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SPECIAL ARTICLE

Myonecrosis After Revascularization Procedures

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The detection of elevated cardiac enzyme levels and the occurrence of electrocardiographic (ECG) abnormalities after revascularization procedures have been the subject of recent controversy. This report represents an effort to achieve a consensus among a group of researchers with data on this subject. Creatine kinase (CK) or CK-MB isoenzyme (CK-MB) elevations occur in 5% to 30% of patients after a percutaneous intervention and commonly during coronary artery bypass graft surgery (CABG). Although Q wave formation is rare, other ECG changes are common. The rate of detection is highly dependent on the intensity of enzyme and ECG measurement. Because most events occur without the development of a Q wave, the ECG will not definitively diagnose them; even the ECG criteria for Q wave formation signifying an important clinical event have been variable. At least 10 studies evaluating >10,000 patients undergoing percutaneous intervention have demonstrated that elevation of CK or CK-MB is associated not only with a higher mortality, but also with a higher risk of subsequent cardiac events and higher cost. Efforts to identify a specific cutoff value below which the prognosis is not impaired have not been successful. Rather, the risk of adverse outcomes increases with any elevation of CK or CK-MB and increases further in proportion to the level of intervention. This information complements similar previous data on CABG. Obtaining preprocedural and postprocedural ECGs and measurement of serial cardiac enzymes after revascularization are recommended. Patients with enzyme levels elevated more than threefold above the upper limit of normal or with ECG changes diagnostic for Q wave myocardial infarction (MI) should be treated as patients with an MI. Patients with more modest elevations should be observed carefully. Clinical trials should ensure systematic evaluation for myocardial necrosis, with attention paid to multivariable analysis of risk factors for poor long-term outcome, to determine the extent to which enzyme elevation is an independent risk factor after considering clinical history, coronary anatomy, left ventricular function and clinical evidence of ischemia. In addition, tracking of enzyme levels in clinical trials is needed to determine whether interventions that reduce periprocedural enzyme elevation also improve mortality.

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When cardiac enzymes are measured after coronary revascularization procedures, 5% to 30% of patients have elevated levels of creatine kinase (CK) or its MB subfraction (CK-MB), and similar proportions of patients develop electrocardiographic (ECG) changes. Because these findings raise fundamental issues in clinical practice and clinical research, a group of clinical investigators who had produced relevant data recently convened to review the available evidence and to attempt to reach a consensus concerning recommendations for clinical practice and clinical investigation.

This review appears in the midst of a sweeping change in society's view of medical illness and health care delivery, in that evidence of a good clinical outcome is the basis for acceptance

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CK = creatine kinase
CK-MB = creatine kinase, MB isoenzyme
ECG = electrocardiogram, electrocardiographic
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
Tn = troponin
WHO = World Health Organization

of therapeutic approaches. In this context ischemic heart disease can be considered a chronic illness characterized by periods of quiescence punctuated by acute events, including death, myocardial infarction (MI) and symptoms of angina or congestive heart failure. Therapies designed to improve patient outcome in ischemic heart disease generally are considered worthwhile if they improve all three outcomes, particularly if the incremental cost is within the accepted societal range (1). Revascularization, by either coronary artery bypass graft surgery (CABG) or percutaneous revascularization procedures, is increasingly being used in the treatment of symptomatic ischemic heart disease. The relevance of enzyme rises, representing possible myocardial necrosis (myonecrosis) during the procedures, and the extent to which these enzyme rises constitute an undesirable clinical outcome, will be important considerations in the debate about which procedures should be used in which patients.

Because the primary goals of therapy for patients with coronary artery disease are to reduce anginal symptoms and to prevent major ischemic complications, a number of investigators have begun to study ECG changes and elevations in enzyme levels in the circulation after percutaneous procedures, which may reflect myocardial cell damage during the procedure. This issue has been a topic of interest for several decades with regard to CABG (2,3), but uncertainty regarding the usefulness of CK-MB as a measure of perioperative injury arose when increases in enzyme levels were noted in the absence of clinically apparent cardiac damage (4), and this issue has yet to be clarified. The recent introduction of pharmacologic agents designed to reduce the extent or consequences of myocardial injury during surgical treatment and the advent of less invasive surgical techniques have stimulated renewed interest. Scrutiny of enzyme elevations after percutaneous procedures has intensified as enzyme elevations have been observed more frequently with the use of new technologies (5,6).

The impetus for resolving the diagnostic criteria for myocardial necrosis comes from two sources: the clinical issue of whether a patient should be treated differently after such an episode and the uncertain place of isolated enzyme events or ECG changes in assessing the value of a procedure. In clinical practice, new ECG changes or elevated cardiac enzymes may affect the need for hospital admission, the length of hospital stay, the intensity of follow-up or postdischarge pharmacologic therapy. For clinical trials evaluating new and current therapies, differences in these measures may provide a means of distinguishing which therapy is associated with better outcomes. Alternatively, if small "leaks" of cardiac enzymes or periprocedural ECG abnormalities have no significance in terms of patient outcome, counting these events as MIs would be misleading in a therapeutic evaluation.

