Contents

Cardiovascular effects of exercise

Mario Marzilli
Department of Cardiology, University of Siena, Italy

Correspondence: Mario Marzilli, Department of Cardiology, University of Siena, Policlinico Le Scotte, V. Le Bracci, 53100 Siena, Italy.
E-mail: marzilli@unisi.it

Physical inactivity doubles the risk of developing heart disease and increases the risk of hypertension by 30%. It also doubles the risk of dying from cardiovascular disease and stroke. Every year, more than 2 million deaths are attributable to physical inactivity worldwide.

Moderate and high levels of physical activity are associated with a reduced risk of cardiovascular disease and all-cause mortality. Physical activity acts through many metabolic pathways that affect cardio-vascular risk factors. It improves the plasma lipid profile, reduces body weight, decreases blood pressure, reduces platelet aggregation, increases fibrinolytic activity, improves cardiac function, improves cardiorespiratory fitness, and decreases the resting heart rate. Furthermore, exercise training seems to improve endothelium-dependent vasodilatation and increase both urinary excretion of sodium and insulin sensitivity. Long-term exercise has been associated with a decrease in atherogenic activity of blood mononuclear cells and with decreased C-reactive protein concentrations.

Unfortunately, 60–85% of the world population, from both developed and developing countries, are not sufficiently physically active to gain health benefits. Promoting physical activity appears to be an essential component in the prevention of premature cardiovascular disease and all-cause-mortality.

In patients with chronic or post-acute cardiovascular disease, exercise therapy is consistently identified by international guidelines as a central element of cardiac rehabilitation. A recent meta-analysis has confirmed that exercise-based cardiac rehabilitation reduces both cardiac and total mortality, possibly through a direct effect on myocardial oxygen demand, endothelial function, autonomic tone, coagulation and clotting factors, inflammatory markers, and the development of coronary collaterals vessels.

In patients with heart failure, exercise training improves functional capacity and quality of life. The optimal form of training remains undefined, and although intermittent aerobic exercise appears to be effective, strength training alone may not be as effective as the standard approach of continuous aerobic exercise.

A regular physical exercise program improves symptom-free exercise tolerance and myocardial perfusion in patients with stable coronary artery disease, and retards the progression of coronary artery disease over time. Improved endothelium-dependent vasodilatation may represent the most important mechanism to explain the reduction in myocardial ischemia. In patients with stable coronary artery disease, a 12-month exercise training program resulted in a higher event-free survival rate than with standard percutaneous coronary intervention.

Michael Allard, in the basic article of this issue 26 of *Heart and Metabolism*, focuses on the differences in myocardial energy metabolism associated with pathologic and physiologic forms of cardiac hypertrophy. Non-invasive cardiac imaging can be of great help in the differential diagnosis between these two forms of cardiac hypertrophy. In general, as described by Eike Nagel and Ingo Paetsch, echocardiographic techniques are sufficient to diagnose cardiomyo-pathy. In difficult cases, magnetic resonance may provide additional conclusive information.

Editorial

M. Marzilli

Harm Kuipers completes the description of cardiac adaptations to exercise, describing the effects of training on autonomic control and discussing the effects of pharmacologic interventions to improve performance.

Neil Smart and Thomas Marwick review the risk and benefits of exercise in cardiac disease. Their article is rich in useful recommendations to minimize exercise-related adverse events and maximize the benefit to the patient, beginning from the preclinical stage of cardiac disease.

Andrew McLeod offers a number of very useful tips for the construction of an exercise program, including technical and financial aspects.

The benefits of a metabolic approach to the improvement of cardiac function in chronic heart failure are reviewed by Hamayak Sisakyan and illustrated by Mario Marzilli in a case of severe heart failure.

In all, issue 26 of *Heart and Metabolism* offers a comprehensive overview of exercise as an effective addition to the therapeutic strategies for the prevention and treatment of cardiac diseases.

Adaptive and maladaptive cardiac hypertrophy

Michael F. Allard
The James Hogg iCapture Centre for Cardiovascular and Pulmonary Research, Department of Pathology and Laboratory Medicine, University of British Columbia – St Paul's Hospital, Vancouver, Canada

Correspondence: Dr Michael F. Allard, The James Hogg iCapture Centre for Cardiovascular and Pulmonary Research, Room 166, St Paul's Hospital, 1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6.
Tel: +1 604 806 9292, fax: +1 604 806 9247, e-mail: mallard@mrl.ubc.ca

Abstract

The substrate utilization profile of the heart is altered during the hypertrophic response to both pathologic (eg, hypertension) and physiologic (eg, exercise) stimuli. The alterations in substrate catabolism that occur as part of the hypertrophic response are dependent upon the nature of the stimulus leading to cardiac hypertrophy and, as such, differ significantly in pathologic and physiologic forms of cardiac hypertrophy. These alterations in substrate catabolism can be considered adaptive, as in physiologic cardiac hypertrophy, or maladaptive, as in pathologic cardiac hypertrophy, depending upon how they influence functional outcome of the heart after an acute metabolic stress.
■ *Heart Metab.* 2005; 26:5–9.

Keywords: Cardiac hypertrophy, energy metabolism, exercise, pressure-overload, ischemia-reperfusion

Introduction

Prolonged increases in hemodynamic workload lead to cardiac hypertrophy. This response is generally viewed as adaptive because it enables the heart to maintain function [1,2] and normalizes myocardial oxygen consumption [3], all in the presence of elevated hemodynamic workload. However, when consideration is given to the longer term outcome of the hypertrophic response as well as to the functional outcome of the hypertrophied heart after a subsequent acute metabolic stress, it becomes clear that viewing this response as entirely adaptive is too simplistic.

It is well recognized that cardiac hypertrophy occurs in response to prolonged pressure- or volume-overload due to pathologic stimuli such as hypertension or valvular heart disease [4]. As compared to non-hypertrophied hearts, cardiac hypertrophy due to pathologic stimuli is known to be associated with an enhanced risk of sudden death and with the development of heart failure [4]. In addition, such hearts develop larger myocardial infarctions [4] and suffer greater dysfunction following ischemia and reperfusion [5–7]. This latter observation is of importance because cardiac hypertrophy and coronary artery disease are both highly prevalent conditions that commonly co-exist [8]. When the hypertrophic response to pathologic stimuli is considered in this way, so-called pathologic cardiac hypertrophy may be viewed as maladaptive.

Cardiac hypertrophy also develops in response to physiologic stimuli such as endurance exercise training [9–11]. Cardiac functional performance is enhanced in hearts hypertrophied in response to physiologic stimuli and this form of cardiac hypertrophy (ie, physiologic cardiac hypertrophy) is not associated with detrimental long-term outcomes [10,12,13]. The response of physiologically hypertrophied hearts to an acute metabolic stress such as ischemia and reperfusion differs from those hypertrophied by pathologic stimuli. Specifically, post-ischemic recovery of these hearts is enhanced relative to that of non-hypertrophied hearts [11,14]. When these observations are taken into account, the hypertrophic response to physiologic stimuli may be considered truly adaptive in nature.

In addition to enlargement of cardiac myocytes, the hypertrophic response, whether due to pathologic or

physiologic stimuli, is accompanied by qualitative changes within the cardiac myocytes. Energy metabolism is one aspect of cardiac myocyte biology that is well recognized as being altered during the hypertrophic response in both pathologically and physiologically hypertrophied hearts [11,15–17]. Of importance, these changes in energy metabolism are considered to be key determinants as to whether the hypertrophic response is adaptive or maladaptive [1,2,7,11,18]. As such, I will review what is known about the way in which energy metabolism is altered in hearts hypertrophied by physiologic or pathologic stimuli with particular emphasis on how changes in energy metabolism may influence the outcome from ischemia and reperusion, this being an indicator of the adaptive or maladaptive nature of the hypertrophic response. Before embarking on this discussion, a brief overview of energy metabolism in the myocardium will be provided.

Myocardial energy metabolism

Circulating fatty acids, glucose, lactate, amino acids, and ketone bodies as well as intracellular glycogen and triacylglerol can be used by the heart to produce energy [19–21]. However, catabolism of carbohydrates, such as glucose and lactate, and long-chain fatty acids produce most of the energy with the majority coming from fatty acid catabolism (*Figure 1*). After entering the cardiac myocyte through glucose transporters in the sarcolemma, glucose may be incorporated into glycogen or may be degraded to pyruvate in a step-wise manner via glycolysis [20,22,23]. Rates of glycolysis in the heart are determined in large part by the extent of glucose transport and flux rates through reactions catalyzed by hexokinase and phosphofructokinase-1 [22–23]. The pyruvate produced by glycolysis is then either oxidized in the mitochondria or converted to lactate [20,22,23]. The extent of mitochondrial oxidation of pyruvate, which can be derived from lactate or from glycogen, is determined mainly by the activity of the mitochondrial pyruvate dehydrogenase complex [23].

As with glucose, catabolism of fatty acids by the myocardium is controlled at multiple steps, including uptake and intracellular transport as well as transport into the mitochondria where the fatty acids are oxidized by β-oxidation and the tricarboxylic acid

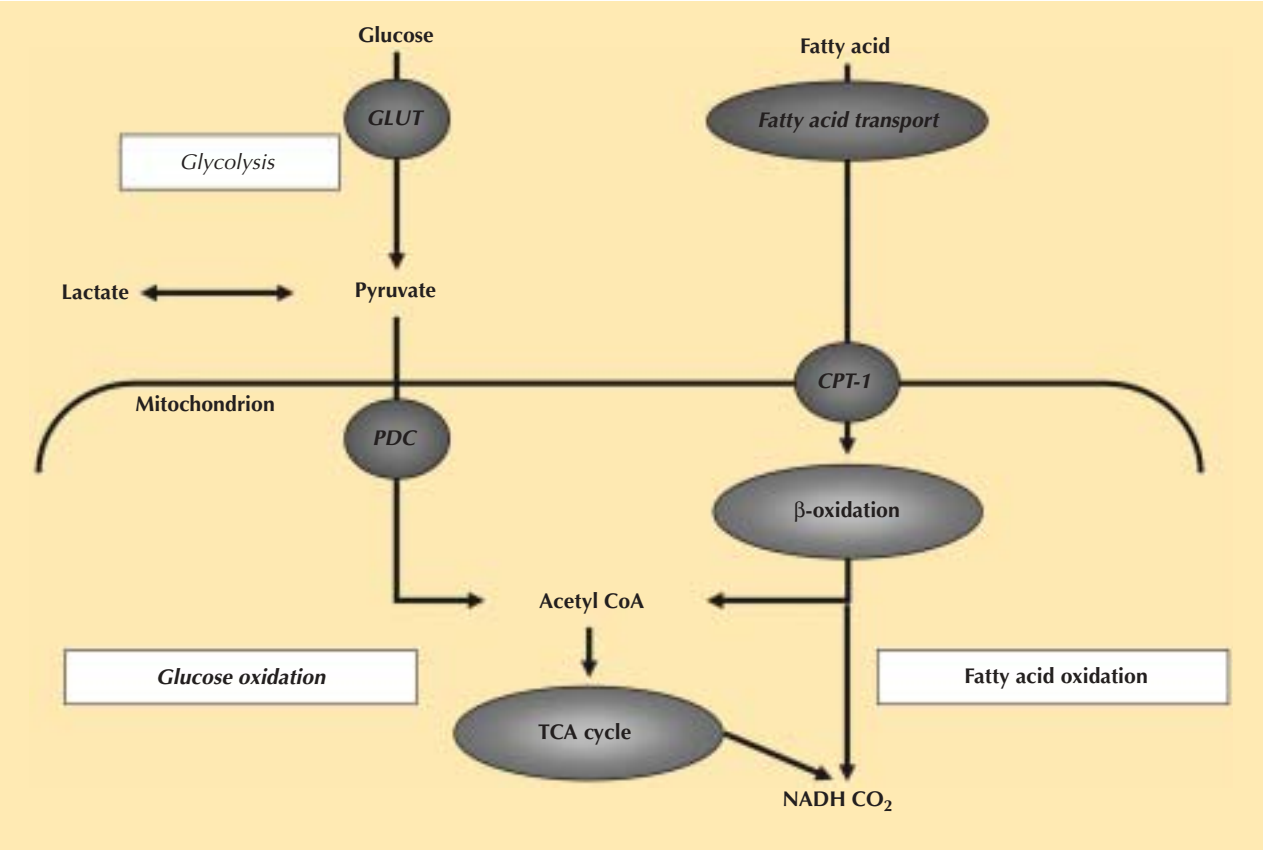

Figure 1. Energy metabolism in the heart. CoA, coenzyme-A; CPT-1, carnitine palmitoyltransferase-1; GLUT, glucose transporters; NADH, reduced nicotine adenine dinucleotide; PDC, pyruvate dehydrogenase complex; TCA cycle, tricarboxylic acid cycle.

cycle [24]. The rate of long chain fatty acid oxidation is governed largely by the rate of transport into the mitochondria which itself is controlled significantly by carnitine palmitoyltransferase-1. It is important to recognize that catabolism of glucose and fatty acid are reciprocally related such that inhibition of fatty acid oxidation, for instance, leads to a compensatory stimulation of glucose use, especially glucose oxidation [20,23].

Energy metabolism in cardiac hypertrophy

Glycolysis and glucose oxidation

Rates of glycolysis are accelerated in hearts hypertrophied by pathologic stimuli before and after ischemia [15–17] (*Figure 2*). Interestingly, rates of glucose oxidation are not correspondingly increased [7,15–17]. Glucose oxidation can, in fact, actually be lower in pathologically hypertrophied hearts than in non-hypertrophied hearts [7]. A corollary of these alterations in glucose catabolism is that the fraction of glucose passing through glycolysis that is oxidized is lower in these hypertrophied hearts. The alterations in glucose catabolism in hearts hypertrophied in response to endurance exercise training stand in stark contrast. Specifically, glycolysis is reduced and glucose oxidation is increased in physiologically hypertrophied hearts compared to non-hypertrophied hearts (*Figure 2*). Correspondingly, fractional oxidation rates of glucose are higher in these hearts.

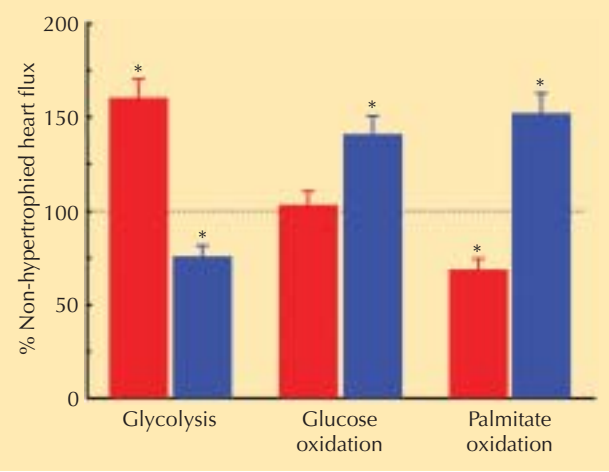

Figure 2. Energy metabolism in pathologic and physiologic cardiac hypertrophy. Red bar, *Pathologic cardiac hypertrophy (n = 6–8);* blue bar, *physiologic cardiac hypertrophy (n = 6 or 7). Values are mean ± SEM and were calculated as (hypertrophied heart flux rate/non hypertrophied heart flux rate) × 100. *P < 0.05 compared with corresponding non hypertrophied heart.*

Fatty acid oxidation

As compared to non-hypertrophied hearts, long-chain fatty acid oxidation is reduced in pathologically hypertrophied hearts [15–17] (*Figure 2*). The substrate utilization profile that develops as part of the hypertrophic response to pathologic stimuli is similar to that in a fetal heart [25], a change considered to reflect the reoccurrence of a fetal phenotype in response to chronically altered cardiac workloads [1,26]. This particular catabolic profile for energy substrates has been observed in a number of different pathologic settings including hearts hypertrophied by pressure overload [16] or volume overload [15], and in hearts hypertrophied of spontaneously hypertensive rats [17], as well as in patients with hypertrophied-failing hearts [27].

As with glucose catabolism, the alteration in fatty acid oxidation in hearts hypertrophied by endurance exercise training [11] differs from that in their pathologic counterpart. Specifically, long-chain fatty acid oxidation rates are accelerated as compared to non-hypertrophied hearts (*Figure 2*). That the profile of energy substrate catabolism differs dramatically between hearts hypertrophied by pathologic stimuli as compared to those hypertrophied by physiologic stimuli indicates that alterations in metabolism induced by prolonged changes in hemodynamic workload are influenced by the nature of the stimulus leading to cardiac hypertrophy.

