Clinical efficacy of intravenous lipoxygenase inhibitor quercetin in patients with acute ST-segment elevation myocardial infarction: results of a prospective randomized open-label trial

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Summary

Objectives: Although significant progress has been made in treatment of patients with acute coronary syndromes (ACS) sometimes outcomes remain unsatisfactory even after early reperfusion. There is experimental data on anti-ischemic properties of bioflavonoid quercetin and its capability to limit size of myocardial infarction (MI) and to prevent left ventricular (LV) remodeling. We have hypothesized that addition of intravenous quercetin to standard therapy would limit size of infarction in patients with acute ST-segment elevation myocardial infarction (STEMI).

Design and Methods: In open-label trial patients admitted for acute STEMI within 6 hrs from symptoms onset were randomized either to quercetin ($n = 93$) or to control group ($n = 105$). Quercetin infusion was started within 30 minutes after admission and was repeated during 5 days. All patients received standard therapy and were consented. Echocardiography was performed on the 1st and 10th day after admission. Mass of necrotic myocardium was calculated using serial serum CK-MB measurements. Diene conjugates and leukotriene C_4 (LTC_4) were assessed at 2, 24, 96, 120, 216 hrs from start of quercetin infusion. Statistical analyses were performed using SPSS 11.0.

Results: Received data proves that quercetin inhibits lipoxygenase activity in vivo and causes remarcable decrease in LTC_4. Steady decrease in serum diene conjugates was observed in quercetin group ($p < 0.05$). Mass of myocardial necrosis was 26.4% less in treatment than in control group (45.4 ± 2.1 and 61.6 ± 2.9 g/eq, $p < 0.001$. Echocardiographic data suggests that early administration of quercetin impacts cardiac hemodynamics preventing LV dilatation and increasing ejection fraction.

Conclusion: Quercetin decreases serum concentration of leucotriene C_4 and inhibits lipids peroxidation. Early administration of quercetin in patients with STEMI decreases mass of myocardial necrosis and facilitates improvement of LV contractility.

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Early reperfusion of cardiac tissue is now considered to be the most efficacious strategy in the prevention of progression towards necrosis of cardiac myocyte and in restoring the cellular function altered by ischemia [1–6]. Functional recovery is not immediate and often depends on the extent of reperfusion injury [2]. Contractile dysfunction (stunning) may last for several hours or even days after the start of reperfusion [7,8]. Cellular mechanisms underlying the reperfusion syndrome may involve over-production of oxygen-derived free radicals, acidosis and/or the development of the inflammatory reaction and cellular Ca^{2+} overload [9].

Previous experimental studies have shown that the use of the bioflavonoid quercetin i.v. form is associated with anti-ischemic effects, limitation of left ventricular (LV) remodelling and stabilization of cardiomyocyte membranes [10–13]. The existing data suggests lipoxygenaze blocking properties of quercetin [10,13]. The aim of the present study was to investigate whether the addition of intravenous quercetin to standard ther-

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apy would limit the infarct size of patients with acute ST-segment elevation myocardial infarction (STEMI).

Methods

In order to evaluate the efficacy of the intravenous form of quercetin, 198 consecutive patients with STEMI (mean age 53.2 ± 0.7 years) were hospitalised within the first 6 hours (3.7 ± 0.1 hours) from the onset of the symptoms. Patients were randomised to the quercetin group and received iv quercetin ($n = 93$), or to the control group ($n = 105$). The infusion of quercetin was started within 30 minutes after admission and was further performed repeatedly during 5 days using an original scheme. All the patients gave informed consent, the study was approved by local ethics committee.

Inclusion criteria were: signs and symptoms of ST-segment elevation acute myocardial infarction (AMI), randomisation within 6 hours from the onset of the symptoms, age ≥ 21 years. Exclusion criteria were: cardiogenic shock (Killip IV), decompensated diabetes mellitus, uncontrolled hypertension, hepatic and severe renal insufficiency (serum creatinine ≥ 265 μmol/l) and coagulopathy.

All the patients underwent 2D echocardiography on the 1st and the 10th day after admission. The mass of necrotic myocardium was calculated using serial serum CK-MB measurements. Diene conjugates and leukotriene C_4 (LTC_4) were assessed repeatedly at 2, 24, 96, 120, 216 hours from the start of quercetin infusion. Statistical analyses were performed using SPSS 11.0 software.

