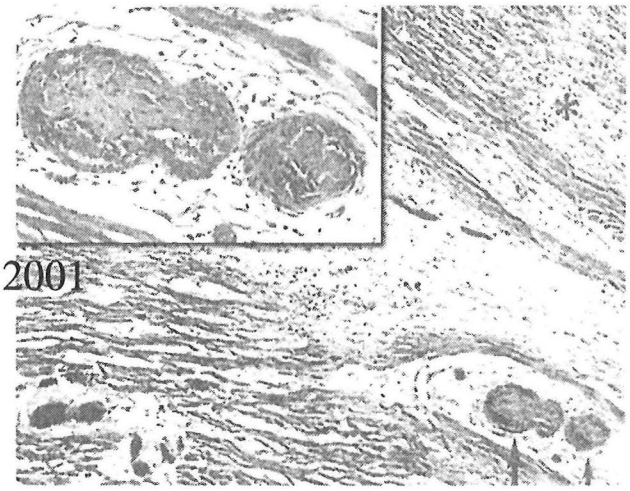
Troponinemia:

Mechanisms and Implications of Minimal Myocardial Injury

Internal Medicine Grand Rounds

1 March 2001



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Dr. Meidell has disclosed no financial interests or relationships with commercial entities related, directly or indirectly, to the topic of this Internal Medicine Grand Rounds. He has disclosed the following general relationships with commercial biomedical or biotechnology concerns: Smith-Kline Beecham, Inc.: past consultant; Valentis, Inc.: past member, Cardiovascular Advisory Board (for predecessor GeneMedicine, Inc.); ThromboGene, Ltd., consultant; Genentech, Inc.: research support Dr. Meidell will be discussing investigational therapeutic trials, and may in this context discuss "off-label" uses of various therapeutic agents.

In 1994, the Clinical Pathology Laboratory at Parkland Memorial Hospital introduced an assay for cardiac troponin I as a component of the "cardiac enzyme" profile. In a recent review, abnormal serum cTnI was the fourth most common reason (behind chest pain, congestive heart failure and atrial fibrillation) for evaluation by the Cardiology Consultation Service, and the most common reason for interservice transfer to the Coronary Care Unit. The Clinical Pathology Laboratory runs dozens of cTnI assays daily, but there remains significant confusion concerning the significance of an abnormal (or in some clinical settings, normal) serum cTnI concentration. Some examples:

Case 1:
A 54 year old man, active cigarette smoker, with a 10 year history of hypertension off therapy for several months, was admitted with a recent history of crescendo pattern chest pain after a 30 minute episode of chest pain at rest. ECG in the ED showed borderline criteria for left ventricular hypertrophy but no dynamic changes and was unchanged from a tracing 1 year previously. Serum CK and CK-MB were normal, and initial serum cTnI was 0.4 ng/ml. He was treated with oral antihypertensives, long acting nitrates, and titrated intravenous unfractionated heparin. Twelve hours after admission, a second cTnI returned 1.7 ng/ml, and he was transferred to the CCU for management of non-Q wave myocardial infarction with heparin and tirofiban and referred for cardiac catheterization.

Case 2:
A 62 year old man with a family history of premature coronary artery disease was admitted to telemetry with new onset resting chest pain suspicious for angina after an ECG in the ED demonstrated 1 mm ST segment depression inferoapically which normalized on subsequent tracings and serial CK-MB and cTnI were normal. On therapy with oral antianginals he remained pain-free for 48 hours and was discharged to follow-up in the COPC clinic.

Case 3:
A 63 year old woman with longstanding poorly-controlled hypertension and renal failure on hemodialysis was admitted from the dialysis center with dyspnea and edema. She had no history of chest pain, but her BP in the ED was 220/120. Prior echocardiography had demonstrated normal left ventricular chamber size, concentric LVH, and moderately depressed left ventricular systolic function with global hypokinesis. ECG showed LVH with repolarization abnormality. Total CK was 195, CK-MB was normal. Serum cTnI was 2.2 ng/ml. The cardiology service was consulted for evaluation of NQMI.

Case 4:
A 71 year old man with no cardiac history underwent elective repair of an abdominal aortic aneurysm. The procedure was uncomplicated except for transient hypotension to 85/60 in the immediate postoperative period. ECG was normal and unchanged from a preoperative tracing. CK was 410, CK-MB was 6 and serum cTnI was 3.1. The cardiology service was consulted for possible transfer for perioperative myocardial infarction.

Did my patient suffer a myocardial infarction? A minor myocardial injury? An "infarctlet"? An "enzyme leak"? Should my patient be treated with a platelet aggregation inhibitor? Low molecular weight heparin? Titrated unfractionated heparin? Should I refer the patient for non-

invasive stress evaluation or coronary angiography and possible transluminal or surgical coronary revascularization? What is the risk for a recurrent cardiac event? Death? Is this cTnI elevation "real"? What's the underlying pathophysiology?

The advent of testing for very sensitive markers of myocardial injury has resulted in these questions being asked of the consulting Cardiologist on a daily basis. Today I'll try to provide information with which some of them may be answered.

Troponins

Is cardiac troponin specific for myocardium?

Troponin is a heterotrimeric complex of proteins that, in association with tropomyosin, form the calcium-sensitive regulatory complex of myofibrils. Troponin I is an ~24kD protein that forms an inhibitory complex with troponin C in the absence of calcium. There are distinct fast and slow skeletal and cardiac isoforms encoded by distinct genes. The cardiac isoform is 31 amino acids longer than the skeletal forms, possessing an N-terminal extension that contains two phosphorylation sites that play a role in modulating calcium sensitivity. In normal cardiomyocytes, >98% of cellular cTnI is assembled into myofibrils. The amino acid sequence of cardiac troponin I (cTnI) shows ~ 40% dissimilarity in comparison to the skeletal muscle isoforms, and cTnI is not expressed in skeletal muscle during ontogeny, muscle regeneration or in response to pathological stimuli (Cummins 1987, Martin 1991).

Troponin T is a 31-36 kD protein that appears to function as an adapter linking troponin C to tropomyosin. TnT's demonstrate both N- and C-terminal heterogeneity reflecting alternative splicing. Like TnI, fast and slow skeletal and cardiac isoforms exist, and are the products of separate genes; the cardiac isoform, cTnT, is encoded by the TNNT2 gene. Mutations in the C-terminal inhibitory domain of cTnT responsible for forms of hypertrophic cardiomyopathy alter calcium sensitivity and reduce force generation at sub-saturating calcium concentrations. Recent observations suggest that post-translational (proteolytic) processing of cTnT may occur in the setting of cardiomyopathy, and may contribute to decreased contractility. Like cTnI, in normal cardiomyocytes, cTnT exists primarily in association with myofibrils, with a very small cytoplasmic pool.

Assays for Cardiac Troponins: Validation and Specificity

How are cTnT/cTnI assayed, and how specific are the assays?

cTnT

Katus and colleagues (1991) developed an immunoassay for cardiac troponin T. The sandwich immunoassay employed two monoclonal antibodies directed against separate epitopes of the cTnT molecule. One of these antibodies showed modest (<15%) cross-reactivity with skeletal isoforms, the other no detectable cross-reactivity. They evaluated the potential of this assay for the detection of myocardial injury in 388 patients with suspected acute myocardial infarction and 101 patients with skeletal muscle injuries. All patients ultimately diagnosed with myocardial infarction demonstrated elevated levels of cTnT in serum. In 37/79 patients ultimately diagnosed

with unstable angina, at least one serum sample showed an elevated cTnT concentration. Specificity for myocardial injury was between 89-94% depending on the threshold value selected.

Subsequently, Antman et al (1993) developed a rapid beside immunoassay for cTnT. This assay was validated on a series of 100 patients presenting to the ED for evaluation of chest pain. MI was defined by CK > upper limits of normal with characteristic rise and fall, and CK-MB > 2.5%. Sensitivity of cTnT for diagnosis of myocardial infarction was 33% at < 2 hours, 50% at 2-4 hours, 75% at 4-8 hours and 86% beyond 8 hours from the onset of symptoms. Specificity was 95-100% at < 8 hours, and 86% beyond 8 hours. This validation study also suggested that serum cTnT concentration predicted prognosis, as 71% of patients with recurrent infarction were cTnT positive on presentation, and 10/34 patients with a positive cTnT had a major adverse cardiac event prior to hospital discharge.

A similar rapid bedside test was developed in 1995 by the Katus group (Muller-Bardorff et al 1995) (Figure 1). Validation studies included 25 healthy volunteers, 62 patients with chest pain but without evidence of infarction, 35 patients with myocardial infarction by CK and CK-MB criteria, 24 radiofrequency ablation patients and 35 patients with unstable angina, and showed good correlation with clinical diagnosis and greater sensitivity than CK-MB assays for identification of myocardial injury.

