

Early release of glycogen phosphorylase in patients with unstable angina and transient ST-T alterations

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Abstract

Objective—To determine whether transient ST-T alterations in patients with unstable angina are associated with an increase in plasma glycogen phosphorylase BB concentrations on admission to hospital.

Design—Prospective screening of patients with unstable angina for markers of myocardial cell damage.

Setting—Accident and emergency department of university hospital.

Patients—48 consecutive patients admitted for angina pectoris (18 with transient ST-T alterations). None of the patients had acute myocardial infarction according to standard criteria.

Main outcome measures—Creatine kinase and creatine kinase MB activities, creatine kinase MB mass concentration, and myoglobin, cardiac troponin T, and glycogen phosphorylase BB concentrations on admission.

Results—All variables except for creatine kinase and creatine kinase MB activities were significantly higher on admission in patients with unstable angina and transient ST-T alterations than in patients without. However, glycogen phosphorylase BB concentration was the only marker that was significantly ($p = 0.0001$) increased above its discriminator value in most patients (16). In the 18 patients with transient ST-T alterations creatine kinase MB mass concentration and troponin T and myoglobin concentrations were significantly ($p = 0.0001$) less commonly increased on admission (in five, three, and two patients, respectively).

Conclusions—The early release of glycogen phosphorylase BB may help to identify high risk patients with unstable angina even on admission to an emergency department. Glycogen phosphorylase BB concentrations could help to guide decisions about patient management.

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Glycogen phosphorylase is the key enzyme of glycogenolysis and has three main isoenzymes: BB (brain), MM (muscle), and LL (liver).¹ The isoenzymes are encoded by three distinct genes and differ in their functional and immunological properties,^{1,2} which makes it possible to develop specific immunoassays.

Glycogen phosphorylase BB (molecular weight 96000 kDa as a monomer) is the predominant isotype in human myocardium where it occurs alongside the MM subtype.³ The release of glycogen phosphorylase from injured myocardium may reflect the burst in glycogenolysis initiated during acute myocardial ischaemia.⁴ This is supported by a rapid increase in serum concentrations of glycogen phosphorylase BB in patients with acute myocardial infarction before concentrations of creatine kinase, creatine kinase MB, myoglobin, and cardiac troponin T increase.⁵ Unstable angina, however, ranges from no myocardial cell damage to non-Q wave myocardial infarction. Myocardial ischaemia induces glycogenolysis and may lead to a transient loss of integrity of the plasma membrane, with a subsequent leakage of soluble cytosolic proteins in more severe cases.⁶ We therefore investigated whether glycogen phosphorylase BB is also released early from the myocardium—that is, on admission to the emergency department—in patients presenting with unstable angina and transient ST-T alterations.

Patients and methods

PATIENTS

The study population consisted of 48 consecutive patients (32 men, 16 women, mean age 63.7 (SD 10.4) years) who were admitted to the emergency department of the department of internal medicine (University Hospital of Innsbruck, Austria) for typical symptoms of angina pectoris. The average delay from the onset of chest pain to admission was 4.6 (4.4) hours (range 1–22 hours). In all patients acute myocardial infarction was ruled out retrospectively from standard criteria of the World Health Organisation.⁷ Patients with a history of recent stroke, myocardial infarction documented within the previous two weeks, valvular heart disease, or cardiomyopathy were excluded.

Standard 12 lead electrocardiography was performed routinely at the time of admission, and recordings were repeated for several times during the hospital stay. All patients were given routine antianginal treatment that included nitrates, β blockers, calcium channel blockers, aspirin, and heparin as needed. The electrocardiograms were evaluated blindly for evidence of reversible myocardial ischaemia, defined as transient ST elevation (≥ 0.1 mV), ST depression (≥ 0.1 mV), and T inversion in at least two contiguous leads of a standard

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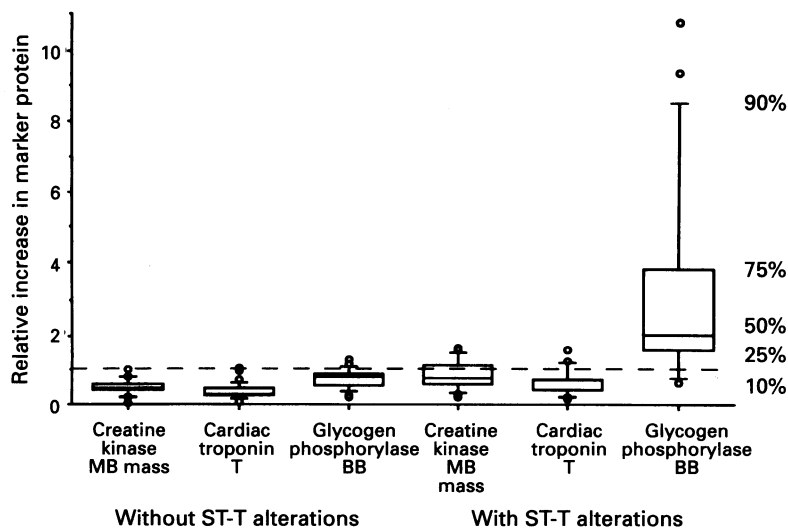
12 lead electrocardiogram. Patients were divided into two groups according to the presence of transient ST-T alterations at presentation.⁸ Neither group differed significantly according to age, sex, or delay ($p \geq 0.27$). On admission a single blood sample was collected in all patients for measurement of creatine kinase and creatine kinase MB activities, creatine kinase MB mass concentrations, and concentrations of myoglobin, cardiac troponin T, and glycogen phosphorylase BB. Creatine kinase and creatine kinase MB activities were repeatedly measured during the hospital stay to exclude acute myocardial infarction.

