

EXERCISE, ANTIOXIDANTS, AND CARDIOPROTECTION

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KEY POINTS

- Cardiovascular disease continues to be the number one cause of death in the United States.
- Coronary artery disease is the major disease of the cardiovascular system; this disease greatly increases the risk of cardiac ischemia-reperfusion injury (i.e., heart attack). Ischemia-reperfusion injury in the heart occurs due to a transient blockage of coronary blood flow followed by the restoration of blood flow.
- Regular exercise lowers the risk of developing coronary artery disease and reduces cardiac injury during an ischemia-reperfusion insult.
- The mechanism to explain exercise-induced protection against ischemia-reperfusion injury (called cardioprotection) is unknown but may be linked to increases of both heat-shock proteins and antioxidants in the heart.
- Animal research suggests that supplementation with nutritional antioxidants reduces ischemia-reperfusion-induced cardiac injury.
- Additional research is required to determine if dietary antioxidants can provide myocardial protection in humans.

INTRODUCTION

Cardiovascular disease (diseases of the heart and blood vessels) continues to be the number one cause of death in the United States as well as other developed countries. Therefore, finding ways to reduce the mortality of cardiovascular disease remains an important public health goal. In this regard, numerous studies reveal that regular exercise is cardioprotective. For example, epidemiological studies indicate that compared to sedentary individuals, physically active people have a lower incidence of heart attacks (Lee et al., 1995). Further, these investigations also demonstrate that the survival rate of heart attack victims is greater in physically active individuals compared to their sedentary counterparts (Berlin & Colditz, 1990).

In addition to the cardioprotective effects of regular exercise, there is also a growing interest in nutritional antioxidant supplementation as a strategy to protect the heart during a heart attack. Indeed, the role that dietary antioxidants play in providing cardiac protection is a rapidly expanding field of research. The purpose of this review is to summarize our current knowledge regarding the cardioprotective effects of both exercise and dietary antioxidants

RESEARCH REVIEW

Cardiovascular Disease: An Overview

Although numerous cardiovascular diseases exist, coronary artery disease (CAD) remains the number one cause of death due to cardiovascular disorders. CAD is caused by a collection of plaque (i.e., buildup of cholesterol, calcium, fibrous tissue) inside a coronary vessel (Barrow, 1992). This collection of plaque inside coronary vessels results in a narrowing of coronary arteries (stenosis) that decreases the delivery of oxygen to the heart due to reduced coronary blood flow.

The events leading to cardiac injury during a heart attack begin with a transient blockage of coronary blood vessels that is usually caused by a blood clot triggered by coronary stenosis. This reduction in blood flow to the heart is called ischemia and is typically followed by a restoration of blood flow (reperfusion) when the clot dissolves. Although commonly known as a heart attack, the overall process of ischemia followed by reperfusion results in cardiac injury and is technically referred to as ischemia-reperfusion (I-R) injury. The magnitude of cardiac injury that occurs during an I-R insult is a function of the duration of ischemia, i.e., a longer period of ischemia results in greater cardiac injury. For example, a relatively short duration of ischemia (e.g., 5 minutes) does not result in permanent cardiac damage but may depress cardiac function for 24–48 hours following the insult. In contrast, a long duration of ischemia (>20 minutes) promotes permanent cardiac injury (i.e., cell death) resulting in a myocardial infarction (Downey, 1990). The severity of a myocardial infarction is significant because cardiac muscle cells are not capable of regeneration; therefore, following myocardial infarction, the pumping capacity of the heart is permanently diminished.

Despite the complexity of the cellular mechanism(s) responsible for the I-R-induced cardiac damage, essential factors leading to I-R-induced cellular injury have been delineated in recent years. Experimental evidence indicates that several interrelated factors including radical production, calcium overload, protein breakdown, cellular membrane damage, and leukocyte (white cell) acti-

vation contribute to I-R injury. Collectively, these factors promote cardiac injury, which can lead to myocardial infarction (Bolli & Marban, 1999; Granger & Korthius, 1995).

Exercise and the Prevention of Cardiovascular Disease

Numerous epidemiological studies indicate that regular physical activity reduces the risk of cardiovascular mortality independent of other lifestyle modifications such as diet or smoking (Berlin & Colditz, 1990; Lee et al, 1995; Paffenbarger et al., 1986). Further, exercise-related protection against cardiovascular disease follows a dose-response relationship; the risk of death from cardiovascular disease becomes progressively lower as total energy expenditure due to physical activity increases from 500 to 3500 kcal/week (Paffenbarger et al., 1986). These data strongly support the notion that increased physical activity is protective against heart disease.

