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ORIGINAL ARTICLE

Procalcitonin in acute myocardial infarction

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Abstract

Objective: Procalcitonin (PCT) is released in severe bacterial infections, sepsis and in infection independent cases such as major surgery, multiple trauma, cardiogenic shock, burns, resuscitation, and after cardiac surgery. The aim of this study was to determine the levels and the kinetics of PCT in AMI and to investigate their possible correlation with the release of IL-6 and CRP. *Design-Patients:* The study included 60 patients (47 men, 63.2 ± 14.8 years) with the diagnosis of AMI at admission. In all patients, serum levels of PCT, IL-6, CK-MB, TnI and CRP were measured at admission, at 3, 6, 12, 24, 48 and 72 h and at the seventh day. *Results:* PCT was elevated in all patients with AMI. It was initially detected in serum approximately 2–3 h after the onset of the symptoms. The median value at admission was 1.3 ng/ml (95% CI: 0.89 to 1.80). The value of PCT showed an increase and reached a plateau after 12–24 h. The median value at 24 h was 3.57 ng/ml (95% CI: 2.89 to 4.55). PCT values fell to baseline (<0.5 ng/ml) by the seventh day. PCT was detected in serum earlier than CK-MB or TnI in 56 of the 60 patients (93.3%). The kinetics of PCT was similar to those of CK-MB and TnI. The maximal values of PCT were positively correlated with the maximal values of IL-6 (r=0.59, *P*=0.00) and of CRP (r=0.65, *P*=0.001). The maximal values of IL-6 were positively correlated with max CRP (r=0.35, *P*=0.045). *Conclusions:* PCT could be considered as a novel sensitive myocardial index. Its release in AMI is probably due to the inflammatory process that occurs during AMI.

Key Words: *Procalcitonin, proinflammatory cytokines, infarction*

INTRODUCTION

Procalcitonin (PCT) is a peptide consisting of 116 amino acids with a sequence that is identical to that of the prohormone of calcitonin (1). Normally the active hormone calcitonin is produced and secreted by the thyroid gland after intracellular proteolytic procession of PCT (2). However, in severe bacterial infections, in sepsis and probably in other conditions, intact PCT, that is not degraded to calcitonin, is found in the blood (3,4). These PCT plasma levels are very stable and, according to some studies, the origin of PCT in these conditions is extrathyroidal (5). In healthy individuals PCT levels are below 0.1 ng/ml and thus below the detection limit of PCT in blood (6). However, the threshold of PCT concentrations that indicate an acute bacterial infection is 0.5 ng/ml, whereas in cases of severe sepsis PCT concentrations range from 10 to 1000 ng/ml (3,7). Additionally, values not exceeding 5 ng/ml are found in infection independent cases such as major surgery or multiple trauma, cardiogenic shock (8), burns, resuscitation and in post cardiac surgery period (9–13). Based on these data some investigators presumed that PCT is also elevated in acute myocardial infarction (AMI). Working in this direction, Buratti et al. (14) were the first to conclude that PCT levels were elevated, but not significantly, during AMI. Furthermore, Remskar et al. (15) found that PCT levels were elevated in AMI, but only if AMI was associated with severe heart failure, resuscitated cardiac arrest or concomitant bacterial infection.

It has been also shown that pro-inflammatory cytokine interleukin-6 (IL-6) and C-reactive protein (CRP) are released in AMI as a response to the ensuing inflammatory process or/and to the tissue injury (16,17). The aim of this study was to investigate the role of PCT in AMI and its possible correlation with the release of IL-6 and CRP.

Methods

The study included 60 consecutive patients (47 men, 13 women, mean age 63.2 ± 14.8 years) with

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Table I. Baseline characteristics of the 60 patients.

	Number of patients
Known (documented) CAD	13 (21.7%)
Previous AMI	7 (11.7%)
Smoking	48 (80%)
Hypertension	33 (55%)
Diabetes	13 (21.7%)
Family history of CAD	17 (28.3%)
Hypercholesterolemia	45 (75%)
Angina in the previous 10 days.	18 (30%)

CAD, coronary artery disease; AMI, acute myocardial infarction

the diagnosis of AMI at admission. The baseline characteristics of these patients are shown in Table I. Forty-one of them presented in the emergency room with an ST elevation AMI within 6 h from symptoms onset and received thrombolysis with rt-pA. Eight patients had ST elevation AMI but did not fulfill the criteria for thrombolysis, and the rest 11 had a non-ST elevation AMI. The mean time (based on the history) from symptoms onset to first sample (at admission) was 2.31 ± 1.13 h. The concomitant therapy included aspirin (100 mgr), clopidogrel (75 mgr) and lipid lowering agents for all patients, β-blockers for 58 (of 60) patients and ACE-inhibitors for 56 (of 60) patients. The severity of left heart failure was estimated according to Killip classification (Table II). Patients with infections or septic condition were excluded from the study.

