Impact of low-level electromagnetic fields on the inducibility of atrial fibrillation in the electrophysiology laboratory

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BACKGROUND Atrial fibrillation (AF) is the most common sustained arrhythmia in adults. Research suggests that autonomic nervous (ANS) system dysfunction contributes to AF pathophysiology. Animal studies have shown that low-level electromagnetic fields (LL-EMF) are potentially capable of AF suppression. This study evaluated the safety and efficacy of LL-EMF in suppressing AF in humans.

OBJECTIVE To investigate the impact of LL-EMF on AF inducibility in humans.

METHODS Patients presenting for ablation of paroxysmal AF were randomized to a sham protocol or LL-EMF (3.2×10^{-8} G at 0.89 Hz) applied via a Helmholtz coil around the head. AF was induced via atrial pacing, and was cardioverted if duration was greater than 15 minutes. The protocol was then run for 60 minutes, followed by reinduction of AF. The primary endpoint was the duration of pacing-induced AF after protocol completion compared between groups.

RESULTS Eighteen patients completed the study protocol (n = 10 sham, n = 8 LL-EMF). Pacing-induced AF duration in the LL-EMF group was 11.0 ± 3.43 minutes shorter than control after protocol completion (CI 3.72–18.28 minutes, $P = .03$). A smaller proportion of LL-EMF patients experienced spontaneous firing initiating an AF episode (0/7 vs 5/6, $P = .0047$). A significantly greater proportion of patients in the control group required direct current cardioversion after 1 hour (0.78 vs 0.13, $P = .02$).

CONCLUSION In patients with paroxysmal AF, LL-EMF stimulation results in shorter episodes of pacing-induced AF and a reduced likelihood of spontaneous firing initiating an episode of AF.

KEYWORDS Atrial fibrillation; Autonomic modulation; Catheter ablation; Electromagnetic fields; Translational research

(Heart Rhythm O2 2021;2:239–246)

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance in adults, with an estimated prevalence of 5.2 million patients in the United States and 1.2 million new cases annually.[1] AF is associated with a significant cardiovascular morbidity and mortality burden, chiefly owing to its role as a causative and exacerbating factor in patients with congestive heart failure, as well as being a significant risk factor for cardioembolic stroke.[2,3] Current management of patients with AF in whom a rhythm-controlling strategy is pursued includes the initiation and escalation of antiarrhythmic drug therapy, direct-current cardioversion (DCCV), and invasive radiofrequency catheter ablation targeting sites in the left and right atria.[2] These therapies have a number of significant limitations. Antiarrhythmic drugs have disappointing long-term efficacy in the maintenance of normal sinus rhythm (NSR) and have a number of serious adverse effects and contraindications in a plurality of AF patients.[4,5] Although catheter ablation is superior to antiarrhythmic drug therapy in the maintenance of NSR,[6] and potentially improves outcomes in patients with systolic heart failure[7,8] it has several serious and potentially life-threatening complications.[9]

Because of these issues, there is growing interest in pursuing alternative methods of AF suppression. Multiple studies have confirmed an intimate relationship between cardiac autonomic nervous system (CANS) dysfunction and the initiation and maintenance of AF.[10] Consequently, several recent studies have demonstrated the ability of autonomic

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2666-5018/

https://doi.org/10.1016/j.hroo.2021.04.004

KEY FINDINGS

- Low-level electromagnetic field stimulation (LL-EMF) is able to suppress the inducibility of atrial fibrillation (AF) in patients presenting for ablation of paroxysmal AF.
- LL-EMF decreased levels of monocyte chemoattractant protein-1 measured in peripheral venous blood.
- LL-EMF represents an interesting new approach for noninvasive management of AF, and requires further study to assess its efficacy in improving clinical AF outcomes.

modulation to suppress and prevent AF in a variety of animal models,[11–14] as well as in humans.[15,16] These studies have utilized a variety of therapeutic modalities, including direct vagus nerve stimulation, renal denervation, catheter ablation of cardiac autonomic ganglionated plexi and transcutaneous stimulation of the auricular branch of the vagus nerve. Another novel, noninvasive method of autonomic modulation involves application of a low-level electromagnetic field (LL-EMF) to the patient's body to affect changes in neural networks innervating the heart. Prior studies have demonstrated the ability of LL-EMF to suppress AF inducibility in animal models of pacing-induced AF and to affect AV conduction.[17,18] The purpose of this study was to investigate the effect of an externally applied LL-EMF on AF inducibility in humans.

