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ORAL PRESENTATIONS

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Treatment of multivessel CAD in diabetics

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Coronary artery disease (CAD) is a major cause of morbidity and mortality among patients with diabetes mellitus. Compared to nondiabetic patients, patients with diabetes are more likely to have CAD. The most often finding in these patients is multivessel CAD, and it is characteristic to have episodes of silent ischemia. Diabetic patients with CAD have a lower long-term survival rate than nondiabetic patients with CAD. About 30% of patients undergoing revascularization are diabetics.

The medical treatment and revascularization management of CAD, including the indications for revascularization, are generally similar in patients with and without diabetes. However, the short- and long-term results of revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery are worse in diabetic patients.

Coronary artery bypass grafting seems to be the preferred revascularization technique in diabetics, especially if long-term survival is anticipated. However, because of residual uncertainties and increased risk for stroke with CABG, clinical judgment is required when choosing a revascularization technique in patients with diabetes.

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Predictors of coronary slow flow/ no reflow following PPCI

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Despite the great reduction in STEMI mortality achieved after introduction of primary PCI, microemboli resulting from coronary plaque disintegration could cause microvascular damage leading to the slow flow or no reflow phenomenon in the coronary arteries. This occurs in 15-30% of patients undergoing primary PCI for acute myocardial infarction and is associated with worse outcomes. Various studies tried to identify clinical, biological and imaging-based predictors for this phenomenon and proved that patients with slow flow/no reflow tend to be older and to have in a significantly higher extent complex coronary lesions and more expressed signs of vulnerability in the culprit lesions. A higher Killip class at presentation has also been associated with no reflow. At the same time, the duration from the onset of symptoms to revascularization has been correlated with the incidence of this phenomenon. Invasive imaging studies including intravascular ultrasound (IVUS) and optical coherence tomography (OCT) identified various morphologic characteristics of atheromatous plaques as being associated with a higher risk for slow flow/no reflow. These imaging-based biomarkers are represented by a high plaque burden, a large necrotic core, large lipid arc (by OCT) or plaque rupture. In general, a large lipid core in the culprit lesion is a significant predictor of no reflow in both STEMI and non-STEMI population. The presence of IVUS-detected attenuated coronary plaques is associated with a 4-fold increase in the risk of no reflow and has been associated with MRI-derived biomarkers of microvascular obstruction. Among biological biomarkers associated with slow flow / no reflow phenomenon, different studies identified neutrophil count, leucocyte count or blood count derived parameters such as red cell distribution width-platelet ratio (a new biomarker for inflammation) or neutrophil-lymphocyte ratio as significant predictors for occurrence of this phenomenon.

Identification of these clinical, biological and morphologic biomarkers prior to PCI could serve for prompt recognition of patients at higher risk for no reflow, in order to initiate specific measures such as manual thrombectomy of protection devices for prevention of microembolisation during PCI.

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Angina with "normal" coronary arteries: a changing philosophy

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An appreciable number of patients with angina have angiografically “normal” or near-normal coronary arteries without significant evidence of flow-limiting disease, a group in which women predominate. Although, it is believed to be, due to early, angiografically undetectable, atherosclerosis-related endothelial dysfunction, coronary microvascular dysfunction or coronary vasospasm of epicardial vessels, the exact mechanisms of coronary ischemia in these groups of patients remain largely speculative, despite preclinical and clinical research advances. Although having "normal" or “near normal” coronary arteries these patients are at risk for potentially fatal events such as myocardial infarction and ventricular arrhythmias. Thus, their prognosis is not benign, as previously thought. Additional testing, such as assessment of endothelial function with acetylcholine and invasive physiological assessment such as coronary flow reserve measurement, may help identify patients at risk for cardiac events. Yet, still to date, in many of these patients are offered no treatment beyond reassurance. Because atherosclerosis is common in these patients, evidence based medical and lifestyle interventions for secondary prevention should be implemented when appropriate.

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The effect of statin pre-treatment on coronary no-reflow phenomenon following PCI

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Prompt reperfusion and restoration of epicardial coronary blood flow to restore viability in the ischemic myocardium is today considered to be mainstay of therapy to reduce morbidity and mortality in acute coronary syndrome (ACS). Despite the proven success of reperfusion therapies and advances in percuatenous coronary intervention (PCI), myocardium viability is not accomplished in many patients with ACS, especially in ST-segment elevation myocardial infarction (STEMI). Coronary no-reflow is defined as suboptimal myocardial reperfusion through a part of coronary circulation without angiographic evidence of mechanical vessel obstruction. The mechanisms and mediators responsible for no-reflow remain speculative, but the end result appears to be severe microvascular dysfunction potentially due to microvascular vasospasm, reperfusion injury, inflammation, distal embolization or thrombus or other debries and individual susceptibility. Coronary no-reflow is associated with negative short and long-term prognosis. The pathophysiology of no-reflow appers to be complex and multifactorial, thus a range of preventive and therapeutic strategies are required in different clinical settings. As a consequence selection of therapy is still under scrutiny. Prevention of individual susceptibility, such as hypercholesterolemia, has recently emergent as an important factor in preventing the coronary no-reflow phenomenon. Hypercholesterolemia is associated with endothelial cell dysfunction and reduction in vascular nitric oxide bioavailability. The establishment of a strongly pro-inflammatory condition is associated with hypercoagulability and may reduce the probability of early successful reperfusion. Statin pretreatment has shown to be effective for preventing no-reflow phenomenon, post-procedural myocardial infarction, and to improve myocardial perfusion after PCI. Statins are attractive because they inhibit neutrophil function and decrease neutrophil-mediated oxidative stress and endothelial injury. These effects might prevent microvascular obstruction caused by plugging of platelets/leukocytes. Statin pretreatment can also, preserve the coronary microvascular permeability.

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Consequences of hypertension on the small brain arteries

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Hypertension (HT) is the most important risk factor for both hemorrhagic and ischemic stroke, where it may affect both the large and small arteries of the brain. As stroke is a heterogeneous disease, identifying the cause in each patient has important clinical and prognostic implications. Acute management and long-term strategies to prevent recurrences may vary considerably between the different subtypes of stroke. Thrombo-embolic occlusions of large arteries are the most common cause of stroke but about one fifth of all ischemic strokes affect the small, deep, arterioles that penetrate the white matter, producing lacunar strokes. Cerebrovascular disease affecting these small arteries may be detected by indirect (biomarkers) or direct methods (brain imaging or hemodynamic studies). Although some biomarkers have been associated with lacunar stroke (asymmetric dimethylarginine ADMA, haptoglobin-1), the specificity and sensitivity are low and the clinical usefulness of blood biomarkers for predicting prognosis in the setting of ischemic stroke has yet to be established. The gold standard method for the detection of small vessel disease is cerebral magnetic resonance imaging (MRI). This technique is crucial for the accurate diagnosis of the topography of cerebral lacunar infarcts and white matter lesions (WML). HT induces long-term remodelling and endothelial dysfunction in the brain arteries and silent subclinical damage may be detected as hyperintensities (white matter lesions – WML) or as hypointensities (Microbleeds – MCBs) on the MRI before stroke onset. Both WML and MCBs are important prognostic factors for stroke, being associated with left ventricular hypertrophy (LVH). In addition, these silent WML and MCBs are the structural pathophysiological substrate of cognitive impairment and vascular dementia. Both SBP and DBP reductions induced by antihypertensive treatment are associated with significant decreases in the incidence of any stroke subtype, but only two observational studies and a meta-analysis suggest that prevention of WML progression and cognitive decline by lowering BP is possible. Concerning the incidence of cognitive decline and its progression to dementia, al least five randomized trials comparing active treatment with placebo have shown beneficial effects, although no specific antihypertensive drug or

