
Impact of Nutrition on Cardiovascular Function

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Abstract: The metabolic sources of energy for myocardial contractility include mainly free fatty acids (FFA) for 95%, and in lesser amounts for 5% from glucose and minimal contributions from other substrates such lactate, ketones, and amino acids. However, myocardial efficiency is influenced by metabolic condition, overload, and ischemia. During cardiac stress, cardiomyocytes increase glucose oxidation and reduce FFA oxidation. In patients with ischemic coronary disease and heart failure, the low oxygen availability limits myocardial reliance on FFA and glucose utilization must increase. Although glucose uptake is fundamental to cardiomyocyte function, an excessive intracellular glucose level is detrimental. Insulin plays a fundamental role in maintaining myocardial efficiency and in reducing glycemia and inflammation; this is particularly evident in obese and type-2 diabetic patients. An excess of F availability increase fat deposition within cardiomyocytes and reduces glucose oxidation. In patients with high body mass index, a restricted diet or starvation have positive effects on cardiac metabolism and function while, in patients with low body mass index, restrictive diets, or starvation have a deleterious effect. Thus, weight loss in obese patients has positive impacts on ventricular mass and function, whereas, in underweight heart failure patients, such weight reduction adds to the risk of heart damage, predisposing to cachexia. Nutrition plays an essential role in the evolution of

Conflict of interest: The author declares no conflict of interest and no funding support to this work.
Curr Probl Cardiol 2018;00:1–30.
0146-2806/\$ – see front matter
<https://doi.org/10.1016/j.cpcardiol.2018.08.003>

cardiovascular disease and should be taken into account. An energy-restricted diet improves myocardial efficiency but can represent a potential risk of heart damage, particularly in patients affected by cardiovascular disease. Micronutrient integration has a marginal effect on cardiovascular efficiency. (Curr Probl Cardiol 2018;00:1–30.)

Energy Metabolism and Heart Function

The cardiomyocyte is a unique muscle cell which possesses the ability to maintain contractile function under varying metabolic conditions. In a healthy heart, under normal physiological conditions, the contractile function is sustained by the production of adenosine triphosphate (ATP), predominantly derived from the fatty acid oxidation (60%-90%), with the balance derived from glucose (30%-40%)¹ and a lesser contributions from lactate, ketones, amino acids, and pyruvate. Pyruvate production derives mainly from glycolysis and lactate oxidation of 10%.²⁻⁴ The primary energy source for cardiac metabolism is supplied by free fatty acids (FFA) and by chylomicrons which cross the cell membrane passively or transported actively by a specific protein.⁵ In the healthy heart, although lipid oxidation represents the principal energy source, the glucose metabolism is essential to maintain physiological cardiac function.²

Glucose uptake from cardiomyocytes is regulated mainly by Glut-4, in response to insulin stimulation and increases during ischemia or work demand (overload).⁶ Glut-4 is dependent upon activation of AMP-activated protein kinase (AMPK), nutria-sensors of the cells.⁷ Glycolysis causes the formation of pyruvate, and its oxidation is the final step of carbohydrate (CHO) oxidation.⁸ Glucose and pyruvate oxidation is inhibited by FFA levels, while increased by the reduction of FFA level⁹ This interaction between fatty acids availability and glycolysis inhibition was first described by Randle and is called “glucose-fatty acid cycle”.¹⁰ In conditions of cardiac stress and overload, the cardiomyocyte energy source shifts towards higher utilization of glucose.

In normal cardiomyocytes, the ATP production is maintained constant by mitochondrial oxidative phosphorylation, even in the condition of overload, eg, intensive exercise or hypertension.¹¹ The increased contractile force is sustained by a concomitant increase in fatty acid and carbohydrate utilization¹² and by the nutritional state¹³ as observed during

overnutrition and restricted calorie balance that significantly changes cardiomyocyte energy metabolism.

During maximal cardiac demand, the healthy heart progressively utilizes lactate for energy.¹⁴ In the condition of cardiac stress, such as in prolonged overload and the hypertrophied heart, cardiac metabolism changes—sparing FFA oxidation, while increasing glucose oxidation.¹⁵ During ischemic heart conditions, glucose becomes the prevalent source of energy for myocardial tissue – both in chronically hypertrophied and normal hearts.¹⁶ In severely ischemic hypertrophied hearts, glycogen degradation is further accelerated, and the consequent reduced CHO availability accentuates the risk of ischemia and reduced contractile performance.¹⁵

In patients with ischemic coronary artery disease (CAD), the low oxygen availability of the myocardium is supplied by optimizing glucose utilization with an improved insulin activity and cardiomyocytes glucose sensitivity. In heart failure (HF) the global cardiac efficiency is impaired due to the reduced mitochondrial energy production¹⁷ via oxidative phosphorylation¹⁸ and these conditions favor an evolution from cardiac hypertrophy to HF.¹⁹ Glucose is the most energetically efficient substrate which is preferentially utilized during conditions of myocardial stress such as overload and HF. In these circumstances, the increased glucose oxidation protects against acute myocardial ischemic injury.²⁰ Furthermore, in HF the myocardium metabolizes ketone bodies which become an essential fuel source for oxidative ATP production.²¹ Ketone body oxidation is metabolically more efficient than FFA oxidation²² and can acutely improve left ventricular function.²³ In the failing heart, ketones bodies represent a preferential source of energy for energy production.²¹ Although ketone bodies oxidation is a more competitive energy pathway compared with other substrates in HF, there is a great limitation due to the ketogenic diet characterized by a high fat and high protein with minimal (50 g/day) or absent intake of carbohydrates,²⁴ not at all tolerated by these patients. However, the effect of the ketogenic diet in patients with cardiovascular disease (CVD) remains to be investigated. Thus, the metabolic flexibility of cardiomyocyte is considerable and is responsive to changes in substrate availability and nutritional status. (Fig 1).

Metabolism in the Heart

FFA

FFA metabolism is less efficient energetically than glucose metabolism although it increases the oxygen consumption.²⁵ However, an excessive availability of myocardial FFA exceeds the oxidative capacity of the

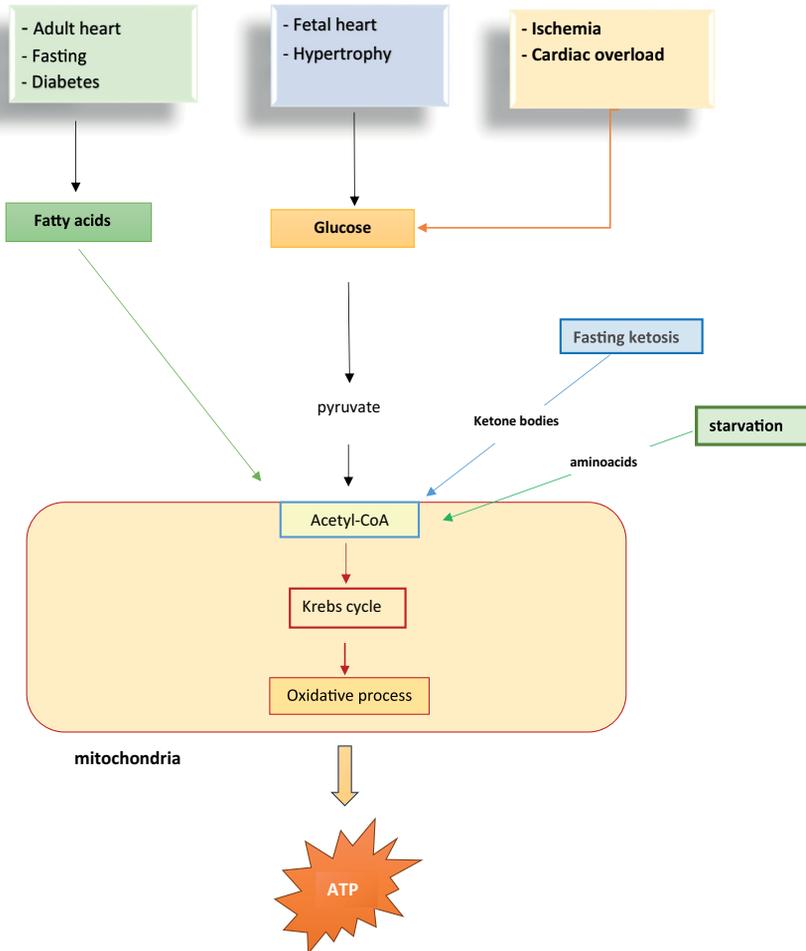


FIG 1. Fatty acids are prevalently oxidized by adult heart, in diabetes, and fasting. Glucose oxidation is prevalent in fetal heart, hypertrophy, cardiac overload, and ischemia. During fasting are oxidized ketone bodies and amino acids.

myocardial tissue favoring the FFA accumulation as intramyocardial lipids, thus causing a “lipotoxicity,” leading to insulin resistance and impairment of the cardiac function.²⁶⁻²⁸ A high intracellular lipids accumulation, as observed in type-2 diabetes, inhibits the glucose oxidation via the phosphorylation of pyruvate dehydrogenase kinase.²⁹

Glucose Metabolism

Glucose crosses the membrane of cardiomyocytes passively or by glucose transporter GLUT4 which regulates the glucose level in the cells. In

contrast to skeletal muscle, in cardiomyocytes, there is also a significant expression of GLUT1, which contributes to cardiac glucose uptake under certain circumstances.³⁰ Various hormones and cytokines regulate glucose metabolism in the myocardium contributing to the development of insulin resistance.³¹

