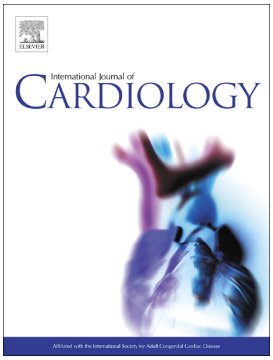

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Abstract

Plaque erosion, fissuring or rupture occurs spontaneously or during coronary interventions. At some residual blood flow, the atherothrombotic debris is washed into the coronary microcirculation, causing physical obstruction, vasoconstriction, inflammation and ultimately microinfarction. Coronary microembolization also contributes to microvascular obstruction in reperfused acute myocardial infarction. Patients with microvascular obstruction after reperfused myocardial infarction have worse prognosis. Cardioprotective strategies to avoid acute coronary microembolization and rescue myocardium from microvascular obstruction have not yet been established in clinical practice. Subclinical coronary microembolization together with release of thrombogenic, vasoconstrictor and inflammatory substances from a culprit lesion can sensitize the coronary microcirculation and contribute to angina in the absence of major epicardial coronary obstruction. Repetitive coronary microembolization can induce progressive loss of functional cardiomyocytes and induce heart failure in the absence of overt myocardial infarction.

Highlights

Acute coronary microembolization after erosion or rupture of an atherosclerotic plaque occurs spontaneously and during coronary interventions.

Coronary microembolization contributes to microvascular obstruction after reperfused acute myocardial infarction.

Coronary microembolization involves physical obstruction, vasoconstriction and inflammation in the coronary microcirculation.

Release of partial debris and soluble thrombogenic, vasoconstrictor and inflammatory substances from the epicardial culprit lesion can sensitize the coronary microcirculation and contribute to angina in the absence of major epicardial obstruction.

Repetitive subclinical coronary microembolization can cause progressive loss of viable cardiomyocytes and ultimately heart failure.

Plaque erosion, fissuring or rupture can occur spontaneously in patients with established coronary atherosclerosis, and plaque rupture is induced iatrogenically/ traumatically by percutaneous coronary interventions (PCI). Particulate debris from the damaged epicardial coronary atherosclerotic lesion together with superimposed thrombotic material, but also soluble factors from the plaque are then washed with the remaining antegrade coronary blood flow into the coronary microcirculation where they cause physical obstruction and enhance vasoconstriction, resulting ultimately in coronary microvascular obstruction.

Spontaneous plaque fissuring with superimposed thrombosis and embolization of the atherothrombotic debris into the coronary microcirculation which then resulted in acute myocardial infarction and sudden cardiac death were first reported by Davies [1,2] and Falk [3]. They described in detail typical autopsy findings of intraluminal microemboli and adjacent microinfarcts. Periprocedural coronary microembolization as a typical complication of PCI was emphasized in two editorials by Topol and Yadav [4] and Erbel and Heusch [5] in 2000 and has received widespread attention since then [6-9]. The reported incidence of coronary microembolization during PCI ranges from 0 to 70%, depending on the method of its assessment by biomarkers or imaging [10], the nature and complexity of the underlying epicardial coronary atherosclerotic lesion [7], the origin in native coronary arteries vs. saphenous vein grafts [7], the technique of the intervention (e.g. atherectomy, rotablation), and the clinical condition of the patient (e.g. stable vs. unstable angina, chronic kidney disease with enhanced coronary calcification etc.) [11].

The embolization of inert particles into the coronary circulation has been used already for decades to induce controlled and diffuse myocardial ischemia in experimental animals and to study its consequences for myocardial metabolism, coronary blood flow and contractile function [12-14]. Therefore, experimental models in dogs [15] and pigs [16-18] to study the pathophysiology of coronary microembolization were readily available, after the clinical importance of coronary microembolization was recognized [4,11,19].

