

## Modulation of Acupuncture on Hypertension

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### 要 旨

アメリカでは心疾患はNo 1 キラーと呼ばれている。特に高血圧が心疾患を起こすリスクファクターとしてその機序解明および新しい治療法の開発にアメリカ国立健康所（NIH）は莫大な研究費用を投入している。近年、鍼治療は代替医学としてアメリカで注目され始めている。著者が所属しているカリフォルニア大学およびハーバード大学を中心に鍼刺激が高血圧に及ぼす影響の基礎および臨床研究が進められている。本総説はアメリカおよび中国で行われてきた高血圧に及ぼす鍼刺激の影響並びに末梢および中枢での作用機序に関する一連の研究を紹介する。これらの実験で自発性高血圧ラットおよび内臓刺激による反射性昇圧ネコ・ラットモデルは使われた。また、鍼が運動による血行動態の反応に与える影響の臨床研究も行われた。鍼刺激は安静時の血圧に影響を及ぼさないが、自発性高血圧および内臓刺激による昇圧反応を有意に抑制した。鍼の効果は10-12時間持続した。将来、高血圧の予防や治療に鍼治療が果たす役割が大きいと期待される。

**Keyword :** Cardiovascular reflex, electroacupuncture, hypertension, opioids

### INTRODUCTION

Acupuncture is one of the few areas of integrative medicine for which the mechanism of cardiovascular action has been explored<sup>1,2)</sup>. Over the last two decades, studies in both China and the United States have used a number of experimental preparations that lend themselves to acupuncture and careful measurement of cardiovascular function<sup>3-11)</sup>. This review paper mainly describes investigations carried out in the United States and China that have explored the peripheral and central neurobiological mechanisms of acupuncture's influence on cardiovascular function, particularly blood pressure.

These studies have been sponsored by the National Institutes of Health, Heart, Lung and Blood Institute. The experimental paradigm used in these studies has been to investigate the influence of acupuncture in a spontaneously hypertensive rats and a feline model of short-term reflex hypertensive responses to visceral organ stimulation, including activation of chemosensitive sensory endings in the gallbladder with bradykinin (BK) or distension of the stomach with a balloon. These conditions simulate sensory nerve stimulation during inflammation and food ingestion, both of which are known to evoke profound sympathoexcitatory reflex

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cardiovascular responses<sup>12,13</sup>. The influence of acupuncture on the hemodynamic response to exercise also has been studied<sup>14</sup> since exercise is well known to raise blood pressure<sup>15</sup>. The rationale for superimposing acupuncture on cardiovascular excitatory reflexes is that, for the most part, acupuncture has little or no influence on baseline blood pressures of normotensive humans or animals<sup>14</sup>. Conversely, elevated blood pressure in genetically hypertensive rats can be lowered by acupuncture for up to 10–12 hours<sup>16</sup>. Here, we review our recent series of experimental studies as well as other groups' studies of the cardiovascular effects of acupuncture on hypertension and show its basic physiological evidence.

#### **ACUPUNCTURE REGULATION OF REFLEX BLOOD PRESSURE ELEVATION DURING GASTRIC DISTENSION AND EXERCISE**

Our group has investigated the ability of acupuncture to regulate reflex elevations in blood pressure in both a rodent (rat) model during activation of mechanosensitive receptors by gastric distension and in humans during exercise<sup>7,10,14</sup>.

Inflation of a balloon in the rat stomach to degrees of distension achieved during food ingestion ( $\leq 20$  mmHg)<sup>10,17</sup>, reflexly increases blood pressure by 20–30 mmHg. We found that 30 minutes of low frequency (2 Hz), low intensity (1–2mA) EA performed bilaterally at the pericardial meridian over the median nerve (Jianshi–Neiguan acupoints, P 5–P 6) as well as at the stomach meridian located over the deep peroneal nerve (Zusanli–Shangquxu acupoints, ST 36–ST 37) but not over the gallbladder meridian, located over the superficial peroneal nerve (Guangming–Xuanzhong control acupoints, GB 37–GB 39), reduced the reflex increase in blood pressure by approximately 45%. The responses

began within 10 minutes of instituting EA and lasted longer following termination of EA at Jianshi–Neiguan (40 minutes) compared to Zusanli–Shangquxu (10 minutes). A new finding in this study was the observation of point specific responses to EA. It demonstrated that stimulation of acupoints over the median nerves caused longer suppression of the reflex blood pressure elevations than stimulating acupoints over the deep peroneal nerves. Furthermore, there was no influence on the reflex cardiovascular response during stimulation of acupoints over superficial somatic nerves. The reduction in cardiovascular reflex blood pressure responses following EA at Jianshi–Neiguan occurred over a range of gastric transmural distension pressures from 5 to 41 mmHg elicited by graded distension of the stomach with a balloon from 5–21 ml. Finally, naloxone administered either intravenously or microinjected unilaterally into the rVLM rapidly reversed the EA–related inhibition of the blood pressure reflex, thus suggesting an opioid–related EA mechanisms in cats during gallbladder stimulation.

