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Complementary supportive cardiac rehabilitation

Abstract

Aim: Physical training increases cardiac exercise capacity, but generally does not affect cardiac function.

Since energy metabolism is closely linked to cardiac function, we assessed the impact of the integrative metabolic approach on the cardiac function during cardiovascular rehabilitation.

Our concept was not to act on one specific enzyme, protein or particular metabolic pathway, but "to improve the flux" supporting normal mechanisms for energy production without increased generation of mitochondrial reactive oxygen species.

Methods: 3 weeks exercise training was undertaken on an upright bicycle ergometer in 30 complementary supportive cardiac rehabilitation sessions. Before each exercise training the patients received magnesium, niacin, coenzyme Q10, biotin, glutathione, vitamin E, thiamine diphosphate, riboflavin, pantothenic acid, pyridoxal, and beta-carotene. Following the exercise training the patients inhaled 95% oxygen 4 l/min provided by oxygen concentrator with ionization lying inside a low frequency pulsed electromagnetic field with intensity of up to 30 microtesla. After oxygen inhalation, the patients received carnitine, arginine, NADH, lipoic acid, selenium, and vitamin C. A cardiopulmonary echocardiograpy exercise test was performed at the start and the end of the three-week session and the patients were asked to evaluate the visual analogue scale.

Results: Arithmetic means of most Ergospiro echocardiographic parameters are lower before and higher after rehabilitation. Exceptions are the values VE/VC02, VD/VT, BR and E/e', where the ratio of arithmetic means is reversed. The correlation coefficients for all 20 pairs of cardiopulmonary echocardiographic variables before and after rehabilitation range from 0, 568 to 0, 952. Most of them are closer to the number 1, that is, most of them show a strong positive association. p values are less than 0, 05 for all 20 pairs of cardiopulmonary echocardiographic variables This means that CSCR statistically significantly improved the results of measurement compared to the results before the rehabilitation.

Conclusion: supporting normal mechanisms/pathways/ for energy production might be the way of supporting cardiac function during cardiac rehabilitation.

Keywords: cardiac rehabilitation, complementary supportive cardiac therapy

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Abbreviations: PDC, pyruvate dehydrogenase complex; TCA cycle, tricarboxylic acid cycle;NEFA, nonesterified fatty acids; PEMF, pulsed electromagnetic field; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AC, adenylate cyclase; CoA, coenzyme A; NAD, nicotinamide adenine dinucleotide; FAD, flavin adenine dinucleotide; ThDP, thiamine diphosphat

Introduction

Prolonged period of exercise training can lead to impressive increase in cardiac exercise capacity but the contribution of cardiac responses is less clear.[1-3] The improvement in functional capacity observed in the training group seems to be related to peripheral factors rather than in central cardiovascular performance./1, 2/ Exercise has a favourable effects on endothelial function,[4] strengthens muscles[5] enhances skeletal muscle aerobic metabolism,[6] reverses resting neuroendocrine hyperactivity in heart failure patients.[6,7] Exercise causes the release of myokines from skeletal muscle, increases mitochondrial biogenesis, improves fatty acid oxidation[8] and increases the availability of nitric oxide.[9] Some studies have shown improvement in V02peak after exercise training[1,5] but others have not.[2,4]

Hambrecht et al have reported favourable effects on remodeling, considering the improvements in LV stroke volume and decrease in LV end diastolic diameter and volume as secondary effects of exercise therapy related to improved peripheral vasodilation.[6] Platt C et al.[10] highlight vascular response associated with improved cardiac function during chronic exercise.

The contribution of myocardial function to the training response, and indeed the benefits of training on myocardial performance have been debated.[1]

Since the energy metabolism is closely linked to cardiac function[11] we assessed impact of the metabolic support on cardiac function during cardiovascular rehabilitation.

We assumed that cardiac metabolic therapeutic approach must be integrative, improving the complete substrate oxidation, i.e. supporting normal mechanism of energy production without increased generation of reactive oxygen species.

