Review article

L-Carnitine and heart disease

Zhong-Yu Wang[a], Ying-Yi Liu[b], Guo-Hui Liu[a], Hai-Bin Lu[c], Cui-Ying Mao[a],*

[a] Department of Cardiology, China-Japan Union Hospital, Jilin University, Changchun, PR China
[b] Department of Anesthesia, China-Japan Union Hospital, Jilin University, Changchun, PR China
[c] College of Pharmacy, Jilin University, Changchun, PR China

ABSTRACT

Cardiovascular disease (CVD) is a key cause of deaths worldwide, comprising 15–17% of healthcare expenditure in developed countries. Current records estimate an annual global average of 30 million cardiac dysfunction cases, with a predicted escalation by two-three folds for the next 20–30 years. Although β-blockers and angiotensin-converting-enzymes are commonly prescribed to control CVD risk, hepatotoxicity and hematological changes are frequent adverse events associated with these drugs. Search for alternatives identified endogenous cofactor L-carnitine, which is capable of promoting mitochondrial β-oxidation towards a balanced cardiac energy metabolism. L-Carnitine facilitates transport of long-chain fatty acids into the mitochondrial matrix, triggering cardioprotective effects through reduced oxidative stress, inflammation and necrosis of cardiac myocytes. Additionally, L-carnitine regulates calcium influx, endothelial integrity, intracellular enzyme release and membrane phospholipid content for sustained cellular homeostasis. Carnitine depletion, characterized by reduced expression of "organic cation transporter-2" gene, is a metabolic and autosomal recessive disorder that also frequently associates with CVD. Hence, exogenous carnitine administration through dietary and intravenous routes serves as a suitable protective strategy against ventricular dysfunction, ischemia-reperfusion injury, cardiac arrhythmia and toxic myocardial injury that prominently mark CVD. Additionally, carnitine reduces hypertension, hyperlipidemia, diabetic ketoacidosis, hyperglycemia, insulin-dependent diabetes mellitus, insulin resistance, obesity, etc. that enhance cardiovascular pathology. These favorable effects of L-carnitine have been evident in infants, juvenile, young, adult and aged patients of sudden and chronic heart failure as well. This review describes the mechanism of action, metabolism and pharmacokinetics of L-carnitine. It specifically emphasizes upon the beneficial role of L-carnitine in cardiomyopathy.

1. Introduction

Heart diseases, particularly chronic heart failure, impact about 25–30 million people globally [1]. Myocardial infarction, left ventricular systolic dysfunction and decreased cardiac muscle contraction and blood-flow are typical features of cardiac failure [2]. Conventional treatments for cardiac arrest include angiotensin-converting-enzyme inhibitors, angiotensin and corticosteroid receptor antagonists, beta-blockers and calcium-channel antagonists [3,4]. These pharmaceutical drugs promote vasodilatation; reduce vascular resistance and blood pressure; increase blood flow and oxygen supply to cardiac muscles, and are either used in isolation or in combinations, depending on patient's condition and needs. However, adverse hematologic/hepatotoxic effects and incidences of hyperkalemia and renal failure have been reported following long-term administration of the drugs [5].

Levocarnitine (L-carnitine; a chemical analog of choline [6]) is a natural and biologically active amino acid derivatives and a micronutrient, which plays an important role in lipid metabolism and mitochondrial defence, and supports several physiological activities. Particularly, propionyl-L-carnitine and acetyl-L-carnitine, the two most commonly studied forms of L-carnitine, help in reducing the accumulation of harmful metabolites generated in coronary thrombosis and embolism. Thus, L-carnitine, and predominantly propionyl-L-carnitine, has been proposed as a treatment for a wide range of cardiac problems, such as, cardiopulmonary arrest, reperfusion injury, coronary infarction, toxic myocardial injury, incidental blood circulatory disturbances, hypercholesterolemia and diabetes [7]. Meta-analyses data indicated a significant role of L-carnitine in averting cardiovascular ailments. The findings showed that predominant protective features following L-carnitine administration included decreased ventricular dysfunction, arrhythmia and discomfort associated with angina pectoris, resulting in diminished cardiac attack and mortality [8]. Additionally, carnitine had a beneficial impact on allied physiological features, such as stress-induced hypertension, diabetic ketoacidosis, hyperosmolar

hyperglycemia, insulin-dependent diabetes mellitus, insulin resistance, obesity, etc. [9,10]. This review article provides an update on metabolism, mechanism of action and pharmacokinetics of L-carnitine, and its role in cardiac dysfunction. Cardiac disorders, particularly, ventricular dysfunction, ischemia and reperfusion injury, cardiac arrhythmias and toxic myocardial injury will be the topics of discussion. The review will also highlight the impact of L-carnitine on cardiovascular disease-associated ailments, such as diabetes and hypertension.

2. Carnitine and acylcarnitine: pharmacokinetics, intermediary metabolism and mechanism of action in coronary artery disorders

2.1. Mode of action of L-carnitine

Within the mitochondrial matrix, conversion of propionyl CoA into succinyl CoA as an intermediate of the citric acid cycle includes stepwise involvement of (1) adenosine triphosphate (ATP) hydrolysis and generation of D-methylmalonyl CoA via propionyl CoA carboxylase catalyst, (2) racemization of D-methylmalonyl CoA to L-methylmalonyl CoA, and (3) mutase-mediated conversion of L-methylmalonyl CoA to succinyl CoA. Owing to the impermeability of CoA-linked compounds, such as propionyl-CoA and its esters, across inner mitochondrial membrane, a conversion to propionyl-L-carnitine is important for mitochondrial transport. Carnitine and carnitine acetyl transferase enzyme, prominently present in mitochondrial matrix, endoplasmic reticulum and peroxisomes, are essential for the mitochondrial transport of their substrates, thus playing a role in cell's energy metabolism [11]. It is believed that augmented carnitine accumulation could control altered oxidative metabolism, glycolysis and ATP production within the damaged myocardium, resulting in protection against cardiac hypertrophy [12]. Hence, propionyl-L-carnitine serves as an important cofactor for fatty acid oxidation, which defines its import role in mediating the entry of fatty acids into the mitochondria to facilitate energy generation in myocardial cells [13].

Following cardiac problems, transport of free fatty acids occurs from the cell membrane to mitochondria for oxidation with the help of cytoplasmic heart-type fatty acid-binding protein (fatty acid binding protein-3) released from myocytes [14]. A fatty acyl-CoA synthetase enzyme activates fatty acids at the outer mitochondrial membrane that involves a catalytic conversion of ATP to pyrophosphate and an adenosine monophosphate-connected fatty acyl chain [15]. Next, an interaction occurs between fatty acyl chain and thioester to generate fatty acyl coenzyme A (CoA) at the outer mitochondrial membrane. Owing to impenetrability of inner mitochondrial membrane, cytosolic interaction of fatty acyl CoA with carnitine in the presence of carnitine palmitoyl transferase enzyme generates acylcarnitine and long-chain fatty acid complex along with free CoA release via catalytic participation of enzyme, carnitine palmitoyltransferase/carnitine acyltransferase I (CPT1/CAT1) (Fig. 1) [16]. Binding of CoA with the carnitine-fatty acid product discharges carnitine and Acetyl CoA molecules via enzymatic involvement of CPT1/CAT1, where carnitine acts as the mediator for fatty acid entry into mitochondria. Stepwise, at first, the influx of long-chain acylcarnitine into mitochondria occurs in lieu of free carnitine through catalytic involvement of carnitine-acylcarnitine translocase. Acylcarnitine then undergoes transesterification that leads to release of free CoA-induced acyl CoA [17]. Within the mitochondrial matrix, acyl CoA undergoes an oxidative conversion to Acetyl CoA. This involves reduction of nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD) to NADH and FADH2, respectively, both of which then enter the oxidative phosphorylation chain.

2.2. Pharmacokinetics of L-carnitine

The "conditionally essential" nutrient, L-carnitine (β-hydroxy-γ-trimethylaminobutyric acid), is an acute necessity for adults and aged, as well as prenatal and post-natal infants and children. Carnitine

deficiency associates with altered free fatty acid, triglyceride and ketone body levels in blood circulation, necessitating exogenous carnitine infusion [18]. "Systemic primary carnitine deficiency" is a genetic defect and an autosomal recessive disorder that leads to several metabolic aberrations. Genetic vulnerability study revealed that targeted recessive mutation at SLC22A5 gene could be a prime reason for plasma carnitine insufficiency [19]. In fact, an altered SLC22A5-regulated generation of functional organic cation transporter 2 (OCTN2) gene resulted in failed fatty acid β-oxidation in the heart. Impact of this disorder varied with patient's age and extremity, and cardiomyopathy, cardiac arrhythmias and fatigue have been reported in both children and matured adults suffering from systemic primary carnitine deficiency [20].

L-Carnitine exists naturally in human cells and tissues and its availability in the physiological system primarily depends on dietary conditions, lean body mass and age [21,22]. Normally, carnitine enters the systemic circulation through food intake in the form of milk-based items and meat, and its cardiac concentration decreases with aging [23,24]. Cardiac carnitine levels demonstrate a swift increase via myocardial tissue-mediated extraction from plasma against a 60-fold concentration gradient [25]. Carnitine can also be incorporated through intravenous route, and it has been observed that dietary intake of carnitine results in decreased and diverse blood carnitine levels compared to intravenous injection [26,27]. Secondly, while oral feeding causes a significant increase in blood carnitine level within 10–12 h, intravenous injection triggers prompt serum uptake reaching a normal blood concentration in 12–13 h [28–30]. The impact emerged stronger when injected as propionyl-L-carnitine, reaching baseline levels in half the time, and excreted as acetylcarnitine through urine within a day [30].

