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Research Article

Integrative Metabolic Therapeutic Approach for Symptomatic Patients with Left Ventricular Dilatation and Reduced Ejection Fraction

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ABSTRACT

Aim: Myocardial energetics has a central role in the pathophysiology of heart failure. Our hypothesis was that cardiac metabolic therapeutic approach must be integrative, improving both the substrate utilization and the complete substrate oxidation, i.e. supporting normal mechanism of energy production without increased generation of reactive oxygen species. Since the energy metabolism is closely linked to cardiac function, we assessed the effect of the integrative metabolic approach on the functional ability and quality of life in patients with heart failure and reduced ejection fraction HFrEF.

Methods and results: We investigated 33 patients with left ventricular dilatation LVIDd> 60 mm and reduced ejection fraction EF<40% in 76 complementary supportive therapy CST periods. Prior to each CST period, therapy was optimized OMT for one month. CST consisted of a 10-day session. In addition to OMT, the patients were treated with carnitine, L-arginine, magnesium, vitamin B, coenzyme Q-10, vitamin E, vitamin C and selenium while lying for 30 minutes inside a pulsed electromagnetic field with intensity of up to 30 micro teslas and inhaling negatively ionized oxygen. Before and after each CST period, patients were asked to evaluate the quality of life using the Minnesota Living with Heart Failure Questionnaire MLHFQ and the visual analogue scale VAS and the EF,LVIDd and NYHA classes were determined. Statistical analysis was based on the t-test, Spearman's rank correlation coefficient and Wilcoxon's signed-ranks test. The longest observation period was 122 months.

After administering the metabolic supportive therapy, a statistically significant improvement $p<0.05$ was noticed in particular items of the MLHFQ, in emotional and physical dimensions. The values of VAS and EF increased whereas the values of NYHA and LVIDd decreased significantly $p<0.001$.

Keywords: HFrEF; Integrative metabolic approach; Complementary supportive therapy.

INTRODUCTION

Heart failure, a life threatening symptomatic syndrome, is usually caused by a myocardial abnormality, even though abnormalities of the valves, pericardium, endocardium, heart rhythm and conduction can also cause HF [1]. Cardiac metabolism occupies a central position in the pathophysiology of HF [2,3] .Metabolic alterations during heart failure, termed metabolic remodeling, are characterized by a shift away from energy production, and along with ATP depletion, they induce other processes, such as structural remodeling and oxidative stress [2]. ATP is the immediate fuel for the heart pump and perturbations in ATP-generating processes result in ATP deficiency affecting the contractile function directly [3]. Genetic studies have shown that a fully integrated metabolic machine is important for normal cardiac function and that selective ablation of components of energy metabolism can cause early or advanced heart failure [4]. Current approaches that are used to manipulate myocardial energy metabolism involve either stimulating glucose metabolism or inhibiting fatty acid metabolism. In our study, we assumed that cardiac metabolic therapeutic approach must be integrative,

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thus improving both the substrate utilization and the complete substrate oxidation, i.e. supporting normal mechanism of energy production, without increased generation of reactive oxygen species. Since the energy metabolism is closely linked to cardiac function, we assessed the effect of the integrative metabolic therapeutic approach on the functional ability and quality of life in patients with heart failure and reduced ejection fraction.

METHODS

Patient population and study design

The study population consisted of 33 patients with left ventricular dilatation LVIDd>60 mm and reduced ejection fraction EF<40% treated in 76 complementary supportive therapy periods.

All patients had persistent signs and symptoms of New York Heart Association NYHA class II-IV. All patients underwent a detailed medical interview, physical examination, laboratory tests and echocardiography. The longest observation period was 122 months.

Quality of life

Quality of life was assessed in two different ways: disease-specific QOL and global assessment. Disease – specific QoL was measured by means of the Minnesota Living with Heart Failure questionnaire [6], assessing with 21-item questionnaire how HF has affected patient's life. The MLHFQ has a scoring range of 0 for no impairment as a result of HF to 105 for maximum impairment. The questions cover symptoms and signs relevant to HF, physical activity, social interaction, sexual activity, work and emotions. Three scores can be determined: an overall score 21 items, 0-105,the physical dimension 8 items,0- 40,and the emotional dimension 5 items,0-25.Higher MLHFQ scores mean a worse QRL.

