**MINI-SYMPOSIUM**

**Spontaneous and interventional coronary microembolisation**

R Erbel

During recent years new imaging techniques have significantly improved the option to study in vivo coronary macro- and microvascular morphology and perfusion, including intracoronary ultrasound and Doppler, positron emission computed tomography as well as magnetic resonance imaging and high frequency transthoracic echocardiography.

**SPONTANEOUS CORONARY MICROEMBOLISATION**

The development of coronary atherosclerosis can be subdivided into five stages according to the American Heart Association. Atheroma and fibroatheroma, stage IV and V lesions, are characterised by lipid core formation. When the ratio of the lipid core to total plaque size increases and the fibrous cap thickness decreases < 60 µm, the risk of rupture is enhanced particularly if an infiltration of macrophages and calcified noduli for 2–6%. Death and acute myocardial infarction, plaque erosion for 35%, fibrous cap thickness decreases < 60 µm, the risk of rupture is enhanced particularly if an infiltration of macrophages indicates signs of inflammation. As these lesions are prone to rupture, they are regarded as vulnerable or plaques at risk. Plaques which are vulnerable are showing more vascular compensatory remodelling than non-vulnerable plaques. Clinical events occur when plaques ulcerate (VIa lesions), show intramural bleeding (VIIb lesions), and form mural or occlusive thrombus based on erosion or plaque rupture (VIIc lesions).

Apparently healthy subjects undergoing necropsy have experienced plaque rupture in 9% of cases, and patients with diabetes and hypertension in 17%. When plaque rupture occurs, this amount of lipid core material (“gruel”) can be washed out and lead to distal embolisation of the coronary tree. Depending on the size of the emboli, macro- or microinfarcts develop. In addition, shed membrane microparticles, with procoagulant potential and apoptosis as a critical determinant of plaque thrombogenicity after plaque rupture, are found. Also the exposed tissue of the plaque ulcer is a strong promotor of coronary thrombosis and contains high concentrations of tissue factors. Thrombus formation within the ulcer can develop and can be washed out, again partly explaining the observation of signs of multiple events. Thrombus formation also seems to be the first step in the healing phase. It also prevents further embolisation of the lipid core material. The atheromatous material often represents the source of a larger thrombus apposition and may immediately or subsequently lead to an enlargement of the infarct zone.

Exposure of denuded intimal layers—plaque erosion—may also produce mural or occlusive thrombus formation and also, like plaque ulceration, lead to type VIIc lesions which are clinically most often found in unstable angina and acute myocardial infarction. Luminal narrowing with increased flow velocity can induce disruption of mural thrombotic material from type VIIc lesions and also result in microembolisation. Even in high grade coronary artery stenosis, cycle flow variation with continuous platelet aggregation formation, increases in flow velocity, thrombi disruption, and microembolisation have been described. Therefore it is not surprising to find signs of coronary microemboli in patients with stable and unstable angina. The major difference between these clinical situations

**Figure 1** Effect of microembolisation on the development of infarctlets, arrhythmias, and ventricular dysfunction, and also on the induction of an inflammatory response which influences cardiac function and can also cause arrhythmias. Modified from Erbel R, Heusch G. Herz 1999;24:551–75.

Abbreviations: CFR, coronary flow reserve; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; TIMI, thrombolysis in myocardial infarction.
seems to be the number of episodes which are present in unstable angina (about 85%) and stable angina (70%), with microemboli in nearly 50% and 40%, and microinfarcts in about 45% and 30% of cases, respectively. Recurrent embolisation caused by remodelling of the platelet thrombus is also found. Platelet-rich thrombemboli have been demonstrated in up to 80% of patients with unstable angina and sudden death. If microembolisation occurs, a wide variety of clinical pictures can be induced, ranging from asymptomatic episodes only detected following analysis of cardiac markers and ECG recordings, up to the no-reflow phenomenon. Signs of subsequent microinfarcts are found even after exercise testing in coronary artery disease, depending on the extent of the disease and the need for further recanalisation. Vulnerable plaques are characterised by signs of inflammation, which can clinically be detected by determining cytokines, but also C reactive protein as well as fibrinogen. What is not yet understood is whether these signs are related to vulnerable plaques or are induced by microembolisation.