Propionyl-L-carnitine activates an action potential across the cell membrane of heart cells. Although significant carnitine accumulation occurs in cardiac tissues, the heart fails to produce carnitine, and hence, true source of carnitine lies in liver and partially in kidney, generated from the amino acids, lysine and methionine [7]. Carnitine deposition occurs principally in the left ventricular region of heart and skeletal muscle tissues [31]. It has been observed that choline insufficiency increases the rate of carnitine metabolism, and carnitine and choline deficiency usually occurs concurrently [32,33]. When heart lacks sufficient carnitine concentration, an increased visceral absorption, followed by enhanced processing within liver, occurs [34,35]. In reality, carnitine concentration within liver increases much rapidly compared to cardiac tissues, particularly after intravenous injection, maintaining a uniform, gentle and steady balance with serum levels [31,36]. Cardiac carnitine concentration depends upon capability of muscle tissues to extricate carnitine through discrete transporter molecules along plasma membrane of myotubes against a strong concentration difference, and usually rises at levels distinctly higher than that present in blood [37]. Owing to impregnable nature of membranes enclosing cardiac muscles, carnitine is retained within the cardiac cell cytoplasm for a long-period [38].

2.3. Metabolic activities of L-carnitine

Enhancement in cytoplasmic concentrations of potentially toxic long-chain acylcarnitine occurs through reversible activation of carnitine acyltransferase. Via reduced carnitine acylcarnitine translocase functioning, an attenuated transport of long-chain acylcarnitine towards the mitochondrial matrix is evident [39]. This results in altered Acetyl CoA levels, causing a deregulated activation of pyruvate dehydrogenase (PDH) multi-enzyme complex, located at the inner mitochondrial membrane. The entire process adjusts the flow of intermediate glycolytic products in the citric acid cycle [40]. Post-ischemic condition associates with decreased PDH level and activity, triggering suppression in glycolytic pathway and lactate uptake, causing reduced cardiac functioning [41]. During hypoxia, reduced cellular carnitine and ATP accompanies deposition of long-chain fatty acid esters,
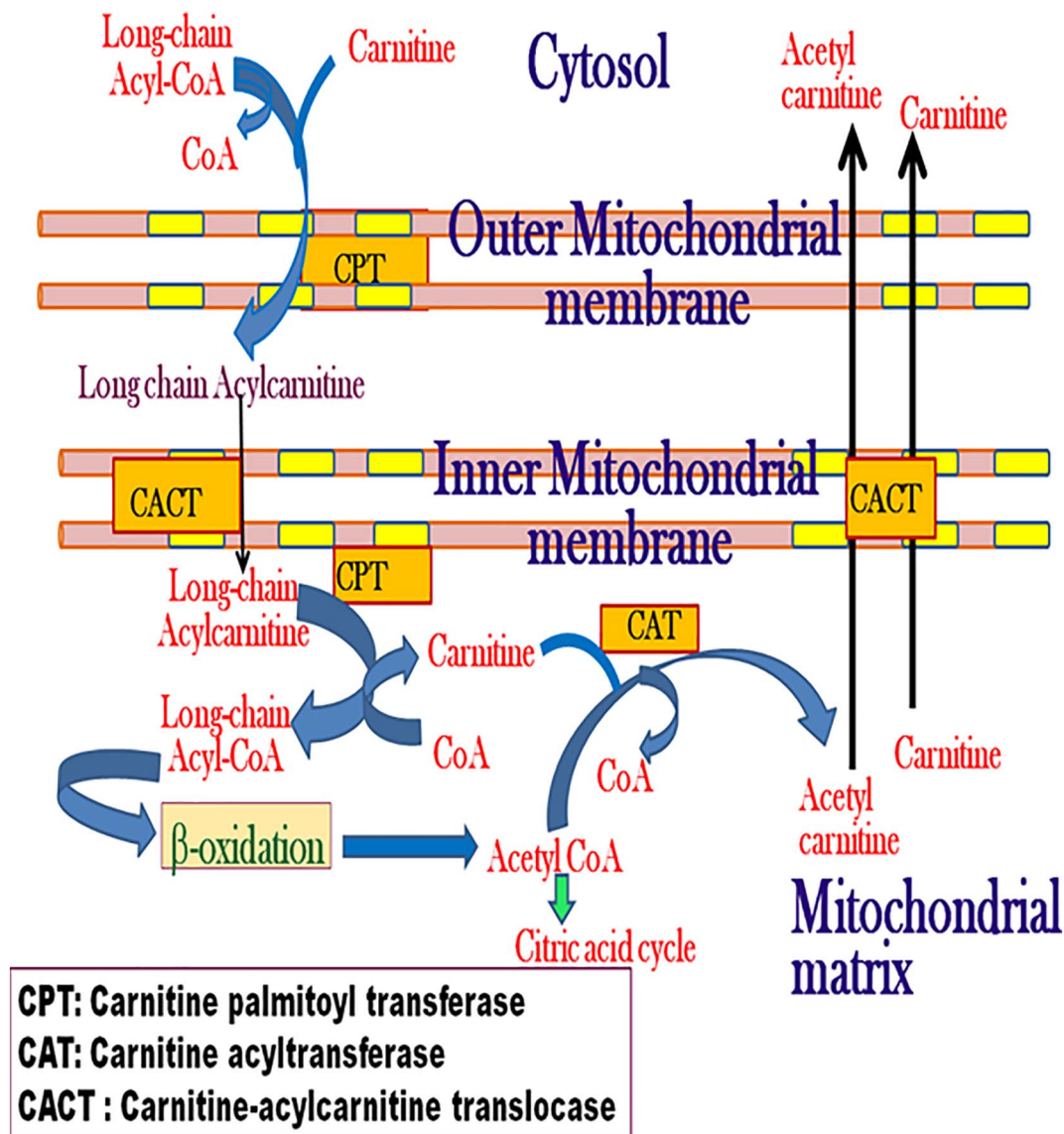
Fig. 1. Carnitine-mediated mitochondrial transport of long-chain fatty acids & fatty acid oxidation. Through a coordinated effort of several key enzymes, long-chain Acetyl CoA is transported into the mitochondria, while acetylcarnitine is transported out.

culminating in enhanced accretion of cytoplasmic acylcarnitine and intramitochondrial CoA complex of long-chain fatty acids [42]. Acyl-carnitine, with both polar and lipophilic properties, mimics detergent action and damages the double-layered lipid membrane, triggering the release of phospholipids, glycolipids and cholesterol [43]. Increased build-up of acylcarnitine is damaging for fatty acyl CoA synthetase as well, responsible for fatty acid biosynthesis and contributing to energy production and cell survival (Fig. 2) [44]. Acylcarnitine deposition disturbs sodium-potassium-ATPase (Na + /K + ATPase) pump and disrupts action potential, polarization, hyperpolarization and depolarization cycle of the cardiac membrane [45]. Additionally, acylcarnitine induces concentration- and time-dependent changes in the resting as well as action potential in situations of 50% repolarization.

Cardiomyocyte cells show augmented inotropy, broadening of repolarization phase and enhanced performance of the enzyme protein kinase C, resulting from the up-regulated functioning of Na + /K + ATPase. This causes alpha-1-adrenergic excitation of the myocardium via reduced activity of alpha-1-adrenergic receptors and thereby a cardiac arrhythmia like condition [46,47]. It also involves a severely altered membrane potential at the endoplasmic and sarcoplasmic reticulum. An associated alteration in performance of voltage-dependent

