Perioperative Myocardial Ischemia and Infarction

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Cardiac complications are a major cause of morbidity and mortality after noncardiac surgery (1–3). However, the exact nature of perioperative myocardial injury remains elusive and an area of continued debate and controversy (2–4). If the etiology and the triggers of perioperative myocardial ischemia and perioperative myocardial infarction (PMI) were known, appropriately taken preventive measures might improve perioperative cardiac outcome. Identification of the etiology and possible triggers of perioperative myocardial ischemia and infarction requires knowledge of their incidence, diagnosis and characteristics, and a basic understanding of the pathophysiology of acute coronary syndromes in the nonsurgical setting.

Incidence and Diagnosis of Perioperative Myocardial Ischemia and Infarction

Incidence

In patients with documented or suspected coronary artery disease (CAD), the reported incidence of perioperative myocardial ischemia varies considerably (between approximately 20% and 60%) (1,3–5). Postoperative myocardial ischemia is more frequent than preoperative (ratio approximately 3:1) and intraoperative ischemia (ratio approximately 5:1). The reported incidence of PMI varies between single digit percentage values and 40% (4). The incidence of perioperative myocardial ischemia and PMI will obviously be affected by their definition and method of detection.

Diagnosis of Perioperative Myocardial Ischemia

There is no accepted standard procedure for the diagnosis of myocardial ischemia. Generally, the diagnosis can be based on hemodynamic (pulmonary artery capillary wedge or left atrial pressure wave), electrocardiographic (ECG), functional (echocardiogram), metabolic (coronary lactate production), biochemical (release of creatine kinase-MB isoenzyme 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 ischemia, the incidence of perioperative myocardial ischemia may vary by a factor of five (6).

Perioperative myocardial ischemia has been predominantly ECG-detected and defined. The reported incidence of perioperative myocardial ischemia will, thus, greatly depend on choice and number of precordial leads, on definition of "ischemic" ST segment change (extent and duration of ST segment change), and on mode of data acquisition (continuous versus intermittent). Holter monitor-detected myocardial ischemia is associated with a sensitivity of 37%–50% and a specificity of 88%–92% (7,8). Continuous 12-lead electrocardiography improves sensitivity to between 61% and 97% (9,10).

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

Diagnosis of Perioperative Myocardial Infarction

Fundamental questions remain regarding definition and diagnostic criteria of perioperative myocardial infarction (MI) (2). According to the definition of the World Health Organisation (WHO), at least two of the following three criteria must be fulfilled to diagnose MI: i) typical ischemic chest pain; ii) increased serum concentration of creatine kinase (CK)-MB isoenzyme; iii) typical electrocardiographic findings, including development of pathological Q-waves. Perioperative

MI is mostly silent; the ECG is often difficult to interpret and frequently does not exhibit characteristic ST segment elevation or Q-waves. Therefore, if the diagnosis of MI is based solely on the classical triad, considerable underreporting of the true incidence of PMI is to be expected, possibly obscuring the etiology and pathophysiology of PMI.

The development of assays for the cardiac troponins T (cTnT) and I (cTnI) that are highly specific and sensitive for myocardial injury formed the basis of a revised definition of MI as proposed by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) (11). Any two of the following criteria satisfy the diagnosis of an acute, evolving or a recent MI: i) typical rise and gradual fall in cardiac troponin concentrations or more rapid rise and fall of CK-MB concentration in combination with at least one of the following: a) typical ischemic symptoms, b) development of pathological Q-waves in the ECG, c) ECG changes indicative of myocardial ischemia (ST segment elevation or depression), and d) coronary artery intervention; ii) pathological findings of an acute MI.