strategy has demonstrated to be superior. In summary, current evidence supports the view that hypertension in mid-life, especially if not treated effectively, is not only crucial to prevent stroke but also to prevent cognitive decline and dementia in late life. High BP in the middle-aged implies a long-term cumulative effect leading to increased severity of atherosclerosis and more vascular comorbidities in late life.

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Lipid metabolism, lipoprotein structure and coronary microvascular dysfunction

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Several experimental and epidemiological studies have proven the relevance of lipoproteins in the different stages of cardiovascular disease development. On one hand, low-density-lipoproteins (LDLs) play a key role in atherosclerosis development and in the onset of atherothrombotic complications by inducing endothelial dysfunction, activating monocytes and promoting their transmigration, inducing changes in the phenotype of vascular smooth muscle cells and increasing tissue factor expression and secretion in several cell types, finally leading to an increase in thrombogenicity. On the other hand, high-density-lipoproteins (HDLs) act as guardians, not only through their role in reverse cholesterol transport, but also because of their anti-oxidant, anti-inflammatory, anti-thrombotic, immunomodulating and cytoprotective properties. However, therapeutic attempts to raise HDL-cholesterol (HDL-C) levels have failed to reduce cardiovascular risk, highlighting that HDL-C levels do not reflect HDL protective properties. Indeed, several HDL subclasses exist depending on their maturation degree. These classes differ not only in their size and density but also in their lipid and protein composition. The existence of this different subclasses has revealed that HDL protective properties are determined by their quality but not through their quantity in terms of the amount of transported cholesterol. In fact, several studies have shown that HDL3 (smaller and denser fraction) are more atheroprotective than HDL2.

Specifically, LDL-C levels predict coronary microvascular dysfunction in coronary artery disease (CAD) patients independently of coronary atherosclerosis, and are inversely correlated with coronary flow reserve in asymptomatic patients without risk factors for CAD. In fact, hypercholesterolemic patients show altered NO bioactivity leading to impaired endothelium-dependent vascular relaxation. In this scenario, HDL protective properties are of great importance. Indeed, epicardial coronary endothelial dysfunction is inversely associated with HDL particles, whereas myocardial perfusion reserve index is directly associated with these micelles. However, how does HDL protein composition affect the microcirculation is yet unknown. In this context, the use of "omic" systems biology approaches, such as proteomics, can help us in elucidating the impact of HDL protein composition on microvascular function and the risk of suffering ischemic heart disease.

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Biomarkers of microvascular dysfunction and ischemia

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In the last years many efforts have been spent in the search for specific biomarkers of the different clinical manifestations of cardiovascular disease. Until now several biomarkers associated to different pathological processes such as inflammation and acute response, stress, plaque instability, coagulation, lipid metabolism, cardiac function and necrosis have been identified. Indeed, proteins involved in each of these steps, if released to the circulation, represent potential biomarkers that can be used for risk assessment, diagnosis and prognosis of disease state.

Within the group of necrosis markers, cardiac troponins have emerged as the gold-standard biomarker for the assessment of the irreversible necrotic damage of the myocardium. Another important group of markers are those involved in cardiac function such as cardiac natriuretic peptides, which have shown to predict mortality in patients with heart failure. Among inflammation markers, C reactive protein (CRP) is the most extensively studied.

Despite the growing knowledge of biomarkers associated to different stages of cardiovascular disease state, currently there are no biomarkers for the detection of microvascular disease and the clinical assessment of microvascular dysfunction is based on highly expensive and invasive imaging techniques. Different studies have proposed proteins involved in endothelial function, inflammation, haemostasis and cardiac function or even adipokines as surrogate markers of microvascular dysfunction. However, those markers are not specific for the presence of microvascular dysfunction or the associated ischemic process. Furthermore, microvascular disease has been widely studied in specific contexts such as kidney dysfunction or diabetes, making difficult the extrapolation of the associated biomarkers with other pathological situations of microvascular disease. In this scenario, the identification of specific, sensitive and reliable biomarkers of ischemia would be very useful for the detection of the ischemic process associated to microvascular dysfunction without the presence of obstructive coronary arteries, and even for risk stratification and prognosis in patients with microvascular disease.

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Microcirculation: a new target in the therapy of hypertension – physiological grounds

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Microcirculation comprises a dense capillary network between arterioles and venules. It is well-known from more than one decade that alterations in microcirculation are linked to progression to cardiovascular events. The physiology of microcirculation is not fully understood and microcirculatory dysfunction could be either the origin as well as a consequence of hypertension. It was demonstrated that the outcome predictive value of microcirculatory structural alteration is similar to the predictive value of the HEART-SCORE. Microcirculatory remodeling a dysfunction is a subclinical event which could precede target organ damage in hypertensive patients. Microcirculatory structural and functional abnormalities could be the sole alteration seen in patients with idiopathic hypertension. Microcirculatory structure and function could be assessed by several clinical methods as Doppler flowmetry of retinal arteries, capillaroscopy, imaging and Doppler coronary microcirculation studies or biopsy examination. There are adaptive changes in microcirculation including Glagov mechanism and neoangiogenesis. In hypertensive patients media to lumen ratio is greater than in normotensive patients and this correlates well with concentric left ventricular hypertrophy. Also there is a striking relation between small vessels remodeling and renal function in hypertensive patients. Mechanisms different from high blood pressure per se could influence microcirculatory maladaptation (i.e. activation of the metalloproteinase complex). The role of current antihypertensive drug therapy in preventing or reversing microcirculatory modifications encountered in hypertensive is not fully understood. Depending on the context antihypertensive therapy could improve microvascular geometry but not normalize it. As the drug effect on microcirculation is dependent on ancillary properties (i.e. vasodilatation) the effect is linked to molecule and not to class; this could explain the discrepancies in literature reported for all classes of antihypertensive drugs (ACEI, beta blockers or antialdosterone drugs).