Ca2 + channels (VOCs), calcium-ATPase pump and sodium-calcium exchanger in the plasma and sarcoplasmic reticulum is reported along with deregulated tissue deposition of acylcarnitine, leading to irregular calcium transfer in the cardiomyocytes. Frequent reports of calcium overload and altered transmembrane electrochemical gradient of calcium following cardiac muscle contraction have also emerged in this condition [48,49]. The inotropic impact of enhanced acylcarnitine appeared quite similar to selective Ca2 + channel activators. An altered expression and activity of Ca2 + and Na + transporters and carriers within cardiac sarcolemma vesicles marked the increased acylcarnitine levels, causing a derangement of cardiac performances and hypertension during ischemia [50]. An enhanced expression of α1-adrenergic receptors at the myocytic surface and liberation of inositol triphosphate associated with the acylcarnitine [51]. The increased Ca2 + mobilisation through VOCs seemed detrimental as it could also result in death of ventricular myocyte cells. A changed dose-dependent calcium overburden has been found to arbitrate contractile dysfunction, mimicking ischemic contracture. Excess acylcarnitine also impaired working of adenine nucleotide translocase (ANT) that translocates ATP, produced by oxidative phosphorylation [52,53]. Inhibiting ANT activity, along the extra-mitochondrial and mitochondrial matrix, affected the
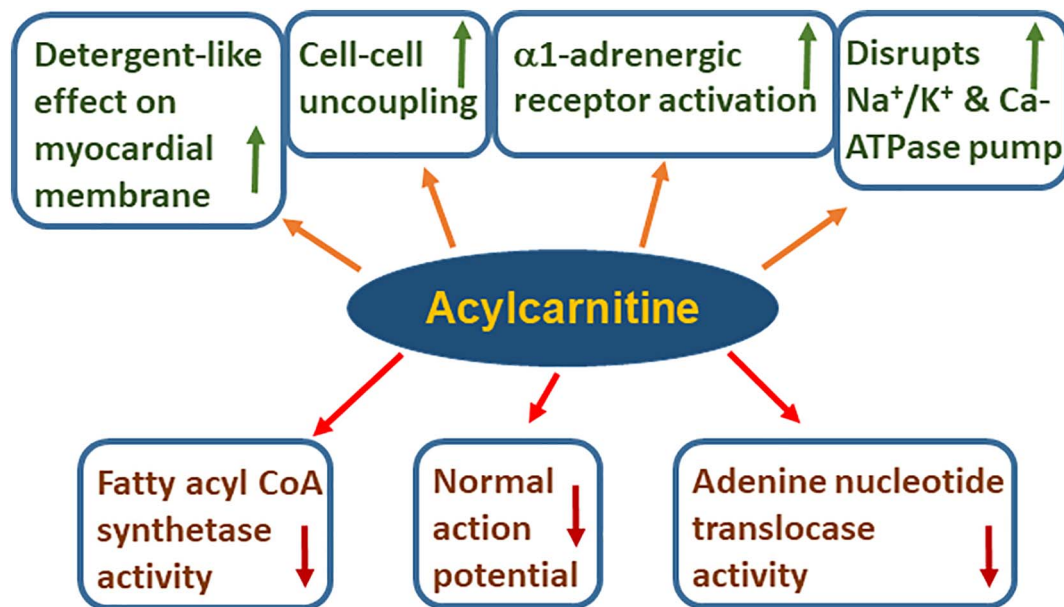
Fig. 2. Toxic role of acylcarnitine deposits in myocardiocyte cells. Individual arrows within the boxes indicate whether the individual effect is supported (upward arrows) or inhibited (downward arrows) by acylcarnitine.

membrane pore-gated ADP and ATP exchange and cellular energy metabolism, without altering mitochondrial permeability transition pore opening. This led to an enhanced generation of mitochondrial reactive oxygen species and oxidative stress, oxidation of ryanodine receptor-RyR2 and S-nitrosylation that trigger diastolic Ca2 + waves [54].

Acylcarnitine blocked endothelial outflow of endothelium-derived relaxing factor (EDRF), mediated by nitric oxide, that stimulates vascular smooth muscle relaxation and regulates vasomotor behaviour cardiac vasodilation [55]. Owing to excess cardiac tissue acetylcholine in ischemic papillary muscle sarcolemma, the resulting decreased amount of EDRF release may be one of the key reasons for the unfavorable consequences following ischemic injury [56]. Accumulation of long-chain acylcarnitine following myocardial ischemia induced an alteration in membrane excitability and electrical propagation, as evident from changed electrophysiological recordings [57]. A coupled onset delay of about 10–15 min has been reported in cell to cell communication, followed by prominent impediment and slowing down of electrical progression, decrease in the gap junctional conductance and disturbed impulse propagation, assessed through whole-cell voltage-clamp techniques. Additionally, redundant and quick accretion of extracellular K + that regulates cardiac refractoriness and spontaneous action potential discharges emanating from oscillatory after-potentials, caused premature diminution in conduction speed. Simultaneously, crossovers of the N-shaped current-voltage link along the voltage axis (zero current line) happened repeatedly, along with attenuated inward rectifier K + current in ventricular myocytes. An enhanced inward Na

+ /Ca2 + exchanger current alongside decreased outward I_{K1} (I_{K1}: Kir2.1 currents, where Kir indicates inward rectifier K + channels) had a greater than an additive effect on the progression of aberrant after-depolarizations. This also generated increased transient inward current and retarded after-depolarization in the cardiomyocyte cells. An inhibited current flow prior to the cellular wave front and decreased speed of inward Na + currents are major factors altering muscle tissue excitability [58].

Under normal conditions, lipid oxidation contributes about 70% of energetic associated with mitochondrial oxidative phosphorylation and ATP generation. The myocardial muscles significantly depend on fatty acid oxidation all through the ischemic condition, wherein CAT1 and β-hydroxyacyl-CoA dehydrogenase activities undergo rapid reduction with compromised energetics, reaching to about 50% compared to normal baseline levels within a day or two of hypoxia [59]. A consistent reduction in oxidative phosphorylation also occurs with a concomitant attenuation in respiration rate and CO_2 generation [60].

3. L-Carnitine and ventricular dysfunction

Ventricular dysfunction shows marked association with fatty acid oxidation within cardiomyocyte cells, with a subsequent augmentation in LPC, unbound arachidonic acid and acyl-carnitine-based molecules, and a reduction in myocardial carnitine levels. The pathological consequences of ventricular dysfunction involve reduced functioning of carnitine transporting enzymes. Hence, supplementation with carnitine has a marked protective effect via suppression of the toxic Coenzyme A
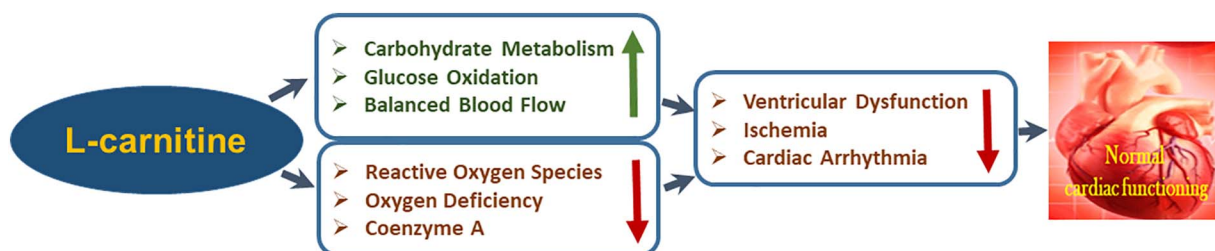

Fig. 3. Pathways promoting L-carnitine-mediated protection against cardiac ventricular dysfunction, ischemia-reperfusion & arrhythmia. L-Carnitine supports carbohydrate metabolism and oxidation along with balanced blood flow, concomitant with reduced reactive oxygen species and CoA, all of which manifests in reduced ventricular dysfunction, ischemia and cardiac arrhythmia, resulting in normal and healthy cardiac functioning.

levels, attenuated reactive oxygen species (ROS) generation, and an ultimate ameliorative impact against cardiac oxygen deficiency and ventricular functional impairment (Fig. 3) [61]. Carnitine also plays an important role in sustaining carbohydrate metabolism [62]. One of the key consequences of carnitine treatment is an augmentation in glucose oxidation, and a concurrent reduction in palmitate oxidation and up-regulation of free fatty acids within cardiac myocytes. Additionally, it has been proven that carnitine inhibits aberrant functioning of the diastole, associated with dilatation and modulation of left ventricles along with the maintenance of cardiac microvascular structure [63]. In a multicentric study (L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico; CEDIM Trial) conducted in 500 patients suffering from severe myocardial infarction, intravenous carnitine treatment within 24 h of cardiac attack at a dose of 6–9 g/d for a year showed significant improvement and recovery from impaired left ventricular functioning. Although the myocardial attack prominently altered left ventricular end-diastolic volume and systolic volume, carnitine-administered patients demonstrated lesser impact compared to placebo. Additionally, reports of cardiac failure and demise dropped significantly, as evident from a rate of 4% and 10% in carnitine-treated patients against 10% and 14% in the placebo, respectively. Carnitine treatment caused a marked shrinkage in infarct volume, determined through electro-cardiography. Carnitine reduced sensation of chest pain and discomfort, left ventricular enlargement, fatigue and edema. Signs of angina pectoris, accompanied by imbalanced myocardial blood circulation and oxygen demand, demonstrated marked down-regulation after carnitine administration as compared to a placebo counterpart. Moreover, carnitine treatment reduced apoptosis and necrosis of myocardiocytes within the left ventricle [64]. Another elaborate study comprising around 50 patients, treated with carnitine at a dose of 2 g/d for a span of three months following myocardial infarction, revealed improvements in exercise continuance and changes in the S wave and T wave electrocardiography (ECG) recordings, characteristic of ventricular depolarization and repolarization [64]. In a study involving protective measures against cardiac collapse among 70 patients in New York, patients undergoing carnitine treatment for three months showed improved cardiopulmonary exercise test on a stationary bicycle, measured by the amount of oxygen consumed, CO_2 produced, respiratory pattern and ECG recording of heart activity [65]. Impact of carnitine treatment has also been studied in children suffering from cardiomyopathy and cardiac muscle and ventricular disorders. A patient study investigating the comparative effects of L-carnitine and angiotensin-converting enzyme inhibitors, treated for seven days to one year in children and adolescents suffering from left ventricular dysfunction, showed that carnitine treatment resulted in noticeable improvements, specifically in terms of higher survival rate and prominently better clinical cardiac health [66].