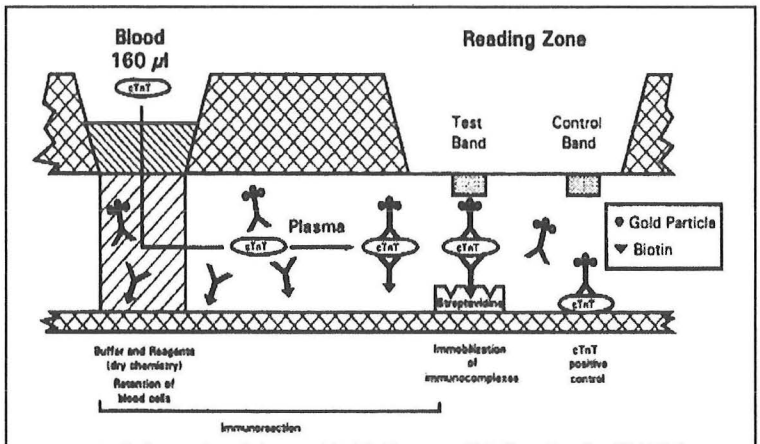

Figure 1: Schematic of the rapid cTnT assay (Muller-Bardorff 1995)

cTnI

In 1992, Bodor and colleagues (1992) reported isolating monoclonal antibodies to cTnI with no observable cross-reactivity to the skeletal muscle isoforms, and described using these antibodies in an assay to detect cTnI in the serum of patients with acute myocardial infarction. A standardized immunoassay (Adams 1993) was validated in a study of 215 subjects (Figure 2), 37 with acute skeletal muscle injury, 10 with chronic myopathies, 9 marathon runners and 159 patients with chronic renal failure on hemodialysis. All subjects had serum assays for CK, CK-MB and cTnI and transthoracic echocardiography for left ventricular wall motion. All 37 patients with acute muscle injury or

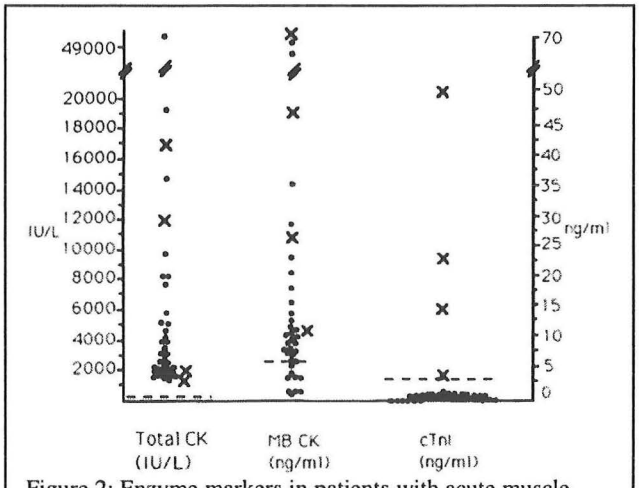

Figure 2: Enzyme markers in patients with acute muscle disease, X: patients with myocardial injury (Adams 1993)

chronic myopathy and 27/159 with renal failure had elevation of total CK. 24/37, 9/10 and 27/159 respectively had elevation of CK-MB. By echocardiography, 4, 1 and 1, respectively, had regional wall motion abnormalities. Serum concentrations of cTnI were elevated only in the six patients with regional wall motion abnormalities on echocardiography. Each of these had electrocardiographic abnormalities consistent with ischemia; all had elevated CK-MB and 2 developed new Q waves. The authors concluded that serum cTnI was highly specific for myocardial injury.

On the basis of these validation studies, clinical assays for both cTnT and cTnI received FDA approval in 1994, and have been in routine clinical use since that time. Elevations of cTnT and/or cTnI are regularly represented as being highly sensitive and specific, and in many settings, including in routine clinical use at Parkland Memorial Hospital, have become a *de facto* "Gold Standard" for identification of ischemic myocardial injury. In broad application, however, cases are encountered in which an abnormal assay for cardiac troponin is the only indication of myocardial injury and/or where clinical suspicion of acute coronary ischemia is low. There remains substantial confusion in interpreting abnormal serum cTnT/cTnI levels, and in understanding the clinical significance of minimal myocardial injury.

Troponinemia following Coronary Intervention: Insights into the Pathophysiology of Minimal Myocardial Injury

What is the significance of a minor elevation of cTnI in patients after coronary intervention?

What is the mechanism of the myocardial injury, if any, identified by an elevated cTnI following coronary intervention?

Evidence of low-grade myocardial injury is common in the setting of percutaneous coronary interventions. In the CAVEAT trial (a prospective trial of PTCA vs. directional atherectomy; Topol 1993), the incidence of periprocedural myocardial injury (using CK-MB criteria) was 8% for PTCA and 19% for atherectomy. In 1-year follow-up (Elliot 1995) there was a significantly higher mortality in patients treated with atherectomy, and most of this occurred in patients with periprocedural infarcts by enzyme criteria.

A similar effect of periprocedural injury on long-term mortality was observed in the three major prospective trials of abciximab therapy in the setting of percutaneous coronary revascularization, EPIC (Topol 1997), EPILOG (EPILOG Investigators 1997, Lincoff 1999) and EPISTENT (EPISTENT Investigators 1998) (Figure 3). In these studies, and in the large Cleveland

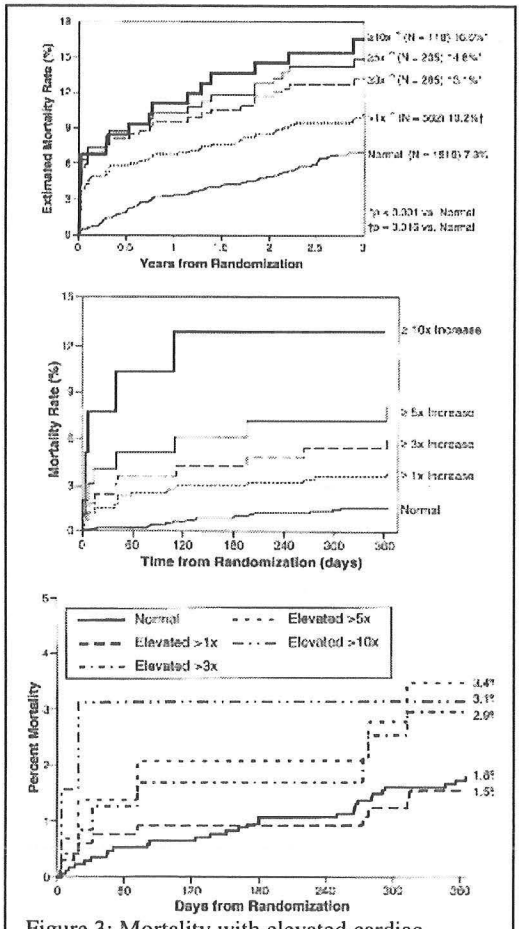

Figure 3: Mortality with elevated cardiac enzymes in TCI trials (Topol 2000)

Clinic series reported by Abdelmeguid et al (1996a, b) total CK or CK-MB were used as the indicator of myocardial injury. A number of studies using cTn as the indicator of myocardial injury, for example that of Ravkilde et al (1994), have reported even higher rates (20%-40%) and have consistently observed an adverse effect on prognosis (reviewed in Topol 2000). The consistent association of enzymatic evidence of injury and an adverse prognosis following TCI led speculation in one consensus paper that "elevated enzymes identify a particular plaque characteristic that could not be identified through other means [and that] might be prone to embolic events at the time of [TCI] and might be associated with a poor outcome for reasons independent of the enzyme elevations" (Califf 1998).

Substantial, albeit indirect, data has accumulated implicating distal embolization as an important pathophysiologic mechanism underlying myocardial injury in association with uncomplicated TCI. The phenomenon of no reflow - an angiographically patent vessel with severely impaired antegrade flow - is well described. It occurs relatively uncommonly in the setting of primary intervention for ST segment elevation myocardial infarction, and even less commonly in the setting of intervention for subtotal coronary occlusion. Ito and colleagues (1996), however, suggest that impaired perfusion following PTCA targeting diseased but not occluded vessels is much more common than appreciated. They reported that in 25% of patients undergoing angiographically successful elective PTCA resulting in normal (TIMI 3) epicardial coronary flow, myocardial contrast echo demonstrated persistent tissue hypoperfusion. Similar perfusion defects have been detected by nuclear perfusion scanning in the setting of coronary rotoblation (Figure 4, Koch 1999) and by MRI in the setting of acute infarction (Wu 1998), where a persistent perfusion defect has been correlated with a very poor short-term prognosis.

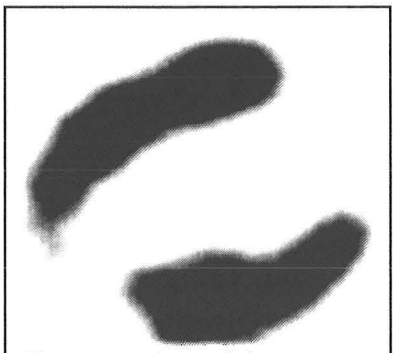

Figure 4: Perfusion defect following rotoblation (Koch 1999)

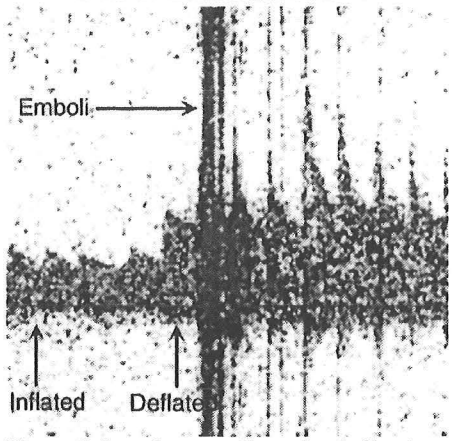

Figure 5: Doppler recording of embolization in carotid angioplasty (Topol 2000).

The presumed mechanism underlying the discrepancy between epicardial coronary flow and tissue perfusion is "microvascular" obstruction resulting from distal embolization of plaque contents and adherent thrombus. Direct evidence of embolization by Doppler is available from studies of carotid intervention (Figure 5) where external monitoring of Doppler signals distal to the site of intervention is technically feasible.

Pathologic studies suggest that distal embolization is not limited to the setting of coronary intervention and that resulting obstruction of intramyocardial vessels is common in the setting of active coronary thrombosis. In 1985, Falk (1985) reported a series of 25 autopsies performed in cases of sudden cardiac death. In 81%, thrombi at the site of occlusion had a "layered" appearance – thrombus material of differing age was present. In 73% of cases, distal embolization of thrombus material with occlusion of small intramyocardial arteries and

associated "microinfarcts" was observed by careful serial sectioning (Figure 6). In some cases, atheromatous plaque material including cholesterol crystals could be identified. Similarly, Davies et al (1986) examined autopsy material from 90 cases of sudden death identified platelet aggregates in intramyocardial vessels and associated "multifocal microscopic necrosis" in 30% (Figure 7). The incidence of intramyocardial platelet aggregates was significantly correlated with an antecedent history of unstable angina (odds ratio 2.2)

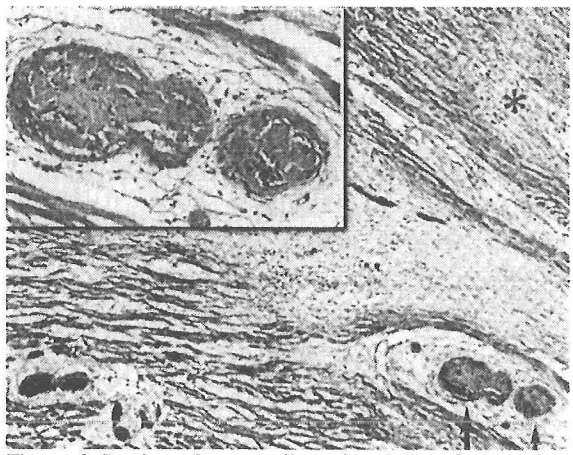

Figure 6: Section of myocardium showing occlusion of intramyocardial vessels with platelet emboli (Falk 1985).

