# ACUPUNCTURE RESEARCH

# Non-Invasive Treatment to Grade 1 Essential Hypertension by Percutaneous Laser and Electric Pulse to Acupoint with Music: A Randomized Controlled Trial\*

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ABSTRACT Objective: To study a non-drug therapy for hypertension disease by combining percutaneous laser and electric pulse stimulation to acupoint with music, and to test the efficiency of the combining treatment to grade 1 essential hypertension. Methods: A total of 174 patients with grade 1 essential hypertension were randomly assigned to 3 groups with a random number table after Chinese medicine (CM) syndrome differentiation: the photoelectric and musical treatment group (Group 1, with a self-developed multi-mode audio frequency pulse photoelectric therapeutic apparatus), acupuncture group (Group 2), and oral placebo group (Group 3), 58 cases per group. The curative effect of each group was evaluated by the changes of blood pressure and CM syndrome integral before and after treatment. Results: Compared with Group 3, there were significant decrease of blood pressure and CM syndrome integral in Group 1 and Group 2 (P<0.01). Compared with Group 2, Group 1 showed the highest decrease in systolic pressure (P<0.017). The total effective rate of anti-hypertension in Group 1 (91.38%, 53/58) was significantly higher than that in Group 2 (74.13%, 43/58) and Group 3 (18.97%, 11/58, P<0.05 or P<0.01); and that in Group 2 was also significantly higher than that in Group 3 (P<0.01). There were significant difference in the total effective rate of CM syndrome integral in both Group 1 (93.10%, 54/58) and Group 2 (84.48%, 49/58) as compared with Group 3 (17.24%, 10/58, P<0.01), while there was no significant difference between Group 1 and Group 2 (P>0.05). Conclusions: The multi-mode audio frequency pulse photoelectric therapeutic apparatus, combining music, laser and electric pulse stimulation, is clinically useful for grade 1 essential hypertension. This "three in one" therapy method is non-invasive, easy and simple to handle. It is expected to be popularized as a new alternative treatment.

**KEYWORDS** laser and electric pulse stimulation to acupoint, musical treatment, multi-mode audio frequency pulse photoelectric therapeutic apparatus, grade 1 essential hypertension

Hypertension has become a major public health problem.<sup>(1)</sup> The global hypertension prevalence rate has showed trend of a yearly increase for the past few years. Surveys showed that the prevalence of hypertension in Europe and North America was 44.2% and 27.6% in 1990,<sup>(2)</sup> while in China in 2002, the prevalence has increased by 5.2%, about 70 million people, compared with that in 1991.<sup>(3)</sup> A study has also shown that hypertension is the biggest single factor in the global disease burden. It is expected by the year 2025, there will be 1.5 billion people suffering from hypertension worldwide.<sup>(4)</sup>

Hypertension is grouped into two categories: essential hypertension (EH) and secondary hypertension. EH is a kind of cardiovascular disease mainly reflected in the increase of systemic arterial pressure<sup>(5)</sup>—about 95% of hypertension.<sup>(6)</sup> Poorly controlled long-term hypertension affects heart, brain,

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and kidney leading to related illnesses, which finally ends in failure of the organs. It is also a significant risk factor for cardiovascular disease and is one of the major factors for cardiovascular death. Therefore, it is urgent for the public health to seek effective methods to control the disease progression in patients with early stage hypertension (grade 1), and reduce complications. (8,9)

The benefits of antihypertensive therapy mainly depend on the lowering of blood pressure. (10) The current early-stage intervention to EH patients is mainly by drug therapy. Although the effect is obvious, the long-term treatments are expensive and have side effects. (11) Furthermore, the necessity of early intervention to patients suffering from early-stage of grade 1 EH is still controversial. (12) For the low-risk of grade 1 hypertension patients without cardiovascular risk factors and the moderate-risk of grade 1 hypertension patients with one or two cardiovascular risk factors, it is recommended that non-drug therapies should be considered on the premise of monitoring blood pressure and risk factors. (13)

Besides changing unhealthy lifestyles, the non-pharmaceutical therapies also include acupuncture and moxibustion therapy, musicotherapy, musical electro-acupuncture therapy, and laser acupuncture therapy, etc. However, there are few studies on the comprehensive application of percutaneous laser and electric pulse stimulation of acupoints combined with music non-invasive treatment. Therefore, this study implemented a novel multi-mode audio frequency pulse photoelectric therapeutic apparatus (MMAFPPTA, an apparatus which has synergistic therapeutic effect by music, laser and electric pulse stimulation, manufactured by Prof. CHEN Zhongben, patent No. CN201445703U) to do a randomized controlled trial on patients with grade 1 EH.

