



Effect of low frequency magnetic field on cardiovascular system

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Abstract The effect of exposing magnetic fields (MFs) with low frequency on human cardiovascular parameters are still unidentified. As a predictor of specific cardiovascular pathologies, estimating the exposure of employees' workplace with dosimeters by changed variability of heart rates is performed in epidemiological studies. Besides, microcirculatory factors such as blood pressure, variability of heart rates or heart rates are concentrated on by laboratory studies. Studies about microcirculatory system's responses to exposing low frequencymagnetic fields are sparse. In the international existing re-evaluation contexts of exposure guidelines, tackling such issues is important for further studies regarding low frequencymagnetic fields, international exposure guideline re-evaluation. In these studies, the potential negative and positive influences of low frequencymagnetic fields and the detections and characterizations of their induced subtle physiological changes should be addressed. The investigation of the micro- and macro-circulatory relationships and the utalization of laboratory geomagnetic shielding are recommended for futher studies. The micro- and macro-circulation, lymph vascular system, and heart are included in the cardiovascular system. Although the cardiovascular system's mechanics and characteristics had a wide discussion in literature which is beyond this paper' scope, a consise description of this system was conducted for the facilitation of understanding the effects of exposing low frequency magnetic fields on human cardiovascular parameters.

Keywords Magnetic field, electromagnetic field, heart, cardiovascular system

1. Introduction

I One of the roles of magnetic fields (MFs) is to be used for the function of heart, so many broad roles of MFs are open for meditation. They are used to for monitoring and diagnosing cardiac data that cannot be easily attained by other techniques. This feature depends on the MFs produced by hearts that are detectable with their signals for providing functional information related to heart condition, e.g., measuring parameters of fetal heart rates (HRs) [1], which cannot be easily performed using standard techniques. The measurement of physiological parameters, including changing of the volume of heart through changing in magnetic susceptibility is another example [2]. Another type of possible dysfunctions may include arrhythmias, disturbances of heart rhythm, or cardiac blood-related disorders, and the key role of MFs is a method of therapy for heart dysfunctions, including a deficiency in flow or weakening of the heart muscle [3]. The third type of possible dysfunctions for MFs is protection of heart. This depends on how to reduce the risks of impaired cardiac function in the future resulted from exposing appropriate MFs, e.g., reducing blood viscosity by using pulse MFs [4] so as to decrease vascular resistances, using pulse MFs to raise the proliferation of endothelial cells [3], or using bio-magnetic procedures to decrease the pressure of blood [5]. The fourth type of vital magnetic reactions of the heart refers to the cardiac influences which are uncontrolled or unintentional, resulted from external sources. Examples may incorporate the potential heart impacts related with electromagnetic treatment applied to other body parts [6] or even changes in the geomagnetic fields [7]. MF techniques and strategies identified with their latent capacity advantage have been proposed and assessed in the previously mentioned types, and sometimes have exhibited



practical advantage for screening and therapy. Albeit some methodologies and techniques have sound establishments in principle, few of them might not be assessed rather than applied. The fundamental reason for this study is to give a framework in which past, present and future MF applications associated with cardiovascular functions can be assessed with regards to the related physiological and physiological establishments.

For 3 decades, studies have investigated the potential effect of MFs exposure [8]. The power grid and electrical appliances generate MFs with a frequency up to 300 Hz. There was evidence that heart rates may be effected by MFs exposure in humans [9] leading to acute cardiac diseases. Savitz et al [10] conducted a cohort study aimed at investigating the effect of mortality due to cardiovascular diseases (CVDs) which occupationally exposed to MFs. They found that the mortality caused by cardiac arrhythmia and acute myocardial infarction (AMI) had positively associated with the exposure to occupational MFs. Despite that this early perception had been marginally supported by some studies, [11] it failed to be replicated by other different studies [12]. This could focus on the advantages of both full histories of career that reduce the possible effect of health worker, and extensive knowledge on potential confounders, though this frequently occurs at the evaluation cost of less occurrence of high exposure and less detailed occupational exposure. However, there are some limitations in the previously mentioned studies on MFs, in which they lack data on individual occupations rather than complete occupational histories, [13] or they missed data on possibly essential confounders [12]. Therefore, such limitations were dealt with by assessing how the exposure to occupational MFs is associated with mortality due to CVDs in a comprehensive community-based prospective cohort study [14] with a full occupational history and extensive knowledge on possible confounders up to baseline.

