

Markers for Perioperative Myocardial Ischemia: What Both Interventional Cardiologists and Cardiac Surgeons Need to Know

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ABSTRACT

All novel markers of myocardial ischemia (ischemia-modified albumin, choline, unbound free fatty acids) lack cardiac specificity. Therefore, for the specific detection of myocardial ischemia selective blood sampling from an inserted coronary sinus catheter is needed, which limits the applicability of these markers in most clinical routine settings. In addition, the superiority of these novel markers over the calculation of myocardial lactate production, the current criterion standard for the laboratory diagnosis of myocardial ischemia, has not been demonstrated so far, and even comparative data is frequently lacking. Further the superiority of these new candidate markers over lactate determination for the diagnosis of myocardial ischemia in peripherally drawn blood samples has not been demonstrated either, and these novel parameters appear not to be a breakthrough for laboratory diagnosis of myocardial ischemia during or after percutaneous coronary interventions or coronary artery bypass grafting. The determination of cardiac troponin I or troponin T is the current criterion standard for the laboratory diagnosis of myocardial damage due to their higher sensitivities and specificities compared to creatine kinase isoenzyme MB. According to current knowledge, troponin increases in peripherally drawn blood samples must be regarded as an indicator of myocardial necrosis which, however, may be limited, only detectable by troponin and may be missed by creatine kinase isoenzyme MB determination. After on-pump coronary artery bypass grafting the generally applied troponin discriminator limits are not valid as there is limited, inevitable cardiac tissue damage occurring during the surgical procedure. Therefore, troponins are significantly increased after reperfusion of the arrested heart over values seen before bypass and also in patients without complications. Perioperative myocardial infarctions can be reliably identified by their characteristic troponin time courses, and both peak concentrations and

time of peak values are diagnostic criteria. Troponin release is lower in off-pump compared to on-pump bypass surgery. Despite the controversy over the significance of troponin elevations after clinically uncomplicated and successful procedures, it is tempting to postulate that less myocardial damage as detected by troponin release is beneficial for the patient. After elective percutaneous coronary interventions, only troponin increases >8-fold the upper reference limit were associated with increased mortality in long-term follow-up.

INTRODUCTION

Currently there is no generally accepted definition of peri-interventional and perioperative myocardial infarction after cardiac surgery based on cardiac marker determination which is supported by guidelines [Alpert 2000]. The clinical significance of minor increases of cardiac markers indicating small or tiny infarcts after otherwise successful and uncomplicated percutaneous coronary interventions (PCI) is uncertain. Myocardial damage in association with aortocoronary bypass surgery (CABG) can be caused by different mechanisms, including a direct trauma from surgical manipulation of the heart, global ischemia from inadequate perfusion or myocardial cell protection, or coronary artery or venous graft embolism and other complications of the procedure. A portion of this damage may be unavoidable, and no marker is capable of precisely distinguishing this damage from myocardial necrosis due to an acute myocardial infarction. However, a frequently used criterion is a CKMB activity of >50 U/L and >5% of total CK activity. Nevertheless, the higher the value for the cardiac biomarker after the procedure, the greater the amount of damage to the myocardium, irrespective of the mechanism. Therefore, myocardial ischemia during CABG or PCI is attempted to be kept to a minimum by cardiac surgeons and interventional cardiologists. But, minor myocardial ischemia is frequent and has to be distinguished from major ischemic events with adverse prognosis. Thus, the diagnosis of myocardial ischemia is clinically relevant, and it is a treatable condition. However, its clinical diagnosis is not always straightforward. The conventional assessment of myocardial ischemia by electrocardiography (ECG) has limited sensitivity during CABG or PCI, because the 12-lead standard ECG is not applicable in the operating room and cath lab. Alternatively, myocardial wall motion can be assessed by echocardiography to detect hypokinesis which is

Presented at the 2nd Integrated Coronary Revascularization (ICR) Workshop for Interventional Cardiologists and Cardiac Surgeons, Innsbruck, Austria, February 24-25, 2005.