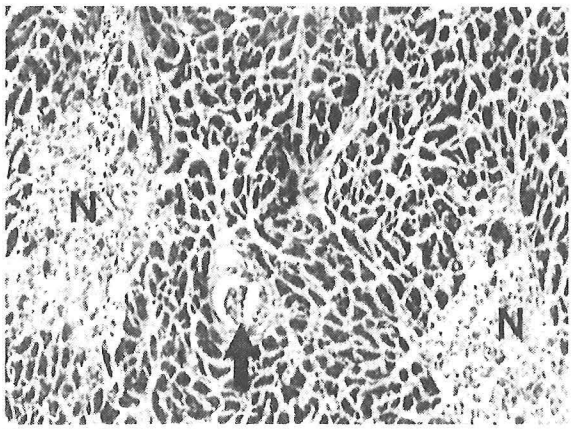

Figure 7: Section of myocardium showing occlusion of intramyocardial vessel and surrounding foci of myocyte necrosis (Davies 1986)

The concept of embolic obstruction of intramyocardial vessels as a mechanism of unstable myocardial ischemia is not new, particularly on this campus. In the 1980's, Willerson and several members of the Division of Cardiology performed an extensive series of experiments in a canine model of acute coronary ischemia. They demonstrated cyclical variations in antegrade coronary flow (termed cyclic flow variations, CFV) arising from platelet aggregation at sites of endothelial injury with spontaneous "reflow" as platelet thrombi dislodged and emobolized downstream (Figure 8). Platelet activation in this model (Ashton 1987) and ultimately in humans (van den Berg 1989) was demonstrated by accumulation of platelet release products in coronary sinus blood. Subsequent studies demonstrated CFV in humans undergoing PTCA with accumulation of serotonin in CS blood (Anderson 1994, Golino 1994).

In aggregate, these studies suggest that an important mechanism of minimal myocardial injury in the settings of transluminal coronary intervention and acute coronary syndromes is the formation of platelet aggregates at sites of endothelial injury, embolization of platelet "microthrombi" with obstruction of intramyocardial vessels, and "microinfarction". Supporting this model are studies in animal models showing that "anti-platelet" therapy inhibits or abolishes cyclical flow variations. Ashton et al (1987) showed that systemic administration of a thromboxane synthase inhibitor, a TxA2 receptor antagonist or a serotonin receptor antagonist inhibited or abolished cyclic flow variations (Ashton 1987). Members of my laboratory collaborated in experiments demonstrating that overexpression of a COX-1 gene to increase local vascular production of prostacyclin effectively eliminated CFVs in a porcine carotid angioplasty model (Figure 8; Zoldhelyi 1996).

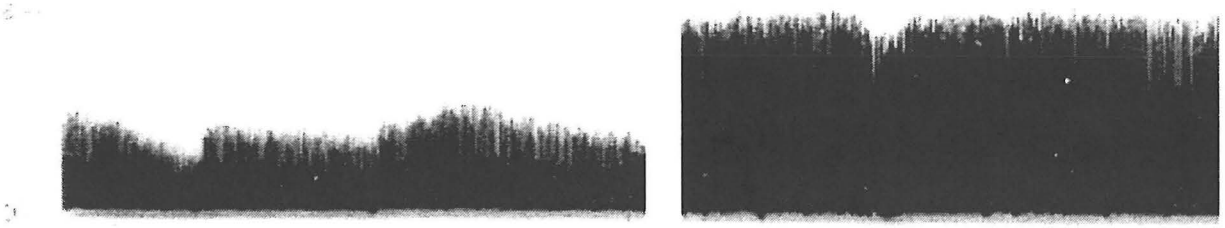

Figure 8: Effect of overexpression of COX-1 on CFV in a porcine PTCA model. Shown is Doppler flow velocity in balloon-injured vessels, left: control, right: AdCOX1 infected.

These observations appear to extend to humans undergoing transluminal revascularization. In 1994, Willerson's group observed CFVs in humans following PTCA, and reported that treatment with abciximab eliminated cyclical reductions in antegrade coronary flow (Anderson 1994), suggesting at least one mechanism underlying the subsequent demonstration that abciximab therapy reduces the incidence of adverse cardiac events following TCI (Figure 9, EPILOG Investigators 1998).

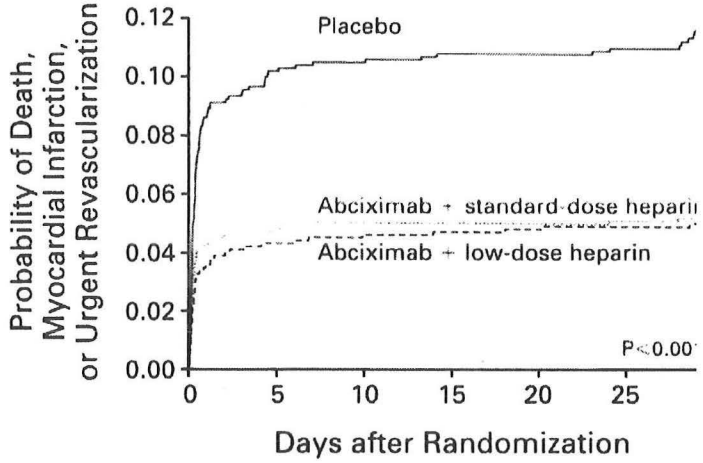

Figure 9: Results of the EPILOG trial of abciximab in TCI.

Recognizing the implications of myocardial injury in the setting of TCI, there have been efforts to develop technologies to limit distal embolization. Catheters with aspiration ports and umbrella-like devices intended to trap or remove debris have been developed (Figure 10). The potential of ultrasonic catheters to disrupt thrombus into fragments small enough to prevent occlusion of intramyocardial vessels is under active investigation.

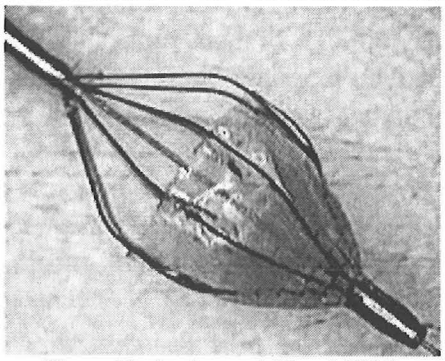

Figure 10: Angioguard (Topol 2000).

To maintain some balance in the discussion, let me acknowledge focusing on a single, probably relatively common mechanism of myocardial injury in the setting of coronary intervention. Obviously, correlations of clinical outcome with release of cardiac proteins following TCI are biased by the occurrence of acute closure from local thrombosis, complex dissection or side-branch occlusion resulting in "macroscopic" infarction. The last of these may be difficult to identify in some cases.

The observation that distal embolization occurs in the setting of TCI with obstruction of intramyocardial vessels, focal necrosis of myocardium and low-level release of myocardial proteins into blood, and that such low level myocardial injury is associated with a significantly

worse prognosis, provides a conceptual framework from which the more general problem of minimal myocardial injury may be approached.

Troponinemia in Acute Coronary Syndromes: Studies in High Risk Populations

In a patient with an acute coronary syndrome, what is the significance of a minor elevation of cTnT/cTnI?

How does prognostic information derived from troponin testing relate to that from ECG?

Does cTn predict significant CAD and/or need for revascularization?

The value of serum troponin concentration as a prognostic variable in high-risk patient populations (patients in whom the diagnosis of acute coronary syndrome is supported by objective evidence of ischemia or underlying coronary artery disease) has been addressed in substudies of several large prospective clinical trials. In general, these studies are of two types, those examining cTnT/cTnI levels in blood obtained at presentation, and those following cTn concentrations serially over the first 24-36 hours.

Immediate cTn levels

The GUSTO IIA trial was a prospective randomized trial of recombinant hirudin for acute coronary syndromes. Patients were enrolled within 12 hours of the onset of chest pain if ECG showed ST elevation, ST depression, T-wave inversion or left bundle branch block. Ohman et al (1996) assayed troponin T concentration in blood samples obtained within 2 hours of admission in 755 patients enrolled in the parent trial. Primary endpoint was the incidence of the composite of death, myocardial infarction or revascularization at 30 days. Overall, 36% of enrolled patients had an elevated serum cTnT concentration (>0.1ng/ml). There was a strong positive correlation between cTnT and both the primary composite endpoint and 30-day mortality (Figure 11) in this high-risk population (72% of patients had Q wave MI). In patients with ST depression or T wave inversion on the qualifying ECG, cTnT concentration also correlated with an ultimate diagnosis of myocardial infarction (by CK-MB criteria), but elevated cTnT concentration at admission did not predict need for revascularization. The cumulative sensitivity of the cTnT assay for adverse cardiac outcomes was 57%, with a specificity of 68%.

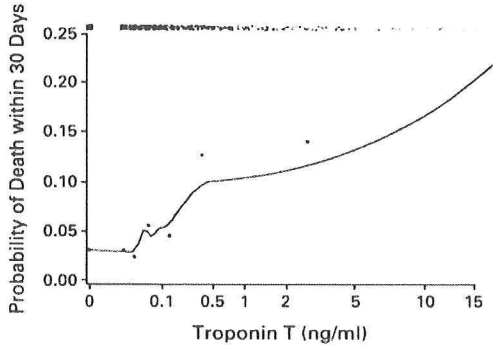

Figure 11: Probability of death within 30d by cTnT level in the GUSTO IIA trial (Ohman 1996).