The upcoming awareness of coronary microembolization in the setting of elective and primary percutaneous coronary interventions about 20 years ago has enormously increased interest in its pathophysiology and its clinical consequences [5,20] Accordingly, devices were developed to prevent coronary microembolization during elective percutaneous coronary interventions and to extract thrombatherosclerotic material during primary percutaneous coronary interventions. However, with the more recent awareness that routine use of protection devices does not improve clinical outcome during elective coronary interventions [21,22] and that also routine thrombectomy does not improve clinical outcome after interventional reperfusion of acute myocardial infarction [23-25], interest in coronary microembolization has quickly vanished. We believe that such current lack of interest in

coronary microembolization and its consequences is premature and that, in fact, it contributes to coronary microvascular dysfunction [26] and heart failure [27,28] in the absence of major epicardial coronary obstruction.

Morphology

By post-mortem angiography and histology in patients who had died from an acute coronary event, typical features of coronary microembolization were identified: intraluminal microthrombi, consisting of platelets, fibrin, atherosclerotic material including cholesterol crystals, and hyalin [1,3,29,30]. These microthrombi were associated with typical microinfarcts in their vicinity, and these microinfarcts were characterized by a pronounced inflammatory reaction.

The morphological features in experimental models of coronary microembolization are remarkably similar, supporting the use of such models for the study of coronary microembolization and its pathophysiology: microinfarcts in close vicinity to embolizing particles with a marked infiltration of polymorphonuclear leukocytes, macrophages and monocytes [15,31,32], but also apoptosis [19,32] are typically seen in dogs and pigs within hours after intracoronary infusion of microspheres (Figure 1).

Pathophysiology

The intracoronary infusion of microspheres in dogs immediately reduces coronary blood flow, and this blood flow reduction is quickly followed by a reactive hyperemia response within minutes [33,34]. The reactive hyperemia response is mediated through endogenous adenosine [33]. The coronary blood flood reserve in response to exogenous adenosine is reduced [34]. An increase in postprocedural baseline coronary blood flow velocity along with a reduced coronary blood flow velocity reserve and an increased creatine kinase release are also typically seen in patients undergoing PCI [35,36], again supporting the use of the above models in the study of coronary microembolization´s pathophysiology.

Regional contractile function in the microembolized coronary artery perfusion territory is immediately reduced along with coronary blood flow, but then- different from coronary blood flow which recovers fully or even exceeds baseline blood flow- does not recover completely [34], and repeated bouts of coronary microspheres infusion add up to a cumulative contractile deficit (Figure 2). In fact, the immediate contractile impairment after infusion of microspheres into the coronary circulation is followed by a further progressive decline of regional contractile function [15], and eventual full recovery- if it occurs- requires a week [37]. The inotropic reserve in response to dobutamine is reduced in microembolized myocardium [34]. With established contractile dysfunction, the microembolized myocardium

is characterized by a perfusion-contraction mismatch [38]. Depending on the size of the microembolized perfusion territory, contractile dysfunction becomes not only apparent on the regional level but also in reduced left ventricular ejection fraction [39]. The observed progressive contractile dysfunction with eventual full recovery is not easily explained by loss of viable cardiomyocytes through necrosis or apoptosis, but more consistent with the slowly developing and eventually resolving inflammatory reaction.

In fact, the inflammatory reaction is associated with increased expression of tumor necrosis factor α (TNFα) on the gene and protein level in microembolized myocardium, and TNFα is a negative inotrope [31,40,41]; accordingly, an antibody to TNFα abrogates the progressive contractile dysfunction which results from coronary microembolization [31]. The enhanced expression of TNFα is dependent on nitric oxide synthase and abrogated by its inhibition with N(ω)-nitro-L-arginine methyl ester [42]. It is also dependent on increased expression of phosphatase and tensin homolog on chromosome 10 (PTEN) and abrogated by PTEN silencing RNA [40]. TNFα, in turn, mediates its negative inotropic action by enhanced formation of sphingosine [42] and reactive oxygen species, oxidative modification of the contractile myofibrillar proteins [43] and ultimately impaired excitation-contraction coupling [44].

