[Original]

The Effect of Long-Term Pulsing Electromagnetic Field Stimulation on Experimental Osteoporosis of Rats

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Abstract : The author performed experiments in order to investigate what biological effect on the bone would be produced by long-term pulsing electromagnetic field (PEMF) systemic stimulation. In some of the mature female rats used as experimental animals, bilateral ovariectomy and right sciatic neurectomy were performed in order to make a model of osteoporosis. PEMF stimulation was produced by repetitive pulse burst (RPB) waves at a positive amplitude of 25 mV, negative amplitude of 62.5 mV, burst width of 4.2 ms, pulse width of 230 μ s and 12 Hz, with the magnetic field strength within a cage being set at 3-10 Gauss. PEMF stimulation over 6 months did not produce any effects on the physiologically aged bones. PEMF stimulation also did not produce any effects on losed cortical bone in osteoporotic hindlegs. On the other hand, an increase of bone volume and bone formation activity was observed in the cancellous bone of osteoporotic hindlegs. These findings suggested that PEMF stimulation exerted a preventive effect against bone loss of osteoporotic hindlegs. Furthermore, an observed increase in bone marrow blood flow seemed to be related with this increase of bone volume and bone formation activity.

Key words : rat, osteoporosis, pulsing electromagnetic fields, bone marrow blood flow.

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Introduction

Recent attention has been paid to the phenomenon that bone formation may be promoted by micro-electrical current stimulation. In 1953, Yasuda (1984) expanded his biodynamic research relating to callus formation and demonstrated that bending of the long tubular bone was associated with development of electrical current. He called this "piezoelectric phenomenon". Furthermore, by passing direct micro-electrical current through the rabbit femoral bone, he found a large amount of callus at the negative pole, and he called this "electrical callus" because it was generated by electrical current. In 1955, Yasuda *et al.* (1984) reported first the clinical applications of the phenomenon to the treatment of fresh fracture, delayed union, pseudoarthrosis, Perthes disease and bone cyst. Later in and after the 1960s, Bassett (1962), Bassett & Pawluk (1964), Friedenbergs & Brighton (1966), Friedenbergs *et al.* (1970, 1974), Brighton & Heppenstall (1971) and Krauss & Lechner (1972) published their experimental and clinical reports on promotion of bone union by micro-electrical current.

Electrical stimulation is produced by various methods, such as direct current, pulse wave, alternating current, electrolet teflon membrane and pulsing electromagnetic fields (PEMF). Unlike direct stimulation, PEMF stimulation is noninvasive and can provide uniform magnetic fields over a relatively extensive area. Therefore, this can be more easily applied to living bodies. The biological effect of PEMF stimulation on the bone has been reported as to not only the promotion of bone union of fractures but also the promotion of bone union in congenital pseudoarthroses (Bassett *et al.*, 1981; Sutcliffe & Goldberg, 1982) and improvement of blood flow in avascular necroses (Rinsky *et al.*, 1980). However, the mechanism of the biological effect on the bone has not yet been fully clarified.

The purpose of this study is to investigate whether long-term PEMF stimulations are able to prevent bone loss due to pathological osteoporotic conditions.

Materials and Methods

1. Material

A total of 94, 8 months Wister female rats (multiparous IV, weighing about 200–250 g) was studied. Of these animals, 64 received a pre-treatment of bilateral ovariectomy and right sciatic neurectomy, and were called the operated group. Of this group, some rats began to receive PEMF stimulation 3 months after the pre-treatment lasting over a period of 6 months. Depending on experimental conditions, 94 rats were divided into 4 groups of unoperated/unstimulated (control), unoperated/stimulated (u/s), operated/unstimulated (o/u) and operated/stimulated (o/s). These rats were sacrificed at 3, 6 and 9 months after the beginning of the experiment as shown in Table 1.

2. Cage and generator of PEMF stimulation

Both the cage and the generator of PEMF stimulation were made in this department. Cages, each measuring $28 \times 38 \times 16$ cm, were piled up in 4 layers, and 2 or 3 rats were fed in each cage and allowed free access to Nihon Clea's pellets (CE-2) and tap water. Rats of the stimulated group were placed in the piled-up cages the outside of which was coiled around with Holmar's copper wires (0.80 mm diameter). These wires were connected to the generator of PEMF. Repetitive pulse burst (RPB) with a burst width of 4.2 ms, pulse width of 230 μ s and 12 Hz was passed through this coil from the generator of PEMF and the magnetic field strength within these cages was set at 3–10 Gauss (Fig. 1).