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Arterial stiffness and myocardial ischemia

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In the last years a large body of evidence has indicated pulse wave velocity (PWV) and central parameters of blood pressure as independent predictors of cardiovascular mortality. In line with these findings it is important to understand the mechanisms through which arterial stiffness can produce a deleterious effect on the cardiovascular system. In this lecture we will present the conditions that are contributing to the development of arterial stiffness and its main hemodynamic consequences consisting in the increase of PWV, the augmentation of central systolic and the decrease of diastolic blood pressure and their important impact on target organs damage, including the heart. There are pathophysiological premises, experimental studies – like those represented by the series of Watanabe et al., clinical studies and epidemiological data which are sustaining the correlation of arterial stiffness with myocardial ischemia. We will detail the studies which have analyzed the correlation of arterial stiffness parameters with coronary flow velocity reserve and with left ventricular hypertrophy. In different stressing conditions, like exercise, myocardial ischemia can appear in patients with increased aortic stiffness due to the imbalance between high systolic workload and the decreased sub-endocardial flow supply. Moreover, we will discuss the effects of this abnormal ventricular-vascular interaction, specifically in heart failure with preserved ejection fraction. In the end we will highlight the most recent data indicating the prognostic significance of arterial stiffness parameters in patients with acute coronary syndromes, for major cardiovascular events and for the recovery of left ventricular function as well.

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What can be done in the case of an acute coronary syndrome with an unstable coronary plaque in a patient with statin intolerance?

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We present the case of a 71 years old woman, who arrived at the Emergency Room with an anterior ST-elevation myocardial infarction, which was treated by primary PCI on a unstable plaque situated on the proximal left anterior descending artery. Within a few days of discharge, the patient complained of back and lower limb pains and lower limb weakness. We decided to decrease the dose of Atorvastatin from 80 to 40 mg/day but the symptoms persisted. Atorvastatin was then replaced with Rosuvastatin 10 mg/day and the lower limb pain dissapeared.

Starting from this case, we propose to briefly discuss the benefits of statins in secondary prevention, the adverse reactions of statins, the risk factors associated with statin intolerance and to focus on the therapeutic options for the management of the statin „intolerant" patient. Future non-statin strategies as well as an algorythm for statin-induced myopathy are discussed.

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Role and limitations of angiography

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Coronary angiogram is currently the gold standard in diagnostic and therapeutic management of CAD. However, several pitfalls and limitations exists. The non recognition of those limitations may result in sub-optimal patient care (i.e over or under treatment).

Coronary angiogram can define different types of significant stenosis, and treat them accordingly. It defines the severity of the coronary disease (1-3VD), and impose different treatment strategies from PCI, CABG or medical treatment.

It makes analysis of the plaques, from concentric to excentric ones and classifies the thrombotic lesions and classifies the bifurcated lesions properly in order to be stent treated correctly.

Coronary angiography is completed by a quantitatively analysis of the lesions, using QCA. Physicians tend to overestimate the lesion severity compared to QCA. Almost a quarter of the clinically estimated >70% significant lesions, were actually <70% by QCA.

Not identifying/treating a significant lesion may have similar (or even worse...) detrimental consequence than over-treating non significant lesion...

It is so important to appropriately assess %DS and lesion severity in order to: avoid unnecessary stenting, avoid under revascularization and offer the most appropriate revascularization strategy for every given patient. For intermediate lesions FFR usage is very useful.

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Genomics and genetics in hypertension and coronary ischemia

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Genomic studies in cardiovascular diseases have the potential to provide insights into pathophysiology of these complex conditions; define an individual's risk to develop cardiovascular disease or to experience cardiovascular events; and to direct preventative and therapeutic approaches in the spirit of precision medicine. This potential is, however, challenged by the multifactorial nature of cardiovascular diseases; complex interactions between genetic and environmental factors; and slow development of complications over many years and decades; and the heterogeneity of cardiovascular diseases. We will therefore also explore the impact of other omics techniques including proteomics and metabolomics in cardiovascular diseases. Whilst genetic factors are particularly well suited to predict lifetime risk and general response to therapeutic approaches, proteomics and metabolomics integrate genetic and environmental factors. This may have advantages for the description of an individual's cardiovascular health.

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Cardioplegy and protection of microcirculation

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Despite surgical proficiency and innovation, it is obvious that cardiopulmonary bypass (CPB), as well as the cardioplegic cardiac arrest (CCA) have some detrimental impacts on the myocardium , as well on the microcirculation causing endothelial cell dysfunction. Cardiac surgery deals today with low mortality and morbidy rates, but the disease severity, comorbidity rate and operative procedural difficulty increases. Depolarizing potassium cardioplegia is the standard of cardiac protection in the last 40 years, but its disadvantages led to improved cardioplegic agents like "magnesium cardioplegia"," hypocalcemic cardiolplegia" and " esmolol cardiolegia" . Endogenous cardioprotective strategies, like ischemic pre conditioning and post conditioning may provide additional protection. There is no general consensus on cardioplegia composition, way of administration and re-dosing interval; despite this, the outcomes of adult and pediatric cardiac surgery are continuously improving.

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Coronary microvascular dysfunction in cardiovascular disease: lessons from large animal models.

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The contribution of coronary microvascular dysfunction to a variety of cardiovascular diseases, including ischemic heart disease, cardiac hypertrophy and heart failure is being increasingly recognized. I will discuss our studies of coronary microvascular dysfunction in swine models of cardiac remodeling, ischemic heart disease, and metabolic perturbations. The results from these studies indicate that microvascular dysfunction is a key feature of these pathophysiological states, indicating that the coronary microcirculation represents an important therapeutic target for the treatment of cardiovascular disease.

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Microvascular angina in left ventricular hypertrophy - case presentation

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Myocardial ischemia may arise in hypertension independent of coronary artery disease through an interaction between several pathophysiological mechanisms, including left ventricular hypertrophy, increased arterial stiffness and reduced coronary flow reserve associated with microvascular disease and endothelial dysfunction.

We report the case of a 52 years old woman hospitalized with acute chest pain without electrocardiographic changes, but slightly elevated serum troponin level (0.150 pg/ml). Her medical history revealed symptoms of exercise induced chest pain for 1 month and hypertension in treatment with 4 different antihypertensive drugs. The electrocardiogram showed left ventricular hypertrophy by Sokolow-Lyon criteria. Echocardiography demonstrated mild concentric left ventricular hypertrophy. Left ventricular ejection fraction was normal with reduced systolic left ventricular myocardial function and diastolic dysfunction grade 1 with normal filling pressure. No wall motion abnormalities were detected. Laboratory tests showed normal renal function, normal glycemic and lipid profiles. No micro albuminuria was present. Twenty-four hour ambulatory blood pressure was on average 130/79 mmHg, but 38 % of systolic and 57% of diastolic measurements were elevated, and the diurnal variation was reduced. Pulse wave analysis, using the device Arteriograph demonstrated that central aortic systolic blood pressure and pulse pressure were in the normal range, PWV was in the upper normal range and Aix was high. The exercise stress test performed after 48 hours of hospitalization was positive for ischemia and the patient was addressed to coronary angiography. Coronary angiography demonstrated non-obstructive coronary artery.