It is well-established that a reduced phosphocreatine/ATP ratio comprises one of the major reasons governing left ventricular damage, marked by significant cardiac energy loss and heart pumping problems [67]. In this situation, attenuated mitochondrial oxidative phosphorylation and resultant suppression in the respiratory cycle plays a critical contributory role. Increased dependence on glycolytic cycle as against the paradigm shift from beta-oxidation catabolic process has also been shown to participate in altered ventricular dilation [68,69]. Biopsies of left ventricular samples, collected while performing open heart cardiac valve surgery, revealed around 45–50% reduced left ventricular ejection fraction and distinct attenuation in overall functioning of electron transport chain and resultant decrease in ATP generation within the cellular respiratory cycle [70]. Interestingly, a reduction in fatty acid transporter protein levels and activities of enzymes participating in medium-chain fatty acid (MCFA) metabolism, particularly medium-chain acyl dehydrogenase, 3-hydroxyacyl-CoA-dehydrogenase and mitochondrial creatine kinase, characterized the left ventricular systolic dysfunction. The study proved recovery from ventricular dysfunction upon treatment with MCFA in the form of octanoyl-L-carnitine,

although marked improvements in respiratory rates were not evident when administered with palmitoyl-carnitine [71]. Meta-analyses data revealed that advantageous impacts of L-carnitine comprised decreased serum levels of calcium ion-regulated brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptides (NT-proBNP), released by cardiac ventricles following unwarranted extension of cardiomyocytes [72]. Quantitative data showed a 50–60% decrease in serum concentrations of BNP and NT-proBNP, subsequent to oral L-carnitine administration in young and chronic heart failure patients [1]. Another study in choline-deficient rats demonstrated that increased myocardial dysfunction and enhanced serum BNP levels had a link with inflammatory lesions and impaired mitochondrial energy metabolism. Conversely, L-carnitine treatment (200 mg/Kg body weight through drinking water) induced protective antioxidative and valvular anti-inflammatory effects [72,73], and attenuated the influx of inflammatory molecules across the myocardial membrane. L-Carnitine could also suppress nitric oxide production, cardiac fibrosis and hypertrophy, endothelium disruption, mitochondrial cytochrome *c* levels and apoptosis and death of cardiomyocyte cells, which resulted in reduced serum BNP levels [74,75].

L-Carnitine effectively reinstates myocardial energy levels with significant refinement in cardiac histology. Carnitine inhibits xanthine oxidase, nitric oxide synthase and monoamine oxidase activities that are primarily responsible for myocardial superoxide and hydrogen peroxide generation, nuclear factor kappa B-mediated inflammation and an ultimate left ventricular remodelling [76,77]. Moreover, L-carnitine reduces endothelin-mediated functioning of NADPH oxidase, causing attenuated vascular and cardiac superoxide levels and an eventual optimum performance of the mitochondrial respiratory chain. While angiotensin converting enzyme II inhibitors help relaxing blood vessels of left ventricles and regulates hypertension, L-carnitine additionally induces partial restoration of endothelium-dependent acetylcholine relaxation [78]. L-Carnitine also causes a reduction in angiotensin II-mediated collagen release, partnered by augmented fatty acid desaturase (FADS) enzyme levels that promote fatty acid unsaturation. FADS-induced arachidonic and prostacyclin finally results in decreased deposition and thickening of connective fibre tissues at the left ventricle and a consequent better survival of cardiac fibroblasts in pathogenetic conditions [79]. Enhanced expression and proteolytic activity of matrix metalloproteases (MMPs) are intricately linked to chronic heart failure, concomitant with a down-regulated expression of inhibitors of MMPs (TIMPs). Although less studied, few reports claim that L-carnitine competently suppresses this MMP and TIMP imbalance, and thereby reduces undesired left ventricular remodelling [80].

4. L-Carnitine and ischemia-reperfusion injury

Impediment in smooth blood circulation during hypoxia and ischemia causes instantaneous attenuation in the cardiac oxygen pressure, resulting in an aberrant oxidation-reduction cycle of the mitochondrial electron transport chain [81]. Ischemia-reperfusion impairs normal NAD + /NADH and FAD/FADH2 redox pair and induces disturbance of catabolic β-oxidation pathway and disruption in the mitochondrial carnitine shuttle, triggering augmented acyl Coa and long-chain acylcarnitine levels at the inner mitochondrial membrane. The long-chain acylcarnitine undergoes undesired and increased deposition (about 3–4 folds) within the cytoplasm and sarcolemma of myocytes within a time span of 1–2 min following cardiac ischemic attack [82]. Clinical conditions of ischemia-reperfusion injury mainly stem from malfunctioning and morphological defects of the heart, and loss in metabolic elasticity along with severe impairment of left ventricles [83]. Altered catabolic and anabolic phenotypes are key characteristics of myocardial pathology, and the preceding condition of left ventricle and arterial fibrils regulates the functioning of citric acid cycle and metabolic energy uptake. These factors ultimately play an important role in damage and recovery subsequent to myocardial infarction and

ischemic damage [84]. A study involving 37 patients with cardiac ischemia-reperfusion damage, between the age group 18–20, demonstrated a reduced glucose uptake and pyruvate dehydrogenase reaction, increased lactase efflux and lactate dehydrogenase activity and altered plasma levels of ketonic compounds, such as beta–hydroxybutyrate and β-hydroxybutyryl-carnitine [85]. Plasma metabolite analyses showed diminished glucose and leucine and isoleucine amino acids and up-regulated alanine (generated via pyruvate transamination) levels. A remarkable increase in the small and medium-chain acylcarnitines, particularly acetylcarnitine, Acetyl CoA, acyl CoA intermediates and β-hydroxybutyrylcarnitine were also obtained within the plasma eluent. The clinical study indicated a necessity for dichloroacetate treatment, that activates the functioning of pyruvate dehydrogenase, in combination with L-carnitine, for enhanced generation of mitochondrial carnitine ester levels and suppression of Acetyl CoA accumulation [86].

Enlarged ischemic heart shows diminished accumulation of free carnitine owing to its attenuated generation and transport, which leads to decreased β-oxidation of long-chain fatty acids across the mitochondrial membrane and an accretion of lethal metabolites. It has been observed that cardiac levels of carnitine are 15–20% and 50% lower compared to normal conditions in the long-term and short term (after 30 min), respectively, subsequent to ischemia-reperfusion. Carnitine treatment restrained post-ischemic diminution of mitochondrial adenine nucleotide, and the impact increased dose-dependently with exogenous carnitine administration. This concept underwent confirmation through studies monitoring myocardiocyte survival following ischemic-reperfusion in rat hearts, at a temperature range of 20–30 °C. In this condition, L-carnitine intricately participated in myocardiocyte metabolic processes, even during homogeneous myocardial cooling and artificially performed electromechanical quiescence, by maintaining ventricular blood volume and pressure and upholding cardiac muscle contraction and retrograde diastolic flow in the aorta [87]. Systematic studies in animal models revealed that L-carnitine treatment up-regulated glucose metabolism and prompted higher glycogen synthesis, which caused recuperation from ischemia-induced cardiac damage. Fatty acid oxidation largely generated the necessary energy for cardiac muscle functioning [88].

A free radical-induced degeneration of the inner mitochondrial membrane all through ischemia and reperfusion is also known. Additionally, a competition emanates between RyR2 S-nitrosylation and RyR2 oxidation levels, which happens alongside an irreversible oxidation at the thiol sites of RyR2. Imbalance between nitroso/redox factors contributes towards $Ca2+$ leak at the sarcoplasmic reticulum and causes a reduction in the binding affinity of the immunophilin protein FKBP12.6 (that plays an important role in excitation-contraction coupling within cardiomyocyte cells) to the calcium-channel [89,90]. A concomitant oxidation at the cys-21 site on RyR1 has also been observed at the cytoplasmic domain of calcium channel. Reduced ANT performance attenuates the ATP/Adenosine diphosphate levels and activation of ATP synthase as well. An associated inhibition of the respiratory oxidative chain leads to enhanced mitochondrial ROS production from the electron transport chain [44].