Glucose is an oxygen sparing substrate that generates more ATP per mole of oxygen compared to fatty acids, and when the availability of oxygen is decreased, it can produce energy through glycolysis. Imaging studies using the fluorodeoxyglucose-positron emission tomography FDG-PET have shown that the ischemic myocardium in the fasting state changes the energy source switching from fatty acids to glucose. Preserving myocardial viability,³² and the degree of elevation in myocardial glucose uptake is predictive of cardiac function recovery after revascularization.³²

In patients with a nonischemic CAD, whole body substrate oxidation rates did not differ from that observed in the no-CAD group.³³ In ischemic CAD patients, their myocardium will adapt to the condition of limited oxygen availability, although oral glucose loading does not acutely increase myocardial CHO oxidation, evidences limited metabolic flexibility. These data indicate that there is a remarkable chronic requirement and utilization of glucose in patients with ischemic CAD.³⁴ The ability of ischemic myocardium to upregulate glucose extraction by overexpressing glucose transporters is limited^{35,36} and some evidence indicates that physiological plasma glucose levels and insulin activity are essential to increase glucose delivery to tissues, thereby playing a protective role.³⁷⁻³⁹ In agreement with this, hypoglycemia has been shown to extend the area of necrosis in the ischemic heart,⁴⁰ and recent trials addressing excessive glucose reduction following the therapy in type-2 diabetes patients found an increased rate of cardiovascular events and mortality, correlated with the frequency of hypoglycemic episodes.⁴¹ However, the switching from FFA to glucose substrate utilization is not completely benign. In fact, the increased use of glucose changes the glutation-related and mTOR pathways favoring hypertrophy and oxidative stress.⁴² Activation of mTORC1, a major regulator of cell growth, promotes protein synthesis and responds to stress, and nutrients, particularly amino acids and glucose.⁴³ AMPK is low and activated by exercise overload and ischemia and regulates the glucose uptake with an insulin-independent mechanism⁴⁴ (Fig 2).

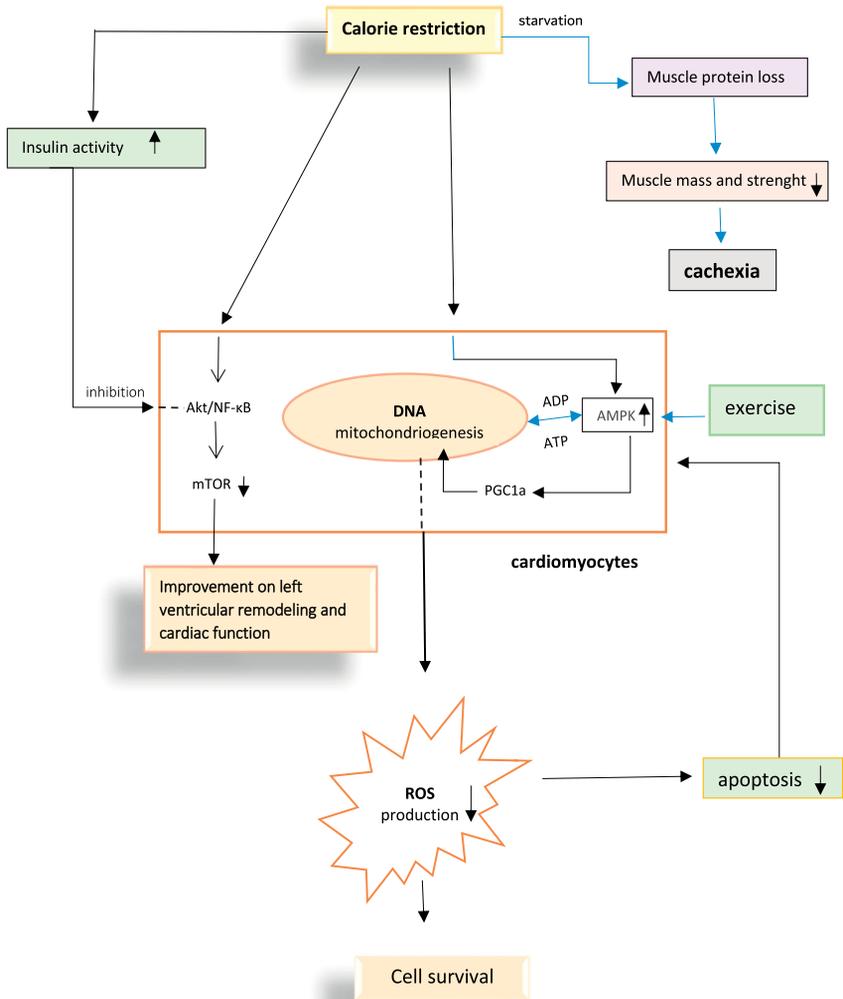


FIG 2. Caloric restriction improves insulin sensitivity that inhibits directly the Akt/NF- κ B and increase the AMPK in the cell. NF- κ B inhibits phosphorylation of mTOR and reverses left ventricular remodeling and cardiac function The activation of both signaling act directly on mitochondria in the cardiomyocytes. AMPK and PGC1 increase mitochondrial biogenesis and autophagy. The increased efficiency of mitochondria reduces the ROS production and improvement of cell survival and apoptosis. Prolonged starvation reduces the muscle mass and strength favoring cachexia.

Protein and Amino Acids

In chronic heart failure (CHF) patients, a reduced circulating level of amino acids was observed, that is correlated with HF severity.⁴⁵ Amino acids have a regulatory effect on myocardium protein turnover^{46,47} and raise the oxygen consumption and glucose oxidation.⁴⁸ Amino acids have the physiological function to stimulate mitochondrial energy production under anaerobic conditions⁴⁸ and activate the protein synthesis in cardiomyocytes⁴⁷ in the presence of glucose and insulin that accelerates the formation of peptides chains.⁴⁹ A higher amino acid levels, more specifically branched chain amino acids (BCAA), are oxidized by the heart, and a 7% of O₂ consumption is required proceeding through the formation of CoA derivative⁴⁹ suggesting a role as metabolic fuels and a primary anabolic effect on the human heart.⁴⁶ Amino acids availability is crucial for heart and depends solely on serum amino acids levels.⁵⁰ Myocardial tissue uses amino acids for protein synthesis which is regulated by the availability of the circulating amino acids, by the availability of oxidative substrates, by the oxygen delivery, and the availability of anabolic hormones.⁴⁷

However, recent reports found that an abnormal amino acids metabolism (included BCAA) were correlated with pathologic remodeling after myocardial infarction⁵¹ and a higher concentration of serum level of BCAAs was correlated with increased risk of CVD, especially stroke, in a population with high cardiovascular risk.⁵² A high level of BCAAs was correlated with cardiac diseases⁵³ and that a defect in the catabolism of BCAA is implicated in the pathogenesis of HF⁵⁴ associated with elevated oxidative stress, and profound metabolic changes in the heart. BCAA catabolism in the myocardium is an underconsidered part of metabolic dysfunction and could explain therapeutic target for the disease.

In patients with CHF, Aquilani et al⁴⁵ found a reduced arterial amino acids levels that were correlated with the severity of left ventricular dysfunction. In the study NYHA class II, III, and IV have been evaluated, and all class-patients received an adequate nutritional intake. In patients in NYHA class IV group which received the nutritional intake of kcal 2132 ± 482/day (29.2 kcal/kg/day), protein 1.3 g/kg/day and CHO 3.6 g/kg/day and lipids 1.2 g/kg/day, the level of essential and BCAAs were found extremely reduced compared to healthy (Fig 3). Nutritional intake was not responsible for the low amino acids level. However, these data show that a diet with normal caloric and protein intake in HF patients needs along much time to restore the normal circulating level of amino acids probably due to malabsorption and that protein ingestion should be

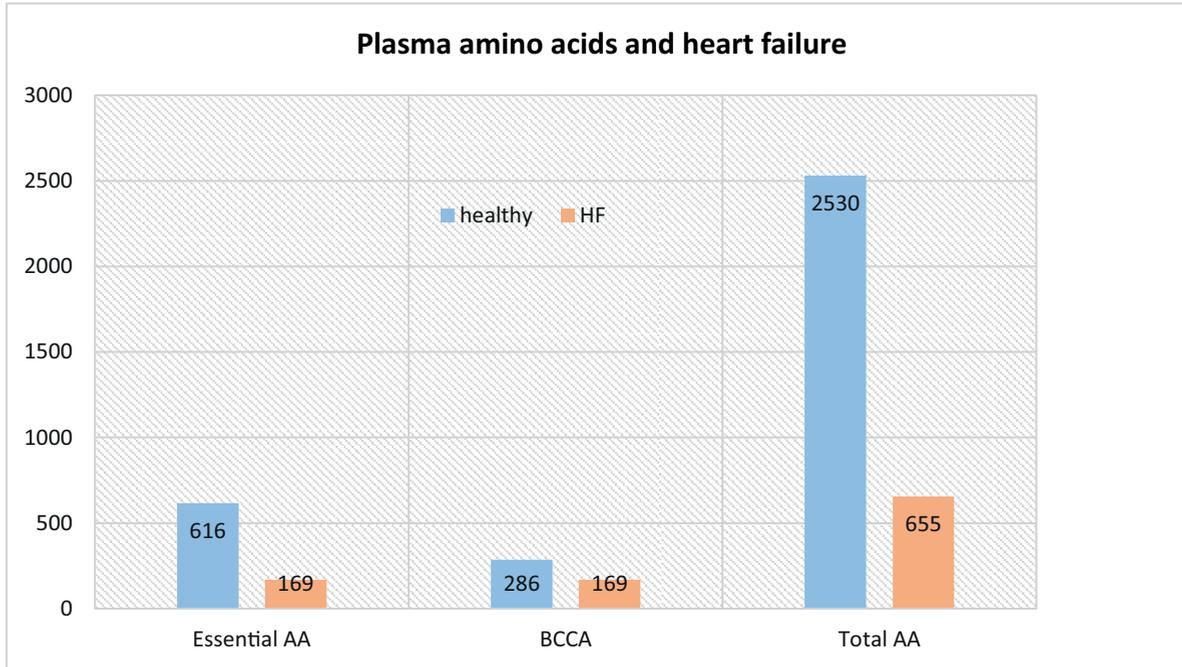


FIG 3. Serum level of total amino acids (AA), essential amino acids (essential AA) and branched chain amino acids in healthy (orange) and FH patients (blue) (from Aquilani et al⁴⁵ modified, with permission). (Color version of figure is available online.)

supplemented with essential amino acids. Unfortunately, in this study, the plasma level of anabolic hormones such as insulin, testosterone, estradiol, and IGF1 was not detected and this could have explained in part this aspect.

