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Triggers of perioperative myocardial ischaemia and infarction

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Cardiac complications are a major cause of morbidity and mortality after non-cardiac surgery.[58 64] However, the exact nature of perioperative myocardial injury remains elusive and an area of continued debate and controversy.[50 64] If triggers of perioperative myocardial ischaemic events could be identified, appropriately taken preventive measures might improve perioperative cardiac outcome. Identification of possible triggers of perioperative myocardial ischaemia and infarction requires knowledge of their incidence, diagnosis and characteristics; of the pathophysiology of acute coronary syndromes (ACS) in the non-surgical setting; and of factors and interventions that have been shown to affect perioperative myocardial injury. The following review will address these areas before attempting to define the possible mechanisms and triggers of perioperative myocardial ischaemia and infarction.

Incidence of perioperative myocardial ischaemia and infarction

Incidence of perioperative myocardial ischaemia

In patients with or at risk of coronary artery disease, the reported incidence of perioperative myocardial ischaemia varies considerably, i.e. between 20 and 63%.[27 46 49 58–61 81–83 87] In studies that examined the incidence of myocardial ischaemia throughout the entire perioperative period, postoperative myocardial ischaemia was consistently found to occur considerably more often than preoperative (ratio approximately 3:1) and intraoperative ischaemia (ratio approximately 5:1).[60 61 81–83 87]

Postoperative myocardial ischaemia seems to be the best predictor of in-hospital and long-term cardiac morbidity and mortality.[11 26 46 59–61 69] It increased the relative risk of experiencing an early postoperative cardiac event (e.g. myocardial infarction, unstable angina, congestive heart failure) by a factor between 9[59] and 21.[46] Postoperative myocardial ischaemia also increased the odds for long-term (30 days to 2 years after surgery) cardiac events (unstable angina, non-fatal myocardial infarction, cardiac death, surgical coronary revascularization) 2.2-fold.[61] In-hospital postoperative myocardial ischaemia preceded long-term adverse cardiac outcome in up to 70%.[46 59]

Incidence of perioperative myocardial infarction

The reported incidence of postoperative cardiac events (the combined incidence of non-fatal myocardial infarction, unstable angina, congestive heart failure, cardiac death) varies between 5.5 and 53%[61 81 82 86 87] and that of postoperative myocardial infarction between 1.4 and 38%.[27 44 46 48 51 61 69 81–83 86 87] Postoperative myocardial infarction increased the odds for long-term cardiac events 20-fold.[61] The various findings would suggest that postoperative cardiac outcome is more affected by postoperative factors that cause myocardial ischaemia than by the patient's preoperative cardiac status.

Definition and diagnosis of perioperative myocardial ischaemia and infarction

Definition and diagnosis of perioperative myocardial ischaemia

The incidence of perioperative myocardial ischaemia and infarction will obviously be affected by their definition and method of detection. There is no accepted gold standard for the diagnosis of myocardial ischaemia. Generally, the diagnosis can be based on haemodynamic (pulmonary artery capillary wedge and/or left atrial pressure wave), electrocardiographic (ECG), functional (echocardiogram), metabolic (coronary lactate production), biochemical (release of creatine kinase-MB isoenzyme and/or troponin) or regional perfusion (scintigram) parameters. All techniques

have considerable limitations regarding sensitivity and specificity. Correlation between the different techniques is astonishingly poor. Depending on the method used to detect myocardial ischaemia, the incidence of perioperative myocardial ischaemia may vary by a factor of 5.[39]

Perioperative myocardial ischaemia has predominantly been detected and defined by ECG. The reported incidence of perioperative myocardial ischaemia will, thus, greatly depend on choice and number of precordial leads, on the definition of ischaemic ST-segment change (extent and duration of ST-segment change), and on the mode of data acquisition (continuous *vs* intermittent).[57] Holter monitor-detected myocardial ischaemia has a sensitivity of 37–50% and a specificity of 88–92%.[88 101] Continuous 12-lead electrocardiography improves sensitivity to 61–90%[56] and 66–97%.[49]

The reported incidence of ECG-defined myocardial ischaemia will also depend on the suitability of patients for reliable detection of ischaemia-specific ECG changes. Patients with left ventricular hypertrophy and those not in sinus rhythm are not suitable for ECG-derived diagnosis of myocardial ischaemia. In addition, perioperative changes in acid–base balance and electrolytes can affect the ECG in a way that interferes with ischaemia detection. Thus, apart from differences in the prevalence of underlying ischaemic heart disease and in the type of surgical risk, the high variability in the reported incidence of perioperative myocardial ischaemia is probably due to methodological problems.

Definition and diagnosis of perioperative myocardial infarction

Fundamental questions remain regarding the definition and diagnostic criteria of myocardial infarction in general[2] and in the perioperative period in particular.[64] According to the definition of the World Health Organization (WHO), at least two of three criteria must be fulfilled to diagnose myocardial infarction: typical ischaemic chest pain; increased serum concentration of creatine kinase-MB isoenzyme; and typical electrocardiographic findings, including development of pathological Q-waves.[108 115] This definition provides adequate specificity but lacks high sensitivity.