We evaluated tissue level perfusion using the myocardial blush grade technique. Total myocardial blush score was lower. We demonstrated that the patient has impaired tissue level perfusion, and this might be assumed as a surrogate marker of a diseased microvascular disease.

Chronic hypertension is associated with development of cardiovascular complications including atherosclerosis, left ventricular hypertrophy, arterial stiffening and microvascular dysfunction. This can cause symptomatic myocardial ischemia even in the absence of significant epicardial coronary artery stenoses. In hypertensive patients with chest pain and non-obstructive coronary artery disease assessment of vascular function by myocardial blush is useful to identify the cause of symptoms.

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Coronary calcification severity: from risk factors to metabolomics investigations

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Conventional risk factors for atherosclerosis (hypertension, diabetes, dyslipidemia, smoking and obesity) have been shown to predict 10 years clinical outcome, however their impact on the presence of significant (>50%) coronary stenosis is not clear. In Euro-CCAD, a multinational (Denmark, France, Germany, Italy, Spain and the USA) study of symptomatic patents 27.9% had significant stenosis, 5.5% of whom had zero coronary artery calcification (CAC). The most important predictor of coronary stenosis was the log transformed CAC score (B=1.25), followed by male gender (B=0.48). The accuracy of CTCA for predicting >50% stenosis using the CAC score alone was higher (AUC=0.85) than using a combination of the CAC score and risk factors with conventional angiography (AUC=0.81) [1]. The same study showed different predictors of CAC presence according to gender. In addition to the progressive increase in CAC with age, the most important predictors of CAC presence were dyslipidaemia and diabetes (β = 0.64 and 0.63, respectively) in males but diabetes (β = 1.08) followed by smoking (β = 0.68) in females; these same risk factors were also important in predicting increasing CAC scores. In patients aged >70, only dyslipidaemia predicted CAC presence in males and only smoking and diabetes were predictive in females [2]. A recently published meta-analysis has also confirmed that diabetes and hypertension consistently predict the presence and extent of CAC in symptomatic patients [3]. Furthermore, it seems that CAC is not an isolated disease that involves only the coronary arteries but also the arterial trunk (aortic root) of which they emerge. This relationship has recently been shown in patients with aortic stenosis from two European centres, a finding that suggests CAC is a systemic disease [4].

In view of the above it is clear that the CAC has significant clinical implications. The first lipid profiling study demonstrated dysregulations of phosphatidylcholine lipid species in patients with severe CAC, which suggest perturbations in fatty acid elongation/desaturation. The altered levels of the 18-carbon and 20:4 FAC lipids may be indicative of disturbed inflammation homeostasis. The marked sphingomyelin dysregulation in SC is consistent with profound apoptosis [5].

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The microvascular obstruction: the last barrier in the revascularization of acute myocardial infarction

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Microvascular obstruction (MVO) during acute ST-segment elevation myocardial infarction (STEMI) is of the utmost importance since it frequently occurs even after timely culprit artery revascularization.

Literature data suggest that intra-procedural embolism during PCI is not the main player in this important field titled as "the last barrier" in STEMI reperfusion.

Regarding intra-procedural embolism during PCI, the EMERALD and the DEDICATION trials were disappointing with regard to the benefit of distal protection devices.

None of the large thrombus aspiration studies and large recent meta-analysis had proven any benefit of the technique on MVO, left ventricular remodeling or long term survival. Moreover, treated vessels may have contained only a small thrombus burden, as issued in the optical coherence tomography substudy of the TOTAL trial.

The aim of this lecture is to present a new invasive parameter in MVO evaluation and a new insight with regard to the timing of MVO occurrence. We have shown that elevated coronary wedge pressure before interventional reperfusion influences the evolution of high-risk STEMI patients.

As recently stated by Mahmoud and Zijlstra, "thrombus aspiration is not the ultimate solution for myocardial reperfusion in STEMI, because distal embolization and microvascular obstruction might already have occurred to some extent before admission".

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Exercise modalities to treat hypertension

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Hypertension is one of the most important cardiovascular disease risk factors, which has a special importance due to its high prevalence and the related huge medical costs. According to the American College of Sports Medicine (ACSM) exercise reduces resting systemic blood pressure (BP) in normotensive individuals and in those with acute or chronic high BP. Over the years, hypertension develops due to several pathomechanisms. In developed countries, one of the most frequent forms is the obesity related hypertension, which is characterized by the activation of the sympathetic nervous system and the renin-angiotensin system, and sodium retention, but also coupled frequently with other abnormalities, such as increased glucose intolerance (in type 2 diabetes mellitus). On the other hand, with aging vascular remodelling elicits the loss of the elasticity of the conduit vessels leading to stiffening of the arterial vasculature and thus isolated high systolic blood pressure. Also, with aging the ability and efficiency of kidneys to excrete salt became reduced leading to a volume overload of the circulatory system affecting both systolic and diastolic pressures.

Several exercise types are known, which can be classified into three main categories. 1) the aerobic exercises (cycling, walking, running, hiking, playing tennis), which focus on increasing cardiovascular endurance, 2) the anaerobic exercises (weight training), which increase short-term muscle strength, and 3) the flexibility exercises (stretching), which improve the range of motion of muscles and joints. The most effective and recommended physical activity to treat hypertension are the aerobic dynamic exercise trainings (evidence category A).

By a critical overview of the literature, we summarize the effects of various exercise modalities/programs/trainings on blood pressure in normotensive and hypertensive individuals. Then the potential underlying mechanisms of various exercise modalities and physical fitness programs on blood pressure lowering effects are discussed, including neuro-hormonal mechanisms (decreasing serum catecholamine levels connected with the decrease of total peripheral resistance), the effects of exercise on vascular func-

tion (vasodilator and vasoconstrictor mechanisms) and structural adaptations, such as arterial remodelling (arterial stiffness, hemodynamic adaptations). In addition, changes in coronary and skeletal muscle microcirculation, myocardial remodelling and changes in various gene expressions are discussed.

In additions to hypertension, exercise trainings known effects other cardiovascular risk factors (obesity, dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, inflammation, oxidative stress) that are interact with each other. Translation of the results of basic science research on cardiovascular system into clinical exercise modalities and hypertension treatments and efficacies are discussed, such as the Frequency, Intensity, Type, and Time (FITT) principle of exercise prescription as powerful therapeutic approaches.