Unspecific glucocorticoid treatment reduces the increased TNFα expression and attenuates the progressive contractile dysfunction [37]. Atorvastatin reduces the increased expression of PTEN and also attenuates contractile dysfunction [45]. Again supporting the translation of the above experimental data, preprocedural statin therapy in patients is also associated with reduced PCI-related myocardial injury, as reflected by reduced creatine kinase and troponin release [46].

We realize that the above experimental studies reported mostly transient responses to coronary microembolization with inert material and were performed in otherwise healthy animals with an intact coronary circulation. We would expect, however, that such responses are more pronounced in response to atherothrombotic material with its vasoconstrictor, thrombogenic and inflammatory properties, are more pronounced with a compromised coronary circulation and are more pronounced when cumulative upon repetitive coronary microembolization.

Coronary microembolization in cardiac imaging

In patients undergoing elective PCI, those who experience a periprocedural non-ST segment elevation myocardial infarction have typical high intensity signals (HITS), as detected by an intracoronary Doppler wire, which correlate with increased postprocedural troponin and C-reactive protein and with reduced coronary reserve [36]. In diabetic patients undergoing

elective PCI, the amount of HITS not only correlates with postprocedural troponin release but also with adverse clinical outcome during 2 years follow-up [47].

The periprocedural myocardial injury, as reflected by the amount of released plaque material and the release of creatine kinase and troponin, correlates with the necrotic core volume of the culprit lesion on intravascular ultrasound (IVUS) imaging and with the minimal fibrous cap thickness on optical coherence tomography (OCT), but not with lipid burden on near-infrared spectroscopy (NIRS) [48-50].

Cardiac magnetic resonance imaging (cMRI) can not only detect regional and global ventricular dysfunction, but also a persistent decrease in contrast medium first-pass perfusion [18] and also microinfarcts in late gadolinium contrast imaging as patchy or streaky hyperenhanced areas in vivo and, with even better spatial resolution, post-mortem, and these findings again correlate with histology and troponin release [16,18,51]. For the detection by cMRI in vivo, the damaged myocardial area has to exceed 5% of the area of interest [51].

Coronary microembolization vs. cardioprotection

Adenosine is a decisive trigger molecule to induce cardioprotection/ infarct size reduction by ischemic pre-, post-, and remote conditioning [52-55]. The fact, that coronary microembolization induces the release of adenosine with subsequent reactive hyperemia [33,56] raises the question whether or not a preceding event of coronary microembolization, clinically possibly apparent as pre-infarction angina [57], might induce protection from subsequent overt acute myocardial infarction. However, an increase of coronary venous adenosine in response to intracoronary infusion of microspheres in pigs did not decrease, but even somewhat increased infarct size [56]. Conversely, such release and possibly depletion of adenosine from microembolized myocardium might impair the potential of subsequent ischemic preconditioning to reduce infarct size. Indeed, the increase in interstitial adenosine was attenuated by prior intracoronary infusion of microspheres in pigs, but ischemic preconditioning could still reduce infarct size [58]. Apparently, adenosine plays a different role in coronary microembolization and in ischemic preconditioning. Adenosine is released during coronary microembolization and somewhat depleted from its release sources in the myocardium and vasculature, and the released adenosine contributes to coronary hyperemia. However, there is no evidence that the adenosine which is released by coronary microembolization induces protection from injury by subsequent sustained myocardial ischemia and reperfusion.

While there was no interference between coronary microembolization and ischemic preconditioning acutely, the progressively increased TNFα expression over several hours

after intracoronary infusion of microspheres in pigs reduced infarct size from subsequent 90 min severe ischemia and reperfusion, and this delayed „third window of cardioprotection“ was abrogated by TNFα antibodies. Such “third window of cardioprotection” is between the acute and immediate protection by the “first” and the more delayed protection by the “second window of cardioprotection” 24-72 hours after the preconditioning stimulus and has been observed 6 hours after the preconditioning stimulus [59,60].