The development of assays for the cardiac troponins T and I, which are highly specific and sensitive for myocardial injury, formed the basis of a revised definition of myocardial infarction proposed by the European Society of Cardiology and the American College of Cardiology.[105] The following two criteria satisfy the diagnosis of an acute, evolving or recent myocardial infarction: (i) a typical increase and gradual decrease in troponin concentrations or more rapid increase and decrease in creatine kinase-MB concentration in combination with at least one of the following: (a) typical ischaemic symptoms, (b) development of pathological Q-waves in the ECG, (c) ECG changes indicative of myocardial ischaemia (ST-segment elevation or depression), and (d) coronary artery intervention; and (ii) pathological findings of an acute myocardial infarction.

Depending on whether myocardial infarction was defined by WHO criteria[115] or by an increase in serum concentration of troponin I of >1.5 ng ml^{-1} respectively, the incidence of postoperative myocardial infarction was 3 or 12%.[44] Similarly, depending on whether myocardial infarction was defined by the typical creatine kinase-MB isoenzyme criteria or an increase in serum concentration of troponin T of >0.1 ng ml^{-1}, the incidence of postoperative myocardial infarction was 1.4 or 17%, respectively.[51] Creatine kinase-MB is relatively inaccurate in detecting postoperative myocardial infarction.[1] Other definitions of postoperative myocardial infarction include an increase in serum concentration of troponin I $\geqslant$3.1 ng ml^{-1} accompanied by at least one of the following: typical ischaemic symptoms, ECG changes indicative of myocardial ischaemia (ST-segment depression or elevation) or new pathological Q-waves. By this definition, the incidence of postoperative myocardial infarction was 6.5%.[48]

The question remains whether a reported incidence of perioperative myocardial injury based on traditional definition underestimates the true incidence of clinically relevant myocardial injury or whether a reported incidence based on serum concentrations of troponins overestimates it. When using exclusively biochemical markers, specificity may be sacrificed for sensitivity. Another question is whether biochemical marker-defined myocardial injury carries the same predictive value as traditionally defined infarctions, and whether mechanisms and triggers are identical in both cases.

Characteristics of postoperative myocardial ischaemia

The majority of postoperative myocardial ischaemia in high-risk patients tends to develop on the day of or the day after surgery, most ischaemic episodes starting at the end of surgery and during emergence from anaesthesia.[48] The vast majority (more than 90%) of postoperative episodes of myocardial ischaemia are silent.[46 60] Postoperative ST-segment changes are almost exclusively episodes of ST-segment depression rather than elevation.[27 48 56 59 60]

The findings on the relationship between short-term changes in haemodynamics and the incidence of postoperative myocardial ischaemia are contradictory. Most studies did not find any association between changes in heart rate and postoperative ST-segment changes[59 60 87] or troponin release.[89] In one study, however, all episodes of ST-segment depression were preceded by increases in heart rate.[48] Overall evidence would suggest that heart rate is not a reliable independent predictor of postoperative ST-segment depression and troponin release.

Characteristics of postoperative myocardial infarction

Clinical and electrophysiological characteristics

Most postoperative myocardial infarctions occur early after surgery and are asymptomatic,[6] and most of them (60–100%) are of the non-Q-wave type.[6 27 46 49] The vast majority of perioperative myocardial infarctions are preceded by episodes of ST-segment depression.[46 48 69 81 82] Long-duration (single duration >20–30 min or cumulative duration >1–2 h) ST-segment change, rather than merely the presence of postoperative ST-segment depression, seems to be the important factor associated with adverse cardiac outcome.[46 69 83] Short ischaemic episodes (<10 min) did not correlate with postoperative myocardial infarction and cardiac complications.[46 48] However, seven patients with postoperative myocardial ischaemia lasting longer than 2 h did not sustain an ischaemic cardiac event.[27]

Pathological characteristics

In an autopsy study from the 1930s, fatal perioperative myocardial infarction was accompanied by thrombosis of the coronary artery supplying the infarcted area.[68] Following fatal perioperative myocardial infarction, the vast majority (93%) of 42 autopsy heart specimens showed significant atherosclerotic coronary artery obstruction.[20] There was evidence of plaque disruption in 55%, and evidence of plaque haemorrhage in 45% of 42 autopsy heart specimens. In more than half the patients, the site of infarction could not have been predicted from the severity of the underlying stenosis.

Such findings are similar to those in autopsies after acute myocardial infarction in the non-operative setting, suggesting that perioperative myocardial infarction has a coronary pathology similar to that of myocardial infarction in the non-operative setting with regard to coronary plaque haemorrhage, rupture and thrombus formation. Acute plaque disruption in the infarct-related coronary artery seems to be common, but the severity of underlying coronary artery stenosis does not predict the infarct territory. Such similarities would suggest that perioperative and non-perioperative myocardial infarctions occur by similar mechanisms.