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Features of an Ideal Laboratory Marker of Myocardial Ischemia

1. Detection of ischemia whether or not necrosis is present
2. Specific for myocardial ischemia
3. Rapid rise with convenient duration of increase
4. Increase in proportion to the extent of myocardium involved
5. Reliable pre-analytical and analytical performance
6. Simple and rapid measurement in peripheral venous blood samples

an early event during myocardial ischemia. However, echocardiography is not always readily available or applicable as well. Thus, it is essential to find a reliable, easy applicable marker which detects myocardial ischemia very early during cardiac interventions, before irreversible damage has occurred. Therefore, a reliable laboratory parameter of myocardial ischemia would be of clear clinical benefit. The characteristics of such an ideal marker are listed in the Table. However, obviously such a marker is currently not available.

Myocardial lactate production is the current criterion laboratory standard for the detection of myocardial ischemia. Its biochemical basis is that the myocardium under physiological conditions uses lactate as an energy substrate, and that during ischemia the myocardium switches from a lactate consumer to a lactate producer. The limitation for the measurement of lactate production is the need for local venous blood sampling via a coronary sinus catheter and simultaneous arterial blood sampling in order to calculate myocardial lactate net release. This invasive procedure is certainly not applicable in most clinical routine settings.

Further, cardiac troponin I and troponin T (cTnI, cTnT) are the current criterion standard for the laboratory diagnosis of myocardial damage, and this review is a critical appraisal of the interpretation of cardiac troponin concentrations after CABG and PCI and a novel marker of myocardial ischemia, ischemia-modified albumin (IMA), which has already been cleared by the US Food and Drug Administration for the early exclusion of acute myocardial infarction [Apple 2005]. Other novel research parameters (e.g., choline, unbound free fatty acids) have been proposed for the detection of myocardial ischemia recently [Apple 2005]. However, these markers are not discussed in detail, because routine assays or data on the use of these markers for the detection of myocardial ischemia during PCI or CABG are not available so far.

CARDIAC TROPONIN

The determination of cTnI or cTnT has replaced creatine kinase isoenzyme MB (CKMB) measurement as the criterion standard for the laboratory diagnosis of myocardial damage [Mair 1997]. The superior troponin's clinical value is due to its higher sensitivity to smaller myocardial damage and its virtually total specificity for cardiac damage. However, cardiac troponins need 4-10 hours after symptom onset to appear in peripherally drawn venous blood samples and are no early markers of myocardial damage. The current Joint European Society of Cardiology and American College of Cardiology Guidelines for the definition of acute myocardial infarction require the rise

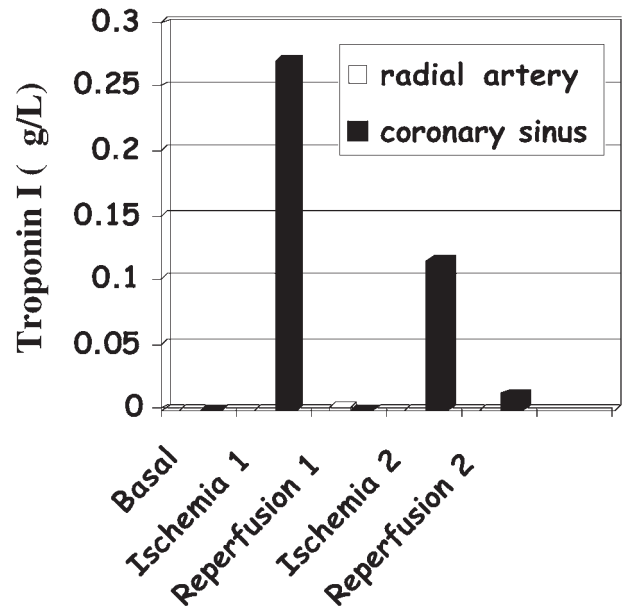


Figure 1. Local troponin release from stunned myocardium. Data from a patient undergoing off-pump CABG with preconditioning by 2 cycles of ischemia with subsequent reperfusion each of 3 minutes duration before doing the LIMA-LAD anastomosis (adapted from Suleiman 1999). The troponin increased only locally in coronary sinus blood samples without a concomitant increase in systemic arterial blood.