Complementary supportive cardiac rehabilitation

The work load on the bicycle started with 50% of the peak work load from the cardiopulmonary echocardiography exercise test, and then gradually increased by either 10 or 15 W/min. Heart rate and rhythm were recorded continuously by 12-lead ECG and blood pressure was measured automatically at the 2 minutes interval. Exercise was symptom, blood pressure, heart rate and arrhythmias limited. Before each exercise training the patients received magnesium, niacin, coenzyme Q10, biotin, glutathione, vitamin E, thiamine diphosphate, riboflavin, pantothenic acid, pyridoxal and beta carotene. Immediately after supervised exercise training patients were

inhaling 95% oxygen 4 l/min provided by oxygen concentrator with ionization/Oxicur 5000 ion S/using face mask. At the same time the patients were lying inside a low -frequency pulsed electromagnetic field with intensity of up to 30 microtesla/QRS 101/. After oxygen inhalation patients received carnitine, arginine, NADH, lipoic acid, selenium, and vitamin C. (Figure 1)

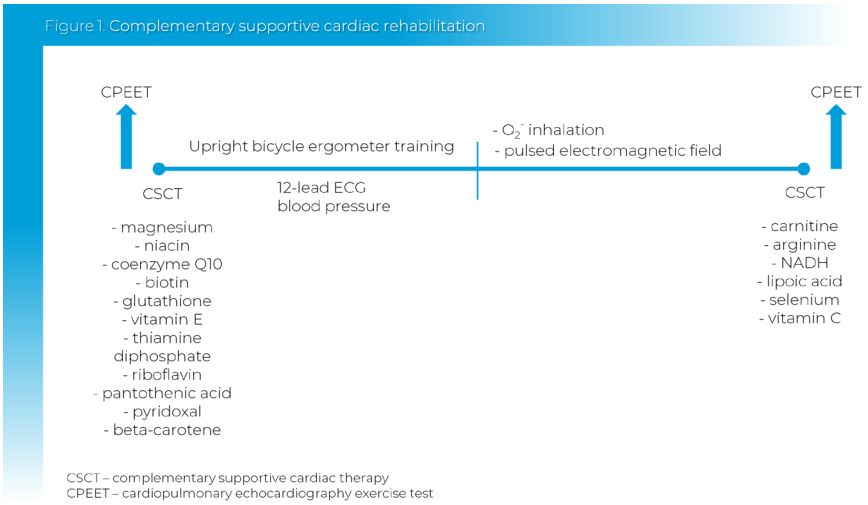

Figure 1 Complementary supportive cardiac rehabilitation

A cardiopulmonary echocardiograpy exercise test was performed on an upright bicycle ergometer/Schiller 911 S/ with 1-minute increase/either 10 or 15 Watts/min/ in work rate, at the start and end of the three-week metabolic exercise training.

Ergospirometric system was based on the AT-104 ECG, with Ganshorn LF8 Power Cube gas analyser/Schiller/. A continuous single breath stroke analysis was carried out for recording the volume of oxygen uptake/V02/, volume of carbon dioxide output/VC02/ and Minute Ventilation/VE/. Additional parameters such as peak V02, aerobic threshold, max 02 pulse, delta V02/delta WR, PETC02, VE/VC02 slope, VD/VT, RER and breathing reserve/BR/were analyzed. Peak V02 was defined as the V02 value relative to body weight in ml/min/kg, and as the highest 30 s average during the last 60 s of exercise. Gas analyzers and flow probes were calibrated before each test. There was continuous ECG monitoring and blood pressure was measured automatically at the 2 minutes interval. Exercise data were stored on disk and analysed off-line/SDS-104 Program.

Patients were imaged in the supine left lateral position using a commercially available system/Vivid E 95, General Electric Healthcare, Milwaukee, WI, USA/in the three standard apical views. We used hybrid technique combining TVI and 2D strain. 2D gray scale images were obtained at a frame rate of 55-90 frames/s and Colour Doppler images were saved with a colour frame rate of 100-140 frames/s. Measurement is performed off –line.