Angiographic characteristics

When compared with a matched control group without perioperative death or myocardial infarction, patients who experienced perioperative myocardial infarctions had more angiographic evidence of extensive coronary artery disease (as reflected by a larger number of affected coronary arteries, high-grade stenoses and collateralized total occlusions).[22] However, high-grade stenoses were an uncommon cause of complications. Inadequate collateralization of total occlusions seemed to have been the most common cause of infarction. In addition, in a third of the patients with perioperative cardiac events, a culprit site could not be identified (i.e. the coronary artery supplying the infarcted territory).[22]

In agreement with the latter finding, coronary angiography performed in three patients within 7 days of postoperative myocardial infarction revealed chronic, severe coronary artery disease but no angiographically visible thrombus or ruptured plaques.[48] Such findings are consistent with the possibility that, in some patients with severe but stable coronary artery disease, postoperative myocardial infarction may develop because of prolonged myocardial ischaemia rather than because of acute plaque rupture and/or coronary thrombosis.

Pathophysiology of myocardial ischaemia

Myocardial ischaemia is characterized by an imbalance between myocardial oxygen supply and demand. Supply- or low-flow ischaemia (reduction in oxygen supply due to coronary vasoconstriction, intracoronary platelet aggregation or thrombus formation) is mostly responsible for myocardial infarction and unstable angina. Demand- or high-flow ischaemia is mostly responsible for ischaemic episodes in chronic stable angina (increase in myocardial oxygen demand, as in tachycardia, exercise or emotional stress) in the presence of fixed coronary artery stenoses. Often, myocardial ischaemia results from both a reduction in supply and an increase in demand.

Endothelial function is impaired in coronary artery disease, and is an important cause of myocardial ischaemia. Stimuli that are accompanied by activation of the sympathetic nervous system, by increases in circulating catecholamines and by increases in coronary blood flow secondary to an increase in myocardial oxygen demand (e.g. during exercise, mental stress or increase in heart rate) induce vasodilatation in normal coronary arteries. However, in atherosclerotic coronary arteries with endothelial dysfunction these stimuli can lead to paradoxical vasoconstriction.[99 116] Acute myocardial ischaemia intensifies these paradoxical vascular responses. Such limitation of coronary flow as a result of paradoxical coronary vasoconstriction, and the inability of vessels to dilate near the site of an atherosclerotic plaque, may result in regional myocardial supply- or low-flow ischaemia.

The most common electrocardiographic finding during episodes of symptomatic or silent myocardial ischaemia in patients with chronic stable angina pectoris is ST-segment depression. When ischaemia is confined predominantly to the subendocardium, the overlying ECG leads show ST-segment depression.[71] This subendocardial pattern is typical of spontaneous ischaemic episodes of angina pectoris or during symptomatic or asymptomatic ('silent') ischaemia induced by exercise or by a stress test. Less obstructive thrombi and/or those that consist of less robust fibrin and more platelet aggregates usually produce ST-segment depression and/or T-wave inversion.

Pathophysiology of myocardial infarction

Myocardial infarction is defined as the death of myocardial myocytes due to prolonged ischaemia.[105] When intraluminal thrombi attach to a ruptured plaque, total occlusion of an epicardial coronary artery may occur, resulting in total interruption of nutrient blood flow to the myocardium. The situation may be worsened by distal embolization of microthrombi and by coronary vasoconstriction induced by local, mediator release-induced or systemic sympathetic activation. If coronary blood flow is interrupted for longer than 30 min, myocardial infarction may result. Persistent coronary artery occlusion will cause a progressive increase in infarct size. Loss of functional myocardium results in impaired left ventricular function, which may impair quality of life and usually leads to premature death.[8]

Any attempt to define triggers of acute coronary syndromes (ACS) must take into account the extreme variations in clinical presentation. At one end of the spectrum are those patients who suffer a sudden cardiac death or a myocardial infarction without any preceding episode of angina, and not followed by recurrent instability. At the other end of the spectrum are those patients who develop a myocardial infarction after episodes of unstable angina over a period of days to weeks, and who often develop postinfarction angina and/or reinfarction. It is conceivable that the triggers of instability differ between such groups of patients.

