These strands of extruded DNA can bind the contents of

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the neutrophil granules and other proteins, eg, myeloperoxidase or tissue factor. The NETs can constitute a solid-state reactor that generates oxidants such as hypochlorous acid and stimulates coagulation locally. Platelets interacting with the basement membrane can activate, release their granular contents, including chemokines that can recruit further leukocytes, and form the nidus of a white thrombus.

Yahagi et al. (15) suggested that fatal plaque erosion associates more commonly with hypertriglyceridemia, diabetes mellitus, female sex, and old age. The morphology of lesions that produce thrombosis caused by superficial erosion differs radically from the features associated with fibrous cap rupture. Superficially eroded lesions contain few macrophages or T lymphocytes, inflammatory cells considered pathogenic in plaque rupture. Rather than depleted collagen, the lesions associated with superficial erosion contain abundant proteoglycan and glycosaminoglycans.

Instead of a paucity of SMCs, eroded lesions can contain abundant arterial SMCs. Plaques complicated by fibrous cap fracture typically harbor large necrotic, lipid-rich cores. In contrast, the more fibrous lesions associated with superficial erosion generally lack prominent central lipid cores.A loss of intimal endothelial cells defines lesions that provoke thrombosis by the mechanism denoted as superficial erosion **(16)**.

Quillard et al. (17) have implicated engagement of the innate immune receptor Toll-like receptor 2 in promoting the susceptibility of endothelial cells to apoptotic stimuli. Hyaluronic acid, a prominent constituent of the extracellular matrix of eroded lesions, could serve as an endogenous ligand of Toll-like receptor 2, implicated in promoting endothelial cell apoptosis.

Experiments that have evaluated gain and loss of Toll-like receptor 2 function in mice support these observations.Indeed, hyaluronan and its receptor, CD44, colocalize along the plaque/thrombus interface in eroded plaque but not in ruptured or stable plaque. Accumulation of hyaluronan and expression of CD44 along the plaque/thrombus interface of eroded plaques may promote de-endothelization, resulting in CD44-dependent platelet adhesion and subsequent thrombus formation, mediated in part by a direct action of hyaluronan on fibrin polymerization **(18)**.

Thrombosis caused by superficial erosion occurs in 2 phases. The first hit, mediated, for example, by Toll-like receptor 2, would jeopardize endothelial viability or adherence, leading to a breach in the integrity of the endothelial monolayer overlying the atherosclerotic plaque. The denuded patch on the intimal surface would then attract platelets that could undergo activation by contact with collagen and other components of the arterial extracellular matrix usually protected from the blood compartment by the endothelial lining of the intima. The second hit, mediated by the release of granular contents from activated platelets and the local production of chemoattractants for polymorphonuclear leukocytes, would beckon these granulocytes to join the platelets at local sites of endothelial denudation. In turn, the activation of polymorphonuclear leukocytes could generate structures known as neutrophil extracellular traps, made up of strands of unwound DNA released by the dying granulocytes.This uncoiled DNA becomes decorated with proteases, tissue factor, and pro-oxidant enzymes that could propagate local

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amplification of an innate immune response, thrombin activation, and fibrin generation and entrap further platelets and fibrin strands in an evolving thrombus **(19)**.

This hypothetical scenario posits a mechanism of thrombosis that is independent of the chronic inflammatory cells typically implicated in fibrous cap rupture: macrophages and T lymphocytes. Rather, this schema implicates different arms of innate immunity in thrombus initiation, propagation, and stabilization. These mechanistic differences with fibrous cap fracture have potential therapeutic implications **(20)**.

Plaque without thrombus:

In patients with ACS without plaque thrombus, a functional alteration of coronary circulation likely causes acute ischemia involving large epicardial coronary arteries or the coronary microcirculation. Epicardial coronary vasospasm may occur in patients in whom coronary angiography does not demonstrate an obstructive atherosclerotic plaque **(21)**. In the CASPAR study (Coronary Artery Spasm in Patients With Acute Coronary Syndrome), coronary angiography failed to show culprit lesions in ≈30% of patients with suspected ACS. Intracoronary acetylcholine administration elicited coronary spasm in nearly 50% of these patients. Similar findings pertained to a Japanese population.Coronary artery spasm also may cause coronary instability in patients with obstructive atherosclerosis **(22)**.