Systolic velocities, strain rate and end systolic strain were obtained by locating the sample volume in the mid anteroseptal, basal inferno-lateral, and mid inferior segment. Early diastolic velocities were analysed separately in the middle of the basal lateral and basal septal segments.

Key parameters of global cardiac performance were EF, SV and GLS.

EF and LV volumes were assessed by 4D bi-plane volume measurement using full matrix array with manually traced endocardial borders including trabeculae and the papillary muscles. All the echocardiographic assessments were interpreted by one cardiologist.

Health status was evaluated using the visual analogue scale with a grade ranging from 0/the worst possible health status/ to 100/the best possible health status.[12]

Statistical analysis were performed using programme SPSS Statistics for Windows version 25. The values of p<0, 05 were considered statistically significant.

Results

Baseline patient's characteristics are listed in Table 1.

Table 1 Baseline characteristics of patients before 30 sessions of the complementary supportive cardiac rehabilitation

Age (years)/mean ± ISD	64,1±7,2
Male gender (%)	60
AETIOLOGY (%)	
Ischemic heart disease	17
Cardiomyopathia	5
Artificial aortic value	3
Arterial hypertension	5
Medication (%)	
ACE-I	11
ARBs	7
Beta Blockers	22
Nitrates	9
Digitalis	2
Amiodarone	1
Oral anticoagulants	2
Anti platelets	17
Atrial fibrillation	2
EF (%) (mean + ISD)	54,5±6,1
SR I/S (mean +ISD)	-0,28±0,05
Peak V02 ml/kg/min (mean +ISD)	11,8±3,8
dV02 /dWR ml/mm/W	8,1±2,9
Visual analogue scale	11

EF, ejection fraction; ACE- I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; SR, strain rate; Peak $V0_2$, highest oxygen uptake; dVO_2dWR, oxygen uptake related to work increase

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All patients have completed the study, and exercise program compliance was 100%. Arithmetic means of most Ergospiro echocardiographic parameters are lower before and higher after rehabilitation. Exceptions are the values VE/VC02, VD/VT, BR and E/e', where the ratio of arithmetic means is reversed. The correlation coefficients for all 20 pairs of cardiopulmonary echocardiographic variables before and after rehabilitation range from 0, 568 to 0, 952. Most of them are closer to the number 1, that is, most of them show a strong positive association. p values are less than 0, 05 for all 20 pairs of cardiopulmonary echocardiographic variables.

Table 2 Cardiopulmonary echocardiography exercise test values before and after 30 complementary supportive cardiac rehabilitation sessions

	Arithmetic mean		Correlation coefficient	t value	p value
	Before	After			
Duration, sec	371	469	0,939	-6,368	<0,001***
Load, W	74	95	0,941	-3,942	<0,001***
Peak V02 ml/ kg/ min	11,8	13,9	0,928	-4,824	<0,001***
Peak V02 (%)	52,3	59,8	0,834	-3,750	0,002**
ATV02 ml/ kg/ min	8,8	11,1	0,801	-4,102	0,001***
d VO_2 W R ml/min/W	8,1	11,2	0,635	-3,781	0,001***
02 pulse ml/beat t	9,4	11,6	0,834	-3,214	0,005**
Peak R ER	0,98	1,01	0,673	-2,334	-0,033*
PET C02 mmHg	33,9	37,12	0,618	-2,768	0,012*
VE/VC02 slope	34,1	24,9	0,628	5,994	<0,001***
VD/VT	0,32	0,23	0,568	3,482	0,003**

- statistical significance up to 5%, ** - statistical significance up to 1%, *** - statistical significance up to 0,1%

Table 2a Cardiopulmonary echocardiography exercise test values before and after 30 complementary supportive cardiac rehabilitation sessions