Table 1. World Health Organization Definition of Acute Myocardial Infarction

Criteria	Definite AMI	Possible AMI
History		
Typical	×	×
Atypical	×	×
ECG changes		
Unequivocal	×	
Equivocal		×
Serum enzyme changes		
Unequivocal	×	
Equivocal		×

AMI = acute myocardial infarction; ECG = electrocardiographic.

Diagnostic Methods

Despite nearly universal agreement that episodes of myocardial necrosis are to be avoided whenever possible, the continuing evolution of diagnostic technology makes the precise clinical definition of myocardial infarction a moving target. The classic definition is the standard set by the World Health Organization (WHO) almost 20 years ago (Table 1) (7). A decade ago a clinical definition of acute MI evolved which is based on an evaluation of both total CK and CK-MB and the ECG. With this definition, which was based on the evaluation of CK and CK-MB by an immunoassay, a patient who had at least a doubling of total CK with >5% of the total representing the CK-MB would be classified as having an MI. More recently, CK-MB assays are predominantly mass assays, whereas total CK assays remain immunoassays. In these circumstances, a 5% proportion of two different assays may be misleading as they measure different components (mass and activity) (8). Therefore, the diagnosis of acute MI now mostly rests on an abnormal (above the upper normal range, most commonly 5 to 10 μg/ml, depending on assay characteristics) CK-MB mass level in addition to ECG findings. However, many patients with symptomatic episodes of acute myocardial ischemia have enzymatic evidence of myocardial necrosis associated with an increased risk of poor clinical outcomes but do not meet WHO criteria (9). In one series, 10% of patients with an elevated CK-MB measurement had a normal total CK (10), whereas a second series demonstrated a 22% 1-year mortality rate in patients with minimally elevated CK-MB, mostly due to comorbid medical conditions (11). The release of some CK-MB may be expected as a routine sequela of CABG, but some investigators have shown a qualitative relation between release of CK-MB and poor outcome. Similarly,

studies have demonstrated that elevations of CK-MB above the upper limit of normal occur commonly after percutaneous transluminal coronary angioplasty (PTCA), but the threshold for defining an MI in this setting remains an enigma.

Not only are the appropriate enzyme criteria uncertain, but the criteria for interpretation of the ECG in the diagnosis of MI are also not as clear as commonly believed. Development of new Q waves is uncommon after a percutaneous intervention, with reported incidences of Q wave MI of 1% to 3%, but other ECG changes are common, and the meaning of QRS changes after surgical treatment has been the source of considerable debate (12).

Methodology of Determining Q Wave MI

A variety of Q wave criteria have been proposed for determining whether an ECG reflects new myocardial necrosis, including 1) a new 2-grade Q wave worsening of the Minnesota code; 2) a new 1-grade worsening of the Minnesota code with major ST-T wave worsening; 3) new 30-ms Q waves in two contiguous leads; 4) new 30-ms Q waves in two contiguous leads at least 1 mm deep; 5) new 40-ms Q waves; and 6) pathologic Q waves (13–20). Incident rates of Q wave events can vary considerably depending on the definition used. Of the various Q wave criteria proposed, the Minnesota code is one of the few validated coding systems used extensively in epidemiologic studies and large-scale clinical trials (13–15). The Minnesota Q wave codes categorize changes in the anterior, inferior and lateral lead groups based on the width and depth of the Q wave and Q/R wave ratio. A distinction is made between Q wave and QS complexes. In autopsy series, the specificity of major Q wave codes for myocardial necrosis exceeds 90% (21,22). In patients with autopsy evidence of MI, 30% to 40% of patients will have major Minnesota code Q waves and 60% will have major or minor Minnesota code Q waves. The sensitivity of Minnesota code Q wave criteria is greater in patients with recent evidence of MI.

The recently revised WHO criteria use the Minnesota code to define Q wave evidence of MI (13). The new development of a 2-grade Q wave worsening or a 1-grade Q wave worsening with major ST segment elevation or depression is defined as a definite MI on the ECG. When the Minnesota code is used for serial comparison, the NOVACODE or other serial comparison algorithm should be used to adjust for biologic noise resulting in minor threshold changes that can produce false positive diagnoses (14).

The evolution of myocardial ischemia or necrosis can result in significant ECG changes over time. In the Program Of Surgical Control of Hyperlipidemia (POSCH), 34% of subjects with codeable Minnesota code Q wave items lost a codeable Q-QS pattern after an average 2.2 years (23). Ascertainment of major ST-T wave abnormalities during acute ischemia will be dependent in part on the timing of ECG acquisition. Q waves may develop instantaneously or over several hours or days. Large-scale clinical trials of patients with spontaneous myocardial ischemia, persistent for >30 min and associated with ST segment elevation >1 mm, have found abnormal cardiac enzyme panels in >90% of patients, and new Q waves develop in 70% to 80% of patients without a previous history of MI. Evaluation of ECGs for new Q waves in a critical care setting may be further confounded by inconsistent patient position and lead placement, especially in an unstable patient. ECG scoring systems to determine the extent of myocardial necrosis may provide additional incremental information on prognosis, but have not been widely applied to detection of MI (24).