Table 1. Classification of experimental conditions of rats

Group	No. of rats sacrificed			
	3 months	6 months	9 months	Total
Unoperated/unstimulated (control)	6	5	9	20
Unoperated/stimulated			10	10
Operated/unstimulated	9	11	15	35
Operated/stimulated		12	17	29
Total	15	28	51	94

Fig. 1. Diagram showing the outline of 12 Hz repetitive pulse burst (RPB). The magnetic field strength within the cage reached 3 Gauss at the central part and 10 Gauss at the marginal part.

3. Item of observation

For reference, body weights were measured every month, and serum-Ca, -P and -ALP levels were measured by an autoanalyzer (Olympus' improved model of ACA 8000) at the time of sacrifice.

a) Soft X-ray observation

After complete removal of soft tissues, the right femur was put on an aluminium plate (2 mm thick) and irradiated together with the aluminium slope wedge at exposure conditions of 5 mA, 34 KVp and 60 min and at a distance of 45 cm. The length of the femur was measured by a slide caliper and then the indices were calculated at the central part of the femur by the microdensitometry (MD) method (Inoue *et al.*, 1980, 1981).

b) Measurement of the bone strength

Using the stretching/compressing tester (Shimadzu's Autograph S model), strength of the right tibia was tested under the bending load. The tibia was placed on a supporting table (2.0 cm span) in such a way that its middle part was loaded from the medial to the lateral side, and the loading to the rupture was measured by delineating the load-time curve under the condition of a full-scale weight of 10 kg, cross head speed of 5 mm/min and chart speed of 40 mm/min.

c) Measurement of bone marrow blood flow

Using a UH meter PHG-201 (Unique Medical), which contained the hydrogen clearance system, bone marrow blood flow was measured at the diaphysis of the right femur. Under the anesthesia, a 0.4 mm diameter hole was drilled at the diaphysis, and a platinum electrode of 0.3 mm diameter was inserted into bone marrow quickly as a barrier electrode and fixed in the hole. Plate-type silver chloride electrodes as non-barrier electrodes were embedded under the skin of the thigh. When the respiratory conditions of these rats were stabilized at 70–90/min, they were allowed to inhale hydrogen together with room air, and these clearance

curves were measured. Blood flows were calculated according to the method of Aukland *et al.* (1964) and Whiteside *et al.* (1977a).

d) Light-microscopic observation

Using the Yoshiki (1983) method with H. E. staining which was retreated with cyanuric chloride during fixation, decalcified samples were prepared from the cross section of the right femur at its middle part and the sagittal section of this bone at its distal metaphysis. Furthermore, undecalcified samples of the same parts were also prepared according to the method of Konno & Takahashi (1983), and some of them were examined by Villaneuva bone staining, while others by Villaneuva Goldner staining. Bone histomorphometry by Cosmozone 98 (Nikon), the system for picture analysis, was also used on these decalcified samples. Parameters used were those proposed by Takahashi (1983).

Results

All groups showed weight increases with time, which was more prominent in the operated groups than in the unoperated ones. PEMF stimulation did not have any influences on body weight (Fig. 2). No specific changes were observed for serum-Ca, -P and -ALP levels (Table 2).

Macroscopic examination of soft X-ray pictures of the right femur in the operated groups revealed osteoporotic changes in the cancellous bone together with thinning of the cortical bone width as early as 3 months. After that, those changes did not show any

Fig. 2. Changes in body weight.

C : Unoperated/unstimulated (Control) group

U/S : Unoperated/stimulated group

O/U : Operated/unstimulated group

O/S : Operated/stimulated group

* $P < 0.05$ ** $P < 0.01$ (t-test vs. control group)

Table 2. Biochemical findings of serum samples

Group	Month	N	Ca(mEq/ℓ)		P(mg/dl)		ALP(U)	
			Mean	SD	Mean	SD	Mean	SD
Unoperated/unstimulated (control)	3	4	5.6	0.9	6.1	2.0	27.5	8.6
	6	4	5.2	0.2	3.7	1.0	14.9	1.9
	9	9	5.1	0.3	4.0	0.9	18.3	2.0
Unoperated/stimulated	9	8	5.1	0.2	3.4	1.7	20.0	2.4
Operated/unstimulated	3	9	4.4	0.5	6.8	0.9	25.9	4.6
	6	9	4.8	0.5	5.1	1.4	23.0	5.7
	9	15	5.1	0.2	4.5	1.7	24.2	2.5
Operated/stimulated	6	12	4.3	0.6	4.5	1.0	17.1	5.5
	9	16	5.2	0.4	4.7	2.2	20.8	4.6

marked progressions. There was no difference between the stimulated group and the unstimulated one (Fig. 3).

