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Creatine Kinase-MB Fraction and Cardiac Troponin T to Diagnose Acute Myocardial Infarction After Cardiopulmonary Resuscitation

MARCUS MÜLLNER, MD, MICHAEL M. HIRSCHL, MD, HARALD HERKNER, MD, FRITZ STERZ, MD, THOMAS LEITHA, MD, MARKUS EXNER, MD, MICHAEL BINDER, MD, ANTON N. LAGGNER, MD

Vienna, Austria

Objectives. **This study sought to evaluate the diagnostic value of the biochemical markers creatine kinase (CK), creatine kinase-MB fraction (CK-MB) and cardiac troponin T (cTNT) to diagnose acute myocardial infarction (AMI) after cardiopulmonary resuscitation (CPR).**

Background. **Elevations of CK and CK-MB after CPR are a frequent finding and might be associated with ischemic myocardial injury, as well as physical trauma to the chest.**

Methods. **Patients who had cardiac arrest and primary successful resuscitation were included in the study. The diagnosis of AMI was confirmed or ruled out by means of typical electrocardiographic findings, thallium-201 myocardial scintigraphy or autopsy, if death occurred during the hospital period, in 39 primary survivors of sudden cardiac death. In 24 patients (62%) the diagnosis of AMI was established. Serum cTNT, CK and CK-MB were measured, and the CK-MB/CK ratio was calculated on admission and after 12 h.**

Results. **On admission all markers of myocardial injury proved to be weak methods for the diagnosis of AMI. After 12 h cTNT as well as CK-MB exhibited a similar diagnostic performance; CK and the CK-MB/CK ratio proved to be worthless. Sensitivity and specificity for a cTNT cutoff value of 0.6 ng/ml, 12 h after cardiac arrest, were 96% and 80%, respectively. For a CK-MB cutoff value of 26 U/liter, sensitivity was 96% and specificity was 73%.**

Conclusions. **Cardiac TNT and CK-MB are valuable tools in detecting AMI as the cause of sudden cardiac death. However, there is a considerable lack of sensitivity and specificity. Cardiac injury is probably caused not only by AMI, but also by myocardial damage related to CPR efforts.**

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Detection or exclusion of acute myocardial infarction (AMI) as the cause of sudden cardiac death may be of potential benefit for both diagnostic and therapeutic procedures (1). Diagnosis of AMI is usually based on history, typical electrocardiographic (ECG) changes or elevation of the serum MB fraction of creatine kinase (CK-MB) (2). After cardiopulmonary resuscitation (CPR), a history often cannot be obtained and electrocardiography may not be diagnostic because of persistent left bundle branch block or non–Q wave infarction. Elevations of serum CK and CK-MB after CPR are not only caused by AMI, but are also associated with mechanical and electrical trauma to the chest during CPR (3,4).

Cardiac troponin T (cTNT), a polypeptide subunit of the myofibrillar regulatory troponin complex found in striated muscles, can be detected by specific monoclonal antibodies to cTNT (5) and is highly sensitive and specific for myocardial injury (6).

From the Departments of Emergency Medicine, Nuclear Medicine, Pathology and Dermatology, Vienna General Hospital, University of Vienna Medical School, Vienna, Austria.

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Address for correspondence: Dr. Marcus Müllner, Department of Emergency Medicine, Vienna General Hospital, University of Vienna Medical School, Waehringer Guertel 18-20/6D, 1090 Vienna, Austria.

The aim of the present study was to evaluate the diagnostic possibilities of the biochemical markers CK, CK-MB and cTNT to detect AMI after successful CPR.

Methods

Patients. The patients in this study were selected from those patients served by the Department of Emergency Medicine at the Vienna General Hospital, a tertiary care university hospital. The study period was from May 1, 1995 through December 1, 1995. The performance of this study was approved by the local ethics committee.

Inclusion criteria. Patients more than 18 years of age who had a witnessed out of hospital cardiac arrest on ventricular fibrillation and received chest compressions and direct current countershock during CPR, with a return of spontaneous circulation for a duration of 12 h or more, were eligible for inclusion in the study. *Cardiopulmonary arrest* was defined as the absence of both spontaneous respiration and palpable pulse. *Return of spontaneous circulation* was defined as electrical activity on the ECG and palpable pulses.