The Selvester QRS score is another method that has been validated for estimating the size of anterior, inferior and posterolateral infarcts (25–28). A set of three screening criteria for the Selvester system has been shown to achieve high specificity in control populations (95%) and moderate sensitivities for identifying anterior (67%), inferior (90%) and posterolateral (45%) infarction (29,30). The term "new significant Q waves in at least two anatomically contiguous leads" is commonly used in definitions of new MI. Using the Selvester system, this definition for the various leads would be Q waves ≥30 ms for leads I and aVL (lateral); ≥30 ms for leads II and aVF (inferior); ≥30 ms for leads V_5 and V_6 (apical); any Q wave length for leads V_1 to V_3; and ≥20 ms for lead V_4 (anterior) (31).

Despite the acceptance of the clinical importance of Q wave MI, the relation between Q wave formation and subsequent outcome after PTCA has not been intensively investigated. Only the National Institutes of Health PTCA registry (32) has documented subsequent increased mortality. After CABG, QRS changes are common, and new Q waves have been associated with subsequent mortality (16), but conduction disturbances are common, causing difficulty in interpretation. The recent finding in both the Bypass Angioplasty Revascularization Investigation (BARI) (33) and Emory Angioplasty Surgery Trial (EAST) (34) of a higher rate of Q wave MI after CABG than after PTCA has raised the question of whether these Q waves represent the same entity as a Q wave in a medically treated patient. Preliminary reports showed no differences in systolic function despite the higher rate of Q waves in surgically treated patients.

General Meaning of Elevated Cardiac Enzymes

The interpretation of elevated CK and CK-MB as markers of myocardial necrosis is based on the systematic study defining the pathogenic mechanisms of CK release from the myocardium. In human myocardium CK is present in high activity as a dimer composed of two subunits (35–37). Approximately 15% of total CK activity in human myocardium is composed of the MB isoenzyme, 75% of the MM isoenzyme and the remaining 10% of a separate isoenzyme—the mitochondrial isoenzyme (CK-MT), present as an octamer (35,36,38). Although all CK-MT activity is bound to mitochondrial membranes, ~50% of the CK-MM and CK-MB activity is bound to myofibrils (39). Creatine kinase catalyzes the reaction that

transfers high energy phosphate groups between creatine phosphate and adenosine triphosphate. The presence of the intact enzyme is critical to normal myocardial function. Biochemical inhibition of CK interferes with the full range of cardiac performance in isolated hearts (40). Studies in transgenic mice (41,42) show that the B-knockout is lethal, whereas the M-knockout, MT-knockout and double knockout survive with remarkable histologic changes. The M-knockout has an increase in mitochondrial mass, and the myocardium in the double knockout appears almost identical histologically to insect flight muscle with dense packages of mitochondria between thin bundles of myofibrils (41,42). The critical role of CK is further attested by an apparent absence of phenotypic polymorphism (43), although post-translational modification of CK-MB in plasma produces CK-MB "isoforms" (44).

Several experimental studies have identified the pathologic conditions necessary for CK release from the myocardium. A close correlation between CK release and disruption in cellular ultrastructure has been documented in anoxic isolated heart preparations from several species (45). In a canine preparation of ischemia and infarction, elevation of serum CK is seen in the presence of histologic evidence of micronecrosis or frank infarction (46). Although only one-seventh of total tissue CK is recoverable in serum (47,48), the amount of CK released correlates with the size of experimental infarcts (49,50). Creatine kinase is released in response to anoxic injury in relation to the ability to maintain or recover a cellular potassium gradient—an accurate index of irreversible cell injury (51). Several other metabolic derangements, such as irreversible loss of mitochondrial respiratory function and unrestorable dissociation of the CK-MT from mitochondrial membranes, precede measurable decreases in myocardial CK in the postischemic isolated rabbit heart (52). Moderate irreversible derangements in mitochondrial respiratory function and global left ventricular function precede decreases in total myocardial CK activity in the isolated ferret heart (53).

The pathogenic mechanisms of myocardial enzyme release include depletion of high energy phosphate compounds (46,47,49,50,54), H^+ and phosphate accumulation leading to solubilization of bound CK (45,52) and leakage of enzyme through disrupted sarcolemma (48,51). Although the specificity of other markers such as troponins I and T for myocardial necrosis is not firmly established (55,56), the majority of studies indicate that CK-MB is not released in the absence of myocardial necrosis (45–53), although some disagreement exists.