Adaptive and maladaptive alterations in energy metabolism in cardiac hypertrophy

As mentioned, the hypertrophic response enables the heart to meet the demands of a chronically elevated hemodynamic workload and, in this sense, has been viewed as adaptive in nature. However, it has been suggested that the alterations in the heart that occur as part of this response, including changes in substrate catabolism, have an impact upon the functional outcome of the heart when faced with a subsequent acute metabolic stress which occurs in the setting of myocardial ischemia and reperfusion, for instance [28]. The functional outcome after ischemia and reperfusion can, therefore, be used as a means to determine if the changes induced as part of the hypertrophic response are adaptive or maladaptive.

Based upon results from a variety of sources, post-ischemic functional outcome of hearts hypertrophied in response to physiologic stimuli is greater [11,14], while that of hearts hypertrophied in response to pathologic stimuli is lower than that of non-hypertrophied hearts [5–7] (*Figure 3*). With the preceding comments in mind, the hypertrophic

response to physiologic stimuli can be considered adaptive, but the response to pathologic stimuli can be considered maladaptive. The dramatically different functional outcomes in these two forms of hypertrophy (*Figure 3*) are associated with equally dramatic differences in catabolic profiles for energy substrates (*Figure 2*). Given the well recognized link between function and metabolism in the heart [1], it is logical to consider the possibility that alterations in energy substrate catabolism contribute to the adaptive or maladaptive nature of the hypertrophic response, particularly when the hypertrophied heart is exposed to an acute metabolic stress.

Evidence from experimental and clinical studies suggests that the catabolic fate of glucose is an important determinant of post-ischemic myocardial function [23,29]. In particular, the extent of oxidative versus non-oxidative catabolism of glucose appears to be of great functional significance. For instance, it has been shown that pharmacological treatments that stimulate glucose oxidation and/or reduce glycolysis improve functional recovery of the non-hypertrophied heart following ischemia [23,29]. In hearts hypertrophied in response to pathologic stimuli, two agents that modulate energy metabolism, namely dichloroacetate [7] and trimetazidine [30], have been shown to normalize post-ischemic function and did so in association with stimulation of glucose oxidation and reduction of glycolysis. By altering the fate of glucose, these agents serve to shift the balance from non-oxidative to oxidative glucose catabolism, a profile resembling that seen in hearts hypertrophied by physiologic stimuli and a profile associated with a functionally beneficial outcome after ischemia.

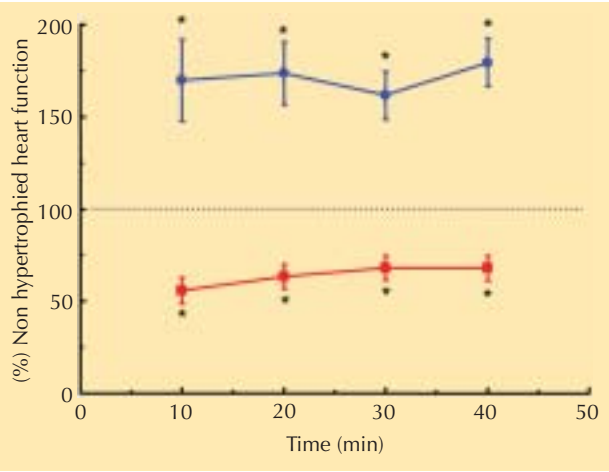

*Figure 3. Postischemic functional recovery in pathologic (□; n = 18) and physiologic (○; n = 13) cardiac hypertrophy. Values are mean ± SEM and were calculated as (hypertrophied heart function/corresponding non hypertrophied heart function) × 100. *P < 0.05 compared with corresponding non hypertrophied heart.*

Taken together, these data provide support for the concept that the extent of oxidative versus non-oxidative glucose catabolism is an important determinant of post-ischemic function and that differences in the balance between oxidative and non-oxidative fates are, at least in part, responsible for the dramatically different outcomes observed between the two forms of hypertrophy. It has been suggested that the cellular mechanism linking the fate of glucose to heart function is related to proton production [31], with a higher production of protons associated with a detrimental functional outcome. The stoichiometry of non-oxidative as compared to oxidative glucose catabolism indicates that net protons are produced when the ATP generated by non-oxidative glycolysis is hydrolyzed [31]. Thus, as compared to non-hypertrophied hearts, non-oxidative glucose catabolism and, therefore, proton production are accelerated in hearts hypertrophied by pathologic stimuli which contribute to the poor outcome [7]. In contrast, non-oxidative glucose catabolism and proton production are reduced in hearts hypertrophied by endurance exercise training, a change that might partly explain their improved post-ischemic function [11]. In a similar way, agents that serve to shift the balance from non-oxidative to oxidative glucose catabolism, such as trimetazidine or dichloroacetate, are functionally beneficial because they reduce net proton production [23,31–33]. Such a reduction favors recovery of intracellular pH, which limits calcium overload by successive H^+/Na^+ and Na^+/Ca^{2+} exchange, and therefore reduces the energetic cost associated with the maintenance of ion homeostasis [23]. This would in turn lead to improved post-ischemic contractile function and efficiency [23].

Conclusions

The substrate utilization profile of the heart is altered during the hypertrophic response to both pathologic and physiologic stimuli. The alterations in substrate catabolism that occur as part of the hypertrophic response are dependent upon the nature of the stimulus leading to cardiac hypertrophy and, as such, differ significantly in pathologic and physiologic forms of cardiac hypertrophy. These alterations in substrate catabolism can be considered adaptive, as in physiologic cardiac hypertrophy, or maladaptive, as in pathologic cardiac hypertrophy, depending upon how they influence functional outcome of the heart after an acute metabolic stress.

Acknowledgement

This work was supported by operating grants from the Canadian Institutes of Health Research and the Heart and Stroke Foundation of British Columbia and Yukon. ■

REFERENCES

1. Taegtmeyer H. Genetics of energetics: transcriptional responses in cardiac metabolism. *Ann Biomed Eng*. 2000;28(8):871–876.
2. Young ME, Laws FA, Goodwin GW, Taegtmeyer H. Reactivation of peroxisome proliferator-activated receptor alpha is associated with contractile dysfunction in hypertrophied rat heart. *J Biol Chem*. 2001;276(48):44390–44395.
3. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest*. 1975;56(1):56–64.
4. Frohlich ED, Apstein C, Chobanian AV, et al. The heart in hypertension. *N Engl J Med*. 1992;327(14):998–1008.
5. Gaasch WH, Zile MR, Hoshino PK, Weinberg EO, Rhodes DR, Apstein CS. Tolerance of the hypertrophic heart to ischemia. Studies in compensated and failing dog hearts with pressure overload hypertrophy. *Circulation*.1990;81(5):1644–1653.
7. Anderson PG, Allard MF, Thomas GD, Bishop SP, Digerness SB. Increased ischemic injury but decreased hypoxic injury in hypertrophied rat hearts. *Circ Res*. 1990;67(4):948–959.
8. Wambolt RB, Lopaschuk GD, Brownsey RW, Allard MF. Dichloroacetate improves postischemic function of hypertrophied rat hearts. *J Am Coll of Cardiol*. 2000;36(4):1378–1385.
9. Kannel WB. Vital epidemiologic clues in heart failure. *J Clin Epidemiol*. 2000;53(3):229–235.
10. Frey N, Olson EN. Cardiac hypertrophy: the good, the bad, and the ugly. *Annu Rev Physiol*. 2003;65:45–79.
11. Richey PA, Brown SP. Pathological versus physiological left ventricular hypertrophy: a review. *J Sports Sci*. 1998;16(2):129–141.
12. Burelle Y, Wambolt RB, Grist M, et al. Regular exercise is associated with a protective metabolic phenotype in the rat heart. *Am J Physiol Heart Circ Physiol*. 2004;287(3):H1055–H1063.
13. Moore RL, Korzick DH. Cellular adaptations of the myocardium to chronic exercise. *Prog Cardiovasc Dis*. 1995;37(6):371–396.
14. Moore RL, Palmer BM. Exercise training and cellular adaptations of normal and diseased hearts. *Exerc Sport Sci Rev*. 1999;27:285–315.
15. Bowles DK, Farrar RP, Starnes JW. Exercise training improves cardiac function after ischemia in the isolated, working rat heart. *Am J Physiol*. 1992;263(3 Pt 2):H804–H809.
16. El Alaoui-Talibi Z, Guendouz A, Moravec M, Moravec J. Control of oxidative metabolism in volume-overloaded rat hearts: effect of propionyl-L-carnitine. *Am J Physiol*. 1997;272(4 Pt 2):H1615–H1624.
17. Allard MF, Schonekess BO, Henning SL, English DR, Lopaschuk GD. Contribution of oxidative metabolism and glycolysis to ATP production in hypertrophied hearts. *Am J Physiol*. 1994;267(2 Pt 2):H742–H750.
18. Vincent G, Khairallah M, Bouchard B, Des Rosiers C. Metabolic phenotyping of the diseased rat heart using 13C-substrates and ex vivo perfusion in the working mode. *Mol Cell Biochem*. 2003;242(1–2):89–99.
19. Lehman JJ, Kelly DP. Gene regulatory mechanisms governing energy metabolism during cardiac hypertrophic growth. *Heart Fail Rev*. 2002;7(2):175–185.
20. Saddik M, Lopaschuk GD. Myocardial triglyceride turnover and contribution to energy substrate utilization in isolated working rat hearts. *J Biol Chem*. 1991;266(13):8162–8170.
21. Neely JR, Morgan HE. Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle. *Annu Rev Physiol*. 1974;36:413–457.
22. Henning SL, Wambolt RB, Schonekess BO, Lopaschuk GD, Allard MF. Contribution of glycogen to aerobic myocardial glucose utilization. *Circulation*. 1996;93(8):1549–1555.
23. Depre C, Rider MH, Hue L. Mechanisms of control of heart glycolysis. *Eur J Biochem*. 1998;258(2):277–290.
24. Stanley WC, Lopaschuk GD, Hall JL, McCormack JG. Regulation of myocardial carbohydrate metabolism under normal and ischaemic conditions. Potential for pharmacological interventions. *Cardiovasc Res*. 1997;33(2):243–257.
25. Lopaschuk GD, Belke DD, Gamble J, Itoi T, Schonekess BO. Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim Biophys Acta*. 1994;1213(3):263–276.
26. Lopaschuk GD, Spafford MA, Marsh DR. Glycolysis is predominant source of myocardial ATP production immediately after birth. *Am J Physiol*. 1991;261(6 Pt 2):H1698–H1705.
27. Tian R. Transcriptional regulation of energy substrate metabolism in normal and hypertrophied heart. *Curr Hypertens Rep*. 2003;5(6):454–458.
28. Davila-Roman VG, Vedala G, Herrero P, et al. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 2002;40(2):271–277.
29. Taegtmeyer H. Metabolism-The Lost Child of Cardiology. *J Am Coll Cardiol*. 2000;36(4):1386–1388.
30. Lopaschuk GD, Rebeyka IM, Allard MF. Metabolic modulation: a means to mend a broken heart. *Circulation*. 2002;105(2):140–142.
31. Grist M. Trimetazidine beneficially alters glucose metabolism in hypertrophied rat hearts. *Faseb J*. 2002;16:A491.
32. Lopaschuk GD, Wambolt RB, Barr RL. An imbalance between glycolysis and glucose oxidation is a possible explanation for the detrimental effects of high levels of fatty acids during aerobic reperfusion of ischemic hearts. *J Pharmacol Exp Ther*. 1993;264(1):135–144.
33. Liu Q, Docherty JC, Rendell JC, Clanachan AS, Lopaschuk GD. High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. *J Am Coll Cardiol*. 2002;39(4):718–725.

Risks and benefits of exercise in cardiac disease

Neil Smart, Thomas H. Marwick
University of Queensland, Brisbane, Australia

Correspondence: Mr Neil Smart, University of Queensland Department of Medicine, Princess Alexandra Hospital, Brisbane, Qld 4102, Australia. Tel: +61 7 3240 5346, fax: +61 7 3240 5399, e-mail: nsmart@soms.uq.edu.au

Abstract

Recent meta-analyses have identified significant benefits of exercise-based cardiac rehabilitation, although inherent risks of exertion may remain. We undertook an extensive literature search to identify systematic reviews, meta-analyses and studies of exercise training in cardiac patients, in order to provide an evidence-based assessment of the relative hazards and benefits of exercise training in cardiac patients. Exercise-based cardiac rehabilitation appears to be effective in reducing cardiac deaths and admissions to hospital, improving functional capacity, quality of life, and most cardiac risk factors. We conclude that the growing evidence suggests exercise training to be a safe and effective therapeutic strategy for cardiac patients.

■ *Heart Metab.* 2005;26:10–14.

Keywords: Exercise training, myocardial infarction, heart failure, mortality, quality of life

Background

Exercise training became a component of cardiac rehabilitation 30 years ago. Subsequent data have shown that exercise is considered beneficial for cardiac patients in terms of improved mortality, morbidity, quality of life, functional capacity, and cardiac and vascular function [1]. Nevertheless, some health professionals remain skeptical about inherent risks of training, despite higher levels of fitness being associated with lower risk of all-cause and cardiac mortality in healthy, hypertensive, normotensive, and diabetic [2] cohorts.

We sought evidence of the relative merits and hazards of exercise training for cardiac patients (*Table I*). MEDLINE, Medscape, and the Cochrane Controlled Trials Registry were searched for meta-analyses, systematic reviews and individual studies of exercise training in cardiac patients. Data relating to training procedures and outcomes were reviewed.

Exercise therapy after myocardial infarction

Mortality and morbidity benefits

Two recent meta-analyses of cardiac rehabilitation programs reported the findings summarized in *Table II* [3,4]. The reduction in overall and cardiac mortality ranges from 20% to 30%, with little difference between comprehensive rehabilitation and exercise training only. In a meta-analysis of patients undergoing cardiac rehabilitation, quality-of-life assessment was unequivocal in demonstrating benefit, which was shown by 18 different instruments used in 11 studies [4]. The effect of rehabilitation on rates of revascularization could not be determined by meta-analysis because of the small number of studies and heterogeneity between trials [3].

Exercise training compared with lifestyle guidance

A recent analysis [4] showed that comprehensive cardiac rehabilitation was not clearly superior to exercise only. To an extent, this is surprising, as cessation of smoking may reduce all-cause mortality by 36% in coronary artery disease [5], although this appears substantial compared with therapies such as decreasing cholesterol. Perhaps the explanation for similar effects of exercise training and control of risk factors is that the former may effect the latter. Indeed, a 12-month German study of coronary artery disease showed exercise training to provide superior event-free survival and exercise capacity at lower cost (from reduced rates of admission to hospital and repeat revascularizations) compared with angioplasty [6].

Patients with heart failure

Mortality

Table III summarizes findings from two recent reviews of exercise training in patients with heart failure [7,8].

Functional capacity

Peak oxygen consumption (VO_2) remains a strong independent predictor of cardiac mortality in men and women: values greater than 13–14 mL/kg per min may confer a 50% reduction in cardiac mortality, whereas a 1 mL/kg per min increase may be associated with a 10% lower cardiac mortality [9]. Both resistance and aerobic exercise promote 15–

Table I. Commonly reported benefits and risk of exercise in cardiac patients.

Benefits	Risks
Reduced all-cause and cardiac mortality Reduced admissions to hospital Improved quality of life Improved cardiac risk factors Improved cardiac and vascular function	Sudden death Exercise-induced myocardial infarction/other cardiac event

Table II. Findings from two recent meta-analyses of cardiac rehabilitation.

	Joliffe et al [3]	Taylor et al [4]
Number of patients	7683 (2582 exercise only)	8940
Cardiac mortality exercise CR vs usual care	Reduced 31%	
Comprehensive CR vs usual care	Reduced 26%	
All-cause mortality		Reduced 20% (relative risk 0.80; 95% CI 0.68 to 0.93)
Cardiac mortality		Reduced 26% (relative risk 0.74; 95% CI 0.61 to 0.96)
Non fatal myocardial infarction	No effect	

CI, confidence interval; CR, cardiac rehabilitation.

Table III. Findings from two meta-analyses of exercise training in patients with heart failure.