The effect of protein intake on the progression of CVD and HF remains to be fully elucidated. Epidemiologic studies have found that a high intake of protein with the diet had no deleterious effect on CVD and HF^{55,56} while the greater incidence of CVD was observed in middle age women.⁵⁷ In rats with HF induced by pressure overload, a high protein intake with the diet did not affect cardiac mass, left ventricular volumes or ejection fraction, or myocardial mitochondrial oxidative capacity, but the survival was significantly reduced.⁵⁸

Insulin Effects on the Ischemic Heart

Insulin activity, reducing plasma glucose level, plays an important anti-inflammatory effect on the heart counteracting left ventricular and mitochondrial dysfunction in ischemic myocardial tissue, although, the complexity of insulin signaling within the myocardium is not fully elucidated.⁵⁹ Higher plasma glucose levels have a deleterious effect on cardiac function,⁶⁰ impairing cardiomyocytes function at the nuclear level⁶¹ and reducing diastolic and systolic function.⁶² The acute overingestion of glucose activates an inflammatory process and the reactive oxygen species generation⁶³ through the NF- κ B (nuclear factor κ B), the most sensitive transcription factor to redox signaling.⁶⁴ Glycemic control is beneficial to reduce the risk of mortality in type-2⁶⁵ and type-1 diabetes.⁶⁶ Hyperglycemia in the acute care setting in HF patients was associated with increased mortality. Improving glucose control and insulin sensitivity in type-1 diabetes patients significantly reduces the risk of microvascular complications and CVD.⁶⁷ The amount of carbohydrates ingestion is extremely important in the development of the inflammatory process, which is regulated by insulin activity.⁶⁸ Insulin activity, reducing plasma glucose level, plays an important anti-inflammatory effect on the heart counteracting left ventricular and mitochondrial dysfunction in ischemic myocardial tissue, although, the complexity of insulin signaling within the myocardium is not fully elucidated.⁵⁹ Insulin has a vasodilator effect, by increasing arterial blood flow at the microcirculatory level and stimulating nitric oxide formation,⁶⁹ which has an anti-inflammatory, antithrombotic, and antioxidant effect,⁷⁰ by modifying directly the inflammatory molecules involved in this process.⁷¹ Insulin infusion had an inhibitory effect on Reactive Oxygen Species production and NF- κ B expression in obese, insulin-resistant

subjects.⁷² Insulin possesses anti-inflammatory effects, as documented in intensive care unit patients,⁷³ in patients who undergo to coronary artery bypass grafting,^{74,75} in acute myocardial infarction^{76,77} and burned patients.⁷⁸ In patients with type-2 diabetes after myocardial infarction, long-term insulin administration improved survival and reduced the incidence of reinfarction,⁷⁷ confirming that excessive serum glucose levels are a strong predictor of mortality. Liepinsh et al⁷⁹ demonstrated that a chronic postprandial metabolic state, characterized by insulin elevation and consequent increased glucose and lactate utilization, has a protective effect against myocardial infarction.

However, insulin resistance has a detrimental effect on metabolic regulation, is a determining factor in the development of metabolic syndrome,⁸⁰ and is correlated with left ventricular diastolic dysfunction and structural alterations.⁸¹ Insulin resistance promotes the development of HF,⁸² independently from ischemic cardiac disease.^{83,84} In cardiac hypertrophy induced by pressure-overload as aortic stenosis, insulin resistance, and reduced mitochondrial oxidative capacity are the early metabolic alteration favoring the progression toward HF.⁸⁵ Experimental clinical models in humans and animals have revealed an interdependence between insulin resistance and HF.⁸⁶ Insulin resistance in HF is associated with increased serum concentrations of proinflammatory cytokines, catecholamines, catabolic steroids,⁸⁷ and even with reduced testosterone and adiponectin levels in males.⁸⁸ The mechanism of action of insulin is complex and well summarized by Riehle et al.⁵⁹ Improvement in the biologic activity of insulin, after moderate weight loss and an appropriate diet in overweight and obese patients with ischemic cardiac disease, could be part of an overall therapeutic strategy to improve cardiovascular function and reduce HF events.

Effect of Weight Loss on Heart Function

Weight loss following a restricted calorie diet in obese patients is associated with metabolic and neurohumoral adaptations that may contribute to lifespan extension.⁸⁹ Calorie restriction improves mitochondrial function, DNA repair, and autophagy,⁹⁰ and stimulates stem cell regeneration.

In obese subjects, many clinical studies have shown that weight reduction significantly improves cardiac function (see [Table](#)). Weight loss improved both left ventricular mass and cardiac function.⁹¹⁻⁹⁵ In obese patients with HF, intentional weight loss increased the cardiac efficiency and the quality of life.⁹⁶ Hypocaloric diets, with carbohydrate or fat restriction, associated with modest weight loss, reduce the triglycerides depot in the cardiomyocytes by approximately 25%.⁹⁷ However, Zamora

TABLE. Effect of weight loss on cardiac functions

Authors	Patients	Age	BMI	Intervention	Duration	Effects
Utz, 2013 (106)	38	45	29	Hypocaloric diet	6 months	Weight loss reduced myocardial triglyceride content
Guglin, 2013 (103)	433	56.3	27.9	Spontaneous	3 months	Both RV and LV systolic function improves
Kardassis 2012 (101)	44	41.5	42.5	Bariatric surgery	10 years	Left ventricular volume, stroke volume and cardiac output primarily associated with lean body mass,
Haufe, 2012 (104)	170	44	32.9	Hypocaloric diet (low CHO and low fat)	6 months	Low CHO and Low fat diet improved left ventricular mass
de la Fuentes, 2009 (102)	60	47	37	Diet women: 1200-1500 kcal/d; men:1500-1800	2 years	Moderate weight loss in obese subjects is associated with beneficial changes in cardiovascular structure and function.
Corrao, 2000 (105)	32	45	32	Hypocaloric diet	4 months	Improvements in LV structure and function.

LV, left ventricular; RV, right ventricular.

et al⁹⁸ found that the spontaneous weight loss of about 5% in patients with HF is associated with long-term mortality. These discrepancies could be explained by the different effect of nutritional intake between a balanced calorie-restricted diet and spontaneous weight loss in HF patients. In obese patients with atrial fibrillation, a long-term sustained weight has been shown to substantially reduce arrhythmia burden and maintain sinus rhythm compared to controls.⁹⁹ De Lucia et al¹⁰⁰ have recently demonstrated that a long-term calorie restricted diet in HF patients improved the cardiac sympathetic innervation and inotropic reserve. In obese (??) chronic HF patients, a weight-reducing nutritional intervention was associated with improvement in NYHA classification and decreased HF-related rehospitalization.¹⁰¹ In patients with coronary artery disease, without HF, Ellsworth et al¹⁰² found that a weight loss of 7%-10% determined a down-regulation of the genes which modulated the vascular endothelium and decreased the cardiovascular risk. After 1 year, insulin level, C-reactive protein, and leptin levels were significantly reduced, and these changes were not observed in the control group.

In patients with metabolic syndrome, the restriction of calories and carbohydrate intake have been found to improve insulin sensitivity, postprandial hyperglycemia, and reduce cardiovascular risk, independently of the weight loss.¹⁰³ In other studies, body fat reduction following bariatric surgery improved ventricular and overall cardiac function in type-2 diabetes patients, also resulting in improved glycemic control.^{104,105}

Effect of Calorie Restricted Diet on Heart Function

A caloric restricted diet has a beneficial effect on metabolism reducing the development of atherosclerosis,¹⁰⁶ preventing hypertension and cardiac hypertrophy,¹⁰⁷ reducing the pathogenesis of cardiac hypertrophy pressure overload-induced.¹⁰⁸ Furthermore, caloric restriction improves myocardial function by reducing the senescent process of myocardium suppressing mTOR and increasing autophagy.¹⁰⁹ De Lucia et al¹⁰⁰ demonstrated that caloric restriction in male rats with HF improved cardiac function and inotropic reserve favoring sympathetic cardiac innervation and β -adrenergic receptor levels in the myocardium. However, the antiaging effect of caloric restriction on the myocardium has an opposite effect in old age compared to young age subjects.¹¹⁰

Caloric restriction acts mechanistically accelerating cardiac autophagy and reducing ATP content but modulated by AMPK,¹¹¹ and short-term calorie restriction improved AMPK myocardial expression in both young and old hearts.¹¹² AMPK plays an important role in protecting cardiac

function and homeostasis and myocardial adaptation to starvation.¹¹¹ The AMPK signaling becomes less responsive with advancing age, and after prolonged caloric restriction leads to cellular stress and dysfunction in cardiac contractility.¹¹³