The detection of CK-MB in serum, however, is not entirely specific for myocardial necrosis. Skeletal muscle has a fourfold higher CK content than myocardium (35,36,57), contains measurable CK-MB activity (2%) (35,36,57) and has a lower fraction of bound CK (10%) (39). Because irreversible injury is not required for CK release from the large mass of skeletal muscle, ~2% to 4% of circulating background CK activity in normal serum is composed of CK-MB activity that is predominantly of skeletal muscle origin (48,58,59). The clinical diagnosis of myocardial necrosis is thus based on serial sampling showing a characteristic pattern of rise in CK-MB activity after an episode of possible myocardial injury (14). Within 4 to 6 h after the onset of acute MI, both total CK and CK-MB activities rise above the threshold level. The delay in the appearance of CK activity in serum is attributed to the time required for ischemic injury to result in irreversible myocardial high energy phosphate depletion, solubilization of bound intracellular CK, transfer of CK to myocardial lymph through disrupted sarcolemma and diffusion into the central circulation (48). Creatine kinase activity peaks within 10 to 20 h after the onset of infarction and returns to baseline within 2 to 3 days (58,59). Therefore, the characteristic rise and fall of CK or CK-MB activity after coronary angioplasty is highly likely to be related to the presence of myocardial necrosis.

The timing of the CK rise, peak and fall, as well as the magnitude of peak CK changes, is dependent on the timing of the coronary occlusion and reperfusion of the culprit artery. Because most ischemic episodes in patients with acute ischemic syndromes are asymptomatic, spontaneous ischemic episodes before or during revascularization procedures cannot be excluded. Some of these spontaneous episodes are likely to be sufficiently severe to be associated with CK release. However, because the onset of the asymptomatic episode was unrecognized and the revascularization procedure altered the kinetics of CK release, the precise timing relation between the revascularization procedure and the peak CK may be very difficult to interpret. Reperfusion shortens the time to peak CK, increases the absolute peak and makes the fall more rapid. Because most revascularization procedures improve flow in the culprit artery, the characteristic CK release pattern and subsequent washout into systemic blood seen in de novo MI would be expected to be altered after a percutaneous revascularization procedure whenever there is CK release.

It is unclear whether thresholds can be determined for enzymatic markers such as CK and CK-MB and whether these thresholds are specific enough to differentiate between routine myocardial damage due to the procedure and myocardial injury severe enough to adversely affect long-term outcome. There are also limitations in the application of ECG criteria for the identification of perioperative infarction: minor ECG changes may be seen with pericardial inflammation, and conduction disturbances frequently conceal significant myocardial damage. Newer markers such as troponin T and I appear to have higher specificity for myocardial necrosis and may be more favorable for use in the perioperative period, but the appropriate thresholds for prognostically significant injury remain unclear.

Although newer markers of myocardial necrosis have been shown to have considerable promise (60–62), CK-MB remains the reference standard for diagnosis (63). Myocardial tissue contains a variety of molecular species (or components), many of which also exist in skeletal muscle. These nonspecific macromolecules, such as myoglobin (64), CK isoenzymes (65) and myosin light chains (66), have been found to be excellent early markers of MI, as they frequently appear in serum within 1 to 2 h of the onset of symptoms. However, these tests lack

cardiac specificity, which makes them useful as screening tests but not as diagnostic tests for periprocedural MI.

The troponin complex is a group of three proteins (TnT, TnI and TnC) that act together to regulate muscle contraction through the tropomyosin complex. Although this complex exists in both cardiac and skeletal muscle, the isoforms of TnI and TnT have significantly different protein structures, allowing sensitive assays to be developed for their cardiac-specific forms (66). The proteins TnT and TnI have been shown to have prognostic value beyond CK-MB in acute ischemic syndromes (61,62), but both analytes have long circulating half-lives (5 to 14 days), so that new episodes of necrosis cannot easily be separated from earlier episodes. Both TnT and TnI have a high level of sensitivity and specificity for the diagnosis of acute MI (63,67). Several investigations have used TnT or TnI to diagnose periprocedural infarction (56,68–70). In one study, 60% of patients having angioplasty had elevated TnT (>0.04 ng/ml), whereas elevated CK was observed in only 16%. In all patients who had a balloon inflated for >5 min TnT was elevated (56). The clinical significance of the TnT elevations remains to be established because none of the patients studied had any significant adverse events. Further studies are required to evaluate the implications of the high rate of elevation of the cardiac troponin markers to diagnose minor MI and its significance.

Surgical Revascularization

Although currently available data on surgical revascularization are more limited than are data on percutaneous revascularization, there is substantial empiric evidence to support the common sense concept that patients with perioperative ischemic injury fare less well than those without damage. Perioperative MIs as determined by ECG criteria are associated with worse long-term outcome (71). Small transient increases in CK-MB, representing <1.5% of the total CK, may occur routinely, but larger CK-MB elevations with and without ECG changes have been associated with evidence of myocardial damage by perfusion imaging and pathologic examination (3,72,73). More recent data in patients with cardiac disease undergoing noncardiac surgery also confirm that perioperative ischemic events are predictive of subsequent complications (74), but the threshold separating routine perioperative elevation from substantial damage of prognostic importance is not clear.

The parallels between surgical and percutaneous revascularization suggest a similar need for high quality data in the perioperative period to clarify the relation between elevation of biochemical markers and subsequent cardiac morbidity. In the meantime, it appears that perioperative events involving injury to a large amount of myocardium are associated with increased risk and poorer outcome. Identification of new Q waves in a postoperative ECG or elevation of CK-MB five times or more above the normal limit, representing >3% total CK, are considered quantitative evidence of important myocardial injury in the perioperative period. A gradient of risk similar to that suggested by data for percutaneous interventions may exist for surgical patients, but at this time the prognostic implications of lesser elevations of CK-MB or increases in other biochemical markers are uncertain.