Indeed, a classic study by **Bertrand et al. (23)** found that ergonovine induced spasm in 20% of patientswith recent myocardial infarction and in 40% of patients with unstable angina. In another study, acetylcholine induced spasm in 20% of white patientsand in 60% of patients with myocardial infarctionwithin the previous 14 days.Japanese people have ahigher prevalence of coronary spasm than whites forunknown reasons **(24)**.

Microvascular spasm also can cause myocardial ischemia.This mechanism likely operates in patients with Takotsubo cardiomyopathy,which frequently occurs in the absence of obstructive atherosclerosis, although ≈15% of these patients exhibit concomitant obstructive atherosclerosis **(25)**.

Microvascular spasm can also contribute to ischemia in the face of angiographically normalappearing epicardial coronary arteries. Microvascular ischemia often manifests as angina pectoris but can also cause non–ST-segment–elevation ACS as defined by electrocardiographic alterations and biomarker evidence of myocyte injury**(Figure 5)**.Smooth muscle cells in the media layer of coronary arterial vessels can contract in response to stimuli from the autonomic nervous system (eg, acetylcholine), local responses to autacoids (eg, histamine), and pharmacological stimuli. Local hyperreactivity of smooth muscle cells mediated mainly by enhanced Rho kinase activity results in spasm in response to constrictor stimuli. Normal endothelial cells produce endogenous vasodilator substances, including nitric oxide (NO). Coronary spasm can also contribute to plaque instability by causing endothelial damage, as shown in an infarction-prone strain of the Watanabe heritable hyperlipidemic rabbit. Either macrovascular or microvascular spasm can result from impaired vasodilatation or from vasoconstrictor stimuli acting on hyperreactive vascular SMCs **(26)**.

Shimokawa et al. (27) demonstrated SMC hyperreactivity in a coronary segment in pigs after adventitial exposure of a coronary segment to an inflammatory stimulus (IL-1β).

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Shimokawa (28) suggested that an increase in Rhokinase activity was a major mechanism of SMC hyperreactivity.

Perivascular fibrosis in the coronary microvasculature can contribute to myocardial ischemia. This observation highlights the potential contribution of fixed structural changes in coronary arterioles beyond impaired endothelial vasodilator function as a contributor to myocardial ischemia in the absence of obstructive disease of the epicardial coronary arteries **(29)**.

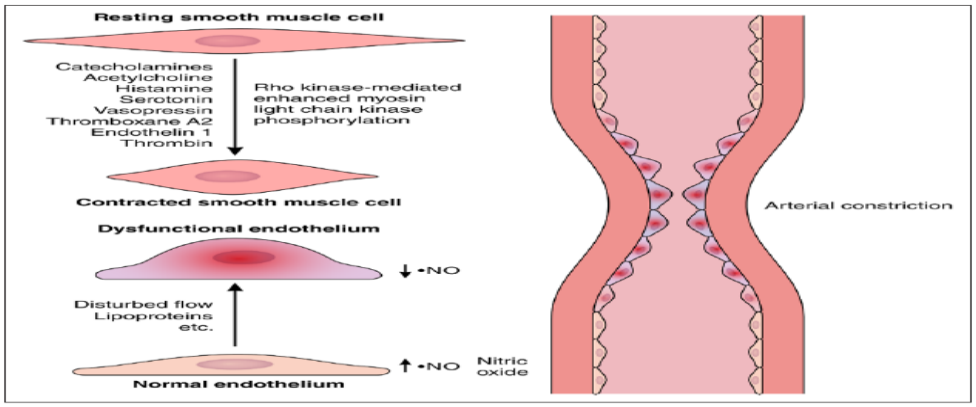

Figure (5): Cellular mechanisms of arterial epicardial spasm relevant to acute coronary syndrome pathogenesis.