Global health assessment 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 [7].

Echocardiography

Echocardiography was performed before and after each CST period. All patients underwent a detailed M-mode and two-dimensional echocardiography in the left lateral decubitus position using commercially available system with a 3, 5 MHz transducer. Standard M-mode and two- dimensional measurements were obtained according to the guidelines of the American Society of Echocardiography [8]. For the measurement of LVEF the modified biplane Simpson's rule was used, obtained from apical four-and two- chamber views. All the echocardiographic assessments were performed and interpreted by one cardiologist.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 17.0 and were based on the t-test, Spearman's rank correlation coefficient and Wilcoxon's signed-ranks test. All quantitative data were expressed as mean +-SD. The values of $p<0.05$ were considered statistically significant.

RESULTS

Baseline characteristics of heart failure patients before the first CST period are shown in Figure 1.

Age (years)	56,1 +6,8
Male gender (%)	84,8
AETIOLOGY (%)	
Idiopatic cardiomyopathy	33,3
Ischaemic cardiomyopathy	39,4
"Burnt out" hypertensive	24,3
Viral myocarditis	3
NYHA (mean + 1 SD)	3,06 + 0,82
II/III (%)	66,7
IV (%)	33,3
EF(%)	32,3 + 5,5
LVIDd (mm)	69,5 + 4,6
VAS (mean + 1SD)	39,85 + 11,42
Atrial fibrillation (%)	18

Medication (%)	
ACE-I	72
ARBs	18
Beta Blockers	82
If-channel blockers	12
Nitrates	76
Diuretics	100
MRAs	51
Digitalis	31
Amiodarone	62
Oral anticoagulants	18
Antiplatelets	55

NYHA - New York Heart Association; EF – ejection fraction; LVIDd – left ventricular end-diastolic diameter; VAS – visual analog scale; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin II receptor blocker; MRA – mineralocorticoid receptor antagonist

Figure 1: Baseline Characteristics of Heart failure patients before first CST period

Descriptive statistical analysis, i.e., analysis of the arithmetic mean, standard deviation and coefficient variation of individual items of Minnesota Living with Heart Failure Questionnaire suggests that the some of the biggest problems for patients before therapy were the lack of air, fatigue and lack of energy ,depression, as well as difficulties in doing sport, recreation and hobbies. The major reduction and significant improvement is in the four problems. The sense of depression after treatment was lower by 2.26, difficulties in breathing were reduced by 1.48, the feeling that the person was a burden on their family or friends was reduced by 1.48 and the feeling of anxiety or worry was reduced by 1.39 Figure 2.

MLHFQ	Before CST			After CST			
	Arithmetic mean	Standard deviation	Variation coefficient	Arithmetic mean	Standard deviation	Variation coefficient	Arithmetic mean difference
1. Swelling of joints and legs	2,91	1,86	64	1,73	1,587	92	1,18
2. Need for rest during the day	3,88	0,893	23	2,91	0,98	34	0,97
3. Difficulty in walking or climbing stairs	3,97	0,918	23	2,97	0,918	31	1,00
4. Difficulty in performing daily activities	3,76	1,032	27	2,61	1,029	39	1,15
5. Difficulty in travelling	2,88	1,763	61	2,58	1,696	66	0,3
6. Difficulty in sleeping	3,00	1,639	55	2,33	1,339	57	0,67
7. Difficult relationships with friends and family	1,67	1,689	101	1,48	1,503	102	0,19
8. Difficulty in earning for a living	2,55	1,986	78	2,36	1,868	79	0,19
9. Difficulty in getting involved in sports, recreation	4,03	0,847	21	3,03	0,883	29	1,00
10. Difficulties in sexual life	2,42	2,016	93	2,03	1,794	88	0,39
11. Reduced appetite	2,09	1,702	81	1,64	1,365	83	0,45

Figure 2: Results of Descriptive statistical analysis (arithmetic mean, standard deviation and variation coefficient) before and after CST.