and fall of biochemical markers of myocardial necrosis, preferentially cardiac troponins, in the appropriate clinical context [Alpert 2000]. Despite the merits of troponin determination in the majority of clinical settings the clinical significance of mild to moderate troponin increases after elective, clinically successful and uncomplicated CABG or PCI remains heavily debated among cardiac surgeons and cardiologists.

A frequently asked question is, whether small troponin increases actually always reflect myocardial necrosis. Suleiman and coworkers [Suleiman 1999] reported limited troponin release in response to short regional ischemia reperfusion cycles of 3 minutes each in patients undergoing off-pump CABG before performing the left internal mammary artery (LIMA)—left anterior descending artery (LAD) anastomosis (see Figure 1). According to these results stunned myocardium obviously releases small amounts of cardiac troponin, which can be only detected in coronary sinus blood samples and not in the systemic circulation. Thus, the general consensus and believing is that troponin increases in peripheral venous blood reflect myocardial necrosis which may be limited and not associated with CKMB increases above the upper reference limit [Alpert 2000, Mair 1997] and that cardiac troponins can be only detected outside the coronary circulation if the release in the coronary sinus is large, which is the case after myocardial necrosis.

Cardiac Troponin after Coronary Artery Bypass Grafting Acute CABG for Evolving Myocardial Infarction. Cardiac troponin release during and after uncomplicated emergency CABG in patients with evolving myocardial infarction

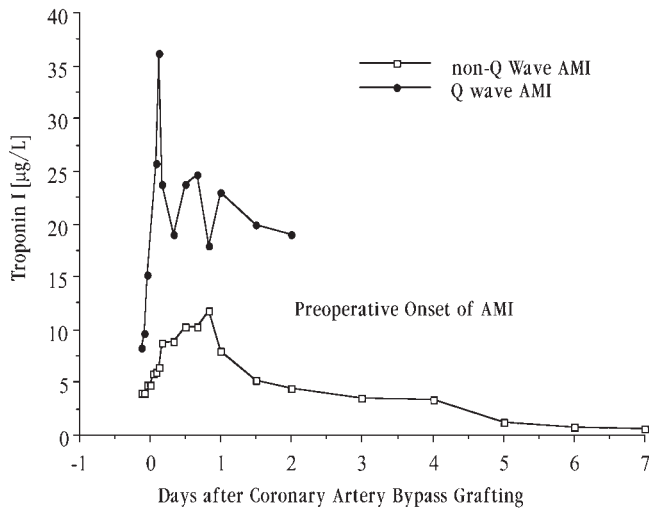


Figure 2. Cardiac troponin I release in two patients with emergency coronary artery bypass grafting for evolving myocardial infarction. AMI indicates acute myocardial infarction.

with already preoperatively elevated cardiac troponin concentrations (see Figure 2) should not be interpreted as perioperative myocardial infarctions as the onset of myocardial infarction was before start of surgery, and the procedure may limit myocardial infarct size but cannot prevent the development of myocardial infarction. Increased preoperative cTnT concentrations were associated with a higher frequency of perioperative myocardial infarction and heart failure [Carrier 1998].