Antman et al (1996) examined the relationship between serum cTnI concentration and 42-day mortality in 1404 patients in the TIMI IIIB trial. The trial enrolled patients between 21-76 with documented coronary disease and chest pain at rest 5 min - 6 hrs in duration thought to be ischemic within the preceding 24 hours. 573 of 1404 patients had elevated serum cTnI levels on

admission. Patients with elevated cTnI levels had a higher incidence of ST segment abnormalities on ECG (57 vs. 33%), and were less likely to have had a prior myocardial infarction (31 vs. 47%), prior antianginal therapy or a prior angiogram showing significant CAD (22 vs. 40%). 1150 patients underwent angiography. cTnI status did not predict either occluded vessels or the extent of thrombus present at angiography. cTnI concentration was elevated in 25% of patients without CK-MB evidence of myocardial infarction, and 75% of those with elevated CK-MB levels. Figure 12 shows mortality rate at 42 days according to magnitude of cTnI elevation. Only in those patients in whom blood samples were obtained more than six hours from the onset of symptoms was there a strong correlation with mortality.

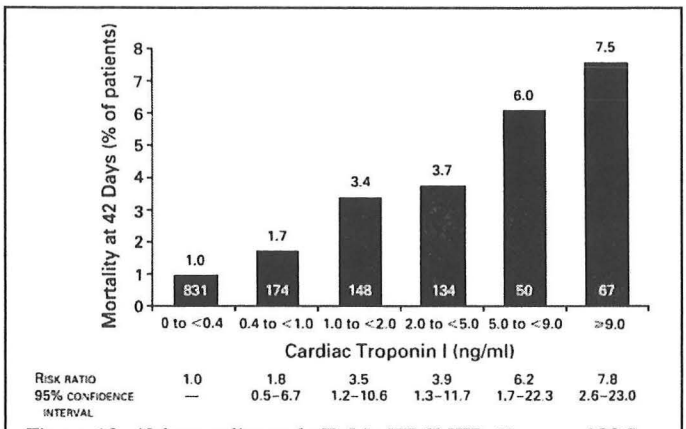

Figure 12: 42d mortality and cTnI in TIMI IIIB (Antman 1996).

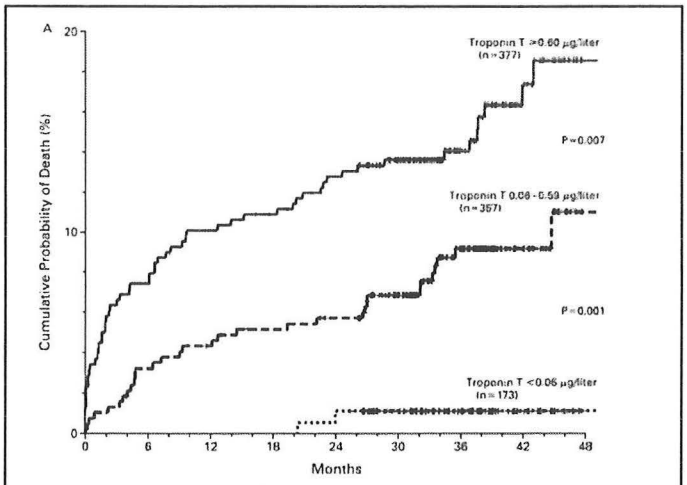

Figure 13: Mortality in the FRISC trial by cTnT level (Lindahl 20000).

Lindahl et al (1996) reported the experience from the FRISC trial (randomized study of low molecular weight heparin in patients with acute coronary syndromes). In 593 patients with unstable chest pain and either ECG changes or known CAD, the risk of death or myocardial infarction was 4.4% in patients with cTnT<0.06 ng/ml, 11.4% for cTnT 0.06-0.18 ng/ml and 14% for cTnT > 0.18 ng/ml (Figure 13). An important finding in the FRISC data is that a differential risk for mortality identified by cTnT status persisted throughout the follow-up period (up to 4 years).

It is difficult to draw conclusions applicable to the way cardiac troponin is used as an indicator in the current clinical environment from the data available in these substudies of the GUSTOIIA, TIMI IIIB and FRISC trials. First, because each of these studies did not distinguish patients with/without infarction by CK-MB criteria, the correlation between cTnT/cTnI levels and outcome reflects to some degree identification of those patients with a myocardial infarction by conventional criteria. Secondly, because of the kinetics of troponin release following ischemic myocardial injury, stratifying patients on the basis of cTnT/cTnI at presentation identifies patients presenting early/late relative to the onset of symptoms, and to the extent that early therapy may impact prognosis, biases the analysis.

Serial assays of cTn

The first study examining serial measurements of cTnI in patients with suspected acute coronary syndromes was published by Galvani et al (1997). They evaluated 106 patients with a clinical diagnosis of unstable angina, chest pain within 48 hours of admission and ST-T wave abnormalities on initial electrocardiogram, with serial cTnI measurements at 8 hour intervals for 3 days. Patients were treated with aspirin, unfractionated heparin and intravenous nitrates (beta blockers and calcium channel antagonists were allowed at the discretion of the attending physician). Thirteen patients met diagnostic criteria for myocardial infarction by CK-MB criteria and were excluded from analysis. Of 91 patients with complete data, 7 had elevated levels of cTnI on admission, and 15 had detectable elevation 8 hours after an initially normal value. In patients with persistently normal cTnI, there were no deaths and 4 subsequent infarcts (5.8%) in 30 days, compared to 2 deaths (9.1%) and 4 infarcts (18.2%) in those developing cTnI elevation. Cardiac event rates during one year follow-up were 10% vs. 32% (differences at 30 days and 1 year were significant).

A second substudy of the GUSTO IIA trial addressed the ability of serial cTnT measurements to refine short-term prognosis in patients with initially normal values, and to predict course beyond 30 days (Newby 1998). Mortality at 30 days was 10% in patients with an abnormal initial cTnT, 5% in 308 patients evolving an abnormal cTnT after admission, and 0% in 166 patients with a persistently negative cTnT. Only age and ECG stratum (ST depression or a combination of ST elevation and ST depression) were better predictors of 30-day mortality than cTnT. Abnormal cTnT on serial testing also correlated with the incidence of shock and congestive heart failure, but did not predict need for either transluminal or surgical revascularization. Figure 14 shows 1-year survival as a function of cTnT status.

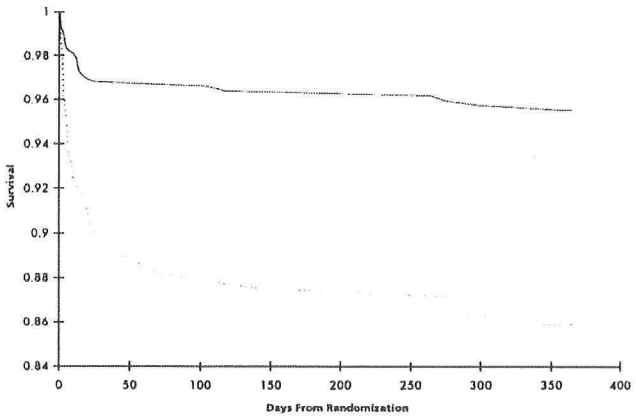

Figure 14: Survival as a function of cTnT status in the GUSTO IIA trial (Newby 1998).

The prognostic implications of minimal myocardial injury in the setting of an acute coronary syndrome are independent of the marker by which the minimal injury is detected. In the PURSUIT trial, a prospective randomized study of eptifibitide therapy in 10,948 patients with chest pain and ECG changes or an elevated CK-MB, 8250 patients had serial CK-MB

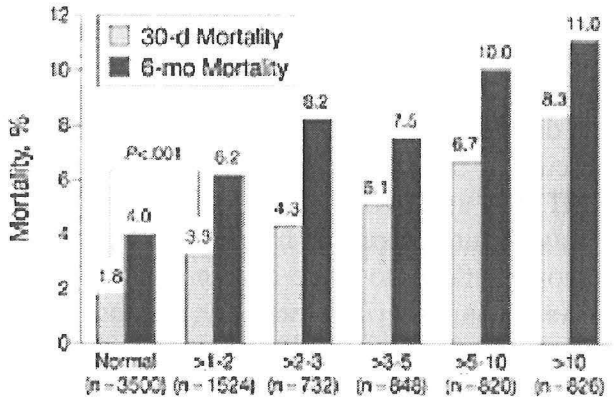

Figure 15: Mortality by CK-MB in the PURSUIT trial (Alexander 2000).

measurements available for analysis. Alexander et al. (2000) examined the relationship between minor elevations of CK-MB and mortality at 30 days and 6 months (Figure 15). There was a strong and continuous relationship between evidence of myocardial injury and mortality at both time points. The relationship was even stronger for elevation of CK-MB occurring after admission than with the qualifying episode of chest pain, consistent with prior observations of the negative prognostic impact of recurrent infarction (Benhorin 1990, Mueller 1995). In the context of the PURSUIT data, the correlation between elevated cTnT/cTnI and the incidence of death or myocardial infarction in patients with an acute coronary syndrome simply extends the relationship between minimal myocardial injury and adverse clinical outcome to even smaller myocardial injuries (those detectable by cTn release but not by increased CK or CK-MB).

Relationship between cTnT/cTnI and ECG as predictors of outcome

ST segment depression on ECG has been shown to be an important indicator of high risk in patients with acute coronary syndromes in substudies of the RISC (Nyman 1993), TIMI-III (Cannon 1997) and GUSTO IIB (Savonitto 1998) trials. In the last, for example, in a high-risk population (chest pain and ECG abnormalities), the risk of 30-day death or myocardial infarction (reinfarction) was 5.5% in patients with only T-wave inversion, 10.9% in patients with ST segment depression and 12.4% in patients with both ST segment elevation and ST segment depression on the qualifying electrocardiogram. One-year follow-up confirmed the ongoing prognostic implications of presenting ECG findings, as shown in Figure 16. Despite the prognostic power, like troponin status, ECG findings did not predict subsequent revascularization.

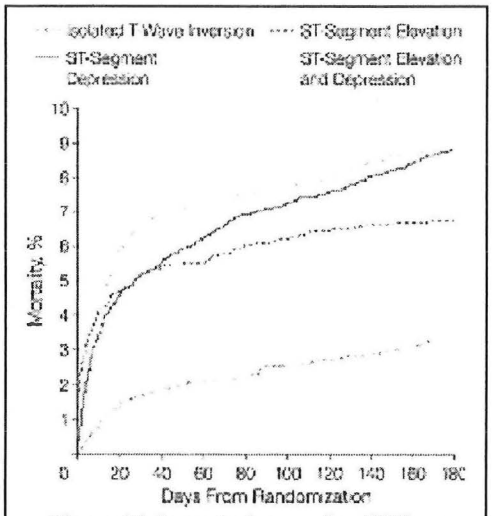

Figure 16: Impact of presenting ECG on prognosis in the GUSTO IIB trial (Savonitto 1998).

