Heart Metab. (2014) 63:23–28

Focus on trimetazidine: effects on diet and the heart

Roberto Ferrari
Department of Cardiology and LTTA Centre, University Hospital of Ferrara and Maria Cecilia Hospital, GVM Care & Research, E.S. Health Science Foundation, Cotignola, Italy

Correspondence: Roberto Ferrari, MD, Chair of Cardiology, Azienda Ospedaliero-Universitaria di Ferrara, Ospedale di Cona, Via Aldo Moro 8, 44124 (Cona) Ferrara, Italy.
E-mail: fri@unife.it

Abstract

Trimetazidine, a clinically effective antianginal agent that has no negative inotropic, chronotropic, or vasodilator properties, mediates a general improvement in cardiac metabolism. It has been suggested that trimetazidine may exert its antianginal effect by inhibiting fatty acid oxidation and improving glycolysis and glucose oxidation. Trimetazidine is a partial inhibitor of long-chain 3 ketoacyl-coenzyme A thiolase, the enzyme catalyzing the last step of free fatty acid β-oxidation; therefore, inhibiting fatty acid oxidation. The inhibition of free fatty acids oxidation with trimetazidine in coronary artery disease patients with or without diabetes improved cardiac metabolism at rest and during stress. For this reason, the recent European Society of Cardiology guidelines on stable coronary artery diseases suggest that trimetazidine be used as an add-on drug that improves cardiac metabolism. ■ Heart Metab. 2014;63:23–28

Keywords: Adenosine triphosphate; angina; ATP; ATP/O_2; β-oxidation; cardiac metabolism; fatty acid oxidation; ischemia; trimetazidine.

Trimetazidine is a clinically effective antianginal agent that has no negative inotropic, chronotropic, or vasodilator properties. Thus, trimetazidine is different from the "classical" antianginal agents such as nitrates, β-blockers, calcium channel blockers, or ivabradine as it does not affect myocardial oxygen consumption and blood supply. Experimentally, the beneficial effect of this agent has been attributed to the preservation of myocardial energy stores,[1] reduction in intracellular acidosis,[2] calcium overload,[3] and free radical injury caused by ischemia.[4] It follows that the effects of trimetazidine are mediated by a general improvement in "cardiac metabolism," which is threatened and/or altered in: (i) the condition of transient oxygen deficiency such as angina; (ii) prolonged ischemia such as myocardial infarction (MI); or (iii) chronic hypoxia such as heart failure (HF). A relevant question is what the overused wording "cardiac metabolism" means and how it is altered in pathological conditions and, more relevantly, how it can be changed for the better by trimetazidine, which is the main topic of this issue of Heart and Metabolism.

The purpose of this short review is to analyze the meaning of "cardiac metabolism" for the clinician and to address the existing evidence that trimetazidine exerts an antianginal effect. By no means is the purpose to review the complexities of heart metabolism, which has been properly addressed elsewhere.[5,6,7] The idea is to try to provide the reader with the essential information to help decide when, why, and in which patients to add trimetazidine to the classical

Heart Metab. (2014) 63:23–28

Abbreviations

CAD: coronary artery disease; **CoA:** coenzyme A; **FFA:** free fatty acids; **HF:** heart failure; **MI:** myocardial infarction

antianginal agents. As the prevalence of type 2 diabetes mellitus is rapidly increasing and as the distinct metabolic profile of diabetes appears to be important for increasing the risk for coronary artery disease (CAD), a subchapter is dedicated to this topic.

The daily work of the human heart is simply extraordinary: approximately 100 000 beats and more than 9000 liters of blood is ejected into the circulation, which travels about 136 000 km (this is how long our ultramicroscopic circulation is!) in 27 seconds. Obviously, to sustain such continuous work (for all of our life, night and day), the heart consumes a great amount of energy in the form of adenosine triphosphate (ATP), which is produced by the mitochondria (provided there is enough oxygen to support mitochondrial oxidation) and is transferred to the cytosol. Although it is difficult to be precise, it is estimated that the daily energy production of cardiac mitochondria ranges between 10 to 30 kg of ATP. It may sound impossible, but it is not. It is a continuous cycle: ATP is produced by the mitochondria and it is immediately utilized mainly in the cytosol to allow the synchronous contraction of the myofilaments (systole) and the extrusion of Ca^{2+} from the myofilaments to the sarcoplasmic reticulum, the extracellular space, or into the mitochondria (diastole). Of course, ATP is also necessary to support several other processes that are linked to the maintenance of the myocyte structure and function. There is no doubt that the heart is the highest energy-consuming organ in the body; consequently, it contains the highest number of mitochondria compared with other organs. This also explains why the heart is so dependent on oxygen delivery through the coronary arteries to feed mitochondrial oxidation. Interestingly, the myocardial oxygen reserve is almost nonexistent and is just enough to support a few heartbeats. Similarly, the myocardial ATP pool is very limited; the main myocardial energy reserve is represented by creatine phosphate (CP).