Methods

Patients were eligible for the study if they were presenting for a first ablation for paroxysmal AF, defined as AF occurring for periods <7 consecutive days. Exclusion criteria included age less than 18 or greater than 85 years, left ventricular ejection fraction <40%, persistent AF, stroke or myocardial infarction within the past 6 months, greater than moderate valvular stenosis or regurgitation as assessed by preprocedure transthoracic echocardiogram or presence of a prosthetic heart valve, or prior ablation for AF. Basic demographic and medical history information were collected on all participants, including age, sex, race, ethnicity, comorbid medical conditions, medications, and basic transthoracic echocardiogram measures of cardiac structure and function.

This was a prospective, randomized, double-blind sham-controlled trial. The institutional review board at the University of Oklahoma Health Sciences Center reviewed and approved the study protocol, and the study was conducted in accordance with the principles in the Declaration of Helsinki. All patients gave written informed consent prior to study participation, and the study was registered with the Food and Drug Administration through clinicaltrials.gov (NCT03593486). Patients were enrolled upon presentation to our electrophysiology (EP) lab for ablation of paroxysmal AF. After informed consent was obtained, the patient was randomized to 1 of 2 protocols that were preprogrammed into the magnetic field stimulator. As described below, one of the protocols was an active stimulation protocol, and one was sham (ie, no stimulation delivered). These were named "Stim 1" and "Stim 2" in the computer. Because the specifics of the protocol were programmed into the stimulator by the device manufacturer, neither investigators nor study participants knew which of these 2 protocols were sham vs active. Investigators were blinded to group assignment.

Regarding preprocedure care, our practice is to discontinue antiarrhythmic drugs for 5 half-lives prior to the procedure, with the exception of amiodarone, which is discontinued for 6 weeks. Patients taking Coumadin for stroke prophylaxis continue uninterrupted, while patients taking direct oral anticoagulants (eg, apixaban, rivaroxaban, or dabigatran) had this medication discontinued 24 hours prior to the procedure. After enrollment, the patient was brought to the EP lab for the procedure and placed on the lab table with their head positioned in the magnetic coil. Our practice is to perform AF ablation under general anesthesia utilizing a volatile anesthetic (typically sevoflurane or desflurane), a paralytic (typically rocuronium or vecuronium), and an intravenous propofol infusion. Patients did not receive inotrope or vasopressor infusion during the study protocol. Vascular access was obtained in the bilateral common femoral veins, and diagnostic catheters were placed in the right atrial appendage, coronary sinus, and His position.

Baseline measurements

Because the study was limited to patients with paroxysmal AF, patients began the study in NSR. Before the experimental protocol began, baseline electrophysiologic intervals (AH, HV) were recorded, as is standard practice for all patients presenting for EP study. Pacing from the right atrial appendage and distal coronary sinus (3 o'clock position in the left anterior oblique projection) was used to measure right atrium and left atrium atrial muscle effective refractory periods (AMERP), respectively (drive cycle length 600 ms, with S1-S2 interval decrements of 10 ms). The presence of spontaneous firing prior to AF induction was also noted. Burst atrial pacing was then utilized (decrementing from 250 ms to either 200 ms or the shortest cycle length that captured the atrium 1:1, whichever resulted in AF induction first) to induce AF. Measurements of the duration of pacing-induced AF, number of burst pacing attempts required to induce AF, and the AF cycle length (averaged over 30 consecutive beats) were recorded. Burst pacing was performed until any single episode of AF occurred that lasted longer than 30 beats, or 15 attempts, whichever came first. In 11 patients (5 sham, 6 LL-EMF), 5 cc of venous blood was drawn from the central venous sheaths to measure baseline levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8 and monocyte chemoattractant protein (MCP)-1. Serum was saved frozen at -80°C. Investigators analyzing these samples were blinded to group assignment. Patients remaining in AF after 15 minutes underwent DCCV to NSR.

Figure 1 Study device. The device is designed for the patient's head and upper neck to lie in the center of the electromagnetic field created by the Helmholtz coil situated around the headrest. The device connects to an external stimulator, which provides the specified field strength and stimulation frequency.

This was to negate the effects of any acute electrophysiologic remodeling that might have made the patient more prone to remain in AF after the protocol was complete, which could have reduced the efficacy of the procedure.

