



Effects of acupuncture with needle manipulation at different frequencies for patients with hypertension: Result of a 24- week clinical observation

Lili Zhang^{a,b}, Hilary Lai^{a,b}, Li Li^{a,b,c}, Xiaoli Song^{a,b}, Guanran Wang^d, Xiaonong Fan^{a,b,c}, Jian Liu^{a,b,c}, Sha Yang^{a,b,c}, Shu Wang^{a,b,c,*}

^a Acupuncture Department, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, PR China

^b National Clinical Research Center for Acupuncture and Moxibustion, Tianjin, PR China

^c Tianjin Key Laboratory of Acupuncture and Moxibustion Science, Tianjin, PR China

^d Department of Medicine, Heilongjiang University of Traditional Chinese Medicine, Harbin, PR China

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ABSTRACT

Objectives: To investigate whether the manipulation parameter of the twirling frequency in acupuncture affects the blood pressure when acupuncture is applied on the acupoints ST9 and LR3 in a human body.

Design: A randomized, controlled trial.

Interventions: A hundred and twenty patients with hypertension were randomized into four treatment groups. A twirling frequency of 120 twirls per minute or 60 twirls per minute were respectively applied on the acupoints ST9 or LR3. Each patient received five acupuncture sessions a week over a period of 12 weeks, with a follow-up period of a further 12 weeks. The outcome was assessed by using an ambulatory blood pressure monitor.

Results: A hundred and twenty twirls per minute on ST9 could overall improve the BP (24hDBP, mSBP, mDBP, dDBP, nSBP and nDBP). Sixty twirls per minute on ST9 improved the 24hDBP, dSBP, dDBP and mDBP; 120 twirls per minute on LR3 did not show any anti-hypertensive effect, while 60 twirls per minute on LR3 improved the dSBP and dDBP. The results indicated that the acupuncture effect on BP, the onset of anti-hypertensive effect, the occurrence of the effect, and the duration of the effect depended on the frequency of needle manipulation on the same acupuncture point.

Conclusions: As one of the important factors of the effects of acupuncture, the manipulation parameter's impact has its specificity for different acupoints. Thus, in the future, close attention needs to be paid to this clinically.

Trial Registration: Chinese Clinical Trial Registry: Chi CTR-TRC-12002582.

1. Introduction

Across the world hypertension, affects one-third of young adults, almost two-thirds of people over the age of 60, and approximately three-quarters of people over the age of 70.¹ In 2010, more than 300 million adults in China had hypertension, and the number continues to increase.² Across the World Health Organization's regions, approximately 62% of stroke and 49% of myocardial infarctions are caused by hypertension.³

Current pharmacological treatments for hypertension can decrease the morbidity and mortality of stroke, heart failure, and heart attacks, but are limited by the high cost and poor adherence.⁴ A Cochrane

review showed that anti-hypertensive drug therapy did not reduce the mortality and morbidity in adults with mild hypertension. About 9% of patients discontinued this pharmacological treatment because of the adverse effects.⁵ Since the current pharmacological treatment for hypertension entails shortcomings, the use of acupuncture to solely treat hypertension or combined with western medicine has increased during the past few years.

Currently, trials evaluating anti-hypertensive effects of acupuncture have shown diverse results. In 2013, the American Heart Association classified acupuncture as a *Class III, no benefit, Level of Evidence B* recommendation for blood pressure (BP)-lowering efficacy⁶ based on two systematic reviews and meta-analysis.^{7,8} Since 2013, one meta-analysis

Abbreviations: 24hSBP, 24-h systolic blood pressure; 24hDBP, 24-h diastolic blood pressure; mSBP, morning systolic blood pressure; mDBP, morning diastolic blood pressure; dSBP, daytime systolic blood pressure; dDBP, daytime diastolic blood pressure; nSBP, nighttime systolic blood pressure; nDBP, nighttime diastolic blood pressure

* Corresponding author at: Acupuncture Department, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 314 West Anshan Avenue, Tianjin 300193, PR China.

E-mail address: wangs2008@163.com (S. Wang).

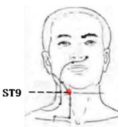
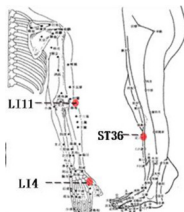


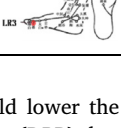
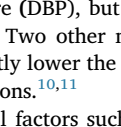
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Table 1
Group Definitions and Acupuncture Regime.

