Probable controversy of cardiac resynchronization therapy on the adaptive energy metabolism of hypertrophied and insufficient heart in Democratic Republic of Congo.

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Abstract

Background: It is reported that 20 to 30% of patients are not responders to this treatment (Cardiac Resynchronization Therapy). The reasoning in this merely theoretical paper shows the plausible danger that can be brought by measurements apparatus, in the occurrence the CRT especially when it is sophisticated.

Objective: In Physical Cardiochemistry field our overall purpose is to bring a contribution to heart health. It is needful to draw attention for caregivers and manufacturers, especially with respect to the magnetism these apparatuses may exhibit.

Methods: The Observation and documentary research are used. It is recalled hereby successively energy metabolism in healthy cardiomyocyte, adaptive energy metabolism of a hypertrophied and insufficient heart, cardiac resynchronization therapy and energy metabolism of the cardiomyocyte with its potential effects on both glucose oxidation and fatty acids oxidation.

Results: It is shown a plausible interaction between oxygen magnetic field, paramagnetic by nature, and pacemaker and/or defibrillator electromagnetic field according to the sacral principle of "*like dissolves like*" with all evil consequences on patients.

Conclusion: It will be necessary to evaluate later not only the behavior of the various energetic substrates of a hypertrophied heart as a function of the variation of the magnetic field strength but also the content of the probable substances produced in the presence of a magnetic field and with a potentially harmful effect on cardiac function. Convinced technology has its setbacks, the pacemakers and/or defibrillators manufacturers are invited to a greater rigor, greater caution and sustained care in building these devices. In next publication study of a case (CRT-D), where the diabetes has been observed, will be outlined.

Keywords: Cardiac Resynchronization Therapy (CRT); Glucose oxidation; Fatty acid oxidation; Oxygen; Paramagnetism; Hypertrophied and insufficient heart.

1. Introduction

The heart is an organ rich in lipids, and in mitochondria. The human heart produces about 30 kg of adenosine triphosphate (ATP) per day (80 µmoles.g^{-1}.min^{-1}) mainly from fatty acids (FA) oxidation [1]. Cardiovascular diseases are the leading cause of mortality and morbidity in the world. In particular, arterial hypertension and myocardial infarction predispose to the development of heart failure [2-5]. The hypertrophied and insufficient heart is characterized by the change of use of heart substrates in energy metabolism associated with a deficiency content of high-energy phosphate, mitochondrial dysfunction and high glucose dependency [6,7]. In order to improve cardiac efficiency, cardiac resynchronization therapy (CRT) is proposed. The CRT creates a magnetic field susceptible to influence the reaction of oxygen which is an essential molecule in the mitochondrial oxidative metabolism. This review analyzes the influence of the likely interaction of the magnetic field created by the CRT and oxygen on glucose and fatty acids oxidations which might affect the adaptive mechanism of energy metabolism of an already hypertrophied and insufficient heart.

2.Theoretical survey

2.1. Energy metabolism in a healthy cardiomyocyte

The fatty acids (FA) and glucose are the main source of energy for cardiomyocyte [8]. However, FA are the preferred energy source, but expensive in terms of oxygen and susceptible to entail harmful effects. The fatty acids, by the beta oxidation, provide the majority of cofactors required for mitochondrial oxidative phosphorylation [9].

Energy metabolism in a cardiomyocyte has been described by several authors including Fillmore et al in 2014 [9]. The fatty acid is converted to acyl coA by fatty acyl CoA synthetase (FACS) and then enters the mitochondria through CPT 1, CPT 2 and carnitine translocase (CAT). Beta oxidation oxidizes acyl coA to acetyl coA which enters the Krebs cycle. The cycle produces the reduced equivalents (NADH and $FADH_2$) that allow the oxidative phosphorylation to produce ATP via the respiratory chain of the mitochondrial membrane. The oxidation of the fatty acids consumes much more oxygen (0.177 mole of oxygen per mole of ATP).