Debate continues as to the appropriate cut-off values of troponin concentrations for defining a clinically relevant MI. Initial cut-off values (cTnI >1.5 ng/mL and cTnT >0.1 ng/mL for certain assays) were derived from titration of troponin concentrations to a population of patients with clinically diagnosed MI. However, even small increases in serum concentrations of cardiac troponins are associated with adverse cardiac outcome in patients with or without ST segment elevation acute coronary syndrome (12). Considering the high specificity of cardiac troponins for myocardial cell injury, the recent consensus document of the ESC and the ACC on the re-definition of MI states that in the presence of documented myocardial ischemia, even minor increases in troponin serum concentration to greater than the 99th percentile of the normal population should be regarded as MI. As most troponin assays still lack adequate precision at such low concentrations, slightly higher cut-off values based on <10% imprecision are recommended.

In the frequent absence of typical symptoms and ECG signs of acute MI, the diagnosis of PMI has to rest heavily on changes in biochemical markers. Cardiac troponins appear to be better suited to identify PMI than CK-MB isoenzyme (13). Depending on the biochemical marker and the cut-off values, in the same study the overall incidence of PMI varied between 2.8% (CK-MB >10%), 9% (conventional cut-off values of cTnI >1.5 ng/mL and/or cTnT >0.1 ng/mL), and 23% (low level cut-off values of cTnI >0.6 and/or cTnT >0.03 ng/mL) (14). Only 5.6% of patients fulfilled the revised definition of MI (presence of at least two of three criteria: prolonged chest pain, elevated CK-MB or troponin, ischemic ECG changes). However, without routine measurements of serum concentrations of biochemical markers and continuous ECG monitoring for three postoperative days, MI would have been diagnosed in only those 3.6% of patients who experienced prolonged chest pain or symptoms of congestive heart failure.

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 cardiac 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. Irrespective of whether one refers to small increases in serum concentrations of troponin as "myocardial infarction" or "subclinical myocardial injury" or "at risk," even minor increases in serum concentrations of troponins (cTnI >0.6 and/or cTnT >0.03 ng/mL) and CK-MB (CK >170IU and CK-MB/total CK >5%) during the first three postoperative days were associated with 50%–100% increases in long-term mortality after major vascular surgery (follow-up period 1–5 yr; mean, 32 mo) (15). Larger, conventional increases in troponin concentration (cTnI >1.5 and/or cTnT >0.1 ng/mL) and CK-MB (CK >170IU and CK-MB/total CK >10%) were associated with twofold and almost fourfold higher long-term mortality, respectively. Postoperative increases in cTnT >0.1 ng/mL correlated with postoperative cardiac events (admission for unstable angina, nonfatal MI, cardiac death) within the first 6 mo after noncardiac surgery (16), and routine cTnI measurements during the first three postoperative days enabled prediction of all cause mortality within the first 6 mo after vascular surgery (17). Furthermore, prolonged postoperative myocardial ischemia and increases in postoperative cardiac troponin concentrations correlated strongly (13,15). Postoperative myocardial ischemic episodes of >30 min and >60 min were associated with 2.6-fold and 3.7-fold increases in long-term mortality, respectively (15). Taken together, existing evidence clearly suggests that even small increases in serum concentrations of cardiac troponins in the perioperative period reflect clinically relevant myocardial injury with short-term and long-term consequences on outcome. Perioperative measurements in high-risk patients enable prompt initiation of appropriate further diagnostic and therapeutic measures which may affect long-term cardiac outcome.

Characteristics of Perioperative Myocardial Ischemia and Infarction

Characteristics of Perioperative Myocardial Ischemia

Postoperative myocardial ischemia seems to be the best predictor of in-hospital and long-term cardiac morbidity and mortality (18,19). It increased the relative risk of experiencing an early postoperative cardiac event (e.g., MI, unstable angina, congestive heart failure) by a factor of nine (18) to 21 (20). Postoperative myocardial ischemia also increased the odds for long-term (30 days to 2 yr postoperatively) cardiac events (unstable angina, nonfatal MI, cardiac death, surgical coronary revascularization) 2.2-fold (21). In-hospital postoperative myocardial ischemia preceded long-term adverse cardiac outcome in as much as 70% of patients (18,20). The majority of postoperative myocardial ischemias in high-risk patients tends to develop on the day of or the day after surgery, with the majority of ischemic episodes starting at the end of surgery and during the emergence of anesthesia (13). The vast majority (more than 90%) of postoperative episodes of myocardial ischemias are silent (20,22). Postoperative ST segment changes are almost exclusively ST segment depressions rather than elevations (9,13,18,20).