2. MFs effects on oxidative stress in heart

MFs with low frequencies are commonly used in various equipment and electrical appliances, including kitchen appliances, TV sets and computers. Recently, MFs have been considered therapeutic agents and commenced to be increasingly used in medicine. Growing interest of researchers has been noticed in biological effects of MFs on target cells and tissues. Various species' biological systems may have been subjected to different changes biochemically and physiologically, which were initiated by very low frequency MFs [15].

Biochemical changes in a cell results from membrane potential or trans-membrane ionic transfer which modifies cell functions. Between neighboring atoms, chemical bonds with following free radicals' productions can be effected by MFs [16]. Besides, free radical life-span of cell can be increased by MFs [17]. Free radicals described as "reactive oxygen species and reactive nitrogen species (RNS)", are causative factors in the oxidative damage of cellular molecules as well as structures, including nucleic acids, proteins and lipids. In particular, cellular structures, including biological membranes, which are full of unsaturated fatty acids (UFAs), are exposed to free radical attacks [18]. In cell membranes, lipid peroxidation process is promoted by free radicals reacting with UFAs. The end lipid peroxidation product called Malondialdehyde (MDA) is "a highly toxic molecule implicated in a range of pathologies by producing oxidative damage in tissues". The heart is more vulnerable to free radical damaging effects than other tissues due to high consumption of oxygen. A living organism has defense systems against different oxidants. Against lipid peroxidation, cells are protected by some of these systems, including glutathione peroxidase (GSH-Px), antioxidant vitamin A, C & E, catalase (CAT), glutathione (GSH), and superoxide dismutase (SOD). These antioxidant defense systems can be deteriorated by a magnetic field which leads to oxidative stress [17].

3. Effects magnetic field on heart rate variability

In some cases, a recently changing waveform with MF band frequencies has been applied. Electric fields are induced by MFs over time whether the biological tissues are conductive or not. Carriers, such as ions, begin to carry the electric charge after the induction of electric fields. It was proved that tissue treatment is affected by some factors, including the induced electric fields' density, because it also has the character of physical energy. Growing interest is attracted by the high-induction magnetic stimulation (HIMS) because of its short-time considerable effect. Motor impacts are triggered by HIMS application via the muscle fibers contractions, without the device contacting muscles' treated areas [19]. Choosing an appropriate technique depends on the



assessment and monitoring of cardiac activity affected by HIMS application. The heart rate variability (HRV) is “considered to be an indicator of the activity of the autonomous nervous system”. In the 1960s, early studies were investigated, and the HRV experimental effect was a topic of different studies. According to available studies, it can be claimed that HRV is “a suitable indicator of both the autonomous nervous system as well as pathological conditions” [20]. This study aimed at examining and analyzing the cardiac activity, precisely the ECG signal. Inside the chest area of animal model, HRV and variations of heartbeats intervals were assessed throughout the HIMS application. Standard HRV assessment approaches, including time and frequency domain, were used for the analysis of biophysical stimulations before, during, and after the HIMS application. Additionally, nonlinear assessment methods were included in the analysis. The evaluation is essential to assess HRV as well as its complexity because signals with maximum complexity are appeared to be produced by organisms with best healthy states. The signal’s complexity is associated with its structural richness and correlations across multiple time scales [21]. Using nonlinear analysis of signals, depended upon the trajectory reconstruction within phase spaces, is increasing particularly in medical studies. The required recurrences of one data set of time series are visualized through dynamic systems’ recurrence enabled by the recurrence quantification analysis which is defined as “a multidimensional method which allows monitoring the dynamics of a whole system” [22]. Accordingly, standard evaluation approaches in time and frequency domain were used to investigate the HIMS effect on the cardiac activity. The monitored system dynamics were also described by such approaches with the help of the recurrence quantification analysis and basic nonlinear methods.

