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Effects of ribose on exercise-induced ischaemia in stable coronary artery disease

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There is no established treatment specifically aimed at protecting or restoring cardiac energy metabolism, which is greatly impaired by ischaemia. Even after reperfusion, myocardial content of ATP remains low for more than 72 h. Long-term post-ischaemic dysfunction and irreversibility of ischaemic damage have been associated with low ATP content. Evidence that the pentose sugar ribose stimulates ATP synthesis and improves cardiac function led us to test the possibility that ribose increases tolerance to myocardial ischaemia in patients with coronary artery disease (CAD).

20 men with documented severe CAD underwent two symptom-limited treadmill exercise tests on 2 consecutive days; we postulated that the ischaemia induced might bring about changes in ATP metabolism lasting for several days. Patients whose baseline tests showed reproducibility were randomly allocated 3 days of treatment with placebo or ribose 60 g daily in four doses by mouth. Exercise testing was repeated after treatment on day 5. At that time mean (95% confidence interval) treadmill walking time until 1 mm ST-segment depression was significantly greater in the ribose than in the placebo group (276 [220–331] vs 223 [188–259] s; $p=0.002$). The groups did not differ significantly in time to moderate angina. In the ribose-treated group the changes from baseline to day 5 in both time to ST depression and time to moderate angina were significant ($p<0.005$), but these changes were not significant in the placebo group.

In patients with CAD, administration of ribose by mouth for 3 days improved the heart's tolerance to ischaemia. The presumed effects on cardiac energy metabolism offer new possibilities for adjunctive medical treatment of myocardial ischaemia.

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Introduction

Although myocardial ischaemia has profound effects on the heart's energy metabolism, there is no available treatment specifically aimed at preventing or correcting the changes. This is an important limitation of current treatment, since normal heart function and tissue preservation constantly require large amounts of energy derived from the hydrolysis of ATP. ATP is believed to be the main intermediary between energy-creating and energy-requiring reactions in myocardial cells. ATP stores in the heart are very limited—sufficient for less than 1 min of contraction.¹ During myocardial ischaemia, content of ATP and creatine phosphate, the chief reserve source of high-energy phosphate, declines rapidly.^{2,3} When reperfusion occurs (spontaneously or as a result of therapeutic measures) before the tissue is irreversibly damaged, creatine phosphate content returns to normal within minutes; thus, cellular

energy-producing mechanisms are intact.⁴ By contrast, despite reperfusion, ATP concentrations take 72–96 h to recover,^{5,6} and a recovery time of more than 7 days has been reported after global ischaemia.⁶ Low myocardial ATP content has been associated with extended post-ischaemic dysfunction such as is observed in stunned myocardium. In some studies, ATP concentrations correlate with irreversibility of ischaemia, cell death, and the preservation and return of contractile performance after ischaemia.^{2,7}

Factors that prevent faster post-ischaemic restoration of ATP concentrations have been identified. Myocardial ischaemia leads to degradation of ATP, and the dephosphorylated derivatives diffuse out of the myocyte into the extracellular space where they are no longer available as precursors for immediate ATP resynthesis in the salvage pathway.^{8,9} Spontaneous or therapeutically induced reperfusion augments such loss of ATP metabolites. Thus, when blood flow is re-established, restoration of ATP content depends primarily on de-novo synthesis. This process is slow in the heart¹⁰ because the essential precursor 5-phosphoribosyl-1-pyrophosphate (PRPP) is in short supply.¹¹ Exogenous ribose, a pentose sugar, bypasses rate-limiting steps in the oxidative pentose phosphate pathway that generates this precursor. This sugar increases the myocardial pool of the precursor¹² and accelerates ATP synthesis.^{12,13} Ribose-induced increases in ATP concentrations have been associated with improved post-ischaemic ventricular performance in animals,^{14,15} and less severe ischaemic cell damage has been reported.¹⁶ There is strong evidence that ribose would be able to have these beneficial effects in man too.^{3,9,17–19} In this study we tested the hypothesis that ribose increases tolerance to myocardial ischaemia in patients with coronary artery disease (CAD).