The findings on the relationship between short-term hemodynamic changes and the incidence of postoperative myocardial ischemia are contradictory. Most studies found no association between changes in heart rate and postoperative ST segment changes or troponin release. Overall evidence would suggest that heart rate is not a reliable independent predictor of postoperative ST segment depression and troponin release.

Characteristics of Perioperative Myocardial Infarction

Clinical and Electrophysiological Characteristics. Perioperative MI increased the odds for long-term cardiac events 20-fold (21). Most (>80%) PMIs occur early after surgery, are asymptomatic, are of the non-Q-wave type (60%–100%), and are most commonly preceded by ST segment depression rather than ST segment elevation (3,4,10,14,23). In-hospital postoperative myocardial ischemia preceded long-term adverse cardiac outcome in up to 70% of patients (20). Long-duration (single duration >20–30 min or cumulative duration >1–2 h), rather than merely the presence of postoperative ST segment depression, seems to be the important factor associated with adverse cardiac outcome (20). Short-duration ischemic episodes (<10 min) did not correlate with postoperative MI and cardiac complications (20). ECG evidence of myocardial ischemia was strongly associated with postoperative low level and conventional increases in troponin serum concentration (14).

Pathological Characteristics. After fatal PMI, the vast majority (93%) of 42 autopsy heart specimens showed significant atherosclerotic coronary artery obstruction (24). There was evidence of plaque disruption in 55% and of plaque hemorrhage in 45% of 42 autopsy heart specimens. In more than half the patients, the site of infarction could not have been predicted based on the severity of the underlying stenosis. In a retrospective histological analysis of 26 cases of fatal PMI, coronary plaque rupture was associated with almost 50% ($n = 12$) of all MIs (25). Intracoronary thrombus was observed in nine cases (35%). In eight of these (31% of all cases), the thrombus was present at the site of a plaque that occluded the coronary vessel by ≥50%. Total coronary occlusion was observed in five cases (19% of all cases). The MI was transmural in 62% of cases and circumferential in 19%. Pathological evidence of a previous left ventricular MI existed in 21 (81%) patients, and clinical evidence of a previous MI existed in the remaining five (19%) patients. Multivessel and left main CAD were present in 88% and 23% of cases, respectively.

The findings are similar to those in autopsies after acute MI in the nonoperative setting, suggesting that PMI has a coronary pathology similar to that of MI in the nonoperative setting with regard to underlying CAD, coronary plaque hemorrhage, 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 necessarily predict the infarct territory. The high incidence of histologically confirmed transmural infarctions seems to be in contradiction to the ECG finding of almost exclusively non-Q-wave PMIs. Conversely, the presence of circumferential PMIs is consistent with a myocardial oxygen supply/demand mismatch as being the main trigger of myocardial injury. However, myocardial oxygen supply/demand mismatch and plaque rupture are not mutually exclusive mechanisms, and MIs may develop by different mechanisms at different locations in the same patient. Overall, the findings suggest that perioperative and non-perioperative MIs develop by similar mechanisms and may thus be susceptible to similar preventive (and therapeutic) strategies.

Angiographic Characteristics. Autopsy results and preoperative findings on dobutamine stress echocardiography were analyzed retrospectively in 32 patients who died after major elective vascular surgery (26). All of the 16 (50%) patients who suffered a PMI had exhibited inducible ischemia during preoperative stress testing. Although in 13 (81%) of these patients the PMI was located in a coronary artery territory that had also demonstrated stress-induced myocardial ischemia, in nine of them (56%)

pathological evidence of MI was present in a coronary artery territory that had not shown stress-induced myocardial ischemia. Coronary angiography performed in three patients within 7 days of PMI revealed chronic severe CAD but no angiographically visible thrombus or ruptured plaques (13). The various findings are consistent with perioperative plaque rupture at sites other than critically narrowed coronary artery stenoses and with the possibility that in some patients with severe but stable CAD, PMI may develop primarily on the basis of prolonged myocardial ischemia.