Free fatty acid and carbohydrate metabolism

The wording "cardiac energy metabolism" refers to the complex biochemical process that allows the heart to produce enough ATP to support its function and the physiological maintenance of the myocyte structure. As it is shown in *Figure 1*, the ultimate

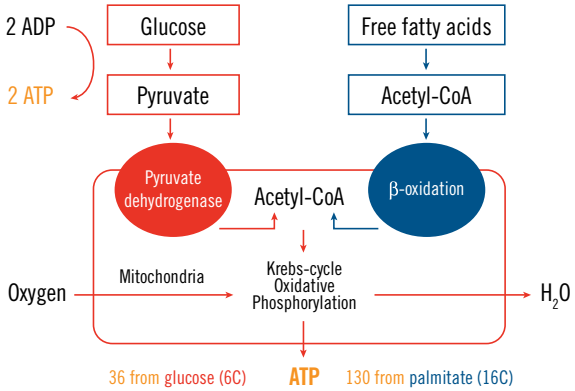

Fig. 1 *Schematic representation of aerobic cardiac metabolism.*

major source of mitochondrial energy production lies in extracellular carbohydrates and free fatty acids (FFAs). Interestingly, the heart has the unique ability to use either carbohydrates (mainly glucose and lactate) or FFAs with continuous alternation between the two, according to their arterial concentrations (ie, after a meal, as the arterial concentration of carbohydrates increase, glucose is the preferred substrate). The metabolism of these substrates merges because, ultimately, they both produce acetyl-CoA, a 2-carbon molecule that is oxidized via the Krebs cycle. In this way, their intrinsic chemical energy can be released for ATP production by oxidative phosphorylation.[5-7] Carbohydrate and FFA degradation to acetyl-CoA, however, involves different metabolic routes, β-oxidation for FFA and glycolysis for carbohydrates *(Figure 1)*.

The metabolism of FFAs is complex. FFAs are generally bound to plasma proteins, namely albumin. They cross the heart membrane (sarcolemma) by passive diffusion, probably with the involvement of a specific intracellular binding protein in the cytosol and are activated at the expense of ATP and coenzyme A (CoA) to form long-chain acetyl-CoA. These cannot enter the mitochondrial matrix where the enzymes for their β-oxidation are located. For this purpose, carnitine is required. Due to the activity of the carnitine transport system, long-chain acetyl-CoA reaches the inner mitochondrial space and can enter the β-oxidation cycle, where their long molecule (16 to 18 carbon) is demolished into several acetyl-CoA molecules that only have 2 carbon

fragments. The cleavage occurs at the level of the second carbon atom, which is the β-position. During the fragmentation of the FFAs, the intrinsic energy contained in the long molecule is released with the formation of $FADH_2$ and $NADH_2$, which in turn, are able to provide the protons required for the eventual production of ATP. In the presence of oxygen, the actual ATP production from FFAs depends on which FFA is involved. If we take palmitic acid as an example, 35 ATP are produced during β-oxidation. In addition, each molecule of palmitic acid (16 carbon) produces 8 acetyl-CoA, which, when passing through the Krebs cycle, generates a total of 131 ATP. ATP is used for activation of acetyl-palmitoyl-CoA. Thus, the total ATP production per one molecule of palmitic acid is 130 ATP molecules, with an ATP/O_2 ratio of 130/23 (meaning that 23 oxygen molecules are used during the entire process), providing an ATP/O_2 ratio of 5.6.[7]

Carbohydrates are broken down by glycolysis, the process that converts one molecule of glucose (actually glucose-6-phosphate, a molecule with 6 carbons) to 2 molecules of pyruvate (a molecule with 3 carbons). For each glucose converted to pyruvate, 4 molecules of ATP are made, but 2 are used to form glucose-6 phosphate, so the net ATP synthesis is 2 ATP. Glycogen, which represents the carbohydrates stored in the myocardium, can form glucose-6-phosphate without requiring ATP. Therefore, for each 6-carbon units of glycogen broken down to pyruvate, 4 ATP will be generated. Such a small production of ATP occurs in the cytosol, not in the mitochondria and, therefore, does not require oxygen. This is particularly relevant under the condition of ischemia (ie, during an angina attack) as it is the only way to allow the formation of ATP in the absence of an oxygen supply. As a result of such a peculiarity of ATP production in the absence of oxygen, glycolysis represents the so-called "anaerobic" metabolism[7] and is the reason why glucose is a better substrate than FFAs for the ischemic heart.