5. L-Carnitine and cardiac arrhythmia

Cardiac arrhythmias have been reported to cause around 300,000–400,000 deaths in the USA every year. In most cases, prior incidences of cardiac problems appear unreported, with autopsy samples clearly demonstrating unsynchronized contraction of cardiac muscle fibers [91]. These events provide a clear indication that cardiac arrhythmias and unanticipated cardiac failures are likely consequences of coronary arterial blood clotting that restrict systemic blood flow, followed by temporary and momentary myocardial ischemia and essential cellular oxygen and glucose deprivation [92]. A distinct link has been found with the small muscle diameters, with prominently elevated acylcarnitine in these ischemic-muscles [7]. An increased acidification

owing to imbalance in the amount of CO_2 released and diffused in small-diameter muscles, and a consequent altered pH has also been observed [93]. This culminates in reentrant arrhythmias in ischemic myocardium. Augmented acylcarnitine concentration and reduced CATI activity also triggers deposition and retention of LPC within myocardial cellular and subcellular chambers. This associates with inhibited functioning of several enzymes, owing to decreased pH, that catabolizes LPC in the sarcolemma of cardiac myocytes [94]. Specifically, a down-regulated functioning of (1) lysophospholipase that mediates the conversion of LPC to glycerophosphoryl choline and fatty acid; (2) Coenzyme A-LPC acyltransferase, responsible for generation of diacyl-phosphatidylcholine involving the interaction of acyl CoA and LPC; (3) lysophospholipase-transacylase that triggers self-interaction of LPC to release diacyl-phosphatidylcholine and glycerophosphoryl choline are generally observed. A concomitant incidence of altered cardiac electrical activity, measured through ECG, has also been reported in cardiac arrhythmia. The effect of acylcarnitine involves competitive inhibition of lysophospholipase-transacylase and lysophospholipase enzymes [95]. Conversely, carnitine contributes by suppressing mechanical and electrical impairments in the myocardial tissues, which could cause an absolute deterrence of cardia arrhythmia [96]. This carnitine-mediated cardioprotection has distinct correlation with superior oxidative-phosphorylating capability in mitochondrial populations, without altered adenine nucleotide-translocase functioning. In a study on Guinea pigs with artificially induced arrhythmia, L-carnitine inhibited the growth of conduction block in micro-patterned cardiomyocyte cells and eliminated aberrant cardiac muscle cell firing and atrioventricular nodal reentrant tachycardia and fast heart rhythm, typical of arrhythmia [97]. A study involving the electrophysiologic mechanism in adult mongrel dogs also proved that intravenous injection with L-carnitine caused α-adrenoceptor-mediated cellular uncoupling at the gap junctions via protein kinase C-signalling, with concurrent hindrance to sodium channel functioning in the cardiac tissues [98].

6. L-Carnitine and toxic myocardial injury

Myocardial injury is a physiological occurrence, whose severity may cause morbidity, multi-organ failure and an eventual mortality. Frequently, this type of myocardial ischemia-reperfusion injury appears as an outcome of cardiac surgery and cardiopulmonary bypass, with significant contribution from hyperactivated leukocytes, neutrophil and endothelial cells [99]. Events contributing to toxic myocardial damage prominently include increased oxidative biochemical reactions in the myocytes, promoting free radical generation and nitric oxide-dependent endothelial impairment. These altered intravascular bioactivities trigger platelet activation, venous thrombosis and pulmonary embolism. Generation of pro-inflammatory cytokines and chemokines, particularly tumor necrosis factor-alpha, macrophage inflammatory protein, interleukin (IL)-6 and IL-8, and a suppressed expression of anti-inflammatory cytokine, such as IL-10, chemokine ligand-2, etc., in the cardiac myocytes are common features of myocardial injury. Especially, an altered equilibrium among pro- and anti-inflammatory cytokines and chemokines is a critical factor governing extent of myocardial injury [97]. Aldosterone antagonists, that enhance endothelial nitric oxide-synthase functioning and thereby control vascular characteristics, local blood circulation and platelet activation and aggregation, until now, served as therapeutics for toxic myocardial degeneration [100]. Nonetheless, carnitine prominently promoted functional recovery and restored aerobic metabolism process during cardioplegic arrest in patients experiencing tissue damage during open-heart surgery (Fig. 4).

Myocardial necrosis, associated with aluminium phosphide (an insecticide) exposure, mimics ischemia-like condition that hampers 70% performance of mitochondrial respiratory chain and cardiac metabolism and induces ventricular dilatation and dysfunction, often culminating in an absolute heart collapse. Phosphine gas serves as an active
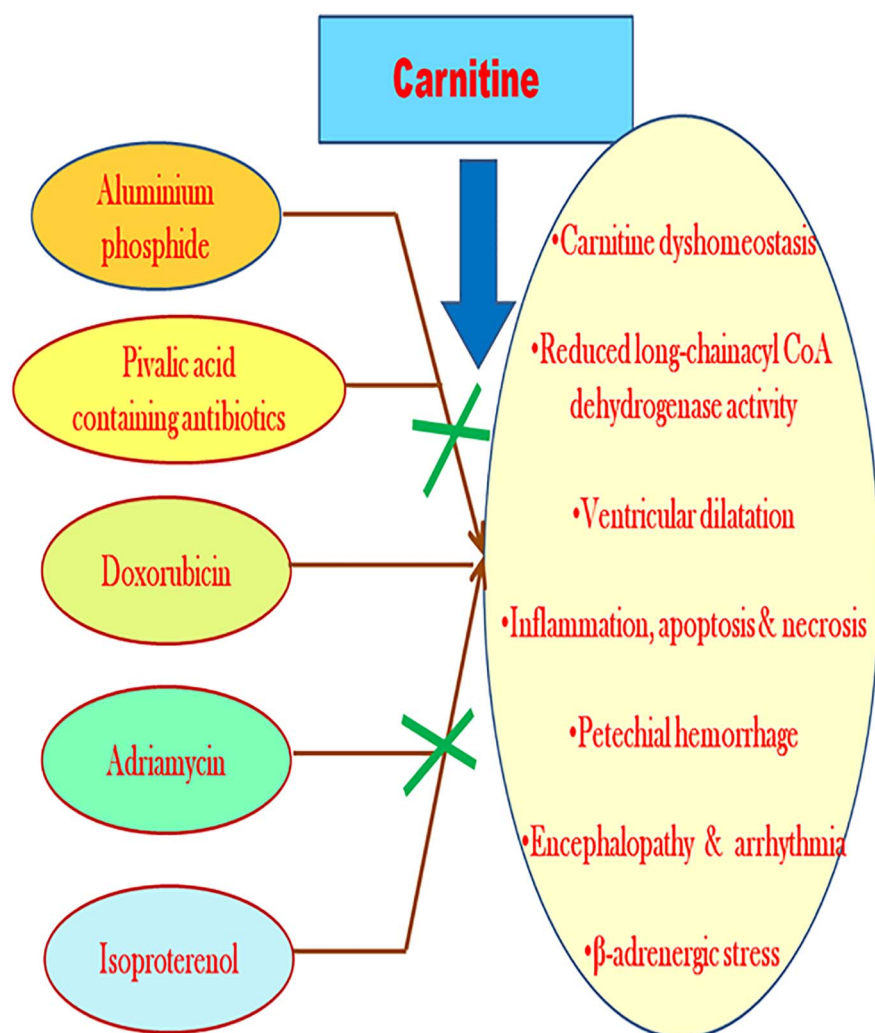
toxic constituent of aluminium phosphide that undergoes rapid entry into the blood circulation via respiration, food items, skin and epithelial mucosal layers. Decreased long-chain acyl-CoA dehydrogenase activity and cardiac hypertrophy are typical features of severe myocardial aluminium phosphide toxicity, and L-carnitine administration plays marked role in the recovery process. Additionally, L-carnitine regulates blood volume in cardiac cycle, without affecting left ventricular blood ejection, which arbitrates protection against congestive cardiac failure [101]. In situations of modest carnitine insufficiency, treatment with selective β-adrenoceptor agonist, isoproterenol, aggravates myocardial damage. An in vivo study in rats showed that a slight decrease in the cardiac carnitine levels increases the susceptibility of cardiac collapse, particularly for cases undergoing isoproterenol treatment. Sub-cutaneous isoproterenol injection in carnitine-deficient rats progressively elevated systolic and diastolic blood pressure, heart beat, pulse rate, respiratory secretions, cytokine release and apoptosis, added to deep and asymmetrical breathing. Upon ventricular macroscopic morphology, following isoproterenol infusion in carnitine-deficient conditions, rat hearts had a flaccid and fibrous look, with petechial hemorrhages evident on the cardiac epicardium. Thus, carnitine-lacking phenotypes are prone to relentless heart problems owing to cardiac fragility in patients experiencing β-adrenergic stress [102]. An epidemiological study from Faroe Islands, Denmark, showed that patients treated with pivalic acid-containing antibiotics died, with signs of encephalopathy and cardiac arrhythmia. Thorough investigation revealed that the patients had mutated SLC22A5 gene and a residual OCTN2 activity significantly lower (3–20%) than their normal counterparts.

Additionally, treatment with pivalic acid caused a depletion of plasma carnitine concentrations through increased pivaloyl-carnitine, and thereby acylcarnitine production, and undesired urinary carnitine excretion. All these conditions triggered a combined loss in physiologic and systemic carnitine levels and altered carnitine homeostasis, and via radically lessened carnitine stores and enhanced carnitine demands caused severe cardiac complications. Thus, currently antiretroviral pivalic acid-based antibiotics are generally prescribed with carnitine supplementation for mitigating carnitine deficiency-induced cardiac problems [103].

The anticancer anthracycline-based antibiotic, doxorubicin, caused serious cardiac toxicity via increased oxidative stress-induced tissue damage. Doxorubicin impaired the equilibrium between oxidant and anti-oxidant enzymes, resulting in profound ROS generation, altered expression and activities of superoxide dismutase, lipid peroxidase, catalase and glutathione peroxidase enzymes. Several incidences have proven a lethal role of doxorubicin as well. Doxorubicin caused a dose-dependent reduction in cardiac FABP3 and OCTN2 gene expression, attenuating ATP-dependent energy metabolism and carnitine levels. An experimental observation in rats administered intraperitoneally for ten successive days with carnitine (200 mg/Kg body weight) revealed a marked reversal from therapeutic doses of doxorubicin-induced cardiac injury, without interfering with the anti-tumor activity of doxorubicin [104]. Carnitine supplementation with doxorubicin enriched its levels in lymphocytes, restored immune functioning and blood pressure and reduced biochemical oxidative stress, and thereby served as a protective agent countering cardiovascular remodelling [105]. Another

broad-spectrum anthracycline antibiotic, adriamycin, demonstrated irreversible cardiac degeneration in about 40% cancer patients, clinically limiting its use in cancer treatment. L-Carnitine co-treatment with adriamycin served as a mitochondrial substrate for anaplerotic reactions, and successfully restored a normal cardiac biological environment [106].