Percutaneous Revascularization

Multiple institutions have now reported follow-up studies of percutaneous revascularization, and the evidence strongly supports a relation between the appearance of CK-MB in the circulation and poorer clinical outcomes during subsequent clinical evaluations. Elevated enzymes are associated with a higher risk of death, subsequent MI and a need for repeat revascularization procedures. The level of risk seems to increase as a continuous function, with no obvious threshold effect or "cutoff" value. Subsequent risk is clearly elevated in patients with abrupt vessel closure, side branch occlusion, thrombus formation or major dissection, but even when these complications are not reported by the clinician, the risk of subsequent poor outcome remains increased when an elevated CK-MB is measured after the procedure. In patients with low level elevations of CK-MB, the in-hospital risk appears to be low, but the intermediate- and long-term risk appears to be elevated. Attempts to adjust for other prognostic factors have found enzyme rises to be independently predictive of adverse outcomes.

Klein et al. (5) initially reported that 15% of a consecutive series of 249 patients treated with angioplasty in 1989 and 1990 had elevations of total CK or CK-MB. Acute symptomatic events were evident in almost half the patients whose CK-MB became elevated in the presence of normal CK. Based on these findings, the investigators made a plea for more follow-up studies with larger numbers of patients.

In the most detailed long-term follow-up study to date, Abdelmeguid et al. (75) demonstrated a direct relation between elevation of CK and CK-MB and risk of acute or chronic complications in 4,863 consecutive patients who had a successful percutaneous procedure. After excluding patients with an unsuccessful procedure, 88 patients with transient abrupt closure in the laboratory followed by successful opening of the vessel were compared with 4,775 patients without abrupt closure. The mortality rate of patients with abrupt closure and no rise in CK-MB was no different from that of patients with successful procedures without abrupt closure. However, when CK-MB was elevated, the mortality rate was significantly higher. In a multivariable regression analysis, an increase in CK-MB was the most important independent predictor of adverse outcomes in follow-up. This relation remained significant after controlling for a variety of clinical, morphologic and procedural factors.

In a follow-up study, these investigators evaluated the baseline characteristics, cardiac enzymes and clinical outcomes of 4,797 patients with successful percutaneous procedures (76). Patients with elevated CK levels more often had thrombus-associated lesion characteristics, saphenous vein graft lesions and use of directional atherectomy. Characteristics associated