Support for the prognostic power of electrocardiographically detected ischemia, via continuous multi-lead ST segment monitoring, was provided in a substudy of the CAPTURE trial (Klootwijk 1998; a prospective randomized trial of abciximab therapy for refractory unstable angina with electrocardiographic changes despite therapy with heparin and intravenous nitroglycerin in patients with coronary angiography demonstrating a significant lesion suitable for transluminal revascularization). 332 patients underwent continuous computerized ST segment monitoring. The endpoint was the combined incidence of death or myocardial

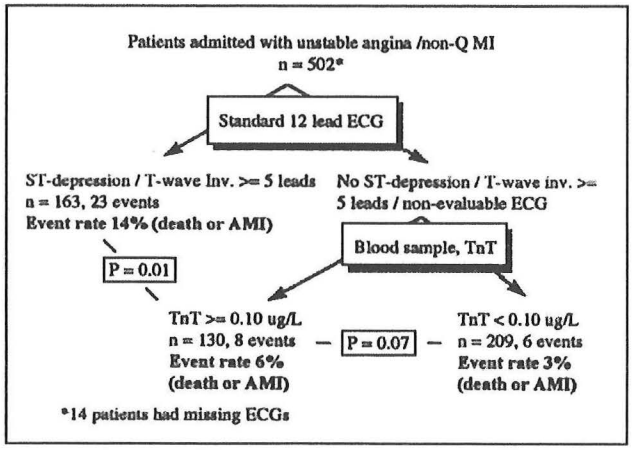

Figure 17: Results and triage strategy from the TRIM trial (Holmvang 1998).

infarction within 5 days. Recurrent ischemia was detected in 18% of patients, and conveyed a 3-4 fold increased risk for death or non-fatal myocardial infarction. In the absence of recurrent ischemia, overall event rate was 5%, and the event rate in patients treated with abciximab was <2%.

The interaction between ECG and biochemical markers of myocardial injury in predicting prognosis was evaluated formally in a substudy of the Thrombin Inhibition in Myocardial Ischemia (TRIM) trial (Holmvang 1998). Blood samples were obtained within 6 hours of admission from 516 patients with chest pain thought to be ischemic who had either ECG changes or a history of coronary artery disease (retrospectively 309 with NQMI, 190 with USA) and assayed for cTnI, cTnT, myoglobin and CK-MB. The endpoints were the combined incidence of death/non-fatal infarction and the incidence of death/MI/refractory angina requiring intervention. Figure 17 summarizes the principal findings of the TRIM substudy. cTnT level did not provide independent prognostic information alone, but did stratify those patients without ischemic ECG changes into groups at intermediate and relatively low risk.

In a substudy of the FRISC trial examining by multivariate analysis predictors of death from cardiac cause within 2 years of enrollment (Lindahl 2000), both cTnT and ECG findings at presentation contributed independent prognostic information (Figure 18).

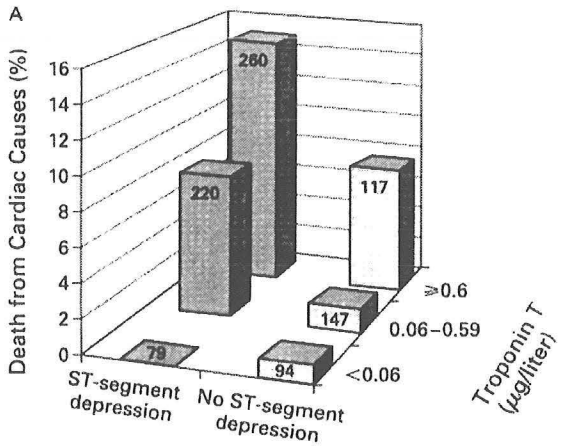

Figure 18: cTnT, ECG and Mortality in the FRISC trial (Lindahl 2000).

Predicting Coronary Artery Disease: Correlating cTnT/cTnI and Angiography

Investigators in the CAPTURE trial (abciximab peri-PTCA in patients with refractory unstable angina) examined the correlation between baseline cTn status and angiographic findings – lesion severity, the presence of visible thrombus and TIMI flow grade, in 853 patients (Heeschen 1999). In the parent trial, 31% of patients had an elevated baseline cTnT, and in patients managed conventionally, an elevated cTnT correlated with a 5-10 fold higher incidence of death and myocardial infarction. Patients underwent baseline angiography, were treated with the study drug (aspirin, heparin and aspirin, heparin and abciximab) for 18-24 hours, and then underwent repeat angiography and PTCA of the culprit lesion. There was a weak correlation between cTn status and lesion complexity; 72% of patients with elevated cTnT had angiographically complex (B2,C) lesions vs. 54% of patients without a cTnT > 0.1 ng/ml. There was also a minor correlation with TIMI flow grade; 75% of cTnT negative patients vs. 60% of cTnT positive patients had TIMI 3 (normal) antegrade flow in the target vessel. On initial angiography, thrombus was visible in 7.4% of patients, 14.6% of those cTnT positive vs. 4.2% of those cTnT negative. During pre-PTCA therapy, thrombus resolved in 26.5% of placebo treated patients vs. 49.5% of patients treated with abciximab. Lesion complexity, TIMI flow grade and visible thrombus all lacked predictive value with regard to MI-free survival at 6 months, while, as noted previously, cTnT status was a strong predictor of outcome. The authors conclude that because

angiography is a poor predictor of lesion complexity, it may be preferable to look at the consequences of the lesion (cTn) rather than angiographic characteristics.

Roe (1999) and Galvani et al. (1997) similarly observed that cTnI status is a poor predictor of coronary anatomy. In the latter study, coronary angiography was performed in 70% of patients, and there were no significant differences in the existence, extent or severity of angiographic coronary disease as a function of cTnI status.

Like troponin concentration, ECG, while correlating with clinical outcome, is a relatively poor predictor of coronary anatomy. In the GUSTO IIB electrocardiographic substudy (Savinitto 1998), there were only minor differences in the extent of coronary artery disease as a function of the nature of the electrocardiographic abnormality (single vessel CAD 1.5 fold more likely in patients with ST segment elevation, and 3-vessel disease ~ 1.5 fold more likely in patients with ST segment depression on the qualifying ECG). ECG findings at presentation did not predict subsequent need for revascularization.

Predicting Benefit from Therapy: Troponin and the Treatment of ACS

Last month, Dr. Richard Lange (2001) presented Grand Rounds on the management of acute coronary syndromes. In his presentation, Dr. Lange noted that the benefit of aggressive antiplatelet, anticoagulant and early revascularization strategies appears to accrue to patients at higher initial risk. To focus that point with reference to markers of myocardial injury:

In the CAPTURE trial, a prospective randomized trial of abciximab therapy in the periprocedural (PTCA) period for refractory unstable angina, abciximab was shown to reduce the combined incidence of death and myocardial infarction before PTCA, and at 72 hours, 30 days and 6 months relative to conventional management. Hamm et al (1999), in a substudy of this trial, analyzed the beneficial effect of abciximab as a function of baseline cTnT status. The data are summarized in Figure 19. For patients with baseline cTnT levels below 0.12 ng/ml, the incidence of the death/MI was insignificantly higher in patients treated with abciximab. In contrast, in patients with elevated cTnT levels, abciximab therapy significantly reduced the incidence of death/MI at all 3 follow-up times. Neither ST segment depression nor baseline CK-MB levels correlated significantly with beneficial therapeutic effect (although a trend similar to that with cTnT was observed). The assumption is that high levels of troponin in patients with unstable angina reflect an active thrombotic process with distal embolization of platelet thrombi originating from the culprit lesion, and that therapy with a platelet aggregation inhibitor reduces the incidence of thrombus formation and may facilitate

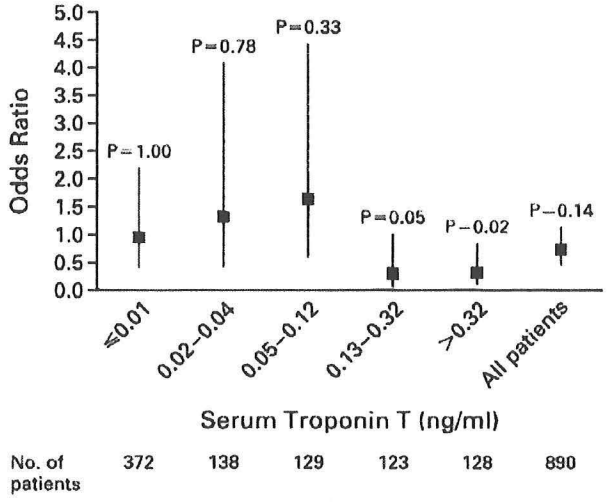

Figure 19: Effect of abciximab as a function of cTnT in the CAPTURE trial (Hamm 1999).

resolution of distal microemboli. Specifically, the authors suggest that an elevated serum troponin may serve as a surrogate marker of active thrombosis.

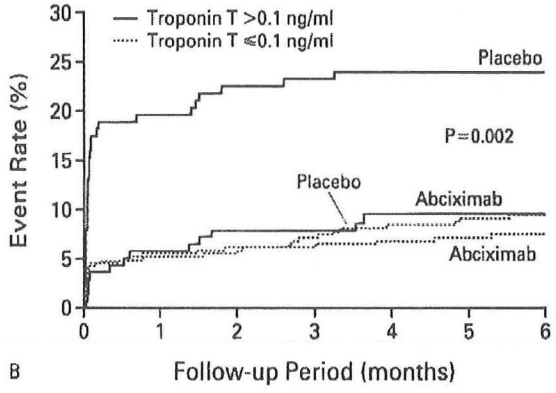

Figure 20: Cardiac event rates in the CAPTURE trial (Hamm 1999).

