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.1 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 indicates signs of inflammation.2 As these lesions are prone to rupture, they are regarded as vulnerable or plaques at risk.3 Plaques which are vulnerable are showing more vascular compensatory remodelling than non-vulnerable plaques.4 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).5

Apparently healthy subjects undergoing necropsy have experienced plaque rupture in 9% of cases, and patients with diabetes and hypertension in 17% of cases.6 Rupture (fig 1) accounts for > 60% of all thrombi associated with sudden coronary death and acute myocardial infarction, plaque erosion for 35%, and calcified noduli for 2–6%.7 Signs of plaque rupture are found in 85% of patients with unstable angina, but also in 15–25% with stable angina.8 Pathological and clinical studies have revealed multiple lesions, not only limited to a single coronary vessel but also in more than one vessel in unstable angina in mean (SD) 1.3 (1.4) hearts and in stable angina in 1.1 (1.3) hearts.9 Clinically 2.1–2.6 complicated lesions per patient were found in acute coronary syndromes with elevated cardiac markers, with a wide range from 0–6 lesions.10 These lesions are not limited to the dominant vessel with the culprit lesion, but are also found in the remaining coronary tree.

The development of multiple layering suggests repetitive, periodically occurring plaque rupture during life. Meanwhile the healing process of plaque rupture itself could be detected by intravascular ultrasound. Thrombus formation within the ulcer seems to be part of this healing process which results later in an attachment of the fibrous cap to the vessel wall, leading to plaque thickening. This mechanism seems to lead to progression of coronary artery disease, particularly when the effect of multiple events at the same site is taken into account.

Quantitative pathological anatomic analysis showed in fibroatheroma, thin walled atheroma, and ruptured plaques a mean (SD) necrotic core area of 1.2 (2.2), 1.7 (1.1), and 2.8 (5.5) mm² and a ratio of the necrotic core to the plaque size of 15 (20%), 23 (17%), and 34 (17%), respectively.5 Using similar definitions by intravascular ultrasound quantification the plaque ulcer measured 12 (13) mm² within a plaque size of 72 (53) mm².11 The ulcer volume measured up to 50 mm³.12 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 promoter 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.\textsuperscript{12}

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 microinfaracts are found even after exercise testing in coronary artery disease, depending on the extent of the disease and the need for further revascularisation. 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 microinfaracts (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 patients with unstable angina (about 85%) and stable angina (70%), with a concomitant microinfarct in nearly 50% and 40%, and microinfarct in unstable angina (about 85%) and stable angina (70%).

Of utmost importance is the finding that plaque rupture often occurs in the absence of a flow limiting stenosis, and can even be present when coronary angiography is negative or suggestive of a normal anatomy. This is found in up to 15% of unstable patients. Nearly 90% of patients with acute myocardial infarction have stenosis < 70\%\textsuperscript{15}

Since significant coronary luminal narrowing cannot explain the symptoms and signs of myocardial ischaemia, other pathophysiologic mechanisms have to be considered in addition to microembolisation:

- intermittent coronary spasm enhanced by plaque rupture with activation of platelets and leucocytes and release of vasoactive mediators, such as serotonin and endothelin
- imbalance of vasoconstriction and vasodilatation caused by endothelial damage and dysfunction, which may be enhanced by plaque haemorrhage (type VI b lesion)
- cyclic flow variations with recurrent platelet aggregation and thrombus formation and washout
- thrombus formation after plaque fissuring or rupture (type VI c lesion) which is not totally blocking the coronary artery, but may or may not embolise, as demonstrated by angiography and intravascular ultrasound
- plaque rupture and ulceration with microembolisation of plaque debris (type VI a lesions).