## **METHODS**

# **Diagnostic Criteria**

Western medicine (WM) diagnostic criteria for grade 1 hypertension is: systolic blood pressure (SBP) 140–159 mm Hg and/or diastolic blood pressure (DBP) 90–99 mm Hg. (13)

# **Chinese Medical Syndrome Differentiation**

Patients were diagnosed as 4 syndrome types of Chinese medicine (CM) according to syndrome

differentiation: Gan (Liver) fire hyperactivity syndrome, yin-deficiency and yang-hyperactivity syndrome, excessive phlegm-dampness syndrome, and yin-yang deficiency syndrome.<sup>(19)</sup>

#### **Inclusion Criteria**

Patients could be included if they (1) were coincided to the WM diagnostic criteria and the CM syndrome differentiation criteria for grade 1 hypertension; (2) age ranged 25–69 years and body mass index (BMI) was 18–30; (3) at the early stage of grade 1 EH; (4) never took antihypertensive drugs or had stopped antihypertensive drugs for at least 2 weeks; (5) signed informed consent forms, voluntarily accepted the therapies and followed the study plan.

#### **Exclusion Criteria**

The exclusion criteria were as follows: (1) patients with secondary hypertension; (2) patients with hypertensive disorders in pregnancy; (3) patients with cardiovascular or cerebrovascular diseases or other vital organs chronic diseases; (4) patients with mental disorders or inability to cooperate with researchers.

#### **Patients**

One hundred and seventy-four patients with grade 1 EH participated in this clinical study in the First and Fifth Affiliated Hospitals of Sun Yet-sen University, and Guangdong Hospital of Traditional Chinese Medicine from July, 2011 to February, 2013. Patients were assigned into 4 CM syndrome types according to syndrome differentiation: 54 with Gan fire hyperactivity syndrome, 57 with yin-deficiency and yang-hyperactivity syndrome, 48 with excessive phlegm-dampness syndrome, and 15 with yin-yang deficiency syndrome. The patients with different syndromes were randomly assigned to 3 groups with a random number table, the photoelectric and musical treatment group (Group 1), the acupuncture group (Group 2) and the oral placebo group (Group 3), with 58 patients in each group (Figure 1). This clinical trial was approved by the Medical Ethics Committee of the Fifth Affiliated Hospital of Sun Yet-sen University (No. 2010S35).

#### **Therapeutic Method**

MMAFPPTA is shown in Figure 2. (1) The instrument's working principle is shown in Figure 3. Multi-mode audio information (such as music tracks) was processed by pulse width modulation audio frequency and was converted into electrical signal

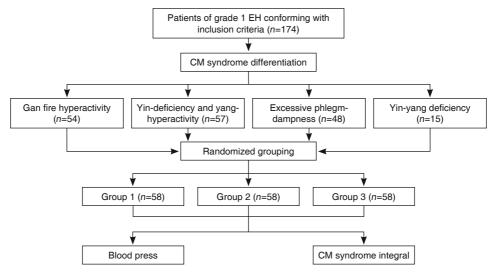


Figure 1. Flowchart of Clinical Trial

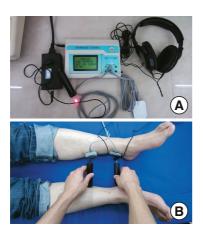


Figure 2. MMAFPPTA

pulses with the equal strength and width (stress time), and the pulse changed with the audio frequency signal strength. This could control the laser output by semiconductor laser unit and the voltage of electrical stimulation output by surface electrode patch, and finally acted on the patients' acupoints. Meanwhile, the patients could listen to the music, of which the original audio signal was amplified. (2) Signal source of pulse audio frequency: selected from "relaxation to decompress" CD album (edited by Prof. ZHUO Da-hong from the First Affiliated Hospital of Sun yatsen University, and was published by Guangzhou

Pacific Audio and Video Company). (3) Instrumental parameter: the output pulse voltage was 0 to 110 V; small semiconductor laser (wavelength: 650 nm, laser spot diameter: 0.5 cm, power: 50 mW).