Up to very recently, ulcerative, fissured and/or thrombotic coronary plaques that are characterized histologically by a central lipid core, inflammatory cell infiltrate and fibrous cap thinning have been termed 'vulnerable'.[73] The popular view that a vulnerable plaque constitutes the final common pathway that leads to the atherothrombotic events ignores not only the numerous, diverse triggers of acute coronary events but also the contributory role of blood rheology and coagulation ('high-risk blood'). A more dynamic and inclusive concept seems appropriate.[16 43 67]

Structural (central lipid core, thin cap) and functional (plaque thrombogenicity, intraplaque inflammatory cell infiltrate) factors interact in an unpredictable fashion. Exogenous factors (e.g. mechanical stress, vasomotor tone, infection, blood viscosity and coagulability) further modify such interaction, making the final outcome even less predictable. The transition from stable coronary artery disease to the ACS of non-Q-wave and Q-wave infarction and unstable angina is characterized by coronary plaque disruption and subsequent thrombosis, which constitute the major pathogenetic components of unstable or vulnerable plaques.[67] However, at least in some cases and irrespective of the presence of unstable or stable plaques, a thrombogenic state or high-risk blood is likely to contribute to ACS.[33]

Comprehensive post-mortem studies no longer support the view that rupture of atheromatous (vulnerable) coronary plaques are the result of mostly localized mechanical shear stress forces, and that a single type of culprit coronary plaque is the only cause of instability.[19 92] Inflammatory mechanisms and structural and functional plaque characteristics have received increasing attention.[13 67 111]

Structural and functional characteristics of acute coronary syndromes

In contrast to stable coronary artery disease, ACS are characterized by complex coronary plaques and stenoses, coronary endothelial erosions, plaques fissures, fresh thrombi, and plaque inflammation.[67 111] The factors leading to unstable plaques (which ultimately trigger ACS) are structurally and functionally multiple and complex. In some cases, thrombogenic 'high-risk' blood may be required to trigger ACS.

Structurally vulnerable plaques

Plaques with a central lipid core of >40% of the total lesion area and a cap thickness of ≈65–150 mm are potentially vulnerable to mechanical stress and/or inflammatory weakening of their collagen structure, and they may rupture even if they cause a stenosis that is not visible on X-ray angiography.[67] In the context of the perioperative period, it is important to remember that the prevalence of structurally vulnerable plaques is also high in patients with stable coronary artery disease[13] and correlates with the total atherothrombotic burden.[23] However, it is impossible to predict the time it will take the structurally vulnerable plaque to become unstable, or the trigger that causes the plaque to rupture (i.e. mechanical stress, coronary vasospasm, widespread acute inflammatory endothelial activation, or the chronic inflammatory component of atherosclerosis).

Functionally vulnerable plaques

In a substantial percentage of culprit lesions, thrombosed plaques without detectable fissures were observed.[19] In such cases, plaque vulnerability is probably caused by thrombogenic or high-risk blood and/or local proinflammatory cytokines that trigger thrombosis, sometimes even in the absence of inflammatory cell infiltration and a lipid core.[111]

Complex coronary artery stenoses

Complex coronary artery stenoses, consisting of a variable combination of plaque fissuring and thrombosis, appear to be the hallmark morphological characteristic of ACS. However, the fate of these complex coronary stenoses is highly variable. They may remain complex but become functionally stable, or they may even become smooth after having undergone remodelling. This explains why a substantial fraction of patients with stable coronary artery disease demonstrate angiographically complex lesions.

Thus, neither complex (as typically found in ACS) nor flow-limiting coronary stenoses (as typically found in stable angina) are isolated morphological substrates of instability. However, multiple angiographically complex lesions correlated with instability[37] and elevated C-reactive protein (CRP) concentrations.[117]

Coronary endothelial erosions

Although fissure of the culprit lesion is the prominent finding in some patients with ACS, in 20–40% of ACS cases coronary thrombi have been observed to overlie atherosclerotic plaques without disruption of the fibrous cap, but with endothelial lesions underneath or above stenotic or non-stenotic plaques of variable morphological characteristics (e.g. with or without inflammatory cell infiltrates, with or without a lipid core).[14 24 28 100 109 111] The thrombi overlie plaques with only superficial endothelial erosion. These erosions are particularly common in young victims of sudden death, in smokers and in women. Under such conditions, thrombus formation may depend on hyperthrombogenicity-inducing systemic factors, such as hypercholesterolaemia, increased concentrations of catecholamines, diabetes, smoking, infection, a hypercoagulable state (with elevated serum concentrations of fibrinogen, von Willebrand factor, and factor VII) and a defective fibrinolytic state (with increased serum concentrations of plasminogen activator inhibitor 1 and decreased concentrations of tissue plasminogen activator and urokinase).[18] Systemic factors, including elevated low-density lipoprotein cholesterol, cigarette smoking, hyperglycaemia and others, are associated with increased blood thrombogenicity.[90] As erosion of plaques without the typical features of a vulnerable plaque (fissuring, thin fibrous cap, lipid-rich core) may result in ACS, the generic term 'high-risk' plaque may be more appropriate than 'vulnerable' plaque.[67]

Plaque inflammation

In ACS, 30–40% of coronary thrombi overlie plaques that often contain inflammatory cell infiltrates, are denuded of endothelium, and often, if not mostly, have luminal inflammation.[4 12 109] Activated T cells in the non-culprit arteries and systemic circulation[15 104] were demonstrated in patients with unstable angina. These findings are consistent with recent evidence that the serum concentration of CRP better predicts the risk of myocardial infarction and stroke than total and low-density lipoprotein cholesterol concentrations.[95] The incidence of elevated CRP serum concentrations is less than 50%, 70% and 100% in patients with very early myocardial infarction not preceded by unstable angina, severe unstable angina, and very early acute myocardial infarction preceded by unstable angina, respectively.[54 55] In addition, the persistence of elevated markers of systemic inflammation predicts recurrence of instability.[9] However, inflammatory cell infiltration is not uncommon in patients with stable coronary artery disease.[100]