Stimulation protocol

The study device is a Helmholtz coil attached to a commercially available EMF stimulator. The Helmholtz coil allows for placement of the system around the participant's head and upper neck (Figure 1). This stimulation site is intended to target the brainstem and vagus nerve as it exits the jugular foramen. The system is designed to create an isotropic magnetic field with a field strength from 1 to 99 pico-Tesla (pT) and a frequency range of 0.01 Hz to 50 Hz. After baseline measurements were recorded, the stimulator was set to the protocol to which the patient was randomized (stim 1 or stim 2) and turned on.

The active stimulation protocol is specifically targeted for vagal stimulation. The rationale and evidence for LL-EMF as a biological stimulus has been previously described, and is based on several hypotheses and assumptions put forth by Saxena and colleagues.[19] Briefly, for any given molecule of mass *m,* a strength and frequency of an applied magnetic field can be specified that will impart energy to the molecule to perform biological action. Field strength is calculated using the following equation:

$$mc2 = BvLq \quad (1)$$

where m is molecular mass, c is the speed of light, v is the relative velocity of the "carrier" of the molecule (ie, the patient), L is the length of the "carrier" (ie, patient height), and q is a unit charge in coulombs.[19] Appropriate stimulation frequency is then calculated using the following equation:

$$F = qB / 2\pi m \quad (2)$$

where q is the molecule's charge, m is molecular mass, and B is the previously calculated field strength.[19]

It must be acknowledged that the exact mechanism whereby EMF is able to affect biological action is incompletely understood. Yu and colleagues[18] were able to demonstrate a reduction in AF inducibility by targeting vasostatin-1 in a dog model using a field strength of 0.034 μG at 0.952 Hz. Because of differences in molecular weight between dog and human vasostatin-1, and variability in the "l" parameter caused by application of the LL-EMF to only a portion of the patient's body, the stimulation parameters need to be modified. After we discussed these issues with Saxena et al,[19] the parameters 0.032 μG at 0.89 Hz were selected, though it must be acknowledged that these were empirically chosen.

During the stimulation time, transseptal puncture and mapping of the left atrium was performed, as is standard practice for this procedure, but no ablation was performed. After the 60-minute protocol was complete, right and left atrial AMERP were again measured as described previously. The presence or absence of spontaneous firing was again noted prior to burst pacing. The same pacing protocol as described previously was then employed, noting the number of attempts required to induce AF, duration of pacing-induced AF, AF cycle length, and measurements of right atrial / left atrial AMERP, AH, and HV. In the same 11 patients as before, another 5 cc venous blood sample was drawn (within 5 minutes of protocol completion) prior to retesting, stored, and analyzed as previously described.

The primary endpoint of the study is the duration of pacing-induced AF after the 1-hour study protocol compared between sham and EMF groups. Other endpoints analyzed included the proportion of patients experiencing spontaneous firing after stimulation, the proportion of patients requiring DCCV after stimulation, AF cycle length, number of attempts required to induce AF, electrophysiologic intervals (right atrial / left atrial AMERP, AH, HV), and levels of TNF-α, IL-6, IL-8, and MCP-1 compared between the 2 groups. Safety endpoints include procedure duration, incidence of subjective neck or back pain reported after the procedure, and the incidence of major complications known to be associated with the ablation procedure (pericardial effusion, major bleeding, stroke, conduction system damage requiring temporary or permanent pacing, esophageal or phrenic nerve injury, myocardial infarction, and death).

Statistical analysis

A mixed linear model, with adjustment for the respective baseline values, was used to compare the change in each continuous variable before vs after stimulation between groups, including electrophysiologic as well as inflammatory

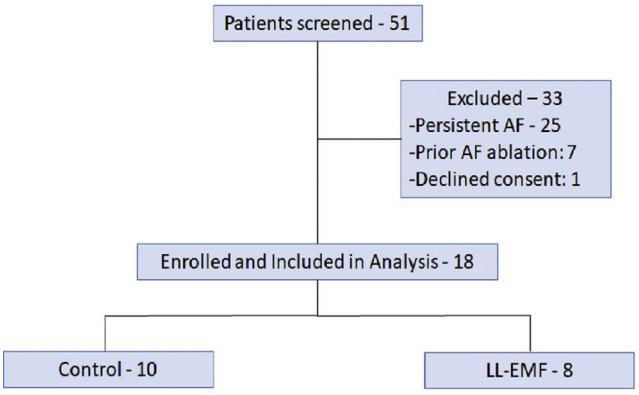

Figure 2 Screening and enrollment flow. AF = atrial fibrillation; LL-EMF = low-level electromagnetic fields.