In all patients serum levels of PCT, IL-6, CK-MB, Troponin I (TnI) and CRP, were measured at admission, at 3, 6, 12, 24, 48 and 72 h and at the seventh day.

Forty healthy volunteers, who constituted the control group for PCT and IL-6 were also included. The criterion for considering all these patients as healthy for coronary artery disease was a negative stress test (treadmill test, heart scintigraphy or stress echocardiography). This population did not differ statistically with the patient population, as regards the demographic characteristics (age, sex). In the healthy volunteer population, measurements of PCT and IL-6 were done from two different samples with an interval of seven days between them.

Table II. Characteristics and in-hospital clinical status of the 60 patients with AMI.

	Number	Percent
Male	47	78.3
Thrombolysis	41	68.3
ST elevation	49	81.7
Non ST elevation	11	19.4
Killip classification		
I	26	43.3
II	22	36.7
III	7	11.7
IV	5	8.3
Deaths	2	3.3
Cardiac arrest	4	6.7
Mechanical ventilation	4	6.7
Angioplasty (urgent)	8	13.3

The protocol of the study was approved by the Ethical Committee of KAT hospital and all patients had signed an informed consent.

Isolated serum samples were kept at −70°C in cryovials for long-term storage. PCT levels were measured in human serum samples using a commercially available non-isotopic kit, immuno-luminometric assay, (LUMItest PCT, BRAHMS, Germany). Briefly, 20 μl serum, standard or control, in duplicates, were added in test tubes, coated with anti-PCT antibody and incubated for 1 h at room temperature in the presence of 0.25 ml tracer, a luminescence labeled monoclonal antibody solution. After incubation, tubes were washed with washing buffer four times and left to drain any remaining drops. Lumitest Basiskit (BRAHMS) was used for Lumiscence measurements on a Lumat LB 9507 (BERTHOLD) luminometer, with suitable internal software. The functional sensitivity (defined as the lowest analyzed concentration that was determined with an inter-assay CV < 20) has been assessed as being 30.3 ng/ml with probability of 95%. BRAHMS PCT LIA shows a high precision in the determination of serum concentrations. The intra-assay CV and the inter-assay CV are 6–10% in relevant PCT concentration range.

IL-6 levels were measured in human serum samples using a commercially available ELISA kit (DIACLONE, France), based on a solid phases sandwich enzyme linked-immuno-sorbent assay. Briefly, 100 μl serum, in duplicates, were added in microplate wells, coated with monoclonal antibody IL-6, followed by washings and an incubation with a secondary antibody (streptabidin-peroxydase). Further washing and substrate solution (TMB) leads to the detection of IL-6, present in the samples. Reaction is stopped with H_2SO_4 2N and final measurements were reading on a microplate reader EL311sx (BIOTEC). Calculations followed the four parameters curve.

TnI levels were measured with AXSYM system (ABBOTT). The AXSYM troponin-I ADV assay precision is less than or equal to 10% total CV with 95% confidence for concentrations from 0.27 ng/ml up to 4.00 ng/ml.

CRP levels were measured in human serum samples using the CardioPhase hs CRP kit of the company DADE BEHRING in the nephelometric analyzer BN PROSPEC of DADE BEHRING. Briefly, polystyrene particles coated with monoclonal antibodies specific to human CRP are aggregated when mixed with samples containing CRP. This aggregates scatter a beam of light passed through the sample, the intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result is evaluated by comparison with a standard of known concentration.