In the event of plaque rupture, thrombus growth depends not only on the size and thrombogenicity of the fissured plaque, but also on the number and activation of exposed inflammatory cells.[33] Inflammatory activation of the endothelium can turn its physiological vasodilatory and antithrombotic properties into pathological vasoconstrictor and prothrombotic properties. In addition, the inflammatory response of the circulating blood may activate coagulation.[97]

Plaque progression

Plaque progression is often abrupt and mostly unpredictable.[16] Three facts are worthwhile recalling. First, plaque progression and clinical outcome are not always closely correlated, and each is poorly predicted by clinical and angiographic variables. Most plaques that underlie a fatal or nonfatal myocardial infarction stenose angiographically the respective coronary artery by less than 70%. Approximately 60% of those infarcts are caused by rupture of plaques which carry the characteristics of 'vulnerability' (i.e. large thrombogenic core of lipid and necrotic debris, and a thin ruptured cap). Secondly, plaques often progress episodically in relation to episodes of thrombosis (which, in turn, are triggered by plaque rupture, erosion, endothelial activation or inflammation). In the absence of a hypercoagulable state, thrombi may remain mural rather than become occlusive, and may thus produce few if any symptoms (unless they embolize).[66] If subsequent lysis is incomplete and is followed by re-endothelialization, the plaque will grow. Thirdly, plaques in a given patient often progress largely independently.[36]

These are all reasons for the unpredictability of individual patient outcome. Part of this unpredictability is probably related to fluctuations of risk factors and triggers (e.g. physical activity, mental stress, environmental temperature, smoking, infection, hydration and blood pressure). However, most of the independent plaque behaviour in a given patient is probably due to pronounced heterogeneity of plaque histology and to differences in the physical forces to which plaques are exposed.[25 35]

Pathogenesis of plaque rupture

The pathogenesis of plaque rupture involves both biochemical and physical factors. Rupture of the intimal surface is the result of a combination of cellular processes that promote plaque instability and physical (haemodynamic) processes that influence the magnitude and distribution of stress on the plaque. When intimal rupture occurs, the content of the plaque is important. Unstable plaques contain twice as much tissue factor and plasminogen activator inhibitor-1 than stable plaques.[107]

Passive plaque disruption is related to physical forces, and it occurs most frequently where the fibrous cap is weakest. Three main factors determine the vulnerability of the fibrous cap: (i) circumferential wall stress or cap fatigue; (ii) the location, size and consistency of the atheromatous core; and (iii) blood-flow characteristics, particularly the impact of flow on the proximal aspect of the plaque.[23]

The size of the thrombus that forms at the site of plaque rupture and the clinical consequences will depend on several key factors: the depth of injury, the composition of the plaque, the magnitude of the stenosis, and the extent of platelet activation and intrinsic fibrinolytic activity.[28] The degree of plaque disruption (ulceration, fissure or erosion) and substrate exposure is a key factor in determining thrombogenicity at the local coronary artery site. Both plaque composition and its propensity to rupture are major determinants of future ischaemic events.[18] These many variables explain why coronary lesions that are angiographically fairly small may progress acutely to severe stenosis or total occlusion, and may account for as many as two-thirds of the patients who develop unstable angina or other ACS.[23]

Physical factors in plaque rupture

ACS follow a circadian rhythm.[73 74] This indicates that cardiac events do not occur entirely randomly and may be triggered by external activities. The likelihood of plaque rupture may be increased after awakening by the 20–30 mm Hg increase in systolic blood pressure that occurs during the morning hours. The parallel increase in heart rate not only increases myocardial oxygen demand and decreases myocardial oxygen supply by decreasing diastolic filling time, but may also predispose to myocardial ischaemia by affecting the rheological properties at the site of a plaque and by predisposing the plaque to rupture. In the morning hours, increased vascular tone (placing additional haemodynamic stress on the plaque), platelet hyperreactivity, increased blood viscosity, a nadir of fibrinolytic activity, and reduced level of tissue plasminogen activator have been observed.[106] Interestingly, and possibly relevant to the perioperative setting, the diurnal variation in plaque rupture is eliminated by β-blockers and by aspirin.[93]

Consistent with the finding of a circadian rhythm of ACS, plaque rupture is more common during various kinds of strenuous physical activity, including exercise stress testing and emotional stress.[72] In all of these situations, the sympathetic nervous system is activated. This leads to increased plasma concentrations of catecholamines, blood viscosity, and increases in blood pressure and heart rate, which are accompanied by detectable increases in platelet aggregation and decreases in fibrinolytic activity that both tend to favour thrombosis.[38] This combination of increased prothrombotic and reduced fibrinolytic activity could initiate propagation and total occlusion of the coronary artery by a mural thrombus overlying a small plaque erosion that might otherwise have been harmless. Similar physiological processes may trigger ischaemic cardiac events in the perioperative period (a time that is characterized by comparable adrenergic stimulation) and increased prothrombotic and reduced fibrinolytic activity.