Of high relevance is the autophagic process induced by prolonged starvation in cardiac myocytes. In cultured cardiomyocyte cells, glucose deprivation activates the autophagic flux increasing Sirt1, required for the deacetylation of FOXO1 which is essential for maintaining left ventricular function during severe caloric restriction.¹¹⁴ Metabolic remodeling at the myocardial level precedes structural alterations activating the target of rapamycin complex 1 (mTORC1), a major regulator of cell growth, resulting in increased protein synthesis and hypertrophy.¹¹⁵ Autophagy is an essential biologic mechanism to maintain cellular and tissue renovation and health.¹¹⁶ The regulation of autophagy is not only a response to the starvation but in some tissue occurs actively without starvation.¹¹⁷ Metabolic alteration including glucose and amino acids oxidation may be responsible for mitochondrial dysfunction and antecedent to HF.¹¹⁸ Excessive activation of autophagic flux can favor the transition to HF.¹¹⁹

Very-low-calorie diets can also be dangerous for cardiovascular metabolism and function.¹²⁰ Van der Meer et al¹²¹ showed that in 14 healthy men a very-low-calorie diets (471 kcal/day, 50.2 g carbohydrates, protein, and 6.9 g fat) for a period of 3 days resulted in an increase in myocardial deposition of triglycerides and decreases in left ventricular diastolic function, without changes in ejection fraction. Similar results were reported by Reynolds¹²² after a 2-day fast. The increased deposition of triglycerides in cardiomyocytes is a consequence of the excessive plasma NEFA levels, as observed in type-2 diabetes and obesity.¹²⁰

Severely Restricted Diet and Mortality Risk

Even though weight loss has beneficial effects on cardiac function in obese patients, severely restricted diets can cause a detrimental effect on cardiac function and increase mortality risk in patients who have low body mass index (BMI)^{123,124} as well as healthy adults.¹²⁴ Significant weight loss (ie, intentional or unintentional) can profoundly affect cardiac metabolism, particularly in persons with known CAD.¹²⁵ Low BMI can be associated with immobility, poor nutrition,¹²⁶ and frailty in the elderly, but is often not considered in a typical clinical evaluation.¹²⁷ Notably, some HF patients have a reduced hunger sensation, nausea, and spontaneously restrict food intake.¹²⁸ Despite its high incidence in geriatric

patients, malnutrition is rarely recognized and treated¹²⁹ and is often missed as a clinical sign in patients with chronic HF.¹³⁰ Spontaneous weight loss should be treated aggressively because it represents a higher risk of muscle wasting and cachexia.¹³¹ Among healthy obese subjects, weight loss generally does not reduce mortality risk.¹³²

Effect of Starvation on Cardiac Function

Prolonged calorie restriction has a deleterious effect on cardiac physiology and function. Cordero-Reyes et al¹³³ showed that energy starvation in HF patients caused metabolic alteration through reduced mitochondrial number but not a reduction in mitochondrial electron transport capacity. Deficient carbohydrate diets (≤ 800 kcal/daily) may negatively impact vascular endothelial function while maintaining recommended carbohydrate intake generates a more favorable vascular profile.¹³⁴ In mice, a restricted caloric diet (by 40%) for 30 weeks showed a decreased ventricular mass and cardiomyocyte contractility, elevated phosphorylation of AMPK, and depressed phosphorylation of mTOR and ULK1.¹³⁵ These data suggest an indispensable role of AMPK in the maintenance of cardiac metabolism under prolonged caloric restriction through autophagy regulation.¹³⁵

Starvation, as observed in patients affected by anorexia nervosa, is associated with tissue alteration and many medical complications¹³⁶ and induces a significant deleterious effect on cardiac function.¹³⁷ The most concerning are those related to the cardiovascular system, such as serious arrhythmias or structural cardiac alterations which lead to increased mortality.¹³⁸ During starvation protein and fat catabolism are increased, which lead to loss of cellular volume and atrophy of various tissues, including brain, liver, intestine, kidney, and muscle, in addition to the heart muscle. Morphologic studies by ultrasound have shown decreased cardiac mass, reduced cardiac chamber volumes, and mitral valve prolapse.^{139,140} Congestive HF has also been described as a cause of death in anorexia nervosa.¹⁴¹ Siegel et al¹⁴² described a grossly normal heart that weighed 250 g with focal inflammation of the conduction system in association with massive weight loss due to dieting. Isner et al¹⁴³ described a reduced cardiac weight of 120-140 g, with a grossly normal aspect. Histologically, it has been reported that widespread interstitial fibrosis in the papillary muscles and myxoid material deposition occurs, which can be responsible for rhythm disturbances in patients with anorexia nervosa.¹⁴⁴ In some anorexic patients, the cause of death was associated with

fibrosis and myxoid material deposition which are a direct consequence of starvation.¹⁴⁴ In patients following severe restrictive diets, a mild QTc prolongation has been observed,¹⁴⁵ but the QTc interval was not correlated with the disease severity¹⁴⁶ but was negatively associated with serum potassium concentrations.¹⁴⁷

Nutrition in Chronic HF Patients

In patients with chronic HF, food intake is extremely important to improve the quality of life and survival rate. Overweight and mildly obese patients with CVD, compared with underweight patients, have a better prognosis as expressed by the obesity paradox concept.¹⁴⁸ BMI has been shown to be inversely correlated with all-cause mortality,¹⁴⁹ and overall cardiovascular mortality is reduced with higher BMI.^{150,151} An increase in BMI of 5 units decreases the risk of mortality by 10%.¹⁵² Notably, the mortality rate is increased at the high end of the extreme of the BMI distribution resulting in a U-shaped pattern, with increased mortality at both the lowest and highest BMI.^{153,154}

Moreover, after adjustment for confounding factors,¹⁵⁵ the group with the lowest BMI (<18) exhibited the highest mortality. The obesity paradox could be partially explained by a significantly lower sympathetic activation in obese CHF patients¹⁵⁶ (impact of visceral obesity upon the metabolic syndrome). Importantly, however, only BMI has been used as the criterion for obesity in these studies, while fat-free mass and muscle mass are arguably more important given that they are stronger predictors of LV mass than fat mass.

Macronutrient ingestion influence blood substrates which has a significant effect on the insulin-sensitive tissue.¹⁵⁷ A reduction in calorie intake exerts a profound effect on weight loss representing the principal factor of reducing all metabolic syndrome components, independent from diet composition.¹⁵⁸ Daily caloric intake of about 125 kJ/kg (=29 kcal/kg) and a daily protein intake of 1.2-1.4 g/kg body weight is recommended for elderly patients at normal weights.¹⁵⁹ In overweight and obese patients less energy intake is required (20-24 kcal/kg/day). A reduction in dietary fat intake to about 25% of total caloric intake (0.6-0.8 g/kg/day) is adequate because high-fat diets associated with low-carbohydrate predispose to insulin resistance.¹⁶⁰ In overweight patients, restricted calorie diets cause an improvement in insulin resistance independent of macronutrient composition. Ketogenic diets improve insulin resistance,¹⁶¹ and low carbohydrate and high protein diets enhance metabolic equilibrium and reduce cardiovascular risk.¹⁶² The reduction in calorie intake is effective to

reduce body fat independent of diet composition, but a diet with high-CHO and low-fat composition is more effective in reducing the markers of MetS.¹⁶³ A relatively high-carbohydrate diet is suggested during submaximal exercise because it increases the rate of whole-body fat oxidation and reduces the rate of muscle glycogenolysis.¹⁶⁴

Weight loss induced by a very low CHO and high-saturated-fat diet is detrimental to cardiac function and has a detrimental effect on CVD risk factors.¹⁶⁵ Nilsson et al¹⁶⁶ found that a low CHO-high fat diet in mice for 2 weeks caused an increase in body fat and a reduction in lean mass; after 4 weeks cardiac function also deteriorated. Low CHO-high fat diets impair cardiomyocytes function was reduce the myocardial response to ischemia. The increased fatty acid oxidation in the presence of reduced CHO availability compromises the recovery of left ventricular function.¹⁶⁷ Also, low CHO-high fat diets have been shown to be a limiting factor in endurance athletes in whom the adaptation to training and performance benefits are negated.¹⁶⁸ Low CHO-high fat diets may have some clinical applications, but this does not appear to be the case in patients with CVD or those with dyslipidemia or insulin resistance.¹⁶⁹ In the myocardium, oxidation of fatty acids is inhibited proportionate to the increased availability of fatty acids causing contractile dysfunction.¹⁷⁰ This metabolic change, if protracted for an extended time (weeks or months), can cause measurable damage to the cardiac tissue causing a dramatic lipid deposition within cardiomyocytes upon fasting.

Increasing FFA oxidation results in a reduction in glucose oxidation but causes a decrease in cardiac function and efficiency.¹⁷¹ CHO metabolism reduces FA oxidation and cardiac alteration under stress conditions of cardiac overloads, such as exercise, hypertension, and hypertrophy.¹⁷² Improving glucose utilization by myocardial tissue is an effective strategy to prevent the progression of cardiac dysfunction such as that associated with pathologic hypertrophy.¹⁷³ A high polyunsaturated and saturated fatty acid intake was significantly associated with 1-year mortality in patients with chronic HF.¹⁷⁴ In patients without HF, higher plasma FFA were associated with a 12% higher risk of HF.¹⁷⁵

Nutritional Intake in CHF Patients

The major nutritional dysfunction in HF patients is represented by malnutrition. Various clinical studies have found that patients with CHF are in a prevalent malnutrition state varying from 54%¹⁷⁶ to 60%-69%,¹⁷⁷ and the prognostic value of malnutrition, assessed by the Controlling Nutritional Status, demonstrated that represent the best predictor of

death.^{178,179} After 1-year follow up, the mortality rate was 65% between patients malnourished and frail while only 1% between those who were neither frail nor malnourished.¹⁸⁰ However, an excess of nutritional intake leads to cardiac dysfunction and HF.¹⁸¹ It appears evident that an adequate nutritional intake in HF patients is recommended.