Slow coronary flow phenomenon

The coronary slow flow phenomenon (CSFP) is an angiographic clinical entity, characterized by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis. Although it is well-known to interventional cardiologists for approximately four decades, the pathogenic mechanisms are incompletely understood. Rather than representing a simple angiographic curiosity, CSFP has direct clinical implications, as it has been linked to clinical manifestations of myocardial ischemia, lifethreatening arrhythmias, sudden cardiac death, and recurrent acute coronary syndromes **(30)**.

Karakayaet al. (31) suggested that a combination of morphological and functional abnormalities in small vessels and epicardial coronary arteries accounts for the etiology of CSFP. Another feature of CSFP, probably requiring special consideration is its frequent occurrence in association with more widespread vascular abnormalities. Cerebral blood flow velocity is significantly lower in patients with CSFP. Endothelial abnormality appears to be a generalized process affecting both coronary and peripheral vasculature. Furthermore, in intravascular ultrasound investigation, **Camsari et al. (32)** found that there was a significant correlation between coronary intima-media thickness (IMT) and carotid IMT.

In contrast, aortic distensibility and aortic strain, another predictor of subclinical atherosclerosis, were lower in patients with CSFP. It is reasonable to assume that early atherosclerosis is not restricted to the coronary circulation but also extends to large peripheral conduit arteries in patients with CSFP **(33)**. **Wang et al. (34)** hypothesized that CSFP is not an isolated local observation but may be part of generalized vascular disturbance. CSFP may be caused by the interplay between local features coronary arteries and systemic pathophysiologic factors.

Although a number of formal definitions have been proposed, the CSFP essentially consists of a delay in the

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progression of the contrast injected into the coronary arteries during coronary angiography. This condition, which may affect one or all coronaries, was originally described by. Since then it has been accepted as an independent clinical entity, which is called 'CSFP', 'coronary slow flow syndrome' 'syndrome Y', or "primary" coronary slow flow **(35)**.

Importantly, 'primary' CSFP should be distinguished from the delay in the contrast progression in the context of coronary reperfusion therapy such as angioplasty or stenting for acute myocardial infarction, or other "secondary" causes of coronary slow flow. These include coronary artery ectasia, coronary artery spasm, valvular heart disease, or connective tissue disorders **(36)**.

Incidence:

CSFP is observed in approximately one percent of the patients undergoing coronary angiography, especially in patients presenting with acute coronary syndrome (usually unstable angina). In the Thrombolysis In Myocardial Infarction (TIMI)-IIIA study, 4% of patients presenting as unstable angina but with normal/insignificant epicardial coronary artery disease (CAD) showed impaired angiographic filling suggestive of CSFP **(37)**. **Mangieri et al. (38)** reported an incidence of 7% of this phenomenon in patients suspected to have CAD, however the documentation of slow flow was visual without any objective criteria.

Pathogenic mechanisms:

The pathophysiological mechanisms of CSFP remain uncertain. The coronary circulation is traditionally considered as a two-tier model. The first tier consists of epicardial vessels, which are also referred to as "conductance vessels" as these do not pose any resistance to blood flow. The second compartment consists of "small vessels" of <400 µm ("resistive vessels") which primarily regulate myocardial blood flow in the absence of any significant obstructive epicardial stenosis **(39)**.

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Yaymaci et al. (41) investigated the presence of stress-induced myocardial ischemia in patients with CSFP by measuring two metabolic indicators of ischemia i.e. coronary arteriovenous oxygen content difference and lactate production. Although majority of patients developed anginal pain with atrial pacing, only few (17%) revealed evidence of metabolic ischemia. Thus, angina pectoris in most patients with CSFP does not originate from myocardial ischemia as demonstrated by metabolic parameters.