While increasing total energy expenditure from exercise is important in the prevention of heart disease, does exercise intensity also play a role? The answer to this question appears to be “yes.” For example, Lee et al. (1995) reported that only energy expenditure during relatively high-intensity physical activity (>5-6 times resting metabolic rate, e.g., slow running, recreational swimming, mowing the lawn with a hand mower) was associated with a reduction in cardiovascular-related deaths in adult men. A strong link between exercise intensity and reduced mortality from cardiovascular disease has also been supported by other studies (Shephard & Balady, 1999).

Exercise And Reduced Risk For Cardiovascular Disease: Biological Mechanisms

The biological mechanism responsible for exercise-induced protection against cardiovascular disease continues to be investigated. In this regard, it is clear that regular exercise reduces several cardiovascular risk factors, including hypertension, diabetes mellitus, obesity, blood lipids, risk of thrombosis (blood clotting), and endothelial (blood vessel) dysfunction (Shephard & Balady, 1999). Therefore, it appears that the association between exercise and reduced cardiovascular mortality rates is due to the reduction in one or more risk factors.

Exercise-Induced Protection Against Cardiac Injury During Ischemia-Reperfusion

While it clear that regular exercise reduces the risk of developing cardiovascular disease, it is also well established that exercise training improves myocardial tolerance to I-R (Bowles et al., 1992; Demirel et al., 2001; Hamilton et al., 2001; Powers et al., 1998). This exercise-mediated cardioprotection is observed in ischemia of both moderate duration (i.e., 5-20 min) and long duration (i.e., >20 min). Specifically, recent studies indicate that endurance exercise training reduces myocardial injury resulting from an I-R insult (Demirel et al., 2001; Powers et al., 1998).

Mechanisms of Exercise-Induced Cardioprotection

At present, the mechanisms behind the exercise-induced myocardial protection against I-R injury are unknown. Nonetheless, at least three primary mechanisms could explain the cardioprotective

effect of exercise: 1) improved collateral circulation; 2) induction of myocardial heat shock proteins; and 3) improved myocardial antioxidant capacity. Although the development of collateral circulation may occur in some animal species following many months of endurance training, evidence indicates that the beneficial effects of short-term exercise are not due to the development of collateral blood vessels (Yamashita et al., 1999). Hence, by elimination, it appears that the exercise-induced cardioprotection associated with short-duration endurance training is due to an increase in myocardial levels of heat shock proteins and/or an increase in antioxidants.

Proteins play an important role in maintaining homeostasis in cardiac and other cells. Damage to existing proteins or impaired protein synthesis during I-R results in a disturbance of cellular homeostasis. To combat this type of disturbance, cells respond by synthesizing a group of proteins termed “heat shock proteins.” These proteins are induced by a variety of stressful conditions, including elevated body temperature and prolonged exercise (Powers et al., 1998). Importantly, numerous studies indicate that increased cellular levels of heat shock proteins can provide protection against cardiac I-R injury (Hutter et al., 1994; Marber et al., 1995).

Although an exercise-induced increase in myocardial heat shock proteins is a potential mechanism to explain the cardioprotection associated with exercise, a recent study indicates that exercise training in a cold environment provides cardioprotection during I-R injury but does not elevate myocardial levels of heat shock proteins (Hamilton et al., 2001). Thus, while increases in myocardial heat shock proteins can promote improved post-ischemic function, other mechanisms could also be responsible for exercise-induced cardioprotection.

Improved protection against radical-mediated cardiac injury is another potential mechanism to explain exercise-induced cardioprotection during an I-R insult. Radicals are highly reactive molecules that are produced during myocardial I-R. Indeed, it is now clear that radicals play a key role in myocardial injury during I-R (Downey et al. 1990). Antioxidants are molecules that are capable of removing radicals and therefore prevent radical-mediated cellular injury. Cells contain several naturally occurring enzymatic and non-enzymatic antioxidants. Primary enzymatic antioxidant defenses include superoxide dismutase, glutathione peroxidase, and catalase. Important non-enzymatic defenses are compounds such as glutathione and the vitamins E and C. Each of these antioxidants is capable of quenching radicals and preventing cellular injury.