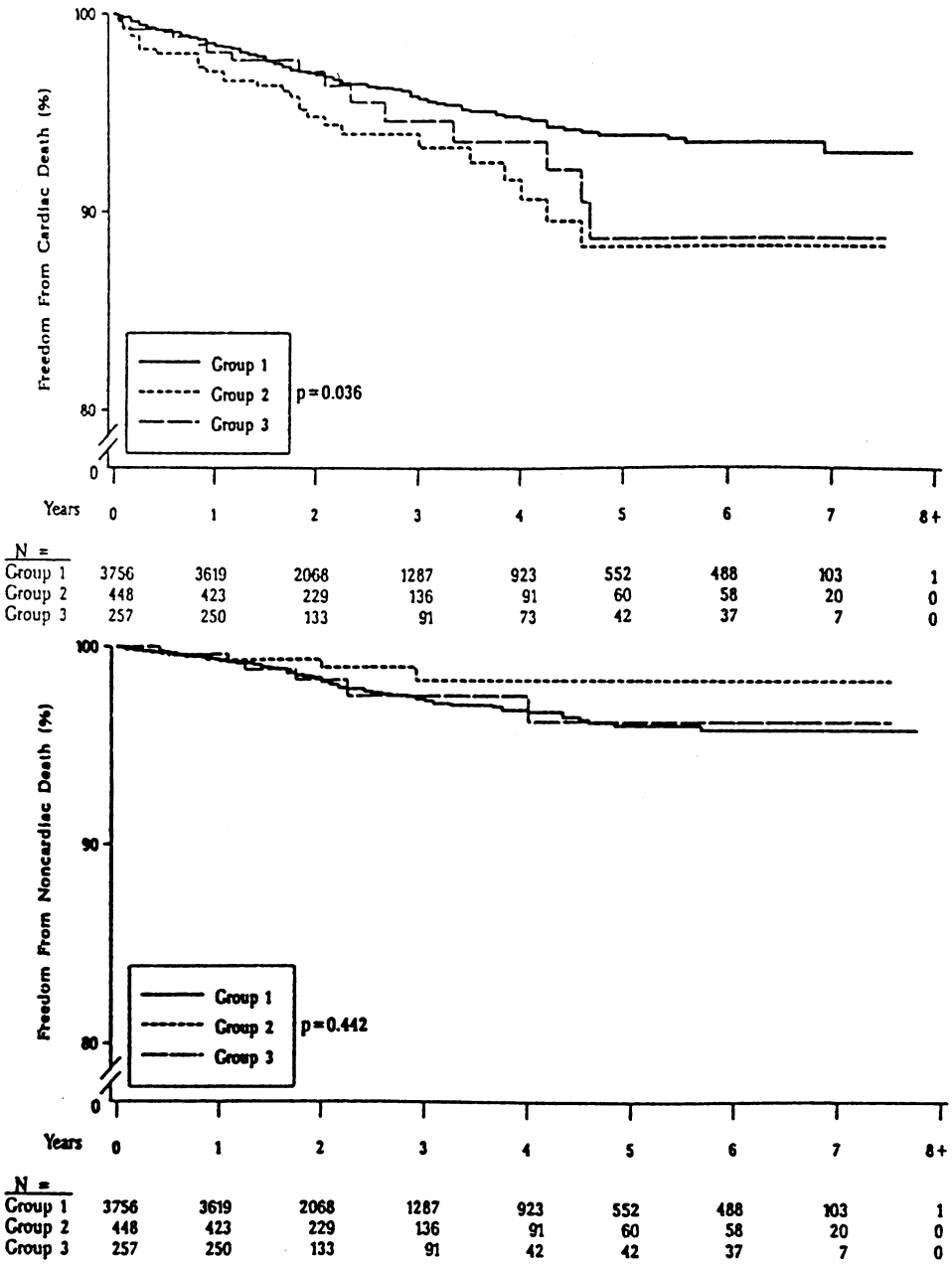

Figure 1. Plots showing freedom from cardiac (**top**) and noncardiac (**bottom**) death according to postprocedural cardiac enzyme level. Reprinted, with permission, from Abdelmeguid et al. (77).

with CK elevation included a coronary embolism during the procedure, a history of recent MI, minor procedural complications (transient abrupt closure), hypotension, vein graft procedures, complex lesions, large dissections and severe preprocedural stenoses. A continuous relation was observed between the level of CK-MB and the risk of death over an average follow-up period of >3 years (Fig. 1).

In a more recent study, Abdelmeguid et al. (77) evaluated 4,484 patients at the Cleveland Clinic whose maximal CK was less than two times the upper limit of normal. Recent MI (<36 h), "salvage" atherectomy for failed PTCA and chronic total occlusion procedures were excluded. Within this restricted group, a continuous relation was also found between the level of CK-MB elevation and the risk of death in follow-up, again with no evident threshold (77). Kugelmass et al. (6) evaluated 565 patients treated with directional atherectomy and stenting at a single institution. Elevation of CK-MB with a peak value <50 IU/liter occurred in 11.5% of patients and was associated with no significant increase in adverse 2-year outcomes. In contrast, the 2.3% of patients with a CK-MB level >50 IU/liter had a significant increase in poor outcomes. Enzyme elevation was associated with a greater extent of coronary disease and more adverse lesion morphologic characteristics.

Harrington et al. (78) reported on findings in 1,012 patients enrolled in the randomized Coronary Angioplasty Versus

Table 2. Studies of Enzyme Elevation

Study (ref no.)	Year	Procedure	Threshold Value	No. of Pts	Above Threshold	Level of Increased Risk
Oh et al. (91)	1985	Elective PTCA, successful	CK-MB >2% of total CK	128	20%	None detected
Klein et al. (5)	1991	Elective PTCA, successful	CK-MB ≥5% of total CK	249	15%	None detected
Kugelmass et al. (6)	1994	DCA or stenting, successful	CK-MB 10–50 IU/liter (>1–5× ULN)	565	8.2%	None detected
			CK-MB >50 IU/liter (>5× ULN)		2.3%	↑ Death
Harrington et al. (78)	1995	DCA or PTCA, both successful and unsuccessful	CK-MB ≥3× ULN	1,012	11%	↑ Composite of death, MI, repeat revascularization
Abdelmeguid et al. (75)	1995	DCA or PTCA, successful, with and without transient AC	Total CK > ULN	4,863	Without AC, 12%; with AC, 50%	↑ Death
Abdelmeguid et al. (76)	1996	DCA or PTCA, successful	Group 2, 2–5× ULN	4,664	Group 2, 123%	↑ Death
			Group 3, >5× ULN		Group 3, 61%	↑ Death
Abdelmeguid et al. (77)	1996	PTCA or DCA, successful	CK 100–180 IU/liter; CK-MB ≥4%	4,484	10%	↑ Death
			CK 181–360 IU/liter; CK-MB ≥4%		6%	↑ Death
Redwood et al. (98)	1996	DCA, Rotablator, ELCA	CK-MB 1–4× ULN	1,897	—	↑ Death
			CK-MB >4× ULN		—	↑ Death
Kong et al. (99)	1996	PTCA	CK >125 IU/liter; CK-MB >4%	2,812	9%	↑ Death, MI
Tardiff et al. (82)	1996	PTCA	CK-MB 1–3× ULN	2,432	14%	↑ Death
			CK-MB 3–10× ULN		8%	↑ Death

AC = abrupt closure; CK = creatine kinase; CK-MB = creatine kinase, MB fraction; DCA = directional coronary atherectomy; ELCA = excimer laser coronary angioplasty; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; Pts = patients; ref = reference; ULN = upper limit of normal; ↑ = increased.