Sezgin et al. (42)reported evidence of endothelial dysfunction in patients with CSFP using simple method of measuring flow-mediated vasodilation (FMD) of the brachial artery. It has been suggested that FMD is predominantly due to endothelial release of nitric oxide (NO). There was a strong and inverse relationship between CTFC and percentage of FMD in patients with CSFP thereby suggesting that endothelial NO activity is impaired in these patients.**Sezginet al. (43)** demonstrated that baseline and peak exercise endothelin-1 plasma

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concentrations were higher and nitric oxide plasma concentrations were lower in slow coronary flow patients. In addition, patients with slow coronary flow had raised level of plasma homocysteine and asymmetric dimethylarginine, a nitric oxide synthase inhibitor, both of which have a detrimental effect on endothelial function. Decreased adiponectin concentrations and paraoxonase activity, two significant markers of endothelial dysfunction have also been shown to be responsible for the etiopathogenesis of CSFP **(44)**.

Endothelin-1 (ET-1) and NO are important molecules that modulate vasodilatory response to stress (rapid atrial pacing/exercise). Recently published studies have highlighted the imbalance between ET-1 and NO release in patients with CSFP as compared to controls with normal coronary flow**.**Furthermore, in patients with CSFP, coronary sinus ET-1 levels also increased significantly as compared to femoral artery ET levels. Even correlation of ET-1 levels and intimal thickness of coronary artery using IVUS has been reported. It is possible that CSFP results from imbalance of ET-1, a potent vasoconstrictor leading to deregulation of vascular tone even in the very early stages of plaque formation **(45)**.

Clinical manifestations:

CSFP is a frequent angiographic observation, with a reported incidence of 1%-7% in patients undergoing diagnostic angiography because of clinical suspicion of cardiovascular disease. Clinically, this phenomenon occurs most commonly in young men and smokers, and patient admitted with acute coronary syndrome **(36)**.

The clinical course is complicated, with over 80% of patients experiencing recurrent chest pain, most occurring at rest, necessitating readmission to the coronary care unit in almost 20% of affected patients. Most importantly, coronary slow flow has been described to be associated with life-threatening arrhythmias and sudden cardiac death, probably due to increased QTc dispersion in these patients **(33)**.

Further, **Yilmaz et al. (46)**delineated the clinical and laboratory features of CSFP compared to the control subjects without CSFP. Metabolic syndrome was more frequent in CSFP in the presence of higher total cholesterol, low-density lipoprotein-cholesterol, fasting glucose and body mass index levels. **Ozcanet al. (47)** observed that insulin resistant states and impaired glucose tolerance correlate with CSFP occurrence. A common underlying pathophysiologic mechanism of the metabolic syndrome and CSFP may be endothelial dysfunction.

Diagnosis and evaluation:

CSFP in coronary angiographic studies was initially described subjectively by visual judgement. A semiquantitative assessment of coronary blood flow is the thrombolysis in myocardial infarction (TIMI) flow grade classification, which reflects the speed and completeness of the passage of the injected contrast through the coronary tree **(48)**. Currently, by using CTFC as a quantitative index of coronary flow, coronary angiography is the only tool for the diagnosis and assessment of CSFP. Yet, owing to its invasiveness, this method does not permit long-term clinical follow-up and dynamic treatment evaluation. Recent advances of transthoracic Doppler echocardiography (TTDE) have enabled the non-invasive demonstration of coronary flow patterns in the left anterior descending (LAD) coronary artery **(40)**.

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Wang and Nie(49) measured coronary flow in the distal LAD using TTDE technique with a high success rate (92.3%) **(Figure 6)**. Patients with CSFP exhibited lower coronary diastolic velocities of LAD, which was negatively correlated with CTFC **(Figure 7)**. TTDE may provide a useful tool for the monitoring of treatment effect and long-term follow-up for CSFP.

