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Review

Caloric restriction and heart function: is there a sensible link?

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Calorie restriction (CR) is defined as a reduction in calorie intake below the usual *ad libitum* intake without malnutrition. Ample of clinical and experimental evidence has demonstrated that CR is capable of retarding aging process and development of cardiovascular disease. Although suppression of reactive oxygen species production and inflammation plays a central role in the favorable cardiovascular effects of CR, the health benefit of CR is believed to be ultimately mediated through a cadre of biochemical and cellular adaptations including redox homeostasis, mitochondrial function, inflammation, apoptosis and autophagy. Despite the apparent beneficial cardiovascular effects of CR, implementation of CR in the health care management is still hampered by apparent applicability issues and health concerns. Here we briefly review the cardiac consequence of CR and discuss whether CR may represent a safe and effective strategy in the management of cardiovascular health.

Keywords: caloric restriction; metabolism; cardiac function; cardiac geometry

Calorie restriction and health

Calorie restriction (CR) is defined as a reduction in calorie intake below the usual *ad libitum* intake without malnutrition. In general, the daily caloric intake subjected to CR has been restricted to 50% to 70% of the average food intake in subjects eating *ad libitum*[1, 2]. CR was first reported to retard aging and prolong median and maximal life span in the 1930s[3]. Over the last several decades, CR has been widely studied which exhibits an apparent beneficial impact on longevity, age-associated diseases, and attenuation of functional decline, across a broad variety of species (including rats, mice, fish, flies, worms and yeast)[4, 5]. Moreover, CR provides protection against a cadre of chronic diseases including diabetes mellitus, neurodegenerative diseases, autoimmune disorders[6–8] and cancer[9–12]. CR has been shown to alter a variety of physiological parameters especially reduced metabolic rate and oxidative damage, resulting in a decrease in the incidence of cardiovascular diseases[13]. In response to energy deficiency, experimental animals experience a drastic decrease in both fat mass and lean body mass. Muscle mass is overtly reduced, although the rate of loss of function and mass/body weight with the aging process is attenuated[9, 14–16]. Metabolic rate may decrease tran-

siently although studies have indicated similar metabolic rate per kg lean body mass to that of *ad libitum* fed rodents in long-term CR protocol[17]. Body temperature, systolic and diastolic blood pressure all decrease[18, 19] along with the reduced sympathetic activity[20]. CR-treated animals are more spontaneously active and display superior cognitive abilities compared to their *ad libitum* counterparts[21, 22].

The most prominent mechanism that may be responsible for the beneficial health and physiological effects of CR are usually mediated through increased insulin sensitivity which results in reduced plasma glucose and insulin concentrations and improved glucose tolerance[23]; reduced levels of oxidative stress (decreased oxidative damage to proteins, lipids and DNA)[24], increased resistance to various types of stress including heat, oxidative and metabolic stress[25] as well as enhanced immune function[26].

Impact of CR on aging

An inverse relationship between calorie intake and lifespan has been revealed in mice, suggesting a key role for regulators of energy metabolism in the mechanism of CR. Accordingly, CR-induced metabolic reprogramming may be a key event in the mechanism of lifespan extension[27, 28]. The age when CR is started, the severity of restriction, and strain or genetic background of animals determine the magnitude of life extension. The only mammals in which CR has clearly been shown

to slow primary aging and extend maximum lifespan are rats and mice[29–31]. In rodents, initiating a 30% to 60% reduction in calorie intake below usual *ad libitum* intake early in life (from shortly after weaning to age 6 months) caused a proportionate 30% to 60% increase in maximum lifespan, whereas a 44% reduction in calorie intake started in adulthood (12 months) extended maximum lifespan by only 10% to 20%[32]. Data from rodents found that CR increases longevity by preventing or delaying chronic diseases including diabetes, atherosclerosis, cardiomyopathy, autoimmune diseases, kidney and respiratory diseases, and cancer[3, 30–32]. In addition, CR is capable of decreasing neurodegeneration in the brain and enhancing neurogenesis in animal models of Alzheimer's disease, Parkinson disease, Huntington disease and stroke[27, 32–34]. However, reduction of chronic diseases does not completely explain the increased lifespan and preservation of function at more youthful-like states in calorie-restricted rodents. In particular, approximately one third of these experimental rodents die without any evidence of apparent organ pathology[35].

