Microcirculatory dysfunction in ST-elevation myocardial infarction: cause, consequence, or both?

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Aims Despite advancements over the past years, normal reperfusion at the myocardial level is not achieved in approximately every other patient with ST-elevation myocardial infarction. In the current work, we aimed at reviewing the role of the coronary microcirculation in the development and outcome of this acute coronary syndrome entity.

Methods and results A PubMed/Medline search was performed with the key words acute coronary syndrome, acute myocardial infarction, coronary artery disease, endothelial dysfunction, microcirculation, and reperfusion. The synthesis of the information points to myocardial microcirculatory dysfunction as a consequence of a primary epicardial event, based on the vulnerable plaque concept. As an alternative theory, microcirculatory dysfunction may contribute to the clinical course of the acute coronary event, based on the vulnerable patient concept. The pros and cons of these two viewpoints are to be discussed and their influence on patient management is to be considered.

Conclusion Microcirculatory dysfunction in ST-elevation myocardial infarction can be cause, consequence or both according to non-traditional and traditional concepts.

KEYWORDS
Acute coronary syndrome; Myocardial infarction; Endothelium; Microcirculation

Introduction

The diagnosis and treatment of patients with acute coronary syndromes (ACS), including ST-elevation myocardial infarction (STEMI), has been the subject of intense investigation and the focus of multiple randomized clinical trials over the last two decades.1-3 As a consequence, prompt implementation of both pharmacologic and mechanical approaches to reopen the occluded epicardial coronary artery and to reperfuse the ischaemic/hypoxic myocardium is now considered to be mainstay of therapy to reduce morbidity and mortality in acute STEMI.1 Despite the proven success of restoration of epicardial coronary blood flow in a reasonably timely fashion, reperfusion on the myocardial level is not accomplished in ≈50% of patients with STEMI and of negative prognostic implication.4-7 (Figure 1). The common denominator of prevailing theories for this phenomenon is the development of myocardial microvascular dysfunction as a consequence of the primary epicardial event and/or perhaps of reperfusion per se.8-10 (Figure 2). As an alternative explanation, however, one may postulate that pre-existing and/or simultaneous dysfunction of the myocardial microcirculation is of primary pathophysiological significance (Figure 3). These traditional and non-traditional views of microcirculatory impairment in STEMI are the objective of this review.

Traditional pathophysiologic construct: secondary dysfunction of the myocardial microcirculation in ACS

Over the last two decades, the working hypothesis has been that STEMI is primarily an epicardial or a large vessel event as a result of plaque rupture or erosion, leading to thrombus formation with subsequent complete occlusion of the “culprit” vessel and evolving hypoxic myocardial cell death.11 The concept of plaque rupture and erosion gained scientific credibility, as an attractive explanation for the initially puzzling observations that STEMI and even sudden cardiac death may not be the consequence of a pre-existing severely obstructive epicardial stenosis.12,13 This hypothesis was primarily based upon the luminal images of coronary arteries at the time of coronary angiography in patients prior to the development of acute myocardial infarction (AMI).

At the time of AMI, the angiographic display of an occluded epicardial artery with intra-luminal thrombus and slow or even absent coronary flow that persists after recanalization led to the widely accepted opinion that the coronary microcirculation is an innocent bystander in the initial phase of the acute...
Figure 1 Prognostic merit of two surrogates of myocardial perfusion, readily available during clinical practice: recovery of electrocardiographic ST-segment elevation (**STR, full ≥70%, partial <70%) and myocardial blush (MB, closed 0/1, open 2/3), as highlighted by data from the CADILLAC trial. Reproduced with permission of the European Society of Cardiology.