Patients and methods

We studied 20 men, aged 45–69 years, who had CAD documented by coronary arteriography ($\geq 75\%$ narrowing of at least one main vessel) and a history of angina induced by normal daily activities (table). 3 patients had had myocardial infarctions previously. Before entry to the study each patient had to have a positive treadmill test. An exercise test was judged positive when there was ischaemic ST-segment depression (≥ 1 mm [0.1 mV], horizontal or downsloping, persisting for at least 80 ms after the J point in the electrocardiogram) and angina during the first 9 min of exercise according to the Bruce protocol. Results of exercise tests were accepted as reproducible when the times of onset of ST-segment depression and of moderate angina on day 2 were within 60 s of the respective times on day 1. 4 patients who met all other entry criteria did not show reproducibility and were therefore excluded. During the study, patients continued their usual medication (nitrates, calcium-channel antagonists, beta-blockers) provided it did not change during the 72 h before the first exercise

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BASELINE CLINICAL CHARACTERISTICS OF STUDY PATIENTS

Patient	Age (yr)	Stenosis*	Treatment
Ribose group			
1	68	75% LAD, 99% RCA	B, C
2†	53	99% LAD, 50-60% CX, 75% RCA	B, C, N
3	50	100% LAD, 50% CX, 99% RCA	B
4	61	90% LAD, 99% CX, 100% RCA	C, N
5†	56	100% RCA	B, C, N
6	53	99% CX, 100% RCA	C, N
7	64	75-90% LAD, 75-90% CX, 90% RCA	B, C, N
8	55	99% LAD, 40% CX, 50% RCA	C, N
9	65	75-99% LAD, 99% CX, 75% RCA	C, N
10	45	100% LAD, 50% CX, 100% RCA	B, N
Placebo group			
11	53	99% LAD	B
12	53	75-99% LAD, 75-99% CX, 75-99% RCA	B, N
13	62	70% LAD, 70% CX, 80% RCA	B
14	69	100% LAD, 50% CX, 99% RCA	B, N
15	45	90% LAD	B, N
16†	50	100% LAD, 75% CX, 90% RCA	C, N
17	52	75% LAD, 50% CX, 100% RCA	B, C, N
18	67	100% LAD, 75-100% CX, 100% RCA	B, N
19	60	90% LAD, 100% RCA	B, C, N
20	62	70% LAD, 50% CX, 90% RCA	B, N

LAD = left anterior descending artery; CX = circumflex artery; RCA = right coronary artery; B = beta-blockers; C = calcium-channel antagonists; N = nitrates.

*An artery with $\geq 70\%$ stenosis was considered diseased.

†Had previously had myocardial infarction.

test. On each day of exercise testing, morning doses were withheld until after the test. Reasons for exclusion were unstable angina, myocardial infarction within the previous 3 months, previous heart surgery, evidence of heart failure, left main coronary artery stenosis, valvular heart disease, any other non-coronary heart disease, any disorder rendering the ST segment in the exercise electrocardiogram unclear (eg, left bundle branch block), and compromised gastrointestinal absorption. Study patients had to be able to perform treadmill walking exercise and had no symptomatic peripheral vascular disease. All patients gave informed written consent. The study protocol was approved by the University of Munich Medical School Ethics Committee.

Exercise tests were done on a motor-driven treadmill according to the Bruce protocol. All patients were familiar with the procedure. The skin was prepared for a 12-lead electrocardiogram by shaving, cleansing with acetone, and abrasion with emery paper. At the first exercise test, lead position was marked with permanent dye for precise application on subsequent tests. During exercise, 3 standard electrocardiographic leads were continuously monitored. ST-segment deviation was measured in all leads by a computerised system with subsequent manual over-reading. In cases of discrepancy between the computer-processed signal and real-time electrocardiography recordings, the latter were used for analysis. On each day with exercise tests scheduled, the patient came to the laboratory after an overnight fast without having taken any drugs that morning. All three exercise tests for each patient were done under identical external conditions, at the same time of the morning with constant room temperature and humidity. All exercise tests were carried out by the same physician. If ST-segment depression did not occur in post-treatment exercise tests before the exercise was stopped at the onset of moderate angina, total exercise time was used for time to ST depression. Patients were instructed to continue exercise until they had angina of moderate severity (chest pain of such severity that the patient would normally stop activity).

Because the carryover effects of ribose are unknown, a crossover design was judged inappropriate. If a patient showed reproducible exercise tests on days 1 and 2 he was randomly allocated, by means of a table of random numbers, treatment with ribose or placebo for 3 days (starting after the exercise test on day 2 and continuing to day 4). A final exercise test was done on day 5 to assess treatment effects. We postulated that two consecutive exercise tests to the point of myocardial ischaemia would induce changes in cardiac energy metabolism lasting for more than 72 h.