Pathophysiology of Myocardial Ischemia and Infarction

Pathophysiology of Myocardial Ischemia

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

Endothelial function is impaired in CAD, and is an important cause of myocardial ischemia. 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 a rise myocardial oxygen demand (e.g., during exercise, mental stress, 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 (27,28). Acute myocardial ischemia intensifies these paradoxical vascular responses. Such limitation of coronary flow as a result of paradoxical coronary vasoconstriction and inability of vessels to dilate near the site of an atherosclerotic plaque may result in regional myocardial supply or low-flow ischemia.

The most common ECG finding during episodes of symptomatic or silent myocardial ischemia in patients with chronic stable angina pectoris is ST segment depression. When ischemia is confined predominantly to the subendocardium the overlying leads show ST segment depression. Such subendocardial pattern is typical for spontaneous ischemic episodes of angina pectoris or during symptomatic or asymptomatic ("silent") ischemia induced by exercise or 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 death of myocardial myocytes resulting from prolonged ischemia. 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 is worsened by concomitant local mediator release-induced or systemic sympathetic-induced coronary vasoconstriction and distal microthrombi embolization. If coronary blood flow is interrupted for longer than 30 min, MI may result. Persistent coronary artery occlusion will cause 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.

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

Characteristics of Acute Coronary Syndromes

Structural and Functional Characteristics

Until very recently, ulcerative, fissured or thrombotic coronary plaques that are characterized histologically by a central lipid core, inflammatory cell infiltrate and fibrous cap thinning have been termed "vulnerable" (29). The popular view that a vulnerable plaque constitutes the final common pathway that leads to the atherothrombotic events not only ignores 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 (30–32). Morphological/structural (central lipid core, thin cap) and functional (plaque thrombogenicity, intraplaque inflammatory cell infiltrate) plaque components interact in an unpredictable

fashion. Exogenous factors (e.g., mechanical stress, vasomotor tone, infection, blood viscosity, coagulability) further modify such interaction, making the final outcome even less predictable. The transition from stable CAD to the ACSs of non-Q-wave and Q-wave infarction and unstable angina is characterized by coronary plaque disruption and subsequent thrombosis that constitute the major pathogenetic components of "unstable" or "vulnerable plaques" (30). 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 postmortem 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 (34,35). Inflammatory mechanisms and structural and functional plaque characteristics have received increasing attention (36,37). In contrast to stable CAD, ACS are characterized by complex coronary plaques and stenoses, coronary endothelial erosions, plaques fissures, fresh thrombi, and plaque inflammation. The factors leading to unstable plaques (which ultimately trigger ACS) are structurally and functionally multiple and complex. In some cases, a thrombogenic "high-risk" blood may be required to trigger ACS. It is impossible to predict the time it will take a structurally vulnerable plaque to become unstable and the trigger that causes the plaque to rupture (i.e., mechanical stress, coronary vasospasm, widespread acute inflammatory endothelial activation, or chronic inflammatory component of atherosclerosis). In case of thrombosed plaques without detectable fissures, plaque vulnerability is probably caused by thrombogenic or high-risk blood or local proinflammatory cytokines that trigger thrombosis, sometimes even in the absence of inflammatory cell infiltration and a lipid core.

In 20%–40% of ACS, coronary thrombi have been observed to overlie atherosclerotic plaques without disrupture 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). Thrombus formation may depend on hyperthrombogenicity-inducing systemic factors (e.g., hypercholesterolemia, increased concentrations of catecholamines, diabetes, smoking, infection), a hypercoagulable state (with elevated serum concentrations of fibrinogen, von Willebrand factor, and factor VII), or a defective fibrinolytic state (with increased serum concentrations of plasminogen activator inhibitor 1 and decreased concentrations of tissue plasminogen activator and urokinase). As erosion of plaques without the typical features of a vulnerable plaques (fissuring, thin fibrous cap, lipid-rich core) may result in ACS, use of the generic term "high-risk" plaque may be more appropriate than "vulnerable" plaque (30).