Treatment Group	Main Acupoints and Manipulation Parameter	Matching Acupoints and Manipulation Parameter
ST9-H (ST9 High-Frequency) Group	 Bilateral needle insertion at ST9 Insertion depth: 0.8–1 <i>cun</i> Twirled 120 times within 1 minute	 Bilateral needle insertion at LI4 Insertion depth: 1 <i>cun</i> Angle: about 360 degrees Twirled 60 times within 1 minute
ST9-L (ST9 Low-Frequency) Group	 Bilateral needle insertion at ST9 Insertion depth: 0.8–1 <i>cun</i> Twirled 60 times within 1 minute	 Bilateral needle insertion at ST36 and LI11 Insertion depth: 1 <i>cun</i> Angle: Less than 90 degrees Twirled 120 times within 1 minute
LR3-H (LR3 High-Frequency) Group	 Bilateral needle insertion at LR3 Insertion depth: 0.5–0.8 <i>cun</i> Twirled 120 times within 1 minute	
LR3-L (LR3 Low-Frequency) Group	 Bilateral needle insertion at LR3 Insertion depth: 0.5–0.8 <i>cun</i> Twirled 60 times within 1 minute	

has shown that acupuncture could lower the Systolic blood pressure (SBP) and Diastolic blood pressure (DBP), but it was limited by methodological flaws in the studies.⁹ Two other meta-analyses supported that acupuncture could significantly lower the BP in patients who were taking anti-hypertensive medications.^{10,11}

We have reported that several factors such as the patients' condition, placebo effects, acupoint selection, and manipulation parameter may have led to these contradictions. Many acupuncture trials explored the efficacy of acupuncture, however the question remains of whether the acupoints selected are the best for treating a specific condition for a specific group of patients because of the acupoint specificity.¹²

In the theory of acupuncture therapy, the manipulation parameter is often neglected, yet it is significant in the evaluation of the efficacy of acupuncture. Therefore, conventional evidence regarding the efficacy of acupuncture treatment for hypertension may be inadequate. The work reported here was designed to assess the performance of how different acupuncture twirling frequencies could reduce BP.

2. Methods

2.1. Study design

The study was a randomized, controlled trial.

2.2. Study participants

Eligibility criteria included: (1) essential hypertension with stable BP between 140/90 mm Hg and 159/99 mm Hg (clinic blood pressure); (2) age between 35 years old and 70 years old; (3) duration of hypertension less than 15 years; and (4) no anti-hypertensive medication, no medical contraindications to acupuncture, no history of cerebrovascular events, diabetes, endocrine disorders and renal insufficiency. Pregnant or lactating women or patients participating in any other concurrent clinical trials were excluded. All participants provided a written informed consent.

This study was conducted on 120 participants with mild hypertension (Sample size based on Lee H and Kim SY's (2009) study required to achieve 80% power at a level of significance of 5% was calculated. We anticipate an improvement of 6 mmHg diastolic BP by acupuncture with manipulation method). A hundred and twenty participants were recruited and randomized into one of four acupuncture groups with the ratio of 1:1:1:1. An independent statistician generated a random list of numbers using the SPSS software and concealed all group assignments in opaque envelopes. Each patient received a random number after enrollment. The acupuncturist could only open the corresponding envelope before the first acupuncture treatment for an appropriate treatment protocol.

2.3. Ethics

This trial protocol was approved by the local institutional review board and the ethics committee (the First Hospital affiliated to Tianjin University of Traditional Chinese Medicine Ethics Committee, Tianjin, China (TYLL2012 [K] 001)). All aspects of the study were conducted and adhered to in accordance with the Declaration of Helsinki. Participants were given sufficient time to decide whether to participate in the study or not, and signed a written consent form before commencement of the studies. Participants were allowed to withdraw from the study at any time during the research.

2.4. Intervention

With years of clinical experience in the treatment of cardiovascular and cerebrovascular diseases, academician Shi Xuemin, during the 1970s, formulated the *Huo Xue San Feng (HXSF)* acupuncture regime for hypertension. Since then this regime has been widely applied at the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine. The main acupoints are the ST9 or LR3, and the matching acupoints are LI4, LI11, and ST36. A twirling manipulation parameter of 120 times with a high frequency and a twirling manipulation parameter of 60 times with a low frequency was applied within one minute at the main acupoints in different groups (Table 1).