Excisional Atherectomy Trial (CAVEAT) comparing excisional atherectomy with angioplasty. Atherectomy was associated with a greater incidence of enzyme-positive events, and threefold or greater increases in CK-MB were associated with higher rates of repeat revascularization, longer hospital stay and greater cost. Surprisingly, these enzyme rises were also associated with a higher rate of 1-year mortality (79). Even in the absence of clinically recognized abrupt closure, enzyme elevation was associated with adverse clinical outcomes in CAVEAT.

Topol et al. (80) published the long-term outcomes of patients entered into the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial as a function of CK-MB elevation. A stepwise increase in the 3-year rise of death was observed, ranging from a risk ratio of 1.47, with an increase in the CK-MB ratio between one and two times the upper limit of normal, to a risk ratio of 2.40 for patients with an elevation more than 10 times the upper limit of normal. Recently, a number of institutional and group experiences with cardiac enzymes have been reported in abstract form (Table 2). In the most extensive series reported to date, Redwood et al. (81) compared 499 patients treated with direct coronary atherectomy who had CK-MB elevations one to four times the upper limit of normal with 1,148 patients treated with directional coronary atherectomy without an enzyme rise and with 250 patients with a greater enzyme rise. The low level enzyme elevations were associated with a threefold increase in major in-hospital complications and in late mortality. Data from both the Integrelin to Manage Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT II) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO II) trials have supported these findings (82,83). These studies also documented a substantial increase in medical costs for patients with elevated cardiac enzymes.

Most recently, a detailed single-center analysis from Northwestern evaluated 253 consecutive patients with elevated CK and 120 control patients in a case-control study (84). Elevation of CK was a significant independent predictor of cardiac mortality (Fig. 2) and mortality or subsequent MI, even after considering coronary anatomy and left ventricular function, and this relation did not have an obvious threshold. Based on these findings the investigators and editorial reviewers (85) recommend routine assessment of CK and CK-MB.

Several recent randomized studies have failed to find a relation between low levels of CK-MB release and higher late mortality (86,87). These trials tended to enroll patients with good left ventricular function and a modest extent of disease.

Mechanisms

At least two possible processes require discussion in terms of mechanisms. The first is the mechanism responsible for CK

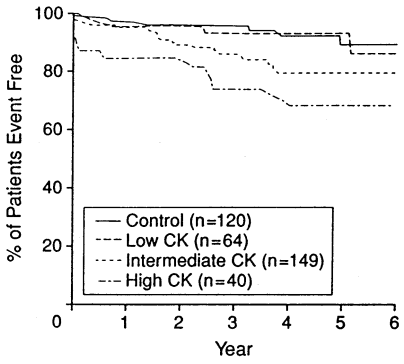

Figure 2. Event-free survival curves for cardiac mortality are shown for the patient subgroups with high (>3.0 times normal), intermediate (1.5 to 3.0 times normal) and low (>1.0 to <1.5 times normal) CK elevations and for the control group. Freedom from cardiac mortality after elective PTCA was significantly lower for patients with high and intermediate CK elevations compared with patients with low CK elevations and control subjects (p = 0.007). Reprinted, with permission, from Kong et al. (84).

release and the second is the mechanism responsible for adverse clinical outcomes. The mechanism(s) responsible for CK release are either related to myocellular necrosis (e.g., occlusion due to embolization, side branch occlusion, with subsequent reperfusion and washout) or not related to myocellular necrosis. In the latter case, possible mechanisms include profound ischemic injury but retention of cell viability, enzyme induction or perhaps some other, as yet undescribed, process. The mechanism(s) responsible for the adverse outcome event could be as simple as those associated with other types of myocellular necrosis (e.g., poor left ventricular function, heightened adrenergic state contributing to ischemia or arrhythmogenesis, arrhythmogenesis itself related to refractory period dispersion). Alternatively, it could be that the characteristics of the vessel wall (e.g., endothelial dysfunction, inflammation) or plaque (e.g., soft core, thin cap, high stress) that lead to micronecrosis initially make the vessel or plaque relatively more vulnerable to additional rupture or disruption over the follow-up period and result in an adverse outcome event.

Several studies have attempted to explore the basis for leakage of cardiac enzymes during an angioplasty procedure. In a study of 357 balloon inflations in 38 patients, ECG evidence of myocardial ischemia was noted after an average of 20 s of balloon inflation, whereas elevations of CK were not observed in patients with an ischemia duration <5 min (88). These findings have been corroborated in 110 patients in whom no significant CK-MB elevation was observed during a 15-min balloon inflation with no ECG evidence of ischemia (89). Several investigators have reported that percutaneous interventions without clinically recognized complications are not associated with a significant leak of myocardial enzymes (68,89–91), while others have found minor elevations in CK-MB in a minority of patients in whom no clear evidence for ischemia could be documented (5,92). The most common cause for elevated enzymes from available studies after angioplasty is minor branch occlusion during the procedure, which occurs in approximately one-third of all patients with elevated enzymes (5,70,91), whereas angiographic evidence of thrombus in the vessel is associated with CK-MB elevations in 13% to 40% of patients. Other documented causes have included intimal dissection, coronary spasm and distal embolization (5). Distal embolization has been noted to be particularly common in patients undergoing a percutaneous intervention in saphenous vein grafts (93). In a series of 155 procedures, independent predictors of distal embolization with subsequent enzyme release included diffusely diseased vein graft (p = 0.002), presence of thrombus (p = 0.006), ulcerated lesion surface (p = 0.007), large plaque volume (p = 0.02) and marked eccentricity (p = 0.03) (93). Thus, thrombosis either of a side branch or by distal embolization appears to be a major culprit for enzyme leakage after angioplasty. This concept is further supported by the findings of a high rate of periprocedural infarctions and abrupt closure in patients with thrombus-laden lesions (94,95).