Exclusion criteria. Patients who had a history of MI before this event were excluded from the study, as were patients whose cardiopulmonary arrest was associated with trauma, hypothermia, drowning, drug overdose or a primary respira-

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CK = creatine kinase
CK-MB = creatine kinase–MB fraction
CPR = cardiopulmonary resuscitation
cTNT = cardiac troponin T
ECG = electrocardiogram
IQR = interquartile range
MI = myocardial infarction
SPECT = single-photon emission computed tomography

tory arrest. To assess whether the patient had a prior history of MI, the patient (if he or she had recovered) and/or the patient's relatives, as well as the physician, were interviewed. Prior MI was presumed if the patient had a history of chest pain and documented unequivocal changes on the ECG or unequivocal changes in serum enzymes, or both (2).

Treatment was in accordance with the American Heart Association's guidelines for basic and advanced cardiac life support and for postresuscitative care (7). All patients received standard intensive care treatment such as controlled mechanical ventilation and sedoanalgesia with midazolam (0.2 mg/kg body weight per h), fentanyl (0.004 mg/kg per h) and low dose dopamine (1.5 μg/kg per min). Other medications were left to the discretion of the attending physician.

Data collection. Acquisition of out-of-hospital data was performed retrospectively on the arrival of each patient according to the "Utstein style," the recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest (8). Evaluated data included time of cardiac arrest, duration of the interval from time of collapse to beginning of basic or advanced life support, duration of the interval from time of collapse to return of spontaneous circulation, out-of-hospital medication, first ECG rhythm and the patient's history. The interval between recognition of collapse and time of calling the emergency medical system was estimated by one of the investigators who personally interviewed one or more witnesses. For the interval from cardiac arrest to initiation of basic or advanced life support, we presumed no sufficient systemic blood flow (i.e., duration of no blood flow) (9). The interval from initiation of life support to return of spontaneous circulation was presumed to be representative of duration of low blood flow.

Diagnosis of AMI. The diagnosis of AMI was established if one or more of the following tests revealed a positive result.

Electrocardiography. Acute MI was presumed if the 12-lead ECG displayed ST segment elevations >0.2 mV in two precordial leads or >0.1 mV in two limb leads and subsequent development of Q waves within the hospital stay (10). If the ECG was not diagnostic for AMI a myocardial scintigraphy or autopsy, or both, was performed.

Dipyridamole stress thallium-201 single-photon emission computed tomography (SPECT) protocol. We chose a dipyridamole stress thallium-201 SPECT protocol, which was performed within 3 weeks after admission, to determine not only AMI but also the viability in myocardial segments showing reduced function and to detect inducible myocardial ischemia (11) so that management of the tested patients could be facilitated.

All tests were performed in the morning in the fasting state, and the patients were prohibited from having caffeinated beverages and coronary and blood pressure medication in the 24 h before testing. Dipyridamole (Boeringer, Ingelheim, Germany) was given intravenously (0.7 mg/kg) over 5 min, followed by a low level (25 W) bicycle stress test over 4 min, the injection of 100 MBq of thallium-201 and continuation of bicycle stress for 1 more min. Single-photon emission computed tomographic scintigraphy (180° rotation, 6° steps, 64 × 64 matrix, 45 s/frame; no prefiltering, low bandpass-filtered backprojection) was performed within 5 min after thallium-201 injection and repeated at 3 h of redistribution with a large field of view gamma camera equipped with a low energy general-purpose collimator. Slices of the left ventricle, reoriented according to the short, vertical and horizontal length axes of the heart, were visually assessed by two investigators. In patients with irreversible segments, SPECT scintigraphy was repeated after reinjection of 37 MBq of thallium-201. Myocardial infarction was presumed if the segments were still irreversible after reinjection.