More recent studies suggest that reducing calorie intake can also increase the lifespan in nonhuman primates[36, 37]. There are two longevity studies (one at the University of Wisconsin, the other at the National Institute on Aging) examining the long-term effects of CR on aging in rhesus monkeys[38]. Up-to-now, the experimental data have shown that a number of metabolic, hormonal and structural adaptations taken place in CR-treated rodents also exist in CR monkeys. A 20-year longitudinal adult-onset CR study in rhesus monkeys at the Wisconsin National Primate Research Center revealed that moderate CR lowered the incidence of aging-related death. Fifty percent of control fed animals survived as compared with 80% of the CR animals. Furthermore, CR delayed the onset of age-associated pathologies. Specifically, CR reduced the incidence of diabetes, cancer, cardiovascular disease, and brain atrophy[27]. In addition, immune senescence and sarcopenia are attenuated in calorie restricted monkeys[39]. Taken together, emerging evidence from ongoing research of CR in monkeys suggest that this nutritional paradigm may be universal among species with regards to extension of life span and retardation of aging.

It is likely that certain physiological and psychological consequences elicited by CR seen in animals may distinctly impact human life. It is rather difficult to determine whether CR has beneficial effects on longevity in humans because there are little validated biomarkers that may serve as surrogate markers of aging. Furthermore, it is impractical to conduct randomized, diet-controlled, long-term survival studies in human[40]. Nonetheless, data from epidemiological studies suggest that CR may offer beneficial effects on the factors involved in the pathogenesis of primary and secondary aging and life expectancy in humans. Data from a series of studies conducted by the Calorie Restriction Society, a group that practices self-imposed CR with a belief that diet restriction extends lifespan, were recently reported[41–43]. Compared with control individuals consuming a Western diet, calorie restricted individuals exhibited similar alterations in metabolic and organ function reported previously in calorie restricted rodents. The main parameters for metabolic and organ function include low percentage of body fat, low systolic and diastolic blood pressure, markedly improved lipid profile, increased insulin sensitivity, reduced plasma concentration of inflammatory markers, low circulating growth factors, and low serum concentration of T_3[41–43]. Interestingly, left ventricular diastolic function (*ie*, parameters of viscoelasticity and stiffness) in calorie restricted individuals was somewhat similar to those who were ~16 years younger[43] and is consistent with the beneficial cardiac effects of CR seen in mice[44]. Nonetheless, further large scale study is in need to determine the human metabolic and functional adaptive responses to CR.

Impact on cardiovascular system

CR exerts a protective effect on cardiovascular system. Evidence from both experimental animals and human has demonstrated that CR decreases basal heart rate[29, 45]. In addition, Mager and coworkers recently depicted that rats maintained on a CR diet display increased heart rate variability[46]. High heart rate variability is usually associated with improved cardiovascular function, whereas low heart rate variability is usually indicative of poor cardiovascular function. Other than heart rate, CR may also participate in the regulation of blood pressure. Hypertension is a major risk factor for coronary artery disease and stroke[47]. Both systolic and diastolic blood pressures are significantly reduced in rats maintained on a CR diet[48]. Similarly, monkeys also display reduced blood pressure following CR diet[37].

Progressive CR induces a dose-dependent increase in myocardial triglyceride content and a dose-dependent decrease in diastolic function in lean healthy men[49]. Viljanen and colleagues showed that myocardial free fatty acid uptake was reduced after a short-term low calorie diet resulting in overt weight loss. Furthermore, these changes were in parallel with the reduction of left ventricular mass, cardiac work, and perfusion at rest and a subtle reduction in myocardial triglyceride content[50].

It has been shown that diastolic dysfunction is favorably affected by CR in human[43]. Interestingly, changes of diastolic function in CR subjects were very similar to lifelong CR mice[44]. CR possesses cardiac-specific effects which may offset aging-associated changes in diastolic function. These beneficial effects on cardiac function might be mediated by the effect of CR on blood pressure, systemic inflammation and myocardial fibrosis[43]. Further evidence revealed notable effect of CR on endothelial function[22]. CR is capable of improving endothelium-dependent vasodilatation[51]. It is plausible to speculate that CR improves endothelial function in the non-obese, probably via decreased production of ROS. CR lowers most major coronary heart disease (CHD) risk factors, including plasma low density lipoprotein cholesterol (LDL-C) concentration, total cholesterol/high density lipoprotein cholesterol (HDL-C) ratio, C-reactive protein (CRP) concentrations, and the homeostasis model assessment for insulin resistance (HOMA-IR) index[52].

CR reduces levels of oxidative stress in cardiovascular

system by alleviating oxidative modifications of proteins and DNA and decreased levels of lipid peroxidation in the heart[24, 53, 54]. CR reduces inflammatory processes which triggers atherosclerosis, as indicated by reduced levels of leukocytes and circulating levels of tumor necrosis factor α (TNF-α) and other inflammatory cytokines[1, 55]. By suppressing atherosclerosis, CR should ultimately reduce the risk of cardiovascular disease and stroke.