	Arithmetic mean		Coefficient	t value	p value
	Before	After			
BR (%)	53	41	0,912	4,817	<0,001***
VE l/m in	34,8	39,9	0,952	-3,840	<0,001***
LVEF %	54,5	62,8	0,828	-6,281	<0,001***
LVSV ml	52,8	64,2	0,712	-6,334	<0,001***
LV GLS%	-16,2	-16,9	0,756	2,783	0,017*
Vs cm/sec	3,73	4,38	0,891	-4,931	<0,001***
SR 1/S	-0,28	-0,38	0,878	-4,021	0,001***
Ve' cm/s	6,82	7,96	0,889	-5,683	<0,001***
E/e'	12,1	9,04	0,838	4,321	0,001***
VAS	63,72	84,3	0,881	-4,328	<0,001***

- statistical significance up to 5%, ** - statistical significance up to 1%, *** - statistical significance up to 0,1% PV02, highest oxygen uptake, ATV02 oxygen uptake at anaerobic threshold; $dV0_2/dWR$, oxygen uptake related to work increase, p02 pulse. oxygen pulse at peak exercise; pRER, peak respiratory exchange ratio; PETC02, end-tidal partial pressure of carbon dioxide; VENC02 slope, minute ventilation to carbon dioxide output slope; pVD/VT dead space/tidal volume ratio; BR, breathing reserve; EF, ejection fraction; SV, stroke volume; GLS, lobal longitudinal strain; Vs, systolic myocardial velocity; SR, strain rate; Ve. Early mitral diastolic annular velocity; E/e, LV, filling pressure; LV, left ventricular; VAS, visual analogue scale

This means that complementary supportive cardiac rehabilitation statistically significantly improved the results of measurement compared to the results before the rehabilitation.

Discussion

Apart from reducing numerous cardiovascular risk factors including diabetes mellitus, hyperlipidemia and hypertension chronic exercise evokes important molecular, structural, and functional changes.[10] Responses of the heart to chronic exercise can be organ-level reponses, cellular reponses and response in signaling pathways.

Cardiac remodeling at the tissue level caused by exercise training can increase left ventricular mass by 20% or more. Exercise-induced "physiological hypertrophy" is believed to be cardioprotective while disease-associated "pathological hypertrophy" is part of an adverse remodeling process including cardiac fibrosis, electrical remodeling, and activation of a fetal gene program.[10] Exercise improves cardiomyocite contractility and Ca2+ sensitivity.[13] Powering this contractile activity requires chemical energy. Normally, 70% to 90% of cardiac ATP is produced by the oxidation of fatty acids, which is the pivotal process for the heart's energy production.[14] During pathological remodeling of the heart cardiomyocytes revert to a fetal metabolic state, reducing metabolism of fatty acids and shifting back toward glycolisis as the primary pathway for energy production.[15] Most approaches that are used to manipulate myocardial energy metabolism involve either stimulating glucose metabolism or inhibiting fatty acid metabolism.[16]

In our study we accepted the general concept that the flux through energy-providing pathways determines the functional state of the tissue.[11]

Our concept was not to act on one specific enzyme or protein or particular pathway but "to improve the flux" supporting normal mechanism of energy production without increased generation of mitochondrial reactive oxygen species.

Regulation and control of flux through a metabolic pathway is a shared property of many different intra- and extracellular effectors and cannot be achieved by any single enzyme acting in isolation. In addition to product inhibition there are other factors which need to be taken into account such as the overall activity of the enzyme and availability of cofactors for the reaction.[11] (Scheme 1)