All participants received 60 acupuncture sessions within 12 weeks at the acupuncture clinic of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine. Licensed acupuncturists administered the treatments. The acupuncture protocol was developed in adherence with the *Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)* guidelines for conducting this acupuncture studies.¹³ The different treatment groups and main acupuncture parameters are defined in Table 1. All patients received an acupuncture treatment following a predefined regime using 0.25*40 mm needles (Hwato needle, manufactured by Suzhou Hua Tuo Medical Instruments Co., Ltd., China). The needle retention time was 30 min.

2.5. Quality control

Acupuncturists who performed the acupuncture therapies had passed the Chinese National Medical Licensing Examination and had at least five years of experience in acupuncture. Prior to the trial, they attended the Standard Operating Procedure of Acupuncture Training for standardized acupuncture processes such as interaction with patients, acupoint selection, and manipulation techniques.

2.6. Outcomes evaluation

Physicians who had no knowledge of the group allocation

Table 2
Cases of Abnormally High Blood Pressure at Enrollment.

		ST9-H	ST9-L	LR3-H	LR3-L
SBP	24h \geq 130 mm Hg	14	20	15	18
	daytime \geq 135 mm Hg	13	17	10	14
	nighttime \geq 120 mm Hg	19	18	17	22
	morning \geq 135 mm Hg	12	13	12	10
DBP	24h \geq 80 mm Hg	23	25	19	22
	daytime \geq 85 mm Hg	21	18	15	18
	nighttime \geq 70 mm Hg	26	24	22	28
	morning \geq 85 mm Hg	17	19	12	14

conducted the evaluation of the outcomes. BP was evaluated by an ambulatory blood pressure monitor (MOBIL-O-GRAPH NG Vers. 20, Germany) at baseline, 6 weeks, 12 weeks, 16 weeks, 20 weeks and 24 weeks after randomization. The daytime (06:00–22:59) BP was measured once every 30 min. The nighttime (23:00–05:59) BP was measured once every hour. The participants were forbidden to drink tea, coffee or other sedative-hypnotics. According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014)¹⁴, a high-level BP is defined as a 24-h average BP \geq 130/80 mm Hg, daytime average BP \geq 135/85 mm Hg, and/or nighttime average BP \geq 120/70 mm Hg.

Outcome measures was changes in the SBP and DBP, including 24-h, daytime, nighttime, and morning (06:00–08:00) from the start to the 3-month follow-up period. Considering that one or two BP indices (24-h SBP/DBP, daytime SBP/DBP or nighttime SBP/DBP) could be normal for many hypertensive patients, only patients with abnormally high BP on enrollment were included in the data analysis (Table 2).

2.7. Statistical analysis

Statisticians in the Statistics Department of the Tianjin Medical University who had no knowledge of the study design, analyzed all data. Demographic information among the groups were compared using the Chi-square test. For the normal distribution data, Repeated Measures ANOVA analysis was used at different observation times. For the skewed distribution data, the Kruskal-Wallis test was employed. The Two-side test was applied and the statistical significant level was set at $p < 0.05$. The outcomes included the 24-h SBP/DBP, daytime SBP/DBP, nighttime SBP/DBP, and morning SBP/DBP. Each data set only included the hypertensive patients at the time of enrollment.

3. Results

From October 2012 to July 2015, 432 patients were screened. A hundred and twenty patients were enrolled and randomized into four groups: ST9-H group (120 twirls/minute at ST9), ST9-L group (60 twirls/minute at ST9), LR3-H group (120 twirls/minute at LR3), and the LR3-L group (60 twirls/minute at LR3). Three hundred and twelve patients who met at least one exclusion criteria were excluded (Fig. 1).

The characteristics of the patients in each group at the start of the studies are shown in Table 3. The gender, age, and the course of hypertension were comparable among the different groups ($p > 0.05$). The cases of abnormally high BP included in the data analysis are shown in Table 4.