Key words: hypertension, sport, vasomotor function, coronary and skeletal microcirculation, metabolic syndrome, inflammation, oxidative stress, FITT principle of exercise

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Blood pressure variability – implications for treatment

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Studies performed in the past 30 years have provided important information on 1) the extent to which blood pressure (BP) varies over the 24 hours and 2) the mechanisms involved and the effects of hypertension and antihypertensive treatment on this phenomenon. Evidence has also been obtained that BP variability carries and independent prognostic significance, i.e. that a greater BP variability value is associated with a greater number of cardiovascular outcomes independently on mean BP. This presentation will summarize the most important evidence so far obtained but also emphasize the major gaps of knowledge in this area, primarily the absence of information on whether a treatment-induced reduction of BP variability adds to the documented protective effect of a reduction of mean BP by treatment. It will then more extensively address the evidence collected in recent years on "long-term" BP variability, e.g. the range of BP values that range of BP values between visits in treated hypertensive patients. It will be shown, in particular, that visit-to-visit BP variability 1) has an adverse independent prognostic value 2) the two factors together improve the ability to determine the extent of cardiovascular protection by treatment and 3)the mechanisms involved in visit-to-visit BP variability remain largely undetermined but a variable adherence to the prescribed treatment is probably involved.

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Coronary Microcirculation: The New Obiective in Patients with STEMI?

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Rapid revascularization by primary percutaneous coronary intervention (PPCI) with stenting is considered to be the treatment of choice for patients with ST-elevation myocardial infarction (STEMI). Despite prompt restoration of epicardial coronary flow, however, normalization of flow at the myocardial or microcirculatory level is not always assured (30-40% of STEMI patients). This phenomenon is associated with larger post-infarction myocardial necrosis, which is a major determinant of morbidity and mortality in STEMI survivors.

A 47-year-old man with no previous medical history presented to the emergency department with 3 hour of acute onset of left-sided chest pain, shortness of breath, and diaphoresis. He reported active tobacco smoking but denied other drug use. He denied any previous episodes of chest pain or exertional symptoms.

On examination, his blood pressure was elevated at 145/90, pulse was 78 beats per minute, and oxygen saturation was 100% on 2.5 liters of supplemental oxygen. His cardiac examination was normal, including no appreciable murmur or pericardial friction rub. The electrocardiogram demonstrated ST-segment elevations in leads V1–V5, along with reciprocal changes in leads III and aVF, concerning for an acute anterior STEMI. His laboratory values were notable for an elevated troponin T and CK-MB.

He was treated with sublingual nitroglycerin, unfractionated heparin, and aspirin in the emergency department which improved but did not completely alleviate his symptoms and brought urgently to the cardiac catheterization laboratory. Coronary angiography showed proximal left anterior descending artery (LAD) sub occlusion. After intra-coronary injection of nitroglycerin and balloon predilation, the stent was deployed at a nominal inflation pressure, but TIMI II flow persisted. Repeated intracoronary bolus doses of adenosine and a GP IIb/IIIa inhibitor were administered. A final angiogram showed TIMI II flow distal to the mid LAD. At this point, the patient's chest pain was completely resolved, along with some resolution of ST segments. An echocardiogram was performed and demonstrated akinesia of the left ventricular antero-septal wall. Echocardiography performed after 3 months demonstrated

apical dyskinesia, a reduced left ventricular ejection fraction, abnormal longitudinal strain in the apical segments and reduced global longitudinal strain.

Impaired microvascular reperfusion is considered the consequence of numerous pathophysiological mechanisms: ischaemia-related injury, reperfusion-related injury, distal embolization, and individual susceptibility (both genetic and due to pre-existing coronary microvascular dysfunction) of the microcirculation to injury. The most important clinical predictor of microvascular injury is ischemia duration, but ischemic extent also plays an important role. Contemporary strategies in PPCI to protect the myocardium include reduced ischemic time, platelets inhibitors, vasodilators (adenosine, verapamil, and nitroprusside), new antithrombotic agents, statins, thrombus aspiration, etc. Future trials should explore the effects of integrated treatments aimed at prevention and treatment of coronary microvascular dysfunction.

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Fractional Flow Reverse (FFR) for invasive evaluation of coronary ischemia

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Fractional flow reserve (FFR) is the gold standard for invasive evaluation of the functional severity of a coronary stenosis. FFR is defined as the ratio between the maximum flow in a coronary with stenosis, as compared to the maximum flow in the same artery with ideal normal diameter. In practice, this ratio is measured with a pressure wire, as a ratio of pressures across the stenosis, in conditions of maximum flow, obtained with maximal coronary vasodilation. FFR below 0.8 proved to identify patients who benefit from revascularization using percutaneous coronary interventions (PCI). Decisions based on FFR proved to offer a better outcome and MACE-free survival for patients, as compared to decisions based on angiography alone. Intracoronary vasodilation (adenosine e.g.) is often used by beginners, while intravenous systemic vasodilation with adenosine is preffered by experienced teams and for pullback investigations, in long lesions. FFR is reproducible and can be used for decision making in various lesion types, including multivessel disease, left main, bifurcation lesions, jailed side branches after coronary stenting, serial stenosis and diffuse disease. FFR should be interpreted in relation with the clinical setting. In non-ST elevation acute coronary syndromes, FFR is accurate and safe for both culprit and non-culprit vessel stenosis. In the setting of ST elevation acute coronary syndromes, FFR may be unreliable for the culprit lesion, but is accurate for the non-culprit lesions. Myocardial infaction is associated with microvascular dysfunction, therefore coronary flow reserve and maximal coronary flow at vasodilation are lower and FFR fail to decrease as much as in the absence of myocardial infarction, for a given stenosis. In order to evaluate culprit lesion functional severity post-STEMI, one should wait for the microvasculature stunning to resolve; duration may vary, but it typically is around one week. For a given stenosis, FFR inversely correlates with the mass of viable myocardium supplied. Experience with FFR, in randomized trials, clearly support its presence in guidelines, in a wide range of clinical and lesion settings.

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Is deffer PCI a better alternative for myocardial revascularization?

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Functional myocardial revascularization of ischemic territory in acute phase of STEMI patient is not only anatomical revascularization, but obtaining optimal microcirculation of culprit lesion. A damaged microcirculation, named slow/no reflow, has an 11-40% incidence in STEMI cases and prognostic importance like decreased ventricular function with heart failure and increased mortality at 5 years after index event. The mechanisms of this phenomenon are multiple distal microembolisation, vasoconstrictors mediators, free oxygen radicals eliberated from manipulation of activated atheroma plaque. Treatment of no/slow flow phenomenon is limited and partially inefficient with nytroglicerine, adenosine etc. That's why prevention is the key to obtain a good prognostic results in treating STEMI pacients.

There are few studies with limited pacients numbers to detect the best prevention method, like schorting ischemic time, thrombaspiration for high thrombus burden, 2b3a glycoprotein inhibitors, distance preconditioning, postconditioning with repeated postdilatation, deffer stenting and pharmacological stabilization of activated atheroma plaque

We choose to treat our STEMI cases with no reflow high risk (vessel >3mm sized, high thrombus burden, long lesion, young pacient, first hours debut), with an pharmaco-invasive attitude (make diagnostic angiography, obtain TIMI 3 flux in culprit lesion by thrombaspiration or undersized low pressure balloon predilatation, pharmacological therapy (glycoprotein 2b3a administration for 12-24 hours, statin, duble antiagregation) and redo angiography in the first five days with/without stenting). Deffer stenting and active medications may be a good alternative to prevent microcirculation alteration by mediators delivered after extensive instrumentation of activated atheroma plaque. Our results are good so far, but we have a limited number of these pacients and we expecte result of large trials(literature reported just 2 small studies DEFFER STEMI and DANAMI 3-DEFER) to validate this methods of no/slow flow prevention.