Glucose enters the cardiomyocyte through GLUT 1 and 4, undergoes glycolysis and produces acetyl coA by dint of pyruvate dehydrogenase (PDH). Acetyl coA enters the Krebs cycle to produce ATP. The oxidation of glucose consumes less oxygen compared to that of the FA (0.156 mole of oxygen per mole of ATP). The 2/3 of oxygen used by the cardiomyocyte are consumed by the oxidation of FA [10].
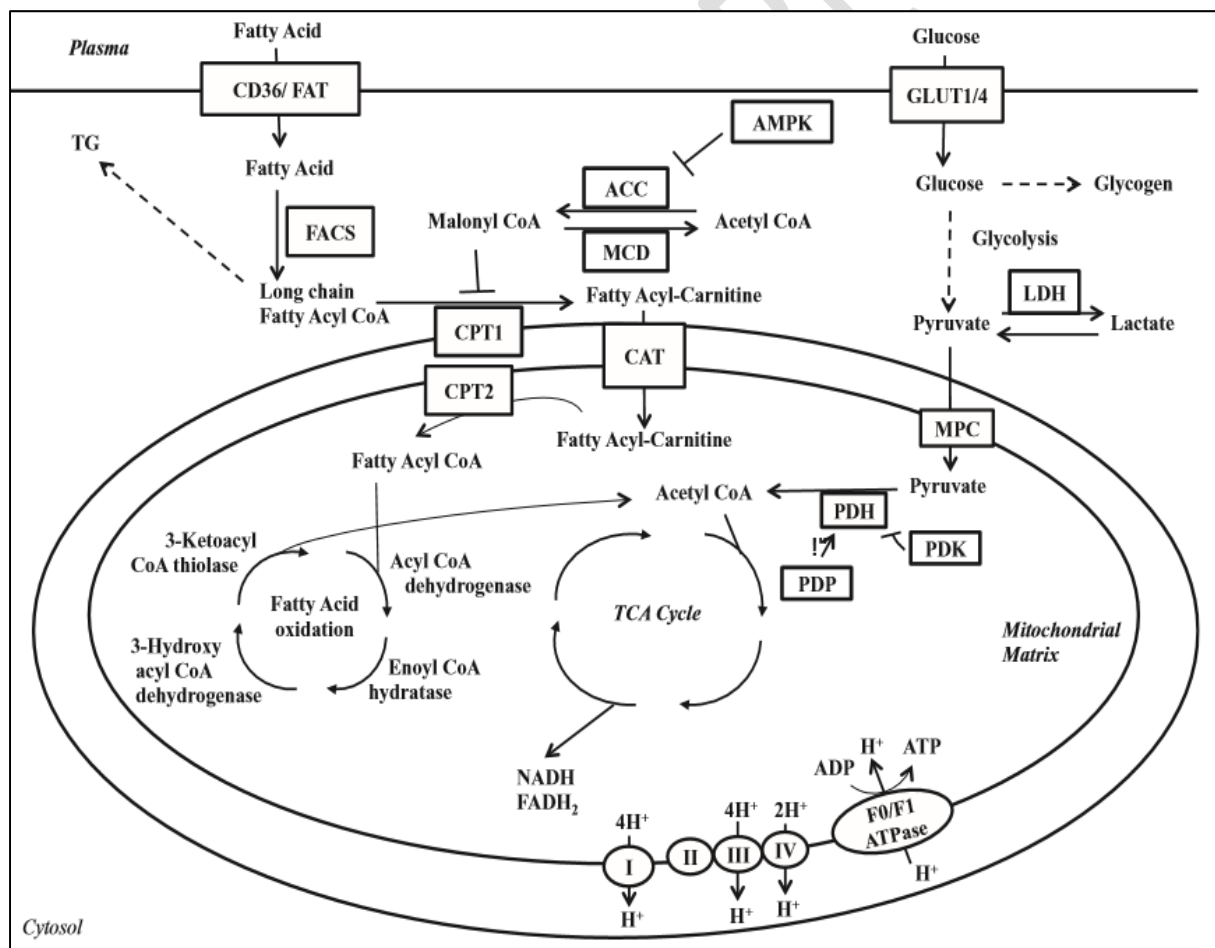

Fig.1. **Overview of oxidation of fatty acid and glucose in the heart** [9].

ACC, acetyl CoA carboxylase; AMPK, AMP-activated protein kinase; CPT, carnitine palmitoyl transferase; CAT, carnitine translocase; FACS, fatty acyl CoA synthetase; FAT, fatty acid transporter; GLUT, glucose transporter; LDH, lactate dehydrogenase; MCD, malonyl CoA decarboxylase; MPC, mitochondrial pyruvate carrier; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatase; TCA, tricarboxylic acid; TG, triacylglycerol.

2.2.Adaptive energy metabolism (metabolic shift) of a hypertrophied and insufficient heart

Different studies suggest a metabolic flexibility (shift) of the cardiomyocyte of a hypertrophied and insufficient heart. Indeed, it has been observed a modification of the use of energy substrate: the energy metabolism that is normally 70% at the dependency of FA is redirected towards the privileged metabolism of glucose [6,11]. The sick hypertrophied cardiomyocyte is deficient in energy because its ability to produce ATP has decreased: the Phosphocreatine / ATP ratio is shaken, the hypertrophied heart becomes unable to convert chemical energy into mechanical work [12].