Factors and interventions affecting perioperative cardiac outcome

Definition of possible triggers of perioperative myocardial ischaemia and infarction may be helped by looking at factors that have been shown to increase perioperative cardiac events and interventions that have been shown to reduce such events.

Factors associated with postoperative myocardial ischaemia

Postoperative myocardial ischaemia has been shown to be associated with postoperative anaemia,[78] postoperative hypothermia[29 30] and pain.[7 62] Anaemia, hypothermia and pain will all activate sympathetic tone with the adverse effects on cardiovascular function and coagulation. The result will be an increase in myocardial oxygen consumption in the presence of a decrease in delivery.

Interventions associated with improved perioperative cardiac outcome

β-Adrenoceptor antagonists

Perioperative β-blocker therapy can provide a 60–65% reduction in the likelihood of non-fatal myocardial infarction and cardiac death.[5 63 84] The protective effect of perioperative β-blocker therapy on perioperative cardiac outcome in patients with suspected or documented coronary artery disease may well be due to its ability to reduce the incidence and severity of perioperative myocardial ischaemia.[112]

The exact mechanism by which β-adrenoceptor antagonists reduce postoperative myocardial ischaemia remains to be determined. In the heart, β-adrenoceptor blockade improves myocardial oxygen balance by reductions in heart rate, blood pressure and contractility. A reduction in blood pressure and pulse rate at rest or with exercise with β-blockers may reduce the propensity for plaque disruption by reducing circumferential stress on the fibrous caps of lipid-rich plaques. In addition to these possible benefits, β-blockers also have anti-arrhythmic properties.

In the central nervous system, β-blocker therapy leads to a reduction in peripheral sympathetic nerve discharge. The biochemical effects of β-adrenoceptor blockade include anti-atherogenic effects (e.g. decreased endothelial injury), increased production of prostacyclins, inhibition of platelet accumulation, and decreased affinity of low-density lipoprotein to proteoglycans in the vessel wall.

α_2-Adrenoceptor agonists

α_2-Adrenoceptor agonists reduce perioperative mortality and myocardial ischaemia after non-cardiac surgery, and myocardial infarction after vascular surgery.[70 79 80 113] The mechanism of their protective effect is likely to be manifold. α_2-Adrenoceptor agonists attenuate perioperative haemodynamic instability,[70] inhibit central sympathetic discharge,[75] reduce peripheral norepinephrine release[21] and dilate poststenotic coronary vessels.[40]

Aspirin

Early postoperative administration of aspirin improved outcome after coronary artery bypass surgery.[65] Aspirin is known to reduce cardiac events in patients with acute coronary syndromes and in patients not known to have coronary heart disease.[17] It eliminates the diurnal variation in plaque rupture.[93] Compared with controls, patients with unstable angina have more than twice the blood concentrations of interleukin-6, CRP and macrophage colony-stimulating factor.[41] These concentrations decreased after 6 weeks of aspirin treatment. Aspirin will, of course, reduce platelet aggregability, but its ability to reduce future myocardial infarction appears greatest in individuals with serological evidence of increased inflammation.[94] Thus, the anti-inflammatory effect of aspirin may be additive to its antithrombotic effect in patients with plaque instability.

Statins

A retrospective case–control study provided evidence that the preoperative use of statins may be associated with reduced perioperative mortality in patients undergoing major vascular surgery.[85] Patients on preoperative statin therapy had a more than 4-fold reduction in perioperative mortality. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A. Their direct effect on vascular function may result in coronary plaque stabilization.[52] Statins possess anti-inflammatory action and reverse endothelial dysfunction.[52] The beneficial effect of statins on perioperative outcome was comparable between users and non-users of β-blockers.

Mechanisms and triggers of perioperative myocardial injury

All studies consistently found an association between perioperative myocardial ischaemia (defined by ST-segment changes) and perioperative cardiac morbidity. Furthermore, postoperative cardiac complications were preceded almost universally by long- rather than short-duration ST-segment changes, the ST-segment changes consisted almost exclusively of depression rather than elevation, and most postoperative myocardial infarctions were of the non-Q-wave rather than the Q-wave type. These characteristics of perioperative myocardial ischaemia may have several explanations: (i) prolonged perioperative myocardial ischaemia leads to myocardial infarction; (ii) repeated and prolonged ST-segment depression reflects the onset of a permanent cardiac event (e.g. myocardial infarction); and (iii) perioperative myocardial ischaemia and infarction are two separate events that both develop on the basis of underlying coronary artery disease.