It is now well known that exercise can elevate myocardial antioxidants (Powers et al., 1993, 1998). Further, new evidence reveals that as little as 1-3 days of exercise can elevate myocardial levels of the antioxidant enzyme, superoxide dismutase (Demirel et al., 2001; Yamashita et al., 1999). In this regard, there is also evidence that elevating myocardial levels of superoxide dismutase is associated with cardioprotection (Chen et al., 1998; Wang et al., 1998; Yamashita et al., 1999). A recent study has provided direct evidence to link exercise-induced increases in superoxide dismutase to cardioprotection. Indeed, Yamashita et al. (1999) demonstrated that blocking the exercise-induced elevated level of super-

oxide dismutase in the heart results in a loss of exercise-induced cardioprotection. Nonetheless, although the results of these experiments are promising, one study rarely provides a complete answer to a complex question. Therefore, additional experiments will be required to provide definitive evidence that an increased level of myocardial superoxide dismutase is the sole mechanism responsible for exercise-induced cardioprotection.

Nutritional Antioxidants and Cardioprotection

Given the important role that radicals play in I-R-mediated cardiac injury, it is not surprising that there is growing interest in the possibility that supplementation with nutritional antioxidants will provide cardioprotection. Although numerous antioxidants have been studied, three naturally occurring antioxidants have been linked individually or in combination to protection against I-R-induced cardiac injury (Table 1).

| Antioxidant | Overview and mechanism of protection against radicals | Research linking antioxidant with cardioprotection |
|-------------------|---|--|
| Vitamin E | Mostly widely distributed antioxidant in nature. Vitamin E, a generic term, refers to 8 different structural variants of tocopherols or tocotrienols. They are lipid soluble antioxidants that protect against radical-mediated damage to cell membranes. | Coombes et al., 2000 ab |
| Vitamin C | Water-soluble, naturally occurring antioxidant. Two-fold role as antioxidant: 1) recycles vitamin E; and 2) directly scavenges radicals. | Mickle et al., 1989 |
| Alpha lipoic acid | A naturally occurring, water-soluble antioxidant that can recycle vitamin C. Alpha-lipoic acid is also capable of directly scavenging radicals within the cell. | Coombes et al., 2000ab |

Table 1. Three common dietary antioxidants provide protection against ischemia-reperfusion-induced cardiac injury.

Of the antioxidants listed in Table 1, vitamin E and alpha-lipoic acid have received the most recent experimental attention with reference to cardioprotection. Specifically, research using animal models reveals that dietary supplementation with these antioxidants results in myocardial protection against I-R injury (Coombes et al., 2000ab). It is important to note that the myocardial protection from I-R injury is likely due to the synergism between these two antioxidants as opposed to their individual antioxidant qualities. For example, while alpha-lipoic acid is capable of directly scavenging radicals, this antioxidant also recycles vitamin C. Vitamin C, in turn, restores vitamin E to its antioxidant capacity during periods of radical stress. Hence, it is now clear that nutritional antioxidants work as a team to protect cells from radical mediated damage.

Although animal studies suggest that dietary supplementation with antioxidants provides protection against I-R-induced cardiac injury, it is unclear if antioxidant supplementation can provide the same protection in humans. Further, given that some antioxidants

can be toxic when consumed in very large doses, the decision to use dietary antioxidant supplements should be approached with caution and advice from a well-trained nutritionist. Given the strong therapeutic potential of antioxidants, a major research challenge for the future is to determine the safe and optimal daily intake of nutritional antioxidants.

PRACTICAL APPLICATIONS

- Regular exercise training can reduce the risk of cardiovascular disease and provide cardioprotection against I-R injury.
- Current evidence suggests that exercise-induced cardioprotection is dependent upon both the duration and intensity of exercise. Although definitive exercise guidelines for optimal protection are not available, 30 minutes of daily exercise performed at a relatively high intensity of exercise (e.g., slow running) has been shown to reduce the risk of heart disease and provide cardioprotection.
- Evidence indicates that nutritional antioxidants can provide cardioprotection in animals. Therefore, consuming the RDI of nutritional antioxidants is a prudent dietary goal.
- While it is clear that consumption of dietary antioxidants is an important nutritional goal, it is possible that consuming large doses of nutritional antioxidants is not advantageous and could be potentially harmful.

SUMMARY

It is well established that exercise training lowers the risk of developing cardiovascular disease. Further, it is now clear that exercise reduces myocardial oxidative injury following an I-R insult. The mechanism to explain this exercise-induced cardioprotection remains unclear and continues to be investigated. Potential mechanisms include induction of cardiac heat shock proteins and/or improved myocardial antioxidant capacity.