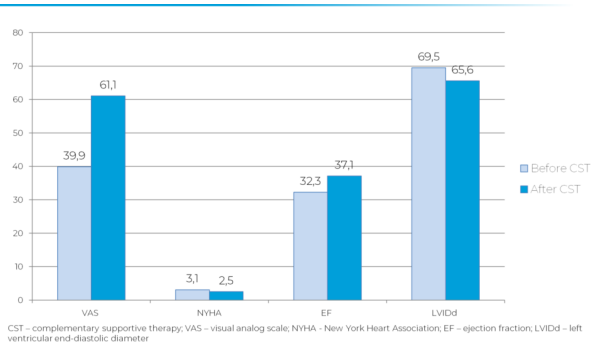
Given that individual MLHFQ items belong to physical item 2-7 as well as 12 and 13 or emotional dimension [17-21] they are shown in Figure 3.

DIMENSION	Before CST			After CST		
	Arithmetic mean	Standard deviation	Variation coefficient	Arithmetic mean	Standard deviation	Variation coefficient
Physical dimension	3,44	0,875	25	2,55	0,869	34
Emotional dimension	3,02	1,099	36	2,07	0,932	45

Figure 3: Results of Descriptive statistical analysis (arithmetic mean, standard deviation and variation coefficient) based on particular dimensions before and after CST.

Based on the arithmetic means before and after the CST, there is a marked improvement, i.e. reduction in difficulties including those of physical reduction by 0.89 and also emotional nature decrease by 0.95.

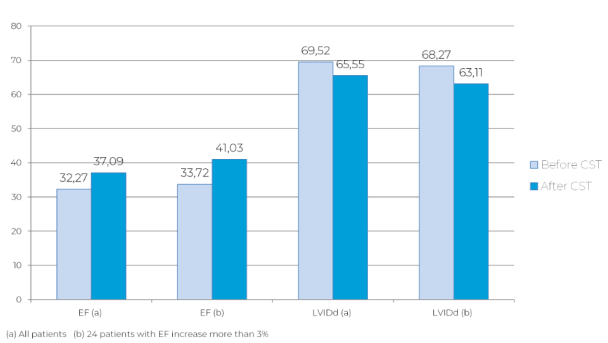
Graph 1 visually presents the average values of individual indicators before and after CST.



CST – complementary supportive therapy; VAS – visual analog scale; NYHA - New York Heart Association; EF – ejection fraction; LVIDd – left ventricular end-diastolic diameter

Graph 1: Average values of VAS, NYHA, EF, LVIDd before and after CST.

Graph 2 presents mean EF and LVIDd in all patients a and in 24 patients with EF increase more than 3% b before and after CST. In all patients mean EF increase was 4.8% and in group b mean EF increase was 7.3%.



(a) All patients (b) 24 patients with EF increase more than 3%

Graph 2: Mean EF and LVIDd before and after CST.

Out of 9 patients with EF increase lower than 3%, 6 had ischemic cardiomyopathy with scars, 2 had dilated cardiomyopathy and one had hypertensive hypertrophic cardiomyopathy.

Figure 4 shows the results of comparing patient responses to individual MLHFQ items using Wilcoxon's test prior to CST in relation to the status after CST. With the aid of Wilcoxon's non-parametric test applied to 21 variables, the evidence showed that there is a statistically significant difference p<0.1%.The exception is only in question 15, where there is no statistically significant change in the financial inability of purchasing medication after CST compared to the condition before CST.

MLHFQ	Z	P	Statistical significance
1. Swelling of joints and legs	-4,594	<0,001	* * *
2. Need for rest during the day	-5,184	<0,001	* * *
3. Difficulty in walking or climbing stairs	-4,963	<0,001	* * *
4. Difficulty in performing daily activities	-4,802	<0,001	* * *
5. Difficulty in travelling	-2,5	0,012	*
6. Difficulty in sleeping	-4,147	<0,001	* * *
7. Difficult relationships with friends and family	-2,449	0,014	*
8. Difficulty in earning for a living	-2,121	0,034	*
9. Difficulty in getting involved in sports, recreation	-5,260	<0,001	* * *
10. Difficulties in sexual life	-3,606	<0,001	* * *
11. Reduced appetite	-3,873	<0,001	* * *

