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

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plays an essential role in the evolution of 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 2020;45:100391.)

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 level[9] 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 utilization[12] and by the nutritional state[13] 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 production[17] via oxidative phosphorylation[18] 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 oxidation[22] 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

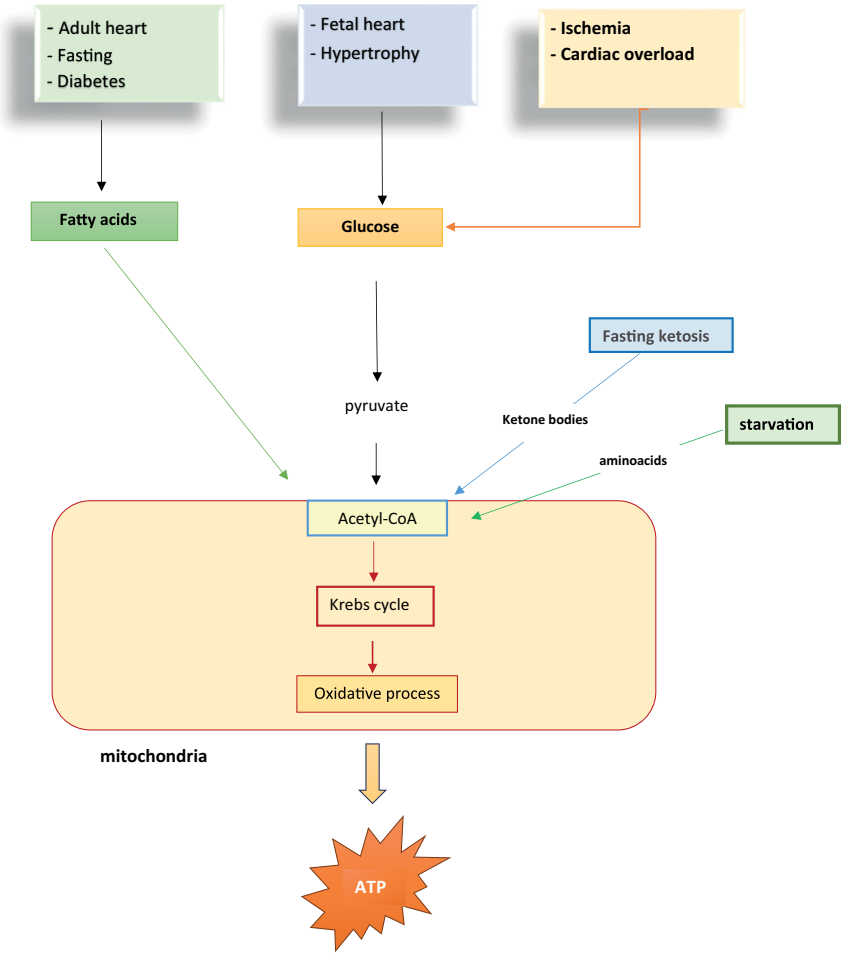

FIG 1. Fatty acids are prevalently oxidized by adult heart, in diabetes, and fasting. Glucose oxidation is prevalent in fetal heart, hypertrophy, cardiac overload, and ischemia. During fasting are oxidized ketone bodies and amino acids.

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 mechanism[44] (Fig 2).