Results

The study groups did not differ in terms of demographic characteristics (sex, age), time to admission and main clinical characteristics (history of hypertension, angina and prior MI). All the patients received conventional therapy at the discretion of a physician. The summary of received treatments is presented in Table 1.

Study results have demonstrated substantial inhibition of lipids super-oxidation which was associated with steady decrease in the serum diene conjugates level which is detectable already at 2 hours after the start of drug infusion with maximal effect achieved at the 5th day of MI (Figure 1). This pattern persisted throughout the 10-days study period. Furthermore, our data proved that quercetin inhibited lipoxygenase activity in vivo and rendered significant decrease in LTC_4 levels during the entire study period (Figure 2).

Peak levels of CK-MB were similar in both study groups and comprised 0.23 ± 0.01 mccat/l in the quercetin and 0.26 ± 0.01 mccat/l – in the control groups. This implies that patients were comparable in terms of baseline infarct size. Time to the peak of CK-MB was greater in the control group (13.9 ± 0.6 vs 9.9 ± 0.4 hours in the quercetin group, $p < 0.001$). The mass of myocardial necrosis calculated using the dynamics of serum CK-MB was 26.4% less in the treatment rather than in the control group (45.4 ± 2.1 and 61.6 ± 2.9 g/eq, $p < 0.001$), which resulted from the shortening of CK-MB normalization times in the quercetin group as compared to the control group (37.5 and 49.0 hours, respectively, $p < 0.001$) (Figure 3). Relatively early the peak of

Table 1.
Concomitant medications and procedures

	Quercetin ($n = 93$), %	Control ($n = 105$), %	*P*-value
TLT	45.2	48.6	NS
PTCA	27.9	20.0	NS
Aspirin	100.0	96.2	NS
Beta-blockers	98.9	95.2	NS
ACE inhibitors	69.9	79.0	NS
Heparin	98.9	98.1	NS
Nitrates	95.7	88.0	NS

PTCA – percutaneous transluminal coronary angioplasty; TLT – thrombolytic therapy.

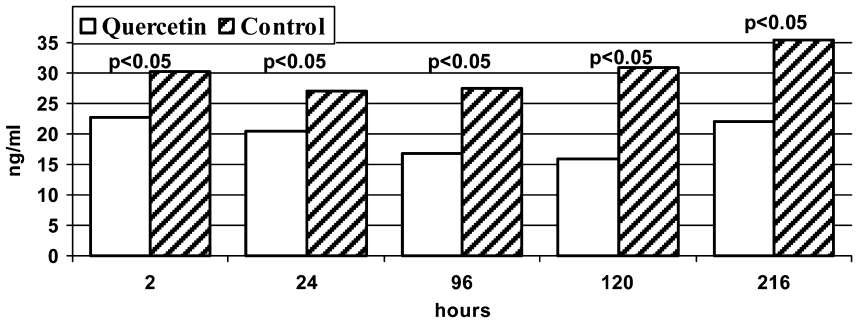

Figure 1. Dynamics of diene conjugates in patients with acute myocardial infarction.

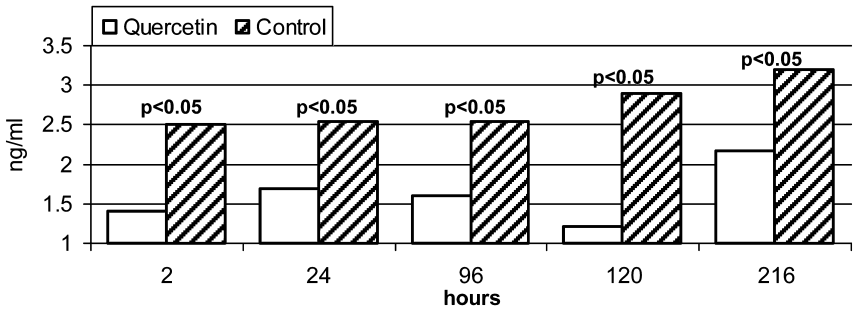

Figure 2. Dynamics of leucotriene C_4 in patients with acute myocardial infarction.