Different from ischemic preconditioning which has either little interference with coronary microembolization or even results in a third window of cardioprotection from coronary microembolization, protection by ischemic postconditioning is attenuated by coronary microembolization. This is a clinically relevant problem since ischemic postconditioning in patients with reperfused acute myocardial infarction involves further manipulation of the culprit lesion with the potential to induce coronary microembolization, unless there is direct stenting [61]. In a pig model of reperfused acute myocardial infarction, intracoronary infusion of microspheres at immediate reperfusion extended the infarct zone, such that ischemic postconditioning still protected, but the resulting infarct size was larger than without coronary microembolization [62].

The interaction of ischemic pre-, post-, and remote conditioning with coronary microembolization is apparently very complex. All forms of ischemic conditioning protect not only the myocardium but also the coronary microcirculation from injury by ischemia/ reperfusion [63-65]. Specifically, coronary microembolization can either induce delayed protection through enhanced TNFα expression or has no effect on acute ischemic preconditioning or attenuates the protection by ischemic postconditioning. However, it appears that the reduction of infarct size by ischemic conditioning interventions is more robust than the reduction of microvascular obstruction/no-reflow. In fact, infarct size reduction by local and remote ischemic preconditioning and by local ischemic postconditioning is not associated with reduced no-reflow areas in pigs, however the role of coronary microembolization in this setting is probably minor. [66]. There is currently no information available whether local or remote ischemic pre- or postconditioning protects from injury by coronary microembolization.

In vitro characterization of coronary aspirate from patients undergoing PCI

The use of an occlusion/ aspiration device in patients undergoing PCI not only protects from coronary microembolization and its consequences but also permits the retrieval of the stagnant blood column and its further analysis ex vivo. Larger particulate debris is retained while running the plasma through a filter, and atherothrombotic particulate debris typically

includes platelet aggregates, fibrin, hyalin, and atherosclerotic material, including cholesterol crystals and calcium [67].

Microparticles, anucleotic phospholipid vesicles with a diameter between 0.1 and 1.0 µm, are also released during PCI and they carry typical markers of platelet or endothelial origin [68]. Erythrocyte aggregation in coronary aspirate is enhanced after PCI [69].

However, there is not only particulate debris but also a number of soluble factors which are released during PCI, notably serotonin, thromboxane A2 [70,71], TNFα [71,72] and endothelin [73] (Figure 3). Serotonin, thromboxane A2 and endothelin induce vasoconstriction in rat mesenteric bioassay arteries [70,71,73] whereas TNFα induces endothelial dysfunction and thus augments vasoconstriction [71]. Serotonin from human post-stent aspirate also induces vasoconstriction in the rat coronary microcirculation and impairs left ventricular function [74] The release of TNFα from stent implantation into saphenous vein grafts correlates with the reduction of plaque volume on postprocedural IVUS and with restenosis after 5 months follow-up [72], in particular in patients with diabetes mellitus [75]. Native coronary arteries release less particulate debris but more endothelin than saphenous vein grafts when undergoing PCI [73]. Patients with chronic kidney disease release more particulate debris and calcium but less serotonin than patients without kidney disease when undergoing PC [76]. Aspirate from patients receiving a paclitaxel-eluting stent into their saphenous vein grafts induces less vasoconstriction than that from patients receiving bare-metal stents [77]. Apparently, the coronary aspirate and its particulate and soluble constituents carry a specific signature, depending on the patients´ co-morbidities, complexity of the culprit lesion, saphenous vein grafts vs. native coronary arteries, and the implanted stent [67].