This alteration of metabolism is believed to be caused by mitochondrial dysfunction due to the decrease of the factors of mitochondrial biogenesis PPARγ-coativator-1α (PGC-1α), nuclear respiratory factors (NRF1/2), mitochondrial transcription factor A (Tfam) [13,14] and the production of oxygenated reactive species altering mitochondrial DNA [15].This dysfunction would lead to a decrease of oxygen consumption in mitochondria [13-18], thereby decreasing cardiac efficiency.

In order to improve cardiac efficiency, some studies demonstrate a reorganization of mitochondrial metabolism by lowering the use of FA [19-22] (in dogs [23-25], rat hearts [26-29] or even their suppression [30], while the increase in deposition of ^{18}F-fluorodeoxy-glucose (^{18}F-FDG) and oxidation of cardiac glucose has been proven (in humans [21,31,32]). In the studies of Young [33], only glucose oxidation was significantly increased while experiments in dogs [23-25] and rat hearts [26-29] had demonstrated the uptake increased glucose. In sum, the upstream different theses plead for a metabolic change in an hypertrophied and insufficient heart towards a fetal energy metabolism characterized by a decrease of mitochondrial oxidative metabolism and an increase of the glycolysis [8,25,34]. This change of energy metabolism would be likely due to a change of activity of transcription proteins such as hypoxiainducible factor-1 α (increased), PPAR α (decreased) and PPAR γ co-activator-1 (PGC-1) (decreased) [8,26,27]. High rates of glycolysis and low rate of glucose oxidation can cause a decoupling of glycolysis and of glucose oxidation with as a consequence the production of

protons [8]. These protons are driven out of the cell by the Na^+/ H^+ exchanger. The sodium (Na) exits out of the cell by Na^+/Ca^{2+} exchange and there will be an increase of Ca^{2+} in the cell. ATP is then used to remove Ca^{2+} from the cell. It is thus reoriented out of contractile function thereby decreasing cardiac efficiency [9].

2.3. Cardiac resynchronization therapy and energy metabolism of the cardiomyocyte

Approximately one-third of hypertrophied and deficient hearts have intraventricular electrical disturbances resulting in asynchronous ventricular contraction, altering thus the efficiency of the heart pump [35,36]. The CRT consists in installing a pacemaker and / or a defibrillator, it is indicated in systolic heart failure with stages dyspnea NYHA II / III / IV, an ejection fraction ≤ 35% and QRS duration ≥ 120 ms. It is noted that 20 to 30% of patients are not responders to this treatment [37]. This category of patients could justify the controversy of this medical act. According to the universal principle of *"like dissolves like"* [38], the stimulator and / or the defibrillator behave differently in the presence of another magnetic moment. The application of a magnet on a stimulator is susceptible to induce asynchronous stimulation [39], an increase in the amplitude of the stimulation and a temporary suspension to the adaptation of the heart rate to the effort. However, the magnet does not induce these effects on defibrillator besides the possible deactivation of ventricular antiarrhythmic therapy that is solved by dint of the setup of the apparatus [40].

Although studies have not shown the universal effect of a clinical magnet (of magnetic field intensity greater than 90 gauss) applied to a pacemaker / defibrillator [40], patients which are refractory to this treatment suggest a possible interference of the magnetic field of the implant on the energetic metabolism of the cardiomyocyte. Precisely a possible interference of the magnetic field of oxygen and that of the cardiac implant can alter adaptive mitochondrial oxidative metabolism.

Indeed, the oxygen molecules are paramagnetics. They behave as small magnets having a pre-existent magnetic momentum to the inductive field (Fig.2) [41,42].
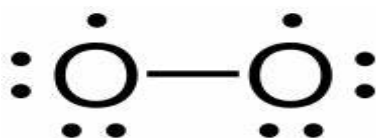

Fig.2. The Real Structure of Oxygen

In the absence of inductive field, these ones are randomly oriented because of thermic commotion and the resultant magnetization is not zero. The action of external field tends to orient those magnets in parallel between them and in the same sens with the magnetizing field. This alignment is partially destroyed by thermic agitation which tends to modify the dipoles orientation in the field direction; an equilibrium is established for which the atoms contribute positively to the field action because a permanent magnetization is superimposed to inferred magnetization.

The resultant induction is then more intense than in the empty. It is important to know that the external field acts on the magnetic moments which exist spontaneously in some certain atomic or molecular edifices. The result is the electrons circulation on their orbits together with electronics and nuclear spins [41,43].