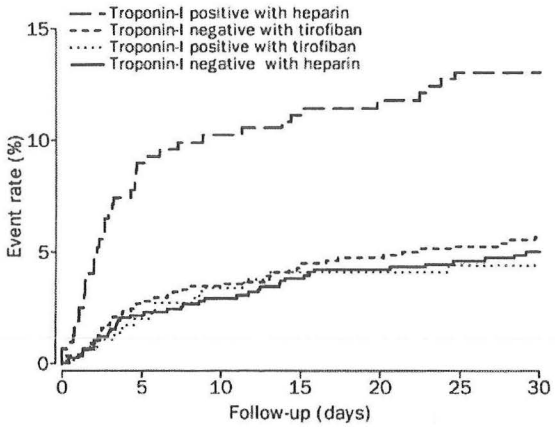

Figure 21: Event rates in the PRISM trial (Heeschen 1999)

Similar results (Figures 20 and 21) correlating response to tirofiban in patients with acute coronary syndromes have been reported from the PRISM trial (Heeschen 1999). PRISM enrolled 2222 patients with accelerating or rest chest pain within 24 hours with new ECG changes, CK > 2-fold normal, history of MI or coronary revascularization, history of an abnormal stress study or a prior coronary angiogram showing >50% luminal diameter narrowing in at least one vessel. Patients were treated with aspirin and randomized to either heparin or tirofiban, with a primary endpoint of death, MI or recurrent ischemia at 48 hours. Of enrolled patients, 60% had undetectable cTnI levels, and the frequency of mortality/infarction in this group was low and did not differ with treatment arm (0.6% vs 0.7%). As shown in Figure 21, for patients with cTnI levels > 1 ng/ml, there was a beneficial effect to therapy with the platelet aggregation inhibitor. The event rate curves from PRISM (Figure 21) are remarkably similar to those from CAPTURE (Figure 20). Troponin positive patients not receiving a platelet aggregation inhibitor are at substantially higher risk than either cTn negative patients, or cTn positive patients receiving aggressive therapy. A similar correlation between therapeutic benefit from enoxaparin (in comparison to unfractionated heparin) in patients with an acute coronary syndrome and ST depression and/or T wave inversion on initial electrocardiogram has been reported in the TIMI 11B trial (Antman 1999).

A more comprehensive approach to risk and the effect of treatment has been presented by Antman et al. (2000). The authors applied regression analysis to the populations of the TIMI 11B and ESSENCE trials of LMWH in acute coronary syndrome to identify predictors of outcome and beneficial effect of LMWH therapy. Using the 7 predictors identified (age > 65; 3 risk factors for CAD; prior coronary stenosis > 50%; ST deviation on ECG; >2 anginal events in preceding 24 h; ASA in last 7 days; elevated CK-MB or cTn level), they were able to stratify the TIMI 11B study population into risk groups with combined rates of death/MI/refractory ischemia requiring revascularization ranging from 4.7% to 40.9%. They further observed that the beneficial effect of enoxaparin therapy in the TIMI 11B and ESSENCE trials appeared in those patients at relatively higher risk (TIMI Risk Score >3, Figure 22).

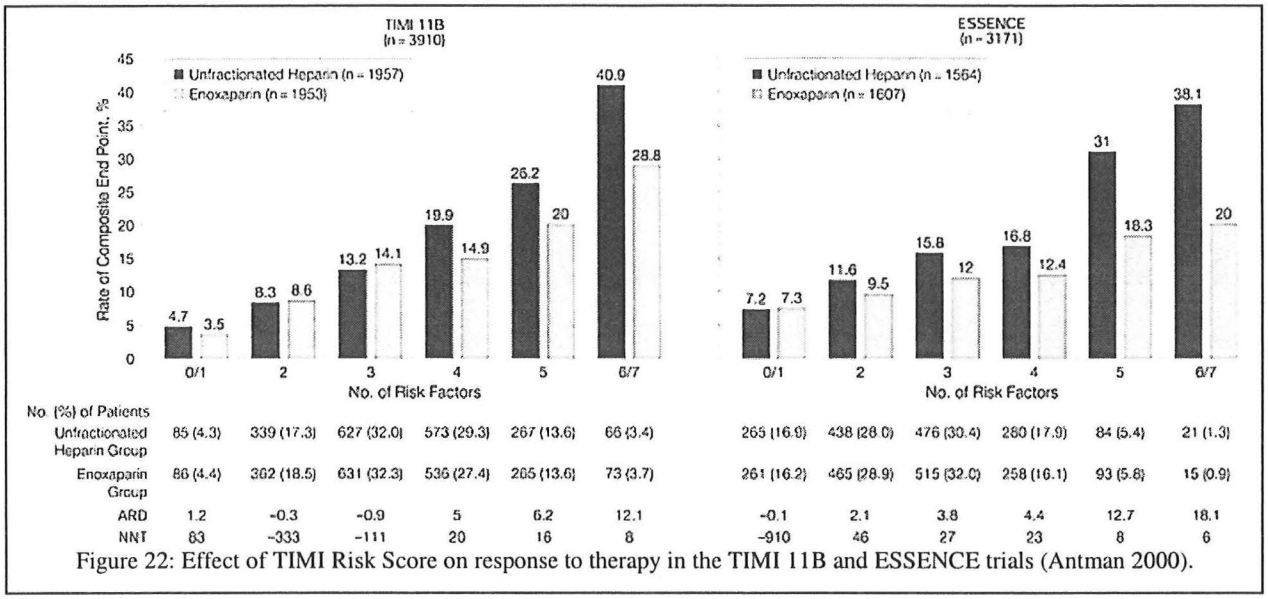

Figure 22: Effect of TIMI Risk Score on response to therapy in the TIMI 11B and ESSENCE trials (Antman 2000).

Summary: CTnT/cTnI and Risk Stratification in Acute Coronary Syndrome

The available data concerning cTnT/cTnI testing and prognosis in high-risk populations (e.g. patients with chest pain associated with dynamic ECG changes or with documented coronary disease) support several conclusions:

i. Evidence of minimal myocardial injury identifies among patients with ACS a subgroup at clearly higher risk for cardiac death or recurrent myocardial infarction in both the short and intermediate term (e.g. 1 year: ~10% mortality, 20-30% reinfarction rate).
ii. The relationship between myocardial injury and adverse outcome is a function of the magnitude of the injury, and this relationship holds down to the limits of detectability, even with the very sensitive cTnT/cTnI assays.
iii. Patients without evidence of myocardial injury are at lower risk, but in those with ECG abnormalities, the risk, at least for recurrent infarction, remains substantial despite negative cTnT/cTnI status – i.e. an abnormal ECG, particularly ST segment depression, identifies a patient at significant risk of subsequent adverse cardiac event regardless of troponin status.
iv. Troponin status predicts outcome and beneficial effect of aggressive antithrombotic therapy, but does not predict the existence, extent, severity or complexity (thrombus) of angiographic coronary artery disease, or the need for subsequent revascularization.

On the basis of the data available, several authors (Braunwald 2000, Roberts1998, Ohman 2000) have advocated employing markers of minimal myocardial injury (and specifically cTnT/cTnI levels) to guide approach to therapy in patients presenting with acute chest pain syndromes. In his review of the field in 1996, Bertram Pitt pointed out that "*while the ability to stratify patients with unstable angina by detection of subclinical myocardial necrosis is important, the concept is not new.*" He cited the work of Willerson (1975) and colleagues here at U.T. Southwestern. Using ^{99m}Tc-pyrophosphate (infarct-avid) scanning, Dr. Willerson's group was able to identify patients with the clinical diagnosis of unstable angina without CK elevation who had a positive

^{99m}Tc-PYP image. Such patients had evidence of "*myocardial necrosis at autopsy, and a relatively poor prognosis*". Dr. Pitt further argued that while elevated cTnT levels "*clearly identify a high-risk group ...what is really needed is confidence in identifying a truly low-risk group*" (<1% incidence of ischemic events per 6 mo-1yr), pointing out that a negative cTn identifies a subset with a 3-4% 6-month risk of ischemic events, and thus does not eliminate the necessity for further pre-discharge evaluation (e.g. stress testing).

Troponinemia in Chest Pain Syndromes: Studies in Low Risk Populations

How sensitive and specific are cTnT/cTnI for myocardial injury in a population at relatively low risk, i.e. patients presenting to an emergency department with chest pain?

In most series, of patients presenting to emergency departments with acute chest pain syndromes, <15% show classical clinical markers of myocardial infarction (Lee 1987). The problem is to separate the ~35% of patients with unstable angina from the 50%+ whose pain is not of ischemic origin (Fox 1999). The application of a diagnostic test for myocardial injury to the broad population of patients presenting with chest pain syndromes poses a significantly different problem than the use of the same test in a population selected for high risk (e.g. chest pain with dynamic ECG changes). First, studies on populations meeting, more or less, the latter criteria, generally show rates of myocardial infarction (by CK-MB criteria) of 15-40%, and where angiographic data are available, rates of significant coronary artery disease >70%. The central issues are risk stratification and therapeutic guidance. In ED chest pain patients, infarction rates are generally <10%, and as many as 60-70% of patients ultimately have no evidence of acute ischemic heart disease. In this broad population, the initial issues are diagnosis and admit/discharge decision. Secondly, for the high-risk inpatient, serial testing over an extended period of time poses no particular difficulty and very limited incremental cost (~$15/assay). Practical considerations dictate that to be of value in an emergency department setting, a test must yield diagnostic/prognostic information in a relatively brief (generally <8-12 hours) period.