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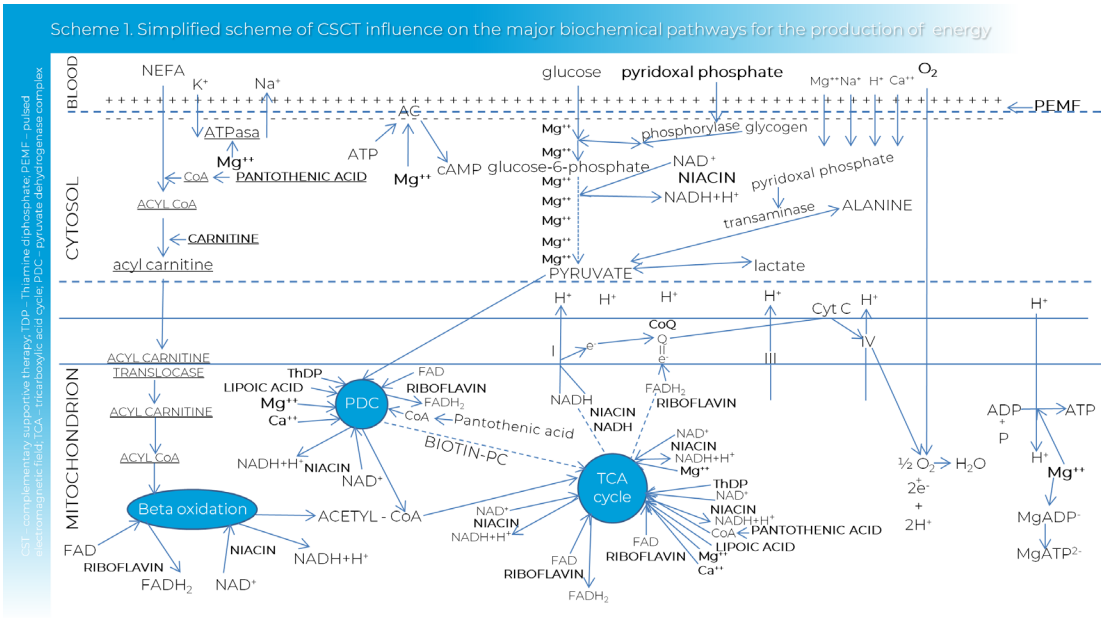

Scheme 1 Simplified scheme of CSCT influence on the major biochemical pathways for the production of energy

The mammalian heart is an obligate aerobic organ. The principal purpose of oxygen respiration and the principal use of breathed in oxygen is to generate ATP in oxidative phosphorylation. Oxygen serves as the terminal electron acceptor in the electron transport chain, and in the absence of sufficient oxygen, electron transport ceases and cardiac energy demands are not met, i.e. there is no regeneration of ATP.[17] Oxidative phosphorylation, quantitatively the main source of ATP,[11] depends on the production of reducing equivalents and the passage of electrons along the respiratory chain. The oxidative phosphorylation is under triple control, i.e. by ADP, oxygen and substrate.[17,18]

In the normal myocardium the production of ATP is strictly coupled to the myocardial oxygen consumption.[19] The release of the protons and entry of the electrons into electron transport chain is dependent on oxygen consumption. Oxygen uptake during exercise is inextricably linked to increased rates of high-energy phosphate utilization.[20] Force and velocity development of the myocite are tightly correlated with ATP utilization and oxygen consumption.[21] So, oxygen consumption and ATP regeneration are two processes mutually dependant and inseparable. The relative concentration of ADP in the cytosol control not only the rate of electron transport and oxidative phosphorylation, but also the turnover rate of the citric acid cycle, the rate of pyruvate oxidation and glucose utilization. Thus, whenever hydrolysis of ATP is increased, a whole sequence of enzyme-catalyzed reactions and transport mechanisms is set into motion.[11]

Our patients inhaled 95% negatively ionized oxygen, 4 l/min using face mask for ½ hour. Ionized oxygen inhalation therapy is at the same time oxygen inhalation therapy and ionization therapy where oxygen serves as an ions carrier.[22]

Beyond its indispensable role in cardiac energy metabolism oxygen plays a central role in other biological processes that can be determinants of cardiac function, including the generation of ROS, the generation of NO and the determination of cardiac gene expression patterns. However, the role of oxygen and oxygen-associated processes in the heart is complex. Oxygen can be both vital and deleterious contributing to cardiac dysfunction and death.[17] The dark side of oxygen relates to the fact that each oxygen atom has one unpaired electron in its outer valence shell, and molecular oxygen has two unpaired electrons. Thus atomic oxygen is a free radical and molecular oxygen is a/free/ bi-radical. Concerted tetravalent reduction of oxygen by the mitochondrial electron-transport chain is considered to be a relatively safe process; however, the univalent reduction of oxygen generates reactive intermediates. When ROS, a normal by-product of cellular aerobic metabolism overwhelms cellular antioxidant defences, the result is lipid peroxidation of the cell membrane and of the membranes of cellular organelles.[23] Animal studies have delineated that antioxidants and ROS defense pathways can ameliorate ROS-mediated cardiac abnormalities.[24] In our complementary supportive cardiac therapy we counterbalanced the increased generation of mitochondrial ROS using intracellular antioxidant molecules such as coenzyme Q, vitamin E, vitamin C, beta-carotene, glutathione, and lipoic acid.[17,25]