MLHFQ	Z	P	Statistical significance
12. Difficulties in breathing	-5,092	<0,001	* * *
13. Fatigue and lack of energy	-5,035	<0,001	* * *
14. Stay in hospital	-3,494	<0,001	* * *
15. Financial inability to purchase medicines	-1	0,317	
16. Negative side-effects of medication	-3,568	<0,001	* * *
17. Feeling of being a burden to family and friends	-3,772	<0,001	* * *
18. Lack of self-control	-2,810	0,005	* *
19. Feeling of anxiety or worry	-5,098	<0,001	* * *
20. Poor concentration and memory	-4,630	<0,001	* * *
21. Depression	-5,154	<0,001	* * *

* Statistical significance up to 5%; * * Statistical significance up to 1%; * * * Statistical significance up to 0,1%; MLHFQ – Minnesota Living with Heart Failure Questionnaire; CST – complementary supportive therapy

Figure 4: Results of the comparison of patients responses to particular questions regarding problems in performing daily activities based on Wilcoxon's test before CST and in relation to the condition after CST.

The results of the comparison before and after CST for each particular dimension using the t-test for dependent samples suggest that there are statistically significant changes or statistically significant improvements to individual groups of questions or individual dimensions given that p<0.05 in both emotional and physical dimensions Figure 5.

VARIABLES		Arithmetic mean	Standard deviation	t	p	Statistical significance
Physical dimension	Before CST	3,44	0,875			
	After CST	2,55	0,869	19,83	<0,001	* * *
Emotional dimension	Before CST	3,02	1,099			
	After CST	2,07	0,932	15,97	<0,001	* * *

Figure 5: Results of t-tests in comparing arithmetic means before and after CST.

Figure 6 shows the results of comparing individual indicators before and after CST using the t-test for dependent samples. The conclusion is that the changes after CST are statistically highly significant in relation to the condition before CST given that p<0.001 in all four indicators. Therefore, improvement of the VAS, NYHA, EF and LVIDd indicators after CST is not small or accidental. VAS and EF increased significantly whereas the NYHA and LVIDd indicators decreased significantly, which both indicate a significant improvement after CST compared to the condition before CST.

		Arithmetic mean	Standard deviation	t	p	Statistical significance
VAS	Before CST	39,85	11,421			
	After CST	61,06	13,507	12,688	<0,001	***
NYHA	Before CST	3,061	0,827			
	After CST	2,485	0,606	6,804	<0,001	***
EF	Before CST	32,27	5,530			
	After CST	37,09	6,292	18,594	<0,001	***
LVIDd	Before CST	69,52	4,570			
	After CST	65,55	6,119	6,302	<0,001	***

CST – complementary supportive therapy; VAS – visual analog scale; NYHA - New York Heart Association; EF – ejection fraction; LVIDd – left ventricular end-diastolic diameter

Figure 6: Results of t-tests in comparing arithmetic means before and after CST.

Results of correlation analysis before and after CST for each dimension and indicators of patient condition are shown in the Figure 7. The Pearson correlation coefficients show that there is a positive and statistically significant correlation between the values given in Figure 7. The values before CST compared to values after CST are in strong correlation with the VAS, NYHA and LVIDd indicators and in a very strong correlation with physical dimensions, emotional dimensions and EF indicator.

VARIABLES	N	Pearson's correlation coefficient	p	Statistical significance
Average physical dimension before CST	76	0,96	<0,001	***
Average physical dimension after CST				
Average emotional dimension before CST	76	0,96	<0,001	***
Average emotional dimension after CST				
VAS Before CST	76	0,72	<0,001	***
VAS After CST				
NYHA Before CST	76	0,81	<0,001	***
NYHA After CST				
EF Before CST	76	0,98	<0,001	***
EF After CST				
LVIDd Before CST	76	0,81	<0,001	***
LVIDd After CST				

*** Statistical significance up to 0,1%; CST – complementary supportive therapy; VAS – visual analog scale; NYHA - New York Heart Association; EF – ejection fraction; LVIDd – left ventricular end-diastolic diameter

Figure 7: Results of correlation analysis before and after CST.