Elective On-pump CABG. Apart from the clinically obvious cases with early graft occlusion with hemodynamic instability, new regional wall motion abnormalities or the development of new Q-waves in the ECG in the appropriate clinical context, the diagnosis of perioperative myocardial infarctions is difficult after CABG, and the clinical significance of perioperative non-Q-wave myocardial infarctions remains to be controversially discussed in the literature [Barron 1998, Galianes 1998, Mahaffey 2001, Newman 2001]. Despite uncertainties on the prognostic implications of perioperative non-Q-wave infarctions it is clear that the higher the troponin values after cardiac surgery the greater the myocardial damage is, and myocardial damage should be minimized. After on-pump CABG the usual upper reference limits of cardiac markers are invalid as a consequence of inevitable cardiac tissue damage (e.g., cardioplegic cardiac arrest, cannulation of the great veins with right atriotomy) occurring during the surgical procedure. The extent of this increase depends on the surgical procedures and the different techniques of cardioprotection (e.g., cardioplegic cardiac arrest or intermittent aortic cross-clamping, antegrade, retrograde or combined cardioplegia, crystalloid or blood-containing cardioplegic solutions). Further, the combination of CABG with valve surgery was associated with higher troponin concentrations than either procedure alone [Lasocki 2002], and the postoperative autotransfusion of mediastinal shed blood which is hemolytic and may contain considerable amounts of cardiac troponins can interfere with the diagnosis of perioperative myocardial infarction during the early postoperative

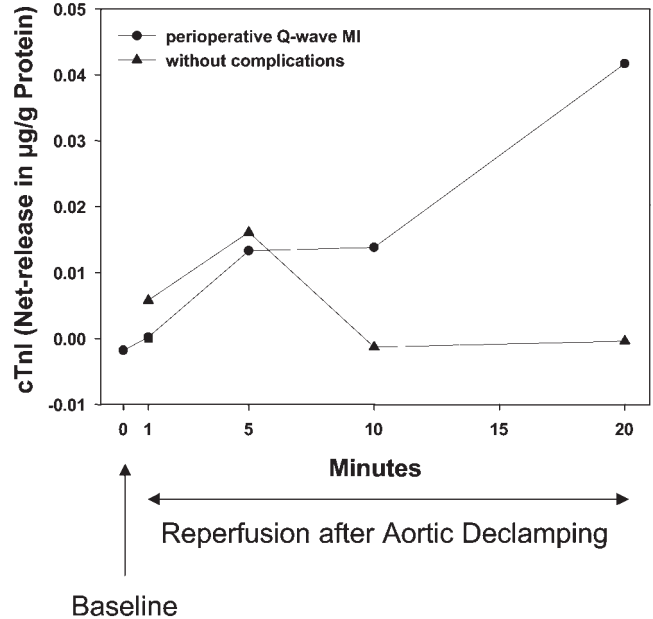


Figure 3. Early myocardial net cardiac troponin I release in two representative patients undergoing elective on-pump CABG. MI indicates myocardial infarction; cTnI, cardiac troponin I.

hours [Hannes 1994]. Troponin release in uncomplicated, elective on-pump CABG patients does not correlate closely with aortic cross-clamping time. We were the first to report on cTnT and cTnI release in patients with elective on-pump CABG [Mair 1991, 1994]. cTnT and cTnI reliably identified patients with perioperative Q-wave myocardial infarction, but there is some limited troponin release in uncomplicated patients as well. There is a continuum of troponin release from the uncomplicated patients, patients with minor ischemic events and complications to the clinically clearly defined patients with perioperative Q-wave infarctions, and a wider range of myocardial damage not always indicated by CKMB measurements is obviously common even in patients currently not classified as having perioperative myocardial infarctions. Thus, it is a challenge to define troponin discriminator values at different time points after CABG for the detection of clinically relevant complications which impair prognosis. Troponin starts to increase in coronary sinus blood samples as early as 5 minutes after aortic declamping [Bleier 1998] (see Figure 3) and within a few hours in the systemic circulation, and both troponins stay increased for several days. Troponin time courses in patients with perioperative myocardial infarction differ significantly from those in uncomplicated patients (see Figure 4), troponin values are markedly higher within the first postoperative hours and stay much higher than in uncomplicated patients for days [Carrier 2000, Mair 1991]. cTnT peak values are found around postoperative days 3 to 4. In on-pump CABG cTnT concentrations do not exceed 1.0 µg/L in uncomplicated cases. With cTnI the situation is more complex as there are several commercially available assays which are not standardized so far, and absolute concentrations may differ markedly between assays. As a consequence published decision limits are only