Pyruvate is subsequently converted, this time by an aerobic (oxygen requiring) metabolism to acetyl-CoA. This process occurs in the mitochondrial matrix and requires the activity of a complex enzyme named pyruvate dehydrogenase that allows pyruvate to enter the mitochondria and catalyze the reactions, converting pyruvate into acetyl-CoA.[5,6,7] During this process and with the entry of acetyl-CoA into the Krebs cycle, a further 36 ATP molecules are made, providing an ATP/O_2 ratio of 6, slightly higher than that of palmitate. However, it should be considered that 2 ATP are also formed in the cytosol without any oxygen consumption, yielding a total of 38 ATP per molecule of glucose with an ATP/O_2 ratio of 38/6, providing an ATP/O_2 of 6.3.

Clinical effects of metabolism on heart function

During ischemia, due to the reduction in oxygen availability, there is a severe restriction of mitochondrial function, which leads to accumulation of acetyl-CoA accompanied by potential harmful effects including detergent-provoked damage of membranes and the obvious inhibition of ATP production. At the same time, anaerobic glycolysis is accelerated with an increase in glucose uptake and glycogen degradation because of the breakdown of the remaining ATP and CP (the energy reserve of the myocardium). Pyruvate, however, can no longer enter into the mitochondrial matrix and it is converted into lactate, which is washed out by the myocytes into the extracellular space. Such an accumulation of end products that includes lactate, $NADH_2$, and protons has harmful effects accelerating the ischemic process. Clinically, the release of protons and lactate causes intracellular and extracellular acidosis and, consequently, the typical angina pain *(Figure 2)*. At the same time, acidosis interferes with all of the intracellular calcium movements through the sarcolemma and the sarcoplasmic reticulum. Clinically, this results in the regional left ventricular (LV) dyskinesia or even akinesia, which is always present and coincides with the angina pain. In addition, the concomitant decline of ATP in the ischemic myocytes causes a reduction in the uptake of calcium into the sarcoplasmic reticulum and a

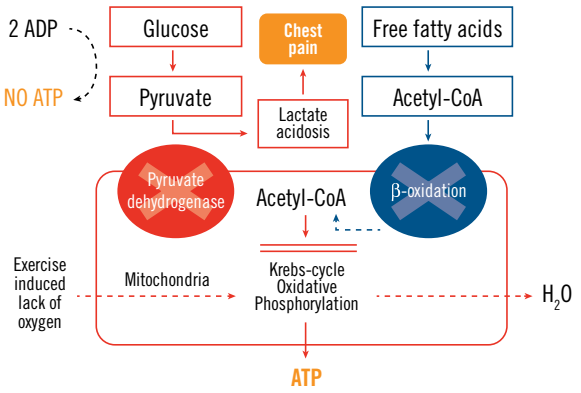

Fig. 2 *Schematic representation of the changes during exercise-induced transient ischemia.*

decreased activity of the sarcolemma calcium pump, with an increased calcium level in diastole and poor diastolic relaxation. Electrophysiologically, increased cytosolic calcium can also result in arrhythmias dependent on the formation of delayed depolarization. The accumulation of FFAs, consequent to the inactivation of mitochondrial function, also promotes further ischemic damage. An increased level of FFAs or of their metabolic byproducts will cause membrane damage, directly or indirectly, by the formation of lysophosphoglycerides. Increased membrane damage is likely to be associated with arrhythmias, particularly in the presence of high circulating catecholamines. Membrane damage further alters calcium metabolism, resulting in massive overload of the ion with severe relaxation impairment.[8,9,10] *Figure 3* shows the drastic delete-