7. Summary and conclusion

Myocardial injury involves diverse metabolic derangements, characterized predominantly by aberrant left ventricular functions, culminating in grave clinical repercussions in the heart. If left untreated at early stages, critical complications such as congestive cardiomyopathy, dysrhythmias, deep venous thrombosis and pulmonary embolism may develop. Predominantly, inherent or toxic metabolite-induced carnitine deficiency and an associated abnormal fatty acid metabolism are proven deregulatory phenomena impeding normal ventricular performance, and appear as key reasons for arrhythmia and ischemic-reperfusion damage and myocardial injury. Accordingly, L-carnitine treatment has developed as a preventive and therapeutic strategy against mild to severe cardiac disorders. Although several studies successfully attested capability of L-carnitine as an ameliorative agent against cardiac collapse, critical challenges lie in discerning the integrated role of cardiac and pharmacokinetic factors and physiological vital organs, such as the brain, liver, kidney, etc. in carnitine-mediated protection. Most importantly, impact of L-carnitine in patients who underwent cardiovascular surgeries remains less explored. Hence, large multicentric clinical trials with carnitine supplementation in chronic dysfunctional heart patients seem important, both for pre- and pro-surgery cases. These novel clinical studies would enlighten unknown links between hypertrophied hearts, reduced mechanical performance, L-carnitine depletion and L-carnitine-mediated therapy for cardiac failure, and additionally inform their mutual links with other vital organs, leading to improved quality of life and long-term beneficial impact against myocarditis.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

[1] X. Song, H. Qu, Z. Yang, J. Rong, W. Cai, H. Zhou, Efficacy and safety of L-carnitine treatment for chronic heart failure: a meta-analysis of randomized controlled trials, Biomed. Res. Int. 2017 (2017) 6274854.

[2] P.G. Roan, M. Buja, S. Saffer, C. Izquierdo, H. Hagler, B. Duke, L.D. Hillis, J.T. Willerson, Effects of systemic hypertension on ischemic and nonischemic regional left ventricular function in awake, unsedated dogs after experimental coronary occlusion, Circulation 65 (1982) 115–125.

[3] B. Lipworth, D. Skinner, G. Devereux, V. Thomas, J. Ling Zhi Jie, J. Martin, V. Carter, D.B. Price, Underuse of beta-blockers in heart failure and chronic obstructive pulmonary disease, Heart 102 (2016) 1909–1914.

[4] P. Kolkhof, C. Nowack, F. Eitner, Nonsteroidal antagonists of the mineralocorticoid receptor, Curr. Opin. Nephrol. Hypertens. 24 (2015) 417–424.

[5] G. Sidorenkov, G. Navis, Safety of ACE inhibitor therapies in patients with chronic kidney disease, Expert Opin. Drug Saf. 13 (2014) 1383–1395.

[6] J.R. Pieklik, R.W. Guynn, Equilibrium constants of the reactions of choline acetyltransferase, carnitine acetyltransferase, and acetylcholinesterase under physiological conditions, J. Biol. Chem. 250 (1975) 4445–4450.

[7] M.A. Arsenian, Carnitine and its derivatives in cardiovascular disease, Prog. Cardiovasc. Dis. 40 (1997) 265–286.

[8] J.J. DiNicolantonio, C.J. Lavie, H. Fares, A.R. Menezes, J.H. O'Keefe, L-Carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis, Mayo Clin. Proc. 88 (2013) 544–551.

[9] Z.T. Bloomgarden, Obesity, hypertension, and insulin resistance, Diabetes Care 25 (2002) 2088–2097.

[10] R.H. Eckel, K.G. Alberti, S.M. Grundy, P.Z. Zimmet, The metabolic syndrome, Lancet 375 (2010) 181–183.

[11] F. Di Lisa, R. Menabo, N. Siliprandi, L-Propionyl-carnitine protection of mitochondria in ischemic rat hearts, Mol. Cell. Biochem. 88 (1989) 169–173.

[12] M.F. Allard, B.O. Schonekess, S.L. Henning, D.R. English, G.D. Lopaschuk, Contribution of oxidative metabolism and glycolysis to ATP production in hypertrophied hearts, Am. J. Phys. 267 (1994) H742–750.

[13] A.P. Wong, A. Niedzwiecki, M. Rath, Myocardial energetics and the role of micronutrients in heart failure: a critical review, Am. J. Cardiovasc. Dis. 6 (2016) 81–92.

[14] N. Fillmore, J. Mori, G.D. Lopaschuk, Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy, Br. J. Pharmacol. 171 (2014) 2080–2090.

[15] D.G. Mashek, L.O. Li, R.A. Coleman, Long-chain acyl-CoA synthetases and fatty acid channeling, Futur. Lipidol. 2 (2007) 465–476.

[16] S. Sharma, S.M. Black, Carnitine homeostasis, mitochondrial function, and cardiovascular disease, Drug Discov. Today Dis. Mech. 6 (2009) e31–e39.

[17] M.C. Hunt, M.I. Siponen, S.E. Alexson, The emerging role of acyl-CoA thioesterases and acyltransferases in regulating peroxisomal lipid metabolism, Biochim. Biophys. Acta 1822 (2012) 1397–1410.

[18] C.J. Rebouche, Carnitine function and requirements during the life cycle, FASEB J. 6 (1992) 3379–3386.

[19] P.L. Magoulas, A.W. El-Hattab, Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management, Orphanet J. Rare Dis. 7 (2012) 68.

[20] J. Rasmussen, O.W. Nielsen, A.M. Lund, L. Kober, H. Djurhuus, Primary carnitine deficiency and pivalic acid exposure causing encephalopathy and fatal cardiac events, J. Inherit. Metab. Dis. 36 (2013) 35–41.

[21] A.J. Liedtke, S.H. Nellis, L.F. Whitesell, C.Q. Mahar, Metabolic and mechanical effects using L- and D-carnitine in working swine hearts, Am. J. Phys. 243 (1982) H691–697.

[22] J. Bremer, Carnitine—metabolism and functions, Physiol. Rev. 63 (1983) 1420–1480.

[23] C.J. Rebouche, A.G. Engel, Carnitine metabolism and deficiency syndromes, Mayo Clin. Proc. 58 (1983) 533–540.

[24] L.L. Bieber, Carnitine, Annu. Rev. Biochem. 57 (1988) 261–283.

[25] N.R. Marquis, I.B. Fritz, The distribution of carnitine, acetylcarnitine, and carnitine acetyltransferase in rat tissues, J. Biol. Chem. 240 (1965) 2193–2196.

[26] P. Harper, C.E. Elwin, G. Cederblad, Pharmacokinetics of intravenous and oral bolus doses of L-carnitine in healthy subjects, Eur. J. Clin. Pharmacol. 35 (1988) 555–562.

[27] C.J. Rebouche, C.A. Chenard, Metabolic fate of dietary carnitine in human adults: identification and quantification of urinary and fecal metabolites, J. Nutr. 121 (1991) 539–546.

[28] P.G. Welling, J.H. Thomsen, A.L. Shug, F.L. Tse, Pharmacokinetics of L-carnitine in man following intravenous infusion of DL-carnitine, Int. J. Clin. Pharmacol. Biopharm. 17 (1979) 56–60.

[29] T. Uematsu, T. Itaya, M. Nishimoto, Y. Takiguchi, A. Mizuno, M. Nakashima, K. Yoshinobu, T. Hasebe, Pharmacokinetics and safety of L-carnitine infused i.v. in healthy subjects, Eur. J. Clin. Pharmacol. 34 (1988) 213–216.

[30] A. Marzo, G. Cardace, C. Corbelleta, E. Bassani, E. Morabito, E. Arrigoni Martelli, Homeostatic equilibrium of L-carnitine family before and after i.v. administration of propionyl-L-carnitine in humans, dogs and rats, Eur. J. Drug Metab. Pharmacokinet. Spec No 3 (1991) 357–363.

[31] E.P. Brass, C.L. Hoppel, W.R. Hiatt, Effect of intravenous L-carnitine on carnitine homeostasis and fuel metabolism during exercise in humans, Clin. Pharmacol. Ther. 55 (1994) 681–692.

[32] M.A. Mehlman, D.G. Therriault, R.B. Tobin, Carnitine-14C metabolism in choline-deficient, alloxan-diabetic choline-deficient and insulin-treated rats, Metabolism 20 (1971) 100–107.

[33] O.W. Griffith, Mammalian sulfur amino acid metabolism: an overview, Methods Enzymol. 143 (1987) 366–376.

[34] T. Nakagawa, M. Sunamori, A. Suzuki, The myocardial distribution and plasma concentration of carnitine in patients with mitral valve disease, Surg. Today 24 (1994) 313–317.