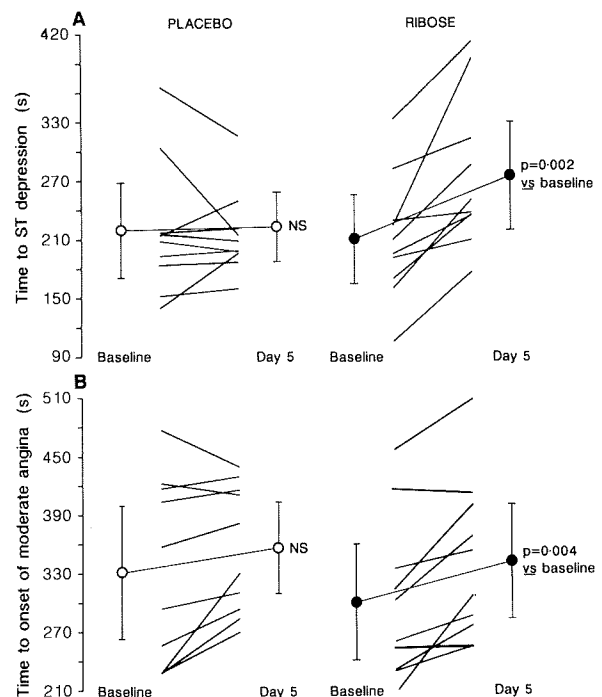
Patients in the ribose group received 60 g D-ribose daily, dissolved in water, in four doses of 15 g. Because of possible hypoglycaemic responses to ribose²⁰ patients were asked not to take ribose while fasting. The dosage was based on reports of animal experiments that showed the efficacy of high doses of ribose¹⁴ and on human studies^{21,22} showing that 60 g per day is well tolerated and not associated with gastrointestinal side-effects. The placebo solution contained mainly an equicaloric amount of glucose. It was identical to ribose solution in taste, colour, and appearance as assessed by a pretrial experiment with 10 hospital staff. Purity of substances was checked by the hospital pharmacy.

The sample size was prospectively chosen on the grounds of clinical practicability. The paired *t* test was used for within-group comparisons. Analysis of covariance was used to adjust for baseline measurement in between-group comparisons. $p < 0.05$ (two-tailed) was considered to indicate significance.

Results

In the ribose-treated group, the mean walking time until 1 mm ST-segment depression was significantly greater on day 5 than at baseline (figure, A), whereas there was no significant change in time to ST depression in the placebo group ($p = 0.67$). 2 ribose-treated patients did not show ST depression on day 5, so time to the onset of moderate angina was used in the analysis. After treatment, the time to ST depression (day 5) was significantly longer in the group that had received ribose than in the placebo-treated group (mean and 95% confidence interval [CI] 276 [220-331] vs 223 [188-259] s; $p = 0.002$).

The time to onset of moderate angina also increased significantly from baseline to day 5 in the ribose group (figure, B); there was an increase in this variable in the placebo group but it did not achieve significance ($p = 0.062$). There was no significant difference between the ribose and placebo groups in mean time to onset of moderate angina on



Treadmill walking times until ST-segment depression (A) and onset of moderate angina (B).

Baseline = average of results on days 1 and 2 for each patient; day 5 = after 3 days treatment. Mean and 95% confidence intervals given for each group.

day 5 (343 [284–402] vs 357 [310–404] s; $p=0.53$). There were no significant changes in heart rate, systolic blood pressure, or rate-pressure product.

Ribose was generally well tolerated. 2 patients had episodes of slight discomfort 30 min and 2 h, respectively, after the first 15 g dose of ribose. The symptoms were not typical of hypoglycaemia, and plasma glucose was not measured. Neither patient experienced any more symptoms during further treatment. 1 patient reported mild gastrointestinal discomfort during day 4 (3rd treatment day). In the ribose group, serum uric acid increased to 440–500 $\mu\text{mol/l}$ (7.4–8.4 mg/dl) in 3 patients, and 2 patients had moderately high aminotransferase and gammaglutamyl transpeptidase activities in serum. 1 of the latter was taking lovastatin, which is known to cause rises in serum aminotransferases. The other had a history of symptomless increases in aminotransferases for the previous year; there was no indication of acute myocardial infarction. The patient had drunk alcohol before and during the study. He was feeling well and refused further evaluation.

Discussion

Although myocardial ischaemia is primarily regarded and treated as a disease of myocardial perfusion, it is the changes in myocardial metabolism that bring about the detrimental effects of ischaemia. The effects of cardiac ischaemia on the heart's energy metabolism are not limited to the period of reduced perfusion. ATP is low for several days even after brief periods of ischaemia and despite reperfusion.^{5,6} Ischaemic episodes followed by reperfusion are common in patients with CAD. They are also characteristic of commonly used therapeutic interventions such as thrombolysis, percutaneous transluminal coronary angioplasty, and surgical revascularisation, all of which are inevitably associated with substantial disturbances of cardiac energy metabolism. The lack of medical treatment aimed directly at impaired cardiac energy metabolism is therefore surprising.