marker data. The Tukey-Kramer method was used to adjust for multiple comparisons. Residual plots were created to evaluate the appropriateness of modeling assumptions, including normality of the residuals and constant variance. The Fisher exact test was used to compare the proportion of patients who experienced spontaneous firing initiating an episode of AF after the 1-hour stimulation period, as well as the proportion of patients who required DCCV after the 1-hour stimulation period. The Wilcoxon signed rank test was used to compare the change in levels of each inflammatory mediator before vs after LL-EMF stimulation within the active protocol group separately. Continuous and categorical demographic data are presented as mean ± standard deviation or percentages, as appropriate. Baseline characteristics were compared using the Student *t* test or Wilcoxon rank sum test, or χ^2 test or Fisher exact test (if more than 20% of the expected counts from the contingency table were less than 5 or if any of the expected counts were 0), where appropriate. The proportion of patients who developed adverse events were compared between the intervention and control groups using a χ^2 test or Fisher exact test.

As this was a pilot study, no prior studies exist regarding the use of EMF to suppress AF inducibility in humans. The study by Stavrakis and colleagues[15] utilized a similar protocol, albeit with tragus stimulation as the means of autonomic modulation. Pacing-induced AF duration in the stimulation group was 10.4 ± 5.2 minutes (mean ± standard deviation) vs 18.5 ± 5.6 minutes in the control group. Assuming a power of 0.8 and a 2-sided significance level of 0.05, we determined we would need a total of 9 paired (pre- vs post-intervention) comparisons in each group (18 total patients) to detect this difference.

Results

From September 2018 through April 2019, a total of 51 eligible patients presented to our EP lab for ablation of AF. Patient flow during screening and enrollment is demonstrated in Figure 2. Baseline characteristics are listed in Table 1. As shown, there were no significant differences in measured baseline characteristics between the sham and active protocol groups.

Electrophysiologic effects of LL-EMF stimulation are summarized in Table 2. Of note, the protocol–time interaction was negative for all continuous variables. With respect to the primary outcome, the adjusted pacing-induced AF duration was not significantly different at baseline between the sham and LL-EMF group (9.28 ± 7.4 minutes vs 4.73 ± 6.47 minutes, $P = .53$). The adjusted pacing-induced AF duration was significantly shorter in the EMF group compared to the sham group after 1 hour (difference 11.00

Table 1 Baseline characteristics

	Control (n = 10)	EMF (n = 8)	*P* value
Age (years)	59 (57–63)	59.5 (54.5–64)	.78
BMI	33.5 (27.2–36)	27.5 (22.97 – 32.1)	.21
Male	5 (0.5)	3 (0.38)	.66
Time from diagnosis (months)	36 (24–60)	24 (18–66)	.69
Hypertension	5 (0.5)	4 (0.5)	>.9
Diabetes	1 (0.1)	3 (0.38)	.27
Coronary disease	0 (0)	1 (0.13)	.44
Obstructive sleep apnea	5 (0.5)	4 (0.5)	>.9
Ejection fraction (%)	55 (55–59)	55 (55–59.5)	.6
CHA_2DS_2VASc score	1 (0-1)	2 (1–2)	.4
Beta-blocker	4 (0.4)	4 (0.5)	>.9
ACEi/ARB	0 (0)	2 (0.25)	.18
Amiodarone	0 (0)	2 (0.25)	.18
Other AAD	6 (0.6)	5 (0.63)	>.9
Left atrial size (cm)	4.5 (4.28–5.16)	4.07 (3.63–4.92)	.26
Left ventricular septal thickness (cm)	1.1 (1.05–1.2)	1.1 (1.1–1.25)	.7
Cryoballoon ablation	7 (0.7)	5 (0.63)	>.9

All categorical variables were analyzed using Fisher exact test because of low expected counts in the contingency table. The Wilcoxon rank sum test was used to compare continuous variables because of the small sample size. Data are presented as median (interquartile range) or count (proportion).

AAD = antiarrhythmic drug; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index.