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

Plaque progression is often abrupt and mostly unpredictable. 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 MI stenose angiographically the respective coronary artery by <70%. Approximately 60% of those infarcts are caused by rupture of plaques that carry the characteristics of "vulnerability" (i.e., large thrombogenic core of lipid and necrotic debris and a thin ruptured cap). Plaques often progress episodically related 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). If subsequent lysis is incomplete and is followed by re-endothelialization, the plaque will grow.

Plaques within a given patient often progress largely independently. 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, blood pressure). However, most of the independent plaque behavior in a given patient is likely attributable to pronounced heterogeneity of plaque histology and to differences in the physical forces to which plaques are exposed.

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 (hemodynamic) processes that influence the magnitude and distribution of stress on the plaque. When intimal rupture occurs, the content of the plaque is important.

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) 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. 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. The degree of plaque disruption (ulceration, fissure, or erosion) or 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 ischemic events. These many variables explain why angiographically fairly small coronary lesions 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.

ACS follow a circadian rhythm (38,39). This indicates that cardiac events do not occur entirely randomly and may be triggered by external activities. Consistent with the finding of circadian rhythm of ACS, plaque rupture is more common during various kinds of strenuous physical activity, including exercise stress testing and emotional stress (40). In all of these situations, the sympathetic nervous system is activated. This leads to increased plasma concentrations of catecholamines, blood viscosity, and of blood pressure and heart rate, which are accompanied by detectable increases in platelet aggregation and decreases in fibrinolytic activity that both tend to favor thrombosis. 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 ischemic cardiac events in the perioperative period that is characterized by comparable adrenergic stimulation, and increased prothrombotic and reduced fibrinolytic activity.

Mechanisms of Perioperative Myocardial Ischemia and Infarction

All studies consistently found an association between perioperative myocardial ischemia (defined by ST segment changes) and perioperative cardiac morbidity. Furthermore, postoperative cardiac complications were preceded almost universally by long-duration rather than short-duration ST segment changes, ST segment changes consisted almost exclusively of depression rather than elevation, and most PMIs were of the non-Q-wave type rather than the Q-wave type. These characteristics of perioperative myocardial ischemia may have several explanations: i) prolonged perioperative myocardial ischemia leads to MI; ii) repeated and prolonged ST segment depression reflects the onset of a permanent cardiac event, (e.g., myocardial infarction); iii) perioperative myocardial ischemia and infarction are two separate events that both develop on the basis of underlying coronary artery disease (5).

There is pathological evidence that the pathogenesis and pathophysiology of PMI (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) resembles that in the nonsurgical setting. Conversely, the combination of consistent increases in heart rate preceding the ischemic episodes, ST segment depression rather than elevation during literally all ischemic episodes, non-Q-wave rather than Q-wave myocardial infarctions in all cases of myocardial infarctions, lack of angiographically visible thrombus or ruptured plaques in patients who underwent coronary angiography after PMI, and complete reversal of ECG changes to baseline in all but one of the patients with ischemia (including those with infarction) was highly suggestive that prolonged stress-induced myocardial ischemia is the likely primary cause of PMI.

Although ST segment depression usually reflects subendocardial ischemia and is often regarded as reversible injury, it is not inconsistent with a MI. Elderly patients, in particular, may present with MI without ST segment elevation. In most studies on perioperative cardiac ischemic events, the study populations consisted largely of elderly patients. Thus, prolonged ST segment depression may reflect ongoing myocardial ischemia (ultimately leading to MI) or it may reflect the beginning of an evolving MI.

Although postoperative cardiac complications were mostly associated with only long-duration ST segment depression, not all investigations found such an association. In addition, most studies did not find a correlation between acute increases in heart rate and myocardial ischemia and infarction. Such lack of consistent association between heart rate and length of postoperative ST segment depression on one hand and adverse cardiac outcome on the other would argue for nonischemic causes of ST segment depression in the perioperative period (e.g., hyperventilation, electrolyte changes, drug effects, positional changes), for compensatory mechanisms to myocardial ischemia (e.g., preconditioning as a result of multiple brief episodes of myocardial ischemia and coronary reperfusion), or for functional collateral perfusion (5).