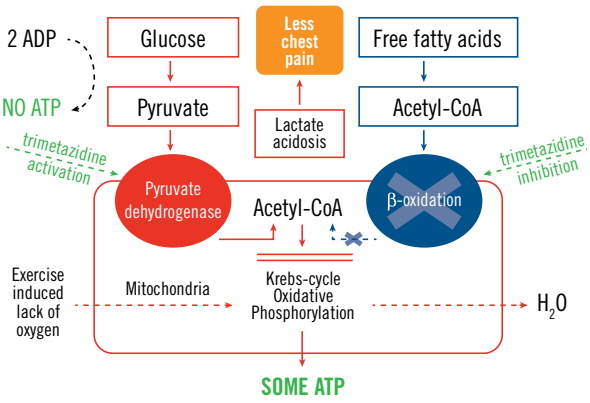

Fig. 3 *Effect of palmitate vs glucose on an ischemic heart.*

rious effect of palmitate vs glucose as a substrate for isolated rabbit hearts perfused under ischemic conditions (coronary flow reduction from 24 to 3 mL/min). When FFA (palmitate) is used as an ischemic substrate, diastolic pressure starts to increase after 15 minutes of ischemic perfusion suggesting severe relaxation impairment. On reperfusion, there is a partial recovery of the pre-ischemic developed pressure suggesting that myocytes are still viable. At the end of reperfusion, mitochondrial calcium is not increased and their capacity to produce ATP is retained. On the contrary, substitution of glucose with palmitate causes massive, irreversible damage after 30 minutes of ischemic perfusion.

Trimetazidine mode of action

The data reported in *Figure 4* are relevant to explain the mechanism of action of trimetazidine as it has been suggested that it may exert its antianginal effect by inhibiting fatty acid oxidation and improving glycolysis and glucose oxidation.[10-12] Fantini et al[11] demonstrated that trimetazidine reduces in vitro mitochondrial respiratory activity in a substrate depended manner: palmitate oxidation is markedly reduced, but not that of pyruvate, glutamate, or citrate. Later, Kantor et al[13] showed that in isolated rabbit hearts under aerobic conditions, trimetazidine does not influence substrate metabolism, while under ischemic conditions it causes a switch in the source of acetyl-CoA for the Krebs cycle from fatty acid β-oxidation to glucose oxidation. This is not due to a direct stimulation of pyruvate dehydrogenase (PDH), but rather an indirect stimulation of PDH secondary to less fatty acid oxidation, which is because β-oxidation is a key determinant of PDH activity.[14] Trimetazidine is a partial inhibitor of long-chain 3 ketoacyl-CoA thiolase, the enzyme catalyzing the last step of β-oxidation.[13] This, in turn, stimulates PDH and oxidation of pyruvate, with activation of anaerobic glycolysis.