Micronutrients

Micronutrients have been proposed to have a benefit in improving clinical management of HF patients.¹⁸² A sodium-restricted diet (2000-4000 mg/day) with a reduction in total fluid ingestion to 1.5 l/day has been suggested to result in clinical improvements in HF functional class.¹⁸³ Lennie et al¹⁸⁴ showed that higher sodium intake (more than 3 g daily) increased the risk of rehospitalization more than 2 times compared to patients with lower sodium diets. Further analysis showed no advantages related to further sodium reduction in patients with stable HF.¹⁸⁵

Omega-6 and omega-3 are essential fatty acids that mediate cellular inflammatory responses¹⁸⁶ and decrease the risk of serious arrhythmias and sudden death.¹⁸⁷ The American Heart Association has recently expanded the list of Class recommendation for Omega 3 prescription in CVD patients for their medical benefits.¹⁸⁸ Although many supplements have been suggested for HF patients including coenzyme Q10, carnitine, and vitamin D, the potential benefits to cardiac function remain to be proven.¹⁸⁹ The administration of multiple micronutrient supplementations in chronic stable HF patients taken for 12 months provided no evidence of any benefit.¹⁸⁵

Antioxidant vitamins (vitamin C, E, and β -carotene) did not show positive evidence for a protective effect on CVD and mortality.¹⁹⁰ However, the serum level of vitamin E was negatively associated with endothelin function.¹⁹¹

Coenzyme Q10 is a component of cellular membranes and is involved in the production of ATP in the mitochondria improving the electron transport chain and reducing the redox reaction. In patients with chronic HF, the administration of CoQ10 (100 mg x 3 times daily) was safe and reduced some cardiovascular complications.¹⁹² However, the beneficial effects remain uncertain, and larger randomized clinical trials on CoQ10 supplementation in patients with CVD are needed.¹⁹³ Daily intake of resveratrol at the dose of 150 mg/daily of for 4 weeks did not improve metabolic markers related to cardiovascular health.¹⁹⁴ Sciatti et al¹⁹⁵ in a review evaluating the effect of micronutrients in patients with HF

concluded that a beneficial role remains to be demonstrated and large clinical trials with a single supplement method are required.

Future Perspectives

Clinical trials in patients with HF with specific calorie-restricted diet prescription with high CHO and protein and low fats contents are necessary to evaluate the myocardial efficiency. A low-calorie diet of 1200-kcal/daily in obese patients was safe for a long period up to 16 weeks,¹⁹⁶ and no different effect in improving insulin resistance between high vs the low glycemic index of CHO was found.¹⁹⁷ Calorie restriction with different modalities such as intermittent fasting (60% energy restriction on 2 days per week) or periodic fasting (a 5-day diet providing 750-1100 kcal) and time-restricted feeding improved insulin resistance and the risk factors for CVD¹⁹⁸ have been evaluated in healthy and overweight human subjects with positive effects. However, further investigation on the effect of a restricted calorie diet and with balanced macronutrients in patients with CVD and HF is necessary. Furthermore, in association with nutrition, the anabolic hormone level should be considered at the same time.

Conclusion

Nutrition has an essential impact upon the recovery of heart function in patients with CVD and HF for improving energy metabolism and energy transfer, and for reducing HF mortality. Macronutrients regulate cardiomyocyte activity which can be improved by the optimization of glucose uptake, improved insulin activity, and by reduced fat intake. Weight loss, through excess fat loss, is useful for obese and type-2 diabetes patients, while some evidence points to weight loss being detrimental to underweight patients for whom mortality risk may be increased. Thus, from a clinical perspective, dietary interventions should be personalized, based on consideration of anthropometrics data representing states of excess adiposity, underweight, or low lean body mass.

Overweight and obese individuals should adopt a gradual restriction of calories from unhealthy fats and refined carbohydrates while maintaining lean body mass through ingestion of healthful fats, complex carbohydrates, and appropriate protein intake consistent with body mass requirements.

Overweight and obese subjects need a calorie-restricted diet, targeted to a 40% reduction in caloric ingestion and based on basal energy

expenditure with high protein, low-fat composition improving insulin activity and glucose utilization by cardiomyocytes. In lean or underweight subjects, the diet should be nutritionally balanced, and isocaloric to maintain and preserve lean body mass calorie ingestion should counteract the risk of malnutrition to prevent cardiac cachexia and increased risk of cardiac mortality.

REFERENCES

1. Gertz EW, Wisneski JA, Stanley WC, et al. Myocardial substrate utilization during exercise in humans. Dual carbon-labeled carbohydrate isotope experiments. *J Clin Invest* 1988;82:2017–25.
2. Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. *Cardiovasc Res* 1997;34:25–33.
3. Carley AN, Severson DL. Fatty acid metabolism is enhanced in type 2 diabetic hearts. *Biochim Biophys Acta* 2005;1734:112–26.
4. Rosano GM, Fini M, Caminiti G, et al. Cardiac metabolism in myocardial ischemia. *Curr Pharm Des* 2008;14:2551–62.
5. Schaffer JE. Fatty acid transport: the roads taken. *Am J Physiol Endocrinol Metab* 2002;282:E239–46.
6. Young LH, Coven DL, Russell RR 3rd. Cellular and molecular regulation of cardiac glucose transport. *J Nucl Cardiol* 2000;7:267–76.
7. Coven DL, Hu X, Cong L, et al. Physiological role of AMP-activated protein kinase in the heart: graded activation during exercise. *Am J Physiol Endocrinol Metab* 2003;285:E629–36.
8. Randle PJ. Fuel selection in animals. *Biochem Soc Trans* 1986;14:799–806.
9. Lopaschuk GD, Belke DD, Gamble J, et al. Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim Biophys Acta* 1994;1213:263–76.
10. Randle PJ, Garland PB, Hales CN, et al. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963;1:785–9.
11. Balaban RS, Kantor HL, Katz LA, et al. Relation between work and phosphate metabolite in the in vivo paced mammalian heart. *Science* 1986;232:1121–3.
12. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005;85:1093–129.
13. Taegtmeyer H. Energy metabolism of the heart: from basic concepts to clinical applications. *Curr Probl Cardiol* 1994;19:59–113.
14. Kaijser L, Berglund B. Myocardial lactate extraction and release at rest and during heavy exercise in healthy men. *Acta Physiol Scand* 1992;144:39–45.
15. Sambandam N, Lopaschuk GD, Brownsey RW, et al. Energy metabolism in the hypertrophied heart. *Heart Fail Rev* 2002;7:161–73.
16. Schonekess BO, Allard MF, Henning SL, et al. Contribution of glycogen and exogenous glucose to glucose metabolism during ischemia in the hypertrophied rat heart. *Circ Res* 1997;81:540–9.

17. Neubauer S. The failing heart—an engine out of fuel. *N Engl J Med* 2007;356:1140–51.
18. Sharov VG, Todor AV, Silverman N, et al. Abnormal mitochondrial respiration in failed human myocardium. *J Mol Cell Cardiol* 2000;32:2361–7.
19. Rosca MG, Tandler B, Hoppel CL. Mitochondria in cardiac hypertrophy and heart failure. *J Mol Cell Cardiol* 2013;55:31–41.
20. Ussher JR, Wang W, Gandhi M, et al. Stimulation of glucose oxidation protects against acute myocardial infarction and reperfusion injury. *Cardiovasc Res* 2012;94:359–69.
21. Aubert G, Martin OJ, Horton JL, et al. The failing heart relies on ketone bodies as a fuel. *Circulation* 2016;133:698–705.
22. Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins Leukot Essent Fatty Acids* 2004;70:309–19.
23. Zou Z, Sasaguri S, Rajesh KG, et al. dl-3-Hydroxybutyrate administration prevents myocardial damage after coronary occlusion in rat hearts. *Am J Physiol Heart Circ Physiol* 2002;283:H1968–74.
24. Prabhakar A, Quach A, Zhang H, et al. Acetone as biomarker for ketosis buildup capability—a study in healthy individuals under combined high fat and starvation diets. *Nutr J* 2015;14:41.
25. Nagoshi T, Yoshimura M, Rosano GM, et al. Optimization of cardiac metabolism in heart failure. *Curr Pharm Des* 2011;17:3846–53.
26. Huss JM, Kelly DP. Mitochondrial energy metabolism in heart failure: a question of balance. *J Clin Invest* 2005;115:547–55.
27. An D, Rodrigues B. Role of changes in cardiac metabolism in development of diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2006;291:H1489–506.
28. Yagyu H, Chen G, Yokoyama M, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. *J Clin Invest* 2003;111:419–26.
29. Atherton HJ, Dodd MS, Heather LC, et al. Role of pyruvate dehydrogenase inhibition in the development of hypertrophy in the hyperthyroid rat heart: a combined magnetic resonance imaging and hyperpolarized magnetic resonance spectroscopy study. *Circulation* 2011;123:2552–61.
30. Abel ED. Glucose transport in the heart. *Front Biosci* 2004;9:201–15.
31. Frias MA, Montessuit C. JAK-STAT signaling and myocardial glucose metabolism. *JAKSTAT* 2013;2:e26458.
32. Di Carli MF, Asgarzadie F, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. *Circulation* 1995;92:3436–44.
33. Bressler P, Bailey SR, Matsuda M, et al. Insulin resistance and coronary artery disease. *Diabetologia* 1996;39:1345–50.