**INTERVENTIONAL CORONARY MICROEMBOLISATION**

When Andreas Grünzig introduced percutaneous transluminal coronary angioplasty (PTCA) in 1977, he thought that embolisation may be induced, but he found no wash out of plaque material into the distal coronary artery in experimental studies. Using PTCA a rise of cardiac markers was noticed only rarely, despite the fact that ECG recordings detected SFT segment changes in a large group of patients. The systemic determination of the new cardiac markers troponin T or I and the introduction of coronary stenting, as well as rotational angioplasty in percutaneous coronary intervention (PCI), led to a 5- to 10-fold increase of cases with so called “infarctlets”.\textsuperscript{14,15}

The prevalence of these laboratory findings was higher in patients with unstable than stable angina (34% vs 10\%), higher in patients after stenting than after PTCA (22% vs 4\%), and higher after recanalisation than after angioplasty of coronary artery stenosis. In patients undergoing coronary rotational angioplasty the highest percentage of patients with “infarctlets” (37\%) was observed. Independent predictors were high grade complicated type C lesions (American College of Cardiology/American Heart Association classification) and coronary dissection induced by PCI. Also plaque burden, but not cross sectional area at the reference or lesion site, was significantly related to rise of cardiac markers after PCI.\textsuperscript{16}

Analysis of coronary flow reserve (CFR) before and after PCI demonstrated that an improvement and even a normalisation could be reached.\textsuperscript{17} But an abnormal flow reserve persisted after PTCA in 23\% of patients, with a concomitant reduction in relative coronary flow reserve in up to 80\%. Using coronary stenting the rate of normalised CFR could be increased compared to PTCA alone. Even so, in more than 20\% of patients a reduced flow reserve was present, despite an open vessel with no residual stenosis and normal flow characteristics in other areas of the heart.\textsuperscript{18}

But an elevation of baseline coronary flow velocity could be detected, which was highest during rotational angioplasty and lower after stenting, resulting in a reduced CFR despite an increase in baseline (maximal) flow. Experimentally, an increase in baseline coronary flow velocity was observed when coronary microembolisation was induced leading to a reduced CFR, because maximal flow velocity remained constant or decreased slightly.\textsuperscript{19} With further microembolisation baseline flow velocity decreased, too. These findings were dependent on the size of the microemboli.\textsuperscript{20} Clinically, coronary flow impairment was associated with an elevation of both troponin and creatine phosphate kinase, supporting the idea of procedural related embolisation caused by plaque disruption, squeezing, and redistribution, resulting in myocardial injury.\textsuperscript{21} 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 injury.\textsuperscript{22} 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 thermography seem to be a very promising tool.

Postprocedural cardiac marker increase is neither rare nor a prognostically insignificant event, which has been shown by most studies.\textsuperscript{23} Importantly, marker 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.\textsuperscript{24,25}

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 postprocedural elevation of cardiac markers and improvement of coronary flow, supporting a cardioprotective effect in coronary interventions.\textsuperscript{26} 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, fails 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 thrombosis 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, vessels 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 enhancement of the myocardium in echocardiography have less improvement of ventricular function than areas with complete opacification. Full contrast opacification after reopening of the infarct related vessel is 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 complete 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 can 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 interventional induced microembolisation after plaque rupture, which can be repetitive, recurrent, and lead to a significant reduction of myocardial and microvasculature 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.

**Authors’ affiliations**

Correspondence to: Dr Raimund Erbel, Department of Cardiology, University Essen, Hufelandstrasser 55, D-45122 Essen, Germany; erbell@uni-essen.de / www.uni-essen.de/cardia

**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.

C Y Loong
E Reyes
S R Underwood
c.loong@rbh.nthames.nhs.uk

Stress
Rest
Spontaneous and interventional coronary microembolisation

R Erbel

*Heart* 2003 89: 986-989
doi: 10.1136/heart.89.9.986

Updated information and services can be found at:
http://heart.bmj.com/content/89/9/986

These include:

**References**
This article cites 24 articles, 13 of which you can access for free at:
http://heart.bmj.com/content/89/9/986#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Clinical diagnostic tests (4779)
- Drugs: cardiovascular system (8842)
- Intervventional cardiology (2933)
- Percutaneous intervention (964)
- Acute coronary syndromes (2742)
- Hypertension (3006)
- Diabetes (842)
- Echocardiography (2127)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/