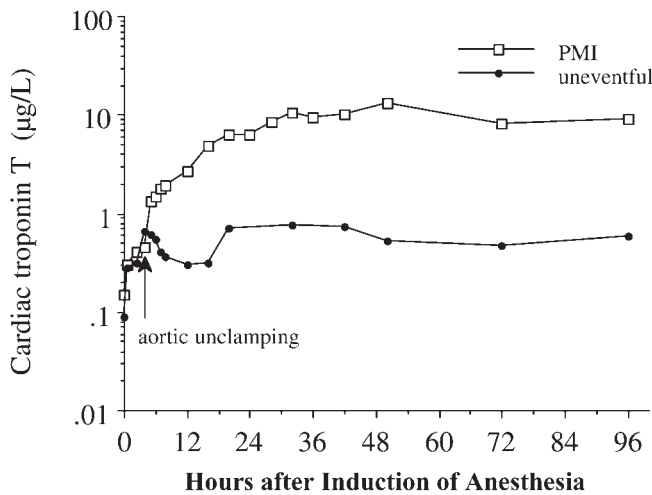


Figure 4. Troponin T time courses in two representative patients undergoing elective on-pump CABG. PMI indicates perioperative myocardial infarction.

valid for the assay used in the particular publication and cannot be applied for other cTnI assays. Patients with perioperative myocardial infarction show a continuing cTnI increase, whereas cTnI in uncomplicated cases peaks within 6-12 hours after surgery [Mair 1994]. Frequently there is a prolonged increase in cTnI rather than a distinct peak. The increase and peak for cTnI parallel that for CKMB, however, cTnI stays increased on average 3 days longer than CKMB. In case of perioperative myocardial infarctions, cTnI concentrations start to increase with aortic declamping, peak on or about the first postoperative day and remain increased until at least the fifth postoperative day. A consistent finding of all published studies on cTnI after elective on-pump CABG surgery is that cTnI does not exceed the 30-fold upper reference limit of the assay used in uncomplicated patients. cTnT and cTnI seem to be comparably useful for the diagnosis of perioperative myocardial infarction although there is only little direct comparative data [Bonney 1998]. Both, cTnI and cTnT release after on-pump CABG predict short- and long-term morbidity and mortality [Benoit 2001, Lasocki 2002, Lehrke 2004, Simeone 1999]. Long-term survivors had markedly lower cTnT concentrations than non-survivors on postoperative days 1 to 4, and the optimum time point for prediction of cardiac mortality was on the second day post surgery [Lehrke 2004].

Elective Off-pump CABG. The situation in patients with elective off-pump CABG substantially differs from CABG patients with use of standard cardiopulmonary bypass. In this subgroup of CABG patients the generally used upper reference limits for troponin assays can be applied. A consistent finding of all published studies is that troponin release is lower in off-pump compared to on-pump CABG [Ascione 1999, Bonatti 1998, Braun 2000, Khan 2004, Kilger 2000, Koh 1999]. Despite the controversy over the significance of these troponin elevations, particularly those after clinically uncomplicated and successful procedures, it is tempting to postulate that less myocardial damage as detected by troponin