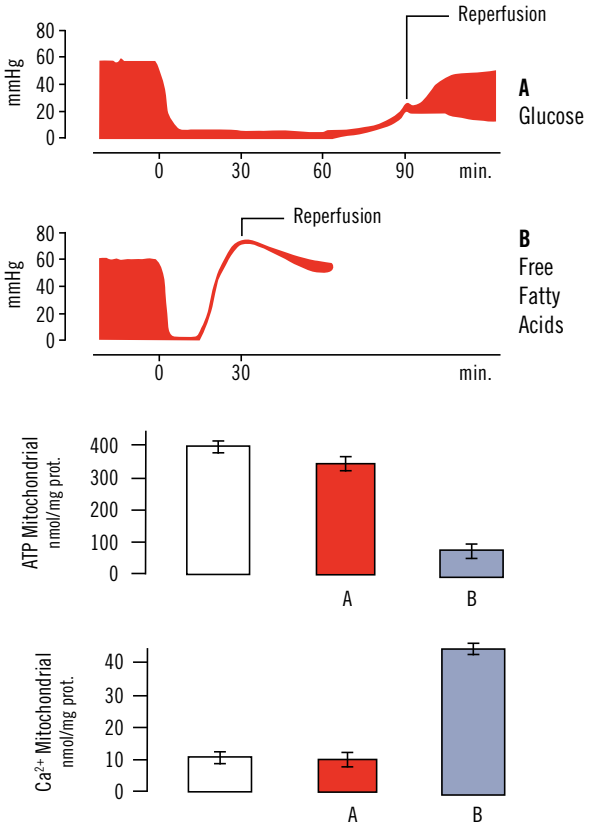

Fig. 4 *Metabolic effect of trimetazidine. Effects of different substrate (glucose A and palmitate B) on the mechanical (upper panels) and isolated mitochondrial function of isolated and perfused rabbit hearts under aerobic ischemia (coronary flow 3ml/min) and aerobic reperfusion. At the end, mitochondria were harvested and their ATP production and Ca^{2+} content determined. Palmitate caused a massive increase of diastolic pressure (index of impaired relaxation) already after 30 mins of ischemic perfusion and no recovery during reperfusion. Glucose exerted a protective effect. Adapted from O. Visioli, F. Di Lisa, R. Raddino, R. Ferrari. Estaratto dal volume: GUISEPPE GIUFFRIDA, Attualita in tema di cardiopatia ischemica. Edizioni luigi pozzi - Roma. Copyright © Edizioni Luigi Pozzi s.r.l.*

Numerous experimental studies, in addition to those reported in *Figure 4*, have demonstrated that stimulation of glucose oxidation both during and after ischemia can benefit the ischemic heart.[15,16] By improving the coupling of glycolysis with glucose oxidation, proton production is decreased, resulting in decreased tissue acidosis and an improvement in cardiac efficiency. As a result, selective stimulation of glucose oxidation by trimetazidine may explain the anti-ischemic and anti-anginal effects of this agent by increasing the coupling between glycolysis and glucose oxidation. There is less proton production and acidosis, thus causing less angina pain and increasing the exercise time to angina and to electrocardiogram-ST alteration during exercise. These effects of trimetazidine are depicted in *Figure 4* and summarized in *Table I*. In summary, trimetazidine inhibits fatty acid oxidation secondary to an inhibition of long-chain 3-ketoacyl CoA thiolase. This results in an improved coupling of glycolysis with glucose oxidation, less acidosis, and more anaerobic ATP production.

Effects of trimetazidine on cardiac metabolism
• Inhibition of FFA β-oxidation
• Activation of pyruvate dehydrogenase
• Shift of metabolism from FFA to glucose
Under ischemic condition, this results in:
• Better cardiac energy via anaerobic ATP
• Less lactic acid, less acidosis, less angina
• Prolongation of exercise time to angina and to 1 mm ST depression in absence of hemodynamic effects

Table I *The effects of trimetazidine on cardiac metabolism.*

Type 2 diabetes and cardiac metabolism

Diabetes mellitus is an important predictor of future cardiovascular events in patients with and without ischemic heart disease.[17,18] Patients with diabetes, but without overt CAD have a prognosis similar to CAD patients without diabetes, and patients with diabetes and CAD have a cardiovascular death rate double that of patients without diabetes and CAD.[19] The diffuse distribution of atherosclerosis in patients with type 2 diabetes is related, in part, to the metabolic derangements of diabetes and, in part, to the clustering of different risk factors, such as elevated blood pressure, central obesity, and an altered lipid profile.

An important effect of diabetes at a myocardial level is the switch from carbohydrate oxidation to FFA and ketone oxidation. As observed in diabetic patients, elevated levels of acetyl-CoA and FFA inhibit PDH and pyruvate flux. In ischemia, these metabolic abnormalities result in an increased lactate release and are associated with calcium overload and, eventually, cell death leading to contractile dysfunction. In diabetic patients, levels of both FFAs and fatty acid esters are elevated. However, although FFA metabolism is elevated, esterified fatty acid is decreased. In addition to these changes in circulating FFAs, diabetes causes an increase in myocardial triglyceride content. The consequence is impaired ventricular performance, independent of blood pressure and significant CAD, which supports the existence of a condition termed 'diabetic cardiomyopathy'.[20]

Optimizing cardiac metabolism could become a new approach to the management of ischemic heart disease in diabetic patients. Clinical manipulations of metabolic substances are intended to shift the ischemic myocardium from FFA to glucose utilization.[21] Studies conducted in isolated perfused hearts confirmed that a switch from FFA to glucose exerts favorable effects on the diabetic heart.[21] In a prospective DIGAMI study (Diabetic Patients Receiving Insulin–Glucose Infusion during Acute Myocardial Infarction), the long-term mortality in diabetic patients admitted for acute myocardial infarction was reduced by 30% in 1 year with 24h glucose–insulin–potassium infusion followed by multidose insulin treatment. A meta-analysis of all of the trials on glucose–insulin–potassium infusion showed a 28% reduction in mortality at a 1-year follow-up, and this therapeutic regimen has been recommended for all diabetic patients suffering an acute myocardial infarction.[22]

Conclusion

In conclusion, the inhibition of FFA oxidation with trimetazidine in CAD patients with or without diabetes improved cardiac metabolism at rest and during stress, and therefore, reduced the decrease in LV function caused by chronic hypoperfusion and repetitive episodes of myocardial ischemia. For this reason, in the recent ESC Guidelines on chronic ischemia, trimetazidine is recommended as an add-on drug acting by improving cardiac metabolism. In addition, trimetazidine should be considered for the treatment of patients with diabetes and CAD with or without LV dysfunction.