The length of the right femur slightly increased with aging, but no differences were observed among these four groups (Fig. 4).

In the operated groups, the middle part of the right femur showed an increase in Δ value and a decrease in MCI value by the MD method, while there were no significant differences between the stimulated groups and the unstimulated ones. Δ GSmin, Δ GSmax and Σ GS/D values, generally accepted as indices of the bone density, were found to be significantly lower in the operated groups. However, the bone density tended to be higher in the o/s group than in the o/u one (Table 3).

In the 3-point bending test of the right tibia, the operated groups showed a decrease in the rupture-inducing loading volume, but showed a recovering tendency at 9 months. However, there was no significant difference between the stimulated group and the unstimulated one (Fig. 5).

The marrow blood flow in the diaphysis of the right femur was found to be significantly lower at 3 months after the beginning of the experiment in the operated group than in the unoperated one. But after that, the flow in the operated group gradually increased subsequently, especially the flow of the o/s group showed a value considerably closer to the one of the control group at 9 months (Fig. 6).

Histologically, the cortical bone of the operated groups showed a decrease in the bone volume (Fig. 7), which was supported by the measurement of the cortical-total area ratio (Table 4). However, there were no differences between the stimulated group and the unstimulated one. In the cancellous bone, the operated groups showed thinning and decreasing of the trabecular bone with decreasing of the osteoid (Fig. 8). These were reflected in decreases of the trabecular bone specific volume (tVsp), mean trabecular thickness (MTT) and relative osteoid volume (ROV) under the histomorphometry. Furthermore, the operated groups showed a decrease in the fractional formation surface (FrFs). As to the effect of PEMF stimulation, there were no differences between the control group and the u/s one, while all of tVsp, MTT, ROV and FrFs were found to be greater in the o/s group

than in the o/u one (Table 4).

Discussion

The effect of electrical stimulation on the bone has been investigated mainly from the aspect of promotion of bone union. Bassett *et al.* (1982) reported that the clinical application of PEMF stimulation yielded good results in about 80% of the patients with 1007 ununited fractures and 71 failed arthrodeses. Furthermore, Bassett (1984) reported that in nonunions and delayed unions, the fracture gap is bridged by fibrocartilage and blocks vascular invasion for months or years until calcification has occurred. Normally, calcifica-

Fig. 3. Osteoporotic changes of the femur in the operated groups.

tion of this tissue ensues, setting the stage for vascular penetration, chondroclasis, and replacement by fiber and lamellar bone. PEMF stimulation not only increases the calcium content of chondrocytes but also appears to trigger calcification of the "blocking" fibrocartilage so that the normal final phases of fracture healing can follow. However, much is still unknown about the extremely complicated mechanism of PEMF stimulated bone induction. There has also been few reports on the effect of PEMF stimulation on various conditions of bone except bone union.

The essential pathology of osteoporosis may be described as a decrease in the total mass of bone below levels needed for mechanical support (Heaney, 1965). No etiology

Fig. 4. Length of the right femur.

C : Unoperated/unstimulated (Control) group

U/S : Unoperated/stimulated group

O/U : Operated/unstimulated group

O/S : Operated/stimulated group

* $P < 0.05$ (t-test vs. control group)

Table 3. Index values at the middle part of the right femur by the microdensitometry method

Group	Month	N	D(mm)		d(mm)		MCI		ΔGS_{min} (mmAl)		ΔGS_{max} (mmAl)		$\Sigma GS/D$ (mmAl)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Unoperated/unstimulated (Control)	3	4	3.13	0.10	1.89	0.10	0.394	0.038	1.22	0.09	2.05	0.13	1.35	0.06
	6	2	3.25	0.02	1.86	0.02	0.408	0.004	1.28	0.04	2.02	0.01	1.36	0.05
	9	9	3.19	0.12	1.93	0.14	0.395	0.033	1.27	0.14	2.11	0.18	1.41	0.14
Unoperated/stimulated	9	10	3.18	0.23	1.93	0.13	0.391	0.028	1.31	0.09	2.03	0.10	1.41	0.10
Operated/unstimulated	3	5	3.11	0.11	2.06	0.09	0.337	0.013	1.06	0.09	1.87	0.19	1.21	0.10
	6	10	3.10	0.16	2.14	0.12	0.309	0.031	0.99	0.06	1.81	0.12	1.14	0.05
	9	15	3.16	0.17	2.17	0.08	0.315	0.017	1.03	0.10	1.91	0.08	1.21	0.07
Operated/stimulated	6	11	3.08	0.13	2.10	0.11	0.317	0.026	1.04	0.15	1.89	0.34	1.20	0.19
	9	17	3.18	0.11	2.16	0.14	0.323	0.031	1.09	0.11	1.98	0.15	1.27	0.10

Fig. 5. Loading volume inducing rupture of the right tibia in the 3-point bending test.