Coronary microembolization vs. coronary microvascular dysfunction - a perspective

Coronary microembolization is only one of several pathomechanisms which contribute to coronary microvascular obstruction after reperfused acute myocardial infarction [65,78,79]. The physical obstruction of coronary microvessels with particulate debris causes sustained myocardial ischemia without eventual reperfusion; as such it is most likely not amenable to cardioprotective interventions after it has occurred. In contrast, the soluble thrombogenic, vasoconstrictor and inflammatory molecules which are released with PCI are potentially amenable to specific inhibitory approaches. However, the evidence for such specific protection of the coronary microcirculation by ischemic conditioning or vasodilators (adenosine, sodium nitrite, nitroprusside, verapamil) is not really convincing at this point [11,64,71,80]. More research is needed here (Figure 4). At this point, microvascular obstruction after reperfused acute myocardial infarction carries an adverse prognosis.[81,82]

In clinical practice, during elective coronary interventions, coronary microembolization is inferred from periprocedural increases in biomarker enzymes such as creatine kinase and/or troponin. These periprocedural increases in biomarkers of cardiac injury are mostly transient and only minor, and they are rarely associated with overt clinical events. While we have become aware of coronary microembolization mostly from acute and interventional coronary settings, its routine prevention in such settings appears to not improve clinical outcome, and it therefore may not be of too great importance here. However, we have learned a lot about coronary microembolization and also about the release of soluble substances from such acute and interventional scenarios. The release of particulate debris and soluble vasoconstrictor,thrombogenic and inflammatory substances from the epicardial culprit lesion could in fact be subclinical and more chronic, and the true significance of it could be a sensitization of the coronary microcirculation (e.g. by TNFα, [71]) and the progressive loss of viable cardiomyocytes upon repetitive coronary microembolization. In particular, coronary microvascular dysfunction and heart failure appear to have an unfortunate liaison [28], in which coronary microembolization could play a significant role. Vice versa, coronary microembolization and release of vasoconstrictor, thrombogenic and inflammatory substances may not only compromise the coronary microcirculation and ventricular function, but also have more overt clinical consequences when the coronary microcirculation and ventricular function are already compromised, thus creating a vicious cycle.

Legends

Figure 1A. Patchy microinfarct (hematoxylin-eosin staining, phase-contrast microscopy) and embolizing microspheres. **B.**Marked infiltration of leukocytes. scale bar = 100 µm. from [15] with permission.

Figure 2. Repeated intracoronary injection of microspheres (arrows) reduces coronary blood flow (CBF) and regional systolic wall thickening (PWT) immediately. Coronary blood flow recovers and even somewhat exceeds baseline flow. Systolic wall thickening does not fully recover, and there is a cumulative contractile deficit after repeated microembolization. from [34] with permission.

Figure 3. Increased concentrations of serotonin, thromboxane A 2 and TNFα, but not of endothelin, epinephrine, norepinephrine and tissue factor in coronary aspirate plasma after stenting of saphenous vein grafts. Data from [71].

Figure 4. Schematic diagram of coronary microembolization and its consequences. modified from [11]