Smart and Marwick [7]	Piepoli et al [8]
No deaths directly related to exercise in more than 60 000 patient exercise hours Only one study showed significant mortality benefit Mean increment in peak VO_2 was 16%	Significant reductions in mortality (35%, $P=0.015$) and admissions to hospital (28%, $P=0.011$) Weakest patients may benefit most (eg, elderly, low LVEF, least fit) Must treat 17 patients to save 1 death in 2 years

LVEF, left ventricular ejection fraction; VO_2, oxygen consumption.

17% increments in peak VO_2 in patients with heart failure [10]. In patients undergoing cardiac rehabilitation, increments of 35–50% in peak VO_2 are possible in compliant patients with initial peak metabolic equivalent of task units (METS) less than 5 [11].

Quality of life

A recent review of changes in quality of life after exercise training in patients with heart failure reported significant increments in 11 of 16 studies [10].

Exercise for preclinical disease

Effects of aging

Current evidence supports a 10% per decade decline in functional capacity of men and women, regardless of activity level. The decline may be due to reductions in maximal heart rate and lean body mass. Exercise training does not influence declines in maximal heart rate, but lean body mass can be maintained [12].

Diabetes

The STENO-2 study (Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes) [13] showed a significant (50%) reduction in relative risk in those who underwent lifestyle modification including exercise training. Stratified analyses indicate that both physical inactivity and adiposity are important determinants of the risk of mortality in diabetic men, and this association was independent of body mass index [14]. Exercise training in patients with type 2 (non insulin-dependent) diabetes mellitus improves baroreflex sensitivity, exercise capacity, muscle strength and glucose control. These beneficial effects in refractory autonomic regulation and glucose control may be associated with the improved prognosis in type 2 diabetes [15].

Obesity

Generally, exercise training does not expend many calories, suggesting that modification of risk factors may be effectively achieved by a combination of dietary and exercise interventions. However, in the short term, body weight reduction has been shown to be able to modify the autonomic profile favorably in a population of normotensive, severely obese individuals. The reduction in heart rate and increased parasympathetic activity may contribute consistently to reducing the risk of cardiovascular morbidity and sudden cardiac death in this group of patients [16].

Hypertension

Exercise training of patients with hypertension may help to control their hypertension and regress left ventricular hypertrophy [17].

Risks

Strategies to minimize exercise-induced events

Exercise training, 4 weeks after myocardial infarction, has been performed without complication [18]. After an uncomplicated recovery period, 4–6 weeks after an event (myocardial infarction or an episode of heart failure) may be the optimum time to begin exercise.

Supervised outpatient trials may produce better rates of adherence than home exercise, possibly because of poor motivation and concerns about safety [19]. Strategies improving compliance with home exercise require regular contact with the patient and methods of verifying the patient's adherence to the regimen. Nevertheless, it is possible to sustain peak VO_2 and quality of life in a 'home' exercise program 12 months after discharge from cardiac rehabilitation [20]. A tailored exercise program may optimize health benefits while minimizing the risk of exertional events. Periodic measurement of functional capacity, either directly or indirectly, may protect against under- or overestimation of the optimal training intensity.

Risks of cardiac events or death

The additional risk of cardiac arrest from exercise has been estimated subjectively at 100-fold during or after vigorous exertion [21]. *Table IV* summarizes the findings of large analyses in three groups of patients.

Mechanisms of risk

A high-intensity (90% peak VO_2) exercise-induced platelet hypercoagulable state may increase the risk of acute and fatal cardiac events [22]. However, evidence exists that low-intensity (55% peak VO_2) exercise does not present a risk of thrombosis.

Table IV. Risk of sudden death in exercise training of cardiac patients.

	Patient group		
	General cardiac	Heart failure	Healthy
Study	Van Camp and Peterson [24]	Smart and Marwick [7]	Thompson et al [25]
Number studied	51 303	2347	7620
Patient hours per death	783 972	60 000 +	396 000
Activity	Cardiac rehabilitation	Strength/aerobic	Jogging

After cardiac rehabilitation, statistically significant reductions in QT and JT dispersion have been reported. These may reduce the subsequent risks of malignant ventricular arrhythmias and sudden cardiac death [23].

Conclusions

Exercise training is safe and effective in reducing cardiac deaths and admissions to hospital, improving functional capacity, quality of life and cardiac risk factors in cardiac patients. However, the populations studied have been predominantly male and middle aged, and the ethnic origin of participants has seldom been reported. Nonetheless, the failure of many cardiac patients to be referred for exercise rehabilitation represents a lack of application of evidence-based medicine. ■

REFERENCES

1. Hamm LF, Kavanagh T. The Toronto Cardiac Rehabilitation and Secondary Prevention Program: 1968 into the new millennium. *J Cardiopulm Rehabil*. 2000;20:16–22.
2. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care*. 2004;27:83–88.
3. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2001:CD001800.
4. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2004;116:682–692.
5. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. *Cochrane Database Syst Rev*. 2004:CD003041.
6. Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation*. 2004;109:1371–1378.
7. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med*. 2004;116:693–706.
8. Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;328:189.
9. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol*. 2003;42:2139–2143.
10. Lloyd-Williams F, Mair FS, Leitner M. Exercise training and heart failure: a systematic review of current evidence. *Br J Gen Pract*. 2002;52:47–55.
11. Balady GJ, Jette D, Scheer J, Downing J. Changes in exercise capacity following cardiac rehabilitation in patients stratified according to age and gender. Results of the Massachusetts Association of Cardiovascular and Pulmonary Rehabilitation Multicenter Database. *J Cardiopulm Rehabil*. 1996;16:38–46.
12. Hawkins S, Wiswell R. Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training. *Sports Med*. 2003;33:877–888.
13. Pedersen O, Gaede P. Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the Steno-2 study. *Metabolism*. 2003;52(8 suppl 1):S19–S23.
14. Katzmarzyk PT, Janssen I, Ardern CI. Physical inactivity, excess adiposity and premature mortality. *Obes Rev*. 2003;4:257–290.
15. Loimaala A, Huikuri HV, Koobi T, Rinne M, Nenonen A, Vuori I. Exercise training improves baroreflex sensitivity in type 2 diabetes. *Diabetes*. 2003;52:1837–1842.
16. Facchini M, Malfatto G, Sala L, et al. Changes of autonomic cardiac profile after a 3-week integrated body weight reduction program in severely obese patients. *J Endocrinol Invest*. 2003; 26:138–142.
17. Hagberg JM, Park JJ, Brown MD. The role of exercise training in the treatment of hypertension: an update. *Sports Med*. 2000;30:193–206.
18. Stewart KJ, McFarland LD, Weinhofer JJ, Cottrell E, Brown CS, Shapiro EP. Safety and efficacy of weight training soon after acute myocardial infarction. *J Cardiopulm Rehabil*. 1998;18:37–1844.
19. Johnson NA, Heller RF. Prediction of patient nonadherence with home-based exercise for cardiac rehabilitation: the role of perceived barriers and perceived benefits. *Prev Med*. 1998;27:56–64.

20. Smith KM, Arthur HM, McKelvie RS, Kodis J. Differences in sustainability of exercise and health-related quality of life outcomes following home or hospital-based cardiac rehabilitation. *Eur J Cardiovasc Prev Rehabil*. 2004;11:313–319.
21. Cobb LA, Weaver WD. Exercise: a risk for sudden death in patients with coronary heart disease. *J Am Coll Cardiol*. 1986;7:215–219.
22. Ikarugi H, Shibata M, Shibata S, Ishii H, Taka T, Yamamoto J. High intensity exercise enhances platelet reactivity to shear stress and coagulation during and after exercise. *Pathophysiol Haemost Thromb*. 2003;33:127–133.
23. Kalapura T, Lavie CJ, Jaffrani W, Chilakamarri V, Milani RV. Effects of cardiac rehabilitation and exercise training on indexes of dispersion of ventricular repolarization in patients after acute myocardial infarction. *Am J Cardiol*. 2003;92:292–294.
24. Van Camp SP, Peterson RA. Cardiovascular complications of outpatient cardiac rehabilitation programs. *JAMA*. 1986;256:1160–1163.
25. Thompson PD, Funk EJ, Carleton RA, Sturner WQ. Incidence of death during jogging in Rhode Island from 1975 through 1980. *JAMA*. 1982;247:2535–2538.

Imaging: hypertrophic cardiomyopathy and athlete's heart

Ingo Paetsch, Eike Nagel
Department of Cardiology, German Heart Institute, Berlin, Germany

Correspondence: Eike Nagel, Department of Cardiology, German Heart Institute, Augustenburger Platz 1, 13 353 Berlin, Germany. Email: eike.nagel@DHZB.de

Abstract

Imaging methods like echocardiography and cardiac magnetic resonance (CMR) can be useful for differentiation between hypertrophic cardiomyopathy (HCM) and training induced (physiologic) left ventricular hypertrophy. While echocardiography remains the first line method for the assessment of left ventricular dimensions and wall thickness, CMR imaging offers additional information with regard to myocardial texture characterization and assessment of intramyocardial motion components. Contrast enhanced CMR detects even subtle areas of (intra)-myocardial fibrosis which are frequently found in HCM patients and the amount of fibrotic tissue has been shown to correlate with patient prognosis. In addition, CMR myocardial tagging allows to measure systolic and diastolic motion components with diastolic function being normal in physiologic hypertrophy, while most HCM patients have abnormal diastolic function.

In some cases, however, a definitive diagnosis can only be made after deconditioning of the athlete (=interruption of training): CMR imaging with its high reproducibility for the determination of left ventricular volumes and mass is particularly valuable to prove the serial regression of physiologic left ventricular hypertrophy over time while in HCM patients hypertrophy persists.

■ *Heart Metab.* 2005;26:15–19.

Keywords: Hypertrophic cardiomyopathy, physiological mycocardial hypertrophy, echocardiography, cardiac magnetic resonance imaging

Introduction

Imaging can play a crucial role in the differential diagnosis between hypertrophic cardiomyopathy and the athlete's heart. Even though the final diagnosis may be made only after reduction of training in some cases, imaging may provide essential information in most patients. Echocardiography is the first method to be used. Magnetic resonance techniques provide information, such as a more accurate determination of wall thickness and muscle mass, the detection of myocardial fibrosis, and the ability to assess intramural myocardial motion components, including cardiac twisting and untwisting. These data may aid better discrimination between those with hypertrophic cardiomyopathy, and athletes (see flow chart for the different diagnostic steps in Figure 1). In addition the criteria for differential diagnosis between dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy is summarized in *Table I*.

Magnetic resonance techniques

As most physicians are well informed concerning echocardiographic techniques, but may have a less specific knowledge on magnetic resonance imaging, the major magnetic resonance methods that are applied in the patients under discussion will be reviewed briefly here.

Assessment of left ventricular dimensions, wall thickness and muscle mass

Magnetic resonance imaging is superior to all other imaging methods for the assessment of left ventricular

Table I. Differential diagnosis of dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy in athletes.

Suspicious finding	Suspected diagnosis	Athlete's heart	Cardiomyopathy
Increase in LV end-diastolic diameter > 60 mm	Dilated cardiomyopathy	Normal systolic function	Systolic dysfunction
Right ventricular enlargement in combination with conduction abnormalities	Arrhythmogenic right ventricular cardiomyopathy	Normal regional/global systolic function	T wave inversion V1 – V3 Segmental right ventricular wall motion abnormalities Regional right ventricular wall thinning Fatty infiltrations

LV, left ventricular.

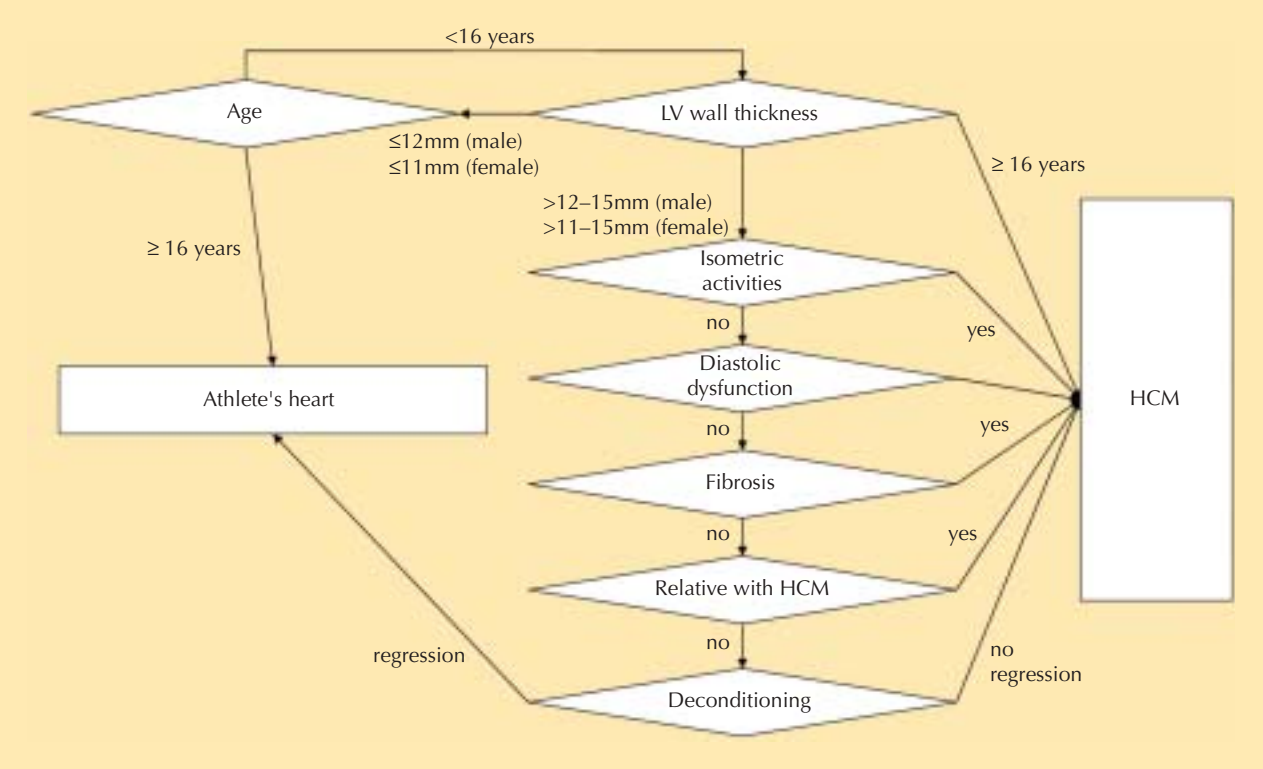

Figure 1. Flowchart for steps in the differential diagnosis between hypertrophic cardiomyopathy (HCM) and athlete's heart. LV, left ventricle.

dimensions, wall thickness and muscle mass. This is because of its three-dimensional visualization independent of any imaging windows, the high contrast between blood and myocardium, and its high temporal and spatial resolution. Today, steady-state free precession techniques are used for this purpose. In these, in contrast to earlier techniques (turbo-gradient echo), the contrast between blood and the myocardium is independent of the inflow of blood (with fresh magnetization) into the imaging slice. Contrast is generated by the inherent differences of magnetization of blood and myocardium. The application of this technique has improved blood–myocardial contrast significantly in long-axis views and in patients with reduced ejection fraction. In addition, steady-state free precession techniques yield an unprecedented accuracy for the depiction of the trabeculae, as the presence of blood between these myocardial structures results in bright signal, independent of its flow, resulting in an even more accurate determination of wall thickness and muscle mass. Magnetic resonance is regarded as the reference standard for the assessment of left ventricular muscle mass [1,2].

Detection of fibrosis

A new technique applied in most patients with suspected cardiomyopathy is the so-called 'late

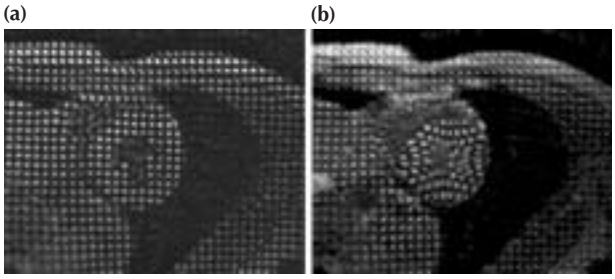

Figure 2. Assessment of intramyocardial motion components and cardiac rotation using myocardial tagging in a patient with hypertrophic cardiomyopathy. (a) End-diastole; (b) end-systole. There is normal myocardial shortening and thickening; however, rotation is completely absent.

enhancement' (or 'delayed hyperenhancement') technique [3]. The standard contrast agents used for magnetic resonance imaging (gadolinium chelates) diffuse from the vascular bed into the interstitium, but not into the cell. Any increase in distribution volume or a reduction in wash-out of the contrast agent will lead to a local enrichment of the drug, which can be visualized with magnetic resonance imaging. Although this technique was originally proposed for the detection of necrosis in myocardial infarction, increasing data confirm its applicability to the detection of any form of fibrosis within the myocardium.