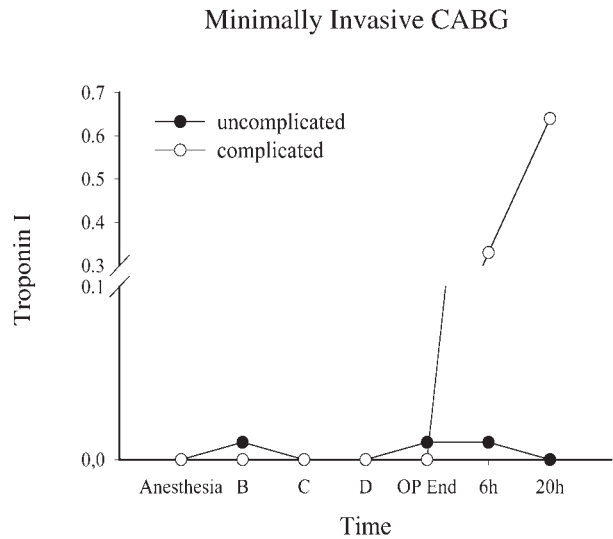


Figure 5. Troponin I time courses in two representative patients undergoing minimally invasive CABG. The troponin I values are given in µg/L. The upper reference limit of the troponin I assay used was .1 µg/L. The patient with perioperative myocardial infarction (complicated) showed a marked troponin I increase, in the uncomplicated patient troponin I concentrations stayed within the reference interval. Data adapted from Bonatti et al [1998].

release is beneficial for the patient. Troponin concentrations in uncomplicated patients frequently stay within the reference interval, small increases (up to 2-3 fold of the upper reference limit) are common and are related to minor ischemic events. In case of perioperative myocardial infarction (see Figure 5) the increases are marked and associated with adverse prognosis [Bonatti 1998]. Increases in troponins after off-pump CABG are linked to cardiac complications, however the data on the prognostic implications of troponin increases are limited compared to on-pump CABG patients.

Percutaneous Coronary Interventions

Primary PCI. Similar to CABG, cardiac troponin release after successful primary PCI in patients with evolving myocardial infarction should not be interpreted as periprocedural myocardial infarctions as the onset of myocardial infarction was before start of PCI, and the procedure may limit myocardial infarct size but cannot prevent the development of myocardial infarction.

Elective PCI. Just as the importance of cardiac troponin elevation after elective, uncomplicated CABG has challenged the surgical community, the significance of troponin increases after elective, uncomplicated PCI has been heavily debated among cardiologists. We were the first to demonstrate that troponin increases are more frequent than CKMB increases after elective PCI and could identify side-branch occlusion even when symptomless as one important factor to be involved [Talas 1992]. Another important determinant for troponin increase is distal microvascular embolization from the plaque during intervention. Dependent on the interventions that a patient underwent cTnI concentrations varied [Mandadi 2004], more than two lesions requiring interven-

tions, more than one implanted stent, age, type B and C lesions, dissection, and ejection fraction <30% were univariate predictors of a 3-fold or higher troponin increase after PCI compared to baseline concentrations [Herrmann 2002, Mandadi 2004]. In the meantime there is increasing evidence for the prognostic significance of troponin release after elective PCI. Minor elevations of cardiac troponins are commonly found in patients undergoing PCI. Peak concentrations of troponin were found 24-48 hours after PCI [Talas 1992]. However, only substantial troponin increases of more than 5-8 times the upper reference limit after elective PCI are related to cardiac events and mortality during long-term follow-up [Herrmann 2002, Nallamothu 2003, Saadeddin 2002]. However, other studies could not confirm the long-term prognostic relevance of troponin increase after uncomplicated, successful, elective PCI [Kini 2004] or found only a relation with in-hospital complications without an incremental risk of adverse intermediate-term clinical outcomes [Fuchs 2000].

Hybrid Coronary Artery Revascularization

The interpretation of troponin concentrations after hybrid coronary revascularization is very complex and depends on the timing of the two coronary revascularization procedures. If the minimally invasive (LIMA) is performed first (off-pump or totally endoscopic on the arrested heart) and the catheter intervention a few days afterward, troponin after CABG must be assessed according to the technique used as discussed above and a baseline value before PCI should be obtained. If baseline values before PCI are already increased only increases of more than 25% from baseline should be considered as significant increase after PCI [Apple 2002]. If the order of procedures is the other way round, preoperative baseline values are usually within the normal range and post-operative troponin concentrations must be interpreted according to the surgical technique used for performing the LIMA graft. Sometimes a simultaneous intervention is performed and usually the surgical technique used has the major impact on postinterventional troponin concentrations. The available data is too limited to suggest discriminator values for prognostically relevant troponin increases after such procedures. In general, the lower the troponin release the smaller the myocardial damage that occurred, and less myocardial damage should be beneficial for the patient.