Effect of CR on cardiovascular disease and cardiopathology

Much of the cardiovascular disease is related to the metabolic syndrome which diagnosis standard including clinical findings of increased abdominal circumference, elevated triglycerides, low high-density lipoprotein-cholesterol, elevated fasting blood glucose and/or elevated blood pressure. It is well established that, beside drug therapy, lifestyle therapies that combine energy restriction and physical activity independently improve a number of cardiovascular disease risk factors including insulin resistance, impaired glucose tolerance, dyslipidemia and hypertension[56–58].

Hypertension and cardiac hypertrophy

Reduced caloric intake lowers blood pressure in hypertension[59–61] and obesity[62], which are usually accompanied with overt cardiovascular anomalies. The mechanisms responsible for this observation have not been clarified. However, decreases in sympathetic nervous activity frequently accompany reduced caloric intake. In the spontaneously hypertensive rats, fasting-induced reduction in blood pressure is accompanied by reduced cardiac norepinephrine turnover[63] and reduced sympathetic support of blood pressure[60]. Reduced plasma norepinephrine levels and decreased sympathetic support of blood pressure have also been observed in aortic coarctation-induced hypertension following CR[59]. There is thus considerable evidence suggesting that reduced sympathetic activity may serve as an important mechanism behind the reduction in blood pressure following decreased caloric intake[64].

The Dahl salt-sensitive rat is model which indices of decompensated, pressure-overload hypertrophy. Seymour reported that CR reduced the degree of change rather than preventing it. CR reduced restrictive pattern development (lower E/A), prolonged early filling deceleration time, and shortened relaxation time. These authors concluded that modest CR, independent of salt intake, reduced hypertension associated decompensated pressure-overload hypertrophy[65].

Ischemia and reperfusion

Shinmura showed that short-term (2 weeks) CR is capable of improving myocardial ischemic tolerance in both young and old Fischer 344 rats. The cardioprotection induced by CR is associated with an increase in AMPK activation[66]. Furthermore prolonged CR (6 months) improves myocardial ischemic tolerance and restores ischemic preconditioning (IP) effect in middle-aged rats, possible through a nitric oxide-dependent

increase in nuclear human silent information regulator type 1 (SIRT1) content[67]. CR also promoted ischemia-induced revascularization in wild-type mice but not adiponectin knockout mice. Adiponectin is known to promote vascular cell function and survival under stressed conditions[66, 67]. It was recently reported that CR may confer resistance to myocardial ischemia-reperfusion injury by increasing adiponectin levels[68]. Lifelong CR drastically attenuates myocardial oxidative stress during ischemia/reperfusion[23] and post-ischemic inflammatory response[69].

IP is able to protect the heart against ischemia reperfusion damage in adult but not in senescent rat hearts. Abete and colleagues found that IP reduces postischemic dysfunction in the hearts from adult and food-restricted but not in the *ad libitum*-fed senescent rats[70]. Nonetheless, exercise training and food restriction individually produce partial preservation of IP in the aging heart[71]. One of the mechanisms responsible for early IP conservation in aging heart may be restoration of the norepinephrine release in response to preconditioning stimulus.

Diabetes mellitus and metabolic syndrome

Major metabolic effects of substantial weight loss in obese patients with type 2 diabetes provide an avenue to understand the mechanisms behind metabolic syndrome. Typical diagnosis of metabolic syndrome requires presence of 3 of 5 characteristics: increased abdominal waist, hyperglycemia, high blood triglycerides, high blood pressure and HDL-C. One of the commonly accepted hypotheses is that the crucial initial event is the increased concentration of circulating free fatty acids (FFAs) and cytokines derived from excess visceral abdominal fat[72]. Increased circulating FFAs is known to decrease glucose uptake by heart and skeletal muscle[72] although it is rather difficult to link chronically increased circulating FFAs to increased blood triglycerides and decreased high density lipoprotein (HDL) in humans. Weight loss in obesity led to decreased waist circumference, decreased circulating glucose and triglycerides, and cytokines. Conversely, increased circulating FFAs taken up by the heart promote accumulation of myocardial triglycerides leading to diastolic dysfunction and lipotoxic cardiomyopathy in human[73]. Overall, these results provide support the concept that excess circulating FFA, as associated with abdominal visceral obesity, is fundamental in the pathogenesis of an increasingly common human disease, namely, metabolic syndrome. It was also indicated that unloading the human body of adipose tissue induces a "reverse metabolic syndrome." Similar to human, type 2 diabetic rats undergo CR or exercise displayed improved plasma levels of glucose, insulin, cholesterol and triacylglycerol and reduced abdominal fat accumulation[74]. Other report also reported reduction in cardiovascular disease risk in type 2 diabetes following CR[75]. Hammer and colleagues reported that a short-term very low-calorie diet increases myocardial triglyceride content and is associated with a decrease in left ventricular diastolic function in patients with well-controlled type 2 diabetes[76]. Furthermore prolonged caloric restriction improves