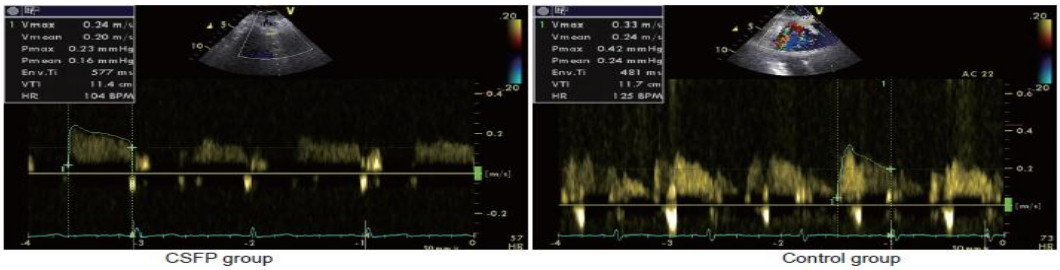

Figure (6): Representative echocardiographic images in the CSFP and control groups

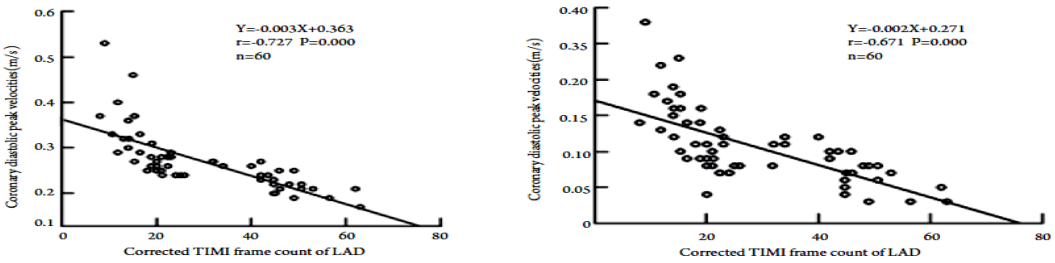

Figure (7): Correlations between corrected TIMI frame count (CTFC) of LAD and coronary diastolic peak and mean velocities

Therapy:

There are no definite treatment modalities for patients with CSFP. Conventional antianginal therapy is of limited value in the chronic management in these patients. Nitrates are ineffective as their biotransformation to active metabolite is diminished due to deficiency of required enzymes in coronary microvessels as compared to larger epicardial coronary arteries **(21)**.

Demirkol et al. (50)observed improvement in myocardial perfusion with dipyridamole infusion using myocardial perfusion SPECT.

Long-term oral therapy with dipyridamole was assessed by **Kurtoglu et al. (51)** in an open-label fashion. Coronary flow returned to normal levels in majority of the vessels as adjudged by using CTFC. This was accompanied with complete relief from chest pain in two-third of patients and decrease in symptoms in the remaining.

Conventional calcium L-channel blockers (diltiazem/verapamil) are of limited value in alleviating symptoms. This is perhaps due to absence of voltage-gated L-type calcium channels in microvessels, as shown by **Perez-Reyes (52)**in the animal models. Instead, the microvascular tone may appear to rely on other types of voltage-gated calcium channels, possibly of the T-type.

Beltrame et al. (53)assessed the acute and long-term clinical benefits of mibefradil in patients with CSFP by exploring its beneficial effects on microvessels. There was significant acute angiographic improvement in coronary flow indices with this drug. CSFP was abolished in approximately threefourth of the vessels at 30 min after the drug intake. Interestingly, the improvement in flow indices occurred primarily in vessels with CSFP as compared to vessels with normal epicardial flow.

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In a randomized, double blind, placebocontrolled, cross-over study, there was substantial reduction in frequency of angina by 56%, episodes of prolonged angina by 74%, and sublingual nitrate consumption by 59% along with improvement in physical quality of life. Since the drug has been formally withdrawn, these observations may stimulate further research with similar molecules. A three-dimensional pharmacophore model consisting of three hydrophobic regions, one hydrogen bond acceptor and one positive ionizable region has been hypothesized for T-type calcium channel blockers **(54)**.

Thus, CSFP continues to intrigue the clinicians. It appears to represent a heterogeneous group of disorders. In some, it may represent an early stage of atherosclerosis with endothelial dysfunction and in others, it may indicate microvascular dysfunction or other unknown disorders **(55)**.