It appears however that in gaseous phase the orbital magnetic moment interacts only with the intense field; in liquids and solids, things are quite different. This blockade of magnetic moments is ascribed to electrostatic interaction between divers orbits of the same molecule or of vicinal molecules. Only the magnetic moments associated to electrons and nuclear spins undergo a directress action of external field. When the electrons are pair, the effect is zero by compensation.

When the edifices have a single electron or no pair electrons, the magnetic moments are then oriented in the external field direction. Those substances present then a positive magnetic susceptibility, they are paramagnetics. The paramagnetism is always superimposed to the diamagnetism [42,44].

2.3.1. Potential effects of cardiac resynchronization therapy on glucose oxidation

In an insufficient heart, the energetic metabolism is preferentially oriented towards the oxidation of glucose [21,31,32,33], which has become the major energy source [6,11,45,46]. Oxygen, a paramagnetic molecule and key element of this metabolism, will tend to become rare during a CRT. Indeed, oxygen is the simple molecule that has a magnetic moment [47]. It is logically attracted by the magnetic field of the cardiac implant, hindering thus the oxidation of glucose which has become the main energy source of a hypertrophied and insufficient heart. Alteration of mitochondrial oxidative metabolism of glucose agraves the decoupling of glycolysis and oxidation of glucose, thereby causing a proton elevation in the cytosol, which,

as described above (Fig.1), will have to be removed from the cell by ionic regulation mechanisms consuming ATP. This unfit use of ATP comes to worsen heart failure already installed that the homeostatic mechanisms seemed to compensate. ATP from glucose oxidation is oriented towards contractile function [48-51] and the ATP provided by glycolysis is preferentially used by the pumps. It upstream follows, in the cytosol, an increase of glucose metabolites that may thus influence the GLUT1 and GLUT4 transporters decreasing the binding affinity to the glucose molecule with a consequence the extracellular increase of glucose susceptible to cause cardiac insulin-resistance. Likewise, Lahbib *et al.* in 2014 studies on cells after incubation in a magnetic field have reported the induction of oxidative stress entailing instability of glucose level and insulin release. The magnetic field is likely to induce a disturbance of the metabolism of free radicals and a rise in their concentration [52,53,54].

2.3.2. Potential effects of cardiac resynchronization therapy on fatty acids oxidation

Although oxidation of FA is not the main energy source of an insufficient heart [19-22], its alteration would be susceptible to compromise the adaptive energy metabolism in place. It is not amazing that the depletion of oxygen in an insufficient heart under a CRT alters the mitochondrial oxidative metabolism of FA, the oxygen being attracted by the magnetic field of the cardiac implant. This alteration of FA oxidation would entail, upstream, an accumulation of FA exposing thus the heart to lipotoxicity that would lead to cardiac dysfunction [12]. These fatty acids can be metabolized to intermediate metabolites (diacylglycerol and ceramides), which will contribute to the establishment of cardiac insulin-resistance and therefore cardiac dysfunction [55,56].

3. Conclusion

The adaptive energy metabolism which aims to increase the efficiency of insufficient heart seems to be disturbed by oxygen depletion. This latter is deviated from its metabolic role to the magnetic field created by the implant (CRT). As a result, at the level of the cardiomyocyte, an alteration of adaptive mitochondrial oxidative metabolism is observed, pushing the heart into energy deficiency, exposure to lipotoxicity and insulin-resistance introducing again the hypertrophied and insufficient heart on an energy dead-end. All these mechanisms contribute to the installation of cardiac dysfunction degrading thus the vital prognosis of patients with hypertrophied and insufficient heart under CRT. This review may partly explain the high rate (20 to 30%) of patients who do not respond to CRT. A new balance

of energy deficiency would be established between the metabolic pathway of glucose and that of FA. Careful study of the expression of genes encoding PDH will give plenty information because it is recognized to be a target at the crossroads of these two metabolic pathways. An increase in FA oxidation inhibits PDH while an increase of glucose oxidation stimulates it.

In addition to the important rate of patients insensitive to the CRT, its high cost restricts its accessibility in poor regions, especially in Sub-Saharan Africa. The research for a new treatment alternative is needful. The resort to the phytotherapy is acceptable, reachable, available and popular for the majority of Africans (80%).

It will be necessary to evaluate later not only the behavior of the various energetic substrates of a hypertrophied heart as a function of the variation of the magnetic field strength but also the content of the probable substances produced in the presence of a magnetic field and with a potentially harmful effect on cardiac function.

Convinced technology has its setbacks, the pacemakers and/or defibrillators manufacturers are invited to a greater rigor, greater caution and sustained care in building these devices taking into account the universal principle of *"like dissolves like"*. In next publication study of a case (CRT-D), where the diabetes has been observed, will be outlined.

Competing Interests

Authors have declared that no competing interests exist.

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