ISCHEMIA MODIFIED ALBUMIN (IMA)

Pathophysiology

This recently cleared test is based on the observation that the affinity of the aminoterminal end of human albumin for cobalt is reduced in patients with myocardial ischemia [Bar-Or 2000]. In principle, in serum of patients with ischemia, cobalt added to serum does not bind to the same extent to the N-terminus of albumin than in sera of controls, leaving more free cobalt to react with dithiothreitol and form a darker color, which is detected using a photometer. The precise mechanisms for the production of IMA during ischemia are not known, but have been localized to modifications of the aminoterminal end of human albumin and are proposed to be related to production of free radicals during ischemia or

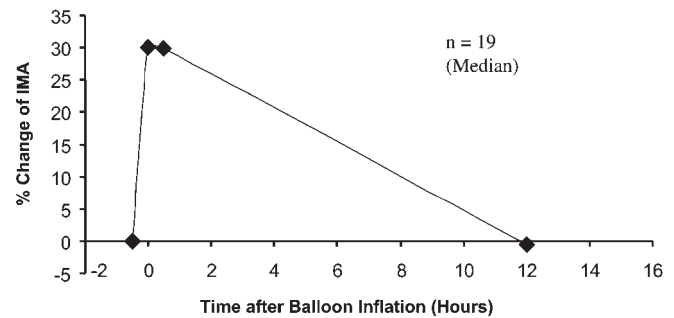


Figure 6. Ischemia-modified albumin (IMA) changes after percutaneous transluminal coronary intervention. Adapted from Sinha et al [2003], data given as median of 19 patients.

reperfusion and binding of metals released from ischemic tissue to albumin [Bar-Or 2001]. The modification of albumin is not specific for myocardial ischemia, and increases can be expected during ischemia in any vascular bed. If IMA is used as a specific marker for myocardial ischemia, similar to lactate, local blood sampling from the coronary sinus is necessary to calculate net myocardial IMA production. Further, structural variants of human albumin at the aminoterminal may lead to reduced cobalt binding and false-positive test results as well [Bhagavan 2003].

Percutaneous Coronary Intervention

PCI is a controlled model of human myocardial ischemia, and it could be demonstrated that IMA concentrations rapidly increase within minutes after balloon inflation (see Figure 6), stay elevated for at least 30 minutes, and decrease to basal levels within 12 hours [Sinha 2003]. There were no cTnT increases detectable in the patients of this study. The study group consisted of 19 patients who had >70% single vessel disease, and all of whom had chest pain or ECG changes indicative for myocardial ischemia during the procedure, and stents were deployed as required. IMA levels were higher in patients with more balloon inflations, higher pressure inflations, and longer inflation duration [Quiles 2003]. IMA levels increased significantly lesser in patients with collateral circulation compared with those without collateral vessels [Garrido 2003]. However, these latter two studies [Garrido 2003, Quiles 2003] show a substantial difference in absolute values with mean increases from baseline 101 to 113 U/mL 10 minutes post-PCI [Garrido 2003] and from baseline 60 to 81 U/mL post-PCI [Quiles 2003]. This suggests that there are only minor IMA increases after PCI, and IMA concentrations vary considerably between individual patients. Further, there is a considerable overlap between normal values and IMA concentrations after PCI, and no data on the prognostic significance of IMA changes after PCI have been published so far.