Despite good prognosis of CSFP patients, the subsequent progress is frequently characterized by remitting, relapsing anginal episodes resulting in considerable impairment in quality of life. Unfortunately, currently available antianginal agents are of limited clinical value. It was shown that dipyridamole and mibefradil, which both influence functional obstruction in arteries <200 µm, normalized CTFC but nitroglycerine, which dilates arteries with diameters >200 µm, did not. Importantly, statins appear beneficial for patients with CSFP, likely in part due to their anti-inflammatory properties **(56)**.

Guneset al. (57)demonstrated that nebivolol can both improve endothelial function and markedly ameliorate symptoms, thereby improving quality of life in patients with CSFP. Besides its beta-receptor blocking activity, nebivolol can cause endothelium-dependent vasodilatation through increased nitric oxide release.

CONCLUSION:

It is challenging to draw a definite conclusion about the impact of SCF on P wave and QT interval given the numerous effective electrocardiogram (ECG) components. However, it is established that in individuals with acute coronary syndrome and sluggish coronary flow phenomena, QT interval and PWD are related.

No Conflict of interest.

REFERENCES:

1- **Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R.** Concept of vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol 2010; 30: 1282–92.

2- **Motoyama S, Ito H, Sarai M, Kondo T, Shaw LJ, Ozaki Y, Narula J.** Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015; 66: 337–346.

3- **Stone GW, Maehara A, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators.** A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011; 364: 226–235.

4- **Kubo T, Maehara A, Mintz GS, Doi H, Moses JW, Stone GW, Leon MB.** The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. J Am Coll Cardiol 2010; 55: 1590–1597.

5- **Cristell N, Cianflone D, Durante A, Moretti L, Li H, Uren NG, Hu D, Maseri A.** High-sensitivity C-reactive protein is within normal levels at the very onset of first ST-segment elevation acute myocardial infarction in 41% of cases: a

eISSN 1303-5150

multiethnic case-control study. J Am Coll Cardiol 2011; 58: 2654–2661.

6- **Scalone G, Niccoli G, Refaat H, Trani C, Crea F.** Not all plaque ruptures are born equal: an optical coherence tomography study. Eur Heart J Cardiovasc Imaging, 2016.

7- **Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A.** The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. N Engl J Med 1994; 331: 417–424.

8- **Schönbeck U, Mach F, Sukhova GK, Murphy C, Bonnefoy JY, Fabunmi RP, Libby P.** Regulation of matrix metalloproteinase expression in human vascular smooth muscle cells by T lymphocytes: a role for CD40 signaling in plaque rupture? Circ Res 1997; 81: 448–454.

9- **Koskinas KC, Sukhova GK, Libby P, Edelman ER, Feldman CL, Stone PH.** Thin-capped atheromata with reduced collagen content in pigs develop in coronary arterial regions exposed to persistently low endothelial shear stress. Arterioscler Thromb Vasc Biol 2013; 33: 1494–1504.

10- **Chatzizisis YS, Coskun AU, Jonas M, et al.** Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007; 49: 2379-93.

11- **Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nuñez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E.** NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010; 464: 1357–1361.

12- **Nakamura S, Inami S, Murai K, Takano M, Takano H, Asai K, Yasutake M, Shimizu W, Mizuno K.** Relationship between cholesterol crystals and culprit lesion characteristics in patients with stable coronary artery disease: an optical coherence tomography study. Clin Res Cardiol 2014; 103: 1015–1021.

13- **Ruiz JL, Weinbaum S, Aikawa E, Hutcheson JD.** Zooming in on the genesis of atherosclerotic plaque microcalcifications. J Physiol 2016; 594: 2915–2927.

14- **Lüscher TF.** Substrates of acute coronary syndromes: new insights into plaque rupture and erosion. Eur Heart J 2015; 36: 1347–1349.

15- **Yahagi K, Kolodgie FD, Lutter C, Mori H, Romero ME, Finn AV, Virmani R.** Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. Arterioscler Thromb Vasc Biol 2017; 37: 191–204.

16- **Hansson GK, Libby P, Tabas I.** Inflammation and plaque vulnerability. J Intern Med 2015; 278: 483–493.

17- **Quillard T, Araújo HA, Franck G, Shvartz E, Sukhova G, Libby P.** TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. Eur Heart J 2015; 36: 1394–1404.