Myocardial tagging

Myocardial tagging is a magnetic resonance technique that allows the placement of 'tags' on the myocardium at end-diastole by regionally modulating the magnetization (*Figure 2*). The tags remain fixed to the myocardium during systolic contraction and diastolic relaxation, and allow for the analysis of intramyocardial motion components (eg, endocardial or epicardial motion or rotation). A major drawback of this technique is the tedious analysis, which has hindered its application in clinical practice. New, nearly fully automated, tools of analysis (eg, harmonic phase, HARP [4]) are available, however, and will rapidly bring this technique into daily use.

Assessment of left ventricular wall thickness

Echocardiographic studies have shown that the vast majority of young athletes have a left ventricular wall thickness less than 12 mm. Only 0.4% of males had a wall thickness greater than 12 mm, and in no female was it greater than 11 mm, prompting further investigation in a study of 720 elite adolescent athletes [5]. In another study, the number was higher, 2.5% of male elite athletes having a wall thickness greater than 12 mm [6]. Most cases of hypertrophic cardiomyopathy exhibit a wall thickness of 20 mm or more; however, some patients with hypertrophic cardiomyopathy may have only a mild hypertrophy – as little as 13 mm [7–9] – thus creating some overlap with competitive athletes. Wall thickness alone may thus not suffice to differentiate between athletes and hypertrophic cardiomyopathy in individuals in whom the wall thickness is between 13 and 15 mm. Suspicion of pathology should be greater if borderline thickness is found in athletes performing isometric activities (weight-lifting, etc) than when it is present in athletes performing endurance sports (rowing, cycling), because left ventricular wall thickness and left ventricular muscle mass are greatest in the latter [10–12]. However, such a thickening of the left ventricular wall is usually in parallel with significant left ventricular enlargement [13].

Training causes a similar increase in thickness of all myocardial segments, with the anterior septum taking the lead. Differences between different segments are usually less than 2 mm and show a smooth transition. In patients with hypertrophic cardiomyopathy, similar thickening of the anterior septum can be observed; however, significant differences between different myocardial segments occur frequently, being most pronounced in patients with hypertrophic obstructive cardiomyopathy, but also in nonobstructive disease. Pathologic hypertrophy tends to be asymmetric and to show abrupt differences in wall thickness; further-

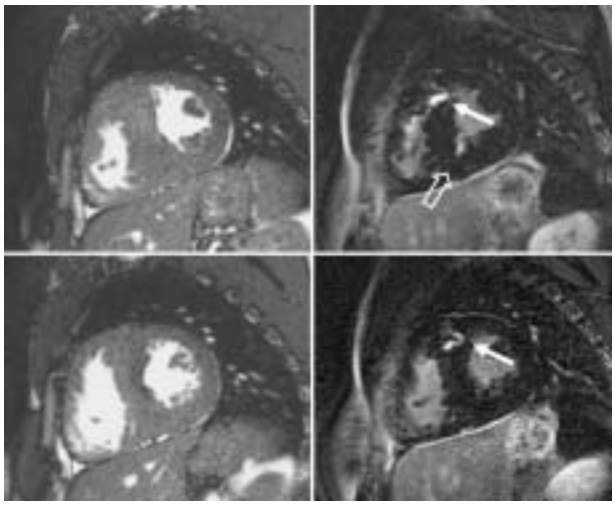

Figure 3. Assessment of left ventricular function, morphology and myocardial structure. Left: Steady-state free precession, end-diastolic images of a cine-loop. Right: Late enhancement images. Top row: Equatorial slice. Bottom row: Basal slice. There are significant regional differences in wall thickness, with abrupt changes typical of cardiomyopathy. In addition, fibrotic tissue can be seen anteroseptal (closed arrows) and mid-inferoseptal (open arrow).

more, frequently, segments other than the anterior septum demonstrate the greatest thickness (*Figure 3*).

Even though echocardiography is well suited to pick up these subtle differences, one should keep in mind that all myocardial segments need to be evaluated quantitatively. In borderline cases (in combination with suboptimal echocardiographic image quality), magnetic resonance imaging may be better suited to achieve reliable visualization and quantification of all myocardial segments. If a borderline diagnosis is made in younger patients (younger than 16 years), follow-up examinations need to be performed, because maximal wall thickness is usually reached after full maturity.

Cavity dimensions

End-diastolic cavity dimensions can give important information in cases with extreme values. A well-trained athlete is likely to have have an enlarged left ventricular end-diastolic diameter (>55 mm), which needs to be discriminated from dilated cardiomyopathy (usually >60 mm) [13]. In contrast, most patients with hypertrophic cardiomyopathy show a rather small diastolic cavity dimension of less than 45 mm. In these patients, however, dilatation of the ventricle may occur over time, and reach similarly high values. Cavity dimensions between 45 mm and 55 mm, which are found in the majority of athletes, do not help in making the differential diagnosis.

Diastolic function

As a rule of thumb, athletes can be expected to have normal diastolic function, independent of their myocardial thickness. In contrast, most patients with hypertrophic cardiomyopathy have abnormal diastolic function. However, individuals with hypertrophic cardiomyopathy, in particular those with mild to moderate hypertrophy, are less likely to show abnormalities. Thus any abnormality in diastolic function confirms the diagnosis of pathology, whereas normal diastolic function does not exclude disease.

Diastolic function may be assessed from the transmitral flow pattern determined with Doppler echocardiography, with an inverted E/A ratio in diastolic dysfunction (A >E; early passive diastolic filling is decreased, late filling during atrial contraction is increased) [14].

Assessment of regional myocardial motion and cardiac rotation and relaxation

With classic imaging techniques, rotational and intramural components of motion are neglected. Studies using myocardial tagging have shown differences in early diastolic rotation (untwisting) between patients with different types of left ventricular hypertrophy. Diastolic untwisting is an important part of diastolic function: it is the most rapid motion component of the healthy heart. In athletes (rowers), early diastolic untwisting is enhanced and rotation velocity increased [15], but patients with hypertrophic cardiomyopathy show a prolongation of diastolic untwisting, with a reduction in rotation velocity. This finding has been related to differences in fiber orientation, with fiber disarray (*Figure 2*).

Similarly, regional differences in shortening and lengthening velocities have been observed by means of tissue Doppler echocardiography [16–20].

Assessment of myocardial fibrosis

Similar to the fibrotic alterations found in myocardial infarction, fibrotic changes [21] or severe fiber disarray with increased interstitial space have an enlarged distribution volume for magnetic resonance contrast agents. These areas show an enhancement in a strongly T1-weighted magnetic resonance scan. Lesions have been found in typical locations in patients with hypertrophic cardiomyopathy, and the amount of enhanced areas correlates with the patient's prognosis [22] (*Figure 3*). The likelihood of a cardiac event was significantly greater in patients with larger fibrotic areas (28.5% of left ventricular muscle mass) than in patients with only mild (8.7%) or no fibrosis.

Family screening

Because of the genetic transmission of hypertrophic cardiomyopathy, family screening may help to establish the diagnosis in borderline cases. The presence of hypertrophic cardiomyopathy in a family member confirms the diagnosis; however, its absence does not exclude it, because the genetic disorder shows incomplete penetration [23]. Potentially, screening could also be performed by DNA analysis; however, the heterogeneity of abnormalities makes this task similarly difficult [23].

Deconditioning

A final step in the diagnosis is the need to refrain from training for several months, which will allow physiologic hypertrophy to normalize, whereas hypertrophic cardiomyopathy will remain unchanged despite the interruption to training [24,25]. Serial examinations should be performed with magnetic resonance rather than echocardiography because of

its greater reproducibility and, thus, ability to detect changes early and allow the patient to resume training again as soon as possible.

Conclusions

The combination of several imaging parameters may prove the presence of pathologic hypertrophy. If no abnormalities are found, the likelihood of cardiomyopathy is low; however, in a few patients deconditioning may be required to enable the final diagnosis to be made. In general, echocardiographic techniques are sufficient; in difficult cases, magnetic resonance imaging may yield additional and valuable information. ■

REFERENCES

1. Moon JC, Lorenz CH, Francis JM, Smith GC, Pennell DJ. Breath-hold FLASH and FISP cardiovascular MR imaging: left ventricular volume differences and reproducibility. *Radiology*. 2002;223:789–97.
2. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29–34.
3. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445–1453.
4. Osman NF, McVeigh ER, Prince JL. Imaging heart motion using harmonic phase MRI. *IEEE Trans Med Imaging*. 2000;19:186–202.
5. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40:1431–1436.
6. Whyte GP, George K, Sharma S, et al. The upper limit of physiological cardiac hypertrophy in elite male and female athletes: the British experience. *Eur J Appl Physiol*. 2004;92:592–597.
7. Henry WL, Gardin JM, Ware JH. Echocardiographic measurements in normal subjects from infancy to old age. *Circulation*. 1980;62:1054–1061.
8. Lauer MS, Larson MG, Levy D. Gender-specific reference M-mode values in adults: population-derived values with consideration of the impact of height. *J Am Coll Cardiol*. 1995;26:1039–1046.
9. Maron BJ. Hypertrophic cardiomyopathy. *Lancet*. 1997;350:127–133.
10. Urhausen A, Monz T, Kindermann W. Sports-specific adaptation of left ventricular muscle mass in athlete's heart. II: An echocardiographic study with 400-m runners and soccer players. *Int J Sports Med*. 1996;17(suppl 3):S152–S156.
11. Urhausen A, Monz T, Kindermann W. Sports-specific adaptation of left ventricular muscle mass in athlete's heart. I: An echocardiographic study with combined isometric and dynamic exercise trained athletes (male and female rowers). *Int J Sports Med*. 1996;17(suppl 3):S145–S151.
12. Urhausen A, Monz T, Kindermann W. Echocardiographic criteria of physiological left ventricular hypertrophy in combined strength- and endurance-trained athletes. *Int J Card Imaging*. 1997;13:43–52.
13. Abergel E, Chatellier G, Hagege AA, et al. Serial left ventricular adaptations in world-class professional cyclists: implications for disease screening and follow-up. *J Am Coll Cardiol*. 2004;44:144–149.
14. Ito T, Suwa M, Imai M, Nakamura T, Kitaura Y. Assessment of regional left ventricular filling dynamics using color kinesis in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr*. 2004;17:146–151.
15. Stuber M, Scheidegger MB, Fischer SE, et al. Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation*. 1999;100:361–368.
16. Rajiv C, Vinereanu D, Fraser AG. Tissue Doppler imaging for the evaluation of patients with hypertrophic cardiomyopathy. *Curr Opin Cardiol*. 2004;19:430–436.
17. Palka P, Lange A, Fleming AD, et al. Differences in myocardial velocity gradient measured throughout the cardiac cycle in patients with hypertrophic cardiomyopathy, athletes and patients with left ventricular hypertrophy due to hypertension. *J Am Coll Cardiol*. 1997;30:760–768.
18. Derumeaux G, Douillet R, Troniou A, et al. Distinguishing between physiologic hypertrophy in athletes and primary hypertrophic cardiomyopathies. Importance of tissue color Doppler [in French]. *Arch Mal Coeur Vaiss* 1999;92:201–210.
19. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation*. 2001;104:128–130.
20. McMahon CJ, Nagueh SF, Pignatelli RH, et al. Characterization of left ventricular diastolic function by tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. *Circulation*. 2004;109:1756–1762.
21. Moon JC, Reed E, Sheppard MN, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004;43:2260–2264.
22. Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2003;41:1561–1567.
23. Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation*. 2003;107:2227–2232.
24. Pelliccia A, Maron BJ, De Luca R, Di Paolo FM, Spataro A, Culasso F. Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. *Circulation*. 2002;105:944–949.
25. Maron BJ, Pelliccia A, Spataro A, Granata M. Reduction in left ventricular wall thickness after deconditioning in highly trained Olympic athletes. *Br Heart J*. 1993;69:125–128.

Constructing an exercise program

Andrew A. McLeod
Poole Hospital NHS Trust, Poole, Dorset, UK

Correspondence: Dr Andrew A. McLeod, Poole Hospital NHS Trust, Longfleet Road, Poole, Dorset BH15 2JB, UK.
E-mail: andrew.mcleod@poole.nhs.uk

Abstract

Exercise programs require consideration of the client group who will participate, and need to focus on the likely available resources. Specific outcome targets need to be considered, and objective evaluation is required to demonstrate benefit for those participating.
■ *Heart Metab.* 2005; 26:20–22.

Keywords: Cardiac rehabilitation, exercise training, exercise prescription, program evaluation, outcome measures

Better to hunt in fields, for health unbought
Than fee the doctor for a nauseous draught,
The wise, for cure, on exercise depend;
God never made his work, for man to mend.

John Dryden

Introduction

The Exercise Program has become an accepted part of almost every cardiac rehabilitation program. Few can accept such *ex cathedra* statements as Dryden's without some qualification, however. The data on which exercise programs are predicated seem secure, but myriad exercise programs abound, with doubtful efficacy for some. It seems best first to define what targets are to be achieved, and then to construct the program. A number of factors need to be considered.

The client group

Is the aim primary or secondary prevention of coronary heart disease? Special groups of patients to be considered include: women, those with diabetes, the obese, patients with heart failure and post cardiac transplant, patients with peripheral arterial disease, those with pulmonary disease, and individuals at very high risk, such as those with implantable defibrillators.

The personnel available

Few program developers will be able to design their ideal syllabus, and then recruit the personnel. The Lifestyle Heart Trial, for example, is unique in cardiac literature in crediting six chefs in a trial that only recruited 48 patients [1].

The likely level of funding

Appropriate monitoring for high-risk patients such as those with heart failure will increase costs.

The compliance factor

A minority of those invited to join traditional exercise programs actually participate. Is the aim to target those without the psychological or financial support, or who will find it difficult to travel to the exercise facility?

The age of the proposed clients

In the elderly, for example, rigorous aerobic training may not be appropriate (although some will participate). Programs that concentrate on strength training (to avoid muscle weakness and increased susceptibility to falls and injury) and flexibility training (to

avoid disability and immobility) may achieve greater health gains overall, although remarkable benefits can be seen in the very elderly [2].

The location of the program

The standard gym or exercise facility program tends to attract a particular type of cardiac patient, usually male, and often at low cardiac risk. Home-based programs offer a better option for many, with equivalent results [3].

The wish to exercise

This differs subtly from compliance. The problem here lies in a client group that has never seen the value of exercise (particularly older women), and the difficulty is in achieving the change in behavior required to commence the exercise program. The initial aim should be to allow the patient greater personal control and responsibility, often by working in groups. The emphasis should be on non didactic teaching (a paradoxical term), together with support. 'Knowledge is necessary but not sufficient to lead to changes in behavior' [4].

Should exercise be on the 'menu'?

This is related to the previous point. The benefits of exercise in almost all cardiac conditions (or associated conditions such as diabetes and obesity) are indisputable. There will be a group of patients however, who will not wish to increase their exercise level, but who may willingly accept the health benefits of other treatments. These include secondary drug prevention (eg, statins, β-blockers, angiotensin-converting enzyme inhibitors), but might also include support for smoking cessation, and dietary modification. Not all clients will wish to take up all the potentially beneficial modifications on offer. Hence the concept of the rehabilitation 'menu'. With this approach, the therapist tailors the treatments, advice, or support on offer to the perceived requirements of the client. Because this is a two-way process, however, the client should explore with the therapist which treatment on the menu is suitable for them.

What is already available?

There is no shame in copying a successful program. Therapeutic plagiarism is beneficial for all.