Coenzyme Q is the electron carrier in mitochondrial electron transport, i. e. redox coenzyme of the respiratory chain and has a possible role as an antioxidant.[26]

Vitamin E protects cell membranes from oxidation and breaks the chain of oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reactions. The importance of peroxyl radical scavenger function is to maintain the integrity of long-chain polyunsaturated fatty acids in the membranes of cells and thus maintain their bioactivity.[25,27]

Vitamin C functions as an enzyme substrate and/or a cofactor in many enzymatic reactions that mediate a variety of essential biological functions. As a powerful antioxidant, it donates electrons to various enzymatic and non-enzymatic reactions, counteracting the action of superoxide radicals and other ROS.[28]

Glutathione as a major antioxidant with the ability to scavange free radicals acts as a reducing substrate for the enzymatic activity of glutathione peroxidase.[17] Selenium functions as cofactor for reduction of antioxidant enzymes, such as glutathione peroxidases.[29] As a potent antioxidant lipoic acid may scavenge hydroxyl radicals, peroxyl radicals and singlet oxygen and increase intracellular glutathione.[30]

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Beta-carotene can quench singlet oxygen and react directly with free radicals, especially peroxyl radicals, which cause lipid peroxidation, and thus helping to minimize damage to cells.[31]

In most instances substrate availability, product removal and enzyme activity are the main factors which control the rate of a biochemical reactions.[11] So, apart from using supplements as antioxidant molecules, we applied them as coenzymes/cofactors in substrate oxidation reactions vital for energy production and as enzyme substrates.

Carnitine performs a number of essential intracellular and metabolic functions and has a fundamental role in the transport of long-chain fatty acids across the inner mitochondrial membrane. Having direct control over the rate of production of acetyl-CoA for TCA cycle, carnitine may indirectly help regulate the rate of glycolysis by increasing the activity of pyruvate dehydrogenase. Incomplete FA oxidation may result in intracellular accumulation of an intermediate of fatty acid metabolism.[32]

Oxidative decarboxylation of pyruvate that assumes a central position in the regulation of fuel supply to the heart, is catalyzed by the multienzyme complex pyruvate dehydrogenase. Pyruvate dehydrogenase complex requires the sequential action of three different enzymes and five different coenzymes or prosthetic groups. These are thiamine diphosphate, lipoic acid, CoA, FAD and NAD.[11]

Thiamine diphosphate, a metabolically active thiamine derivative works as a coenzyme in many enzymatic reactions such as as a pyruvate dehydrogenase complex and alpha keto glutarate dehydrogenase complex. These reactions are instrumental in generating energy. Reduction or inhibition of the reactions diminish synthesis of ATP. In advanced cases of ThDP deficiency heart failure may occur.[28] Alpha-Lipoic acid functions as a prostethic group in mitochondrial alpha-keto acid dehydrogenase complexes including pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase reactions and as such plays a fundamental role in metabolism. Lipoic acid is required for cell growth, mitochondrial activity, and coordination of fuel metabolism.[33]