Figure 2 Illustration of the traditional concept of microcirculatory impairment in the setting of no flow in the proximal LAD compared with preserved flow in the left circumflex coronary artery, as typically seen in acute anterior ST-segment elevation myocardial infarction (upper left panel). The sequence starts with the vulnerable atherosclerotic plaque, which, by rupture or fissure, causes thrombus formation and thereby complete coronary artery occlusion. Embolization of particulate matter, potentially aggravated by PCI, in addition to ischaemia, oxidative stress, and inflammation can lead to dysfunction of the myocardial microcirculation with impairment of myocardial perfusion that can persist or be even intensified after restoration of epicardial blood flow.
coronary event but becomes dysfunctional in its aftermath. In order to explain the dysfunctional state of the coronary microcirculation noted at the time of or soon after the acute coronary event, several pathophysiological mechanisms have been entertained, ultimately relating to either mechanical or functional impairment of the microcirculation.

Mechanical obstruction of the myocardial microcirculation
Distal embolization of atherothrombotic debris has been increasingly recognized over the past years as an important mechanism contributing to myocardial microcirculatory impairment. Indeed, in experimental models, injection of microspheres leads to mechanical obstruction of the myocardial microcirculation in association with alteration of coronary blood flow and the development of myocardial infarction depending on the volume and size of the microspheres. Falk was the first to substantially extend this concept to the clinical arena by providing conclusive support for spontaneous, mainly thrombotic, distal embolization leading to occlusion of small intramyocardial arteries and microinfarctions in patients dying from ACS. These findings resonate with post hoc analyses from the CAPTURE trial, which demonstrated a strong association between cardiac troponin T (cTnT) elevation as a marker of myocardial injury and the presence of thrombus and reduced coronary blood flow on coronary angiography in patients with ACS. In another autopsy-based study, Saber et al. confirmed distal microembolization of atherothrombotic debris in association with myocardial infarction in the vast majority of patients who died after balloon angioplasty or thrombolytic therapy for ACS. This study drew attention to the possibility that interventional efforts may add yet another dimension to myocardial microcirculatory impairment in STEMI. Indeed, using 3-D reconstructive intravascular ultrasound, Sato et al. were able to demonstrate that a reduction in plaque volume during primary percutaneous coronary intervention (PCI) is associated with impairment of the myocardial microcirculation and that the latter is associated with adverse clinical outcomes. The findings from intracoronary Doppler studies provided additional support for the occurrence of distal embolization in PCI in-vivo. Ultimate proof-of-principle was given by the use of distal protection devices, yielding retrieval of atherothrombotic debris, which would have otherwise embolized into the myocardial microcirculation. Nonetheless, the clinical benefits of distal protection devices in primary PCI have remained inconclusive despite the capture of atheromatous material, and the largest trial to date was strikingly neutral, with no evidence of benefit or harm. However, as highlighted by Mizote et al., the benefit of distal protection devices may depend on specific lesion morphology and its association with the potential for distal embolization at the time of PCI. Indeed, it has to be kept in mind that a significant amount of distal embolization may occur before any type of medical or procedural intervention, yielding the myocardial microcirculation dysfunctional and thereby limiting the therapeutic potential of these procedures. Furthermore, impairment of the myocardial microcirculation in the setting of AMI is multifactorial in etiology and would therefore require a multifaceted therapeutic approach. Thus, although the presence of distal coronary embolization is well documented, its ultimate functional and clinical significance in STEMI is to be determined further.

Functional obstruction of the myocardial microcirculation
Extending the concept of embolization, it has to be kept in mind that neither atheromatous nor thromboembolic debris...
in isolation are biologically inert. Moreover, coronary plaques can release bioactive factors, which have the potential to increase the severity of the functional impairment of the coronary circulation. Indeed, coronary microcirculatory vasosnctraction has been noted not only secondary to balloon angioplasty of thoroblastic coronary arterial lesions but even during ischaemia in patients with unstable angina, undergoing invasive coronary testing. Additional and perhaps more persuasive evidence is provided by the experimental model of rupture of atherosclerotic lesions, which leads to a rapids and marked increase in distal vascular resistance as a consequence of severe microvascular vasosnctraction rather than distal embolization. Vasoactive factors, likely to be involved in these pathophysologic events, include endothelin-1, which is a potent vasoconstricting peptide and increasingly expressed in the active plaque. Tissue factor is another prominent example of a bioactive peptide, which is increasingly expressed in active coronary lesions and was shown in the experimental setting to cause a marked reduction of coronary blood flow when released into the coronary circulation. Of additional potential significance are microparticles, which have been associated with impairment in endothelial function in patients with ACS, as a consequence of the regional dissemination of pro-inflammatory and procoagulant activity. Moreover, oxidative stress and ischaemia per se reduce the bioavailability of nitric oxide, further contributing to the dysfunction of the myocardial microcirculation. The extent to which these mechanisms influence the outcome of STEMI is currently uncertain.