Exercise equipment

A recent meta-analysis of cardiac rehabilitation trials that included exercise, undertaken by Joliffe and colleagues for the Cochrane Collaboration [5], has indicated that exercise was the key component in cardiac rehabilitation programs that were associated with reduction in mortality. Not all programs achieve a substantial training effect. In the recent study by Hambrecht and colleagues [6], a vigorous aerobic exercise program conducted on stationary bicycle ergometers was as effective as intervention by percutaneous coronary intervention over a 1-year period, but this required exercise daily. The bicycle offers definite benefit in aerobic programs: the risk of injury is low; heart rate monitoring or respiratory impedance monitoring can accurately quantitate the level of exercise; the external work done can be quantitated accurately. Many patients, however, do not possess the innate quadriceps femoris muscle strength necessary to generate sufficient exercise muscle mass, which results in a substantial increase in oxygen uptake and heart rate. Such patients often find it easier to use a treadmill, which effectively limits them to a fitness center facility. Walking on the flat may not achieve required aerobic levels, however, and individuals in fitness centers are commonly seen exercising on horizontal treadmills. Gravity is a powerful and an extremely useful force in designing an exercise regimen, and even modest slopes considerably enhance oxygen uptake. Home equipment commonly makes use of gravity: for example, stepping up and down one or two stairs; lifting household items to improve upper body strength. In very elderly individuals, however, the ability to walk briskly may be compromised by unsteadiness. In the massively obese, even walking may risk orthopedic injury; for this group, exercise in a swimming pool, with the buoyancy effect of water to minimize injury, can be beneficial.

Assessment of exercise level

Outcome measures of exercise programs should be defined. Some relatively simple techniques have been described (6-min walk test [7], shuttle walk test [8]). Detailed cardiorespiratory gas-exchange techniques are cumbersome and usually only suited to research programs. If treadmill testing or ergometer testing is used, care should be taken to avoid familiarization bias. Heart rates recorded at the same submaximal workload as before the exercise program are valuable. For determining exercise prescription, the Karvonen [9] method for calculating desired levels of exercise during training is simple and accurate, and

has also been validated for patients taking β-blockers. Many programs use the self-estimated 'rating of perceived exertion' conceived by Gunnar Borg's group [10].

Exercise sessions

Some degree of compromise is necessary to set the level of participation required. There is no substitute for an enthusiastic and charismatic leader of a program. Exercise targets should be demanding, but not impossible to achieve. Patients easily lose motivation. Chair-based therapy, which has been used in both arthritis and cardiac patients, can be fun, requires minimal equipment, and is suited to the older or overweight individual. Compliance and adherence can be achieved through the camaraderie of the group, which provides a social as well as a therapeutic function.

If no funding of any consequence is available, very simple forms of exercise can be used. Simply meeting together and walking can be valuable, and is often organized by patient support groups. In the UK, this does not carry the same risk of litigation as in the USA, although this aspect needs to be considered. It may be adequate to have some form of diploma, which can be medically approved or countersigned, to allow simple exercise activity. Freedom from severe ischemia, or demonstrated arrhythmias, and treatment with appropriate drugs may be all that is required.

Conclusion

Exercise programs can range from the very sophisticated to the very simple. Although much publicity obtains for interventional treatments for coronary artery disease, every intervention is as much a failure, and an acknowledgment of failure, of preventive medicine as it is a success. Comprehensive care of the cardiac patient should integrate primary and secondary prevention of heart disease, in addition to intervention. ■

REFERENCES

1. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? *Lancet*. 1990;336:129–133.
2. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330:1769–1775.
3. DeBusk RF. Supervised versus unsupervised exercise training: risks and benefits. In: Wenger NK, Smith LK, Froelicher ES, Comoss PM, eds. *Cardiac Rehabilitation: a Guide to Practice in the 21st Century*. New York: Marcel Dekker, Inc.; 1999:103–108.
4. Newman S, Mulligan K, Steed L. What is meant by self-management and how can its efficacy be established? *Rheumatology*. 2001;40:1–6.
5. Joliffe JA, Rees K, Taylor RS, et al. Exercise-based rehabilitation for coronary heart disease (Cochrane Review). The Cochrane Library; issue 1. Oxford: Oxford Update Software, 2003.
6. Hambrecht R, Walther C, Möbius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease. A randomised trial. *Circulation*. 2004;109:1371–1378.
7. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *BMJ*. 1986;292:693–695.
8. Revill SM, Morgan MD, Singh SJ, et al. The endurance shuttle walk. A new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax*. 1999;54:191–193.
9. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 6th ed. Indianapolis, IN: American College of Sports Medicine.
10. Noble BJ, Borg GA, Jacobs I, et al. A category-ratio perceived exertion scale: relationship to blood and muscle lactate and heart rate. *Med Sci Sports Exerc*. 1983;15:523–528.

New therapeutic approach in chronic heart failure: metabolic intervention with trimetazidine

Hamayak S. Sisakyan
Department of Internal Diseases Diagnostics and Cardiology, University N1 Hospital, Yerevan State Medical University, Yerevan, Armenia

Correspondence: Professor Hamayak S. Sisakyan, Koryun Street 2, Yerevan State Medical University, Yerevan 375025, Armenia. Tel: +347 1 582023, fax: +347 1 541350, e-mail: sisakyan@doctor.com

Abstract

The management of heart failure has improved over the past decade. Angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone inhibitors relieve symptomatology, prevent the progression of heart failure, and improve survival. However, despite the advances in treatment, the prognosis of heart failure remains unfavorable in many patients. In heart failure, myocardial metabolism seems to be directed toward increased oxidation of free fatty acids, which is energy consuming compared with glucose oxidation. Trimetazidine, a metabolic agent with anti-ischemic properties, reduces fatty acid β-oxidation via selective inhibition of 3-ketoacyl-coenzyme A thiolase activity, thereby facilitating energy production via the glycolytic pathway. Switching the substrate energy preference for cellular metabolism is effective in improving the exercise capacity of patients with angina pectoris. At the same time, this effect can also enhance left ventricular function in patients with ischemic cardiomyopathy. We studied the effect of trimetazidine on left ventricular systolic function in patients with ischemic cardiomyopathy, in addition to their standard therapy.
■ *Heart Metab.* 2005; 26:23–26

Keywords: Ischemic cardiomyopathy, left ventricular dysfunction, trimetazidine, myocardial metabolism, echocardiography

Introduction

The management of heart failure has improved considerably over the past decade. Treatment modalities that influence cardiac remodeling and neuroendocrine activation exert beneficial effects by decreasing symptoms, improving quality of life, and reducing high mortality.

Increased energy metabolism through the free fatty acid pathway may be unfavorable in conditions of decreased delivery of oxygen to the heart [1,2]. One of the pathophysiologic metabolic pathways responsible for the progression of heart failure is the induction of insulin resistance, which initiates sympathetic activity, endothelial dysfunction, and increased activity of proinflammatory cytokines [3]. Influencing the energy metabolism of the failing heart by stimulating pyruvate dehydrogenase activity and facilitating glucose oxidation seems attractive from a pathophysiologic and metabolic point of view, as glucose oxidation needs less oxygen and energy [1–3]; the improvement in cardiac energy metabolism will support the enhancement in mechanical efficiency. This hypothesis has been confirmed by the use of trimetazidine in several studies in patients with left ventricular dysfunction and ischemic cardiomyopathy [4–7]. Trimetazidine, through selective inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, increases glucose oxidation by a shift of energy substrate preference from fatty acid to glucose oxidation [8].

Effect of trimetazidine on left ventricular function in patients with ischemic cardiomyopathy

We undertook a study to determine whether modified-release trimetazidine (Preductal MR; 35 mg twice daily), has a positive effect on left ventricular function in patients with ischemic cardiomyopathy, when taken in conjunction with their standard therapy (angiotensin-converting enzyme [ACE] inhibitors, diuretics, and β-blockers).

Seventeen patients were recruited to the study, which was performed at Yerevan State Medical University Hospital, Department of Internal Diseases Diagnostics and Cardiology. One patient was excluded after 1 week because of poor compliance with the standard therapy. Inclusion criteria were: stable clinical condition before entry on standard therapy (ACE inhibitors, β-blockers, diuretics). All patients had an end-diastolic diameter of at least 6.0 cm, and ejection fraction less than 45% as determined by echocardiography. A total of 16 patients with ischemic cardiomyopathy designated as New York Heart Association (NYHA) functional Class II or III were allocated randomly to groups to receive additional treatment with modified-release trimetazidine 35 mg twice daily (eight patients) or to continue with their standard therapy for heart failure (eight patients). They were followed for 3 months. Echocardiography (ATL Ultramark-9 system, Boston WA, USA) was performed at baseline and after 3 months of treatment. All examinations were recorded on videotape and evaluated by two different specialists. Left ventricular dimensions and diastolic and systolic volumes, ejection fraction, and fractional shortening were determined according to the recommendations of the American Society of Echocardiography [9].

All statistical tests reported are two-tailed *t*-tests. Values of $P \leqslant 0.05$ were considered to be significant.

Results

In the trimetazidine group, three patients improved from NYHA Class III to NYHA class II and two improved from NYHA Class II to Class I; among patients receiving conventional treatment, only two had improved functional class. None of the patients in the trimetazidine group worsened their NYHA functional status. During the first day after initiation of treatment and during the entire period of the study, no hemodynamic effect (change in heart rate or blood pressure) or any cardiovascular complication was observed. No serious clinical adverse events were reported by any of the patients.

The echocardiographic study showed a decrease in the end-systolic diameter of the left ventricle in the trimetazidine group, from 5.6 ± 0.8 cm at baseline to 4.92 ± 0.83 cm after 3 months of treatment. In the control group, the left ventricular systolic diameters remained unchanged (*Table I, Figure 1*).

The left ventricular function improved after 3 months of treatment with trimetazidine: the ejection fraction increased significantly ($P < 0.01$) to $41.2 \pm 7.2\%$, compared with a non significant increase to $34.5 \pm 8.1\%$ in the control group. Left ventricular end-diastolic diameter remained constant in both groups after 3 months.

Discussion

The results of our study show that, in patients with moderate chronic ischemic myocardial dysfunction, modified-release trimetazidine is able to relieve symptoms of heart failure and left ventricular function and is well tolerated, without any hemodynamic changes. These findings were not associated with any effects on the patients' heart rates or systolic blood pressures, reflecting the purely metabolic mechanism of action of the drug. To our knowledge, our study is the first to test modified-release trimetazidine with a dose of 70 mg/day in patients with ischemic cardiomyopathy. Although the study population was small, we were able to confirm the safety and tolerability of modified-release trimetazidine despite a daily dose that was increased (70 mg) in comparison with those previously used in clinical studies (20 mg three times a day).

The increase in myocardial contractility during ischemic cardiomyopathy can be explained by the regulation of mitochondrial structure and function, and by the increase in glycolytic adenosine triphosphate (ATP) synthesis [10]. It is possible that hibernated myocardium can be activated by trimetazidine: a favorable effect of trimetazidine on hibernation was demonstrated by Belardinelli and colleagues, who found that trimetazidine improved the contractile response of chronically dysfunctional myocardium to low-dose dobutamine [7,11].

It is well known that the heart has a high rate of energy turnover, with ATP as a basic source of energy. The two coexisting pathways for energy supply are β-oxidation of free fatty acids and breakdown of carbohydrates. The carbohydrate pathway comprises glycolysis and lactate oxidation, producing pyruvate, which is decarboxylated by pyruvate dehydrogenase to acetyl coenzyme A, which in turn enters the final common pathway of the Krebs cycle. Under aerobic conditions, the myocardium generates energy predominantly by oxidation of free fatty acids (70 to 80%), with a smaller contribution from glycolysis (20 to 30%).

Table I. Echocardiographic data of two groups after 3 months of treatment.

	Trimetazidine		Control	
Parameter	Baseline	3 months	Baseline	3 months
LVEDD (cm)	6.5 ± 0.7	6.4 ± 0.7	6.5 ± 5.6	6.3 ± > 7.6
LVESD (cm)	5.4 ± 0.8	4.9 ± 0.8**	5.6 ± 0.7	5.7 ± 0.9
EF (%)	31.7 ± 8.5	41.2 ± 7.2**	29.6 ± 5.0	34.5 ± 8.1
FS (%)	17.0 ± 6.1	23.4 ± 6.0**	13.4 ± 2.6	17.2 ± 5.3

EF, ejection fraction; FS, fractional shortening; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter. **$P < 0.01$ compared with baseline.

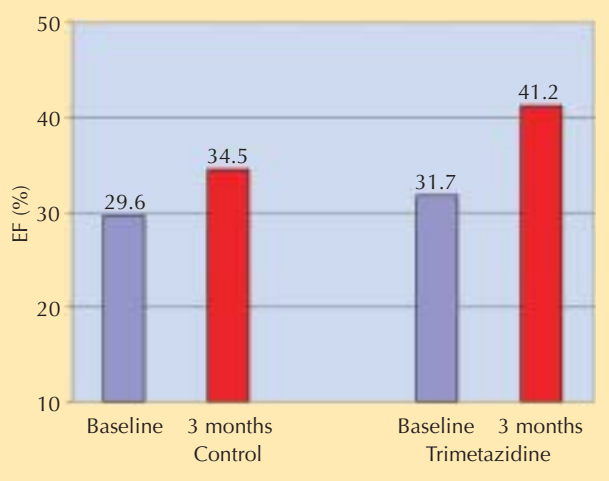

Figure 1. Effect of trimetazidine on left ventricular ejection fraction (EF) in patients with ischemic cardiomyopathy after 3 months compared with conventional therapy, P< 0.05.

The oxidation of glucose ensures the activity of the ion pumps (Na^+/K^+ ATPase and Ca^{2+} ATPase), which preserves the myocyte membrane potential and rapid transport of Ca^{2+} between subcellular compartments [12,13]. The glycolytic and pyruvate pathways require less oxygen per mole of ATP produced than does free fatty acid oxidation. The glucose–fatty acid cycle, described by Randle and colleagues in 1964 [14], preserves the balance between available energy substrates. Glucose utilization is controlled by the availability of, and sensitivity to, insulin, and also by competition with the free fatty acid pathway metabolites. Increased metabolism by the free fatty acid mechanism inhibits the glycolytic pathway, which may be unfavorable in a situation of decreased oxygen delivery to the heart or under other conditions (stress, heart failure, diabetes). Trimetazidine selectively inhibits long-chain 3-ketoacyl coenzyme A thiolase – a key enzyme involved in fatty acid β-oxidation. This compound stimulates glucose uptake, inducing glucose phosphorylation while reducing fatty acid oxidation [15,16].

Brottier and colleagues [4] were the first to demonstrate that patients with ischemic cardiomyopathy treated with trimetazidine for 6 months had ejection fractions (determined by radionuclide angiography) increased by more than 9% compared with a placebo group. The study by Belardinelli and Purcaro [7] in 38 patients with ischemic cardiomyopathy aimed to determine the effect of trimetazidine on cardiac function by echocardiography. The resting ejection fraction in the trimetazidine-treated group increased from 33.1 ± 4.5% to 39.5 ± 5.9% ($P = 0.001$), and the number of dysfunctional segments was reduced from 147 to 137. Low-dose dobutamine improved contractility in 99 of 179 segments, compared with no significant change in patients receiving placebo. This effect in a study of low-dose dobutamine suggests that preserved contractile reserve and viable myocardium may be activated by metabolic intervention with trimetazidine.

The recent study by Vitale and colleagues [5] aimed to assess the effect of trimetazidine on left ventricular function in elderly patients with left ventricular dysfunction, after 6 months. The results have shown that patients receiving trimetazidine had a greater improvement in NYHA class, and a better quality of diastolic function than did those in the placebo group (left ventricular ejection fractions 34.4 ± 2.3% and 27 ± 2.8%, respectively; $P < 0.0001$).

The limitations of our study were the small number of patients and the short (3 months) period of follow-up, which did not allow us to assess mortality with respect to the long-term benefit compared with that associated with other drugs used in chronic heart failure, such as β-blockers or ACE inhibitors.

Our data have provided support for the therapeutic importance of metabolic treatment with trimetazidine in patients with left ventricular dysfunction and ischemic cardiomyopathy.