3.1. BP changes in two ST9 groups

3.1.1. DBP changes in two ST9 groups

Results showed that applying acupuncture with a high-frequency manipulation of 120 twirls/minute at ST9 gradually and continuously decreased the overall DBP during the 12-weeks course of therapy. The 24-h DBP (24hDBP), daytime DBP (dDBP), nighttime DBP (nDBP) and morning DBP (MDBP) were decreased by 5 mm Hg, 5 mm Hg, 3 mm Hg,

and 8 mm Hg respectively ($P < 0.05$) (Fig. 1.A,C,E,G). Three months after the completion of the 12-weeks of treatment, the 24hDBP, dDBP, and MDBP decreased, but the nDBP did not change (Fig. 2. A,C,G).

There were no major changes in the DBP when applying a low-frequency manipulation of 60 twirls/minute at ST9 after the first half of the 12-weeks course of therapy. However, the prolonged reaction of acupuncture continued to exist after the treatment. The 24hDBP, dDBP, and MDBP were decreased by 2–5 mm Hg, 6 mm Hg and 4–7 mm Hg during the 12-weeks course of follow-up ($P < 0.05$) (Fig. 2.B,D,H).

Compared to the 60 twirls/minute on ST9, the 120 twirls/minute on ST9 showed a better anti-hypertensive effect on 24hDBP and MDBP after the six-weeks course of therapy ($P < 0.05$) (Fig. 2.b,h).

3.1.2. SBP changes in two ST9 groups

For patients in the ST9-H group, the morning SBP (mSBP) was decreased by 18 mm Hg to 19 mm Hg during the 12-weeks sessions, while 11 mm Hg to 17 mm Hg after the sessions (Fig. 2.G). The Nighttime SBP (nSBP) was decreased by 5 mm Hg after six weeks of treatment ($P < 0.05$) (Fig. 2.E). No remarkable benefit was seen for the 24-h SBP (24hSBP) or the daytime SBP (dSBP).

In the ST9-L group, the dSBP gradually and continuously decreased by 7 mm Hg during the 12-weeks course of therapy, and the 12-weeks course of follow-up (Fig. 2.D). The 24hSBP could be decreased by 5 mm Hg to 9 mm Hg during the 12-weeks course of follow-up (Fig. 2.B). Yet no remarkable benefit was seen for the nSBP throughout the study.

Compared to the manipulation frequency of 60 twirls/minute at ST9, the manipulation frequency of 120 twirls/minute at ST9 showed a better anti-hypertensive effect on mSBP after the 12-weeks course of therapy ($P < 0.05$) (Fig. 2.g).

3.2. BP changes in two LR3 groups

3.2.1. BP changes in LR3-H groups

There were no significant changes in the SBP and DBP after the 12-weeks course of therapy with acupuncture using the manipulation frequency of 120 twirls/minute at LR3. The outcome of the acupuncture treatments remained effective for some time after the treatment. 24hSBP, dSBP, and mSBP were decreased by 6 mm Hg, 8 mm Hg and 6 mm Hg during the first month of the follow-up period ($P < 0.05$) (Fig. 3.A,C,G). Only 24hSBP and dSBP still remained low during the second and third months of the follow-up period ($P < 0.05$) (Fig. 3.A,C).

3.2.2. BP changes in LR3-L groups

Acupuncture with 60 twirls/minute at LR3 gradually and continuously decreased the dSBP and dDBP during the 12-weeks course of therapy and the 12-weeks course of follow-up ($P < 0.05$). The dSBP and dDBP could be decreased by about 7–8 mm Hg and 4–5 mm Hg respectively (Fig. 3.D). There were no significant changes in the 24-hs, nighttime and morning SBP and DBP.

Compared to the manipulation frequency of 120 twirls/minute at LR3, the manipulation frequency of 60 twirls/minute at LR3 showed a better anti-hypertensive effect on the nDBP during the third month of the follow-up period ($P < 0.05$) (Fig. 3.f).

The table below is a summary of the anti-hypertensive effects in the four groups: the onset of anti-hypertensive effects (6 or 12 weeks of the acupuncture treatment); effect size (the reduction of BP reading), and the duration of the effects (the effect lasting over 3 months after the completion of the acupuncture treatment). The effects of the acupuncture treatment at Renying (ST 9) and Taichong (LR 3) with different manipulation techniques on the BP varied. 120 twirls/minute at ST9 could improve the overall BP (24hDBP, mSBP, mDBP, dDBP, nSBP and nDBP) while 60 twirls/minute at ST9 improved the 24hDBP, dSBP, dDBP, and MDBP. 120 twirls/minute at LR3 did not show anti-hypertensive effects while the 60 twirls/minute at LR3 improved the dSBP and dDBP (Table 5).