[35] M.E. Pierpont, D. Judd, I.F. Goldenberg, W.S. Ring, M.T. Olivari, G.L. Pierpont, Myocardial carnitine in end-stage congestive heart failure, Am. J. Cardiol. 64 (1989) 56–60.

[36] L.J. Ruff, L.G. Miller, E.P. Brass, Effect of exogenous carnitine on carnitine homeostasis in the rat, Biochim. Biophys. Acta 1073 (1991) 543–549.

[37] V. Tanphaichitr, P. Leelahagul, Carnitine metabolism and human carnitine deficiency, Nutrition 9 (1993) 246–254.

[38] T.C. Vary, J.R. Neely, Characterization of carnitine transport in isolated perfused adult rat hearts, Am. J. Phys. 242 (1982) H585–592.

[39] D.F. Pauly, S.B. Yoon, J.B. McMillin, Carnitine-acylcarnitine translocase in ischemia: evidence for sulfhydryl modification, Am. J. Phys. 253 (1987) H1557–1565.

[40] M.S. Patel, N.S. Nemeria, W. Furey, F. Jordan, The pyruvate dehydrogenase complexes: structure-based function and regulation, J. Biol. Chem. 289 (2014) 16615–16623.

[41] H. Schoder, R.J. Knight, K.F. Kofoed, H.R. Schelbert, D.B. Buxton, Regulation of pyruvate dehydrogenase activity and glucose metabolism in post-ischaemic myocardium, Biochim. Biophys. Acta 1406 (1998) 62–72.

[42] L. Owen, S.I. Sunram-Lea, Metabolic agents that enhance ATP can improve cognitive functioning: a review of the evidence for glucose, oxygen, pyruvate, creatine, and L-carnitine, Nutrients 3 (2011) 735–755.

[43] S.W. Sauer, J.G. Okun, G.F. Hoffmann, S. Koelker, M.A. Morath, Impact of short- and medium-chain organic acids, acylcarnitines, and acyl-CoAs on mitochondrial energy metabolism, Biochim. Biophys. Acta 1777 (2008) 1276–1282.

[44] S.M. Marcovina, C. Sirtori, A. Peracino, M. Gheorghiade, P. Borum, G. Remuzzi, H. Ardehali, Translating the basic knowledge of mitochondrial functions to metabolic therapy: role of L-carnitine, Transl. Res. 161 (2013) 73–84.

[45] P. Lombardo, R. Scuri, E. Cataldo, M. Calvani, R. Nicolai, L. Mosconi, M. Brunelli,

Acetyl-L-carnitine induces a sustained potentiation of the afterhyperpolarization, Neuroscience 128 (2004) 293–303.

[46] D.M. Bers, S. Despa, Na/K-ATPase—an integral player in the adrenergic fight-or-flight response, Trends Cardiovasc. Med. 19 (2009) 111–118.

[47] T. Kurz, K.A. Yamada, S.D. DaTorre, P.B. Corr, Alpha 1-adrenergic system and arrhythmias in ischaemic heart disease, Eur. Heart J. 12 (Suppl. F) (1991) 88–98.

[48] I. Bodi, G. Mikala, S.E. Koch, S.A. Akhter, A. Schwartz, The L-type calcium channel in the heart: the beat goes on, J. Clin. Invest. 115 (2005) 3306–3317.

[49] M. St-Onge, I. Ajmo, D. Poirier, M. Laliberte, L-Carnitine for the treatment of a calcium channel blocker and metformin poisoning, J. Med. Toxicol. 9 (2013) 266–269.

[50] A. Baartscheer, M.M. van Borren, Sodium ion transporters as new therapeutic targets in heart failure, Cardiovasc. Hematol. Agents Med. Chem. 6 (2008) 229–236.

[51] M.J. Berridge, Inositol trisphosphate and calcium signalling mechanisms, Biochim. Biophys. Acta 1793 (2009) 933–940.

[52] A. Chevrollier, D. Loiseau, P. Reynier, G. Stepien, Adenine nucleotide translocase 2 is a key mitochondrial protein in cancer metabolism, Biochim. Biophys. Acta 1807 (2011) 562–567.

[53] S.V. Pande, T. Goswami, R. Parvin, Protective role of adenine nucleotide translocase in O2-deficient hearts, Am. J. Phys. 247 (1984) H25–34.

[54] J. Roussel, J. Thireau, C. Brenner, N. Saint, V. Scheuermann, A. Lacampagne, J.Y. Le Guennec, J. Fauconnier, Palmitoyl-carnitine increases RyR2 oxidation and sarcoplasmic reticulum Ca2 + leak in cardiomyocytes: role of adenine nucleotide translocase, Biochim. Biophys. Acta 1852 (2015) 749–758.

[55] E. Tousson, E. Hafez, S. Zaki, A. Gad, The cardioprotective effects of L-carnitine on rat cardiac injury, apoptosis, and oxidative stress caused by amethopterin, Environ. Sci. Pollut. Res. Int. 23 (2016) 20600–20608.

[56] W.C. Sternbergh, R.G. Makhoul, B. Adelman, Nitric oxide-mediated, endothelium-dependent vasodilation is selectively attenuated in the postischemic extremity, Surgery 114 (1993) 960–967.

[57] D. Baetz, M. Bernard, C. Pinet, S. Tamareille, S. Chattou, H. El Banani, A. Coulombe, D. Feuvray, Different pathways for sodium entry in cardiac cells during ischemia and early reperfusion, Mol. Cell. Biochem. 242 (2003) 115–120.

[58] M.C. Wellner-Kienitz, K. Bender, A. Rinne, L. Pott, Voltage dependence of ATP-dependent K + current in rat cardiac myocytes is affected by IK1 and IK(ACh), J. Physiol. 561 (2004) 459–469.

[59] A.J. Morash, A.O. Kotwica, A.J. Murray, Tissue-specific changes in fatty acid oxidation in hypoxic heart and skeletal muscle, Am. J. Phys. Regul. Integr. Comp. Phys. 305 (2013) R534–541.

[60] E.J. Lesnefsky, B. Tandler, J. Ye, T.J. Slabe, J. Turkaly, C.L. Hoppel, Myocardial ischemia decreases oxidative phosphorylation through cytochrome oxidase in subsarcolemmal mitochondria, Am. J. Phys. 273 (1997) H1544–1554.

[61] D.F. Pauly, C.J. Pepine, The role of carnitine in myocardial dysfunction, Am. J. Kidney Dis. 41 (2003) S35–43.

[62] F.B. Stephens, D. Constantin-Teodosiu, P.L. Greenhaff, New insights concerning the role of carnitine in the regulation of fuel metabolism in skeletal muscle, J. Physiol. 581 (2007) 431–444.

[63] J. Kerner, P.E. Minkler, E.J. Lesnefsky, C.L. Hoppel, Fatty acid chain elongation in palmitate-perfused working rat heart: mitochondrial acetyl-CoA is the source of two-carbon units for chain elongation, J. Biol. Chem. 289 (2014) 10223–10234.

[64] S. Iliceto, D. Scrutinio, P. Bruzzi, G. D'Ambrosio, L. Boni, M. Di Biase, G. Biasco, P.G. Hugenholtz, P. Rizzon, Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial, J. Am. Coll. Cardiol. 26 (1995) 380–387.

[65] I. Rizos, Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration, Am. Heart J. 139 (2000) S120–123.

[66] E. Helton, R. Darragh, P. Francis, F.J. Fricker, K. Jue, G. Koch, D. Mair, M.E. Pierpont, J.V. Prochazka, L.S. Linn, S.C. Winter, Metabolic aspects of myocardial disease and a role for L-carnitine in the treatment of childhood cardiomyopathy, Pediatrics 105 (2000) 1260–1270.

[67] H. Lemieux, S. Semsroth, H. Antretter, D. Hofer, E. Gnaiger, Mitochondrial respiratory control and early defects of oxidative phosphorylation in the failing human heart, Int. J. Biochem. Cell Biol. 43 (2011) 1729–1738.

[68] H. Ashrafian, M.P. Frenneaux, L.H. Opie, Metabolic mechanisms in heart failure, Circulation 116 (2007) 434–448.

[69] R. Ventura-Clapier, A. Garnier, V. Veksler, F. Joubert, Bioenergetics of the failing heart, Biochim. Biophys. Acta 1813 (2011) 1360–1372.

[70] N. Stride, S. Larsen, M. Hey-Mogensen, K. Sander, J.T. Lund, F. Gustafsson, L. Kober, F. Dela, Decreased mitochondrial oxidative phosphorylation capacity in the human heart with left ventricular systolic dysfunction, Eur. J. Heart Fail. 15 (2013) 150–157.

[71] M.N. Sack, T.A. Rader, S. Park, J. Bastin, S.A. McCune, D.P. Kelly, Fatty acid oxidation enzyme gene expression is downregulated in the failing heart, Circulation 94 (1996) 2837–2842.

[72] B. Gremmler, M. Kunert, H. Schleiting, K. Kisters, L.J. Ulbricht, Relation between N-terminal pro-brain natriuretic peptide values and invasively measured left ventricular hemodynamic indices, Exp. Clin. Cardiol. 8 (2003) 91–94.