4. MFs effects on cardiac stem cells

In western country, morbidity and mortality are mostly caused by cardiovascular diseases. For heart regeneration, more attention has been paid to the transplantation of cells into the damaged myocardium. So far, the arrhythmogenicity formulated by muscle-derived cells of progenitors as well as the low-certain cardiomyogenic potentials of bone marrow-derived cells of stem/progenitor are two considerable shortcomings to the experimental applicability of adult cells of stems/progenitor in the failure settings of heart [23]. The ideal type of the transplanted cells must be characterized by: “(a) spontaneous disposition to integrate with the target tissue without induction of immune reaction; (b) cardiac commitment; (c) capacity to develop gap junctions with host cells; (d) preferably by some degree of resistance to ischaemia, in order to avoid massive apoptosis, which is currently observed during cell transfer” [24]. Several characteristics of these appear to be fulfilled by cardiac stem cells (CSCs). Actually, wide attention has been paid to the result indicating “the heart contains a reservoir of stem/progenitor cells” [25]. Besides, improving systolic functions and promoting cardiomyocyte regenerations are performed by CSCs gained with this technique when they are injected into border zones of experimental mice’s infarcts [26]. As CSCs are multi-active, renewable and reproductive, they automatically lead to the emergence of endothelial cells, smooth muscle cells and cardiomyocytes. they also form multicellular groups called “cardio spheres” in a semi-suspension culture. With especial attention to the cardiogenic potential of CSCs, there is a need for new approaches through which that differentiation processes are allowed to be modulated with manipulation of minimal cells and without any pharmacological therapy or modification of genes, in order to prove that CSCs therapy is more reliable and clinically feasible. Regulating fracture healing and calcium homeostasis has also been reported by electromagnetic fields (EMFs) [27], which can lead to preventing or repairing damages caused by injuries of heart ischemia-reperfusion. Nevertheless, because of variations in the clinical exposures’ protocols and the static MFs differences, EMFs-based technologies have not been translated clinically [28]. For obtaining completely controlled and reproducible conditions, a system of exposure inside an a-magnetic room was introduced in the current paper for the first time. The paper also evaluated the hypothesis that exposing EMFs to cardiosphere-derived cells and human cardiospheres may have interference with their reproduction, and modulate the cardiac alternative EMFs, tuned to differentiation processes of calcium ion cyclotron energy resonance, without any other intervention. Certain differentiations of human CSCs have been triggered by combining between static and calcium ion cyclotron energy resonance, confirmed via their functional characterizations as well as by analyzing their transcriptional activity and immunophenotype.



5. Results and discussion

Various studies have been conducted in order to identify whether working time of very low frequency MFs utilized for the treatment using MFs has any effect on the free radicals' productions in heart tissues. Exposing rats to very low frequency MFs raised H_2O_2 concentrations as well as lipid peroxidative processes. Besides, plasma's ferric reducing capability and GSH concentrations in heart homogenates were also relatively reduced. The antioxidant defense heart tissues and the generating ROS are not noticeably affected by the exposure to MFs 30 min per day for two weeks. This finding conflicts with the former result which reported that TBARS concentrations in plasma are significantly raised when exposing rats to MFs half an hour per day for 2 weeks. [29]. Besides, the primary antioxidant defenses were not significantly affected by exposing neural culture to MFs of 50 Hz, 1 mT for a week [30]. Likewise, anti-inflammatory cytokine IL-10 productions are increased by exposing mononuclear cells of human peripheral blood to pulsating MFs 50 Hz, 45 ± 5 mT 3 times for 3 hours per stimulation with 24 intervals between stimulations [31]. Lipid peroxidations are frequently utilized as indices to measure damages that occur in the membrane of cells resulting from free radical insults. The biological membrane is a cellular structure substantial with unsaturated fatty acids; therefore, they are likely to be influenced by free radical attacks [32]. In normal conditions, H_2O_2 is "scavenged by catalase (CAT) or glutathione peroxidase (GPx) to water and oxygen". The yielded outcomes are in line with the previously published studies which suggest that antioxidant defense of organisms are reduced by low-frequency MFs, and the antioxidant enzymes' behavior and free radical formations are dependent on the MF working time [33]. Proteins containing sulphhydryl (SH) groups can be abnormally oxidative in case the concentrations of total free-SH groups are reduced, thus contributing to the reduction in the antioxidant ability of plasma indices since the thiol plays a key antioxidant role in protecting cellular and extracellular functions against oxidative stresses [34]. GSH is considered to be "the first-line defense against oxidative damage and radical generation where GSH functions as a scavenger and cofactor in metabolic detoxification of ROS" [34]. Particularly, tissue GSHs play major roles in defenses of antioxidants by ROS direct detoxification. Lipoic acids as potent thiol antioxidants may improve the myocardial condition of glutathione metabolism through the oxidative stress in rats [35]. Oxidative damages may result in a reduction in the GSH and content of total free-SH groups which was induced by very low-frequency MFs. Furthermore, significant decreases in redox ratios (GSH/GSSG) by MFs are inversely linked to oxidative stresses through which the heart membrane is damaged and the ROS are produced. MFs are efficient factors that increase blood flows, favoring bone formations, decreasing the pro-inflammatory molecules' production [36].