**Reperfusion injury**

Reperfusion strategies may not necessarily improve myocardial perfusion under all circumstances. In fact, the term 'reperfusion injury' has been coined to summarize the ultimate clinical sequelae of aggravation of ischaemia-related myocardial injury by the restoration of coronary blood flow, including alterations in myocardial contractile performance (myocardial stunning), myocyte viability (infarction extension), arrhythmogenic threshold (reperfusion arrhythmias), and endothelial function (vascular stunning). Thereby, impairment in endothelial function is one but not the only presentation of reperfusion injury, and likewise, 'no-reflow' is one but not the only presentation of microcirculatory dysfunction and relates to different mechanisms.

Of interest, reperfusion injury has been reported with every modality of reperfusion therapy and postconditioning as the latest supporting evidence. Nonetheless, reperfusion injury has remained a controversial entity from a clinical as opposed to an experimental standpoint. A number of pathophysiologic mechanisms have been postulated with the major focus on the central role of the myocardial microcirculation. Indeed, histological studies have confirmed platelet as well as leukocyte accumulation (plugging) and activation in the myocardial microcirculation, leading to thrombosis, vasosnctraction as well as the release of free oxygen radicals, proteases, and pro-inflammatory mediators. Increase in oxidative stress mediates a reduction in nitric oxide bioavailability as well as activation of the endogenous endothelin and local renin-angiotensin system with an increase in intracellular calcium overload and hypercontracture, as an additional, potentially deleterious consequence. Complement activation leads to the release of histamine and an increase in cell permeability. As a result, endothelial cell and myocyte swelling can be observed as well as the development of luminal protrusion (blebs), interstitial edema, and further stimulation of leukocyte adherence. Independent of their serine protease inhibition and anti-inflammatory activities, interference approaches attribute pro-apoptotic activities to the complement system in ischaemia/reperfusion injury.

The bulk of evidence supporting the entity of reperfusion injury has been obtained from experimental models of ischaemia and reperfusion. The most widely used animal models are based upon an acute occlusion of a normal epicardial artery for a variable period of time followed by the acute release of the occluder. Within the no-reflow specifications for ischaemia and reperfusion injury outlined above, pharmacological interventions that have proven beneficial under experimental conditions include adenosine, adenosine triphosphate (ATP)-sensitive K+ channel opener, calcium channel blocker, Na⁺ exchange inhibitor, GPlIb/IIIa receptor inhibitor, and anti-neutrophil antibodies. All of these interventions have been used in the clinical setting and encouraging results for the reduction of no reflow have been shown in prospective randomized studies only for adenosine and nicorandil. With regard to the Americas and Western Europe, where nicorandil is not as established as in Asia, adenosine appeared as the most promising agent. In this context, the AMISTAD-1 and -2 trials showed a reduction in the size of myocardial infarction; however, ultimately they did not clearly support improved clinical outcome. The apparent lack of translating experimentally successful interventions into established clinical therapies is striking and multifactorial in origin. As summarized by an NHBLI working group report, the main reasons to consider include lack of standardized experimental protocols and reproducibility. For instance, there may be differences in the timing of drug therapy, i.e. before the occluding event in the experimental setting in contrast to administration much later in the course of an evolving MI in the clinical setting. However, this cannot be accounted for all experimental models, and therapeutic windows have been shown in these as well, e.g. the 3 h window for adenosine. Another consideration, underlying the inability to translate the success of the animal experiments into the clinical arena, may be inadequate approximation of the experimental to the clinical setting and fundamental differences between animal models and the mechanisms of STEMI in humans. For instance, the majority of the experimental studies use healthy, juvenile animals, and comorbid conditions such as hypercholesterolemia, diabetes, and hypertension, so prevalent clinically, are therefore not taken into consideration.