Table 2 Electrophysiologic changes

	Control (n = 10)		EMF (n = 8)		
	Baseline	1-hour	Baseline	1-hour	*P* value
AF duration (min)	9.28 ± 7.4	12.18 ± 5.95	4.73 ± 6.47	3.65 ± 5.49	.03
AF cycle length (ms)	202.82 ± 25.27	202.58 ± 25.89	216.78 ± 19.19	230.21 ± 32.14	.13
Attempts at induction	5.3 ± 3.92	3.3 ± 2.45	2.5 ± 2.27	2.88 ± 3.83	.20
RA AMERP (ms)	216 ± 21.19	218.75 ± 22.32	212.4 ± 42.34	222.86 ± 50.24	.25
CS AMERP (ms)	246.67 ± 21.79	245.71 ± 35.52	241.25 ± 30.44	238.57 ± 40.18	.36
AH interval (ms)	77.22 ± 21.57	79.33 ± 22.45	87.5 ± 43.87	97.29 ± 47.31	.52
HV interval (ms)	46.56 ± 7.3	41.71 ± 8.06	43.63 ± 4.66	43.14 ± 3.18	.31

P values are for the comparison of each parameter between electromagnetic field stimulation and sham after the 1-hour protocol after adjustment for the baseline measure. Data are presented as mean ± standard deviation.

AF = atrial fibrillation; AH = atrial-His; CS AMERP = coronary sinus atrial muscle effective refractory period; EMF = electromagnetic field; HV = His-ventricular; RA AMERP = right atrium atrial muscle effective refractory period.

± 3.43 minutes [confidence interval 3.72–18.28 minutes, $P = .03$]) (Figure 3). As noted in Table 2, none of the other electrophysiologic intervals measured were different after the 1-hour protocol compared between the 2 groups.

Because of the decision to perform DCCV if an episode of AF lasted 15 minutes or longer, we also chose to compare the proportion of patients who required DCCV between the 2 groups before and after stimulation. At baseline, a similar proportion of patients in each group required DCCV because the induced episode of AF lasted 15 minutes or longer (6/10 [0.6] in the control group vs 2/8 [0.25] in the LL-EMF group, $P = .19$). AF was terminated by DCCV in all cases lasting longer than 15 minutes, and no patients had spontaneous organization to atrial tachycardia or atrial flutter. In all cases lasting less than 15 minutes, AF terminated spontaneously. After the 1-hour stimulation period, a significantly greater proportion of patients in the control group required DCCV as compared to the LL-EMF group (7/10 [0.7] vs 1/8 [0.13], $P = .02$). Likewise, the proportions of patients experiencing firing after 1 hour were 8 of 10 in the control group vs 0 of 8 in the LL-EMF group ($P = .001$).

Table 3 shows a comparison of levels of inflammatory markers before vs after stimulation in each group in patients with venous blood samples available. MCP-1 was significantly lower in the LL-EMF group compared to the sham group (difference 121.70 ± 50.74 pg/mL [confidence interval 4.70–238.70, $P < .05$]). There were no significant differences in any of the other inflammatory markers after the 60-minute stimulation period.