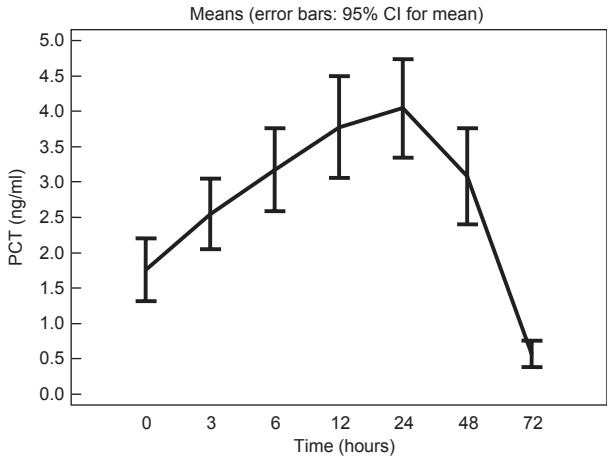

Figure 1. PCT values in patients with acute myocardial infarction.

The assigned value of CRP in N Rheumatology Standard is standardized against the international reference preparation BCR-CRM 470 (N.R: 0–3 mg/l). None of the 60 patients underwent any coronary intervention during the first seven days. Six more patients that were originally included, were finally excluded from the study, since they needed urgent coronary intervention. This strategy was considered acceptable since early invasive strategy has not been shown to be beneficial. This fact was confirmed by the recently published ICTUS trial (18).

Statistics

PCT, CRP, and IL-6 values were not normally distributed and so a non-parametric test was used. The results are expressed as medians and 95% confidence intervals of the medians. Wilcoxon test was chosen. Correlation data were calculated as the Pearson correlation coefficient. A P value <0.05 was considered significant. Medcall statistical program was used.

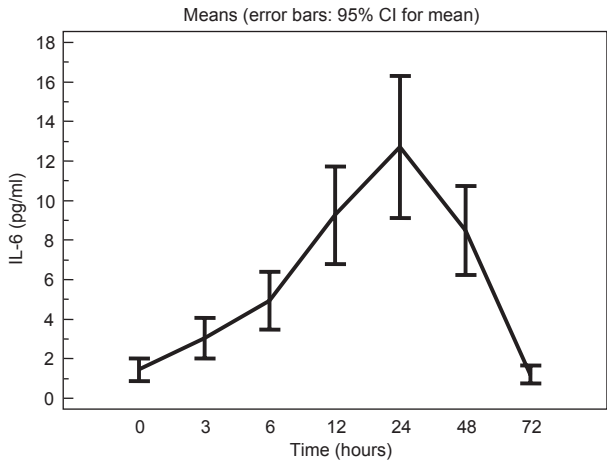

Figure 2. IL-6 values in patients with acute myocardial infarction.

Results

PCT and IL-6 serum levels (<0.5 ng/ml and <0.5 pg/ml, respectively) in all healthy volunteers, were undetectable.

PCT was elevated in all patients with AMI . It was initially detected in serum approximately 2–3 h after the onset of the symptoms. The mean time from symptoms onset to first positive value of PCT ($\geqslant 0.5$ ng/ml) was 2.81 ± 1.44 h. The median value at admission was 1.3 ng/ml (95% CI: 0.89 to 1.80). The value of PCT showed an increase and reached a plateau after 12–24 hours. The median value at 24 hours was 3.57 ng/ml (95% CI: 2.89–4.55). PCT values fell to baseline (<0.5 ng/ml) by the seventh day (Figure 1).

IL-6 levels were detectable in blood approximately 5–8 h after the onset of symptoms. In 36 out of 60 patients IL-6 was undetectable (<0.5 pg/ml) in serum at admission. The mean time from symptoms onset to first positive value (IL-6 $\geqslant 0.5$ pg/ml) was 6.3 ± 2.35 h. The peak value was reached after 24–48 h (median value: 8.09 pg/ml, 95% CI: 4.09–11.93) (Figure 2). IL-6 levels at admission did not differ between patients that had pre-infarction angina and those that had a sudden infarction (median value: 5.36 pg/ml, 95% CI: 0.4–2.43 versus 5.19 pg/ml, 95% CI: 0.2–3.47, $P=0.89$).

PCT was detected in serum earlier than CK-MB or TnI in 56 of the 60 patients (93.3%). The kinetics of PCT were similar to those of CK-MB and TnI.