Group 1: (1) Acupoint selection: bilateral points Taichong (LR 3) and Quchi (LI 11) for Gan fire hyperactivity syndrome; bilateral points Taixi (KI 3) and Sanyinjiao (SP 6) for yin-deficiency and yanghyperactivity syndrome; bilateral points Zusanli (ST 36) and Fenglong (ST 40) for syndrome of excessive phlegm-dampness; bilateral points KI 3 and Guanyuan (RN 4) for yin-yang deficiency syndrome. (2) Acupoint locations: according to "Standard acupoint locations" issued by the World Health Organization. (20) (3) Method of operation: patients were maintained at supine position and the operation area was fully exposed. After cleaning the local skin at the acupoints, the laser acupuncture and electrode were placed on the surface of acupoints. The patients wore headphones to listen to music at the same time. Subsequently, the stimulus signal model was selected and the output signal parameter was set. The treatment time was set to 30 min. (4) Course of treatment: treatment was done once daily, 10 times for a treatment course. The second

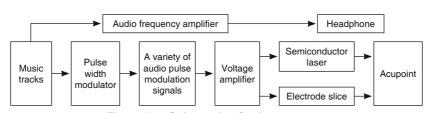


Figure 3. Schematics for Instruments

treatment course was continued after 2-day rest, 3 treatment courses in total.

Group 2: (1) Acupoint selection, location and course of treatment: same with Group 1. (2) Method of operation: patients were maintained at supine position and the operation area was fully exposed. After cleaning the local skin of the acupoints, disposable acupuncture needles were inserted (Hwato brand, purchased from Shanghai Touching Technology Co., Ltd. Needle specifications: diameter is 0.3 mm and the length is 13–50 mm). After the needling sensation was felt, lifting and thrusting or rotating reinforcing and reducing methods were adopted according to the excess and deficiency of syndromes. The needles were in place for 30 min and then removed.

Group 3: (1) Material: placebo starch tablets; specification: 25 mg/tablet. (2) Suggested use: one tablet each time, 3 times per day before meal. (3) Course of treatment: 10 days for a period of treatment, a total of 3 periods.

#### **Curative Effect Observation**

# **Blood Pressure**

The brachial arterial pressure on the right arm before and after treatment was measured 3 times with a 5-min delay between measurements. The evaluation criteria of curative effect in blood pressure were as follows. (1) Marked effect: compared with prior treatment, DBP dropped by over 10 mm Hg and within the normal range; or/and DBP did not drop to normal but has fallen by 20 mm Hg or above. (2) Effect: compared with prior treatment, a. DBP dropped less than 10 mm Hg, but has reached the normal range; b. DBP dropped 10 to 19 mm Hg, but did not reach the normal range; c. SBP decreased by more than 30 mm Hg. (3) No effect: the treatment effect could not meet the above criteria. (19)

#### CM Syndrome Integral

The values of CM syndrome integral before and after treatment were calculated and recorded. The criteria of CM syndrome integral for grade 1 hypertension are shown in Table 1. The main syndromes were classified into none, light, intermediate and heavy levels and scored by 0, 2, 4 and 6, respectively. The minor syndromes were also classified into above 4 levels and scored by 0, 1, 3 and 5, respectively. Tongue and pulse were only taken as dialectical reference, but not scored.<sup>(19)</sup> The evaluation criteria of curative effect in CM

syndrome were as follows. (1) Marked effect: compared with prior treatment, clinical symptoms and signs improved significantly and syndrome integral decreased more than or equal to 70%. (2) Effect: compared with prior treatment, clinical symptoms and signs improved and syndrome integral decreased 30%–69%. (3) No effect: compared with prior treatment, clinical symptoms and signs were not significantly improved or even aggravated, and syndrome integral decreased less than 30%.<sup>(19)</sup>

Table 1. CM Syndrome Integral for Grade 1 Hypertension

CM syndrome	Main syndrome	Minor syndrome
Syndrome of Gan fire hyperactivity	Vertigo, headache, irritability	Flushing, hot eyes, dry mouth, bitter taste, constipation, dark urine, red tongue and yellow tongue coating, wiry and rapid pulse
Syndrome of yin- deficiency and yang-hyperactivity	Vertigo, headache, soreness of waist and knee, dysphoria in chestpalms-soles	Palpitation, insomnia, tinnitus, obliviousness, red tongue and less tongue coating, wiry, thin and rapid pulse
Syndrome of excessive phlegm-dampness	Vertigo, headache, chest congestion, vomiting of phlegm- drool	Palpitation, insomnia, eat little, tastelessness, fat tongue body and greasy fur, slippery pulse
Syndrome of yin- yang deficiency	Vertigo, headache, soreness of waist and knee, extreme chilliness	Tinnitus, palpitation, shortness of breath, nocturia, pale tongue with whitish coating, deep, thin and weak pulse

## Statistical Analysis

The results were presented as mean  $\pm$  standard deviation ( $\bar{x}\pm s$ ). Statistics were assessed using SPSS 19.0. Two independent samples t-test or one-way analysis of variance (ANOVA) was used to compare quantitative variable. Bonferroni test was used to multiple comparisons. Wilcoxon rank sum test or Kruskal-Wallis test was used when data did not conform to normal distribution. Pearson  $\chi^2$  test was used to compare qualitative variable. Differences between means were considered statistically significant when P<0.05.