LABORATORY ANALYSIS

Creatine kinase and creatine kinase MB activities were measured without delay with Merck test kits (Darmstadt, Germany). Creatine kinase MB activities were measured by immunoinhibition. Blood samples for measurement of all other variables were immediately centrifuged, and the plasma was stored at -20°C until analysis. Myoglobin concentration was measured by immunoturbidimetry (Behringwerke AG, Marburg, Germany); creatine kinase MB mass concentrations (Abbott, North Chicago, USA) and cardiac troponin T concentrations (Boehringer Mannheim, Mannheim, Germany) were measured by enzyme immunoassays as previously described.⁹⁻¹¹ Glycogen phosphorylase BB concentration was determined by using a recently developed specific immunoenzymometric assay; this assay does not crossreact with liver or skeletal muscle isophosphorylase.¹² The upper limit of the reference interval (discriminator value) of glycogen phosphorylase BB with this assay was $5 \mu\text{g/l}$.¹³

STATISTICS

All results are expressed as means (SD) except when stated otherwise. χ^2 Tests (with Yates's correction for continuity) and t tests (two tailed) were used for statistical analysis. P values < 0.05 were considered to be significant.



Box plots of glycogen phosphorylase isoenzyme BB concentration, creatine kinase MB mass concentration, and cardiac troponin T concentration in patients with unstable angina on admission to emergency department. Broken line shows discriminator value of each variable.

Results

On admission to the emergency department all variables except for creatine kinase and creatine kinase MB activities were significantly ($p \leq 0.04$) higher in patients with transient ST-T alterations ($n = 18$). In these patients, however, creatine kinase MB mass concentration and myoglobin and cardiac troponin T concentrations were still within the reference range in most patients. Myoglobin concentration was increased in two patients, cardiac troponin T concentration in three, and creatine kinase MB mass concentration in five. By contrast, glycogen phosphorylase BB was significantly ($p = 0.0001$) more commonly increased in patients with transient ST-T alterations than all other biochemical markers tested. It was the only marker that was not only significantly higher ($p = 0.0001$), but also increased above its discriminator value in most patients even on admission to the emergency department ($n = 16$; figure). Myoglobin was not included in the figure because concentrations were above the detection limit ($50 \mu\text{g/l}$) in only some of the patients with ST-T alterations and below the limit in all patients without electrocardiographic changes.

Discussion

An increase in creatine kinase MB mass concentration and in myoglobin and cardiac troponin T concentrations in a subgroup of patients with unstable angina has been previously described in serially collected blood samples during hospital admission.¹⁴⁻¹⁷ We found an early release of glycogen phosphorylase BB into blood in patients with unstable angina and transient ST-T alterations. In these patients glycogen phosphorylase BB was the only marker that was increased above its discriminator value in most of them on admission to the emergency department. The average delay from the onset of chest pain to admission was about 4-5 hours.

The biochemical basis for the rapidity with which glycogen phosphorylase BB is released after myocardial ischaemia is probably its function as a key enzyme of glycogenolysis. In the myocardium glycogen phosphorylase BB exists in association with glycogen and the sarcoplasmic reticulum, forming a macromolecular complex.¹⁸ During myocardial ischaemia this complex is broken down^{19,20} and glycogen phosphorylase BB is released into the sarcoplasm, which results in a large soluble cytosolic pool of the enzyme and a high concentration gradient between the sarcoplasm and the extracellular space. In cases of severe but reversible myocardial ischaemia the permeability of the plasma membrane is simultaneously altered so that soluble proteins can diffuse out of myocytes and be detected in blood as well.⁶ In addition, postmortem studies show that microinfarcts often precede myocardial infarction and sudden death in patients with unstable angina.^{21,22} Unstable angina is a critical phase of ischaemic heart disease. The early release of glycogen

phosphorylase may help to identify high risk patients, even on admission to the hospital, and concentrations of the BB isoenzyme could help to guide decisions about patient management.

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