[73] T. Ogawa, J.P. Veinot, M.L. Kuroski de Bold, T. Georgalis, A.J. de Bold, Angiotensin II receptor antagonism reverts the selective cardiac BNP upregulation and secretion observed in myocarditis, Am. J. Physiol. Heart Circ. Physiol. 294 (2008) H2596–2603.

[74] E. Oyanagi, H. Yano, M. Uchida, K. Utsumi, J. Sasaki, Protective action of L-carnitine on cardiac mitochondrial function and structure against fatty acid stress, Biochem. Biophys. Res. Commun. 412 (2011) 61–67.

[75] A.A. Strilakou, A.C. Lazaris, A.I. Perelas, I.S. Mourouzis, I. Douzis, P.L. Karkalousos, A.T. Stylianaki, C.I. Pantos, C.A. Liapi, Heart dysfunction induced by choline-deficiency in adult rats: the protective role of L-carnitine, Eur. J. Pharmacol. 709 (2013) 20–27.

[76] N. Derin, V.N. Izgut-Uysal, A. Agac, Y. Aliciguzel, N. Demir, L-Carnitine protects gastric mucosa by decreasing ischemia-reperfusion induced lipid peroxidation, J. Physiol. Pharmacol. 55 (2004) 595–606.

[77] S. Savitha, B. Naveen, C. Panneerselvam, Carnitine and lipoate ameliorates lipofuscin accumulation and monoamine oxidase activity in aged rat heart, Eur. J. Pharmacol. 574 (2007) 61–65.

[78] D. O'Brien, P. Chunduri, A. Iyer, L. Brown, L-Carnitine attenuates cardiac remodelling rather than vascular remodelling in deoxycorticosterone acetate-salt hypertensive rats, Basic Clin. Pharmacol. Toxicol. 106 (2010) 296–301.

[79] Y. Omori, T. Ohtani, Y. Sakata, T. Mano, Y. Takeda, S. Tamaki, Y. Tsukamoto, D. Kamimura, Y. Aizawa, T. Miwa, I. Komuro, T. Soga, K. Yamamoto, L-Carnitine prevents the development of ventricular fibrosis and heart failure with preserved ejection fraction in hypertensive heart disease, J. Hypertens. 30 (2012) 1834–1844.

[80] G. Martinez, G. Costantino, A. Clementi, M. Puglia, S. Clementi, G. Cantarella, L. De Meo, M. Matera, Cisplatin-induced kidney injury in the rat: L-carnitine modulates the relationship between MMP-9 and TIMP-3, Exp. Toxicol. Pathol. 61 (2009) 183–188.

[81] L. Zhou, S. Cortassa, A.C. Wei, M.A. Aon, R.L. Winslow, B. O'Rourke, Modeling cardiac action potential shortening driven by oxidative stress-induced mitochondrial oscillations in guinea pig cardiomyocytes, Biophys. J. 97 (2009) 1843–1852.

[82] R.A. Jacobs, A.K. Meinild, N.B. Nordsborg, C. Lundby, Lactate oxidation in human skeletal muscle mitochondria, Am. J. Physiol. Endocrinol. Metab. 304 (2013) E686–694.

[83] S. Neubauer, The failing heart—an engine out of fuel, N. Engl. J. Med. 356 (2007) 1140–1151.

[84] M. Mayr, S. Yusuf, G. Weir, Y.L. Chung, U. Mayr, X. Yin, C. Ladroue, B. Madhu, N. Roberts, A. De Souza, S. Fredericks, M. Stubbs, J.R. Griffiths, M. Jahangiri, Q. Xu, A.J. Camm, Combined metabolomic and proteomic analysis of human atrial fibrillation, J. Am. Coll. Cardiol. 51 (2008) 585–594.

[85] M.S. Sabatine, E. Liu, D.A. Morrow, E. Heller, R. McCarroll, R. Wiegand, G.F. Berriz, F.P. Roth, R.E. Gerszten, Metabolomic identification of novel biomarkers of myocardial ischemia, Circulation 112 (2005) 3868–3875.

[86] R. Jaimes III, S. Kuzmiak-Glancy, D.M. Brooks, L.M. Swift, N.G. Posnack, M.W. Kay, Functional response of the isolated, perfused normoxic heart to pyruvate dehydrogenase activation by dichloroacetate and pyruvate, Pflugers Arch. 468 (2016) 131–142.

[87] B.O. Schonekess, M.F. Allard, G.D. Lopaschuk, Propionyl L-carnitine improvement of hypertrophied rat heart function is associated with an increase in cardiac efficiency, Eur. J. Pharmacol. 286 (1995) 155–166.

[88] J. McHowat, K.A. Yamada, J. Wu, G.X. Yan, P.B. Corr, Recent insights pertaining to sarcolemmal phospholipid alterations underlying arrhythmogenesis in the ischemic heart, J. Cardiovasc. Electrophysiol. 4 (1993) 288–310.

[89] M.T. Ziolo, S.R. Houser, Abnormal Ca(2 +) cycling in failing ventricular myocytes: role of NOS1-mediated nitroso-redox balance, Antioxid. Redox Signal. 21 (2014) 2044–2059.

[90] J. Prestle, P.M. Janssen, A.P. Janssen, O. Zeitz, S.E. Lehnart, L. Bruce, G.L. Smith, G. Hasenfuss, Overexpression of FK506-binding protein FKBP12.6 in cardiomyocytes reduces ryanodine receptor-mediated Ca(2 +) leak from the sarcoplasmic reticulum and increases contractility, Circ. Res. 88 (2001) 188–194.

[91] V.P. Kuriachan, G.L. Sumner, L.B. Mitchell, Sudden cardiac death, Curr. Probl. Cardiol. 40 (2015) 133–200.

[92] G. Boriani, D. Pettorelli, Atrial fibrillation burden and atrial fibrillation type: clinical significance and impact on the risk of stroke and decision making for long-term anticoagulation, Vasc. Pharmacol. 83 (2016) 26–35.

[93] L. Fu, M. Huang, S. Chen, Primary carnitine deficiency and cardiomyopathy, Korean Circ. J. 43 (2013) 785–792.

[94] X. Rousset, B. Vaisman, M. Amar, A.A. Sethi, A.T. Remaley, Lecithin: cholesterol acyltransferase—from biochemistry to role in cardiovascular disease, Curr. Opin. Endocrinol. Diabetes Obes. 16 (2009) 163–171.

[95] L. Patmore, G.P. Duncan, M. Spedding, Interaction of palmitoyl carnitine with calcium antagonists in myocytes, Br. J. Pharmacol. 97 (1989) 443–450.

[96] M. Karmazyn, The 1990 Merck Frosst Award. Ischemic and reperfusion injury in the heart. Cellular mechanisms and pharmacological interventions, Can. J. Physiol. Pharmacol. 69 (1991) 719–730.

[97] A.H. Kulier, L.A. Turner, S. Vodanovic, S. Contney, D.A. Lathrop, Z.J. Bosnjak, Multiple agents potentiate alpha1-adrenoceptor-induced conduction depression in canine cardiac purkinje fibers, Anesthesiology 92 (2000) 1713–1721.

[98] M.A. Kluge, J.L. Fetterman, J.A. Vita, Mitochondria and endothelial function, Circ. Res. 112 (2013) 1171–1188.

[99] S. Wan, A.P. Yim, Cytokines in myocardial injury: impact on cardiac surgical approach, Eur. J. Cardiothorac. Surg. 16 (Suppl. 1) (1999) S107–111.

[100] J. Bauersachs, J.D. Widder, Endothelial dysfunction in heart failure, Pharmacol. Rep. 60 (2008) 119–126.

[101] W. Elabbassi, M.A. Chowdhury, A.A. Fachtartz, Severe reversible myocardial injury associated with aluminium phosphide toxicity: a case report and review of literature, J. Saudi Heart Assoc. 26 (2014) 216–221.

[102] P.L. Giudice, M. Bonomini, A. Arduini, A moderate carnitine deficiency exacerbates isoproterenol-induced myocardial injury in rats, Cardiovasc. Drugs Ther. 30 (2016) 119–127.

[103] J. Kahn, S. Lagakos, M. Wulfsohn, D. Cherng, M. Miller, J. Cherrington, D. Hardy, G. Beall, R. Cooper, R. Murphy, N. Basgoz, E. Ng, S. Deeks, D. Winslow, J.J. Toole,

D. Coakley, Efficacy and safety of adefovir dipivoxil with antiretroviral therapy: a randomized controlled trial, JAMA 282 (1999) 2305–2312.

[104] O.A. Alshabanah, M.M. Hafez, M.M. Al-Harbi, Z.K. Hassan, S.S. Al Rejaie, Y.A. Asiri, M.M. Sayed-Ahmed, Doxorubicin toxicity can be ameliorated during antioxidant L-carnitine supplementation, Oxidative Med. Cell. Longev. 3 (2010) 428–433.

[105] A. Mate, J.L. Miguel-Carrasco, C.M. Vazquez, The therapeutic prospects of using L-carnitine to manage hypertension-related organ damage, Drug Discov. Today 15 (2010) 484–492.

[106] M.M. Sayed-Ahmed, T.M. Salman, H.E. Gaballah, S.A. Abou El-Naga, R. Nicolai, M. Calvani, Propionyl-L-carnitine as protector against adriamycin-induced cardiomyopathy, Pharmacol. Res. 43 (2001) 513–520.