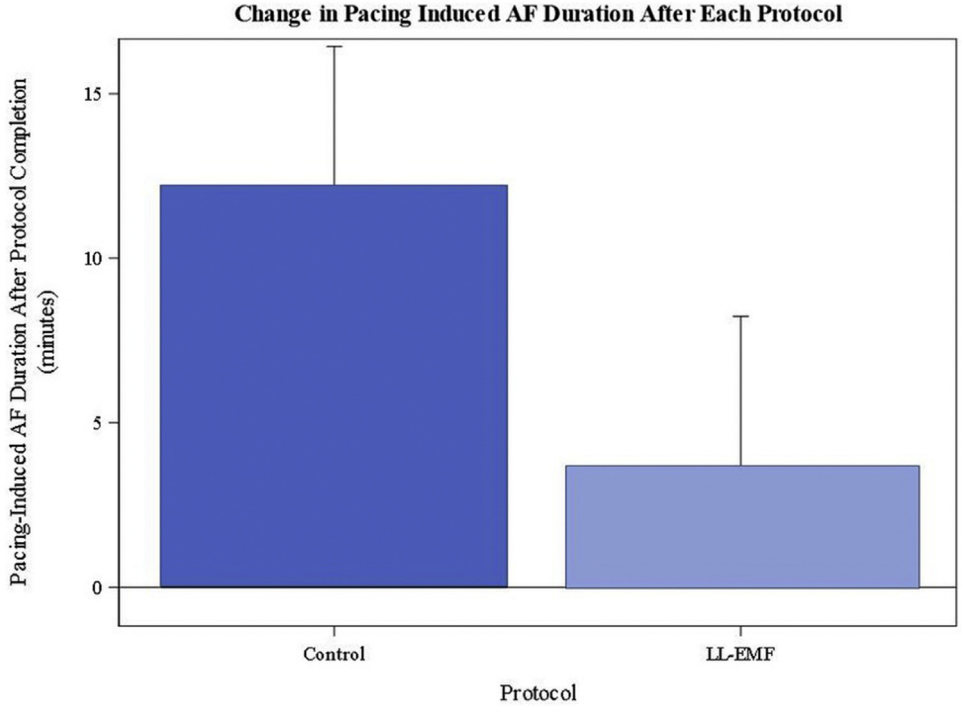

Figure 3 Difference in pacing-induced atrial fibrillation (AF) duration after protocol completion. Bar height represents postprotocol mean pacing-induced AF duration. Whiskers represent confidence intervals on point estimate of pacing-induced AF duration in each group. AF = atrial fibrillation; LL-EMF = low-level electromagnetic field.

Table 3 Changes in inflammatory markers

	Control		EMF		
	Baseline	1-hour	Baseline	1-hour	*P* value
TNF-α (pg/mL)	5.82 ± 4.95	4.41 ± 2.94	2.87 ± 2.46	1.76 ± 1.54	.56
IL-6 (pg/mL)	3.05 ± 2.39	7.82 ± 4.19	2.37 ± 1.64	5.15 ± 2.34	.94
IL-8 (pg/mL)	9.49 ± 7.67	18.77 ± 32.09	7.85 ± 3.55	5.74 ± 1.8	.08
MCP-1 (pg/mL)	306.4 ± 203.03	189.94 ± 111.75	259.33 ± 142.18	137.63 ± 51.46	<.05

P values are for the comparison of each marker between electromagnetic field and sham stimulation after the 1-hour protocol after adjustments for baseline levels of each marker. Data are presented as mean ± standard deviation.

EMF = electromagnetic field; IL = interleukin; MCP = monocyte chemoattractant protein; TNF = tumor necrosis factor.

Discussion

Several studies have demonstrated that ANS dysfunction has a pivotal role in the pathophysiology of AF.[20,21] Previous studies in animal models suggest that LL-EMF can have significant autonomic modulation that can lead to the suppression of AF.[18] In the present study, we investigated—for the first time—the effect of an externally applied LL-EMF on the inducibility of AF in patients with AF. Our investigation included an analysis of AF inducibility, changes in levels of systemic inflammation, and electrophysiologic changes in the right and left atria owing to LL-EMF application. The principal findings of the study were a significantly reduced pacing-induced AF duration in patients exposed to LL-EMF as opposed to sham stimulation, and significantly reduced proportion of spontaneous firing in patients exposed to LL-EMF as compared to sham stimulation. We also noted a significant reduction in MCP-1 levels in the LL-EMF group compared to sham.

Despite the theoretical basis for LL-EMF as a biological stimulus outlined above, the exact mechanism whereby LL-EMF can serve as a vagal stimulus, or why the specific parameters used in this study were effective, remains unclear. Stavrakis and colleagues[15] were able to demonstrate a reduction in AF inducibility using a 60-minute stimulation period. Although the method of vagal stimulation differs in our study, we chose this as a starting point with the hypothesis that LL-EMF would provide a vagal stimulus of similar magnitude as was seen in that study. Additionally, the exact reason why the field strength and stimulation frequency used in our study proved effective remains unclear. As noted above, the stimulation parameters used by Yu and colleagues to target vasostatin-1 in a dog model would be expected to be different than the parameters used to target vasostatin-1 in humans. This is complicated by the fact that the site of stimulation (neck vs whole body) differs between our study and that study, meaning that the "l" parameter in equation 1 would differ in our study (and, in fact, may invalidate the use of this equation altogether given that the EMF is not being applied to the whole body). It is also unknown how differences in patient body size might affect the impact of LL-EMF on autonomic stimulation. These issues were discussed with Dr Jacobsen, and the parameters ultimately used in this study were empirically chosen. Thus, the exact mechanism whereby our specific stimulation parameters were able to suppress AF inducibility remains unclear.