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Cardiac imaging in hypertension

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Uncontrolled and prolonged elevation of blood pressure can lead to hypertensive heart disease. Features of hypertensive heart disease include left ventricular hypertrophy (LVH), diastolic and eventually systolic heart failure. Hypertension also promotes de development of coronary artery disease that manifests clinically as angina or myocardial infarction which can exacerbate cardiac remodeling.

A number of imaging techniques are available in the assessment of hypertensive heart disease including echocardiography, cardiovascular magnetic resonance (CMR), cardiac computed tomography (CCT) and cardiac scintigraphy.

Echocardiography is the most common method that can properly quantify LV mass, global and regional systolic function and diastolic function. Assessment of LV volumes and mass by 2DE is limited by foreshortening, angulation and a reliance on geometric assumptions for calculation, resulting in an underestimation of the true values, particularly in remodeled ventricles. It was shown that 3D echocardiography compared to 2D echocardiography provides superior accuracy values for LV mass, volumes and ejection fraction using CMR as the gold standard. Furthermore, new echo methods like TDI and speckle tracking echocardiography facilitated the assessment of long-axis LV function, which is sensitive to the preclinical phases of heart failure. Tissue Doppler measured velocities and longitudinal strain can be used to differentiate hypertensive heart disease from functional myocardial changes in the athlete's heart or hypertrophic cardiomyopathy.

CCT has a high negative predictive value for ruling out coronary artery disease and it is also appropriate for ventricular mass and volume measurement although issues with the use of nephrotoxic contrast and ionizing radiation persist. Scintigraphic techniques can also be used in the assessment of hypertensive heart disease but their use is greatly limited by the limited spatial resolution.

CMR appears to provide a comprehensive assessment of hypertensive cardiovascular disease, including accurate and reproducible measurement of biventricular function and volumes, tissue characterization and the possibility of serial evaluation without adverse effects.

This lecture will discuss the role of different cardiac imaging techniques in the diagnosis of hypertensive heart disease and the various prognostic parameters that this methods can provide.

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Pathophysiology of coronary microvascular dysfunction: old mysteries and new options

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Coronary microvascular networks play the key role in determining blood flow distribution in the heart. Matching local blood supply to tissue metabolic demand entails continuous adaptation of coronary vessels via regulation of smooth muscle tone and structural dilated vessel diameter. The importance of coronary microcirculation for relevant pathological conditions including angina in patients with normal or near normal coronary angiograms (microvascular angina) and heart failure with preserved ejection fraction (HFpEF) is increasingly recognized. For microvascular angina, clinical studies have shown a prevalence of up to 50% in patients with suspected coronary artery disease as well as a relevant impact on adverse cardiovascular events including cardiac death, stroke and heart failure. Despite a continuously increasing number of corresponding clinical studies, the knowledge on pathophysiological cause-effect relations involving coronary microcirculation is however still very limited. A number of pathophysiological hypotheses for MVA and HFpEF have been suggested but are not established to a degree, which would allow definition of nosological entities, stratification of affected patients or development of effective therapeutic strategies. This may be related to a steep decline in experimental (animal) pathophysiological studies in this area during the last 15 years. Since technology to experimentally investigate microvascular pathophysiology in the beating heart is increasingly principle available, a concerted effort to build "Coronary Microvascular Observatories" to close this gap and to accelerate clinical progress in this area is suggested.

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Microvascular remodelling in the ischaemic heart

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Following myocardial infarction (MI), a requirement for the survival of pre-existing ischaemic cardiomyocytes, as well as newly formed cardiomyocytes, is concomitant formation of new blood vessels. Neovascularisation is a component of the heart's intrinsic repair response, albeit inefficient and recalcitrant to therapeutic augmentation. This may be, in part, due to a lack of understanding of the sources and mechanisms of new vessel formation. With insights gained from developmental coronary vasculogenesis, we have investigated whether embryonic mechanisms are recapitulated in the injured murine adult heart to increase vessel density.

For many years, the origins of coronary vessels were incompletely defined, with the epicardium widely accepted as the primary source of endothelial cells (ECs), as well as smooth muscle cells and adventitial fibroblasts. However, recent studies proposed alternative embryonic sources for ECs, including the sinus venosus and endocardium. Sprouting venous ECs, from the sinus venosus, have been described to invade the myocardium, de-differentiate, expand and re-differentiate into arteries and capillaries. EC contribution from the endocardium has been described to proceed in two phases: an embryonic contribution, controlled by VEGF-A signalling, and an early postnatal contribution, resulting from the trapping of endocardial cells in the inner myocardial wall, during compaction, in the first weeks of life.

Following MI, the quiescent epicardium is reactivated, undergoes rapid expansion and a network of capillaries forms within it. Vessels remodel, acquire smooth muscle support and connect with the existing coronary circulation. While overt angiogenic sprouting can seldom be detected from the coronary arteries or veins, we observed a conspicuous degree of sprouting from veins of the coronary sinus, the adult derivative of the sinus venosus. Sprouting cells express mesenchymal markers, possibly implicating endothelial-mesenchymal transition or de-differentiation and, in cardiac explants post-MI, portions from the atrio-ventricular sulcus exclusively gave rise to vascular sprouts. More recently, we have observed that MI-induced hypertrabeculation and ensuing compaction, a direct recapitulation of the postnatal process, may be an intrinsic mechanism for neovascularisation of the ischemic myocardium. Collectively, our studies provide evidence for the recapitulation of developmental mechanisms, with contributions from all three recognized embryonic EC sources, towards neovascularisation of the ischaemic adult heart.

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Myocardial Ischemia in Patients with Hypertrophic Cardiomyopathy and Normal Epicardial Coronary Arteries

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Hypertrophic cardiomyopathy (HCM) is the most common genetic familial heart disease, with a prevalence of 1:500 in the general population, and is characterized by extreme heterogeneity with regard to phenotypic expression, pathophysiology and clinical course. Many patients have mild or no symptoms and a normal life expectancy, others develop severe symptoms of heart failure, and some die suddenly, often in the absence of previous symptoms and at a young age. About 25% of HCM patients complain of episodes of chest pain. These episodes can be prolonged and atypical for angina pectoris and may often occur at rest, but may also be consistent with classic angina-pectoris provoked by exertion and after meals. Although myocardial ischemia is a pathophysiologic feature of HCM, the relation between myocardial ischemia and these various types of chest pain is unresolved, the mechanisms responsible for myocardial ischemia have not been completely clarified, and myocardial ischemia remains difficult to identify in individual patients.