## **RESULTS**

# **Baseline Characteristics of Study Subjects**

The baseline characteristics of study subjects showed that there was no statistically significant difference in patients' age, gender, course of disease, BMI, SBP, DBP, and CM syndrome integral among

three groups (Table 2).

# Changes of Blood Pressure and CM Syndrome Integral before and after Treatment

Compared with before treatment, the SBP, DBP and CM syndrome integral in Group 1 and Group 2 were significantly reduced after treatment (P<0.01). However, there was no significant difference before and after treatment in the SBP, DBP, or CM syndrome integral for Group 3 (P>0.05, Table 3).

There were statistical differences in SBP, DBP and CM syndrome integral before and after treatment in Group 1 and Group 2 as compared with those in Group 3

(P<0.01, Table 3). The differences in the reduction levels in the three parameters within the three groups were compared by multiple comparisons, which showed that there were statistically significant (adjusted significance level: two-sided  $\alpha = 0.05/3 = 0.017$ , P<0.017, Table 4). Group 1 and Group 2 had significantly higher reduction in all the three parameters compared with Group 3 (P<0.001). There was no significant difference in the reduction in DBP and CM syndrome integral between Group 1 and Group 2 (P>0.017).

#### **Efficacy Comparisons of Blood Pressure**

The total effective rate of anti-hypertension in Group 1 was significantly higher than that in Group 2 and Group

Table 2. Comparison of Patients' Baseline Characteristics among Three Groups

Variable	Group 1 (58 cases)	Group 2 (58 cases)	Group 3 (58 cases)	Statistics	P value
Age (Year, $\bar{x} \pm s$ )	$50.05 \pm 10.74$	$50.19 \pm 10.05$	$49.93 \pm 10.53$	F=0.09	0.991
Gender (Case, male/female)	25/33	27/31	24/34	$\chi^2 = 0.327$	0.849
Course of disease (Year, $\bar{x} \pm s$ )	$3.81\pm2.03$	$3.77 \pm 1.97$	$3.70 \pm 2.04$	F=0.46	0.955
ВМІ	$23.19\pm3.17$	$23.52\pm2.87$	$22.48 \pm 2.76$	F=1.878	0.156
SBP (mm Hg, $\bar{x} \pm s$ )	$150.64 \pm 6.30$	$149.55 \pm 6.62$	$149.79 \pm 6.14$	$\chi^2 = 1.01$	0.603
DBP (mm Hg, $\bar{\pmb{x}}\pm \pmb{s}$ )	$90.91 \pm 5.12$	$91.28 \pm 4.41$	$90.36 \pm 4.82$	$\chi^2 = 1.133$	0.567
CM syndrome integral (Score, $\bar{x} \pm s$ )	$18.24 \pm 7.72$	$18.38 \pm 7.60$	$17.33 \pm 7.56$	$\chi^2 = 0.657$	0.720

Table 3. Comparisons of Blood Pressure and CM Syndrome Integral before and after Treatment ( $\bar{x} \pm s$ )

Group	Case	Time	SBP (mm Hg)	DBP (mm Hg)	CM syndrome integral (Score)
1	58	Before treatment	150.64 ± 6.30	90.91 ± 5.12	18.24 ± 7.72
		After treatment	$128.07 \pm 7.52^{\ast}$	$80.78 \pm 6.47^{\ast}$	$6.05 \pm 3.80^{*}$
		Difference	$22.57 \pm 9.02^{\vartriangle}$	$\textbf{10.14} \pm \textbf{4.85}^{\triangle}$	$\textbf{12.19} \pm \textbf{7.49}^{\triangle}$
2	58	Before treatment	$149.55 \pm 6.62$	$91.28 \pm 4.41$	$18.38 \pm 7.60$
		After treatment	$132.22 \pm 9.81^{\ast}$	$82.81 \pm 6.59^*$	$7.76 \pm 5.00^*$
		Difference	$\textbf{17.33} \pm \textbf{9.76}^{^{\triangle}}$	$\textbf{8.47} \pm \textbf{5.02}^{\triangle}$	$10.62 \pm 6.86^{\vartriangle}$
3	58	Before treatment	$149.79 \pm 6.14$	$90.36 \pm 4.82$	$17.33 \pm 7.56$
		After treatment	$145.78 \pm 11.74$	$88.48 \pm 6.53$	$16.22 \pm 8.29$
		Difference	$\textbf{4.02} \pm \textbf{8.41}$	$\textbf{1.88} \pm \textbf{4.12}$	$1.10 \pm 2.95$