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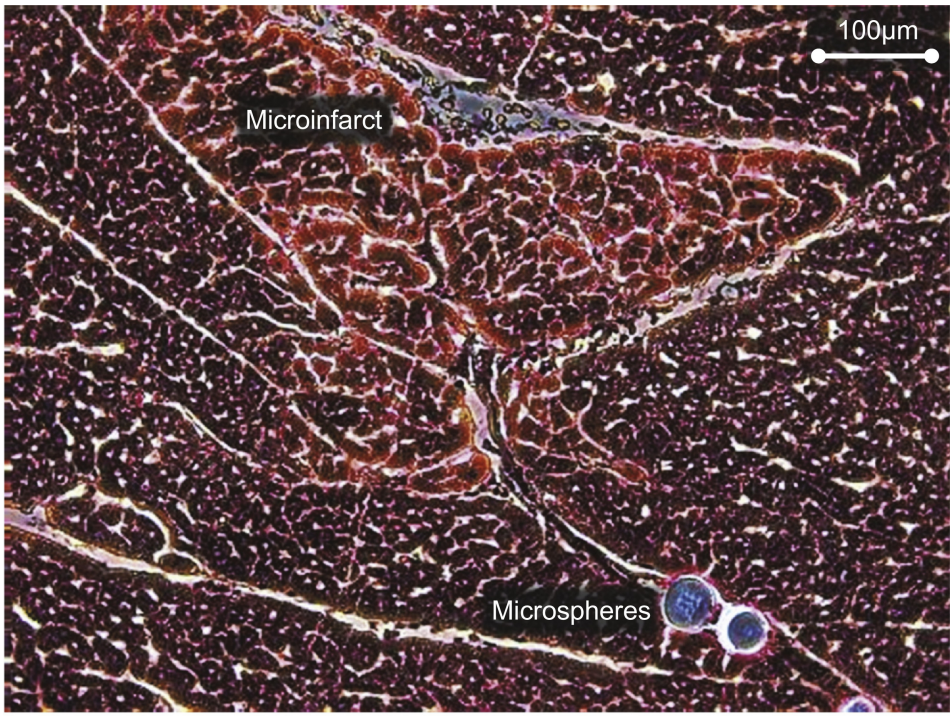