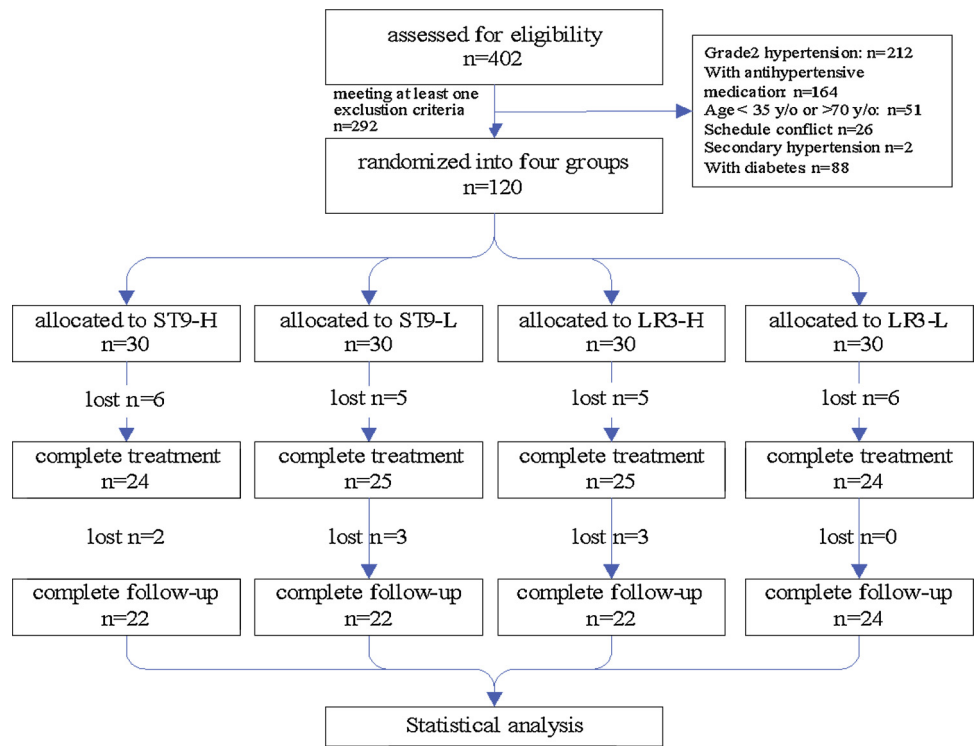


Fig. 1. Study Flowchart.

Table 3
Data Comparisons Among Patients with Mild Essential Hypertension.

Groups	Cases	Gender		Age (Year)	Duration M(P25-P75)
		Male	Female		
ST9-H	29	10	19	56 ± 11	2(1-4.5)
ST9-L	30	8	22	60 ± 5	3(1-5.5)
LR3-H	30	7	23	57 ± 9	3(1-7)
LR3-L	29	8	21	57 ± 11	2(1-3)

Table 4
Cases of Abnormally High Blood Pressure Included in the Data Analysis.

		ST9-H	ST9-L	LR3-H	LR3-L
SBP	24h ≥ 130 mm Hg	9	16	15	15
	daytime ≥ 135 mm Hg	8	14	9	12
	nighttime ≥ 120 mm Hg	13	13	12	19
	morning ≥ 135 mm Hg	9	11	12	9
DBP	24h ≥ 80 mm Hg	18	18	19	17
	daytime ≥ 85 mm Hg	15	13	10	12
	nighttime ≥ 70 mm Hg	21	16	15	22
	morning ≥ 85 mm Hg	11	16	9	11

4. Discussion

Our study was designed to investigate the acupuncture effect on BP, and to verify whether this anti-hypertensive effect is related to the frequency of the needle manipulation. Through the exploration of the acupuncture’s effects on BP in this study, mildly hypertensive patients who did not take any anti-hypertensive medication, and who received five acupuncture treatments per week with different manipulation frequencies at ST9 or LR3 over 12 consecutive weeks, have demonstrated a decrease in their SBP and DBP. Twirling frequencies might elicit anti-hypertensive effects. The results indicated that the acupuncture effect on the BP, the onset of the anti-hypertensive effect, effect size, the occurrence and duration of the effect, can vary based on

the frequency of the needle manipulation on the exact same acupuncture point.