Conclusions

Treatment with modified-release trimetazidine 70 mg/day in addition to standard therapy, over a 3-month period, improves the functional class and systolic function of patients with ischemic cardiomyopathy. This use of trimetazidine was associated with an excellent tolerance profile. ■

REFERENCES

1. Lopaschuk GP. Modulation of energy metabolism as an approach to treating heart failure. *Cardiovasc J S Afr*. 2004;15(45 suppl):52.
2. Marinho NV, Keogh BE, Costa DC, Lamersta AA, Ell PJ, Camici PG. Pathophysiology of chronic left ventricular dysfunction. New insights from the measurement of absolute myocardial blood flow and glucose utilization. *Circulation*. 1996;93:737–744.
3. Young N, Mc Nulty P, Taegtmeyer H. Adaptation and mal-adaptation of the heart in diabetes. Part II. *Circulation*. 2002;105:1861–1870.
4. Brottier L, Barat JL, Combe C, et al. Therapeutic value of a cardioprotective agent in patients with severe ischemic cardiomyopathy. *Eur Heart J*. 1990;11:207–212.
5. Vitale C, Wajngaten M, Sposato B, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur Heart J*. 2004;20:1814–1821.
6. Fragasso G, Piatti MPM, Monti L, et al. Short and long term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. *Am Heart J*. 2003;146:E18.
7. Belardinelli R, Purcano A. Effect of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischemic cardiomyopathy. *Eur Heart J*. 2001;22:2164–2170.
8. Lopaschuk G, Rozak R. Trimetazidine inhibits fatty acid oxidation of the heart. *J Mol Cell Cardiol*. 1998;30:A112.
9. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of two-dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989; 2:358–367.
10. Guarnieri C, Muscari C. Effect of trimetazidine on mitochondrial function and oxidative damage during reperfusion of ischemic hypertrophied myocardium. *Pharmacology*. 1993;46:324–331.
11. Belardinelli R, Georgiou D, Purcaro A. Low-dose dobutamine echocardiography predicts improvement in functional capacity after exercise training in patients with ischemic cardiomyopathy: prognostic implication. *J Am Coll Cardiol*. 1998;31:1027–1034.
12. Renaud JF. Internal pH, Na+ and Ca++ regulation by trimetazidine during cardiac cell acidosis. *Cardiovasc Drugs Ther*. 1988;1:677–686.
13. Ross J Jr. Myocardial perfusion–contraction matching. Implications for coronary heart disease and hibernation. *Circulation*. 1991;83:1076–1083.
14. Randle PJ, Newsholme EA, Garland PB. Regulation of glucose uptake by muscle. *Biochem J*. 1964;93:652–665.
15. 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;86:580–588.
16. Aussedat J, Ray A, Kay L, Verdys M, Harpey C, Rossl A. Improvement of long-term preservation of isolated arrested rat heart: beneficial effect of the antiischemic agent trimetazidine. *J Cardiovasc Pharmacol*. 1993;21:128–135.

Sustained benefit of trimetazidine adjunct to standard treatment in severe heart failure

Mario Marzilli
Department of Cardiology, University of Siena, Italy

Correspondence: Mario Marzilli, Department of Cardiology, University of Siena, Policlinico Le Scotte, V. Le Bracci, 53100 Siena, Italy.
E-mail: marzilli@unisi.it

Abstract

The case is reported of an 81-year-old man with a history of hypertension and a previous silent myocardial infarction who presented to our hospital with New York Heart Association (NYHA) Class III heart failure. Coronary angiography documented diffuse and severe coronary lesions, not suitable for percutaneous or surgical revascularization. High-dose trimetazidine (120 mg/day) was added to standard treatment and the patient was discharged home. He experienced a progressive improvement of symptoms and quality of life that was associated with a reduction in cardiac dimensions and improvement in contractile function. After 10 months, the patient was in NYHA Class I and tolerated the high dose of trimetazidine very well.

■ *Heart Metab.* 2005; 26:27–30.

Keywords: Trimetazidine, heart failure, left ventricular remodeling, electrocardiogram, echocardiogram

Case report

The patient was an 81-year-old gentleman, admitted to hospital on 2 January 2004 because of heart failure (New York Heart Association [NYHA] Class III).

He had been taking hypotensive drugs for more than 40 years. In the year 2000 he was first admitted to hospital for a syncope and discharged with a diagnosis of chronic obstructive lung disease and supraventricular tachycardia.

In January 2003, he began to complain of chest pain and dyspnea on effort. Since December 2003, chest pain had also occurred at rest. A myocardial perfusion scintigraphy obtained in December 2003 showed a marked reduction of tracer uptake in the anterolateral, apical, and inferoapical segments, with limited recovery at rest, consistent with a previous silent myocardial infarction.

On 2 January 2004, he was again admitted to hospital for worsening symptoms of heart failure and chest pain. At the time of admission, he was taking angiotensin-converting enzyme (ACE) inhibitors, nitrates, diuretics, digitalis, and antiplatelet agents.

The electrocardiogram (ECG) showed inverted T waves on the lateral leads (*Figure 1*).

Chest X-rays showed enlarged cardiac dimensions and pulmonary congestion.

The echocardiogram showed a dilated left ventricular cavity (left ventricular end-diastolic volume [LVEDV] 183 mL, left ventricular end-systolic volume [LVESV] 136 mL), a small increase in wall thickness (interventricular septal thickness 12.5 mm; postero lateral ventricular wall thickness [PLVWT] 10 mm), a severe reduction in systolic function (ejection fraction 31.7%), and a dilated left atrium (230 mm^2), with severe hypokinesis of the septum, the apex, and the inferoapical and lateral walls (*Figure 2*).

Coronary angiography was performed and revealed a multivessel coronary artery disease and severe global and regional left ventricular dysfunction, with

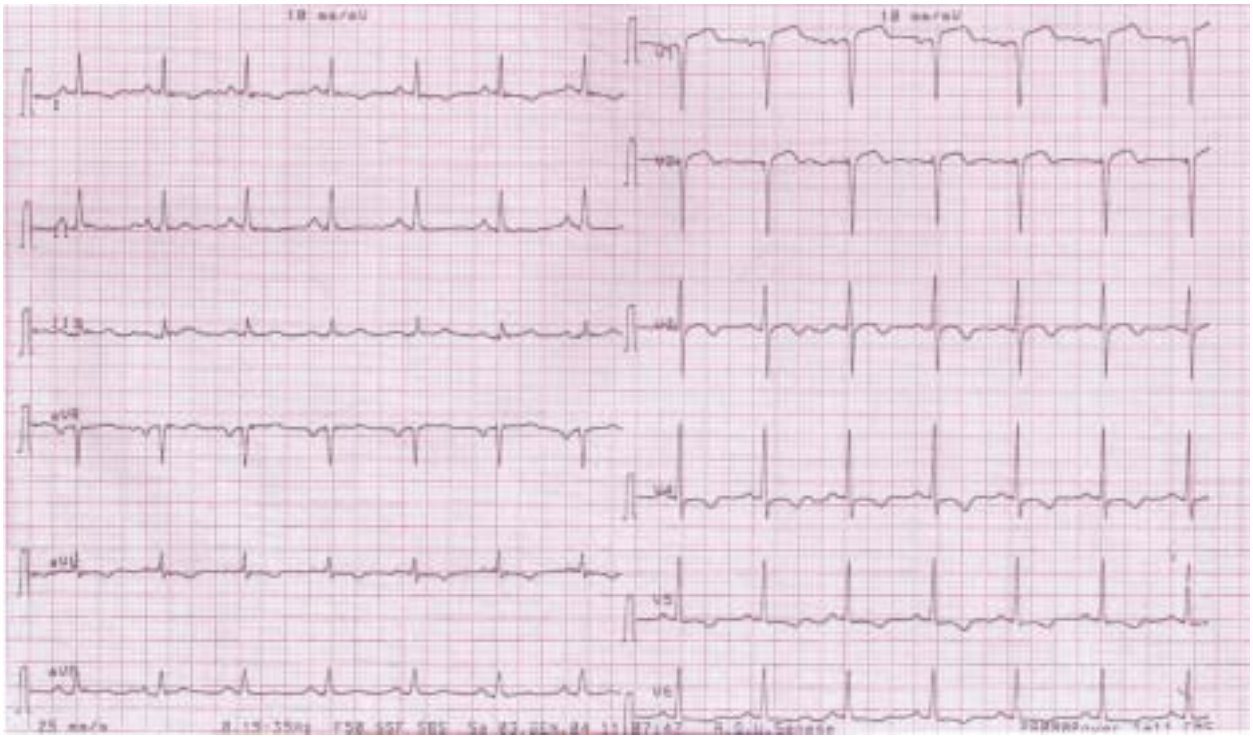

Figure 1. Resting electrocardiogram, January 2004.

a marked increase in left ventricular end-diastolic pressure.

A quality of life questionnaire was administered to the patient with a score of 45/105.

The patient was discharged from hospital on 5 January 2004, with a diagnosis of heart failure, multivessel coronary artery disease, left ventricular dysfunction, and hypertension. Trimetazidine 40 mg three times a day was added to his standard treatment, which now included digitalis, diuretics, ACE inhibitors, statins, nitrates, and low-dose aspirin.

On 23 March, the patient was seen in the outpatient clinic. He reported a significant improvement in symptoms, but physical examination and echocardiogram failed to demonstrate appreciable changes in cardiac chamber dimensions and function.

Seven months later, on 4 October, the patient was seen again in the outpatient clinic. He reported a further improvement in symptoms, which had moved his status from NYHA Class III to Class I, and reported that he had been asymptomatic for chest pain for the previous 4 months.

On the ECG, the T waves had normalized in the left lateral precordial leads, and a significant reduction in the cardiac dimensions was evident on the chest X-rays (*Figure 3*).

The echocardiogram revealed that the left ventricular volumes were reduced (LVEDV 170 mL; LVESV 52 mL) and the ejection fraction had increased to 38.4%. A recovery of contractile function was observed in the lateral wall (*Figure 4*).

The questionnaire on quality of life was re-administered on 11 October and the patient scored 5/105.

Discussion

We report the case of a patient who had survived a silent myocardial infarction at the age of 81 years and had developed a severe ventricular dysfunction.

After acute myocardial infarctions, patients often experience a progressive deterioration of left ventricular function that eventually leads to overt heart failure. This phenomenon, known as left ventricular remodeling, is poorly understood and does not have a specific treatment. Myocardial revascularization may improve symptoms in a patient with postischemic dysfunction and viable myocardium.

In this particular patient, the severity and extension of the coronary lesions, together with associated illnesses and advanced age, made the risk of a revascularization procedure excessive.

Having excluded a myocardial revascularization, we decided to optimize the medical treatment by adding a metabolic agent, trimetazidine, to the standard combination of drugs. Trimetazidine is a cardioprotective agent that shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by selective inhibition of mitochondrial 3-

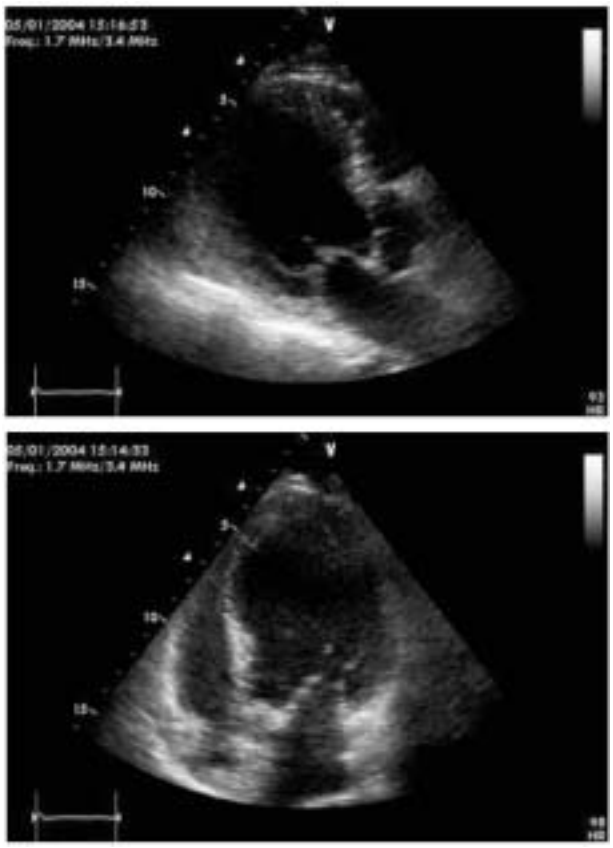

Figure 2. Echocardiographic findings on 2 January 2004. LVEDV = 183 mL, LVESV = 136 mL, end-diastolic diameter [DTD] = 7.46 cm, end-systolic diameter [DTS] = 5.64 cm, ejection fraction 31.7%, E-septum (distance between E point and septum in M-mode)= = 1.8 cm, left atrial area = 23 cm^2, wall motion score index = 1.5.

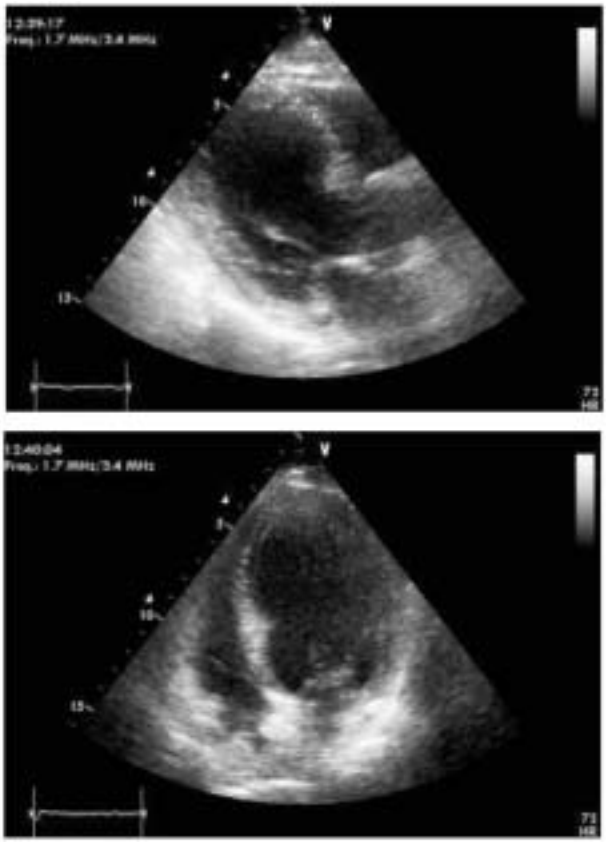

Figure 3. Echocardiographic findings on 4 October 2004. LVEDV = 158 mL, LVESV = 100 mL, end-diastolic diameter [DTD] = 7.14 cm, end-systolic diameter [DTS] = 5.21 cm, ejection fraction 38.4%, E-septum (distance between E point and septum in M-mode = 1.52 cm, left atrial area = 21 cm^2, wall motion score index = 1.25.

ketoacyl coenzyme A thiolase [1]. Because of its purely metabolic mechanism of action, trimetazidine does not interfere with heart rate and arterial pressure, and has minimal, if any, side effects and optimal patients compliance [2,3].

Trimetazidine is commonly used as an antianginal agent and has been shown to reduce the number of ischemic attacks and to improve exercise tolerance in patients with chronic ischemic heart disease, including those with diabetes, patients who have undergone revascularization, and patients with angina resistant to β-blockers and calcium channel blockers [4–7]. It has been shown to improve ejection fraction in patients with dilated cardiomyopathy and to improve the response to dobutamine stress in postischemic ventricular dysfunction [8–10].

The patient we report here appeared to be an ideal candidate for a metabolic approach to the presence of both angina and dyspnea on effort, both resistant to standard treatment. Given the severity of his condition, we decided to use a dose of trimetazidine double that recommended. After the addition of high-dose trimetazidine to his medication regimen, a progressive and significant improvement in symptoms was reported by the patient; furthermore, the amelioration in symptoms preceded objective evidence of improved ventricular function. Prolonged treatment with trimetazidine was associated with further improvement in exercise tolerance and quality of life, and with recovery of contractile function that was evident at echocardiography. ECG changes consistent with attenuation of myocardial ischemia were also observed after 10 months of treatment.

