

Complementary Effect of Exercise in Cardiovascular Medicine

Yeung PK^{1*} and Jodi Tinkel²

¹Department of Medicine, College of Pharmacy, Dalhousie University, Halifax, NS, Canada

²University of Toledo Medical Center, Toledo, OH 43614, USA

Cardiovascular disease, including stroke, is the leading cause of death and disability worldwide, and is an enormous economic burden to our societies [1]. Based on the latest statistics released for heart and stroke disease, an estimated 83,600,000 adults in the United State (US) (>30%) have one form or another of cardiovascular disease (CVD), including more than 90% with hypertension, 18% with coronary heart disease (CHD), close to 10% with myocardial infarction (MI) and 8% with stroke. The total direct and indirect cost in the US alone for treatment of CVD (hospitalization, drugs, home healthcare, etc.), and lots of productivity and morbidity is estimated at close to \$315 billion US per year [2]. Thus, prevention and early treatment of the major CV risk factors could provide huge savings in health care costs worldwide. Despite major advances in treatment of cardiovascular disease, the prevalence of hypertension, ischemic heart disease (IHD) and stroke is still on the rise. Identifying optimal strategies in preventing the development of CV risk factors and slow disease progression remains a therapeutic challenge.

Exercise is increasingly recommended in both primary and secondary prevention strategies to enhance health, reduce risk factors and optimize therapeutic management of cardiovascular diseases [3-9]. Lack of physical activity is recognized as one of four major behavioural, and therefore, modifiable risk factors in the development of CVD [10]. It is believed that regular exercise is one of the most important non-pharmacological tools in reducing overall cardio metabolic risk. Aerobic exercise significantly reduces body weight, blood pressure (BP), blood glucose and lipid levels, and also improves strength, flexibility and quality of life [4]. A single bout of swimming exercise has been shown to sustain left ventricular function after isoproterenol-induced injury in mice, which lasted over 4 weeks after the exercise [11]. Similarly, treadmill exercise has also been shown to have prolonged cardiovascular protective effects against injury induced by isoproterenol in rat [12,13]. In patients with stable systolic heart failure, exercise training can relieve symptoms, improve functional capacity and quality of life, as well as reduce hospitalizations and all cause mortality [14,15]. Conversely, lack of exercise or physical inactivity is a significant cardiovascular risk factor [5]. There is also evidence to suggest that exercise intensity, as well as duration and frequency, is an important variable in determining cardiovascular protection [16,17]. However, applying this evidence into practice must take into account individual differences in baseline fitness, compliance and the independent risk associated with a sedentary lifestyle [18].

The mechanism of cardiovascular protection induced by exercise is not fully elucidated or quantified. It is certainly multi-factorial and includes improvements in cardiovascular risk factors, enhanced fibrinolysis, improved endothelial function, decreased sympathetic tone and other as-yet-undetermined factors [5]. It is known that exercise also activates the neuroendocrine system [19], and triggers release of myokines from skeletal muscle, mediating cross-talk within the cardiovascular system. Some biomarkers such as interleukin-6 (IL-6) can serve as energy sensors and may play an important role in cardiovascular protection [20-22]. Exercise is a form of ischemic preconditioning, and individuals who exercise regularly and experience a clinical ischemic event, such as an MI, have a smaller infarct size and

overall improved left ventricular systolic function [23]. Mechanistically, the beneficial effects of exercise pre-conditioning on endothelial function and the myocardium may be mediated via increased blood flow, enhanced nitric oxide production and bioavailability, changes in neurohormonal release, improvements in oxidant/antioxidant balance and optimization of energy and ATP metabolism [24-26]. It is likely many or all of these factors contribute to the cardiovascular health benefits from exercise.

While it is clear, exercise improves hemodynamic profiles and cardiovascular health [3,6,27-29], very little is known of the significance of interactions between exercise and drug therapy [30,31]. Based on very limited amounts of data available, it is believed that chronic exercise may affect drug absorption by increase in collateral blood flow and changes in gastrointestinal transit times. It may also affect volume of distribution of drugs by the increase in lean body mass (and decreases fatty tissue), plasma protein concentrations and plasma volume that occur with physical conditioning. Changes in hepatic clearance and renal excretion of drugs may also occur as a result of increased hepatic enzyme activities, and/or changes in protein binding. However, these effects are highly variable depending on the drug, as well as physical condition of the patients, as the impact from acute exercise may be different from chronic exercise [32,33]. It has been shown that exercise increased plasma concentrations of propranolol and atenolol, but not carvedilol or verapamil. On the other hand, increasing physical activity in patients taking warfarin has been shown to decrease the international normalised ratio (INR) [30]. In experimental animal models, exercise has been shown to mitigate anthracycline-induced chronic cardiotoxicity in rats [34]. Most recently, we have shown that a brief period of exercise increased absorption, as well as clearance (CL) and volume of distribution (Vd) of diltiazem (DTZ) after subcutaneous (sc) injection in rats [35]. In addition, exercise can also enhance the cardiovascular protective effect of DTZ [36]. These effects are likely to be individual and therapy specific, and at the current levels of physical activity recommended, not likely to have a significant impact in routine clinical practice. Clinicians should however be aware of the potential for such interactions for drugs with a narrow therapeutic range, and in patients who participate in extreme sporting activities may require dosage adjustment [30,31]. More studies are urgently needed in this area to better understand the complex interactions of therapeutic lifestyle interventions and conventional medical therapy.

***Corresponding author:** Yeung PK, Professor of Pharmacy and Medicine, 1Department of Medicine, College of Pharmacy, Dalhousie University, Halifax, Canada, Tel: 902-4943845; Fax: 902-4941396; E-mail: Pollen.Yeung@Dal.Ca

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In summary, lack of regular physical activity is increasingly recognized as a major modifiable contributor to the development of CVD, and it is a significant global health problem. Regular physical activity is rapidly becoming an integral part of recommended therapeutic lifestyle interventions to complement traditional therapy for prevention, treatment and recovery from CVD. A more in-depth understanding of the mechanisms involved in the health benefits of exercise, and the interaction with conventional medicines will further advance prevention and management of CVD, resulting in improved outcomes at lower cost, affecting millions worldwide.

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