34. Hannukainen JC, Lautamaki R, Mari A, et al. Elevated glucose oxidation, reduced insulin secretion and a fatty heart may be protective adaptations in ischemic CAD. *J Clin Endocrinol Metab* 2016;jc20154091.
35. van der Meer RW, Rijzewijk LJ, de Jong HW, et al. Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus. *Circulation* 2009;119:2069–77.
36. Liu L, Shi X, Bharadwaj KG, et al. DGAT1 expression increases heart triglyceride content but ameliorates lipotoxicity. *J Biol Chem* 2009;284:36312–23.
37. Hwang YC, Bakr S, Ramasamy R, et al. Relative importance of enhanced glucose uptake versus attenuation of long-chain acyl carnitines in protecting ischemic myocardium. *Coron Artery Dis* 2002;13:313–8.
38. King LM, Opie LH. Glucose delivery is a major determinant of glucose utilisation in the ischemic myocardium with a residual coronary flow. *Cardiovasc Res* 1998;39:381–9.
39. Hall JL, Henderson J, Hernandez LA, et al. Hyperglycemia results in an increase in myocardial interstitial glucose and glucose uptake during ischemia. *Metabolism* 1996;45:542–9.
40. Libby P, Maroko PR, Braunwald E. The effect of hypoglycemia on myocardial ischemic injury during acute experimental coronary artery occlusion. *Circulation* 1975;51:621–6.
41. Giorgino F, Leonardini A, Laviola L. Cardiovascular disease and glycemic control in type 2 diabetes: now that the dust is settling from large clinical trials. *Ann NY Acad Sci* 2013;1281:36–50.
42. Schisler JC, Grevengoed TJ, Pascual F, et al. Cardiac energy dependence on glucose increases metabolites related to glutathione and activates metabolic genes controlled by mechanistic target of rapamycin. *J Am Heart Assoc* 2015;4.
43. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat Rev Mol Cell Biol* 2011;12:21–35.
44. Russell RR 3rd, Li J, Coven DL, et al. AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. *J Clin Invest* 2004;114:495–503.
45. Aquilani R, La Rovere MT, Corbellini D, et al. Plasma Amino Acid Abnormalities in Chronic Heart Failure. Mechanisms, Potential Risks and Targets in Human Myocardium Metabolism. *Nutrients* 2017;9.
46. Young LH, McNulty PH, Morgan C, et al. Myocardial protein turnover in patients with coronary artery disease. Effect of branched chain amino acid infusion. *J Clin Invest* 1991;87:554–60.
47. Morgan HE, Earl DC, Broadus A, et al. Regulation of protein synthesis in heart muscle. I. Effect of amino acid levels on protein synthesis. *J Biol Chem* 1971;246:2152–62.
48. Burns AH, Reddy WJ. Amino acid stimulation of oxygen and substrate utilization by cardiac myocytes. *Am J Physiol* 1978;235:E461–6.

49. Morgan HE, Jefferson LS, Wolpert EB, et al. Regulation of protein synthesis in heart muscle. II. Effect of amino acid levels and insulin on ribosomal aggregation. *J Biol Chem* 1971;246:2163–70.
50. Schwartz RG, Barrett EJ, Francis CK, et al. Regulation of myocardial amino acid balance in the conscious dog. *J Clin Invest* 1985;75:1204–11.
51. Lai L, Leone TC, Keller MP, et al. Energy metabolic reprogramming in the hypertrophied and early stage failing heart: a multisystems approach. *Circ Heart Fail* 2014;7:1022–31.
52. Ruiz-Canela M, Toledo E, Clish CB, et al. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED trial. *Clin Chem* 2016;62:582–92.
53. Kato T, Niizuma S, Inuzuka Y, et al. Analysis of metabolic remodeling in compensated left ventricular hypertrophy and heart failure. *Circ Heart Fail* 2010;3:420–30.
54. Sun H, Olson KC, Gao C, et al. Catabolic defect of branched-chain amino acids promotes heart failure. *Circulation* 2016;133:2038–49.
55. He J, Wofford MR, Reynolds K, et al. Effect of dietary protein supplementation on blood pressure: a randomized, controlled trial. *Circulation* 2011;124:589–95.
56. Virtanen HEK, Voutilainen S, Koskinen TT, et al. Intake of different dietary proteins and risk of heart failure in men: the Kuopio Ischaemic heart disease risk factor study. *Circ Heart Fail* 2018;11:e004531.
57. Lagiou P, Sandin S, Lof M, et al. Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study. *BMJ* 2012;344:e4026.
58. Ribeiro RF Jr., Dabkowski ER, O'Connell KA, et al. Effect of a high-protein diet on development of heart failure in response to pressure overload. *Appl Physiol Nutr Metab* 2014;39:238–47.
59. Riehle C, Abel ED. Insulin Signaling and Heart Failure. *Circ Res* 2016;118:1151–69.
60. Rubin J, Matsushita K, Ballantyne CM, et al. Chronic hyperglycemia and subclinical myocardial injury. *J Am Coll Cardiol* 2012;59:484–9.
61. Clark RJ, McDonough PM, Swanson E, et al. Diabetes and the accompanying hyperglycemia impairs cardiomyocyte calcium cycling through increased nuclear O-GlcNAcylation. *J Biol Chem* 2003;278:44230–7.
62. Tang WH, Cheng WT, Kravtsov GM, et al. Cardiac contractile dysfunction during acute hyperglycemia due to impairment of SERCA by polyol pathway-mediated oxidative stress. *Am J Physiol Cell Physiol* 2010;299:C643–53.
63. Mohanty P, Hamouda W, Garg R, et al. Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J Clin Endocrinol Metab* 2000;85:2970–3.
64. Dandona P, Aljada A, Chaudhuri A, et al. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 2005;111:1448–54.
65. Carrasco-Sanchez FJ, Gomez-Huelgas R, Formiga F, et al. Association between type-2 diabetes mellitus and post-discharge outcomes in heart failure patients: findings from the RICA registry. *Diabetes Res Clin Pract* 2014;104:410–9.

66. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med* 2014;371:1972–82.
67. Secrest AM, Becker DJ, Kelsey SF, et al. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes* 2010;59:3216–22.
68. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006;116:1793–801.
69. Aljada A, Dandona P. Effect of insulin on human aortic endothelial nitric oxide synthase. *Metabolism* 2000;49:147–50.
70. Mao XM, Liu H, Tao XJ, et al. Independent anti-inflammatory effect of insulin in newly diagnosed type 2 diabetes. *Diabetes Metab Res Rev* 2009;25:435–41.
71. Dandona P, Chaudhuri A, Ghanim H, et al. Insulin as an anti-inflammatory and anti-atherogenic modulator. *J Am Coll Cardiol* 2009;53:S14–20.
72. Aljada A, Ghanim H, Mohanty P, et al. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *J Clin Endocrinol Metab* 2002;87:1419–22.
73. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005;115:2277–86.
74. Visser L, Zuurbier CJ, Hoek FJ, et al. Glucose, insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic clamp: effects on inflammatory response during coronary artery surgery. *Br J Anaesth* 2005;95:448–57.
75. Sato H, Hatzakorzian R, Carvalho G, et al. High-dose insulin administration improves left ventricular function after coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2011;25:1086–91.
76. Zhang L, Zhang L, Li YH, et al. High-dose glucose-insulin-potassium treatment reduces myocardial apoptosis in patients with acute myocardial infarction. *Eur J Clin Invest* 2005;35:164–70.
77. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650–61.
78. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet* 2004;363:1895–902.
79. Liepinsh E, Makrecka M, Kuka J, et al. The heart is better protected against myocardial infarction in the fed state compared to the fasted state. *Metabolism* 2014;63:127–36.
80. Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract* 2003;9:237–52.
81. Hwang YC, Jee JH, Kang M, et al. Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level. *Int J Cardiol* 2012;159:107–11.
82. Ingelsson E, Sundstrom J, Arnlov J, et al. Insulin resistance and risk of congestive heart failure. *JAMA* 2005;294:334–41.

83. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;241:2035–8.
84. Dries DL, Sweitzer NK, Drazner MH, et al. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. *J Am Coll Cardiol* 2001;38:421–8.
85. Zhang L, Jaswal JS, Ussher JR, et al. Cardiac insulin-resistance and decreased mitochondrial energy production precede the development of systolic heart failure after pressure-overload hypertrophy. *Circ Heart Fail* 2013;6:1039–48.
86. Velez M, Kohli S, Sabbah HN. Animal models of insulin resistance and heart failure. *Heart Fail Rev* 2014;19:1–13.
87. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* 1997;96:526–34.
88. Khan RS, Kato TS, Chokshi A, et al. Adipose tissue inflammation and adiponectin resistance in patients with advanced heart failure: correction after ventricular assist device implantation. *Circ Heart Fail* 2012;5:340–8.
89. Redman LM, Ravussin E. Endocrine alterations in response to calorie restriction in humans. *Mol Cell Endocrinol* 2009;299:129–36.
90. Han X, Turdi S, Hu N, et al. Influence of long-term caloric restriction on myocardial and cardiomyocyte contractile function and autophagy in mice. *J Nutr Biochem* 2012;23:1592–9.
91. Kardassis D, Bech-Hanssen O, Schonander M, et al. Impact of body composition, fat distribution and sustained weight loss on cardiac function in obesity. *Int J Cardiol* 2012;159:128–33.
92. de las Fuentes L, Waggoner AD, Mohammed BS, et al. Effect of moderate diet-induced weight loss and weight regain on cardiovascular structure and function. *J Am Coll Cardiol* 2009;54:2376–81.
93. Guglin M, Verma S, Chen R. Association between weight loss and improvement of ventricular systolic function in advanced heart failure. *Congest Heart Fail* 2013;19:186–91.
94. Haufe S, Utz W, Engeli S, et al. Left ventricular mass and function with reduced-fat or reduced-carbohydrate hypocaloric diets in overweight and obese subjects. *Hypertension* 2012;59:70–5.
95. Corrao S, Arnone S, Scaglione R, et al. Effects of a short-term hypoenergetic diet on morphofunctional left ventricular parameters in centrally obese subjects. An echocardiographic study. *Panminerva Med* 2000;42:123–9.
96. McDowell K, Petrie MC, Raihan NA, et al. Effects of intentional weight loss in patients with obesity and heart failure: a systematic review. *Obes Rev* 2018.
97. Utz W, Engeli S, Haufe S, et al. Moderate dietary weight loss reduces myocardial steatosis in obese and overweight women. *Int J Cardiol* 2013;167:905–9.
98. Zamora E, Diez-Lopez C, Lupon J, et al. Weight loss in obese patients with heart failure. *J Am Heart Assoc* 2016;5:e002468.

99. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol* 2015;65:2159–69.
100. de Lucia C, Gambino G, Petraglia L, et al. Long-term caloric restriction improves cardiac function, remodeling, adrenergic responsiveness, and sympathetic innervation in a model of postischemic heart failure. *Circ Heart Fail* 2018;11:e004153.
101. Wang XH, Qiu JB, Ju Y, et al. Reduction of heart failure rehospitalization using a weight management education intervention. *J Cardiovasc Nurs* 2014;29:528–34.
102. Ellsworth DL, Mamula KA, Blackburn HL, et al. Importance of substantial weight loss for altering gene expression during cardiovascular lifestyle modification. *Obesity (Silver Spring)* 2015;23:1312–9.
103. von Bibra H, Strohle A, St John Sutton M, et al. Dietary therapy in heart failure with preserved ejection fraction and/or left ventricular diastolic dysfunction in patients with metabolic syndrome. *Int J Cardiol* 2017;234:7–15.
104. Leung M, Xie M, Durmush E, et al. Weight loss with sleeve gastrectomy in obese type 2 diabetes mellitus: impact on cardiac function. *Obes Surg* 2016;26:321–6.
105. Dzenkeviciute V, Petrulioniene Z, Sapoka V, et al. The effect of weight loss on the cardiac structure and function after laparoscopic adjustable gastric banding surgery in morbidly obese individuals. *Obes Surg* 2014;24:1961–8.
106. Fontana L, Meyer TE, Klein S, et al. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc Natl Acad Sci USA* 2004;101:6659–63.
107. Dolinsky VW, Morton JS, Oka T, et al. Calorie restriction prevents hypertension and cardiac hypertrophy in the spontaneously hypertensive rat. *Hypertension* 2010;56:412–21.
108. Seymour EM, Parikh RV, Singer AA, et al. Moderate calorie restriction improves cardiac remodeling and diastolic dysfunction in the Dahl-SS rat. *J Mol Cell Cardiol* 2006;41:661–8.
109. Shinmura K, Tamaki K, Sano M, et al. Impact of long-term caloric restriction on cardiac senescence: caloric restriction ameliorates cardiac diastolic dysfunction associated with aging. *J Mol Cell Cardiol* 2011;50:117–27.
110. Sheng Y, Lv S, Huang M, et al. Opposing effects on cardiac function by calorie restriction in different-aged mice. *Aging Cell* 2017;16:1155–67.
111. Chen K, Kobayashi S, Xu X, et al. AMP activated protein kinase is indispensable for myocardial adaptation to caloric restriction in mice. *PLoS One* 2013;8:e59682.
112. Shinmura K, Tamaki K, Bolli R. Short-term caloric restriction improves ischemic tolerance independent of opening of ATP-sensitive K⁺ channels in both young and aged hearts. *J Mol Cell Cardiol* 2005;39:285–96.
113. Salminen A, Kaarniranta K. AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network. *Ageing Res Rev* 2012;11:230–41.

114. Hariharan N, Maejima Y, Nakae J, et al. Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac myocytes. *Circ Res* 2010;107:1470–82.
115. Kundu BK, Zhong M, Sen S, et al. Remodeling of glucose metabolism precedes pressure overload-induced left ventricular hypertrophy: review of a hypothesis. *Cardiology* 2015;130:211–20.
116. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. *N Engl J Med* 2013;368:651–62.
117. Mizushima N, Yamamoto A, Matsui M, et al. In vivo analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker. *Mol Biol Cell* 2004;15:1101–11.
118. Wende AR, Brahma MK, McGinnis GR, et al. Metabolic Origins of Heart Failure. *JACC Basic Transl Sci* 2017;2:297–310.
119. Lavandero S, Chiong M, Rothermel BA, et al. Autophagy in cardiovascular biology. *J Clin Invest* 2015;125:55–64.
120. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. *Endocrinology* 2003;144:3483–90.
121. van der Meer RW, Hammer S, Smit JW, et al. Short-term caloric restriction induces accumulation of myocardial triglycerides and decreases left ventricular diastolic function in healthy subjects. *Diabetes* 2007;56:2849–53.
122. Reingold JS, McGavock JM, Kaka S, et al. Determination of triglyceride in the human myocardium by magnetic resonance spectroscopy: reproducibility and sensitivity of the method. *Am J Physiol Endocrinol Metab* 2005;289:E935–9.
123. Ostergaard JN, Gronbaek M, Schnohr P, et al. Combined effects of weight loss and physical activity on all-cause mortality of overweight men and women. *Int J Obes* 2010;34:760–9.
124. Nanri A, Mizoue T, Takahashi Y, et al. Weight change and all-cause, cancer and cardiovascular disease mortality in Japanese men and women: the Japan Public Health Center-Based Prospective Study. *Int J Obes (Lond)* 2010;34:348–56.
125. Pack QR, Rodriguez-Escudero JP, Thomas RJ, et al. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc* 2014;89:1368–77.
126. Tamura BK, Bell CL, Masaki KH, et al. Factors associated with weight loss, low BMI, and malnutrition among nursing home patients: a systematic review of the literature. *J Am Med Dir Assoc* 2013;14:649–55.
127. Byard RW, Bellis M. Incidence of low body mass index in the elderly in forensic cases—a possible marker for frailty syndrome. *J Forensic Sci* 2016;61:676–8.
128. Lennie TA, Moser DK, Heo S, et al. Factors influencing food intake in patients with heart failure: a comparison with healthy elders. *J Cardiovasc Nurs* 2006;21:123–9.
129. Volkert D, Saeglit C, Gueldenzoph H, et al. Undiagnosed malnutrition and nutrition-related problems in geriatric patients. *J Nutr Health Aging* 2010;14:387–92.
130. von Haehling S, Lainscak M, Dohner W, et al. Diabetes mellitus, cachexia and obesity in heart failure: rationale and design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *J Cachexia Sarcopenia Muscle* 2010;1:187–94.

131. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010;1:1–5.
132. Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev* 2009;22:93–108.
133. Cordero-Reyes AM, Gupte AA, Youker KA, et al. Freshly isolated mitochondria from failing human hearts exhibit preserved respiratory function. *J Mol Cell Cardiol* 2014;68:98–105.
134. Jovanovski E, Zurbau A, Vuksan V. Carbohydrates and endothelial function: is a low-carbohydrate diet or a low-glycemic index diet favourable for vascular health. *Clin Nutr Res* 2015;4:69–75.
135. Zheng Q, Zhao K, Han X, et al. Inhibition of AMPK accentuates prolonged caloric restriction-induced change in cardiac contractile function through disruption of compensatory autophagy. *Biochim Biophys Acta* 2015;1852:332–42.
136. Meczekalski B, Podfigurna-Stopa A, Katulski K. Long-term consequences of anorexia nervosa. *Maturitas* 2013;75:215–20.
137. Rose M, Greene RM. Cardiovascular complications during prolonged starvation. *West J Med* 1979;130:170–7.
138. Casiero D, Frishman WH. Cardiovascular complications of eating disorders. *Cardiol Rev* 2006;14:227–31.
139. Olivares JL, Vazquez M, Fleta J, et al. Cardiac findings in adolescents with anorexia nervosa at diagnosis and after weight restoration. *Eur J Pediatr* 2005;164:383–6.
140. de Simone G, Scalfi L, Galderisi M, et al. Cardiac abnormalities in young women with anorexia nervosa. *Br Heart J* 1994;71:287–92.
141. Turillazzi E, Bello S, Neri M, et al. Congestive heart failure as cause of death in an anorexia nervosa fatal case. *Int J Cardiol* 2013;165:e28–9.
142. Siegel RJ, Cabeen WR Jr., Roberts WC. Prolonged QT interval—ventricular tachycardia syndrome from massive rapid weight loss utilizing the liquid-protein-modified-fast diet: sudden death with sinus node ganglionitis and neuritis. *Am Heart J* 1981;102:121–2.
143. Isner JM, Roberts WC, Heymsfield SB, et al. Anorexia nervosa and sudden death. *Ann Intern Med* 1985;102:49–52.
144. Lamzabi I, Syed S, Reddy VB, et al. Myocardial changes in a patient with anorexia nervosa: a case report and review of literature. *Am J Clin Pathol* 2015;143:734–7.
145. Guerrier K, Mitan L, Wang Y, et al. Risk for prolonged QT interval and associated outcomes in children with early restrictive eating patterns. *Cardiol Young* 2016;26:644–9.
146. Krantz MJ, Sabel AL, Sagar U, et al. Factors influencing QT prolongation in patients hospitalized with severe anorexia nervosa. *Gen Hosp Psychiatry* 2012;34:173–7.
147. Koschke M, Boettger MK, Macholdt C, et al. Increased QT variability in patients with anorexia nervosa—an indicator for increased cardiac mortality. *Int J Eat Disord* 2010;43:743–50.
148. Horwich TB, Fonarow GC, Hamilton MA, et al. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;38:789–95.