18- **Franck G, Mawson T, Sausen G, Salinas M, Croce KJ, Libby P.** Flow perturbation mediates neutrophil recruitment and potentiates endothelial injury via TLR2 in mice: implications for superficial erosion. Circ Res 2017; 121: 31–42.

19- **Döring Y, Soehnlein O, Weber C.** Neutrophil extracellular traps in atherosclerosis and atherothrombosis. Circ Res 2017; 120: 736–743.

20- **Crea F and Libby P.** Acute coronary syndromes: The way forward from mechanisms to precision treatment. Circulation 2017; 136: 1155-66.

21- **Sato K, Kaikita K, Nakayama N, Horio E, Yamabe H, Ogawa H.** Coronary vasomotor response to intracoronary

acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: analysis of a single-center study over 20 years. J Am Heart Assoc 2013; 2: e000227.

22- **Bertrand ME, LaBlanche JM, Tilmant PY, Thieuleux FA, Delforge MR, Carre AG, , Laurent JM.** Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. Circulation 1982; 65: 1299–1306.

23- **Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, Mongiardo R, Cianflone D, Sanna T, Sasayama S, Maseri A.** Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction. Circulation 2000; 101: 1102–1108.

24- **Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Ford I, Ruschitzka F, Prasad A, Lüscher TF.** Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med 2015; 373: 929–938.

25- **Arrebola-Moreno AL, Arrebola JP, Moral-Ruiz A, Ramirez-Hernandez JA, Melgares-Moreno R, Kaski JC.**Coronary microvascular spasm triggers transient ischemic left ventricular diastolic abnormalities in patients with chest pain and angiographically normal coronary arteries. Atherosclerosis 2014; 236: 207–214.

26- **Shimokawa H, Tomoike H, Nabeyama S, Yamamoto H, Araki H, Nakamura M, Ishii Y, Tanaka K.** Coronary artery spasm induced in atherosclerotic miniature swine. Science 1983; 221: 560–562.

27- **Shimokawa H.** Williams Harvey Lecture: importance of coronary vasomotion abnormalities: from bench to bedside. Eur Heart J 2014; 35: 3180–3193.

28- **Dai Z, Aoki T, Fukumoto Y, Shimokawa H.** Coronary perivascular fibrosis is associated with impairment of coronary blood flow in patients with non-ischemic heart failure. J Cardiol 2012; 60: 416–421.

29- **Horjeti B, Goda A.** Acute ischemia manifestation in a patient with coronary slow flow phenomenon. J Electrocardiol 2012; 45: 277-9.

30- **Karakaya O, Koçer A, Esen AM, et al.**Impaired cerebral circulation in patients with slow coronary flow. Tohoku J Exp Med 2011; 225: 13-6.

31- **Camsari A, Ozcan T, Ozer C, et al.** Carotid artery intima-media thickness correlates with intravascular ultrasound parameters in patients with slow coronary flow. Atherosclerosis 2008; 200: 310-4.

32- **Arat N, Altay H, Sabah I.** Elastic properties of aorta are impaired in patients with slow coronary flow phenomenon. Indian Heart J 2008; 60: 119-24.

33- **Wang X, Geng LL, Nie SP.** Coronary slow flow phenomenon: a local or systemic disease? Med Hypotheses 2010; 75: 334-7.

34- **Fineschi M, Gori T.** Coronary slow-flow phenomenon or syndrome Y: a microvascular angina awaiting recognition. J Am Coll Cardiol 2010; 56: 239-40.

35- **Gori T, Fineschi M.** Two Coronary "Orphan" Diseases in Search of Clinical Consideration: Coronary Syndromes X and Y. Cardiovasc Ther, 2011.

36- **Diver DJ, Bier JD, Ferreira PE, Sharaf BL, McCabe C, Thompson B, et al.** Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). Am J Cardiol 1994; 74: 531–537.