**Limitations of the traditional construct**

All of the mechanisms outlined above entertain the thought of secondary myocardial microvascular dysfunction limiting the success of tissue reperfusion strategies in AMI. However, it should be emphasized that the central limitation of the clinical studies in the field is their conceptual design. Namely, even if these studies were able to confirm myocardial microcirculatory dysfunction after AMI, they were not
designed to answer the question as to whether this predicted the initial acute coronary event. Furthermore, it has to be taken into consideration that plaque ruptures can remain clinically silent. Even though the exact prevalence is unknown, autopsy studies do outline that healed ruptures are not infrequently encountered upon histopathological review of coronary arteries of sudden cardiac death patients.\(^{51,52}\) In fact, in one intravascular ultrasound-based study, almost one quarter of all ruptured plaques was encountered in patients with stable angina or no symptoms at all.\(^{53}\) Moreover, by serial coronary angiography, one study suggested a delay of at least 3 days from plaque rupture and thrombus formation to the classical clinical presentation of AMI.\(^{54}\) Other studies outlined a closer relationship between trigger and presentation, even though an elevated risk for cardiac events can remain for weeks.\(^{55}\) Furthermore, patients with similar coronary pathoanatomy may present with unstable angina rather than AMI or even sudden cardiac death. Hence, there is fairly broad spectrum in the clinical presentation of an epicardial event, which has remained largely unexplained. While systemic factors such as thrombotic-fibrinolytic balance and local factors such as collateral blood flow have to be taken into consideration, one may also want to question the myocardial microcirculation as a potential modulating factor. There are reports on microcirculatory dysfunction in non-STEMI ACS entities but not to the extent we see with STEMI ACS.\(^{56}\) Hence, for the presentation of the ACS, one may postulate the presence not only of the vulnerable plaque but also of the vulnerable myocardium and its microcirculation.

**Primary dysfunction of the myocardial microcirculation in ACS**

The fact that coronary blood flow is reduced by 50% in the non-culprit coronary arteries in AMI before and after coronary intervention points to global rather than regional myocardial microcirculatory impairment.\(^{57}\) Moreover, in patients without obstructive coronary artery disease (CAD) and/or evidence of coronary epicardial and microvascular endothelial dysfunction during invasive cardiac evaluation, future cardiovascular events, including 38% that could be attributed to ACS, were limited to those with a reduction of coronary blood flow response to intracoronary infusion of acetylcholine.\(^{58}\) These data correspond to the findings of Britten et al., who followed patients with angiographically normal or minimally diseased coronary arteries over an average of 6.5 years and noted a more than three-fold higher cardiovascular event rate in patients in the lowest compared with the highest tertile of coronary flow reserve (CFR) (18 vs. 5%, \(P = 0.019\)) with 36% of all events related to ACS.\(^{59}\) They furthermore confirmed CFR, an indicator of the myocardial microcirculation, as an independent predictor of prognosis.\(^{59}\) Finally, Marks et al. followed patients with chest pain/ischaemic cardiac disease and normal coronary angiograms over a mean period of 8.5 years and noted a nearly three-fold higher mortality for those patients with an abnormal coronary flow reserve (20 vs. 7%; \(P = 0.016\)).\(^{60}\) Hence, the presence of myocardial microcirculatory dysfunction is a strong predictor of clinical outcome, including future acute coronary events, even in the absence of hemodynamically significant epicardial disease.\(^{61}\)