C : Unoperated/unstimulated (Control) group

U/S : Unoperated/stimulated group

O/U : Operated/unstimulated group

O/S : Operated/stimulated group

* $P < 0.05$ ** $P < 0.01$ (t-test vs. control group)

Fig. 6. Bone marrow blood flow in the right femoral diaphysis.

C : Unoperated/unstimulated (Control) group

U/S : Unoperated/stimulated group

O/U : Operated/unstimulated group

O/S : Operated/stimulated group

** $P < 0.01$ (t-test vs. control group)

Fig. 7. Histological picture of the cross section of the right femur at the middle part.
9 months after the beginning of experiment.
H. E. stain retreated with cyanuric chloride during fixation.

Table 4. Bone histomorphometry at 9 month after the beginning of experiment

Group	N	Cortical bone				Cancellous bone					
		Ac/At ratio(%)		tVsp(%)		MTT(μ m)		ROV(%)		FrFS(%)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Unoperated/unstimulated (Control)	9	58.5	1.7	25.6	6.0	74.8	11.4	8.9	3.0	6.4	1.4
Unoperated/stimulated	10	61.5	4.0	26.4	4.0	69.4	2.0	7.3	3.6	7.9	2.2
Operated/unstimulated	15	51.7	3.2	7.5	2.3	53.8	1.9	3.9	0.6	5.5	1.0
Operated/stimulated	17	54.8	6.1	10.3	3.3	57.6	8.7	6.4	3.9	6.6	0.5

The measurement for the cortical bone was done at the cross section of the middle part of the right femur and the measurement for the cancellous bone was done at the distal metaphysis of the right femur (sagittal section).

Ac/At ratio: Cortical-total area ratio, tVsp: Trabecular bone specific volume

MTT: Mean trabecular thickness, ROV: Relative osteoid volume,

FrFS: Fractional formation surface

Fig. 8. Histological pictures of the saggital section of the right femur at the distal metaphysis. 9 months after the beginning of experiment. H. E. stain retreated with cyanuric chloride during fixation.

has yet been established, although various theories including the estrogen deficiency theory by Albright *et al.* (1941) have been proposed. Presently it is presumed that osteoporosis may be induced by complicated interactions among congenital, endocrinological (PTH, estrogen, calcitonin, active vitamin D and adrenal corticosteroid), nutritional (protein and calcium), and mechanical factors. In preparing a model animal of the disease, therefore, investigators have employed a simplified model. So far, immobilization (Saville, 1969), administration of glucocorticoid (Jett *et al.*, 1970), ovariectomy (Aitken *et al.*, 1972; Orimo *et al.*, 1972; Barzel, 1975) and low Ca diet (Bell *et al.*, 1941; Rowland *et al.*, 1967; Salomon & Volpin, 1972) have been used separately or in combination. In this study, the author employed multiparous mature rats partly because they had a normal ovarian function and partly because the effect of physiological growth could be minimized. Furthermore, from the point of view that clinical osteoporosis is predominant among post-menopausal women, the author employed a model with estrogen deficiency by ovariectomy and disused factors by sciatic neurectomy.

In this study, PEMF stimulation histologically did not have any influence on physiological aged bone and on cortical bone of experimental osteoporosis. The findings of the MD method and 3-point bending test support this. On the other hand, the o/s group presented larger values for all of tVsp, MTT, ROV and FrFS than the o/u one. These findings indicate that PEMF stimulation increased bone formation activity and have a preventive effect against bone loss in the cancellous bone of experimental osteoporosis. Furthermore, the increase of bone formation activity was associated with the increase in bone marrow blood flow. Therefore, it may be reasonable to think that there is a relationship between bone marrow blood flow and bone formation activity.