Initial evidence for myocardial ischemia in HCM was derived from post-mortem studies that showed myocardial scarring, and thickening of the intima and medial layers of intramural coronary arteries. During the mid-1980s, cardiac catheterization studies showed that lactate consumption (sampled from the great cardiac vein via the coronary sinus) decreased during atrial pacing in association with reduced venous flow, a finding regarded as convincing evidence of myocardial ischemia. In the late 1980s, Thallium-201 single-photon emission computed tomography (SPECT) identified perfusion defects in patients with HCM, both at rest and after exercise. In 2003, positron emission tomography (PET) measurements of myocardial blood flow under basal conditions and in conditions of near-maximal vasodilatation (after intravenous dipyridamole) allowed calculation of coronary blood flow reserve in patients with HCM. These studies showed that, although myocardial blood flow at rest was similar in HCM patients and control subjects, the increase in blood flow after vasodilatation was significantly reduced in patients compared to controls, reflecting an inability to increase myocardial perfusion and indicating hypoperfusion. In particular, myocardial blood flow was markedly impaired in hypertrophied areas of the left ventricle but was also reduced in nonhypertrophied segments, a finding in agreement with post-mortem

studies showing abnormal intramural coronary vessels throughout the myocardium in patients with HCM.

Cardiac magnetic resonance (CMR), which is more widely available than PET, has proved useful in identifying myocardial damage possibly related to ischemia. CMR perfusion sequences obtained after first pass of gadolinium administration permit assessment of myocardial blood flow, and late gadolinium enhancement sequences can detect and quantify the presence of myocardial fibrosis in patients with HCM. Extensive areas of myocardial fibrosis are identified in patients with end stage HCM, which is characterized by LV wall thinning, cavity dilatation and systolic dysfunction. These observations suggest that abnormal myocardial blood flow caused by microvascular dysfunction may contribute to myocyte death and ultimately repair in the form of replacement fibrosis. In a recent study, published in JACC in 2016, Raphael et al. used Doppler and pressure sensor-tipped guidewire to investigate the impact of myocardial relaxation and contraction on intramyocardial arteries in HCM. The results show that systolic compression of the intramyocardial vessels represent an important impediment to coronary flow in patients with HCM and that this impediment is greater in HCM patients with LV outflow obstruction.

In conclusion, although myocardial ischemia remains difficult to identify in individual patients with HCM, the mechanisms responsible for this pathophysiologic expression of the disease have been in part elucidated. Abnormal intramural coronary arteries with thickened walls and relatively reduced lumen, and abnormal compression of the intramural vessels during systole, appear to play an important role in myocardial ischemia in patients with HCM.

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The role of manual aspiration thrombectomy in the management of STEMI: the role of preserving microcirculation

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The technique of manual aspiration thrombectomy during primary percutaneous coronary Intervention (PCI) for patients with STEMI is based on a mechanical removal of coronary thrombi prior to stent implantation and is believed to confer patient benefit in two distinct aspects. Firstly, via improvement in myocardial perfusion, that could consequently lead to infarct size reduction and better clinical outcomes. Secondly, by ameliorating thrombus burden prior to stent implantation, thus decreasing the rate of stent-related complications (i.e. due to underexpansion or malapposition).

However, two large randomized studies, the TOTAL and the TASTE trials, both showed no difference in clinical outcomes between PCI and thrombectomy versus PCI alone. On top of demonstrating neither in-hospital nor one-year benefit of thrombectomy, the TOTAL trial showed an increased incidence of stroke in patients with manual thrombus aspiration. The absence of improvement in clinical outcomes in the TOTAL and the TASTE trials, contradicted previously published smaller the TAPAS study. Although the results of the TAPAS and the TOTAL seem to be conflicting, in both trials thrombectomy resulted in an improvement of parameters associated with better myocardial perfusion (complete ST-segment resolution (STR) in both studies, MBG ≥2 in the TAPAS and less distal embolization in the TOTAL).

It is difficult to explain why manual thrombectomy did not have the expected impact on outcome of patients undergoing primary PCI for STEMI. Surrogates of myocardial reperfusion, such as complete STR, have consistently been improved by thrombectomy across the trials, even including the overall negative TOTAL trial. However, thrombectomy was not associated with reduced infarct size, as assessed by magnetic resonance imaging or SPECT. Similarly, the theoretical promise to decrease thrombus burden at the site of stent implantation was not realized, as evidenced by the TOTAL-OCT substudy, which showed no difference in thrombus burden before stenting. Importantly, recent patient-level meta-analysis suggests that aspiration in patients with heavy thrombus burden may prevent distal embolization and may be associated with some clinical benefit, but the subgroup findings should be considered exploratory.

The explanation for a lack of clinical benefit may be found in the generally highly complex relationship between surrogates and hard clinical endpoints. In the particular context of a STEMI patient, thrombectomy-associated improvement in surrogates of myocardial perfusion, such as STR or MBG, is only one piece of a complex puzzle that also includes microvasculature-mediated flow resistance, cardiomyocyte response to ischemia and reperfusion injury, stent/procedure-related complications, such as bleeding and contrast-induced acute kidney injury.

Despite the lack of clinical benefit associated with its routine upfront use, manual aspiration thrombectomy appears to remain a useful tool reserved for carefully selected cases with an anticipated high risk of distal embolization or with no-reflow after balloon angioplasty or stent implantation.

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A non-atherosclerotic cause of acute coronary syndrome

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Tako-tsubo syndrome is a cardiovascular disease affecting predominantly postmenopausal women exposed to unexpected strong emotional or physical stress. Patients often present with chest pain, have ST-segment elevation on electrocardiogram, and elevated cardiac enzyme levels consistent with a myocardial infarction, but at the cardiac angiography, left ventricular apical ballooning is present and there is no significant coronary artery stenosis. The etiology of the disease still remains unclear, potentially theories include catecholamine excess, multivessel coronary vasospasm, ischemical cause, and microvascular dysfunction .

We present the case of a 42-year-old Caucasian female who was admitted in the Intensive Care Unit with a two-hour history of chest pain after she had just been told that one of her sons had died in a car accident . She had a history of anxiety disorder, fibromyalgia, irritable bowel syndrome, and gastroesophageal reflux disease.

On admission, vital signs were: BP of 101/78 mm Hg, HR 109 beats/min, respiration rate of 20 breaths/min, O2 sat of 97% on room air, with pain 10/10. The physical exam was normal.

Initial electrocardiogram showed ST elevation in leads I, aVL, and V1–V3, with a rate of 98 beats per minute . Initial cardiac markers were elevated with a troponin I of 5.1 ng/ml (normal, 0.0–0.3 ng/ml), a total CK of 173 U/L (normal, 25–145 U/L), and a CK-MB level of 24.7 ng/ml (normal, 0.0–5.0 ng/ml). Transthoracic echocardiography revealed an akinesia of apicomid-left ventricle (LV) free wall with LV dilatation (LV ejection fraction, 45 %). Emergent catheterization revealed normal coronary arteries, with a right-dominant system, and the ventriculography showed severe hypokinesis of the LV anteroapical wall, and mid to distal septum with apical ballooning.