37- **Mangieri E, Macchiarelli G, Ciavolella M, Barilla F, Avella A, Martinotti A, et al.**Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn 1996; 37: 375–381.

eISSN 1303-5150

38- Brockway R, Brockway M, Brockway B, Hamlin R. Comparison of one- and three-lead ECG to measure cardiac intervals and differentiate drug-induced multi-channel block. J Pharmacol Toxicol Methods 2018; 93: 80-9.

39- Chan A, Isbister GK, Kirkpatrick CM, Dufful SB. Drug-induced QT prolongation and torsades de pointes: Evaluation of a QT nomogram. QJM 2017; 100: 609-15.

40- Tani T, Tanabe K, Kitai T, et al. Detection of severe stenosis and total occlusion in the left anterior descending coronary artery with transthoracic Doppler echocardiography in the emergency room. Echocardiography 2009; 26: 15-20.

41- Yaymaci B, Dagdelen S, Bozbuga N, Demirkol O, Say B, Guzelmeric F, et al. The response of the myocardial metabolism to atrial pacing in patients with coronary slow flow. Int J Cardiol 2001; 78: 151–156.

42- Sezgin AT, Sigirci A, Barutcu I, Topal E, Sezgin N,. Vascular endothelial function in patients with slow coronary flow. Coron Artery Dis 2003; 14: 155–161

43- Sezgin N, Barutcu I, Sezgin AT, et al. Plasma nitric oxide level and its role in slow coronary flow phenomenon. Int Heart J 2005; 46: 373-82.

44- Riza Erbay A, Turhan H, Yasar AS, et al. Elevated level of plasma homocysteine in patients with slow coronary flow. Int J Cardiol 2005; 102: 419-23.

45- Pekdemir H, Cin VG, Cicek D, Camsari A, Akkus N, Doven O, et al. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. Acta Cardiol 2004; 59: 127–33.

46- Yilmaz M, Korkmaz H, Uku O, Kurtoglu E, Bilen MN and Akbulut M. P-wave and QT dispersions on electrocardiography in coronary artery slow flow phenomenon. Kosuyolu Heart J 2017; 20(1): 19-23.

47- Özcan ÖU, Sepehri B, Gürlek A, Erol Ç. Effects of ectasia on electrocardiographic parameters among patients with isolated coronary artery ectasia. MN Cardiol 2015; 22: 26-9.

48- Binak E, Gunduz H, Sahin M, et al. The relation between impaired glucose tolerance and slow coronary flow. Int J Cardiol 2006; 111: 142-6.

49- Wang X and Nie S. The coronary slow flow phenomenon: Characteristics, mechanisms and implications. Cardiovasc Diagn Ther; 1(1): 37-43.

50- Kurtoglu N, Akcay A, Dindar I. Usefulness of oral dipyridamole therapy for angiographic slow coronary artery flow. Am J Cardiol 2001; 87: 777–779.

51- Perez-Reyes E. Paradoxical role of T-type calcium channels in coronary smooth muscle. Mol Interv 2004; 4: 16–18.

52- Beltrame JF, Turner SP, Leslie SL, Solomon P, Freedman SB, Horowitz JD. The angiographic and clinical benefits of mibefradil in the coronary slow flow phenomenon. J Am Coll Cardiol 2004; 44: 57–62

53- Doddareddy MR, Jung HK, Lee JY, Lee YS, Cho YS, Koh HY, et al. First pharmacophoric hypothesis for T-type calcium channel blockers. Bioorg Med Chem 2004; 12: 1605–1611.

54- Olgin JE, Kalman JM, Fitzpatrick AP and Lesh MD. Role of atrial endocardial structuresd as barriers to conduction during human type I atrial flutter: Activation and entrainment mapping guided by intracardiac echocardiography. Circulation 1995; 92: 1839-48.

55- Li JJ, Zheng X, Li J. Statins may be beneficial for patients with slow coronary flow syndrome due to its antiinflammatory property. Med Hypotheses 2007; 69: 333-7.

56- Gunes Y, Tuncer M, Guntekin U, et al. Regional functions of the left ventricle in patients with coronary slow flow and the effects of nebivolol. Ther Adv Cardiovasc Dis 2009; 3: 441-6.

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