The microemboli induced symptoms seem unresponsive to glyceryl trinitrate, but the features have to be analysed in much more detail in the future. Signs of microinfarcts (infarctlets), based on analysis of cardiac markers and ECG recordings and elevation of C reactive protein, are much more often detected than previously reported. Many patients, previously classified as having unstable angina, are now defined as having non-ST segment myocardial infarction. This is found in up to 15% of cases. Recurrent embolisation may be induced, but he found no wash out of the microemboli. When Andreas Grüntzig introduced percutaneous transluminal coronary angioplasty (PTCA) in 1977, he thought that an increase in baseline flow velocity preferably characterises minor forms of embolic myocardial infarction. The overall better correlation between the cardiac marker troponin T/I, outcome, and CFR is explained by the experimental finding that an increase in baseline flow velocity preferably characterises minor forms of embolic myocardial infarction. The important role of inflammation in the presence of vulnerable plaques could be demonstrated by a close correlation between changes of coronary flow velocity after intervention and the pre-interventional level of C reactive protein, indicating that plaques with signs of inflammation are more prone to plaque rupture inducing larger showers of microemboli than those without inflammation. It may be, however, that our techniques are not yet sensitive enough. Catheters enabling theremography seem to be a very promising tool.

Postprocedural cardiac marker increase is neither rare nor a prognostically insignificant event, which has been shown by many studies. Importantly, minor rather than major myocardial injury can be found frequently, with troponin being of higher diagnostic value than creatine kinase. The correlation of cardiac mortality and overall major adverse cardiac events was found to be stronger with postprocedurally increased troponin than with postprocedurally increased creatine kinase. Patients at risk can be identified by determination of troponin within 24 hours after intervention.

Statins are highly effective in primary and secondary prevention of acute myocardial infarction and cardiac death. They induce a stabilisation of the coronary plaques by reducing the inflammatory response and the lipid core, and increasing the collagen content. The endothelial function also improves. These pleiotropic effects explain the cardioprotective profile of statins in ischaemia/reperfusion models. Pretreatment with statins resulted in a more than 90% reduction in the incidence of post-procedural elevation of cardiac markers and improvement of coronary flow, supporting a cardioprotective effect in coronary interventions. This effect can also be related to a reduction in circulating concentrations of C reactive protein with less severe postprocedural microvascular impairment, as a direct proinflammatory effect of C reactive protein on endothelial cells.
Thus, preprocedural statin treatment might improve postprocedural outcome by modulating the target lesion and/or the myocardial microcirculation. Also, preinterventional β-blocker treatment was found to reduce the risk of peri-interventional myocardial injury. Glycoprotein IIb/IIIa receptor inhibitors have also been shown to prevent at least major forms of peri-interventional myocardial injury, but not smaller forms as a result of large amounts of embolising debris in saphenous venous bypass grafts.

In acute myocardial infarction reopening of the occluded coronary vessel by thrombolytic treatment has proved successful in improving ventricular function and/or survival. Combined therapy, however, failed to demonstrate superior results to thrombolytic treatment alone. After thrombolytic treatment only 60% of patients have a full restoration of coronary blood flow (TIMI 3), whereas 20–30% still have reduced flow of TIMI 2. Using PTCA for reopening of occluded coronary vessels, TIMI flow 3 is achieved in 90% of patients. In the beginning of the thrombolytic area, vessels with TIMI flow 2 and 3 have been regarded as patent vessels and this criterion has been used to describe the efficacy of thrombolytic agents. However, patients with reduced coronary blood flow (TIMI 2) have reduced prognosis compared to patients with TIMI flow 3. This prognosis is as poor as if the vessels had never been opened. Using contrast echocardiography, it has been demonstrated that, despite reopening of coronary vessels in acute myocardial infarction, full restoration of myocardial perfusion is incomplete in parts of the patient’s heart. Areas with incomplete restoration of flow and reduced or no contrast opacification of the vessel related vessel may be an indicator of viable myocardium with functional improvement during follow up. Intracoronary Doppler flow velocity measurements demonstrate an increase in coronary flow velocity reserve in recanalised infarcted arteries which is also related to left ventricular recovery.