Pantothenic acid is used in the synthesis of coenzyme A. Pantothenic acid joins thiamine, riboflavin, and niacin in the oxidative decarboxylation of pyruvate and alpha-ketoglutarate.[28] Riboflavin functions as a precursor of coenzymes FAD and FMN for hydrogen or electron transfer. The active forms of riboflavin-flavin adenine dinucleotide function as coenzymes for a variety of oxidative enzyme reactions: in the electron transport chain, the citric acid cycle, beta-oxidation, and pyruvate oxidation. In the oxidative decarboxylation of pyruvate and alpha ketoglutarate, FAD serves as an intermediate electron carrier, with NADH being the final reduced product.. Niacin and niacinamid are precursors of the coenzymes NAD and NADP which act as hydrogen donors or electron acceptors being involved in dehydrogenation reactions. The major role of NADH is to transfer its electrons from metabolic intermediates through the electron transport chain, thereby producing ATP. Niacin is involved in DNA repair as the precursor for nicotinamide adenine dinucleotide.[28,34]

Pyridoxal phosphate functions as a coenzyme for over 100 enzymes, the majority of which are involved in nutrient metabolism. Pyridoxal phosphate is a coenzyme in reactions involving amino acids and coenzyme of glycogen phosphorylase where it is used to break down glycogen.[28]

Biotin, as carboxylase coenzyme, is a carrier for the transfer of "activated bicarbonate" to substrate. Pyruvate carboxylase catalyses the HCO_3- and MgATP-dependent carboxylation of pyruvate to form oxaloacetate. This reaction is considered to play an important anaplerotic role in numerous biological processes. Biotin-dependent carboxylases are widely distributed in nature and have important functions in fatty acid metabolism, amino acid metabolism, carbohydrate metabolism, polyketide biosynthesis, urea utilization, and other cellular processes. These reactions are vital for energy production.[28]

Arginine is a conditionally essential alfa amino acid that is used in the biosynthesis of proteins. It is the immediate precursor of the synthesis of nitric oxide, an intercellular messenger which regulates vasodilation.[35]

Magnesium, the second most abundant intracellular cation is a cofactor for about 300 hundred magnesium activated enzymes. Magnesium is involved in energy production, i. e in ATP metabolism, in glycolysis, oxidative decarboxylation, oxidative phosphorylation, and TCA cycle. Magnesium plays a pivotal role in the reactions of ATP synthase, the central bioenergetics engine. The ATP molecule is usually biologically active in a chelate with a magnesium ion. The Mg2+concentration, remarkably constant and low in the cytosol and tenfold higher in the mitochondrial matrix, mediates ADP/ATP exchange between the cytosol and matrix, MgADP-dependent mitochondrial ATP synthase activity, and cytosolic free ADP homeostasis. After 2 weeks of Mg starvation, cell growth stops and respiration is decreased.[36-40]

The cell membrane is the place where low-frequency pulsed electromagnetic field/PEMF/ interacts within the cell, having a direct action on voltage-gated channels and affecting electrical properties of membranes and their permeability characteristics. PEMF causes cell membrane potential to depolarize by external changes in ion concentration, The construction of a negative cell potential is mainly attributed to the Na-K-ATPase, which is affected by a low–frequency pulsed electromagnetic field.[41,42] Protons can down their concentration gradient only with the help of channel proteins that form hydrophilic tunnels across the membrane.[41] Low-frequency PEMF increases the transport of ions of hydrogen, calcium, sodium, potassium, chlorine and magnesium moving both positive and negative ions in the same directions. Ions stream into the cell and can act on many other pathways and organelles.[41,42] By increasing the entry of Ca++ ions PEMF has an important role in intracellular processes and muscle contraction. Calcium++ and Magnesium ++ both inhibit the kinase and activate the phosphatase reaction, i.e. lead to activation of pyruvate dehydrogenase complex.[11] Ca++by activating isocitrate dehydrogenase and alfa-ketoglutarate dehydrogenase, is used as a regulator in the citric acid cycle and it increases flux through pathway.[43] PEMF increases the oxygen saturation of haemoglobin and significantly increases the diffusion of oxygen in tissues.[42] PEMF elicits non-toxic amount of ROS.[44]

Conclusion

Although our study has relatively small sample size we may say that complementary supportive cardiac rehabilitation improves both cardiac function and cardiac functional capacity. Supporting normal mechanism/pathways/ of energy production might be the way of supporting cardiac function.

Acknowledgments

None

Conflicts of interest

Authors declare that there is no conflicts of interest

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