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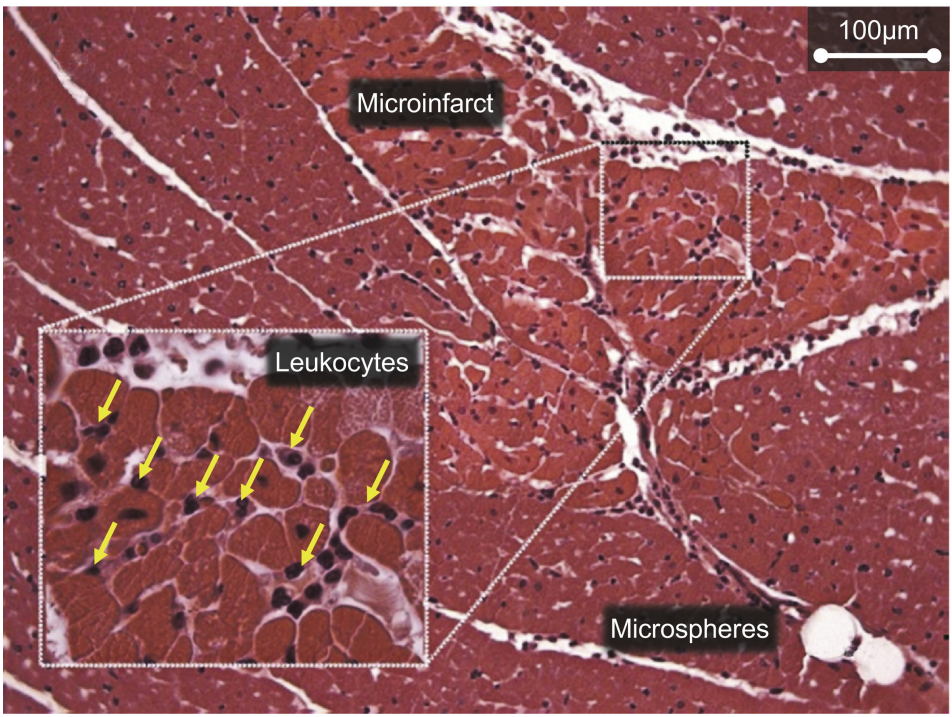
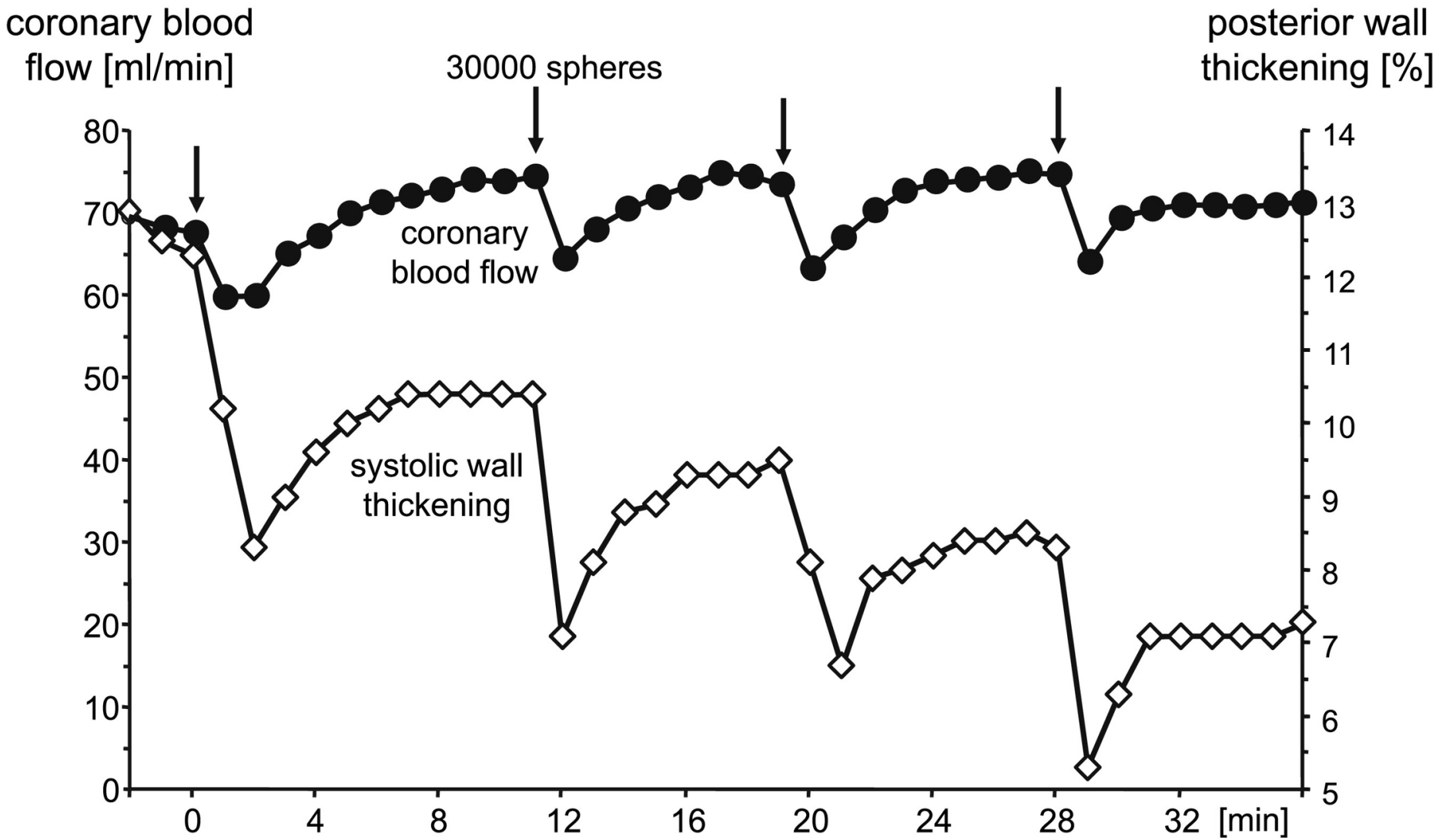