The first large-scale study of troponin testing in an emergency department setting was performed in Hamburg, Germany, and reported by Hamm et al (1997). 773 patients (selected from 870 consecutive with chest pain) presenting to the ED with acute anterior, precordial or left chest pain <12 hours in duration, unexplained by trauma or CXR abnormality and without ST segment elevation on initial ECG had blood obtained within 15 minutes of presentation, 4 hours later, and 6 hours after the onset of symptoms for measurement of cTnI, cTnT, total CK and CK-MB. 47 patients (6%) ultimately met diagnostic criteria for myocardial infarction. In 315 patients the final diagnosis was unstable angina, in 121 stable angina, pulmonary embolism in 12, heart failure in 20 and 258 patients were ultimately felt to have no significant cardiac disease. Of the 773 patients, 16% had at least one positive assay for cTnT, and 22% had a positive assay for cTnI. Of the 47 patients with an ultimate diagnosis of infarction, 94% had an abnormal cTnT assay, and 100% an abnormal cTnI assay. Of those ultimately diagnosed as unstable angina, 22% and 36% had abnormal cTnT and cTnI assays, respectively. Of those with a positive test at any time, 62% had an abnormal assay on the initial sample. Twenty patients had at least one abnormal cTnT or cTnI assay but were ultimately felt to not have acute ischemic heart disease. 7/10 patients with elevated cTnT had renal failure. Of the patients with "false positive" cTnI, 7 had heart failure, 2 pulmonary embolism, and only 1 no evidence of cardiac disease. CK-MB

was elevated in 27 patients without elevated cTn levels, and in none of these patients was ischemic heart disease ultimately documented. Initial electrocardiogram correlated with cTn status. 56% of patients with ST depression, 6% of patients with T-wave inversion and 10% of patients with a normal initial ECG had at least one abnormal troponin assay. Overall, cardiac event rates (death or non-fatal infarction) during 30 day follow-up were cTnI+/-: 19%/0.3%, cTnT +/-: 22%/1.1%. The sensitivity of cTnI and cTnT for predicting cardiac events within 30 days were 94% and 79%, respectively. To synthesize the Hamburg data into a useful form, of 773 ED patients with chest pain and interpretable ECGs:

30 day Cardiac Event Rate in the Hamburg Series

ECG Findings	cTnI Positive	cTnI Negative
Normal or T wave inversion	17.7% (8/45)	0.2% (1/483)
ST segment depression	14.6% (13/89)	1.6% (1/69)

Less favorable data have been reported from the Brigham and Women's Hospital (Wright 1997), citing their experience that "*while serving on the consult service of a large teaching hospital, we occasionally have evaluated patients with chest pain and elevations of cTnI levels in whom we were unable to find any evidence of myocardial injury.*" They reviewed 343 consecutive patients admitted with suspected acute coronary syndrome and in whom at least one cTnI > 1ng/ml was obtained. 146 (45%) had an elevated cTnI with normal CK. Ultimately, 26 (7.6%) were discharged without suspicion of significant ischemic heart disease, although 18 of these had tachyarrhythmia or underlying cardiac disease. Of the 8 patients (2.3% of the initial group and 5.5% of those with normal CK) without obvious heart disease, 5 had LVH by echocardiography, and 3 who underwent angiography had normal coronary arteries. On the basis of these data, the authors speculated that left ventricular hypertrophy alone could cause sufficient subendocardial ischemia to produce detectable myocardial cellular injury. Summarizing this data, of patients admitted and having an abnormal cTnI:

~55%	Myocardial infarction by conventional criteria
~37%	Abnormal cTnI, normal CK, Dx: acute coronary syndrome
~5%	Other acute heart disease (e.g. dysrhythmia, heart failure)
~1.5%	LVH only
~1%	No apparent cardiac abnormality

A larger and more formal series has reported from the same institution (Polanczyk 1998). 1047 patients admitted for acute chest pain underwent serial cTnI, CK and CK-MB testing. 27% had new ischemic ECG changes. 14% of the 1047 patients were ultimately diagnosed with myocardial infarction by conventional criteria, and 37% received a final diagnosis of unstable angina. Major adverse cardiac events (MACE: shock, VT or VF arrest, AV block > 1st degree, IABP, intubation or revascularization) occurred in 9%. The sensitivity, specificity and positive predictive value (PPV) of cTnI for MACE were 47%, 80% and 19% respectively. In the absence of conventional diagnostic criteria for myocardial infarction, the PPV of an abnormal cTnI for MACE was 8%, the negative predictive value was 95%. Significantly, there was no increased risk of MACE in patients with an abnormal cTnI but normal CK-MB and normal ECG (odds ratio 0.7) although the 95% confidence intervals were wide (0.2-2.7). I want to summarize the data from this study in a way slightly different than that presented by the authors. They stratified risk according to three predictors: I) clinical risk (male, worsening anginal syndrome, prior

revascularization), II) new ECG changes, and III) cTnI. The table below gives the MACE rates by risk group:

Major Cardiac Event Rates within 72 hours in the Brigham (Polanczyk 1998) Series

	cTnI Positive	cTnI Negative
Clinical Neg/ECG Neg	1/27	1/217
Clinical Pos/ECG Neg	11/90	24/429
All ECG Positive Patients	32/117	25/167
All ECG Negative Patients	12/117	25/646

Summarizing, patients with no clinical predictors (i.e. women without a history of revascularization and with a low-probability clinical history) and no dynamic ST segment changes on ECG were at relatively low risk (0.5-3%) for early (72h) MACE. Conversely, patients with dynamic ST segment changes on ECG were at relatively high risk (15%-25%) regardless of cTnI status. Patients with conflicting indicators were at intermediate risk (5%-12%), and the predictive value of cTnI in this population (a relatively lower risk population) was limited. It is important to recognize that the series reported by Polanczyk addresses only very early adverse cardiac events. Other series suggest a better predictive value over follow-up periods of 30 days to 1 year. The time window is meaningful, however, in addressing the period before further risk stratification studies might be performed.

Kontos et al (1999) compared troponin testing to myocardial perfusion scanning as an approach to the diagnosis of acute coronary syndrome in patients presenting to an emergency room with a chest pain syndrome. 620 consecutive eligible patients underwent both serial cTnI testing and single photon emission computerized tomography using ^{99m}Tc-sestimibi. cTnI showed superior sensitivity (97% vs. 92%) and specificity (94% vs. 67%) for the diagnosis of myocardial infarction (by CK-MB criteria), but perfusion scanning was significantly better at predicting revascularization (sensitivity 26% vs. 81%). Of 81 patients with significant coronary disease by angiography, 61 had an abnormal perfusion scan, while only 12% had an elevated serum cTnI on serial testing. Offsetting the apparent advantage of perfusion scanning in identifying coronary disease and need for revascularization, 122 patients with neither myocardial infarction nor angiographically significant CAD had an abnormal perfusion scan. On the basis of these data, the authors conclude that cTnI is very effective in identifying patients at lower risk for death/myocardial infarction, but that patients with normal cTnI are not low risk, and that reliance on troponin is not sufficient for the diagnosis of unstable angina, significant coronary artery disease or the need for revascularization.

A group from Houston led by Dr. Roberts (Zimmerman 1999) performed a comparative study of different markers of myocardial injury for the diagnosis of myocardial infarction in 955 consecutive patients over 21 years of age presenting to the emergency department with chest pain of greater than 15 minutes duration. Ultimately, 119 patients (12.5%) met criteria for the diagnosis of myocardial infarction, and 203 (21%) were diagnosed with unstable angina. The sensitivity and specificity of various markers for myocardial infarction by CK-MB criteria) at the time points indicated were:

	6h	10h	18h
cTnI	15.8/96.8	92.3/94.6	95.7/93.4
cTnT	61.7/96.1	86.5/96.4	78.7/95.7
Myoglobin	78.7/89.4	86.5/90.2	57.5/88.8
CK-MB subforms	91.5/89	96.2/90.2	80.9/89.9
Total CK-MB	66/100	90.4/99.6	95.7/99.6

The authors concluded that the CK-MB subform assay provided superior early sensitivity, although serial measurement of cTnI provided the best overall diagnostic accuracy for myocardial infarction. In patients ultimately classified as having unstable angina, CK-MB subforms were increased in 29.5%, myoglobin in 23.7%, cTnI in 19.7% and cTnT in 14.8%.

The Brigham group (Polanczyk 1999) examined several alternative strategies incorporating CK-MB, cTnI, electrocardiography and early exercise testing in varying combinations for the diagnosis of unstable angina in an effort to identify a cost-effective strategy. The approach was retrospective, using 1066 patients from the Brigham and Women's Hospital emergency department. Age adjusted mortality from the Chest Pain Study (Johnson 1999) was employed to generate a cost per year of life saved. Obviously, the results of any such analysis are highly dependent upon the underlying assumptions. In this study, the differences in costs associated with the various strategies were not large, and relatively minor changes in assumptions would shift the favored strategy (measurement of CK-MB followed by exercise testing, use of cTnI only in patients unable to exercise and in patients 65-74 years old). Of more interest in the context of the current discussion is the sensitivity and specificity of the various diagnostic strategies. The authors obtained the figures they used from "real world" experience, an unselected population of more than 1000 patients actually presenting to a major academic center emergency room, and scoring against the ultimate clinical diagnosis made by the patients physicians who were unaware of the results of cTnI testing. The authors report that cTnI testing alone was 86.6% sensitive for a diagnosis of myocardial infarction, 73.1% sensitive for a diagnosis of unstable angina, and 80.4% specific for a diagnosis of MI/USA. The numbers for myocardial infarction are considerably lower than corresponding numbers derived from prospective randomized clinical trials, where the patient populations are substantially higher risk (e.g. dynamic electrocardiographic changes, known coronary artery disease), and have important implications when cTnI testing is employed to guide expensive and potentially dangerous therapeutic intervention (hospital admission, platelet aggregation inhibitors and transluminal revascularization).

To summarize the lessons from studies of cTnT/cTnI testing in relatively low-risk patient populations (i.e. patients presenting to an emergency room with chest pain):

i. Generally, cTnI appears more accurate in diagnosing myocardial injury than cTnT.
ii. Serially negative (>10 hours from presentation) cTnI in the setting of a low risk clinical presentation and no ischemic changes on ECG identifies a patient at very low risk (<1%) for adverse cardiac events within 30 days.

iii. In the setting of higher clinical or electrocardiographic risk, patients with serially normal cTnI assays are at intermediate risk (1.5%-15+%), and require additional diagnostic evaluation prior to hospital discharge.
iv. An abnormal cTnI assay in itself identifies a population at higher risk (>15%) of adverse clinical events, and is >90% specific for acute cardiac (>90% ischemic) disease.
v. "False positive" (no detectable heart disease) cTnI is rare (~1%), but elevation of cTnI occurs in, for example, heart failure, tachyarrhythmia, left ventricular hypertrophy and pulmonary embolus in the absence of detectable acute coronary syndrome or angiographically significant coronary disease.
vi. While cTnI has diagnostic and prognostic value, it does not predict coronary anatomy or need for revascularization.