Acupuncture treatments on ST9 with 120 twirls/minute manipulation could decrease an average 24hDBP by 5 mm Hg on the 6th week. Comparatively, the BP-lowering effect with 60 twirls/minute at ST9 appeared to be gradual. The impact of the twirling frequencies at ST9 is shown to be most beneficial, for example, during the daytime (6:00-22:59), and in the morning (6:00-8:00), where the anti-hypertensive effect is obvious. The ST9-L group could gradually decrease dSBP by 7–12 mm Hg, yet the ST9-H group could decrease mSBP by 11–19 mm Hg. The impact of twirling frequencies at ST9 showed its hypertensive reduction in effect size: ST9-H could decrease morning SBP and DBP by 18 mm Hg, and 8 mm Hg during the 12-weeks treatment, yet ST9-L could decrease that by around 3 mm Hg and 4 mm Hg respectively. Acupuncture on LR3 with 120 twirls/minute of manipulation did not decrease the SBP and DBP during the 12-weeks course of treatment. However, acupuncture with 60 twirls/minute at LR3 could decrease the dSBP and dDBP during the treatment and follow-up periods. The results of the *Stop Hypertension with the Acupuncture Research Program (SHARP)* trial¹⁵ showed the reduction of SBP by 3.6 mm Hg and DBP by -4.3 mm Hg. Professor Flachskampf¹⁶ found that after acupuncture, the average BP could drop by 5.4/3.0 mm Hg, and the daytime BP by 6.5/3.8 mm Hg. Li¹⁷ found that electroacupuncture (EA) at PC5-6 and ST36-37 could decrease the average 24-h BP by 6/4 mm Hg with eight weekly treatments.

Interventions for hypertension were designed according to the records in ancient acupuncture books and recent studies of acupuncture. Frequently used anti-hypertensive acupoints described in the systematic reviews are LR3, LI11, and ST36⁷. The ST9, located next to the carotid sinus, is known as the pressure sensor of the human body that regulates BP. An implantable device, the Rheos Baroreflex Hypertension Therapy System, aims to treat patients with resistant hypertension by electrically activating the carotid baroreflex.^{18,19} Studies showed that the continuous stimulation of the carotid sinus,²⁰ especially the unilateral baroreflex activation,^{21,22} with such a device, could in the long term reduce the BP of patients with resistant hypertension.