Animal studies reveal that supplementation with vitamin E and alpha-lipoic acid can provide protection against I-R-mediated cardiac injury. Currently, it is unknown if nutritional antioxidants can provide cardioprotection in humans; this remains an important area for future research.

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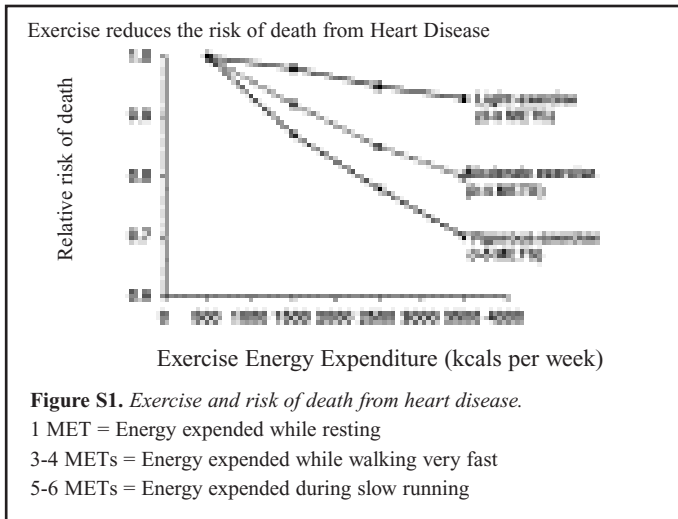
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PROTECTING YOUR HEART WITH EXERCISE AND NUTRITIONAL ANTIOXIDANTS



Cardiovascular disease is a major cause of death throughout the world. Therefore, finding ways to reduce your risk of developing cardiovascular disease and protect your heart in the event of a heart attack is important. Regular exercise and dietary intake of adequate nutritional antioxidants are two lifestyle factors within our control that have been shown to provide protection for the heart (cardioprotection). Examples of activities that provide cardioprotection are running, walking, and cycling. Note in Figure S1 that exercise-related protection against cardiovascular disease follows a dose-response relationship; in other words, the risk of death from cardiovascular disease is progressively lower as exercise energy expenditure increases from 500 to 3500 kcal/week. Notice that exercise of moderate to vigorous intensity provides the most protection against death from heart disease. Table S1 provides an overview of an exercise-prescription designed to provide cardioprotection.

Table S1. Exercise Prescription for Achieving Cardioprotection*

- Perform 30 minutes or more of endurance exercise (3-7 times per week)
- Exercise intensity should reach or exceed 3 METS (equivalent to very fast walk) or higher during workout
- Recommended exercise includes running, walking, swimming, or cycling

* From Lee, I.M., C.C. Hsieh, and R.S. Paffenbarger, Jr., Exercise intensity and longevity: The Harvard Alumni Health Study. *JAMA* 273:1179-1184, 1995.

Nutritional Antioxidants and Cardioprotection

Recent animal studies suggest that dietary supplementation with antioxidants (i.e., vitamin E and alpha-lipoic acid) can provide cardiac protection during a heart attack. Animal studies also show that antioxidant supplementation in drug form (i.e., unnatural antioxidants) slows the progression of coronary artery disease. Nonetheless, it is unclear if antioxidant supplementation can provide the same protection in humans. Further, given that very large doses of some antioxidants could have harmful side effects, the decision to use dietary antioxidant supplements should be approached with caution. Based on our current knowledge of antioxidants, a prudent dietary goal is to achieve the Reference Daily Intake (RDI) for major antioxidant vitamins (e.g., vitamins A, E, C) and minerals (e.g., zinc, copper, magnesium, and selenium) through a varied diet. In other words, the general rule is that most vitamin and mineral dietary requirements are best met by eating foods rather than by ingesting a supplement, and this rule should be followed for antioxidants as well. Hence, achieving the RDI for antioxidant vitamins and minerals through a diet rich in fruits and vegetables is a sound approach toward obtaining the maximum health benefits from antioxidants. Table S2 lists some important food sources of antioxidants.

Table S2. Dietary sources of antioxidant vitamins.

| Antioxidant vitamin | Dietary sources |
|----------------------------|---|
| Vitamin E | Plant oils (e.g., corn, soybean), grains, nuts, asparagus |
| Vitamin C | Citrus fruits, tomatoes, potatoes, green vegetables |
| Carotenoids (Provitamin A) | Carrots, broccoli, spinach, sweet potatoes, peaches, |

Suggested Readings

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