Coronary Artery Bypass Grafting

Up to now, there are no published data on IMA concentrations after CABG. We performed a pilot study (unpublished own results) in patients undergoing on-pump CABG and calculated net-myocardial IMA releases from concentration differences between coronary sinus blood and arterial blood sam-

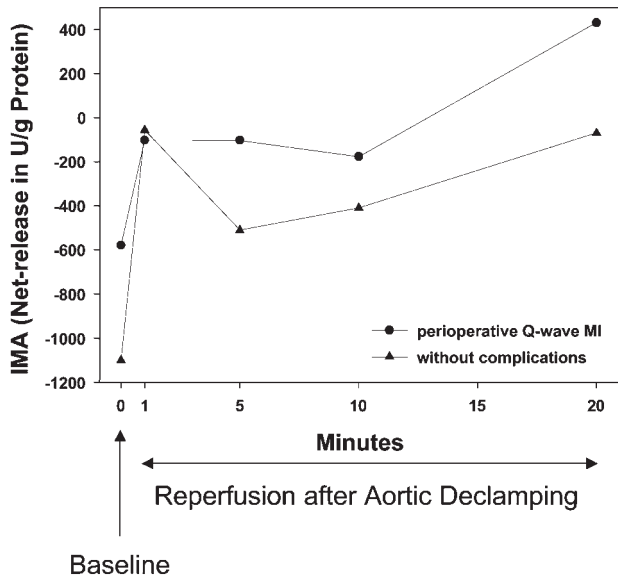


Figure 7. Early myocardial net ischemia-modified albumin release in two representative patients undergoing elective on-pump CABG. IMA indicates ischemia modified albumin; MI, myocardial infarction.

ples. Interestingly, IMA net-releases did not significantly correlate ($r = .2, P = .08$) with myocardial lactate production during reperfusion of the heart after cardioplegic cardiac arrest. IMA net-releases in three patients with clinical signs of perioperative myocardial ischemia were not markedly different from uncomplicated patients. The only prolonged IMA net release at 20 minutes after aortic declamping was found in a patient with perioperative inferior wall myocardial infarction who needed intraoperative graft revision (see Figure 7). However, this patient was also easily identified by its markedly higher troponin net-release compared with the remaining patients at this time point (see Figure 3). According to these preliminary results the diagnostic value of IMA for the detection of intraoperative myocardial ischemia during CABG is limited even when net myocardial production is calculated. The unspecificity of the marker further reduces its diagnostic performance for the detection of myocardial ischemia when IMA is measured systemically in arterial or venous blood samples.

CONCLUSIONS

All novel markers of myocardial ischemia (IMA, choline, unbound free fatty acids) lack cardiac specificity, and, therefore, for the specific detection of myocardial ischemia selective blood sampling from an inserted coronary sinus catheter is needed, which limits the applicability of these markers in most clinical routine settings. In addition, the superiority of these novel markers over the calculation of myocardial lactate production, the current criterion standard for the laboratory diagnosis of myocardial ischemia, has not been demonstrated so far, and even comparative data is still frequently lacking. Further, the superiority of these new candidate markers over lactate determination for the diagnosis of myocardial ischemia in peripherally drawn blood samples has not been demonstrated either, and these novel parameters do not

appear to be a breakthrough for laboratory diagnosis of myocardial ischemia during or after PCI or CABG. The determination of cTnI and cTnT, on the other hand, is the current criterion standard for the laboratory diagnosis of myocardial damage due to their higher sensitivities and specificities compared to CKMB. According to current knowledge, troponin increases in peripherally drawn blood samples must be regarded as an indicator of myocardial necrosis which, however, may be limited, only detectable by troponin and may be missed by CKMB determination.

After on-pump CABG the generally applied troponin discriminator limits are not valid as there is limited, inevitable cardiac tissue damage occurring during the surgical procedure. Therefore, troponins significantly increase after reperfusion of the arrested heart over values seen before bypass also in patients without complications. However, perioperative myocardial infarctions can be reliably identified by their characteristic troponin time courses, and both peak concentrations and time of peak values are diagnostic criteria. Troponin release is lower in off-pump compared to on-pump CABG. Despite the controversy over the significance of troponin elevations after clinically uncomplicated and successful procedures, it is tempting to postulate that less myocardial damage as detected by troponin release is beneficial for the patient. After elective PCI only troponin increases >8-fold the upper reference limit were associated with increased mortality in long-term follow-up.

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