This case illustrates the challenges of distinguishing Takotsubo cardiomyopathy from an acute coronary syndrome. Takotsubo syndrome is a potential life-threatening disease, which can hardly be clinically distinguished from acute coronary syndrome. Further studies will hopefully enable early diagnosis of Takotsubo cardiomyopathy,clarify its etiology, refine therapy regimens and aid in its prevention.

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Non-invasive assessment of coronary microcirculation after primary percutaneous coronary intervention: why, when and how?

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Optimal reperfusion therapy in STEMI patients includes not only opening of the infarct related artery (IRA) with restoration of epicardial coronary flow, but also adequate microvacular blood flow and consequently full tissue reperfusion. The prevalence of slow flow/no-reflow after primary percutaneos coronary intervention (pPCI) in STEMI patients significantly varies (from 5% up to 50%), depending on the applied method and studied population. No-reflow is important predictor of left ventricular (LV) remodeling, LV dysfunction and major adverse cardiac events.

Coronary microcirculation after pPCI can be evaluated by anatomical assessment of myocardial reperfusion (myocardial blush grade - MBG, myocardial contrast echo - MCE, SPECT and PET scan, cardiac magnetic resonance imaging - CMR) and physiological assessment of reperfusion (resolution of ST segment elevation - STR, calculation of microcirculatory resistance index during catheterization, noninvasive and invasive Doppler-derived coronary flow reserve measurements - CFR).

ECG has been used to assess myocardial reperfusion since the introduction of reperfusion therapy. More than 50% reduction in the ST segment elevation 90 min after pPCI is accepted as a mark of successful reperfusion, although several other cutoffs (<30% vs 30-70% and >70%) and timings (1 up to 4 h) had been also used in clinical arena. However, ST-segment changes may be silent in up to 1/3 patients.

Myocardial contrast echocardiography (MCE) is point of care technique, offering assessment of both myocardial mechanic and extent of myocardial reperfusion achieved in the risk area. Despite the phenomenon of reactive hyperemia following reperfusion therapy, MCE due to its high spatial and temporal resolution, can be used to assess microvascular perfusion and extent of no-reflow as early as 5–60 min post-pPCI. After pPCI MCE is valuable predictor of improvement of LV function (with good sensitivity and modest specificity), LV remodeling and long-term clinical outcome including late mortality. MCE

was applied to estimate adjunctive medical therapies to improve microvascular blood flow following STEMI.

Coronary flow reserve (CFR) is the ratio of hyperemic to baseline blood flow (ml/min) or ratio of hyperemic to baseline blood flow velocities (cm/s). CFR represents an integrated measure of flow through both large epicardial arteries and coronary microcirculation. In the presence of patent IRA after pPCI CFR predominately reflects microvascular (dis)function. CFR≥2 is usually taken as normal. CFR can be assessed by transthoracic Doppler echocardiography, PET scan, CMR and most recently with CT.

Transthoracic Doppler (TTD) derived CFR is easy, first line, non-invasive method for CFR assessment with high feasibility for LAD coronary artery. Early after pPCI baseline flow trough epicardial coronary artery with high peak diastolic velocity, short deceleration time systolic retrograde flow is highly suggestive for no-reflow. During hyperemic stimuli (usually adenosine) diastolic peak velocity is increased, but not enough resulting in impaired CFR. Impaired CFR by TTE Doppler after pPCI predicts LV remodeling, poor infarct area recovery and bigger final infarction size. Interestingly even non IRA CFR after STEMI predicts long-term mortality.

Cardiac MRI enables visualization of microvascular obstruction (MVO) after pPCI, a substrate of no-reflow phenomena (hypointense, dark zone within the gadolinium enhancement on T1-weighted sequences) and intra-myocardial haemorrhage (dark hypointense area in the bright oedematous region on T2-weighted images). MVO on cardiac MRI is an independent predictor of adverse clinical outcome, either alone or adjusted for infarct size and left ventricular ejection fraction. Intra-myocardial haemorrhage, although less frequent in humans than in experimental models, correlates with the duration of ischemia and infarct size and is predictor of adverse remodeling and ominous prognosis.

Cardiac Position emission tomography (PET) is a well-validated technique for noninvasive, precise, and reproducible quantification of regional myocardial blood flow (MBF). MBF measurement using PET is used to derive CFR.

Each of above mentioned noninvasive techniques has its relative advantages and limitations. Apart from diagnostic and prognostic purposes they can help to assess and develop new adjunctive therapies to reduce the incidence of no-reflow.

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Treat or not to treat invasively non obstructive unstable lesions

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A 54-year old man, known with arterial hypertensive, diabetes mellitus, smoker and dyslipidaemia, presented to the Emergency Department accusing severe chest pain and dyspnoea for 45 minutes. Symptoms had started a week before, intermittently. The patient hadn't consumed any illicit drugs and had no medical treatment at home. The first electrocardiogram (ECG) showed sinus rhythm, with ST-segment depression in anterior leads. Echocardiography was quoit normal, but troponin seric level was positive for unstable angina.

Patient received standard medication (aspirin 250 mg, clopidogrel 600 mg, enoxaparin 60 mg subcutaneous, and perfusion of nitroglycerine). 24h later angiography was performed and revealed diffuse atherosclerotic coronary artery disease, without critical stenosis, with TIMI flow 3 in all territories, but poor myocardial blush. Also flow fractional reserve (FFR) was performed on left anterior descending artery (LAD) showing no hemodynamically significant stenosis.

Patient received treatment for the cardiovascular risk factors (hypertension, dyslipidaemia, diabetes). He was discharge asymptomatic.

Microvascular coronary dysfunction (MCD) is a syndrome that may occur like chronic angina or acute coronary syndrome. In both cases, the first step in diagnosis is to differentiate from non-cardiac chest pain. It also includes elimination of other causes of acute coronary syndrome (coronary embolization, transient coronary thrombosis, prolonged arterial spasm, stress related cardiomyopathy).

The management of this syndrome is primarily symptomatic and includes monitoring and treatment of possible complications (acute left ventricle failure, pulmonary oedema, ventricular arrhythmias, etc.). Long acting nitrates, beta blockers and calcium antagonist are the first choice MCD treatment.

Prognosis is especially related to the control of all cardiovascular risk factors. In different studies 71% of patients with stable MCD complain of persistence or recurrence of angina, versus only 32% of patients with unstable MCD.

We reported a patient with microvascular coronary dysfunction, with severe symptoms at admission, with poor response to previous medical treatment and without critical stenosis on epicardial coronary artery. MCD is a heterogeneous group of disorders related to several mechanisms that need more prospective studies to identify the specific subgroups at increased risk and their own prognosis.