CRP levels showed an increase in plasma after the 3–6 h, reached a peak value (114.3 mg/l with 95% CI: 72.34–144.32) at approximately 48–72 h and remained elevated until the seventh day. CRP levels at admission were significantly higher in those patients that had pre-infarction angina (unstable angina the previous 10 days) compared with those that had a sudden infarction (median value: 6.2 mg/l, 95% CI: 3.6 to 9.8 versus 27.8 mg/l, 95% CI: 6.8–79.2, $P=0.000$).

A representative example of the time course of plasma PCT, IL-6, CK-MB, TnI and CRP levels, is shown in Figure 3.

The maximal values of PCT were positively correlated with the maximal values of IL-6 ($r=0.59$, $P=0.000$) (Figure 4) and of CRP ($r=0.65$, $P=0.001$). The maximal values of IL-6 were also positively correlated with max CRP ($r=0.35$, $P=0.045$). No correlation between PCT and CK-MB values was found ($r=0.32$, $P=0.08$).

PCT values were significantly higher in patients with pulmonary edema (Killip III) or cardiogenic shock (Killip IV) versus those with Killip I or II. In addition, PCT values were significantly higher in patients with cardiogenic shock (Killip IV) compared with those with Killip I or II or III (Table III, Figure 5).

There was no difference in the max PCT levels between STEMI and NSTEMI patients (median

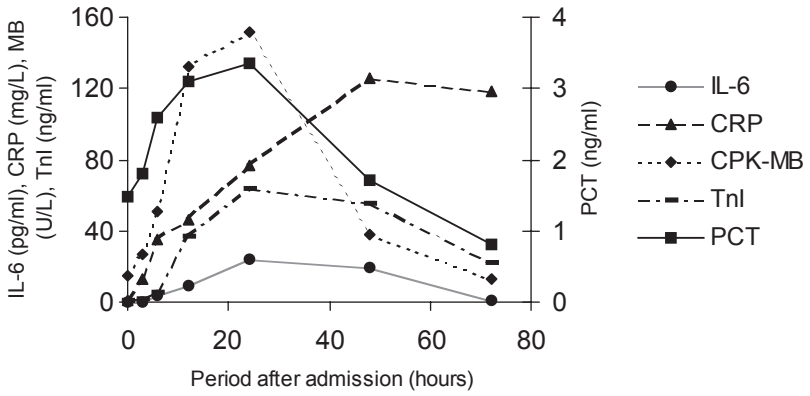

Figure 3. Representative example of time course of plasma IL-6, CRP, CPK-MB, TnI, PCT.

value: 1.25 ng/ml, 95% CI: 0.639–4.05 versus 2.6 ng/ml, 95% CI: 0.61–4.18, P=0.17). Among the STEMI patients there was also no difference in the max PCT levels between thrombolysed and no thrombolysed patients (median value: 1.99 ng/ml, 95% CI: 0.65–9.23 versus 7.35 ng/ml, 95% CI: 2.16–11.78, P=0.15).

PCT levels at admission were significantly higher in patients with pre-infarction angina compared with those that had a sudden infarction (median value: 2.27 ng/ml, 95% CI: 1.58–3.41 versus 0.86 ng/ml, 95% CI: 0.51–1.27, P=0.0023).

The majority of the patients underwent coronary angiography followed by some kind of intervention. Only 8 patients needed urgent intervention.

Discussion

Several studies have demonstrated that elevated PCT levels indicate bacterial infection accompanied by a systemic inflammatory reaction (5,12). Nevertheless, in other infection-independent cases manifesting injury, such as surgery, PCT is also elevated (9–11,19). In these circumstances, PCT is detected very early in blood and because of its stability and long half-life (approximately 20–24 h) remains in measurable levels for a remarkable period (17,20).

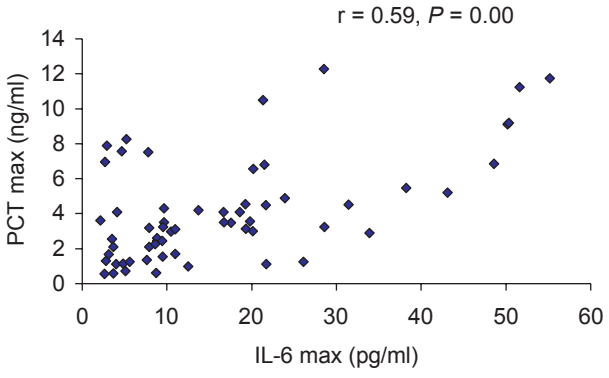

Figure 4. Correlation between PCT max and IL-6 max in the sixty patients with AMI.