149. Lavie CJ, Milani RV, Ventura HO, et al. Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction. *Am J Cardiol* 2007;100:1460–4.
150. Oreopoulos A, Padwal R, Kalantar-Zadeh K, et al. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008;156:13–22.
151. Fonarow GC, Srikanthan P, Costanzo MR, et al. An obesity paradox in acute heart failure: analysis of body mass index and in-hospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. *Am Heart J* 2007;153:74–81.
152. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. *Am J Cardiol* 2012;110:77–82.
153. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368:666–78.
154. De Schutter A, Lavie CJ, Patel DA, et al. Relation of body fat categories by Gallagher classification and by continuous variables to mortality in patients with coronary heart disease. *Am J Cardiol* 2013;111:657–60.
155. De Schutter A, Lavie CJ, Kachur S, et al. Body composition and mortality in a large cohort with preserved ejection fraction: untangling the obesity paradox. *Mayo Clin Proc* 2014;89:1072–9.
156. Farre N, Aranyo J, Enjuanes C, et al. Differences in neurohormonal activity partially explain the obesity paradox in patients with heart failure: the role of sympathetic activation. *Int J Cardiol* 2014;181C:120–6.
157. Hawley JA, Burke LM, Phillips SM, et al. Nutritional modulation of training-induced skeletal muscle adaptations. *J Appl Physiol (1985)* 2011;110:834–45.
158. Hill AM, Harris Jackson KA, Roussell MA, et al. Type and amount of dietary protein in the treatment of metabolic syndrome: a randomized controlled trial. *Am J Clin Nutr* 2015;102:757–70.
159. Kopple JD. National Kidney Foundation KDWG. The National Kidney Foundation K/DOQI clinical practice guidelines for dietary protein intake for chronic dialysis patients. *Am J Kidney Dis: Off J Natl Kidney Found* 2001;38:S68–73.
160. Arkininstall MJ, Bruce CR, Clark SA, et al. Regulation of fuel metabolism by preexercise muscle glycogen content and exercise intensity. *J Appl Physiol* 2004;97:2275–83.
161. Hussain TA, Mathew TC, Dashti AA, et al. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition* 2012;28:1016–21.
162. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr* 2013;97:505–16.
163. Tay J, Brinkworth GD, Noakes M, et al. Metabolic effects of weight loss on a very-low-carbohydrate diet compared with an isocaloric high-carbohydrate diet in abdominally obese subjects. *J Am Coll Cardiol* 2008;51:59–67.
164. Burke LM, Angus DJ, Cox GR, et al. Effect of fat adaptation and carbohydrate restoration on metabolism and performance during prolonged cycling. *J Appl Physiol* 2000;89:2413–21.

165. Keogh JB, Brinkworth GD, Noakes M, et al. Effects of weight loss from a very-low-carbohydrate diet on endothelial function and markers of cardiovascular disease risk in subjects with abdominal obesity. *Am J Clin Nutr* 2008;87:567–76.
166. Nilsson J, Ericsson M, Joibari MM, et al. A low-carbohydrate high-fat diet decreases lean mass and impairs cardiac function in pair-fed female C57BL/6J mice. *Nutr Metab (Lond)* 2016;13:79.
167. Liu J, Wang P, Douglas SL, et al. Impact of high-fat, low-carbohydrate diet on myocardial substrate oxidation, insulin sensitivity, and cardiac function after ischemia-reperfusion. *Am J Physiol Heart Circ Physiol* 2016;311:H1–H10.
168. Burke LM, Ross ML, Garvican-Lewis LA, et al. Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from intensified training in elite race walkers. *J Physiol* 2017;595:2785–807.
169. Noakes TD, Windt J. Evidence that supports the prescription of low-carbohydrate high-fat diets: a narrative review. *Br J Sports Med* 2017;51:133–9.
170. Young ME, Guthrie PH, Razeghi P, et al. Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. *Diabetes* 2002;51:2587–95.
171. Hafstad AD, Khalid AM, Hagve M, et al. Cardiac peroxisome proliferator-activated receptor-alpha activation causes increased fatty acid oxidation, reducing efficiency and post-ischaemic functional loss. *Cardiovasc Res* 2009;83:519–26.
172. Gelinas R, Labarthe F, Bouchard B, et al. Alterations in carbohydrate metabolism and its regulation in PPARalpha null mouse hearts. *Am J Physiol Heart Circ Physiol* 2008;294:H1571–80.
173. Luptak I, Balschi JA, Xing Y, et al. Decreased contractile and metabolic reserve in peroxisome proliferator-activated receptor-alpha-null hearts can be rescued by increasing glucose transport and utilization. *Circulation* 2005;112:2339–46.
174. Colin-Ramirez E, Castillo-Martinez L, Orea-Tejeda A, et al. Dietary fatty acids intake and mortality in patients with heart failure. *Nutrition* 2014;30:1366–71.
175. Djousse L, Benkeser D, Arnold A, et al. Plasma free fatty acids and risk of heart failure: the Cardiovascular Health Study. *Circ Heart Fail* 2013;6:964–9.
176. Aquilani R, Opasich C, Verri M, et al. Is nutritional intake adequate in chronic heart failure patients. *J Am Coll Cardiol* 2003;42:1218–23.
177. Narumi T, Arimoto T, Funayama A, et al. Prognostic importance of objective nutritional indexes in patients with chronic heart failure. *J Cardiol* 2013;62:307–13.
178. Iwakami N, Nagai T, Furukawa TA, et al. Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure. *Int J Cardiol* 2017;230:529–36.
179. Shirakabe A, Hata N, Kobayashi N, et al. The prognostic impact of malnutrition in patients with severely decompensated acute heart failure, as assessed using the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score. *Heart Vessels* 2018;33:134–44.
180. Sze S, Zhang J, Pellicori P, et al. Prognostic value of simple frailty and malnutrition screening tools in patients with acute heart failure due to left ventricular systolic dysfunction. *Clin Res Cardiol* 2017;106:533–41.

181. Chess DJ, Stanley WC. Role of diet and fuel overabundance in the development and progression of heart failure. *Cardiovasc Res* 2008;79:269–78.
182. Lennie TA. Nutritional recommendations for patients with heart failure. *J Cardiovasc Nurs* 2006;21:261–8.
183. Colin Ramirez E, Castillo Martinez L, Orea Tejada A, et al. Effects of a nutritional intervention on body composition, clinical status, and quality of life in patients with heart failure. *Nutrition* 2004;20:890–5.
184. Lennie TA, Song EK, Wu JR, et al. Three gram sodium intake is associated with longer event-free survival only in patients with advanced heart failure. *J Card Fail* 2011;17:325–30.
185. McKeag NA, McKinley MC, Harbinson MT, et al. The effect of multiple micronutrient supplementation on left ventricular ejection fraction in patients with chronic stable heart failure: a randomized, placebo-controlled trial. *JACC Heart Fail* 2014;2:308–17.
186. Heller AR, Theilen HJ, Koch T. Fish or chips. *News Physiol Sci* 2003;18:50–4.
187. Harris WS. The omega-3 index as a risk factor for coronary heart disease. *Am J Clin Nutr* 2008;87:1997S–2002S.
188. Elagizi A, Lavie CJ, Marshall K, et al. Omega-3 polyunsaturated fatty acids and cardiovascular health: a comprehensive review. *Prog Cardiovasc Dis* 2018.
189. Lee JH, Jarreau T, Prasad A, et al. Nutritional assessment in heart failure patients. *Congest Heart Fail* 2011;17:199–203.
190. Stepaniak U, Micek A, Grosso G, et al. Antioxidant vitamin intake and mortality in three Central and Eastern European urban populations: the HAPIEE study. *Eur J Nutr* 2016;55:547–60.
191. Ashor AW, Siervo M, Lara J, et al. Effect of vitamin C and vitamin E supplementation on endothelial function: a systematic review and meta-analysis of randomised controlled trials. *Br J Nutr* 2015;113:1182–94.
192. Mortensen SA, Rosenfeldt F, Kumar A, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail* 2014;2:641–9.
193. Sharma A, Fonarow GC, Butler J, et al. Coenzyme Q10 and heart failure: a state-of-the-art review. *Circ Heart Fail* 2016;9:e002639.
194. van der Made SM, Plat J, Mensink RP. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. *PLoS One* 2015;10:e0118393.
195. Sciatti E, Lombardi C, Ravera A, et al. Nutritional deficiency in patients with heart failure. *Nutrients* 2016;8:E442.
196. Doherty JU, Wadden TA, Zuk L, et al. Long-term evaluation of cardiac function in obese patients treated with a very-low-calorie diet: a controlled clinical study of patients without underlying cardiac disease. *Am J Clin Nutr* 1991;53:854–8.
197. Sacks FM, Carey VJ, Anderson CA, et al. Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. *JAMA* 2014;312:2531–41.
198. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. *Ageing Res Rev* 2017;39:46–58.