So, no clear changes were found to the records before, during and after applying HIMS. Nevertheless, significant differences were found in the data regarding long-term variability parameters before, during and after applying HIMS. Therefore, applying HIMS showed to affect – to some extent – the heart rhythm variability because the experimental variability of signals varied, though it is not clear at first sight. Moreover, no significant transitions, except in the in the low-frequency band during and after applying HIMS, were found in the frequency analysis of data. This low-frequency band is primarily associated with the parasympathetic activity [37]. However, it was indicated that forming conclusions on affecting the heart rhythm of applying HIMS depended upon the frequency analysis is not possible. It also resulted that cardiac activity may not substantially influenced more by applying HIMS. Therefore, linear analysis did not seem to be a suitable choice because the biological process is burdened with fluctuations as mentioned before [38]. On contrary, further works can use such findings as a baseline. Besides, influencing the heart rhythm variability by using parameters corresponding to short and long-term variability can be assumed through using the standard approaches. For such a reason, the recurrence quantification analysis was used in the present paper. This analysis depends upon chaos theory and is considering signal nonlinear behaviors [39]. However, applying HIMS highly resisted by subjects' hearts and a few transitions were significant. Therefore, it was proved that the physiological function of the heart electrical conduction systems has high resistance, and influencing the function of the sinoatrial nodes by low-frequency EMFs in healthy hearts is minimally possible. This can be hypothetically explained and found in the excellent electrical conductivity of the pectoral muscles. An essential portion of electrical currents after their induction, where high-current densities can be closed or created by their current paths, are concentrated on by such conductive environments with well electrical process. Thus, the influence of these



currents can largely be shielded from by the heart itself. The protective procedure of high-induction magnetic stimulations is supported by the results. However, it does not mean that such stimulations could be applied without any risks to the heart area, wherein it is contraindicated, particularly for risk or cardiac patients. [40]. The application of EMFs, HIMS, induced electric currents, or the distance electrotherapy is primarily contraindicated by pacemakers or other electronic surrogates available in the body even though such applications may severely and fatally influence the pacemakers or electronic surrogates. So, the study indicated changes in variability leading to reductions during or after applying the HIMS, though it appears that HIMS has on actual influence on the the heart electrical conduction system. Hence, HIMS application it assumed to have relative influences on cardiac activity. Consequently, variations in the the heart rhythm variability were found; however, increasing the subjects' number and extending the applied pulses' spectrum are recommended in further studies for more clarification [40].

Several research groups recently have paid more attention to investigating the potential effect of MFs exposure to biological systems. Nowadays, still there are scientific debates about the theoretical possibilities of such an association and its non-obvious hypothetical mechanisms. There is considerable proofs manifesting that static MFs with moderate intensity are able to influence several biological processes, especially those whose functions are relatively associated with the characteristics of membrane channels. The influences may mostly be interpreted according to changes in the calcium flux of membranes [41].

The proposed model depends upon the membrane phospholipids' diamagnetic anisotropic properties. It was suggested that the dynamics of these molecules is changed during the exposure of their reorientation to MFs causing an imbedded ion channels deformation [42]. The combined static and alternate MFs, tuned to calcium ion cyclotron energy resonance, influenced the biological system including CSCs. A theory of explaining ICR biologically was elaborated by Lednev [42] in which ions in their protein-binding sites are considered as dipoles, so the transference of energy to the dipoles occurs when ions are exposed to their ICR, as a result, ions are released in solutions. Calcium ions are "essential regulatory components of all organisms". At all cellular growth steps, calcium is involved in the development and regulation, including reproduction, variation, cytoskeleton elements' assembling and disassembling [43].

Reproduction and variation are two mutually exclusive paths. However, since progenitor cells' heterogeneous populations at different commitment phases are represented by cardiospheres and CDCs, several responses can be expected to the reproductive and variative stimuli at all intermediate phases. Exposing MFs enhanced such a process though the cardiospheres are automatically differentiated toward cardiogenic phenotypes [44]. As mentioned before, more improved variative aspects were more allowed by the structure of cardiospheres than that of CDCs.

Therefore, several balances and levels of early cardiac markers' explanation are consistent. The role of calcium dynamics in humans' CSCs variation are yet to be completely elucidated though they are versatile and probable to be dependent upon the type of cell. For enhancing their cardiac regenerative potentials, the reproduction and certain variation modulation formulated through EMFs system could be an effective and safe biotechnological tool with minimal manipulation function [44].

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