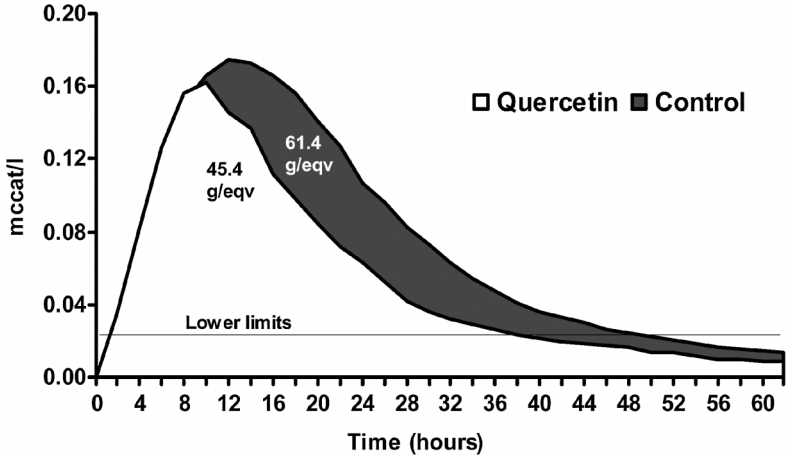

Figure 3. Infarct size index and normalization time of CK-MB.

CK-MB activity could possibly result from more rapid formation of the necrotic zone and the shortening of normalization times and may be associated with the prevention of further damage of cardiac myocytes in the quercetin group. The comparison of the infarct size index in the study groups is represented in Figure 4.

Echocardiographic data suggests that early administration of quercetin impacts cardiac hemodynamics preventing left ventricular dilatation. During 10-days study period end-diastolic index (EDI) and end-systolic indices remained unchanged in quercetin group whereas trend towards increase in EDI was observed among controls. LV ejection fraction significantly increased in the treatment group (8.8%, $p < 0.05$) and slightly increased in the control group (5.9%, $p > 0.05$) (Figure 5).

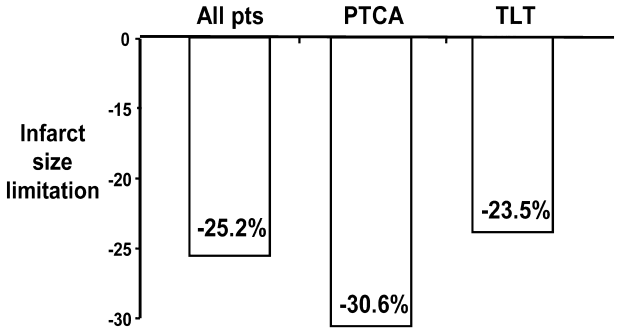

Figure 4. Limitation of infarct size index in patients with acute ST-segment elevation myocardial infarction. PTCA – percutaneous transluminal coronary angioplasty; TLT – thrombolytic therapy.

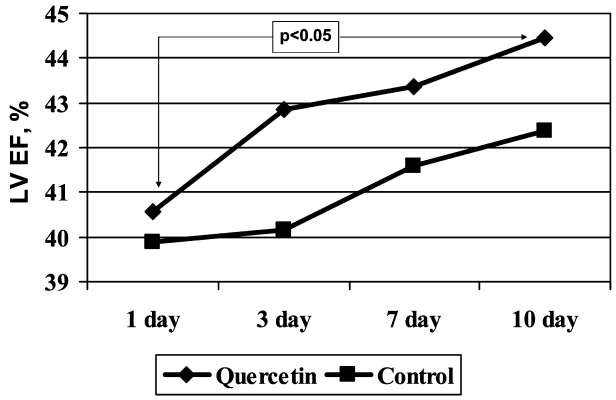

Figure 5. Dynamics of left ventricular ejection fraction.

Discussion

Despite substantial progress in the treatment of patients with acute coronary syndromes (ACS) has been made, mortality following STEMI remains high [14]. The use of conventional medical therapies such as antiplatelets, anticoagulants, β-blockers, nitrates is not always efficacious [15]. Although the early use of revascu-

larization techniques and thrombolytic therapy improves outcomes of the patients with STEMI [4,14], sometimes complete restoration of coronary blood flow cannot be achieved. Reperfusion injury and no-reflow syndrome have been described as a phenomena associated with poor tissue perfusion.