As is evident from Figure 3, the control group experienced an increase in pacing-induced AF duration after the 1-hour study period, while a similar increase was not seen in the LL-EMF group. Thus, LL-EMF appears to have exerted a protective effect, preventing an increase in pacing-induced AF duration, as opposed to causing a decrease in pacing-induced AF duration. The reason for the increase in pacing-induced AF duration seen in the control group is unclear. There was a numerical difference in pacing-induced AF duration at baseline, and although this was not statistically significant, there may have been a greater degree of remodeling in the sham group that translated into an increase in pacing-induced AF duration. Additionally, as noted in Table 2, pacing-induced AF duration in the control group at baseline was 9.28 ± 7.4 minutes, and it is possible that this degree of sustained AF caused enough acute electrophysiologic remodeling or sympathetic stimulation to make AF more inducible 1 hour later. Data in the literature are sparse with respect to the exact timing of electrophysiologic remodeling after AF onset, though several animal studies have been performed to address this question. The classic study by Wijffels and colleagues[22] demonstrated a dose-response effect of pacing-induced AF duration, though on the hours/days time scale. Other studies have shown changes in atrial refractoriness and ganglionated plexus output with as short as 30 minutes of pacing.[23,24] If ganglionated plexi hyperactivity and dysautonomia occur in the acute setting during pacing-induced AF, this provides a theoretical explanation for the beneficial effect of LL-EMF on pacing-induced AF duration noted in our study.

To our knowledge, this is the first study to report on the effect of LL-EMF on spontaneous firing initiating AF. Like the results for pacing-induced AF duration, the proportion of patients who experienced firing was higher in the control group as compared to the LL-EMF group. This again points toward a protective effect of LL-EMF on AF inducibility. As with pacing-induced AF duration, the reason for the increased probability of firing seen in the control group after the 1-hour period is unclear. Although acute electrophysiologic remodeling is a possible mechanism for increased pacing-induced AF duration, this is less likely the mechanism for spontaneous firing, as firing is felt to be a result of CANS remodeling and dysautonomia. One possible explanation is an increase in sympathetic output resulting from the initial pacing-induced AF episode, which could then result in

spontaneous firing and AF induction in patients with a susceptible substrate. If this were true, the salutary effect of LL-EMF may again be related to parasympathetic stimulation, this time by modulating the increased sympathetic outflow brought about by the initial pacing-induced AF episode, which is then able to prevent subsequent firing and AF initiation.

As noted above, there were no significant changes in AMERP as measured from the right atrium or left atrium (via the coronary sinus), or AH or HV intervals when compared between the control and LL-EMF groups (Table 2). Although our study was not powered to detect differences in these parameters, differences in LL-EMF as compared to other methods of parasympathetic stimulation may also explain the lack of effect. Vagal stimulation via LL-EMF may simply be too weak to exert an effect on tissue refractoriness, while pulmonary vein (PV) firing and other electrophysiologic parameters involved in AF maintenance may be "easier targets" (ie, require less parasympathetic stimulation to demonstrate a beneficial effect). Multiple changes in tissue refractoriness, ion channel function, conduction velocity, and action potential duration are required to sustain AF, and it is possible that vagal stimulation via LL-EMF affects each of these parameters differently. Thus, it is possible for LL-EMF to reduce pacing-induced AF duration without having a measurable effect on effective refractory period, as assessed by the extrastimulus testing protocol performed in our study. Alternatively, stimulation parameters calculated to energize a different molecular target (eg, vasostatin-1, which has previously been demonstrated to have a beneficial effect on AF inducibility) may have been able to exert a more targeted vagal effect on the CANS, and could have had a measurable effect on the other electrophysiologic parameters measured in this study. Thus, the lack of effect on tissue refractoriness and AV conduction properties may have been a result of incorrect stimulation parameters, as opposed to a general failure of LL-EMF as a method of vagal stimulation.