It has not yet been fully clarified how local bone and marrow blood flows are related to bone turnover. The presence of a close relation between the two is suggested by the facts that vigorous vascular proliferation is associated with a higher bone formation activity in fracture healing, and that a higher bone blood flow was found to be associated with a high rate of bone growth in experiments (Copp & Shim, 1965; Brookes, 1967; Kane & Grim, 1969). Using a hydrogen washout technique, Whiteside *et al.* (1977b) demonstrated that the regional bone blood flow rate was correlated with the osteoblastic activity. Although it is said that PEMF stimulation promotes vascular proliferation in fracture healing, there are few reports describing the direct reaction of blood flow to PEMF stimulation. In their observation at the level of bone micro-vessels using the vital microscopic chamber, Albrectsson (1980) frequently found bone accretion and resorption at regions with relatively wide vessels (25–60 μm) and increased bone remodelling along with decreased blood flow by PEMF stimulation at 15 Hz (Albrectsson *et al.*, 1984). His findings are contradictory to this study. This reason may be due to regional differences in measuring of blood flow, the method of measurement and PEMF stimulation and the non-unitary biological effect of PEMF stimulation.

Table 5 shows a list of authors who investigated the effect of electrical stimulation on experimental osteoporosis. All of the reports document the effectiveness of electrical sti-

Table 5. Reports on the effect of electrical stimulation on experimental osteoporosis

Investigator	Animal	Bone loss induced by	Stimulation
McElhaney <i>et al.</i> (1968)	rat	plaster cast	transcutaneous D. C., A. C.
Kenner <i>et al.</i> (1975)	rabbit	splinting and casting	direct (electrode) 5 Hz pulsed
Martin & Gutman (1978)	rat	plaster cast	transcutaneous A. C.
Bassett <i>et al.</i> (1979)	rat	muscle removal, neurectomy and plaster cast.	PEMF 10 Hz, 65–72 Hz
Cruss <i>et al.</i> (1983)	rat	muscle removal, neurectomy and plaster cast	PEMF 65–72 Hz
Tadduni <i>et al.</i> (1984)	rat	sciatic neurectomy	direct (plate) 60 kHz signal

mulation in preventing bone loss. Bassett *et al.* (1979) and Cruess *et al.* (1983) were the only investigators that employed PEMF stimulation. In their experiments, they noted that PEMF stimulation promoted proteoglycan and collagen and reduced releases of collagenase and prelabelled Ca, thereby preventing bone loss. The experiments presented here were considerably different from those used in the preparing procedure for model rats, the wave form of PEMF, and the methods of observation. The most important difference was that my experiments first demonstrated the preventive effect of PEMF stimulation against bone loss of osteoporosis in association with the increase in bone marrow blood flow.

Nakagawa *et al.* (1973) noted that they had not experienced any side effects caused by considerably long-term magnetic fields stimulation under 1000 Oe on living bodies. The magnetic fields strength in my experiments was extremely weak. However, because much is also unknown about the biological effect of the magnetic field on living bodies, long-term PEMF stimulation should be carefully used in case of clinical applications.

Conclusions

1. The biological effect of 6 months systemic PEMF stimulation on the bone was investigated in hindlegs of rats.
2. PEMF stimulation did not affect the physiologically aged bone.
3. PEMF stimulation did not have any influence on bone loss at the cortical bone of experimental osteoporosis prepared by bilateral ovariectomy and unilateral sciatic neurectomy.
4. On the other hand, the cancellous bone was found to have an increase of bone volume and bone formation activity indicating a preventive effect against bone loss.
5. An increase in bone marrow blood flow appeared to be involved in this increase of bone volume and bone formation activity.

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実験的骨粗鬆症ラットにおけるパルス電磁場長期刺激の影響

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要 旨: 長期にパルス電磁場全身刺激を与えると、骨にいかなる生物学的な影響が及ぶのかを検討する目的にて実験を行った。実験動物として成熟雌ラットを用いて、一部に両側卵巢摘出術と右坐骨神経切除術を施行し、骨粗鬆症のモデルとした。パルス電磁場刺激は, positive amplitude 25 mV, negative amplitude 62.5 mV, burst width 4.2 ms, pulse width 230 μ s, 12 Hz の repetitive pulse burst (RPB) 波を使用し、ゲージ内磁場強度は3-10 Gauss とした。6ヵ月間の刺激にて、生理的加齢骨では、パルス電磁場刺激による影響は骨力学および組織学的には認められなかった。骨粗鬆症モデルの皮質骨での骨量低下に対しても、パルス電磁場刺激による影響は認められなかった。一方海綿骨においては、パルス電磁場刺激群で bone formation activity が上昇しており、骨量低下に対して予防効果が認められた。この bone formation activity の上昇の発現には、骨髓内血流量の上昇が関与しているものと考えられた。

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