The incomplete restoration of ventricular function and perfusion may be explained by the so-called “no reflow” phenomenon resulting from PTCA—induced microthromboemboli, which may reverse spontaneously. Additionally, differences in collateral blood flow may play a role. Also, abnormalities of microvascular perfusion secondary to leucocyte plugging and microembolisation must be discussed. An increased expression of neutrophil and monocyte adhesion molecules could be shown. They may induce enhanced vasoconstriction, microvascular functional abnormalities caused by serotonin, thromboxane A2 or other substances, and induce local thrombotic effects caused by tissue factor expression secondary to monocyte adhesion. Activated leucocytes may form microaggregates, causing plugging in the microvasculature. New therapeutic options may be based on these findings.

After reopening of coronary vessels in acute myocardial infarction, recurrent chest pain as well as ST segment elevation can be observed in 10–15% of patients. Patients with this phenomenon have elevated creatine kinase, lower ejection fraction, and a worse prognosis than patients with a rapid decline of the ST segment after reopening of the vessel. This is also true for those patients who have permanent ST segment elevation compared to those with a transient ST shift. Permanent ST segment elevation is associated with extensive infarction and reduced recovery of ventricular function.

Coronary blood flow and ventricular function can be improved with glycoprotein IIb/IIIa antagonist treatment to reduce thrombus formation and fragmentation at the lesion site with subsequent distal microembolisation, resulting in improved myocardial perfusion.

**CLINICAL IMPLICATIONS**

These new clinical findings indicate the importance of the coronary microcirculation for clinical cardiology. New methodological techniques to study the coronary microcirculation have demonstrated an interaction between epicardial arteries and the microcirculation. Functional and morphological changes are observed in patients treated for coronary artery disease by interventional cardiology. Nearly 50% of the patients have reduced coronary flow reserve in the reference vessel—that is, microvasculature disease which is present even when no significant coronary luminal narrowing is evident. An interesting explanation may be the presence of spontaneous or interventionaly induced microembolisation after plaque rupture, which can be repetitive, recurrent, and lead to a significant reduction of myocardial and microvascular function even with normal or nearly normal coronary arteries.

Also, for ischaemic cardiomyopathy the pathogenesis could be repetitive coronary microembolisation after multiple plaque rupture and described as multilayered intimal thickening. Inflammation detected by elevation of C reactive proteins or cytokines can in part be the result of ongoing microembolisation.

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**REFERENCES**


IMAGES IN CARDIOLOGY

Significant inducible perfusion abnormality in an asymptomatic patient with hypertrophic cardiomyopathy demonstrated by radionuclide myocardial perfusion imaging

An asymptomatic 21 year old man with non-obstructive hypertrophic cardiomyopathy (HCM) was referred for radionuclide myocardial perfusion imaging for risk assessment.

Adenosine was infused at 140 µg/kg/min over six minutes with submaximal bicycle exercise and thallium-201 (80 MBq) was injected intravenously at three minutes. Stress images were acquired five minutes after injection and rest images one hour after subsequent resting injection of thallium-201 (40 MBq). Conventional emission tomographic imaging techniques were used.

The stress images (left hand panel) show inhomogeneity of tracer uptake in the septum but septal hypertrophy is not obvious and the images might be interpreted as normal. The rest images (right hand panel), however, show that the septum is hypertrophied with high tracer uptake. The ratio of counts in the septum and lateral walls reverses between the stress and rest images. The overall appearance is of a severe inducible perfusion abnormality in the hypertrophied septum, and this is presumably related to impaired perfusion reserve in the region of hypertrophy rather than obstructive coronary disease.

Risk assessment for sudden cardiac death is an integral part of the management of HCM. A high incidence of fixed and inducible perfusion abnormalities has been reported and these may lead to chest pain. However, the association between inducible ischaemia and sudden cardiac death is uncertain. Because stress uptake of tracer may appear normal in a region of hypertrophy, even if there is relative hypoperfusion, stress and rest images should always be compared in patients with known or suspected HCM who undergo radionuclide myocardial perfusion imaging.

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