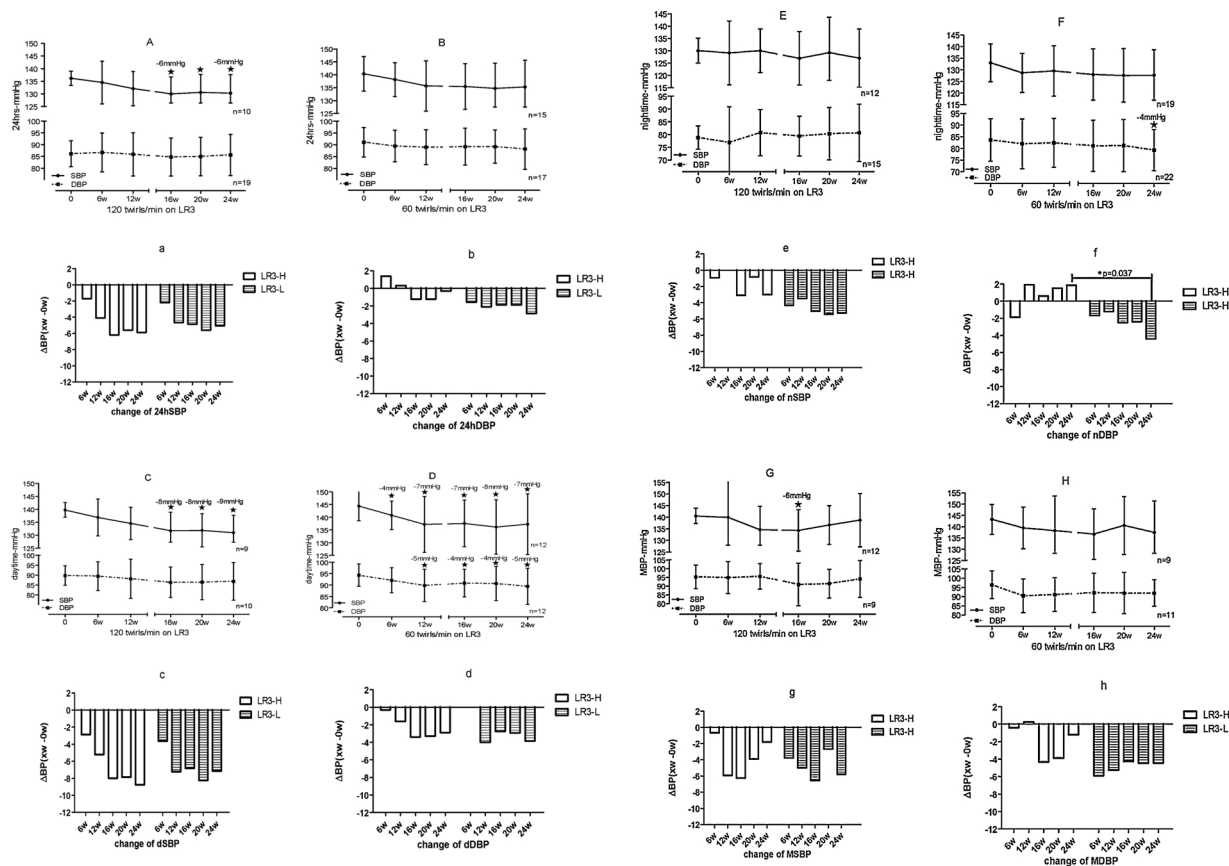


Fig. 3. SBP changes in two LR3 groups. A. 24-h SBP/DBP of patients in LR3-H group; B. 24-h SBP/DBP of patients in LR3-L group; C. daytime SBP/DBP of patients in LR3-H group; D. daytime SBP/DBP of patients in LR3-L group; E. nighttime SBP/DBP of patients in LR3-H group; F. nighttime SBP/DBP of patients in LR3-L group; G. morning SBP/DBP of patients in LR3-H group; H. morning SBP/DBP of patients in LR3-L group; I. change of 24hSBP in the two LR3 groups; J. change of 24hDBP in the two LR3 groups; K. change of dSBP in the two LR3 groups; L. change of dDBP in the two LR3 groups; e. change of nSBP in the two LR3 groups; f. change of nDBP in the two LR3 groups; g. change of mSBP in the two LR3 groups; h. change of mDBP in the two LR3 groups; ★ stands for compared to the BP on 0week, $p < 0.05$. * stands for $p < 0.05$.

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Declarations of interests

The authors declare that there are no conflict of interests.

Author's contributions

SW designed and supervised the study. LLZ contributed to the registration of the trial. LLZ and LL drafted the manuscript. XLS, HL and

GRW contributed to the collection of data. XNF, JL and SY conceived the study, and provided the treatments. All authors read and approved the final manuscript.

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Table 5
The characteristics of the anti-hypertensive effect in the four groups.

	24SBP	24DBP	dSBP	dDBP	nSBP	nDBP	mSBP	mDBP	total
onset time(w)	■ 6 □ 12	■ 6 □ 12	■ 6 □ 12	■ 6 □ 12	■ 6 □ 12	■ 6 □ 12	■ 6 □ 12	■ 6 □ 12	■ 6 □ 12
effect duration (3 m)	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5
effect size (mmHg)	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5	■ 4-5 □ 2-5

□□ stands for ST9-H; □□ stands for ST9-L; ▲ stands for LR3-H; △ stands for LR3-L. (1) The onset time of anti-hypertensive effect: for example, ■6 refers to the onset time of anti-hypertensive effect occurs after 6 weeks of acupuncture treatment in the ST9-H group, while □12 refers to 12 weeks of acupuncture treatment in the ST9-L group. (2) effect duration (3m): the marker refers to the effect lasting 3 months after the completion of the acupuncture treatment. (3) the effect size (the reduction of BP reading): for example, ■4-5 refers to ST9-H group, 24hDBP decreased by 4–5 mm Hg. In the ‘total’ column, we summarized the number of markers. There was no ▲ symbol in the table because that 120 twirls/minute at LR3 did not show anti-hypertensive effects.

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