There is pathological evidence that the pathogenesis and pathophysiology of perioperative myocardial infarction (i.e. acute plaque rupture and coronary thrombosis caused by acute increases in blood pressure, heart rate, coronary vasomotor tone and platelet aggregability and decreased fibrinolytic activity) resemble those in the non-surgical setting.[20] On the other hand, the combination of consistent increases in heart rate preceding the ischaemic episodes, ST-segment depression rather than elevation during literally all ischaemic episodes, non-Q-wave rather than Q-wave myocardial infarctions in all cases of myocardial infarctions, the lack of angiographically visible thrombus or ruptured plaques in patients who underwent coronary angiography after postoperative myocardial infarction, and the complete reversal of ECG changes to baseline in all but one of the patients with ischaemia (including those with infarction)[48] is highly suggestive that prolonged stress-induced myocardial ischaemia is the likely primary cause of postoperative myocardial infarction. Repeated brief ischaemic episodes may well have a cumulative effect and ultimately cause myocardial necrosis.[34]

Although ST-segment depression usually reflects subendocardial ischaemia and is often regarded as reversible injury, it is not inconsistent with a myocardial infarction. Especially elderly patients may present with myocardial infarction without ST-segment elevation.[45] In most studies on perioperative cardiac ischaemic events, the study populations consisted largely of elderly patients. Thus, prolonged ST-segment depression may reflect either ongoing myocardial ischaemia (ultimately leading to myocardial infarction) or the beginning of an evolving myocardial infarction.

Although postoperative cardiac complications were mostly associated with only long-duration ST-segment depression, not all investigations found such an association.[27] In addition, most studies did not find a correlation between acute increases in heart rate and myocardial ischaemia and infarction. This lack of a consistent association between heart rate and the length of postoperative ST-segment depression on the one hand and an adverse cardiac outcome on the other would argue for non-ischaemic causes of ST-segment depression in the perioperative period (e.g. hyperventilation, electrolyte changes, drug effects, positional changes), for compensatory mechanisms to myocardial ischaemia (e.g. preconditioning as a result of multiple brief episodes of myocardial ischaemia and coronary reperfusion,[91] or for functional collateral perfusion).[96]

The preponderance of non-Q-wave infarctions is clearly different from what is found in the non-surgical setting. This, again, would indicate that perioperative myocardial infarctions are more often the result of prolonged ischaemia

than of thrombotic occlusion, similar to the presumed pathophysiology of silent ischaemia.[102] In contrast to the usual coronary thrombotic occlusion after an acute plaque disruption, in the presence of severe but stable coronary artery disease coronary thrombosis may result from a decrease in coronary blood flow and stasis.[31 32] Some patients with stenotic atherosclerotic lesions may develop acute myocardial infarction without evidence for plaque rupture and superimposed thrombus formation. This may happen if there is a marked decrease in myocardial oxygen supply (e.g. prolonged severe coronary vasospasm) or a marked increase in myocardial oxygen demand. These infarcts are located along the least well-perfused inner portions of the ventricular wall and often extend beyond the territory of just one coronary artery.[3] Such decrease in coronary blood flow in the presence of severe coronary artery disease may occur during tachycardia, which considerably shortens diastolic and, thus, coronary filling time[42] and which can narrow atherosclerotic coronary arteries.[76] Myocardial ischaemia-induced coronary vasoconstriction may further decrease coronary blood flow.[98]

It is thus conceivable that coronary thrombosis in the postoperative setting is the consequence rather than the cause of prolonged myocardial ischaemia and postoperative myocardial infarction. This possibility is consistent with the finding that both diabetes mellitus and left ventricular hypertrophy are independent predictors of postoperative myocardial ischaemia.[48] Both conditions are accompanied by limited coronary flow reserve and microvascular dysfunction.[77 103]

Most ischaemic episodes tend to start at the end of surgery and during emergence from anaesthesia.[48] This period is characterized by increases in heart rate, blood pressure, sympathetic tone and procoagulant activity.[10] Increased sympathetic tone can result in increases in blood pressure, heart rate, contractility, coronary vasomotor tone and coronary vascular shear stress. This, in turn, may trigger coronary vasospam, plaque disruption and coronary thrombosis. However, if this were the primary mechanism of postoperative myocardial ischaemia and infarction, ST-segment elevations and more frequent Q-wave infarctions would be expected.

Increases in blood pressure, heart rate and cardiac contractility lead to subendocardial ischaemia by increasing myocardial oxygen demand in the presence of limited or absent coronary vasodilator reserve due to underlying coronary artery disease. In the experimental animal, prolonged (1–4 h) tachycardia-induced ischaemia in the presence of a fixed critical coronary artery stenosis led to a progressive decline in subendocardial blood flow and diffuse subendocardial necrosis.[47]

Surgery induces a state of hypercoagulability on the basis of increased number and reactivity of platelets, increased concentration of fibrinogen and other proteins of the coagulation cascade (factor VIII, von Willebrand factor, α_1-antitrypsin), impaired deformability of erythrocytes, and a decrease in the concentration of proteins that are active in the fibrinolytic system (protein C, antithrombin III, α_2-macroglobulin). Such simultaneous procoagulant and antifibrinolytic activity may trigger coronary artery thrombosis during low-flow conditions in the presence of underlying stable coronary artery disease even in the absence of acute plaque disruption. The ultimate fate of the thrombus and, thus, the extent of jeopardized myocardium will depend on the duration and degree of coronary occlusion, which in turn will depend on the balance between thrombosis and lysis, and on flow conditions (affected by coronary vasomotor tone, perfusion pressure, and the rheological properties of the blood).