DISCUSSION

The primary function of the cardiovascular system is to support cellular respiration. The main purpose of cardiac metabolism is to provide energy for myocardial contraction, ion transport, biosynthesis and degradation [3].In the normal heart, under steady-state conditions, the main metabolic task is to produce ATP for contractile function. Cardiac work strongly depends on ATP generation, and impairment in this process rapidly induces contractile dysfunction [2]. Mitochondrial dysfunction in advanced heart failure has been linked to impaired myocardial energetics [2]. During ischemia, contractile function is associated with ATP content, and the ATP levels after hypoxia and reperfusion of the heart correlate well with myocardial function [9].Studies in animal models and humans have reported a decrease in the PCr ATP ratio, ATP content, and the ATP flux through CK in advanced HF with reduced EF [4].Given that sufficient ATP supply is essential for normal cardiac function, this change has been suggested to be responsible for the transition to systolic dysfunction [4]. Approximately 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 [10]. The remaining 10% to 30% comes from the oxidation of glucose and lactate, as well as small amounts of ketone bodies and certain amino acids [2,3].Typical for the failing heart is a shift from fatty acids to a less ATP-efficient glucose utilization. Wittels and Spann have shown that the content of carnitine in the heart is decreased in homogenates from failing guinea pig hearts and that there is a decreased oxidation of palmitate as early as 1968 [11]. Most studies indicate that fatty acid utilization, which is unchanged or slightly increased in early heart failure, is substantially decreased in advanced heart failure [2,4]. Failing heart has been suggested to be in the state of "fatty-acid overload" suffering from "increased oxygen wastage" and oxidative stress or from accumulation of cardio toxic lipid derivatives [2]. Incomplete FA oxidation may result in intracellular accumulation of an intermediate of fatty acid metabolism. Accumulation of acyl-CoA has been found in association with impaired mitochondrial metabolism and acylcarnitines have been implicated in the pathophysiology of insulin resistance [12,13]. Acute inhibition of FA oxidation in a population of patients with end-stage HF led to a significant worsening of left ventricular function. It is proposed that both glucose and fatty acid oxidation are required for optimal function of the failing heart [14]. In contrast to FA oxidation data on cardiac glucose utilization are less consistent [4].

Glucose oxidation does not correlate with contractile function in HF [2] and there is no correlation between intermediary metabolite levels and cardiac performance [3]. Glucose utilization is increased early in heart failure [4]. In advanced heart failure insulin resistance develops in the myocardium with a decline in glucose utilization [15]. Suggestion is that changes in glucose oxidation may depend on both the stage and the etiology of HF and on the fact that pyruvate may be channeled into anaplerotic pathways to maintain Krebs cycle moieties [2]. However, interpretation of these results is complicated by substantial increases in the concentrations of plasma free fatty acids, glucose, and insulin that are common in heart failure. Although potential metabolic targets for the therapy of the heart failure may include modulation of cardiac FA utilization [12,16] and modulation of glucose metabolism [17] the concept of supplying "better" fuel to improve myocardial efficiency has not received wide acceptance [18], The progression to HF is often long and complex, the time point of assessment will influence metabolic adaptations that are observed [2]. Metabolic and functional cardiac phenotypes and their mechanism differ between HF of different etiologies [2]. In 9 of our patients, even though symptom severity diminished after CST, EF improvement was not reached, especially in patients with ischemic cardiomyopathy with scars.

Alternative pathways play a minor role in the normal heart. In the progression to HF, ATP producing capacity is reduced and alternative pathways may be activated to various degrees maybe providing additional metabolic mechanism influencing contractile function. Potential metabolic targets for the therapy of heart failure may include modulation of cardiac anaplerosis

[2], AMPK activation [19] activation of cardiac glucagon-like peptide-1 receptors [20] and i.e. iron supplementation [21] .However, chronic heart failure is multifactorial and

entails many mechanisms other than those controlled by single gene or enzyme, but one aspect of the process involves cardiac energetics [4].