Troponinemia in Cardiomyopathy, Congestive Heart Failure and Transplantation

What is the significance of an elevated cTnT/cTnI in patients with DCM/CHF?

Progression of non-ischemic cardiomyopathy and chronic congestive heart failure is characterized by progressive myocyte loss. Since the development of sensitive assays for myocardial injury, a number of groups have reported that cTnT/cTnI are detectable in a fraction of patients with non-ischemic cardiomyopathies (La Vecchia 1997, Missov 1997, Chen 1999). In general, abnormal levels of cTnT/cTnI have been observed in patients with decompensated heart failure (e.g. Setsuta 1999, De Carlo 1999), and correlate with a worse left ventricular ejection fraction, higher PCWP and deteriorating cardiac function (e.g. Chen 1999, La Vecchia 2000). In patients hospitalized with acute heart failure, cTnI levels are frequently elevated (incidence 20-80+%). Disappearance of cTnI has been observed in patients improving with therapy, while in patients with refractory and ultimately fatal heart failure, persistently elevated and/or increasing cTnI levels have been observed (La Vecchia 2000). An important limitation in interpreting reports of detectable markers of myocardial injury in patients with cardiomyopathy/heart failure is the absence in most series of angiographic data to exclude causative or coexisting ischemic heart disease, but the suggestion from the available data is that severely decompensated CHF is associated with active myocardial injury in the absence of identifiable discrete ischemic insult.

Smith et al (1997) examined blood samples obtained from 88 patients in the Myocarditis Treatment Trial to determine whether serum cTnI could aid in diagnosis of myocarditis. cTnI levels were elevated in 18/53 (18%) of patients with myocarditis vs. 4/35 (11%) of patients without myocarditis by biopsy criteria. Elevation of cTnI occurred significantly more frequently than of CK-MB, and correlated with symptoms of congestive heart failure of less than one month duration, and with diffuse myocarditis on biopsy suggesting that elevated cTnI may identify an early stage of the disease characterized by active myocyte injury and necrosis.

Elevated cTnT/cTnI have been reported to signal acute rejection in cardiac allograft recipients (Hossein-Nia 1993). Labarrere et al (2000) examined 110 consecutive patients who received a heart transplant between 1989 and 1997 and survived at least 1 year after transplantation. Patients were followed for histological and immunohistochemical biopsy findings, development of coronary artery disease, and graft failure in patients with vs. without elevated serum cardiac

troponin I levels. All recipients had elevated troponin I levels during the first month after transplantation. Troponin I levels remained persistently elevated during the first 12 months in 56 patients (51%) and became undetectable in 54 patients (49%). Persistently elevated troponin I levels were associated with increasing fibrin deposits in microvasculature and cardiomyocytes, and were associated with a significantly increased risk for subsequent graft CAD.

Troponinemia following Cardiac Surgery

What is the significance of elevations of cTnT/cTnI in post-CABG patients?

A cursory computerized search of the Medline database from 1997-present for studies examining cTnT/cTnI in patients undergoing surgical coronary revascularization returned 57 manuscripts in which various approaches to myocardial preservation or minimally invasive approaches to coronary revascularization were studied using cTnT/cTnI as the indicator of myocardial injury. Conspicuously lacking was any functional measure of myocardial performance to validate the serum marker endpoint. Applying a sensitive marker of myocardial injury to the cardiac surgery patient poses a special problem, as some degree of myocyte injury is seemingly inherent to manipulation of the heart. Limited data are available with which to establish a threshold above which cTnT/cTnI are indicative of ischemic injury.

Carrier and colleagues (2000) at the Montreal Heart Institute examined a series of 493 patients undergoing CABG for postoperative cTnT and cTnI levels, using ECG and CK-MB criteria to diagnose perioperative myocardial infarction. In their series, cTnT levels > 3.4 ng/ml were 90% sensitive and 94% specific for infarction, and cTnI levels > 3.9 ng/ml were 80% sensitive and 85% specific for infarction. The negative predictive values of cTn levels below these thresholds were 99%, although the positive predictive values were only 41% and 24%, respectively. The absence of an assessment of wall motion or ventricular performance limits confidence in the reported 6.2% rate of perioperative myocardial infarction. Other recent studies, for example Bonnefoy (1998), Alyanakian (1998), Jacquet (1998) and Sadony (1998) have established threshold values for cTnI between 6.5 and 20 ng/ml as indicative of myocardial infarction as assessed by electrocardiographic and CK-MB criteria.

Not surprisingly, cross-clamp time appears to correlate with release of cTnT into coronary sinus blood. Koh (1998) reported that with cross clamp times >72 minutes increased cTnT release correlated with a delayed return to myocardial lactate extraction and with a lower post-operative left ventricular stroke work index three hours after surgery.

Troponinemia following Non-cardiac Surgery

Are cTnT/cTnI the preferred markers for perioperative MI in patients undergoing non-cardiac surgery?

Non-cardiac surgery also poses difficulties for detecting perioperative myocardial injury not associated with the development of new Q waves, as the extent of skeletal muscle injury often produces an elevation in CK-MB. Several recent series suggest that cTnT/cTnI are more specific for myocardial injury and correlate with adverse cardiac events in the post-operative period. For

example, Lopez-Jiminez and colleagues (1997) measured cTnT serially for 48 hours in 772 undergoing major non-cardiac surgery. In 12% of patients, cTnT levels were elevated in the perioperative period, and elevated cTnT levels correlated with the incidence of in-hospital heart failure and cardiac arrhythmia. Over 6 month follow-up, there were 14 cardiac deaths, 3 nonfatal infarctions and 2 patients admitted for unstable angina. cTnT but not CK-MB was an independent predictor of cardiac events, with an odds ratio of 5.4. Neill (2000) measured cTnT, cTnI and CK-MB and monitored ST depression continuously by Holter for three days in 80 patients undergoing vascular or orthopedic procedures. ECG monitoring detected clinically silent ischemia in 21, and 4 and 6 had elevations of cTnT and cTnI, respectively. Adverse cardiac events occurred in 10% during 3 month follow-up, and the odds ratio for ACE in patients with elevation of cTnT/cTnI were 17 and 13.2, respectively.

In general, the prognostic implications of elevated cTnT/cTnI levels in the perioperative period appear similar, with respect to the subsequent incidence of major adverse cardiac events, to those for patients with acute coronary syndromes, e.g. 10-20% over 6 months to 1 year (Adams 1994). The specificity of cTnT/cTnI for myocardial injury is difficult to assess, as detailed functional studies of myocardial performance as a function of troponin status in the perioperative period are lacking.

Troponinemia in Patients without Identifiable Cardiac Disease

What about elevated cTnT/cTnI in patients with no apparent heart disease?

As discussed previously, in series of unselected patients with elevated cTnT/cTnI levels, a small fraction ultimately prove to have no identifiable acute cardiac disease. In the series from the Brigham and Women's Hospital discussed previously, several such patients ultimately proved to have pulmonary emboli. A more formal study of cTnT in patients with confirmed pulmonary emboli has been reported by Giannitsis and colleagues (2000). In 56 patients, cTnT was elevated in 32% of those with massive or moderate PE, but not in patients with small PE as assessed by clinical criteria. Elevation of cTnT correlated with need for ventilatory and inotropic support, shock and in-hospital and 30-day mortality (odds ratios 12-40).

First generation cTnT assays showed a significant "false positive" rate in patients with renal failure. Second and now, third generation assays appear less prone to spuriously abnormal results in the setting of renal failure (Apple 1998), and several reports have correlated an elevated cTnT with mortality in patients with renal failure (Ooi 1999, Dierkes 2000). Nonetheless, the predictive value of cTnT and cTnI for subsequent adverse cardiac events in patients with suspected acute coronary syndromes has been reported to be significantly lower in patients with renal failure than in those without (Van Lente 1999). In this study, the sensitivity of cTnT for both initial and six-month adverse outcomes was adversely affected by renal insufficiency (0.29 vs. 0.60 and 0.45 vs. 0.56, respectively). cTnI exhibited a similar differential sensitivity (0.29 vs. 0.50 and 0.33 vs. 0.40, renal vs. non-renal, respectively).

Elevations of cTnT/cTnI have been reported in association with a variety of "non-cardiac" conditions, but in the settings described (e.g. cirrhosis, cocaine abuse, sepsis, critical care,

strenuous exercise at high altitude), such elevations seem likely to reflect true subclinical myocardial injury (Pateron 1999, Hollander 1998, ver Elst 2000, Davila-Roman 1997).

Summary

The development of very sensitive assays for myocardial-specific proteins has lowered the threshold of detection for myocardial injury, and done so with improved specificity. Detection of minimal myocardial injury is significant by virtue of predictive value for major adverse cardiac events. The correlation between low but detectable levels of cardiac troponins in blood and the incidence of death, recurrent infarction and recurrent or refractory ischemia probably represents identification of patients with a high-risk substrate, rather than reflecting a direct effect of minimal myocardial injury on prognosis. Because of this correlation, serum cardiac troponin levels have become an important criterion influencing management decisions.

Problems arise when assays for cTnT/cTnI are elevated from the level of a test to the final arbiter of diagnosis and/or management. It is important to recognize what these tests will, and perhaps more importantly, won't do. Cardiac troponin levels will aid in the diagnosis of ischemic heart disease in patients presenting with chest pain syndromes. They will diagnose infarction in patients with confusing creatine kinase levels, but they will not reliably diagnose unstable angina. They will identify among patients with acute coronary syndromes groups at relatively higher or lower, but not truly low risk of adverse outcomes. They will confirm in patients with low-risk chest pain syndromes a statistically favorable prognosis, but they will not exclude significant coronary artery disease. They reliably predict neither the severity of angiographic coronary stenosis, nor the ultimate need for revascularization.

As understanding of the biology of unstable coronary syndromes improves, additional "markers", e.g. C-reactive protein and malondialdehyde derivitized LDL, that appear to convey incremental information are becoming available. With increasingly effective, but potentially dangerous therapeutic tools, it is progressively important to obtain rapid and accurate diagnostic and prognostic information. Troponin assays are a significant improvement, but we remain significant advances in proteomics away from the goal of highly accurate, real-time and minimally invasive diagnostics for suspected acute coronary syndromes.

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