Conclusion

This case demonstrates the benefit of trimetazidine as adjunct to standard treatment in an elderly patient with severe ischemic left ventricular dysfunction, and confirms the good tolerability of this agent even at high dosage. ■

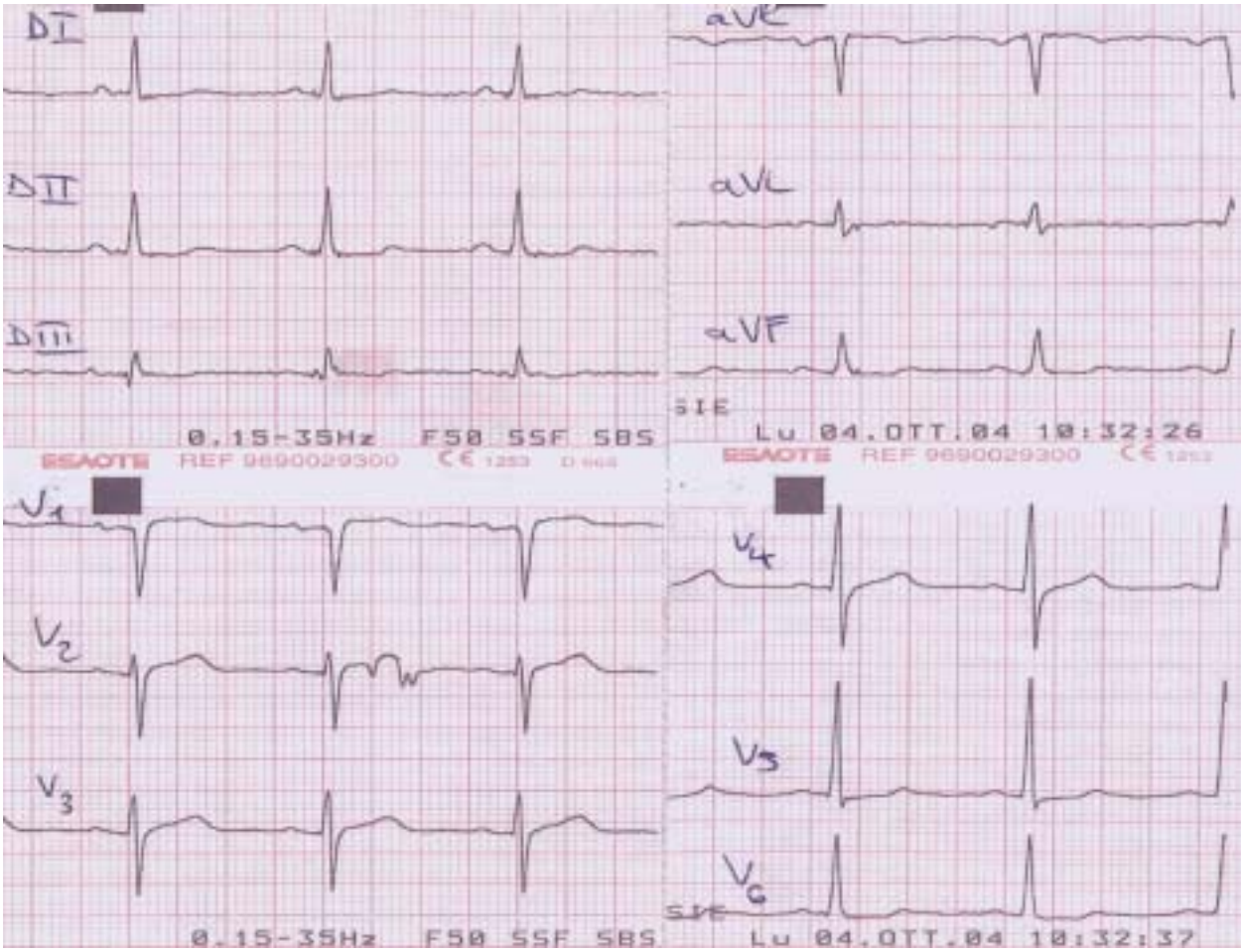

Figure 4. Echocardiogram, October 2004.

REFERENCES

1. 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;86:580–588.
2. Marzilli M, Klein W. Efficay and tolerability of trimetazidine in stable angina: a meta–analysis of randomized, double blind, controlled trials. *Coron Artery Dis*. 2003;14:171–179.
3. Stanley WC, Marzilli M. Metabolic therapy in the treatment of ischemic heart disease: the pharmacology of trimetazidine. *Fund Clin Pharmacol*. 2003;17:133–145.
4. Levy S, for the group of South of France Investigators. Combination therapy of trimetazidine with diltiazem in patients with coronary artery disease. *Am J Cardiol*. 1995;76:12B–16B.
5. Manchanda SC, Krishnaswami S. Combination treatment with trimetazidine and diltiazem in stable angina pectoris. *Heart*. 1997;78:353–357.
6. Michaelides AP, Vyssoulis GP, Bonoris PE, Psaros TK, Papadopoulos PD, Toutouzas PK. Beneficial effects of trimetazidine in men with stable angina under beta-blocker treatment. *Curr Ther Res*. 1989;46:565–576.
7. Marzilli M. Management of ischaemic heart disease in diabetic patients. Is there a role for cardiac metabolic agents? *Curr Med Res Opin*. 2001;17:1–6.
8. Brottier A, Barat L, Combe C. Therapeutic value of a cardioprotective agent in patients with severe ischaemic cardiomyopathy. *Eur Heart J*. 1990;11:207–212.
9. Lu C, Dabrowski P, Fragasso G, Chierchia S. Effects of trimetazidine on ischaemic left ventricular dysfunction in patients with coronary artery disease. *Am J Cardiol*. 1998;82:898–901.
10. Belardinelli R, Purcaro A. Effects of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischaemic cardiomyopathy. *Eur Heart J*. 2001;22:2164–2170.

Cardiac adaptation to exercise

Harm Kuipers
Faculty of Health Sciences, Maastricht University, Maastricht, The Netherlands

Correspondence: Dr Harm Kuipers, Faculty of Health Sciences, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands. E-mail: harm.kuipers@bw.unimaas.nl

Abstract

Regular training elicits specific adaptations to heart structure and function, resulting in increased heart performance and increased exercise capacity. The autonomic control also adjusts to training, and at rest a high parasympathetic tone results in bradycardia with increased stroke volume. Some athletes use drugs to boost sport performance. Androgenic anabolic steroids may alter the serum lipid profile unfavorably. There is no conclusive evidence for cardiac structural and functional changes with the use of these drugs. Erythropoietin not only may enhance sport performance, but also can increase the risk of thromboembolism. Amphetamines can induce acute heart failure, hyperthermia, and sudden death during exercise.
■ *Heart Metab.* 2005;26:31–34.

Keywords: Autonomic nervous system, training, doping, heart

Introduction

Regular physical exercise induces changes in the body that are a physiological adaptation to increased loads. In general, these adaptations are favorable and enable the individual to increase physical performance capacity. Adaptations to training also include the structure and function of the cardiovascular system, in addition to its functional control (*Figure 1* [1]). Strength training induces changes to pressure loads, whereas endurance training requires volume loads and elicits an increased maximal cardiac output, by increasing stroke volume [2]. Compared with the maximal cardiac output in non athletic adults of approximately 25 L/min, that of elite athletes can reach values of up to 30–35 L/min [2].

It has become clear that sport performances and training-induced adaptations are determined mainly by genetic factors and to a limited extent by training [3]. Because of these limitations in training adaptations, athletes may be tempted to use performance-enhancing drugs to push their performance further.

Autonomic control with training

Adaptations to regular exercise also include the autonomic control of cardiovascular function [4,5]. Regular training causes adjustments in the autonomic nervous system that may change the physiological response of the heart and blood vessels to exercise, and increase its functional capacity (*Figure 2*). The speed of depolarization and conduction velocity of myocardial cells determine heart rhythm, which can be changed by different input from the autonomic fibers [4,7]. Increased sympathetic activity leads to increased heart rate and increased contractility, whereas increased parasympathetic input retards heart rate and decreases contractility [4,7]. Endurance-trained individuals are characterized by an increased parasympathetic tone at rest, which is reflected in bradycardia and compensatory increased stroke volume [8] (*Figure 3*). Because of an increased parasympathetic tone and slow pulse rate in the resting state in well-trained athletes, the baroreflex may not always adequately counteract the blood pressure changes associated with sudden changes in posture [10]. Because of this, endurance-trained athletes may be more susceptible than untrained individuals to orthostatic hypotension with sudden changes in posture [10]. A profession that is associated with sudden changes in static pressure from sudden changes in G-forces is that of fighter pilot. Although the author is not aware of relevant published data, it is possible that fighter pilots who are endurance trained and have a pronounced

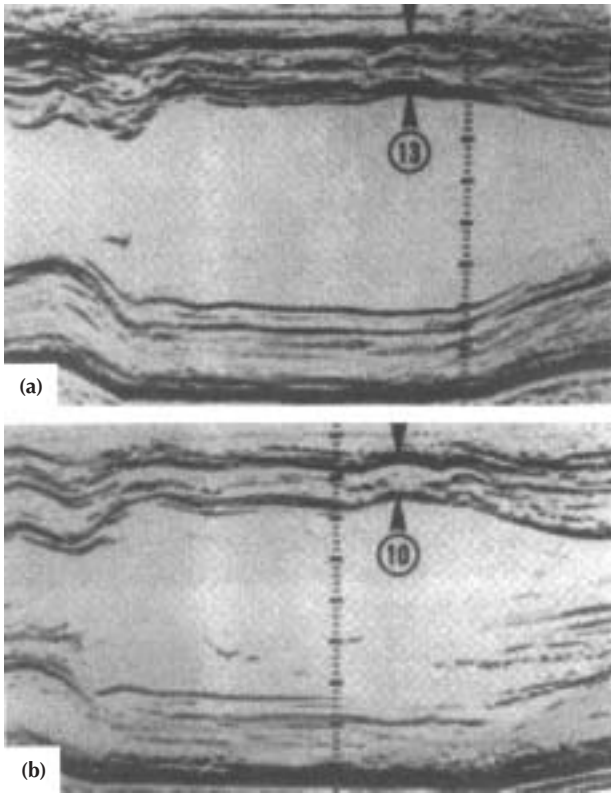

Figure 1. M-Mode echocardiographic tracings obtained from an elite male rower, (a) at the peak of athletic conditioning and (b) after an 8-week period of deconditioning. The ventricular septum shows a reduction in thickness from 13 mm (a) to 10 mm (b). (From Pelliccia and Maron [1], with permission.)

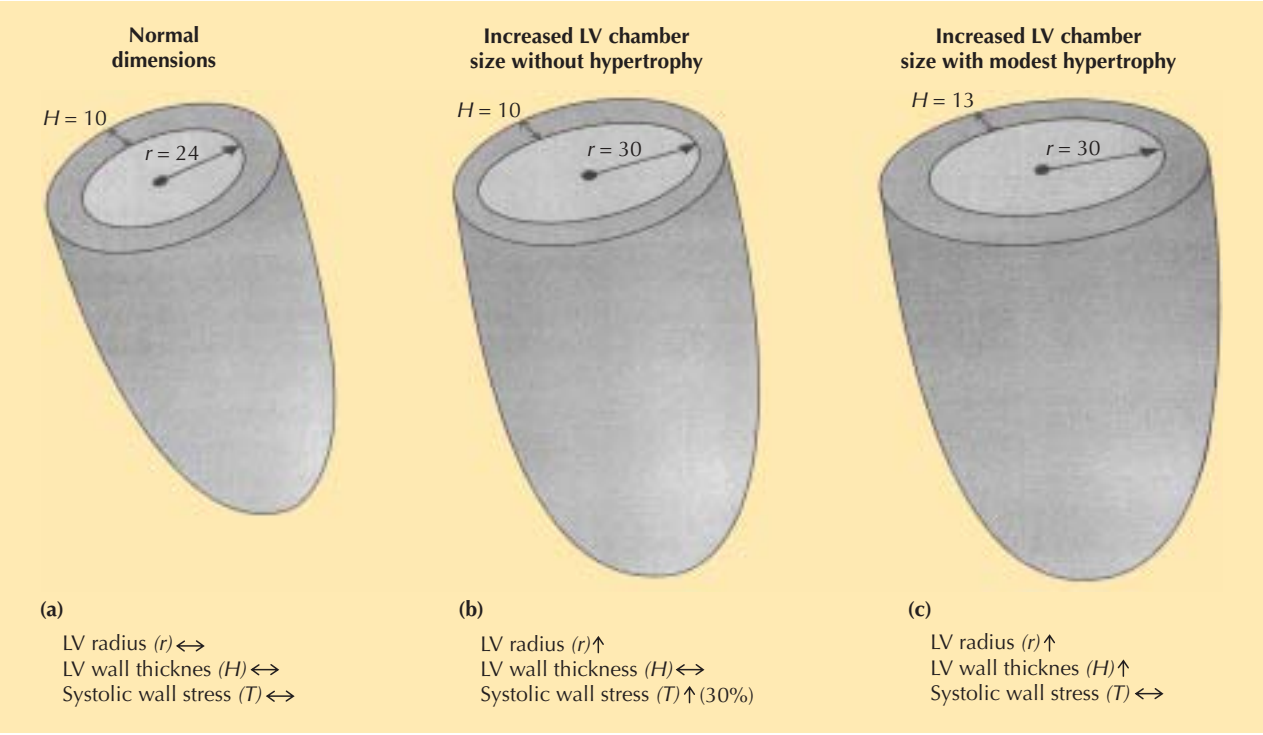

Figure 2. Interaction between left ventricular dimensions and wall stress. (a) Normal left ventricle (untrained). (b) After chamber enlargement without left ventricular hypertrophy (ie, cardiomyopathy. (c) After endurance training (increased ventricular chamber volume and modest hypertrophy). LV, left ventricular. (From Goodman [6], with permission.)

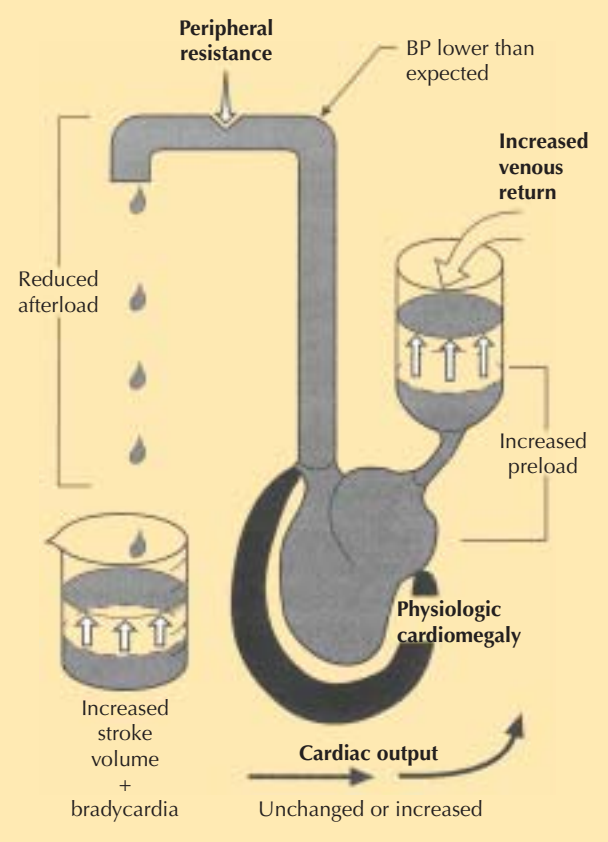

Figure 3. The athlete's heart. As a simplification, the adaptations involved in dynamic exercise training may be regarded as compensatory responses to a chronic volume load, including physiological cardiomegaly. BP, blood pressure. (From Opie [9], with permission.)

bradycardia may have a less adequate baroreflex and a lower G-force tolerance than non trained individuals. In that case, special attention should be given to teaching strategies for coping with high G-forces in flight [11].

Doping in sport and the heart

In sports in which muscle strength and muscle mass are determining factors for success, it has been shown that the use of androgenic anabolic steroids can enhance sport performance [12]. In spite of the positive effects on performance, the use of such drugs may have serious adverse effects that also involve the cardiovascular system. The abuse of androgenic anabolic steroids has been associated with an increased risk for serious cardiovascular events such as myocardial infarction, cerebrovascular accidents, acute heart failure, and thromboembolism [12]. It has been demonstrated that the use of androgenic anabolic steroids can unfavorably affect some risk factors for cardiovascular disease, especially the serum lipid profile. In athletes, administration of high doses of these drugs may lead to decreased concentrations of high-density lipoprotein cholesterol [13]. However, the effects of androgenic anabolic steroid abuse are reversible and, after administration is stopped, serum lipids return to pre-drug concentrations [13].