In our study we accepted the general concept that the flux through energy- providing pathways determines the functional state of the tissue [3]. Regulation and control of flux through a metabolic pathway cannot be achieved by any single enzyme acting in isolation and it is a shared property of many different intra and extracellular effectors. HF is a "metabolic breakdown" and our concept was not to act on one specific enzyme or protein or particular pathway but "to improve the flux", and support normal mechanism of energy production without increased generation of mitochondrial reactive oxygen species Figure 7.

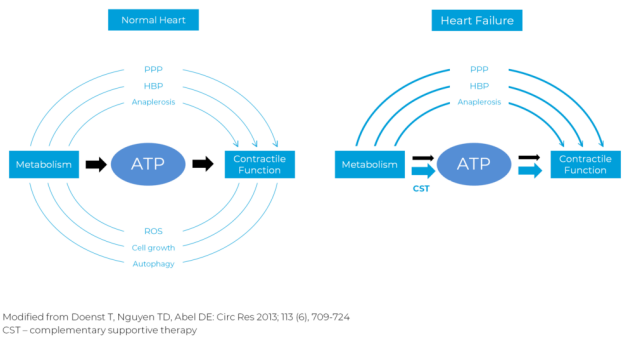


Figure 7: Simplified illustration of the relationship between cardiac metabolism and contractile function, reflecting the role of ATP production and non-ATP producing processes.

SCHEME 1

Scheme 1 presents the way of CST influence on the major biochemical pathways to produce energy. Supplements are applied as coenzymes cofactors in substrate oxidation reactions, as enzyme substrates and or as antioxidant molecules to counterbalance oxidative stress. Oxidative decarboxylation of pyruvate assumes a central position in the regulation of fuel supply to the heart. The conversion of pyruvate to acetyl–CoA is catalyzed by the multi enzyme complex pyruvate dehydrogenase, whose activity is highly regulated by its products acetyl-CoA and NADH [22]. Pyruvate dehydrogenase complex requires the sequential action of three different enzymes: a TDP-dependent pyruvate dehydrogenase, a lipoic acid- dependent dihydrolipoyl transacetylase, and FAD-dependent dihydrolipoyl dehydrogenase and five different coenzymes or prosthetic groups. These are thiamine diphosphate, lipoic acid, CoA, FAD and NAD [3].Thiamine diphosphate, as a pyruvate dehydrogenase coenzyme, turns pyruvate into acetyl-coA or, as an alpha keto glutarate dehydrogenase complex coenzyme, turns alpha-keto glutarate to succinyl-CoA. These reactions are instrumental in generating energy. Reduction or inhibition of the reactions diminish synthesis of ATP. In advanced cases of TDP deficiency heart failure may occur [23]. Pantothenic acid is used in the synthesis of coenzyme A. Acetyl-coA is a common intermediate formed from the catabolism of carbohydrate, lipids and proteins which functions in hundreds of metabolic reactions including degradation reactions resulting in energy production. Pantothenic acid joins thiamine, riboflavin, and niacin in the oxidative decarboxylation of pyruvate and alpha-ketoglutarate [23]. 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. In fatty acid beta-oxidation, acyl-CoA dehydrogenases require FAD. Succinate dehydrogenase is an FAD flavoprotein that removes electrons from succinic acid to form fumarate, which forms FADH2. The electrons are then passed into the electron transport chain by coenzyme Q. Reduction of the oxidized form of glutathione depends on FAD-dependent glutathione reductase. Hydrogen peroxide production from singlet oxygen, which assists in the destruction of

foreign substances, requires riboflavin [23]. Niacin and niacin amid 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.

All of the electrons that enter the electron transport chain come from NADH and FADH2 molecules produced during earlier stages of cellular respiration: glycolysis, beta-oxidation, oxidative decarboxylation of pyruvate and TCA cycle. NADP is a coenzyme in lipid and nucleic acid synthesis [23].

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 [12]. 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 [24,25].

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, Mg ADP-dependent mitochondrial ATP synthase activity, and cytosolic free ADP homeostasis. After 2 weeks of Mg starvation, cell growth stops

and respiration is decreased. ATP synthase becomes rate-limiting for respiration owing to the decrease in the matrix of

Mg ADP [26-30]. 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 [23].