100µm
Microinfarct
Leukocytes
Microspheres

Figure 1


coronary blood flow [ml/min]
30000 spheres
posterior wall thickening [%]
coronary blood flow
systolic wall thickening
80
70
60
50
40
30
20
10
0
14
13
12
11
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16
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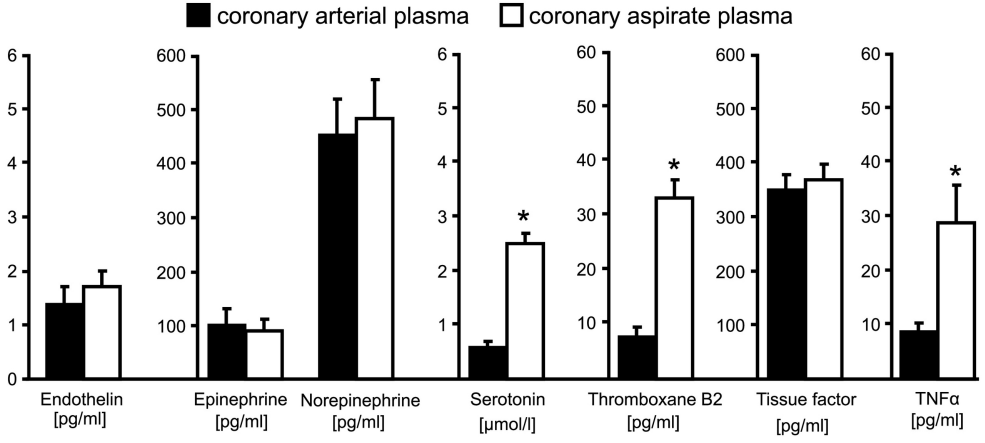
32
[min]

Figure 2


coronary arterial plasma
coronary aspirate plasma
Endothelin [pg/ml]
Epinephrine [pg/ml]
Norepinephrine [pg/ml]
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Thromboxane B2 [pg/ml]
Tissue factor [pg/ml]
TNFα [pg/ml]

Figure 3

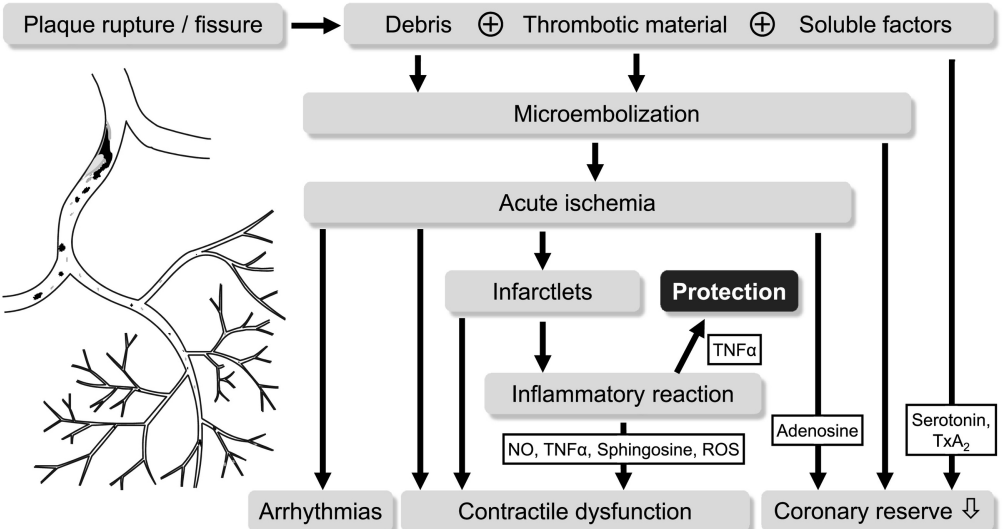
Plaque rupture / fissure
Debris ⊕ Thrombotic material ⊕ Soluble factors
Microembolization
Acute ischemia
Infarctlets
Protection
TNFα
Inflammatory reaction
NO, TNFα, Sphingosine, ROS
Adenosine
Serotonin, TxA2
Arrhythmias
Contractile dysfunction
Coronary reserve ⇩

Figure 4