Autopsy studies. If patients died during their hospital stay, autopsy was performed. Cardiac dissection was performed according to standard procedures (12). The coronary artery tree was examined by transverse cuts at 0.25-cm intervals to localize significant stenosis of coronary arteries as well as thrombotic events. Ischemic damage to the myocardium was evaluated by macroscopic appearance of coagulation necrosis and by staining with nitroblue tetrazolium (13).

Blood sampling. *Determination of CK and CK-MB.* A complete series of routine laboratory tests (including CK and CK-MB) were performed on arrival and 12 h after cardiac arrest. Measurements were carried out with a Hitachi 717 autoanalyzer (Boehringer, Mannheim, Germany). The upper normal value for CK in our laboratory is 80 U/liter, and for CK-MB, 10 U/liter. The percentage of the CK-MB/CK ratio was calculated. The maximal activity of CK-MB after AMI and countershock is to be expected between 10 and 20 h (14–17).

Determination of cTNT. Blood for the determination of cTNT was sampled together with blood for routine laboratory testing on arrival and 12 h after cardiac arrest. Cardiac TNT was measured quantitatively with the ENZYMUN test (Boehringer, Mannheim, Germany). The maximal sensitivity to diagnose AMI is expected to be achieved approximately 12 h after the event (16).

Statistical analysis. Data are expressed as the median value and the interquartile range (IQR). Percentages were determined for dichotomous variables. The Mann-Whitney *U* test was used to compare groups of continuous data. The Fisher exact test was used to compare dichotomous variables. A p value <0.05 was considered statistically significant.

Sensitivity and specificity were calculated according to standard formulas. Receiver operating characteristic curves

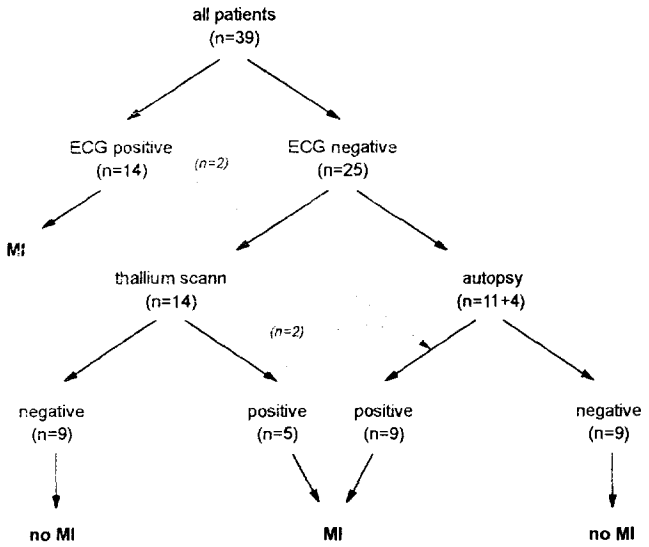

Figure 1. Flow diagram of diagnostic steps to detect myocardial infarction (MI) in 39 patients after cardiac arrest and subsequent cardiopulmonary resuscitation. In four of the patients who underwent autopsy, MI was confirmed by means of the ECG or thallium-201 myocardial scintigraphy (**dotted lines**).

were constructed to visualize the diagnostic performance (18) of serum CK, CK-MB and cTNT on arrival and 12 h after the event in the diagnosis of AMI. The Youden index was calculated for each cutoff value of each biochemical marker of myocardial injury (sensitivity + specificity − 1) (19). The closer the Youden index approaches 1, the better is the diagnostic performance of a test, thus facilitating the definition of a cutoff value.

All data were computed with Microsoft Excel for Windows, version 5.0 and SPSS for Windows, version 6.0.

Results

Within a study period of 6 months, 126 patients were admitted to the emergency department because of cardiac arrest. A total of 42 patients fulfilled the inclusion criteria. Three patients had to be excluded after enrollment because their ECG was not diagnostic and neither thallium-201 myocardial scintigraphy nor autopsy was performed.