Biotin, as carboxylase coenzyme, is a carrier for the transfer of "activated bicarbonate" to substrate. Biotin serves as a coenzyme for four carboxylases in humans. These reactions are vital for energy production [23].

The mammalian heart is an obligate aerobic organ. Constant supply of oxygen is indispensable for cardiac viability and function. The release of the protons and entry of the electrons into electron transport chain is dependent on the consumption of the oxygen. 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 [31]. Irrespective of the etiology, a failing dilated heart requires more oxygen per gram tissue than a non-failing smaller heart [31]. A failing heart is less able to metabolize oxidatively. Oxygen delivery in HF patients is not adequate to meet tissue needs because of decreased cardiac output and slow peripheral blood flow often combined with inadequate oxygen carrying capacity of the hemoglobin caused by anemia and decreased hemoglobin

[32] 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 [31]. 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 [33]. However, the role of oxygen and oxygen-associated processes in the heart is complex; myocardial oxygen consumption must be matched to cardiac function and viability. Oxygen can be both vital and deleterious, contributing to cardiac dysfunction and death. When ROS, a normal by-product of cellular aerobic metabolism overwhelms cellular antioxidant defenses, the result is lipid peroxidation of the cell membrane and of the membranes of cellular organelles [34]. Increased mitochondrial ROS could be an early event triggering structural remodeling and mitochondrial damage and finally cardiac fibrosis and hypertrophy. ROS alter membrane ion pump function in heart muscle and mediating apoptosis ROS contribute to the development and progression of cardiac dysfunction and heart failure [35]. .Animal studies have delineated that antioxidants and ROS defense pathways can ameliorate ROS-mediated cardiac abnormalities [36]. In our CST sessions we counterbalanced the increased generation of mitochondrial ROS using intracellular antioxidant molecules coenzyme Q (ubiquinone), vitamin E, and vitamin C.

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. The existence of a deficiency of CoQ in the cardiac patients' myocardium provides a rationale for restorative therapy [37].

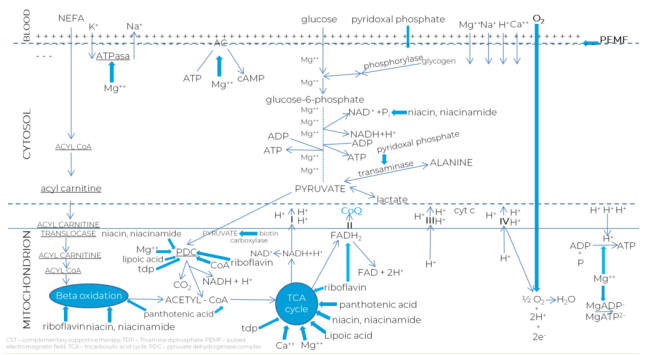
Vitamin E, a lipid-soluble antioxidant, protects cell membranes from oxidation and breaks the chain of oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reactions. The importance of peroxyl radical scavenger function is to maintain the integrity of long-chain polyunsaturated fatty acids in the membranes of cells and thus maintain their bioactivity [38,39].

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 [23]. Selenium functions as cofactor for reduction of antioxidant enzymes, such as glutathione peroxidases. The glutathione peroxidase families of enzymes catalyze certain reactions that remove reactive oxygen species such as hydrogen peroxide and organic hydro peroxides [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. [41, 42].

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 [41,42]. Ions stream into the cell and can act on many other pathways and organelles [43]. By increasing the entry of Ca++ ions PEMF has an important role in intracellular processes and muscle contraction [43]. Ca++ activates pyruvate dehydrogenase phosphatase which in turn activates the pyruvate dehydrogenase complex. Calcium, 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 hemoglobin and significantly increases the diffusion of oxygen in tissues [42]. PEMF elicits non-toxic amount of ROS [44].



Scheme 1: Simplified scheme of CST influence on the major biochemical pathways to produce energy.

CONCLUSION

Integrative metabolic therapeutic approach significantly improved the functional capacity and quality of life in patients with HFrEF. Complementary supportive therapy may contribute to the therapy of patients with heart failure and reduced ejection fraction.

CONFLICT OF INTEREST

None

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