There is some indication from cross-sectional echocardiography and from animal studies that abuse of androgenic anabolic steroids may change cardiac structure and function. Some investigators reported larger ventricular mass and interventricular septal thickness in association with the use of the drugs. Others could not confirm these changes [12]. One prospective study reported echocardiographic changes during use of androgenic anabolic steroids [14], whereas other studies failed to show any significant change to ventricular parameters [12]. Thus, at present, it remains to be established whether the use of androgenic anabolic steroids by athletes does affect cardiac structure and function.

Another drug that is abused, especially in endurance sports, is erythropoietin. It has been shown that the administration of erythropoietin increases hemoglobin mass and oxygen transport capacity, and hence endurance performance [15]. However, with an increase in hemoglobin mass, blood viscosity increases, which may lead to hypertension and thromboembolic events [16]. It is rumored that some athletes use aspirin to prevent thromboembolism. Although never proven, it has been suggested that the sudden death of some young athletes in the late 1980s and early 1990s was associated with the use of erythropoietin. Some large international sport bodies have introduced regular blood testing in athletes in order to monitor their hematological profile and detect and prevent possible manipulation [14].

A drug that was frequently abused in the sport of cycling during the 1960s was amphetamine. In contrast to popular belief, amphetamine is not a strong performance enhancer in high-intensity events; nevertheless, its use is widespread [85]. However, amphetamines may be cardiotoxic and may cause acute infarction and sudden death [18]. In addition, heat dissipation during exercise is impaired, which may lead to hyperthermia and cardiac failure [18]. After some deaths occurred in athletes during competition, the International Olympic Committee put a ban on the use of these drugs. Although no evidence is available, it cannot be ruled out that regular use of amphetamines or other performance-enhancing drugs may cause structural, functional, and possibly irreversible changes to the heart. ■

REFERENCES

1. Pelliccia A, Maron BJ. Outer limits of the athlete's heart, the effect of gender and relevance to the differential diagnosis with primary cardiac diseases. *Cardiology Clinics*. 1997:15:381–396.
2. Astrand PO, Rodahl K, Dahl HA, Strømme SB. Body fluids, blood and circulation. Textbook of Work Physiology. Human Kinetics. 4th ed. Illinois, USA; 2003:127–176.
3. Andersen JL, Scherling P, Saltin B. Muscle, genes and athletic performance. *Sci Am*. 2000;283:48–55.
4. Dickhuth HH, Rocker K, Mayer F, Konig D, Korsten-Reck U. Cardiovascular adaptation to endurance training (athletes's heart). *Herz*. 2004;29:373–380.
5. Kaciuba-Uscilko H, Smorawinski J, Nazar K, Adrian J, Greenleaf JE. Catecholamine reponses to environmental stressors in trained and untrained men after 3-day bed rest. *Aviat Space Environ Med*. 2003;74:928–936.
6. Goodman J, The athletes heart. In: Shepard RJ, Astrand PO, eds. *Endurance in Sport*. Blackwell Science Ltd, London; 1992;68–83.
7. Stein R, Moraes RS, Cavalcanti AV, Ferlin EL, Zimerman LI, Ribeiro JP. Atrial automaticity and atrioventricular conduction in athletes: contribution of autonomic regulation. *Eur J Appl Physiol*. 2000;82:155–717.
8. Carter JB, Bannister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. *Sports Med*. 2003;33:33–46.
9. Opie LH, *The Heart: Physiology, from cell to cirulation* Lippincott-Raven, Philadelphia, USA; 1998.
10. Morikawa T, Sagawa S, Torii R, Endo Y, Yamazaki F, Shiraki K. Hypovolemic intolerance to lower body negative pressure in female runners. *Med Sci Sports Exerc*. 2001;33:2058–2064.
11. Convertino VA. High sustained +Gz acceleration: physiological adaptation to high-G tolerance. *J Grav Physiol*. 1998;5:P51–P54.
12. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med*. 2004;34:1–42.
13. Hartgens F, Rietjens G, Keizer HA, Kuipers H, Wolffenbuttel BHR. Effects of androgenic anabolic steroids on apolipoproteins and lipoprotein (a). *Br J Sports Med*. 2004;38:253–259.
14. Sachtleben TR, Berg KE, Elias BA, Cheatham JP, Felix GL, Hofshire PJ. The effects of anabolic streroids on myocardial structure and cardiovascular fitness. *Med Sci Sports Exerc*. 1993;25:1240–1245.
15. Ekblom B, Berglund B. Effect of erythropoietin administration on maximal aerobic power. *Scand J Med Sci Sports*. 1991;1:88–93.
16. Gaudard A, Varlet-Marie E, Bressole F, Audran M. Drugs for increasing oxygen transport and their potential use in doping. *Sports Medi*. 2003;33:187–212.
17. Gore CJ, Parisotto R, Ashenden MJ, et al. Second generation blood tests to detect erythropoietin abuse in athletes. *Haematologica*. 2003;88:333–344.
18. Karch SB. Stimulants. In: Bahrke, Yesalis, eds. *Performance Enhancing Substances in Sport and Exercise*. Human Kinetics. Illinois, USA; 2002:257–266.

Featured research

Abstracts and commentaries

Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease

Vitale C, Wajngaten M, Sposato B, et al. *Eur Heart J.* 2004;25:1814–1821.

Elderly patients have an increased incidence of ischemic dilated cardiomyopathy, often related to diffuse coronary artery disease. Trimetazidine protects ischemic myocardium by improving myocardial utilization of energy during myocardial ischemia. The aim of the present study was to evaluate the effects of trimetazidine on left ventricular function in elderly patients with ischemic heart disease and reduced left ventricular function. Forty-seven elderly patients (40 men and seven women, mean age 78±3 years) were allocated randomly to groups to receive, in addition to standard therapy, either trimetazidine or placebo, and were evaluated by echocardiography at baseline and after 6 months. Trimetazidine and placebo had no effect on either blood pressure or heart rate (changes compared with baseline: systolic blood pressure 2±5 and 4±6 mm Hg, diastolic blood pressure 1±6 and 3±4 mm Hg, heart rate 3±7 and 5±9 beats/min, for trimetazidine and placebo, respectively). At the end of the study, patients assigned to trimetazidine showed a significantly greater left ventricular function and smaller left ventricular diastolic and systolic diameters and volume indices than patients receiving placebo (left ventricular ejection fraction [LVEF] 34.4±2.3% and 27±2.8%, $P<0.0001$; left ventricular end-diastolic diameter 58.6±1.9 mm and 64±1.7 mm, $P<0.0001$; left ventricular end-systolic diameter 44.5±1.1 and 50±0.8 mm, $P<0.0001$; trimetazidine and placebo, respectively). A significantly smaller wall motion score index was detected in trimetazidine-treated patients than in those allocated to placebo (1.24±0.12 and 1.45±0.19 respectively; $P<0.01$), and the percentage change in LVEF compared with baseline was also significantly greater in trimetazidine-treated patients. Diastolic function improved significantly in the trimetazidine group, but remained unchanged in the placebo group. At follow-up evaluation, patients receiving trimetazidine showed a greater improvement in angina and NYHA class than patients allocated to placebo. Quality of life improved significantly in all patients treated with trimetazidine, but remained unchanged in those allocated to placebo.

Commentary

Cardiac failure is a major problem and increasing in prevalence as populations age. In spite of all the medical advances and in the presence of optimal evidence-based medicine, the prognosis remains poor. Following on from the concept that cardiac failure is associated with increased free fatty acid concentrations secondary to an increased adrenergic state has come the idea that targeted metabolic therapy might be beneficial. As increased free fatty acids cause mitochondrial uncoupling and impaired left ventricular function with a proarrhythmic potential, their presence along with secondarily decreased glucose oxidation perpetuates the heart failure status. Several small studies have shown that trimetazidine reverses this adverse metabolic state and improves left ventricular function. This new study of 47 elderly patients using trimetazidine in addition to modern standard therapy reports improvement in left ventricular systolic and diastolic function, in addition to quality of life, after 6 months of treatment. The importance of recording a benefit in the presence of optimal conventional therapy should encourage further studies looking at long-term (years of) treatment. Improving the quality of life, is of course, important in itself, but if it can be coupled to a better prognosis, then metabolic therapy will be an essential component of the management cardiac failure.

Graham Jackon

Nuclear receptor signaling and cardiac energetics

Huss JM, Kelly DP. *Circ Res*. 2004;95:568–578.

The heart has a tremendous capacity for the generation of ATP, allowing it to function as an efficient pump throughout the life of the organism. The adult myocardium uses either fatty acid or glucose oxidation as its main energy source. Under normal conditions, the adult heart derives most of its energy through oxidation of fatty acids in mitochondria. However, the myocardium has a remarkable ability to switch between carbohydrate and fat as sources of fuel, so that ATP production is maintained at a constant rate in diverse physiological and dietary conditions. This flexibility in selection of fuel is important for normal cardiac function. Although the cardiac capacity for energy conversion and metabolic flux are modulated at many levels, an important mechanism of regulation occurs at the level of gene expression. The expression of genes involved in several energy transduction pathways is dynamically regulated in response to developmental, physiological, and pathophysiological cues. This review is focused on gene transcription pathways involved in short- and long-term regulation of myocardial energy metabolism. Much of our knowledge about cardiac metabolic regulation comes from studies focused on mitochondrial fatty acid oxidation. The genes involved in this key energy metabolic pathway are transcriptionally regulated by members of the nuclear receptor superfamily, specifically the fatty acid activated peroxisome proliferator-activated receptors (PPARs) and the nuclear receptor coactivator, PPARγ coactivator (PGC)-α. The dynamic regulation of the cardiac PPAR/PGC-1 complex in accordance with physiological and pathophysiological states will be described here.

Commentary

The healthy adult heart primarily uses fatty acids and glucose as fuels to generate the large amounts of energy necessary to maintain cardiac work. Mitochondrial oxidation of these carbon substrates normally produces more than 90% of the ATP used for energy metabolism, whereas glycolysis is normally a minor source of ATP production. However, myocardial selection of fuel is highly influenced by a number of physiological and pathological conditions. For instance, in the hypertrophied and failing heart, dramatic metabolic shifts can occur, including a transition from mitochondrial oxidative metabolism towards a greater dependence on glycolytic metabolism. These metabolic transitions can help the heart adapt to cardiac pathologies, but can also have maladaptive influences. The metabolic switches that occur in the heart under a number of pathological conditions are usually accompanied by dramatic changes in the expression of a number of genes of both fatty acid and carbohydrate metabolism. It is now becoming clear that nuclear receptor signaling has an important role in these changes in gene expression. Important players in this nuclear signaling are the peroxisome proliferator-activated receptors (PPARs). For instance, one PPAR isoform, PPARα, is involved in the transcriptional regulation of a number of enzymes involved in fatty acid oxidation. This paper by Huss and Kelly provides an excellent review of the recent advances made in our understanding of the role of nuclear receptor signaling in the control of cardiac energetics. The authors review, not only how nuclear receptors control cardiac energetics, but also how alterations in this nuclear receptor signaling contribute to or alter the course of various cardiac pathologies. The paper also highlights the therapeutic potential of altering nuclear receptor function as an approach to treating heart disease.

Gary Lopaschuk

Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease. A randomized trial

Hambrecht R, Walther C, Möbius-Winkler S, et al. *Circulation*. 2004;109:1371–1378.

Regular exercise in patients with stable coronary artery disease has been shown to improve myocardial perfusion and to retard disease progression. A randomized study was therefore conducted to compare the effects of exercise training and standard percutaneous coronary intervention (PCI) with stenting on clinical symptoms, angina-free exercise capacity, myocardial perfusion, cost-effectiveness, and frequency of a combined clinical endpoint (death of cardiac cause, stroke, coronary artery bypass grafting, angioplasty, acute myocardial infarction, and worsening angina with objective evidence resulting in admission to hospital). A total of 101 male patients aged 70 years were recruited to the study after routine coronary angiography and allocated randomly to groups for 12 months of exercise training (20 min of bicycle ergometry per day) or to PCI. Cost efficiency was calculated as the average expense (in USA dollars) needed to improve the Canadian Cardiovascular Society class status by one class. Exercise training was associated with a higher event-free survival (88%, compared with 70% in the PCI group; $P < 0.023$) and increased maximal oxygen uptake (16%: from 22.7 ± 0.7 to 26.2 ± 0.8 mL/kg; P

<0.001 compared with baseline, $P<0.001$ compared with PCI group after 12 months). To gain 1 Canadian Cardiovascular Society class, US$6956 was spent in the PCI group, compared with US$3429 in the training group ($P<0.001$). Compared with PCI, a 12-month program of regular physical exercise in selected patients with stable coronary artery disease resulted in superior event-free survival and exercise capacity at lower costs, notably because of reductions in re-admissions to hospital and in repeat revascularizations.

Commentary

Percutaneous coronary artery revascularization is performed in a growing number of patients with ischemic heart disease, on the assumption that the procedure ameliorates symptoms and improves prognosis. Several large clinical trials have documented an early symptomatic benefit in patients who have undergone revascularization as compared with medically treated patients. However, follow-up studies have shown this advantage to be lost in a few years.

Much less convincing is the evidence supporting the common belief that PCIs reduce mortality and morbidity in ischemic heart disease. Technical advances in device design and the availability of drug elution stents have rendered PCIs easier to perform and have significantly reduced early and late complications, including restenosis. However, no significant reduction has been reported for morbidity and mortality.

In the meantime, medical therapy also has registered significant progress, with new classes of drug proving effective in acute and chronic coronary syndromes, including metabolic agents, glycoprotein IIb/IIIa inhibitors and hydroxymethyl glutaryl reductase inhibitors.

In this study, the combination of regular physical exercise and standard medical treatment was compared with PCI in 101 patients with stable coronary artery disease. The program of regular exercise proved to be superior to PCI in event-free survival and reduced the overall costs of treatment. This observation adds to a growing body of evidence questioning the 'superiority' of PCI over medical treatment and suggests the need for a critical reappraisal of percutaneous revascularization in stable ischemic heart disease. In patients with mild symptoms and in patients with low to moderate risk, optimal medical treatment combined with a correct lifestyle appears to be the initial strategy of choice, and PCI should be reserved for patients who remain symptomatic despite this regimen.

Mario Marzilli

Glossary

Gary D. Lopaschuk

Dichloroacetate

Dichloroacetate is a molecule that activates pyruvate dehydrogenase (PDH). PDH is the rate-limiting enzyme involved in glucose oxidation. In muscle cells, dichloroacetate activation of PDH results in an increase in glucose oxidation. In the heart, this activation of glucose oxidation has cardioprotective effects during and following ischemia.

Hexokinase

Hexokinase is an important enzyme that phosphorylates glucose to glucose-6-P in the cytoplasm of cells. This allows glucose to be further metabolized. The glucose-6-P can be used as a substrate for glycolysis, a substrate for glycogen synthesis, or as a substrate for the pentose phosphate pathway. However, all of these pathways require that hexokinase first phosphorylate glucose.

Long-chain 3-ketoacyl coenzyme A thiolase

3-ketoacyl-CoA-thiolase (3-KAT) is the last enzyme in the intramitochondrial pathway that is involved in the metabolism of fatty acids (fatty acid β-oxidation). There are 3 different 3-KAT enzymes, with different affinities for long, medium or short chain fatty acids. Long-chain 3-KAT primarily acts on longer chain fatty acid intermediates. Long-chain 3-KAT inhibitors, such as trimetazidine, inhibit the activity of this enzyme, thereby inhibiting fatty acid oxidation. Recent interest has focused on 3-KAT inhibitors as a novel therapeutic approach to protecting the ischemic heart.

6-Phosphofructo-1-kinase

6-phosphofructo-1-kinase (PFK-1) is an enzyme that converts fructose 6-phosphate to fructose 1,6-bisphosphate. PFK-1 is the rate-limiting enzyme of glycolysis. As a result, regulation of PFK-1 is an important mechanism by which glycolysis is regulated.

Pyruvate dehydrogenase (PDH)

Pyruvate dehydrogenase (PDH) is an intramitochondrial complex that converts pyruvate (which primarily originates from glucose or lactate) into acetyl CoA. PDH is the rat-limiting enzyme for the mitochondrialk metabolism of carbohydrates. Maintaining mitochondrial glucose metabolism is an important therapeutic strategy to protect the ischemic heart. Therefore, activating PDH is a potential therapeutic approach to treating heart disease.