Several recent trials of blockade of the platelet glycoprotein IIb/IIIa receptor or potent antithrombotic compounds such as hirudin or bivalirudin during percutaneous intervention have demonstrated a reduction in the occurrence of myocardial necrosis (20,69,96). These findings suggest that preventing platelet aggregation or thrombosis may prevent a substantial proportion of the events. In addition to platelet emboli, embolization of plaque material, particularly with atherectomy devices, could plug smaller vessels downstream. Although side-branch occlusion almost certainly contributes to the overall picture, there is no evidence that it is a major issue in this context.

The fact that all percutaneous revascularization procedures are associated with transient coronary artery occlusion, and occlusions are usually done repeatedly during the procedure, also needs to be considered. Such severe ischemic stress followed by reperfusion could result in washout of any CK induced and leaked as a result of the procedure-related ischemic stress. Some investigators have suggested this from animal models of repeated coronary occlusion without histologic evidence of myocellular necrosis (97).

Prognostic Relation

There are several possible explanations for the relation between enzyme appearance and subsequent adverse outcomes. These include a true effect of myocardial damage, confoundment with more severe underlying disease and the play of chance.

Enzymatic rises may occur predominantly in patients with more severe disease, particularly in those with more diffuse atherosclerosis; from this perspective, it may not be the myocardial necrosis reflected by the enzymes themselves that is creating the risk, but the underlying severity of illness of the patients. Preliminary analyses have been unable to demonstrate that the prognostic import of elevated enzymes is explained by greater underlying disease (75,78). However,

Table 3. Critical Research Questions

What is the appropriate threshold for cardiac enzyme elevation after revascularization procedures to identify patients at risk of long-term clinical sequellae?
In patients with elevated cardiac enzymes, is the worse long-term clinical outcome due to the myocardial necrosis at the time of the procedure, or is it due to the underlying high risk nature of patients who have enzyme elevations in the periprocedural period?
Do elevated cardiac-specific enzymes have the same meaning regardless of the method of revascularization, including: • Routine PTCA • Bypass surgery • Minimally invasive bypass surgery • DCA • Rotablator • Coronary stenting • Laser angioplasty
Which ECG criteria truly best distinguish patients at greatest risk of poor outcome after revascularization procedures?
Which enzyme marker is best for identifying risk after revascularization procedures? • CK-MB • Troponin T • Troponin I

Abbreviations as in Tables 1 and 2.

these analyses did not include detailed evaluations of coronary morphologic characteristics.

A second possibility is that elevated enzymes identify a particular plaque characteristic that could not be identified through other means. Such a plaque might be prone to embolic events at the time of the percutaneous procedure and might be associated with a poor outcome for reasons independent of the enzyme elevations. Given that multiple studies have observed the same relation between enzyme elevation and risk of adverse outcomes, play of chance cannot be used as an explanation.

Recommended Interpretation

More high quality data from consecutive patients with detailed measures of baseline characteristics, procedural details, periprocedural enzymes and clinical outcomes are needed. There is a particular need for longer follow-up of patients, because the life expectancy of many of the patients exceeds 15 years. A series of critical research questions are in need of careful clinical investigation (Table 3).

In the interim, however, a CK-MB elevation more than threefold the upper limit of normal for the reference laboratory should be considered an MI. Elevations below threefold are considered uncertain in terms of their prognostic implications, although currently available data point to a gradient of risk with a modest increase in risk of death for slight elevations. The increase in risk of subsequent cardiac events is clear, however. In the presence of elevated enzymes before the procedures, the interpretation is much more complex.

Recommendations for routine clinical care

1. In the clinical care of patients, a preprocedural and postprocedural ECG should be obtained and the routine measurement of CK and CK-MB is recommended. Ideally, these measurements should be obtained at baseline and 8 and 16 h after the procedures.
2. Patients with elevations of threefold or more above the upper limit of normal for percutaneous intervention or fivefold or more for CABG should be treated as having an MI, especially in the presence of a technical complication of the procedures.
3. Elevations less than three- to fivefold are more uncertain, although any evidence of clinical instability should prompt caution in discharge and activity instructions.
4. Clinical trials involving coronary revascularization should obtain ECGs and measure enzymes as described earlier and at the time of any suspicious clinical event. An independent and blinded Clinical Events Committee is recommended to ensure objective evaluation of the end point.

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