Prevention of complications of ACS requires limitation of metabolic disorders, which occur in cardiomyocytes from the first minutes of ischemia and lead to further progressive myocytes' damage [16]. Therefore myocardial protection techniques from ischemia-reperfusion are being extensively developed [17–19].

Whereas early studies on cardioprotection concentrated on the exploration of metabolic properties of hemodynamically active drugs, nowadays attention is focused on antioxidants, inhibitors of catabolic enzymes and membrane-protective drugs [17]. It has been established that in the settings of acute coronary syndromes phospholipase activation is associated with degradation of the phospholipids membrane bi-layer and accumulation of unsaturated fatty acids (e.g., arachidonic and linolenic acids). The above process along with the activation of oxidases (e.g., lipoxygenase) leads to the three important consequences such as: (1) synthesis of biologically active substances (leukotrienes, lipoxines, lysophospholipids) with pronounced coronaroconstrictory, procoagulant, arrhythmogenic and chemoattractory properties; (2) synthesis of free radicals, especially lipoxygenase-induced; (3) accumulation of polymorphonuclear neutrophils – cells with significant super-oxidative, lipoxygenase and proteolytic properties. The described pathways form a vicious circle and further progression of ischemic cell injury. It could be assumed that the distortion of above relationships via the inhibition of such enzymes as phospholipase A2, lipoxygenase and therefore inhibition of peroxidation could be important in the treatment of AMI and reperfusion syndrome. Worthy of note, that the speed of the development of metabolic disorders requires urgent therapy which could be achieved using intravenous route of administration of drugs.

Distinctive features of an intravenous form of quercetin are potent anti-oxidative effect, inhibition of enzymes responsible for membrane stability (especially lipoxygenase), modulation of nitric oxide levels in damaged tissue and in bloodstream and protection of membrane-associated enzymes responsible for cell ion homeostasis [2]. It has been demonstrated that quercetin inhibits several anti-oxidizing enzymes, namely lipoxygenases [11–13]. A soluble intravenous form of quercetin is relatively new and was developed in late 90-ties. As the results of non-human experimental research and in vitro data may not be readily translated into clinical practice, we have studied several metabolic effects of quercetin in patients with acute STEMI.

Our study proved that quercetin inhibits lipoxygenase in vivo and has anti-oxidative activity decreasing serum levels of diene conjugates. This possibly results in the decrease of myocardial susceptibility to ishcemia/reperfusion. As it has been already noted derivatives of lipoxygenase pathway of arachidonic acid metabolism (leukotrienes, lipoxines) are powerful vasoconstrictors, they stimulate platelet aggregation and have proarrhythmic properties [17].

The extent of necrosis and the speed of formation of the necrotic zone are the main factors determining the prognosis of patients with STEMI [1,2,5,15]. There is a body of evidence that enzymatic estimates of the infarct size correlate with functional and clinical outcomes of AMI patients [20,21]. Therefore, our data on infarct size limitation as a consequence of quercetin use has a sufficient theoretical and experimental background. There is close relationship between the infarct size and the development of heart failure or the onset of cardiac arrhythmias [19]. Timely protection of viable myocardium from progressive injury could be capable of infarct size limitation [8] and prevention of left ventricular remodelling [22]. This hypothesis has been supported by our study results, which demonstrate positive trends in cardiac hemodynamics in the quercetin group as compared to the control group.

Study limitations

This study was randomised but open-labelled and might involve a certain extent of biases associated with this matter. The study was conducted on a relatively small sample size and did not allow extensive subgroup analyses.

In addition, although differences among the study groups in concomitant treatments did not reach statistical significance in the quercetin group, percutaneous coronary intervention was performed 7.9% more often. On the other hand, the control group received ACE inhibitors 10% more frequently and 8% less nitrates which might have some influence on the study results.

Conclusions

An intravenous form of bioflavonoid quercetin irreversibly blocks lipoxygenase pathway of arachidonic acid metabolism, decreases serum concentration of leucotriene C_4 and inhibits lipids peroxidation diminishing levels of diene conjugates. Early administration of intravenous quer-

cetin in patients with ST-segment elevation myocardial infarction decreases the mass of myocardial necrosis and shortens time to peak and normalization of CK-MB. Quercetin prevents left ventricular dilatation and facilitates the improvement of left ventricular contractility. Study results give the background for further randomised placebo-controlled multicenter study for the efficacy of quercetin in the settings of acute coronary syndromes.