Diagnosis of AMI. In 24 patients (62%) the diagnosis of AMI was established (Fig. 1). In four of the patients who underwent autopsy, AMI was confirmed by means of electrocardiography or thallium-201 myocardial scintigraphy (dotted lines in Fig. 1). Patient characteristics, including age and CPR, were similar in both groups (Table 1). Concentrations of biochemical markers of myocardial injury differed between groups on admission (except for CK) and even more 12 h after cardiac arrest (Table 2).

Patients with Q wave MI versus those with non-Q wave MI. Between patients with Q wave MI (n = 14) and those with non–Q wave MI (n = 10) there was no difference according to demographic characteristics (age 66 years [IQR 49 to 74] vs. 62 years [IQR 50 to 67], p = 0.58; 13 males vs. 8 males, p = 0.55) or resuscitation baseline data (duration of no blood flow: 5 min [IQR <1 to 7] vs. 1 min [<1 to 6], p = 0.36; duration of low blood flow: 16 min [IQR 9 to 29] vs. 14 min [IQR 6 to 30], p = 0.93; epinephrine administered during resuscitation: 5.5 mg [IQR 2 to 7] vs. 1 mg [IQR 0 to 7], p = 0.15; cumulative amount of energy of defibrillation administered during resuscitation: 1,760 J [IQR 738 to 2,275] vs. 1,220 J [IQR 700 to 1,990], p = 0.46). The location of the infarction was anterior in 10 patients with Q wave MI and in 8 patients with non-Q wave MI (p = 0.5) and inferior in 4 patients with Q wave MI and in 2 with non-Q wave MI. There was a nonsignificant trend toward higher CK, CK-MB and cTNT values on admission in patients later developing Q wave versus non–Q wave MI (CK: 118 U/liter [IQR 65 to 298] vs. 82 U/liter [IQR 43 to 122], p = 0.13; CK-MB: 22 U/liter [IQR 3 to 46] vs. 7 U/liter [IQR 2 to 42], p = 0.46; cTNT: 0.41 ng/ml [IQR 0.07 to 1.15] vs. 0.15

Table 1. Patient Characteristics Concerning Cardiopulmonary Resuscitation in Patients With (n = 24) and Without (n = 15) Established Acute Myocardial Infarction

	AMI (n = 24)	No AMI (n = 15)	p Value*
Age (yr)	64 (IQR 51–72)	66 (IQR 45–75)	0.9
Men	21 (88%)	9 (60%)	0.05
No flow duration† (min)	2 (IQR <1–6)	3 (IQR <1–10)	0.6
Low flow duration‡ (min)	15 (IQR 8–30)	10 (IQR 3–16)	0.2
Epinephrine (mg)	3 (IQR 0–7)	3 (IQR 0–4)	0.35
Defibrillation energy§ (J)	1580 (IQR 760–2,140)	850 (IQR 400–1,220)	0.06

*p < 0.05 considered statistically significant. †Time from collapse to initiation of life support. ‡Time from initiation of basic or advanced life support therapy to return of spontaneous circulation. §Cumulative amount of energy administered during resuscitation. AMI = acute myocardial infarction; IQR = interquartile range.

Table 2. Serum Concentrations of Biochemical Markers at Hospital Admission and 12 h After Cardiac Arrest and Subsequent Chest Compressions and Defibrillation in Patients With (n = 24) and Without (n = 15) Acute Myocardial Infarction

	AMI (n = 24)	No AMI (n = 15)	p Value*
On admission			
cTNT (ng/ml)	0.23 (IQR 0.07–0.68)	0.05 (IQR 0.02–0.24)	0.04
CK (U/liter)	95 (IQR 63–182)	54 (IQR 39–133)	0.16
CK-MB (U/liter)	21 (IQR 3–41)	2 (IQR 2–20)	0.04
12 h after CA			
cTNT (ng/ml)	3.86 (IQR 1.92–6.53)	0.27 (IQR 0.21–0.58)	<0.0001
CK (U/liter)	1125 (IQR 665–2,085)	108 (IQR 67–730)	0.004
CK-MB (U/liter)	95 (IQR 40–149)	14 (IQR 3–40)	0.0002

*p < 0.05 considered statistically significant. AMI = acute myocardial infarction; CA = cardiac arrest; CK = creatine kinase; CK-MB = creatine kinase–MB fraction; cTNT = cardiac troponin T; IQR = interquartile range.