Notes: \*P<0.01, compared with before treatment; ^P<0.01, compared with Group 3

Table 4. Multiple Comparisons of Differences before and after Treatment in the Three Groups

Indices	Comparative group	$ \overline{R}_i - \overline{R}_j $	$\sigma_{\overline{R}_i\!-\!\overline{R}_j}$	Z	P value
Difference of SBP in pre- and post-treatment	Group 1 vs. Group 2	23.017	9.348	2.462	0.014
	Group 1 vs. Group 3	77.095	9.348	8.247	< 0.001
	Group 2 vs. Group 3	54.078	9.348	5.785	< 0.001
Difference of DBP in pre- and post-treatment	Group 1 vs. Group 2	12.552	9.325	1.346	0.178
	Group 1 vs. Group 3	70.647	9.325	7.576	< 0.001
	Group 2 vs. Group 3	58.095	9.325	6.230	< 0.001
Difference of CM syndrome integral in pre- and post-treatment	Group 1 vs. Group 2	7.802	9.342	0.835	0.404
	Group 1 vs. Group 3	75.164	9.342	8.046	< 0.001
	Group 2 vs. Group 3	67.362	9.342	7.211	< 0.001

Note: adjusted significance level: two-sided  $\alpha = 0.05/3 = 0.017$ 

3 (P<0.05 or P<0.01); and that in Group 2 was also significantly higher than that in Group 3 (P<0.01, Table 5).

Table 5. Efficacy Comparisons of Blood Pressure in the Three Groups

Group	Case	Marked effect (Case)	Effect (Case)	No effect (Case)	Total effective rate (%)
1	58	28	25	5	91.38*△
2	58	21	22	15	<b>74.13</b> <sup>△</sup>
3	58	3	8	47	18.97

Notes: \*P<0.05, compared with Group 2;  $^{\triangle}P$ <0.01, compared with Group 3

#### **Efficacy Comparisons of CM Syndrome**

There were significant difference in the total effective rate of CM syndrome improvement in both Group 1 and Group 2 as compared with Group 3 (*P*<0.01), while there was no significant difference between Group 1 and Group 2 (*P*>0.05, Table 6).

Table 6. Efficacy Comparisons of CM Syndrome in the Three Groups

Group	Case	Marked effect (Case)	Effect (Case)	No effect (Case)	Total effective rate (%)
1	58	30	24	4	93.10*
2	58	26	23	9	84.48*
3	58	3	7	48	17.24

Note: \*P<0.01, compared with Group 3

## DISCUSSION

In CM, hypertension belongs to "vertigo", "headache" and "Gan wind" according to its clinical feature and disease course. (21,22) The main syndrome types of hypertension are Gan fire hyperactivity, yin-deficiency and yang-hyperactivity, excessive phlegm-dampness, and yin-yang deficiency. (18) Therefore, we implemented corresponding treatment for each syndrome: clearing Gan fire, nourishing yin and suppressing yang, invigorating the Pi (Spleen) for eliminating dampness and phlegm, and nourishing yin and yang.

Study by Liu, et al<sup>(23)</sup> showed that LR 3 is the most frequent point in the clinic treatment of EH. Combining LR 3 with LI 11 have the function of clearing Gan fire. Wu, et al<sup>(24)</sup> proved that stimulation at LR 3 and LI 11 can regulate the content of angiotensin converting enzyme and endothelin, protect and repair vascular endothelial cells and lower the blood pressure. KI 3 has the function of tonifying Shen (Kidney) yin and clearing deficient heat. The function of SP 6 is to nourish Gan and Shen, engender liquid, activate blood and dissolve

stasis. Their synergism can nourish yin and suppress yang. Chen, et al (25) found that electroacupuncturing at ST 36 can lower the blood pressure in spontaneously hypertensive rats and regulate the content of peripheral nitric oxide (NO). They speculated that one of the antihypertensive mechanisms may be that the regulation of the NO content in plasma could decrease peripheral vascular resistance and lower hypertension. The function of ST 40 is to harmonize Wei (Stomach), eliminate dampness and phlegm and clear mind. Combined with ST 36, they have the function of invigorating Pi, eliminating dampness, harmonizing Wei and eliminating phlegm. RN 4 has the function of tonifying primordial qi, invigorating the Shen and strengthening yang, which has the function of nourishing yin and tonifying yang with KI 3.