References

[1] Anderson J, Karagounis L, Califf R. Meta-analysis of five reported studies on the relation of early coronary potency grades with mortality and outcomes after acute myocardial infarction. *Am J Cardiol* 1996; 78: 1–8.

[2] Braunwald E. Myocardial reperfusion limitation of infarct size, reduction of left ventricular dysfunction and improved survival. Should the paradigm be expanded? *Circulation* 1989; 79: 441–444.

[3] Ellis AK, Little T, Masud AR, Liberman HA, Morris DC, Klocke FJ. Early noninvasive detection of successful reperfusion in patients with acute myocardial infarction. *Circulation* 1988; 78: 1352–1357.

[4] Hearse DJ. Myocardial Injury During Myocardial Ischemia End Reperfusion: Concepts and Controversies. NY. Raven Press 1992: 13–32.

[5] Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994; 343: 311–322.

[6] Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction: potential mechanisms and early predictors. *Circulation* 1993; 87: 755–763.

[7] Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. *Am J Cardiol* 1994; 74: 1220–1228.

[8] Kloner RA, Bolli R, Marban E, Reinlib L, Braunwald E. Medical and cellular implication of stunning, hibernation, and preconditioning. An NHLBI workshop. *Circulation* 1998; 97: 1848–1867.

[9] Opie LH. The mechanism of myocyte death in ischemia. *Eur Heart J* 1993; 14: S31–33.

[10] Huk I, Brovkovich V, Nanobashvili I, et al. Bioflavonoid quercetin scavenges superoxide and increases nitric oxide concentration in ischemic-reperfusion injury: an experimental study. *Br J Surg* 1998; 85: 1080–1085.

[11] Parkhomenko AN, Kozhukhov SN, Irkin OI, et al. Cardioprotective effects of 5-lipoxygenase inhibitor quercetine in thrombolysed patients with acute myocardial infarction (abstr.). *Eur Heart J* 2000; 21 (Suppl): 476.

[12] Kolchin YuN, Popovich LF, Grabovskii LA, Luik AI, Moibenko AA. The effect of the 5-lipoxygenase inhibitor quercetin on the functional and morphologic manifestations of myocardial lesions in ischemia and reperfusion of the heart. *Kardiologiia* 1990; 30: 72–75.

[13] Kozhukhov S, Parkhomenko A, Moibenko A. Cardioprotective effect of lipoxygenase inhibitor Quercetin in acute myocardial infarction with left ventricular heart failure (abstr). *Eur Heart J* 2003; 24 (Suppl): 620.

[14] Sana S, Kesteloot H, Kromhout D. On behalf of the Task Force of the European Society of Cardiology on Cardiovascular Mortality and Morbidity Statistics in Europe. The burden of cardiovascular diseases mortality in Europe. *Eur Heart J* 1997; 18: 1231–1248.

[15] Van Domburg RT, Sonnenschein K, Nieuwlaat R, et al. Sustained benefit 20 years after reperfusion therapy in acute myocardial infarction. *J Am Coll Cardiol* 2005; 46: 15–20.

[16] Zarco P, Zarco MH. Biochemical aspects of cardioprotection. *Medicographia* 1996; 18: 18–21.

[17] Kubler W, Haas M. Cardioprotection: definition, classification and fundamental principles. *Heart* 1996; 75: 330–333.

[18] Kober G, Pennaforte S, Buck T, Sievert H, Vallbracht C. Myocardial protection during percutaneous transluminal coronary angioplasty. *Eur Heart J* 1993; 14: 6–12.

[19] Kloner RA, Rezkalla SH. Cardiac protection during acute myocardial infarction: where do we stand in 2004? *J Am Coll Cardiol* 2004; 44: 276–286.

[20] Sobel BE. Enzymatic diagnosis of infarction. *West J Med* 1977; 127: 505–509.

[21] Turer A, Mahaffey K, Gallup D, et al. Enzyme estimates of infarct size correlate with functional and clinical outcomes in the setting of ST-segment elevation myocardial infarction. *Curr Control Trials Cardiovasc Med* 2005; 6: 12.

[22] Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the "no-reflow" phenomenon. A predictor of complications and left ventricular remodelling in reperfused anterior wall myocardial infarction. *Circulation* 1996; 93: 223–228.