glucoregulation associated with decreased myocardial triglyceride content and favorable effects on blood pressure and myocardial function in insulin-treated obese patients with type 2 diabetes[77]. These data prove that myocardial triglyceride stores in obese patients with type 2 diabetes are flexible and amendable to therapeutic intervention by caloric restriction.

Other heart diseases

CR reduces the severity of spontaneous cardiomyopathy in rats and prevents age-associated alterations in late diastolic function in mice[78]. CR also improves the survival and myocardial damage in obese mice with viral myocarditis, which is accompanied by increased adiponectin levels in plasma and myocardium[79]. In addition, CR attenuates atherosclerotic formation[34].

Signal transduction mechanism involved in CR

Evidence from animal models and preliminary studies in humans indicates that CR delays cardiac aging and prevents cardiovascular disease. These effects are mediated by a wide spectrum of biochemical and cellular adaptations, including redox homeostasis, mitochondrial function[80], inflammation[81, 82], apoptosis[83], and autophagy[84]. Oxidative stress plays an important role in the pathogenesis of coronary artery disease by mediating expression of inflammatory genes and eliciting oxidative modification of lipoprotein particles[85, 86]. CR seems to confer vasoprotection through attenuation of oxidative stress and antiinflammatory effects in aged animals[13]. CR also increases bioavailability of antiatherogenic NO and improves endothelial function[13]. In addition, CR exerts beneficial effects on a range of systemic cardiovascular risk factors[87, 88].

Over the last decades, a number of nutrient-sensitive proteins have been identified in the health and longevity effects of CR, including the sirtuins, forkhead box transcription factors (FOXOs)[89] and mammalian target of rapamycin (mTOR)[90]. Corton and Brown-Borg provided compelling evidence for the broad participation of the nuclear receptor transcription factor, peoxisome proliferator activated receptor (PPAR) α in CR[91]. The PPAR γ co-activator PGC-1α is a key regulator of genes involved in mitochondrial metabolism. CR increases mRNA levels of PGC-1α in multiple tissues[92]. Regulation of mitochondria through manipulation of SIRT1 and glycogen synthase kinase 3 beta (GSK3β) is a common feature of CR and the stress response[93]. Other transcription factors have also been considered with a key role in CR-elicited biological actions. Heydari and colleagues reported that CR enhanced the heat shock transcription factor 1 (HSF-1) function and thereby promoted the transcription of the important chaperone, heat shock protein 70 (HSP70)[94]. Kim and coworkers proposed an important role of the following redox-sensitive transcription factors in CR-associated actions including nuclear factor kappa B (NF-κB), activator protein-1 (AP-1); and hypoxia inducible factor-1 (HIF-1)[95]. However, much still remains to be determined with regards to the functioning of transcription factors

in long-term CR. Table 1 summaries some of the most important signaling molecules involved in CR-induced biological and physiological responses.

Table 1. CR effect on signal molecule.

Signal molecule	CR effect on signal molecule	Ref No
AP-1	↓	[81, 95]
FOXO	↓	[89, 97]
GSK-3β	↓	[93, 98]
HIF-1	↓	[95, 99]
HSF-1	↑	[94]
HSP-70	↑	[94, 100]
mTOR	↓	[90, 101]
NF-κB	↓	[81, 82, 95, 97]
PGC-1α	↑	[91, 92]
PPAR α	↑	[91, 102]
SIRT1	↑↓	[92, 93, 103]

↑=increase in signal transduction; ↓=decrease in signal transduction.

Conclusion and perspectives

When considering all possible aging interventions evaluated, there is little doubt that CR remains the most robust. Studies in numerous species have demonstrated that CR can increase lifespan, reduce the incidence and delay the onset of age-related diseases, improve stress resistance, decelerate functional decline, and in particular, exert cardioprotection. One of the most pertinent issues in CR research is the relevance of this nutritional intervention in human aging, given the practicality of long term CR in human. More recent research has targeted on the development of "CR mimetics", namely compounds mimicking favorable metabolic effect of CR without restricting caloric intake. Certain compounds, such as resveratrol and rapamycin, have shown some clinical promises with many CR-like effects to promote cardiovascular health and retard cardiac aging in humans[96].

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