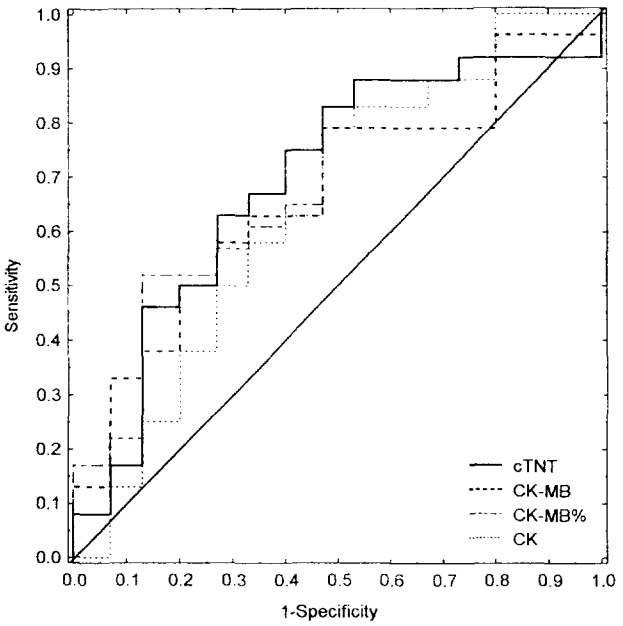

Figure 2. Receiver operating characteristic curves of CK, CK-MB, CK-MB/CK ratio (CK-MB%) and cTNT on admission for the diagnosis of AMI after cardiac arrest and subsequent chest compressions and defibrillation.

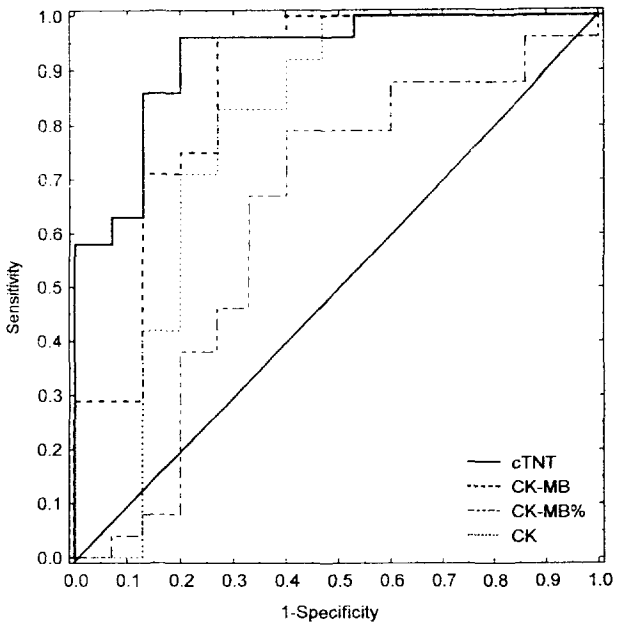

Figure 3. Receiver operating characteristic curves of CK, CK-MB, CK-MB/CK ratio (CK-MB%) and cTNT 12 h after admission for AMI after cardiac arrest and subsequent chest compressions and defibrillation.

ng/ml [IQR 0.07 to 0.42], p = 0.25). Twelve hours after cardiac arrest cTNT was higher in patients with Q wave MI (5.44 ng/ml [IQR 4.1 to 17.63] vs. 1.93 ng/ml [IQR 0.6 to 2.91], p = 0.002). The amount of CK and CK-MB in patients with Q wave MI was 1,350 U/liter [IQR 486 to 2,100] and 93 U/liter [IQR 40 to 184], respectively; in patients with non-Q wave MI the amount of CK and CK-MB was 841 U/liter [IQR 486 to 2,100] and 99 U/liter [IQR 36 to 130], respectively, which did not achieve statistical significance (p = 0.48 and p = 0.77, respectively).