These characteristics make PCT an attractive molecule for study in AMI, since both inflammation and injury are parts of the acute phase reactions in myocardial infarction. Buratti et al. (14) and Remskar et al. (15) have already investigated this issue with interesting and controversial findings. In Buratti et al.'s study (14), a moderate increase in PCT levels was found in 27 of the 44 AMI patients. The maximum PCT values were seen approximately 24 h after the onset of AMI. Remskar et al. (15) found elevated PCT levels only in AMI patients with pulmonary edema (Killip III) and cardiogenic shock (Killip IV). In their study, PCT values reached their maximum values after two to three days. In our study, PCT was increased in all patients with AMI, probably presenting itself as a new myocardial index. Peak PCT values were present in the first 24 h, as Buratti et al. (14) found. Moreover, its kinetics during the acute phase of MI seem more favorable than those of CK-MB and TnI since it appears earlier in serum, reaches its peak at 12–24 h and returns to baseline values at the sixth to seventh day. Alternatively, PCT is not a specific marker. Thus, it plays a role similar to that of myoglobin, but with the advantage of being detectable for longer time, since its half-life is 20–24 h. The definite time from symptoms onset to first sample could not be recorded accurately. However, the measurements of PCT, IL-6 and TnI were done at the same time and so the comparison of their kinetics is probably reliable. In 55 of 60 patients, PCT value at admission was $\geqslant$0.5 ng/ml. The samples could not be taken at exactly the same time from symptoms onset and before admission for all patients and so PCT levels could be elevated even earlier. The fall of PCT levels to baseline indicates that PCT is released in response to a single acute stimulus, since it has been proved that PCT levels remain high when the inflammatory procedure continues (21).

Our findings were different from those of Buratti et al. (14) and Remskar et al. (15) probably because of the accuracy of the laboratory methodology used. Since in AMI PCT values are slightly elevated compared with the other conditions that cause PCT

Table III. Relation of PCT values with the severity of heart failure according to the Killip classification.

Killip I, II, III (55 pts) PCT max: 2.12 (95% CI: 0.93–3.14)	Killip IV (5 pts) PCT max: 6.86 (95% CI: 4.14–9.37)	p=0.000
Killip I, II (48 pts) PCT max: 1.78 (95% CI: 0.73–2.96)	Killip III, IV (12 pts) PCT max: 4.1 (95% CI: 1.59–8.12)	p=0.003

elevation, little differences in laboratory methodologies may reflect significant differences in the results. In our study, a healthy population group was used as control.

PCT induction and plasma levels elevation are closely correlated with the extent and type of systemic inflammation. Normal plasma and serum concentrations of PCT are below 0.5 ng/ml and all values in excess of 0.5 ng/ml are considered abnormal. In our study, all healthy volunteers had concentrations of PCT below 0.5 ng/ml. The values between 0.5 ng/ml to 2 ng/ml are usually considered as slightly elevated. Values of approximately 2 ng/ml to 5 ng/ml are considered as moderately high, whereas those exceeding 5 ng/ml (and especially 10 ng/ml) are considered very high PCT values. The level of PCT concentration is closely correlated with the type, extent and spread of the infection and, in particular, with the systemic manifestations of the inflammatory reaction. Slightly elevated PCT concentrations (0.5–2.0 ng/ml) are observed in bacterial infection, which has triggered a minor systemic inflammatory response (19,22). Additionally, some authors believe that in the infection-independent cases in which PCT is elevated, its value does not exceed 5 ng/ml (9,23–25). In our study all values of PCT in patients with AMI were >0.5 ng/ml and the maximum values were 3.82 ± 2.35 ng/ml. These low PCT levels made us believe that probably during AMI there is only a minor systemic inflammatory response. This inflammation though minor seems to be systematic and not localized, since there are evidences of a pan-coronary inflammation during AMI. The inflammatory nature of PCT induction is proven by the fact that max PCT is positively correlated with both max IL-6 and max CRP, which are inflammatory indices (26–29). Buratti et al. (14) found also positive correlation with max IL-6. The findings of Remskar et al. (15) concerning the higher PCT values found in Killip III and IV conditions were also confirmed by this study.