Through the whole regulation by point stimulation, acupuncture therapy can reduce blood pressure. (14) The mechanisms are neuroregulation (achieved by the changes of neurotransmitter), humoral regulation (the role of some chemicals in blood and tissue liquid on vascular smooth muscle and cardiac muscle) and the regulation of vascular peripheral resistance (reducing blood density and improving micro-circulation, etc.). (26-30) However, its wide application in clinic is limited due to the micro traumatic defects.

Music can regulate patients' stress and anxiety. Modern researches found that music could lower blood pressure and reduce the heart rate. (31,32) A large number of clinical studies have demonstrated that low intensity He-Ne laser intravascular irradiation and semiconductor laser irradiation in vitro could effectively change indexes of blood rheology, prevent thrombosis and ultimately play a role in lowering blood pressure. (33-36) However, in the research and application of laser therapy and electropulse stimulator at present, the signal exciting methods are usually constant or cyclic repetition. It will produce the phenomenon of adaptability and restrain curative effect in clinical treatment, which will directly affect the efficacy of treatment. (37,38) Due to the large alternations of the stimulus intensity, the widespread musical electroacupuncture apparatus will lead to patients discomfort and fear.

The MMAFPPTA in our project adopted the original pulse width modulation audio signal processing technology. The output of electrical stimulation had the characteristics of diversity and aperiodicity, which made the energy changes but the stimulating intensity was

constant. Therefore, the problem of body's fatigue of adaptability, discomfort and scare caused by long term treatment was solved. Gong, et al<sup>(39)</sup> used this instrument to carry out the laser irradiation on Erjian (EX<sub>11</sub>) and fixed electrodes stimulation on ST 36 of hypertensive rats. The results showed that laser irradiation in combination with electrodes stimulation has relatively significant effect in improving blood rheology and played a certain role in delaying the elevation of blood pressure of spontaneously hypertensive rats.

The results of our study showed that the antihypertensive effect of MMAFPPTA was superior to simple acupuncture, especially the significant reduction of SBP, and the antihypertensive and symptoms improved effects are superior to oral placebo, which indicated that comprehensive and multiple treatments by music, laser and electrical acupoint stimulation for early prevention of hypertension offer significant improvements. At the same time, compared with acupuncture therapy, the body surface electrode patch and external low power laser carried by MMAFPPTA were non-invasive and easily operated.

The mechanism of MMAFPPTA include: (1) Basing on the effects of acupoints, laser and music therapies enhance and improve the effects of smoothing emotions and activating blood and dissolving stasis. (2) Audio information of different models through pulse width modulation audio signal processing technology, is converted into electrical signal pulses with the equal strength and width, which can make the patient feel comfortable. (3) The music electrical stimulation signal changed constantly with music, which can prevent the attenuation phenomenon of curative effect caused by the body's adaptability during later treatment. The limitation of this study is that the observation time is relative short and the sample size is small, thus this proposed technique still lacks substantial clinical evidence for the long-term curative effect for hypertension and it requires for future study.

In conclusion, MMAFPPTA, which combines the antihypertensive effects of music, laser and electric pulse stimulation, is a "three in one" therapy method. Our study has shown that MMAFPPTA had effective regulation on the blood pressure of grade 1 EH patients and could improve their symptoms, signs, and quality of life. In addition, the therapy is non-invasive, easy and simple to handle which increases its prospects as a

popular new alternative treatment.

#### **Conflict of Interest**

The authors declared no conflict of interest.

#### **Author Contributions**

Yang ZB, Shi JL, and Chen ZB designed the study. Zhan HR, Hong ZS, Yang ZB and Chen YS wrote the manuscript. Yang ZB, Zhan HR, Hong ZS and Chen YS performed the statistical analyses. Yang ZB, Zhan HR, Hong ZS, Hong HY and Weng ZB carried out the experiment. Chen ZB provided the research apparatus. All authors read and approved the final manuscript.

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