Diagnostic performance of CK, CK-MB, CK-MB/CK ratio and cTNT. On admission all markers of myocardial injury showed to be weak methods for the diagnosis of AMI (Fig. 2). The maximal Youden index for CK, CK-MB, CK-MB/CK ratio and cTNT was 0.23, 0.31, 0.28 and 0.36, respectively. The corresponding cutoff values were 86 U/liter, 18 U/liter, 7% and 0.18 ng/ml, respectively. On admission CK exceeded the upper normal value of 80 U/liter in 15 patients with AMI and in 6 patients without AMI; CK-MB exceeded 10 U/liter in 15 patients with and in 5 without AMI; and cTNT exceeded 0.2 ng/ml in 12 patients with and in 4 patients without AMI. After 12 h, cTNT as well as CK-MB exhibited similar diagnostic performance, whereas CK and CK-MB/CK ratio proved to be almost worthless (Fig. 3). The maximal Youden index was 0.56, 0.69, 0.3 and 0.76 for a CK, CK-MB, CK-MB/CK ratio and cTNT cutoff value of 564 U/liter, 26 U/liter, 7% and 0.6 ng/ml, respectively. Sensitivity and specificity for a cTNT cutoff value of 0.6 ng/ml were 96% and 80%, respectively, 12 h after cardiac arrest. For a CK-MB cutoff value of 26 U/liter, sensitivity and specificity were 96% and 73%, respectively. The upper normal value for CK and CK-MB, as well as a concentration of 0.2 ng/ml for cTNT, was exceeded in all patients with AMI. In patients without AMI, the upper normal value for CK and CK-MB, as well as a concentration of 0.2 ng/ml for cTNT, was exceeded in 11 patients, 9 patients and 12 patients, respectively.

Discussion

The major finding of this study is that in patients resuscitated from cardiac arrest, cTNT concentrations, as well as the absolute amount of CK-MB, are good markers of myocardial injury to diagnose AMI. The CK-MB/CK ratio proved to be of poor diagnostic value in this setting.

Elevations of serum CK and CK-MB in patients who had cardiac arrest and subsequent CPR are a frequent finding (3,4). However, in the two existing studies addressing this question, it could not be determined exactly whether CK and CK-MB elevations were due to skeletal muscular injury or myocardial injury, or both. Further, the value of CK and CK-MB to detect AMI could not be evaluated because of the study design. The present study is, to the best of our knowledge, the first study to determine the diagnostic value of CK-MB and cTNT to diagnose AMI after cardiac arrest.

Diagnostic performance of CK, CK-MB, CK-MB/CK ratio and cTNT. Currently cTNT is said to be as sensitive as but less specific than CK-MB for retrospective diagnosis of AMI (20). In a recent meta-analysis Wu and Lane (20) demonstrated a sensitivity of 97% for CK-MB and 98% for cTNT to detect AMI. Specificity for CK-MB and cTNT in this meta-analysis was 90% and 69%, respectively. It is important to mention that specificity for cTNT in this setting refers to the acuteness and probably also the severity of the event, not to the specificity for

cardiac tissue. The high cardiospecificity of cTNT has already been demonstrated in several studies (16,21–25). After MI, serum cTNT levels are known to be elevated for up to several days (16–17,25–26). This increases the time window to diagnose MI by reducing the ability to differentiate between acute and subacute infarction. Further, it has been shown that cTNT is also detectable in some patients with unstable angina (22), which might precede MI. One recent study addressed the sensitivity and specificity of cTNT in patients after out-of-hospital resuscitation (27). This group found a very high cTNT discriminator level of 4 ng/ml with a sensitivity of 88% and specificity of 95%. The shortcoming of this study (27) is the lack of a satisfactory reference standard for diagnosing AMI after out of hospital cardiac arrest. In our study we defined a much lower cTNT discriminator level of 0.6 ng/ml to diagnose AMI. If we applied a cutoff value of 3.2 ng/ml, the specificity would be 100% with a corresponding sensitivity of 58%. The cutoff values to diagnose AMI in patients without CPR ranged from 0.1 to 0.5 ng/ml (16,23,25). When we applied a cutoff value of 0.6 ng/ml 12 h after the event we found both a higher sensitivity and specificity for cTNT in comparison to CK-MB. Also, the cutoff concentration of 26 U/liter for CK-MB to detect AMI is more than twice the upper normal value than that applied in patients without CPR. It is also noteworthy that cTNT concentrations were elevated >0.2 ng/ml in 12 of 15 (80%) patients without AMI 12 h after cardiac arrest. This implies that a qualitative estimation of cTNT in this patient group is not useful to diagnose AMI unless the discriminator value is set at a level >0.2 ng/ml.