We were able to demonstrate a reduction in MCP-1 concentration in our study, though none of the other inflammatory mediators differed significantly between groups. In the study by Stavrakis and colleagues,[15] they noted a 2.3 $\pm$ 0.3 pg/mL reduction in levels of TNF-α with vagal stimulation, though their study was larger (20 patients in each group), and so our study may have simply been underpowered to detect this difference. Congruent with their study results, we also failed to find a reduction in IL-6 or IL-8 levels with LL-EMF. It may be that levels of inflammatory mediators are differentially affected by a given level of vagal stimulation, though an underlying mechanistic reason for this differential effect is unknown. Additionally, levels of all mediators were low in both groups, as would be expected for an otherwise healthy population of patients undergoing AF ablation. While the degradation kinetics of MCP-1 are not as well characterized as for other inflammatory mediators, it has been estimated to be as short as 10 minutes.[25] Notably, animal models of MCP-1 plasma kinetics have demonstrated a salutary effect of vagal stimulation. Hong and colleagues[26] demonstrated a reduction in MCP-1 levels after vagus nerve stimulation via the tragus in a mouse model of endotoxemia. Similar data were seen in a study of healthy volunteers, where transcutaneous vagal stimulation was noted to reduce levels of MCP-1 as well as IL-8,[27] though exact plasma levels were not reported in that study. Although our study did demonstrate lower MCP-1 levels, this requires further investigation with a larger sample size and control group comparison.

Future directions

A logical question stemming from this research involves the applicability of LL-EMF as a clinical means to reduce AF. In the ambulatory setting, this would require patient access to a device capable of delivering LL-EMF using the parameters described in our study. Magneceutical Health currently manufactures such a device, though its only FDA-approved indication is to "enhance feelings of relaxation." Whether this device (or similar devices) would have efficacy in reducing AF burden in the ambulatory setting will require further study.

Limitations

The present study has several limitations. Principally, the exact mechanism underlying the proposed salutary effect of LL-EMF is unknown. We have outlined the theoretical basis for the biologic effect of LL-EMF, but we must acknowledge that, because of the site of stimulation, variations in patient size, interindividual variations in molecular weight of targeted vagal mediators, and the empirical nature of the stimulation parameters used, inconsistencies remain between the proposed mechanism of LL-EMF stimulation and the effects seen in this study. Thus, drawing a clear mechanistic link between LL-EMF and the treatment effect seen in this study is not possible. Second, the sample size is relatively small, making inferences regarding a true group–time interaction difficult to interpret. Data on several potential confounders (eg, mean volume of fluid administered in each group, AF episode duration prior to study inclusion) were unavailable for analysis, and although randomization should theoretically have alleviated this issue, the small sample size does increase the chance of confounding. This issue is magnified with respect to examination of inflammatory markers, where only a subset of participants had samples available for analysis. Third, we are unable to definitively comment on the source of firing that initiated AF in the control patients, and thus cannot draw a definitive mechanistic link between LL-EMF and reduced likelihood of PV firing, though in general, the proportion of patients experiencing firing in the LL-EMF group was significantly lower than in the control group. Fourth, pacing-induced AF is a nonphysiologic measure, and additional clinical data are required (eg, the effect of LL-EMF on AF burden in the ambulatory setting) to demonstrate the usefulness of LL-EMF in AF suppression clinically. Although there are some data to suggest AF inducibility correlates with AF recurrence after catheter ablation, it is

unknown if AF inducibility in the pristine patient caries the same prognostic significance.[28] Fifth, the decision to perform the study with all patients under general anesthesia likely impacted the study results. Although this effect was likely equivalent across both groups, the magnitude of the effect of LL-EMF would likely have been different had a different anesthetic regimen been used. Finally, we arbitrarily decided to cardiovert pacing-induced AF lasting longer than 15 minutes to reduce the effect of sustained AF on procedural efficacy after completion of the study protocol. If we had allowed AF to continue until it terminated spontaneously, the pacing-induced AF duration (and thus the treatment effect) may have been different when the 2 groups were compared.

Conclusion

In this first-in-human, proof-of-concept study in patients with paroxysmal AF, LL-EMF stimulation results in significantly shorter episodes of pacing-induced AF, as well as a reduced likelihood of spontaneous firing initiating an episode of AF, compared to sham stimulation. Larger studies are warranted to confirm these findings and provide further mechanistic insights.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

The authors have no conflicts of interest to disclose. Study device provided by Magneceutical Health.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients gave written informed consent prior to study participation

Ethics Statement

The institutional review board at the University of Oklahoma Health Sciences Center reviewed and approved the study protocol, and the study was conducted in accordance with the principles in the Declaration of Helsinki.

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