Heart Metab. (2014) 63:23–28

REFERENCES

1. Lavanchy N, Martin J, Rossi A. Anti-ischemia effects of trimetazidine: 31P-NMR spectroscopy in the isolated rat heart. Arch Int Pharmacodyn Ther. 1987;286:97-110.
2. Lagadic-Gossmann D, Le Prigent K, Feuvray D. Effects of trimetazidine on pHi in the rat isolated ventricular myocyte. Br J Pharmacol. 1996;117:831-838.
3. Renaud JF. Internal pH, Na+, and Ca2+ regulation by trimetazidine during cardiac cell acidosis. Cardiovasc Drugs Ther. 1988;1:677-686.
4. Maridonneau-Parini I, Harpey C. Effects of trimetazidine on membrane damage induced by oxygen free radicals in human red cells. Br J Clin Pharmacol. 1985;20:148-151.
5. Knaapen P, Germans T, Knuuti J, et al. Myocardial energetics and efficiency: current status of the noninvasive approach. Circulation. 2007;115(7):918-927.
6. Taegtmeyer H. Energy metabolism of the heart: from basic concepts to clinical applications. Curr Probl Cardiol. 1994;19(2):59-113.
7. Ferrari R, Opie LH. Atlas of the myocardium. Raven Press, New York, 1992.
8. Ferrari R, Ceconi C, Curello S, et al. Oxygen-mediated myocardial damage during ischaemia and reperfusion: role of the cellular defences against oxygen toxicity. J Mol Cell Cardiol. 1985;17(10):937-945.
9. Ceconi C, Curello S, Albertini A, Ferrari R. Effect of lipid peroxidation on heart mitochondria oxygen consuming and calcium transporting capacities. Mol Cell Biochem. 1988;81(2):131-135.
10. Ferrari R. Understanding the new ischemic syndromes: proceedings of a Meeting of the EEC Biomed Concerted Action "The New Ischemic Syndromes": Cortina D'Ampezzo, June, Steinkopff Verlag, 1997.
11. Fantini E, Demaison L, Sentex E, Grynberg A, Athias P. Some biochemical aspects of the protective effect of Trimetazidine on rat cardiomyocytes during hypoxia and reoxygenation. J Mol Cell Cardiol. 1994;26 949-958.
12. Liu B, el Alaoui-Talibi Z, Clanachan AS, Schulz R, Lopaschuk GD. Uncoupling of contractile function from mitochondrial TCA cycle activity and MVO2 during reperfusion of ischemic hearts. Am J Physiol. 1996;270:H72-H80.
13. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res. 2000;86(5):580-588.
14. Randle PJ, Hales CN, Garland PB, Newsholme EA. The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetic mellitus. Lancet. 1963;1:785-789.
15. Lopaschuk GD, Belke DD, Gamble J, Itoi I, Schonekess BO. Regulation of fatty acid oxidation in the mammalian heart in health and disease. Biochim Biophys Acta. 1994;1213:263-276.
16. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischemic conditions: potential for pharmacological interventions. Cardiovasc Res. 1997;33:243-257.
17. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21:1414-1431.
18. Kanters SD, Banga JD, Stolk RP, Algra A. Incidence and determinants of mortality and cardiovascular events in diabetes mellitus: a meta-analysis. Vasc Med. 1999;4:67-75.
19. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229-234.
20. Shapiro LM, Howat AP, Calter MN. Left ventricular function in diabetes mellitus. Methodology and prevalence and spectrum of abnormalities. Br Heart J. 1991;45:122-128.
21. Marzilli M. Management of ischaemic heart disease in diabetic patients. Is there a role for cardiac metabolic agents? Curr Med Res Opin. 2001;17:153-158.
22. Fath-Ordoubadi F, Beatt KJ. Glucose–insulin–potassium (GIK) therapy for treatment of acute myocardial infarction: an overview of randomized placebo controlled trials. Circulation. 1997;96:1152-1156.