PCI can be considered as an iatrogenic form of plaque rupture and allows assessment of the significance of the myocardial microcirculation in a more defined setting. In this regard, it is important to notice that clinical studies of PCI pointed out that patients with pre-procedural CFR impairment were more likely to have post-procedural CFR impairment and procedure-related myocardial injury as well as worse long-term outcome.\(^{21,62}\) These data suggested that pre-existing impairment of the myocardial microcirculation yields greater vulnerability to myocardial injury and thereby implied a primary role of the myocardial microcirculation, at least in PCI-related myocardial injury. A more general applicability of this concept is supported by the higher risk of acute coronary events as well as the injurious consequences of ischemia and reperfusion in patient groups characterized by myocardial microcirculatory dysfunction by cardiovascular risk factor profile.\(^{63}\) In this regard, hypercholesterolemia, diabetes mellitus, and to a lesser extent, systemic arterial hypertension are to be mentioned with the experimental data reviewed previously.\(^{64,65}\) Clinically, an approximately 30% reduction in coronary flow reserve can already be found by dipyridamole PET studies in the asymptomatic early stages of all of these conditions.\(^{56-69}\) The impact of diabetes mellitus on myocardial perfusion impairment and infarct size in patients with AMI undergoing primary PCI is well recognized.\(^{24,70,71}\) In addition, as of recently, there is also evidence that a clustering of the pre-stages of the aforementioned conditions, i.e. the metabolic syndrome, is an independent predictor of poor myocardial perfusion in the setting of AMI and may relate to approximately two times larger infarction size and two times higher occurrence of in-hospital complications.\(^{72,73}\)

Inflammation may be a common link between epicardial macrovascular and myocardial microvascular disease. Indeed, Neri Serneri et al. demonstrated an acute inflammatory process involving the coronary microvessels but not the cardiomyocytes in unstable angina patients. They emphasized that, in this setting, inflammation of the myocardial microcirculation could not be the consequence of myocardial necrosis or even myocardial ischemia but rather due to an immunological process, possibly by downstream spread of immunogenic material from ruptured plaques.\(^{74}\) Intriguingly, IVUS studies highlighted the presence of multiple and not just one plaque rupture in all three and not just one coronary artery in patients with ACS.\(^{75}\) Moreover, widespread activation of neutrophils across the coronary vascular bed has been reported in patients with unstable angina, regardless of the location of the culprit stenosis.\(^{76}\) C-reactive protein (CRP) serum concentration has been identified as an independent predictor of a blunted coronary blood flow response to adenosine and substance P, i.e. endothelium-independent and endothelium-dependent coronary microvascular dysfunction, in patients undergoing elective PCI.\(^{77}\) Similarly, in patients with normal coronary angiograms, a significant inverse correlation was noted between CRP serum concentrations and myocardial blood flow responses to cold pressor testing by 13 N-ammonia and PET imaging.\(^{78}\) Based on these latter findings, one could plausibly speculate that the inflammatory mechanisms linked to plaque rupture also cause microvascular dysfunction.
Further support for this argument may be derived from previous retrospective and prospective randomized trials, which demonstrated a reduction in the incidence and extent of myocardial injury with PCI by pre-treatment with statins, known to improve microvascular function.\textsuperscript{23,79–81} Even more, a very recently published study highlighted a 74\% reduction in the incidence of no-reflow with primary PCI among patients who were taking statins before admission for anterior AMI, suggesting that chronic statin treatment could preserve the microvascular integrity after AMI.\textsuperscript{82} In addition, the GRACE study showed that ACS patients, who were already taking statins when they presented to the hospital, had a 20\% lower risk of developing ST-segment elevation or evolving full acute myocardial infarction.\textsuperscript{83} Similar results were obtained in a smaller-sized study.\textsuperscript{84} On the contrary, early discontinuation with statins has been associated with poorer outcome.\textsuperscript{83,85} Chronic ACE inhibitor therapy at the time of ACS presentation has been indicated to be associated with smaller degrees of myocardial injury and along with statins, beta-blocker, and aspirin with higher rates of infarct-related coronary artery patency.\textsuperscript{86,87} Finally, additional vasofunctional benefits have been ascribed to the GP IIb/IIIa receptor inhibitors.\textsuperscript{88–90} 