On admission none of the variables seemed to be of diagnostic value for the diagnosis of AMI, which has already been described (28,29). All three markers frequently exceeded established upper normal values. For CK and CK-MB this already has been shown (4). The concomitant elevation of cTNT indicates cardiac damage. However, whether this elevation serves as an indicator of unrecognized MI before cardiac arrest or of severe myocardial damage due to cardiac arrest and CPR remains unclear. Admission concentrations in patients with MI were higher at least.

Total CK and CK-MB/CK ratio turned out to be useless tools in the diagnosis of AMI after CPR even 12 h after the event.

Besides AMI as the cause of cardiac arrest, myocardial injury in cardiac arrest patients might be caused by several factors. During cardiac arrest coronary blood flow is presumed to be absent before initiation of life support therapy. During CPR coronary perfusion pressure is reduced to ~10% to 20% of control values (30,31), both factors probably causing ischemic damage. It is also known that defibrillation can cause myocardial muscular damage (32). There is also the possibility of cardiac contusion due to chest compressions. Further, CK and CK-MB elevations might in part also be caused by skeletal muscular injury due to resuscitative efforts. Another possible cause for myocardial damage might be persistent circulatory shock, which is not rare after cardiac arrest with primary successful resuscitation. The design of this study did not allow us to determine which of these factors was responsible for CK-MB and cTNT elevations. Excess release of CK from skeletal muscles can produce a false normal CK-MB/CK ratio, which is a plausible explanation for the low diagnostic value of CK and CK-MB/CK ratio in this patient group. The cross reactivity of cTNT with striated skeletal muscle is expected to be <0.5% (24). Therefore, cTNT was already successfully used to identify increases in CK-MB after physical exercise as noncardiac (21) and also to detect cardiac contusion (33). This might explain the higher sensitivity and specificity of cTNT to diagnose AMI in patients after cardiac arrest and CPR.

When we compared patients with AMI and subsequent Q wave formation on the ECG to patients with AMI but without Q wave formation, we found higher cTNT levels in the former group—probably a measure of infarct size, for the extent of MI is known to be larger if there is Q wave formation (34). The reason why CK and CK-MB did not differ significantly between these groups is most probably the higher myocardial specificity of cTNT as well as a reduced statistical power because of small subgroups.

Study limitations. To create a reference standard to diagnose AMI in our patient group we had to apply several diagnostic tools. Autopsy is presumed to be the reference standard for most diagnostic procedures (35). All our patients survived for more than 12 h, so we expect a coagulation necrosis to be detectable. As for thallium-201 myocardial imaging we presumed AMI only if the patient had irreversible perfusion defects with a sensitivity close to 100% and a specificity ~68% (36,37). The possibility that a patient had an unrecognized MI before the event, and thus did not fulfill the exclusion criteria, also might limit the diagnostic performance of the biochemical markers used in this study. Another limitation of the study is the retrospective evaluation of the prehospital data. Difficulties in conducting clinical studies in cardiac arrest patients are numerous and well recognized (8). We could not do better than using an internationally recognized protocol (8) especially designed for the evaluation of prehospital cardiac arrest data, and assessing the data immediately after arrival in the emergency department.

Conclusions. Although both cTNT and CK-MB are valuable tools in detecting AMI as the cause of sudden cardiac death, there is a considerable lack of sensitivity and specificity, respectively. It is questionable whether other markers of myocardial injury will give more accurate results, for cardiac injury might not be caused only by AMI but also by myocardial damage related to cardiac arrest and CPR efforts.

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