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2022 Beijing Winter Olympics –Spotlight on Cardiac Metabolism

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The world is full of surprises. At the 2022 Winter Olympics in Beijing, trimetazidine (TMZ), a drug known to target cardiac metabolism, came under scrutiny because of its status as a performance-enhancing substance listed by the World Anti-Doping Agency (WADA). Exposure to TMZ was the basis for a controversy surrounding the 15-year old Russian figure skater Kamila Valieva accused of “competitive doping” because of screen-detected TMZ exposure. This is not the first Olympic skirmish surrounding the drug. In 2014, the Chinese swimmer Sun Yang was suspended for three months after testing positive for TMZ. In 2018, the Russian bobsledder Nadezhda Sergeeva was disqualified from the Olympics and banned for eight months after testing positive for TMZ.

Is TMZ really a performance-enhancing substance? This begs another question: When Mother Nature reaches her limits, can the complex network of metabolism be pushed even further to enhance the efficiency of the heart and skeletal muscle, to gain competitive athletic advantage? The principle has been used before, for example with performance enhancers that increase the amount of oxygen in the blood, such as administration of erythropoietin. This strategy also led to the discovery of a gain-of-function mutation in the gene of the erythropoietin receptor, which gave a competitive advantage to one of its carriers, Ero Antero Mäntyranta, a Nordic skier. who won seven medals at the 1960 Winter Olympics in Squaw Valley (1)

And here is where the competition starts:

Even a tiny improvement in the ability to train through fatigue may be the difference between a gold medal or watching the competition on television. Take cardiac metabolism as an example. Like the mammalian body as a whole, the healthy heart is an adaptable metabolic omnivore, able to adjust its substrate use by matching supply and demand (Fig.

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1). The heart is also the most versatile organ in the body regarding metabolic capacity and its ability to convert chemical energy into mechanical energy. The human heart contracts about 100,000 times a day to pump 7000 liters of blood into the circulation. When energy demand increases, coronary flow also increases assuming the sufficient supply of oxygen and nutrients, the latter chiefly in the form of fat and carbohydrates (2). Inside the cell all energy providing substrates enter a highly regulated metabolic network which generates ATP, the critical intermediate of muscle contraction (Figure 1). It has been estimated that the human heart (which weighs about 0.3kg), generates between 6 and 10 kg of ATP in 24 hours.

The question arises: Is it possible then to make myocardial oxidative metabolism even more efficient than it already is? Nature has equipped the heart with metabolic pathways that prefer fat rather than carbohydrates as its main source of energy, not surprisingly, as fatty acids pack more chemical energy than carbohydrates (2). However, a little-appreciated fact is that the efficiency of oxidation for ATP generation in the respiratory chain differs between substrates (Fig. 1). For example, the mitochondrial ATP yield per oxygen atom (P/O ratio) is only 2.33 for long-chain fatty acids like palmitate, while the P/O ratio is 2.58 for glucose (3). Therefore, metabolic interventions aimed at lowering myocardial oxygen demand have been proposed for the treatment of heart failure and of ischemic heart disease, promoting glucose oxidation at the expense of fatty acid oxidation (4). One such intervention is the drug TMZ, which shifts cardiac energy metabolism from long-chain fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (5), resulting in a high P/O ratio (Fig. 1).

A quarter of a century has passed since Stanley, Lopaschuk, and others described the concept of optimizing cardiac energy metabolism pharmacologically (4). This idea is now finding its place on the stage of public awareness. In the case of TMZ, it remains, however, still completely unclear whether this drug may improve athletic performance. In the setting of a healthy heart with normal coronary perfusion, it seems unlikely that TMZ-induced myocardial substrate shifting offers any significant advantage for cardiac function or athletic performance. Would skeletal muscle substrate switch further increase overall peak performance? The answer awaits further research.

Perhaps the WADA and other governing bodies of athletic competition should also be concerned about doping with sodium-glucose cotransporter-2 (SGLT2) inhibitors, not presently on the list of banned substances, with considerations well beyond their potential role as diuretic/masking agents (i.e. agents used to expedite clearance of other banned agents and their metabolites). Initially developed to treat hyperglycemia for patients with type 2 diabetes, the SGLT2 inhibitors have now been proven to reduce the risk for atherosclerotic vascular disease, heart failure, and kidney disease. Beyond lowering blood glucose levels, these drugs as a class, consistently affect a number of pathways that could directly impact myocardial oxygen demand and supply, and thereby theoretically could augment athletic performance. For example, as osmotic/natriuretic diuretics, they could lead to reduced myocardial oxygen demand by reducing intravascular and intraventricular volumes, resulting in reduced blood pressure, ventricular wall tension and resting heart rate. Myocardial oxygen demand could be further reduced by increases in circulating ketone body levels, especially

beta-hydroxybutyrate in the fasting state, a more efficient myocardial metabolic substrate than long-chain fatty acids, with a P/O ratio of 2.5. Also affecting myocardial oxygen supply, the SGLT2 inhibitors increase the hematocrit by increasing red blood cell mass via erythropoietin-mediated mechanisms, that could increase myocardial oxygen delivery much like is done with blood doping and illicit use of erythrocyte stimulating agents. All of these effects, individually or in aggregate, could enhance athletic performance.

As far as the Winter Olympics are concerned, the quadruple jump has caused us to think a) of cardiac metabolism as a model system and b) how nuanced the listing of performance-enhancing agents may be keeping in mind both the safety of athletes and the rules of fair competition.

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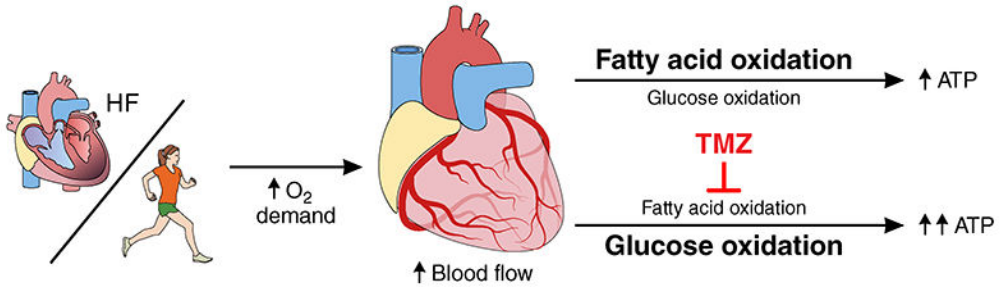

Efficiency

Substrate	P/O ratio
Fatty acids	**2.33**
Lactate	2.46
Ketone bodies	2.50
Glucose	**2.58**

Figure 1: The Essence of Cardiac Metabolism

Inhibition of fatty acid oxidation by trimetazidine (TMZ) enhances ATP production from glucose oxidation.

P/O is the ratio of ATP produced for the amount of O_2 consumed.