Taken together, there is a growing body of multi-layered evidence to suggest that the integrity of the coronary microcirculation plays an integral role in the evolution of STEMI. In line with the concept of the primary significance of the myocardial microcirculation, pre-existing transient or permanent microcirculation dysfunction may contribute to the development and prognosis of ACS via reduction of coronary blood flow, leading to an alteration of shear stress and thereby aggravation of endothelial function on epicardial level as well as aggravation of thrombus formation in an extension of “Folts coronary thrombosis model”\textsuperscript{91} (Figure 3). Coronary thrombus formation as a primary or secondary event in AMI has been debated quite extensively in the past, and some authors would argue that reduction of flow is the primary factor and intracoronary thrombus develops after the onset of myocardial ischaemia, as reviewed by Roberts.\textsuperscript{92} Hence, if the primary role of the coronary microcirculation is to maintain coronary blood flow and to regulate coronary flow reserve prior, during, and after STEMI, this could provide an explanation for several of the unanswered issues on myocardial perfusion in STEMI.

Limitations of the non-traditional pathophysiological construct

One of the main arguments against primary myocardial microcirculatory dysfunction is the finding that ultrastructural evidence of myocardial injury precedes ultrastructural evidence of microvascular injury in experimental models of coronary ligation and reperfusion.\textsuperscript{93} Likewise, a clinical study pointed out that for any time of reperfusion the probability of transmural necrosis was higher than that of microvascular dysfunction, suggesting that microvascular dysfunction lags behind transmural necrosis.\textsuperscript{94} However, other experimental findings suggest that microvascular ‘stunning’ develops independently from myocardial ‘stunning’ in the setting of ischaemia and reperfusion.\textsuperscript{95} Likewise, the clinical observation that ST segment recovery relates to infarct zone wall motion and late survival even in the presence of TIMI 2 and 3 flow and myocardial blush grade (MBG) 2 and 3 points to a potential dissociation between cardiomyocyte function and coronary blood flow.\textsuperscript{96,97} Finally, one study showed that in the early stages of reperfusion, apoptosis occurs first in endothelial cells from small vessels with a subsequent spread to the surrounding myocytes, underscoring again the primary significance of the myocardial microcirculation for cardiomyocyte viability.\textsuperscript{98} The failure of vasodilatory therapy with nitroglycerine to improve clinical outcome in ACS has been raised as a limitation to the non-traditional approach. However, nitroglycerine does not affect the myocardial microcirculation and alternate approaches such as nitroprusside would have to be used to test this hypothesis. A very recently published study gives credit to this theory, showing significantly higher rates of preservation of TIMI 3 flow, corrected TIMI frame count, and MBG with intracoronary injection of nitroprusside than with nitroglycerine in patients with STEMI undergoing primary PCI with distal protection device use.\textsuperscript{99} Furthermore, if microcirculatory impairment relates to endothelial dysfunction and encompasses more than influence of cGMP generation in vascular smooth muscles cells, more specific therapies would be warranted. Unfortunately, no trial has ever been specifically designed to address this question. Hence, while some indirect data exist for chronic statin and ACE inhibitor therapy at the time of ACS presentation, no conclusive data are available that therapies specifically designed to improve microvascular function lead to improved clinical outcome.