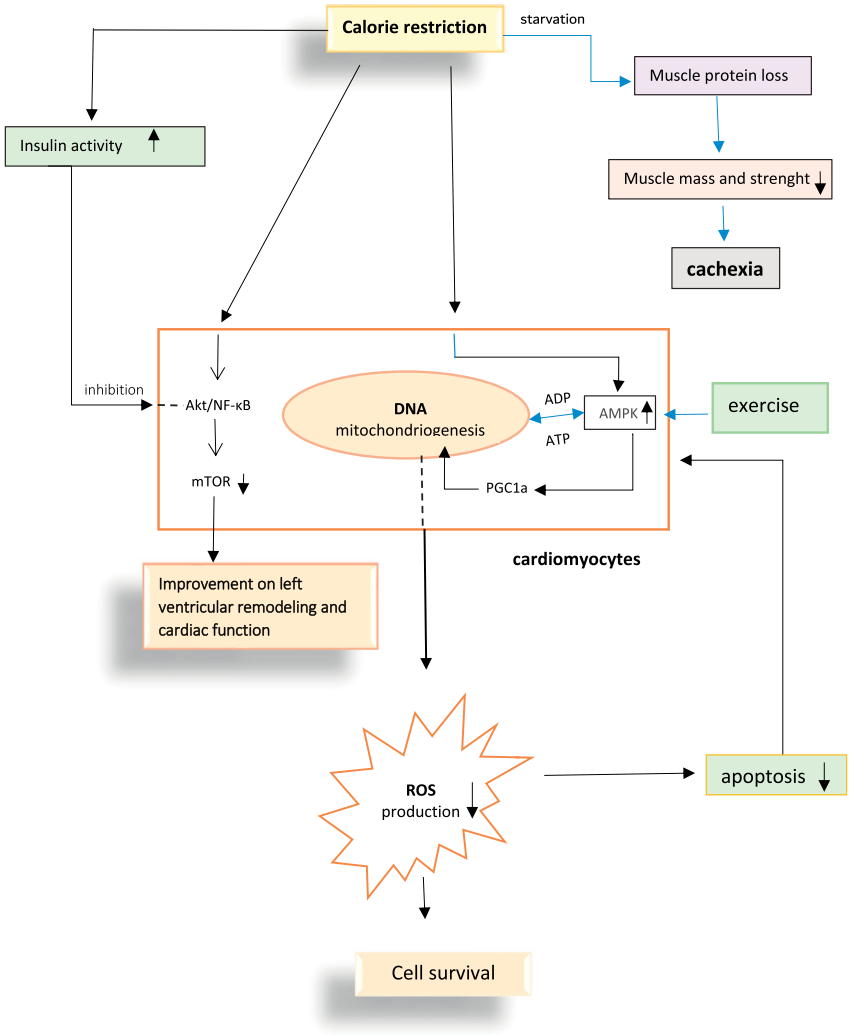

FIG 2. Caloric restriction improves insulin sensitivity that inhibits directly the Akt/NF-κB and increase the AMPK in the cell. NF-κB inhibits phosphorylation of mTOR and reverses left ventricular remodeling and cardiac function The activation of both signaling act directly on mitochondria in the cardiomyocytes. 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 conditions[48] and activate the protein synthesis in cardiomyocytes[47] 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 O_2 consumption is required proceeding through the formation of CoA derivative[49] 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 infarction[51] 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 diseases[53] and that a defect in the catabolism of BCAA is implicated in the pathogenesis of HF[54] 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 al[45] 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 $\pm$ 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

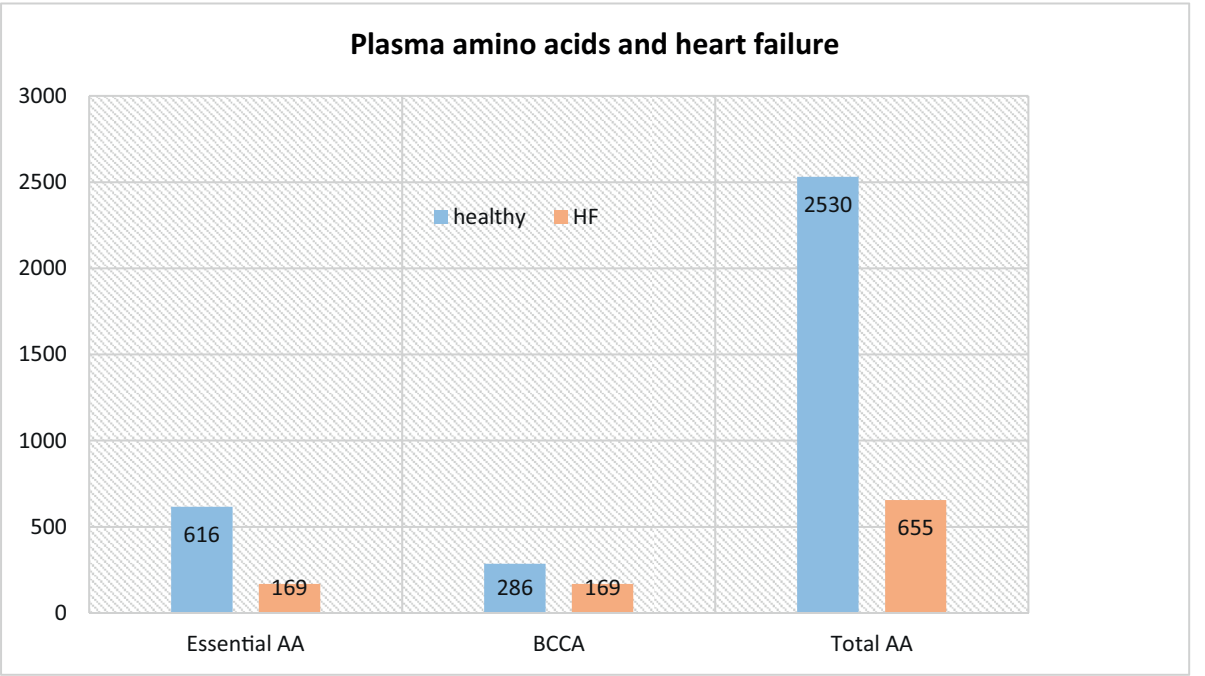

FIG 3. Serum level of total amino acids (AA), essential amino acids (essential AA) and branched chain amino acids in healthy (orange) and FH patients (blue) (from Aquilani et al[45] modified, with permission). (Color version of figure is available online.)

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 level[61] and reducing diastolic and systolic function.[62] The acute overingestion of glucose activates an inflammatory process and the reactive oxygen species generation[63] through the NF-kB (nuclear factor kB), the most sensitive transcription factor to redox signaling.[64] Glycemic control is beneficial to reduce the risk of mortality in type-2[65] 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-kB 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 al[79] 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 al[98] 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 al[100] 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 al[102] 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[100] 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 al[121] 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 Reinolds[122] 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 treated[129] 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 al[133] 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 complications[136] 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 al[142] 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 al[143] 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 severity[146] 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 patients[156] (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 al[166] 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 follows 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 al[184] 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 responses[186] 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 al[195] 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 CVD[198] 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.

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The importance of nutrition in the recovery of heart function in patients with CVD and HF have several potential benefits.

Several perspectives can be drawn from Dr Bianchi's review.

Macronutrients regulate cardiomyocyte activity. Heart function can be can be improved by optimizing glucose uptake, insulin activity, and by reduced fat intake.

Weight loss, through excess fat loss, is useful for obese and type-2 diabetes patients. However, in patients that are underweight weight loss could be detrimental.

Dietary interventions should be personalized, based on consideration of anthropometrics representing states of excess adiposity, underweight, and low lean body mass.

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

Diets in underweight and lean patients, should be nutritionally balanced and isocaloric to maintain and preserve lean body mass in order to prevent cardiac cachexia.

I want to thank Dr Bianchi for an interesting review of nutrition, a very important subject in the management of cardiovascular diseases.