

## Cardioprotective Effects of Intermittent Fasting

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### Abstract

Calorie restriction, a dietary regimen reducing energy intake without causing malnutrition, prolongs lifespan and exerts medical and health benefits such as lowering metabolic risk factors for chronic diseases and ameliorating chronic conditions. Intermittent fasting (IF), a type of calorie restriction regimen, has attracted particular attention as it is cost-effective and more accessible while exerting the same or even enhanced beneficial effects on health and disease in laboratory animals and humans. In this review, we focus on the protective effects of IF on several types of heart diseases including myocardial ischemic injury, age-related cardiac hypertrophy, doxorubicin-induced cardiotoxicity and coronary heart disease risk factors. The findings summarized here implicate IF as a non-pharmacological, non-genetic preventive or therapeutic intervention for certain types of heart disease.

**Keywords:** Intermittent fasting; Heart disease; Calorie restriction; Cardiac injury

### Introduction

Calorie restriction, defined as a dietary regimen reducing energy intake without causing malnutrition, has been shown to enhance physiological health, reduce risk factors for chronic disease and improve chronic conditions [1,2]. Given the fact that intermittent fasting (IF), a form of calorie restriction regimen, is cost-effective and more accessible while exerting the same or even enhanced health benefits, it has attracted particular attention [3,4]. The most common way to undertake IF is that the individuals are completely fasted or severely restrict their food intake every other day, which also termed alternate-day fasting [5]. Another common strategy for IF is that energy uptake is severely restricted for one day or two non-consecutive days each week with or without daily calorie restriction [6]. IF has long been considered a potential preventive or therapeutic intervention for a variety of diseases such as cancer, neurodegenerative disorders, metabolic disease and cardiovascular disease [3]. Here we update the evidences regarding cardioprotective effects of IF in experimental animal models and humans.

### IF and Myocardial Ischemic Injury

In rat models of myocardial infarction, IF protects the hearts from cardiac injury as manifested by reduced infarct size, decreased apoptotic myocytes and inflammation; in addition, IF attenuates post-myocardial infarction cardiac remodelling [7]. The beneficial effects are associated with increased serum adiponectin levels, which have been shown to protect the heart from ischemic injury [8,9]. In a rat model of chronic myocardial ischemia, IF improves the survival of rats with chronic heart failure, attenuates cardiac remodelling, improves cardiac function, stimulates angiogenesis and reduces apoptotic cell death in the border zone of the ischemic hearts [10]. During ischemia-reperfusion, IF protects against cardiac injury in mice through restoration of impaired autophagic flux by stimulating nuclear

translocation of TFEB, a master regulator of autophagy-lysosome gene expression networks [11]. Therefore, IF confers protection to the heart against ischemic injury in experimental animal models.

### IF and Age-Related Cardiac Hypertrophy

IF improves markers for age-related cardiac hypertrophy and heart failure in rats including increased cardiac sarcomeric  $\alpha$ -actin,  $\beta$ -MHC and elevated BNP in the heart and plasma. Moreover, IF ameliorates cardiac parameters including left ventricle weight, left ventricle weight/body weight and cross-sectional area of individual cardiomyocyte, which are increased during ageing. The beneficial effects of IF in the ageing heart are achieved through restoring overactivated ERK1/2 and PI3K $\gamma$  signalling, both of which are associated with pathological cardiac hypertrophy [12]. In addition, IF is able to attenuate oxidative stress, fibrosis and inflammation in the ageing rat heart [13].

### IF and Doxorubicin-Induced Cardiotoxicity

Doxorubicin is one of the most effective anti-neoplasm drugs. However, its clinical use is limited by potential cardiotoxicity. We and others have recently shown that autophagic flux is impaired in the mouse models of doxorubicin-induced cardiotoxicity, which contributes to heart injury [14-16]. Moreover, we have shown that IF is capable of restoring autophagic flux and ameliorating pathological alterations including increased cytoplasmic vacuolization, fibrosis, apoptosis and generation of reactive oxygen species in both acute and chronic doxorubicin cardiotoxicity [16]. Thus, IF could serve as a promising strategy for the prevention and control of doxorubicin-induced cardiotoxicity.

### IF and Coronary Heart Disease Risk Factors

IF is able to alter spectral analysis of blood pressure and heart rate variability and reduce insulin levels in rats, which are risk factors for coronary heart disease [17,18]. IF also lowers coronary heart disease risk factors in humans. For instance, IF improves indicators of

coronary heart disease in obese men and women including reducing body weight, waist circumference, fat mass, low-density lipoprotein cholesterol (LDL-C) and triacylglycerol [19]. In addition, IF-calorie restriction with liquid diet is more capable of reducing risk factors for coronary heart disease compared with IF-calorie restriction without liquid diet in obese women [20,21]. IF with high-protein and low-calorie diet reduces body weight, BMI, blood lipids and enhances arterial compliance in obese men and women [22]. Reduction of coronary heart disease risk factors by IF is associated with modulations of adipokines [19,21].

## Conclusions

Caloric restriction exerts diverse beneficial effects on health and chronic conditions in animal models and humans. However, long-term caloric restriction is difficult to sustain. Although caloric restriction mimetics are more practical, IF offers a more accessible and cost-effective intervention to be realized in humans, and thus receives considerable attention. Importantly, IF has been shown to improve ischemic cardiac injury, age-related cardiac hypertrophy, doxorubicin-induced cardiotoxicity and risk factors for coronary heart disease. Therefore, IF may be considered as a potential intervention for certain forms of human heart disease. However, there are some limitations in current research on cardioprotection of IF in terms of practical applicability. First, IF is not without cardiac adverse effects as reduced diastolic compliance and diminished systolic reserve induced by chronic IF in animal models have been reported [23]. Second, the beneficial effects of IF on myocardial ischemic injury, age-related cardiac hypertrophy and doxorubicin-induced cardiotoxicity have only been shown in preclinical studies and it remains unknown if the results can be translated to humans. Third, although more sustainable, ethic issue should be considered for the execution of long-term IF in humans. Thus, medically supervised clinical trials should be designed and conducted to optimize fasting procedures to confer cardioprotection while minimizing the potential side effects. Nevertheless, IF represents a promising non-pharmacological, non-genetic preventive or therapeutic strategy for several types of heart disease.

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