An additional argument, which may be forwarded against the current concept of a primary role of the microvascular dysfunction, is the good prognosis, including low long-term ACS event rate, in patients with cardiac syndrome X, considered to have functional impairment of the myocardial microvasculature, even though this remains a controversial issue.\textsuperscript{60} On the contrary, one may consider the entity of AMI with normal coronary arteries, which is encountered in up to 12\% of individuals with myocardial infarction undergoing coronary angiography, which may again indirectly point to the significance of the myocardial microcirculation in ACS.\textsuperscript{100} A particular variant of the presentation of STEMI in the presence of non-obstructed epicardial coronary arteries has been increasingly recognized over the past decade: the entity of tako-tsubo cardiomyopathy, ampuła cardiomyopathy, transient apical now also midventricular ballooning syndrome, human stress cardiomyopathy, or broken heart syndrome.\textsuperscript{101,102} Of interest, it was first described with a reference to multivessel coronary artery spasm.\textsuperscript{103} Subsequent studies could confirm provocation of epicardial coronary vasoconstriction by intracoronary injection of acetylcholine in 20–60\% of these patients.\textsuperscript{104,105} More importantly, there is more compelling evidence for microvascular spasm by angiography, nuclear studies, and invasive microvascular testing in this patient population.\textsuperscript{106–111} Hence, while alternative explanations such as transient intraventricular pressure gradient and catecholamine surge by various etiologies are to be considered, this entity highlights the possibility of STEMI due to myocardial microvascular dysfunction. Of further note, deaths due to multisystem organ failure, cardiogenic shock, ventricular fibrillation, and ventricular rupture can occur in the acute phase as well.
Another limitation of the non-traditional concept relates to the question how microvascular function and basal blood flow could deteriorate so acutely and so extensively as to contribute to acute coronary thrombosis, especially as the majority of patients with AMI apparently do not display microvascular dysfunction at the time of assessment. However, limitations of current diagnostic tools do exist and the very recently published results of MRI first-pass perfusion analysis indicate the presence of microvascular impairment in 84% of patients with AMI, suggesting the presence of an ‘iceberg phenomenon’.112 Secondly, acute deterioration in microvascular function and myocardial perfusion has been demonstrated in patients with NIIDDM, e.g. postprandially.113 A dysfunctional endothelium is also increasingly sensitive to catecholamines, which may explain the sudden increase in cardiac events with stressful life events.114 Furthermore, endothelial dysfunction begets a pro-coagulable state, which is of additional significance. In healthy individuals endothelium-dependent vasodilation by forearm venous occlusion plethymography is lower in the evening than in the morning hours and thought to counteract potentially harmful diurnal patterns of sympathetic tone and coagulability.115 However, in patients with angiographically proven CAD, this diurnal variation in endothelium-dependent vasodilation was noted to be absent, conferring a potentially greater risk.115 Then again, these patients were studied at least 3 months after hospitalization for ACS and these findings may therefore not be reflective of the pre-event condition. Hence, there can be sudden changes of factors which influence endothelial function and are themselves influenced by endothelial dysfunction. Nevertheless, a major limitation to argue for or against the non-traditional concept is the lack of tracing data on microvascular function and coronary blood flow just prior to the acute coronary event.

The unavailability of suitable animal models, which mimic the clinical milieu and could be used to test the current hypothesis, has to be listed as yet another limitation. The ideal model should manifest the same large and small vessels disease, similar thrombogenic and platelet aggregation pathways, and a similar response to environmental triggers and risk factors as noted in humans. The lack of a single model that provides an explanation for the pathogenesis of STEMI raises the possibility that STEMI is the consequence of heterogeneous mechanisms with a similar clinical presentation. Thus, future studies should take these possibilities into account in the design of a novel clinical approach for the treatment of STEMI.

If indeed microcirculatory dysfunction is ever demonstrated to be one of the major contributors to the evolution and not just the consequence of an AMI, this could substantially alter future research directions and approaches to therapy. The paradigm that STEMI may be initiated simultaneously at the level of the microcirculation and results in thrombus formation at a site of a non-occlusive epicardial artery may not, however, change clinical practice, which is to restore coronary blood flow and myocardial perfusion. Nonetheless, it could exert an influence upon the selection of adjuvant therapy prior and/or following the revascularization procedure or even a novel design for drug-eluting stents. Moreover, it may underscore our limitations in understanding the mechanisms of STEMI based on the tools that we currently use.

Conflict of interest: none declared.

References