Conclusions

The mechanism(s) and trigger(s) of perioperative myocardial ischaemia and infarction remain poorly understood.[50 58] Existing data are inconclusive and do not allow us to decide definitively whether long-duration subendocardial myocardial ischaemia, or acute coronary occlusion due to plaque disruption or thrombosis, is the primary mechanism of perioperative myocardial injury in the individual patient. This uncertainty is to be expected considering the enormous structural and functional diversity of coronary atherosclerosis, the unpredictability of plaque progression and vulnerability, and the remaining methodological problems of reliably detecting and diagnosing perioperative myocardial ischaemia and infarction.

In many patients with unstable coronary artery disease, numerous mechanisms are responsible for the unstable nature of the disease. These include coronary artery thrombosis, platelet aggregation and emboli, progression of coronary artery disease, coronary artery vasospasm and vasoconstriction, systemic and local inflammation and infection, and increased myocardial oxygen demand in the presence of a fixed stenosis.

In the perioperative period, patients with coronary artery disease may develop a (temporary?) biochemical milieu that predisposes them to widespread plaque degeneration and/or accelerated subsequent thrombus formation. Sudden rupture of a vulnerable plaque may occur spontaneously without apparent reason, or it may follow a particular event, such as extreme cardiovascular demand, exposure to cold, or acute infection.[73 114]

Myocardial infarctions usually occur at sites that previously caused only angiographically determined mild to moderate luminal stenosis.[23 53] This indicates that plaque transformation from the stable to the vulnerable state can be acute and helps to explain the observation that chronic, stable coronary atherosclerosis can transform into acute, potentially life-threatening coronary events at any time. Widespread waxing and waning of coronary inflammation and/or of systemic blood thrombogenicity may contribute to the development of plaque vulnerability, in the absence or presence of underlying structurally vulnerable plaques.

Some patients may remain vulnerable for a period of weeks to months. In such (chronically) inflamed patients it is possible that plaques will suddenly flare up and become unstable, even in the absence of inflammatory cell infiltration and a central lipid core. Plaque rupture may occur without clinical manifestations (silent plaque rupture).

The symptoms associated with unstable coronary syndromes result from myocardial ischaemia that is principally caused by two factors: platelet and thrombus formation and subsequent intense vasoconstriction that results from the local accumulation of thromboxane 2 and serotonin and the reduction in local concentrations of endothelium-derived relaxing factor and inhibitors of platelet aggregation. These events are usually preceded by rupture or erosion of a vulnerable plaque. The thrombotic response to a plaque rupture is probably regulated by the thrombogenicity of the exposed plaque constituents, the local haemorheology (determined by the severity of the underlying stenosis), shear-induced platelet activation, and by systemic thrombogenicity and fibrinolytic activity.[23]

If the plaque disruption is major, with extensive exposure of thrombogenic core material to the blood stream, acute total coronary occlusion with subsequent myocardial infarction or sudden death may develop. If the disruption is minor, the forming thrombus can be non-occlusive and the patient may stay asymptomatic or develop unstable angina or a non-Q-wave infarction. A concomitant increase in coagulability and coronary vasoconstriction (as is common in the perioperative setting) may, however, transform a non-occlusive thrombus to an occlusive thrombus. Ultimately, the balance of thrombosis *vs* thrombolysis is the decisive factor in determining whether the clinical outcome will be myocardial ischaemia or myocardial infarction.

A vast variety of factors and interventions with vastly different mechanisms of action that are known to affect the occurrence of myocardial ischaemia and infarction in the non-operative setting (e.g. temperature, haematocrit, pain, β-blocker, aspirin, statins) have been shown to do the same in the perioperative period. Thus, although the characteristics of coronary artery disease and the perioperative period make it likely that the trigger(s) of perioperative myocardial ischaemia and infarction will vary within and between patients, it is equally likely that the perioperative mechanisms and triggers (biochemical, physical) of myocardial ischaemia and ACS are comparable to those in the non-operative setting. In patients with an old myocardial infarction, stable angina or occult coronary artery disease, the development of postoperative myocardial ischaemia, as reflected by ST-segment depression, can be seen as a positive stress test result. In this case, the non-cardiac surgery is the stress. Taking the analogy of stopping an exercise or pharmacological stress test when signs of myocardial ischaemia develop, it is essential to manage aggressively the various factors that contribute to postoperative stress.

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