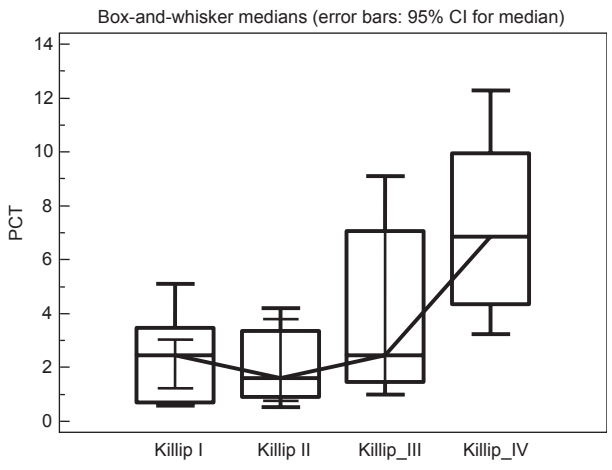

Figure 5. PCT levels in Killip classes.

The conditions under which PCT is induced in AMI remain under question. In experimental studies, the intravenous administration of bacterial endotoxin is followed by a PCT level increase after induction of IL-6 and TNF-α. IL-6 and TNF-α reach peak concentrations approximately 2–3 h and 1.5 h respectively after the endotoxin infection. Peak PCT values are reached within 12–48 h (5,17). The fact that during acute infections PCT levels mirror IL-6 and TNF-α values after a few hours (30) made some authors conclude that PCT is induced by the pro-inflammatory cytokines. In our study, this relation was not found in AMI patients, since the peak values of IL-6 and CRP appear later in blood (24–36 h and 36–72 h respectively). This may means that PCT is related to the induction of IL-6 but is not induced by it. The findings of Liuzzo et al. (31) showing significantly higher elevation of CRP in the AMI patients with pre-infarction unstable angina were confirmed in our study. According to our findings, PCT values were similarly increased in the AMI patients with pre-infarction unstable angina. These relations may show that in this population there is a continuous inflammatory process. However, different pro-inflammatory molecules, as TNF-α, could be involved in this procedure. Furthermore, PCT seems to react more rapidly than IL-6 and CRP in the same inflammatory scenario during AMI. Certainly, as regards IL-6, we should mention that the undetectable levels at admission that were found in 35 of 60 patients and the strange finding that shows earlier increase of CRP, are may be due to the non-high sensitivity of the IL-6 assay that was used. Nevertheless, the whole process seems to be much more complicated, since several measurable markers, such as Amyloid A (32,33) and Visfatin (34), have been presented in newer literature. We concluded that the inflammation, though systematic and extensive, is minor, based on PCT values and the well-established knowledge of the meaning of PCT levels. However, not only these values but also the whole inflammation process as well, is probably affected by the use of medications, such as ACE-inhibitors and lipid lowering drugs, which are known to have anti-inflammatory effects.

Because of the fact that PCT levels in AMI did not exceed the value of 5 ng/ml, we should not overlook the possibility that factors others than bacterial endotoxins could be responsible for the induction of PCT. Based on today's knowledge, we may postulate that bacterial toxins are by far the most potent stimulator of PCT induction. However, several studies concerning, strokes, acute burns, multiple trauma, sterile surgery and other infection-independent cases have suggested that PCT elevation can occur without any measurable concentrations of endotoxins (10,12,25,27). As regards the possible (other than the inflammatory procedure) cause of PCT induction, we found some hypothetical statements that have already been made. Lietzmann (30) has stated that PCT may also be involved in the regulation of vasomotility or interfere with nitrogen monoxide (NO) mediated pathophysiological effects. Steinwald et al. (35) have shown in animal experiments that changes of calcium and phosphate concentrations in the blood are correlated with an increase in calcitonin immunoreactive proteins (including PCT). Finally, Meisner et al. (10,36) noted that in patients undergoing cardiac surgery elevation of PCT was observed when catecholamines were required to maintain adequate circulation.

Limitations

Sensitivity and specificity were not estimated in this study. Although PCT could be considered as a novel, probably sensitive myocardial marker, its specificity in detecting the presence of ischemia (or necrosis) in AMI is under question since many other conditions raise the PCT value, notably infection and cardiac surgery. A well-designed study with the purpose to evaluate the sensitivity and specificity of PCT in AMI is now running. Thus, the advisability of routinely measuring this substance after an AMI remains to be determined.

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