The preponderance of non-Q-wave infarction is clearly different from the nonsurgical setting. This, again, would indicate that PMIs are more often the

result of prolonged ischemia than of thrombotic occlusion, similar to the presumed pathophysiology of silent ischemia. In contrast to the usual coronary thrombotic occlusion after an acute plaque disruption, in the presence of severe but stable CAD coronary thrombosis may, in fact, result from a decrease in coronary blood flow and stasis (41,42). Some patients with stenotic atherosclerotic lesions may develop acute MI without evidence for plaque rupture and superimposed thrombus formation. This may happen in situations of marked decrease in myocardial oxygen supply (e.g., prolonged severe coronary vasospasm) or a marked increase in myocardial oxygen demand. It is thus conceivable that coronary thrombosis in the perioperative setting is the consequence rather than the cause of prolonged myocardial ischemia and PMI.

The majority of ischemic episodes tend to start at the end of surgery and during the emergence from anesthesia (13). This time is characterized by increases in heart rate, blood pressure, sympathetic tone, and procoagulant activity. 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 vasospasm, plaque disruption, and coronary thrombosis. If this, however, were the primary mechanism of postoperative myocardial ischemia and infarction, ST segment elevations and more frequent Q-wave infarctions would be expected.

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 CAD even in the absence of acute plaques disruption. The ultimate fate of the thrombus and, thus, the extent of jeopardized myocardium will depend on 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 rheological properties).

Conclusions

The etiology and triggers of perioperative myocardial ischemia and infarction remain poorly understood. Existing data are inconclusive and do not allow definitive determination whether long-duration subendocardial myocardial ischemia or acute coronary occlusion resulting from 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 ischemia and infarction.

In many patients with unstable CAD, numerous mechanisms are responsible for the unstable nature of the disease. These include coronary artery thrombosis, platelet aggregation and emboli, progression of CAD, 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 CAD may develop a (temporary?) biochemical milieu that predisposes them to widespread plaque degeneration 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.

Myocardial infarctions usually occur at sites that previously caused only angiographically determined mild-to-moderate luminal stenosis. 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 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 ischemia that is principally caused by two factors: platelet and thrombus formation and subsequent intense vasoconstriction that results from the local accumulation of thromboxane 2, 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 plaque rupture is probably regulated by the thrombogenicity

of the exposed plaque constituents, the local hemorheology (determined by the severity of the underlying stenosis), shear-induced platelet activation, and by systemic thrombogenicity and fibrinolytic activity.

If the plaque disruption is major with extensive exposure of thrombogenic core material to the bloodstream, acute total coronary occlusion with subsequent MI or sudden death may develop. If the disruption is minor, the forming thrombus can be nonocclusive 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 nonocclusive thrombus to an occlusive thrombus. Ultimately, the balance of thrombosis versus thrombolysis is the decisive factor in determining whether the clinical outcome will be myocardial ischemia or MI.

A wide variety of factors and interventions with vastly different mechanisms of action that are known to affect the occurrence of myocardial ischemia and infarction in the nonoperative setting (e.g., temperature, hematocrit, pain, β-blocker, aspirin, statins) have been shown to do the same in the perioperative period. Thus, although the characteristics of CAD and perioperative period make it likely that the triggers of perioperative myocardial ischemia and infarction vary within and between patients, it is equally likely that the perioperative mechanisms and triggers (biochemical, physical) of myocardial ischemia and ACS are comparable to those in the nonoperative setting. In patients with an old MI, stable angina or occult CAD, the development of postoperative myocardial ischemia as reflected by ST segment depression can be viewed as a positive stress test result. In this case, noncardiac surgery is the stress. Analogous to stopping an exercise or pharmacological stress test when signs of myocardial ischemia develops, it is essential to manage aggressively the various factors that contribute to postoperative stress.

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