In this study, repeated temporary ischaemia was induced by two exercise tests within 24 h. By this means, we hoped to bring about changes of cardiac energy metabolism lasting for more than 72 h⁵ so that we could test the effects of ribose on tolerance to ischaemia on a subsequent test. Ribose does not affect coronary blood flow, myocardial oxygen consumption, or overall haemodynamics.^{13,19}

Our findings show that in severe CAD oral ribose improves tolerance to ischaemia. The mean increase in treadmill walking time until ST depression with ribose is equivalent to a rise of more than 30%. Interpretation of these data should take into account the fact that the exercise protocol used is characterised by large increments of work per time, thus the observed improvement has greater clinical relevance. ST depression is a widely accepted indicator of ischaemia, and although the precise mechanism has not been established there is ample evidence of a substantial contribution from disturbed ion transport driven by energy-consuming ATPases.^{23,24} Treadmill walking time until the development of moderate angina increased in both groups. This finding is consistent with a strong placebo effect commonly observed in studies involving an active procedure.²⁵ The aetiology of angina is not completely understood. ATP concentrations are only one possible factor. In a study of exercise testing with nuclear magnetic resonance imaging, few patients with CAD reported angina despite demonstrable changes in high-energy phosphate concentrations.³

Some ribose-treated patients improved only slightly (figure). We cannot venture an explanation for this lack of response. Plasma ribose concentrations were not measured, since earlier studies had shown almost complete absorption of ribose taken by mouth.²² We therefore have no proof that adequate blood concentrations were achieved in all patients. Although it has been shown that ribose is effective when administered with various types of cardiac drug therapy,²⁶ the continued treatment in our patients may have affected the results. The study design however reflects the concept that ribose might be used in addition to conventional drug therapy.

The role of overall cardiac ATP concentrations after ischaemia remains controversial. Several studies have found a good correlation between ATP content and heart function,⁷ but no direct link between low ATP content and post-ischaemic dysfunction has been unequivocally shown,²⁷ and a lack of association between ATP concentrations and post-ischaemic recovery has been reported. From the fact that stunned myocardium can be stimulated by inotropic agents, it has been concluded that low ATP concentrations are not the cause of post-ischaemic dysfunction.²⁸ Others have claimed that ATP availability at specific sites of the myocyte is more important than its overall concentration or have found signs of defects in the transduction of energy.²⁹ Nevertheless, the undisputed importance of ATP for all energy-requiring processes in the heart cannot be ignored. It is well known that ATP content is low after ischaemia and recovers extremely slowly after reperfusion. Because ATP is essential, we found it reasonable to assume that lowering of ATP content below a certain point, still unknown, will compromise energy-requiring processes. ATP concentrations about 20% of pre-ischaemic control are associated with irreversible ischaemic injury.^{2,27} Similarly, we assumed that increasing ATP content above these points would be beneficial.

In two trials of patients with CAD, nearly twice as many reversible thallium-201 defects were identified after ribose infusion than after placebo; thus ribose improves the detection of viable ischaemic myocardium. Perlmutter et al^{18,19} speculated that this is the result of metabolic effects of ribose on ²⁰¹Tl kinetics. Administration of ribose leads to symptomatic improvement in patients with myoadenylate deaminase deficiency, the commonest inherited enzyme disorder of skeletal muscle.²¹

Reports on the use of ribose in human beings mention no lasting or damaging side-effects. Reported untoward effects include diarrhoea, gastrointestinal discomfort, nausea, headache, and hypoglycaemia.^{20,21} Ribose-induced insulin secretion has been postulated as an explanation^{19,20} but this was not found consistently.¹⁸ We took precautions to avoid hypoglycaemia. Patients received ribose orally in divided doses and were not in a fasting state when they took it. They were also educated about the symptoms of hypoglycaemia and its self-treatment. In cell cultures human lymphocyte proliferation is inhibited by high ribose concentrations.³⁰ At concentrations associated with high-dose oral administration,^{21,22} however, we found no inhibiting effect (unpublished). Labelled ribose enters the myocardium and the label is found in adenine nucleotides such as ATP.¹²

Our results suggest that ribose can effectively influence cardiac energy metabolism. Further studies to determine its usefulness as adjunctive drug therapy for myocardial ischaemia are warranted. Metabolic cardioprotection with ribose might be especially advantageous for patients undergoing heart surgery or in unstable CAD with jeopardised myocardium.

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