The effect of 30 minutes of low frequency (2 Hz), low intensity (1–2 mA) EA at several sets of acupoints, including : 1) Jianshi–Neiguan (P 5–P 6) found along the pericardial meridian over the median nerves, 2) Hegu–Lique (LI 4 –LU 7) along the large intestine and lung meridians overlying the median and ulnar nerves and 3) Guangming–Zuanzhong (GB 37–GB 39) located along the gallbladder meridian over the superficial peroneal nerve, on the hemodynamic response to exercise was evaluated in healthy adult subjects of both sexes<sup>14</sup>. Subjects completed one of two exercise protocols involving electronically braked bicycle ergometry. One protocol involved a ramp increase in workload, increasing 10 watts each minute to exhaustion. The second protocol was a constant load that was

individualized for each subject to allow them to exercise to exhaustion in 8–12 minutes. During the second protocol we assessed the subjects' breath to breath maximal oxygen consumption and anaerobic (lactate) threshold by measuring their gas exchange. EA at any of the three sets of acupoints did not alter resting blood pressure. We found that in 70% of subjects, EA at either the Jianshi–Neiguan or Hegu–Lique acupoints, but not at the Guangming–Xuanzhong acupoints, reduced exercise-induced increases in systolic and mean arterial blood pressures but not diastolic blood pressure or heart rate. EA reduced the blood pressure responses during both exercise protocols. Additionally the calculated rate–pressure product, an index of myocardial oxygen demand was reduced by EA. Furthermore, the absence of effect during stimulation of the Guangming–Xuanzhong acupoints suggests that this acupoint can be used as a good negative control point in studies of the cardiovascular effects of acupuncture, to assess the magnitude of placebo-related responses during acupuncture<sup>18)</sup>.

#### DEPRESSOR EFFECT OF ACUPUNCTURE IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

Yao et al.<sup>16)</sup> used awake adult SHRs and their normotensive control Wistar–Kyoto rats (WKY) to study the effect of acupuncture on them. The femoral arterial blood pressure and heart rate were continuously recorded on a polygraph. In some rats, the splanchnic nerve discharge was also recorded. The sciatic nerve was stimulated with 3 Hz repetitive rectangular pulses of 0.2 ms duration for 30 minutes to mimic EA. The current intensity was started at a level of 4–8 times the twitch threshold ( $0.1 \pm 0.05$  mA) and then increased every 5–10 minutes, reaching 10–25 times that of the twitch threshold in the final 5–10 minutes of the stimulation

period. A few minutes after the onset of stimulation, the rats showed relaxation and lay quiet in the cage. After the stimulation stopped, many rats fell asleep for hours but were easily woken up by light probing or pinching the tail.

In awake and free moving SHR, their blood pressure and heart rate during the control period were about 160 mmHg and 400 beats/min. Stimulation of the sciatic nerve with a low frequency and low current for 30 minutes induced a light pressor response (about 10 mmHg) and increases of heart rate (about 35 beats/min). However, after the cessation of the sciatic nerve stimulation both the blood pressure and heart rate decreased toward the pre-stimulation levels within a few minutes, followed by a further reduction in 1–3 hours. The lowest blood pressure is about 20 mmHg below the pre-stimulation level. The blood pressure did not fully recover to its high level until 12 hours after the termination of sciatic nerve stimulation. While in the WKYs, the same sciatic nerve stimulation also produced an increase in blood pressure and heart rate. However, the post-stimulation depressor response was less pronounced and of shorter duration as compared with the response in SHR. The blood pressure usually returned to the pre-stimulation control level within 2 hours.

This result demonstrate that prolonged low frequency acupuncture-like stimulation of the sciatic nerve induced a long-lasting depressor response that is more pronounced in hypertensive than in normotensive rats. This is again consistent with clinical observations that acupuncture lowers high blood pressure in hypertensive patients while it causes no significant BP alterations in normotensive subjects.

The splanchnic nerve discharges of SHR increased by about 20% during the stimulation of sciatic nerve, but decreased along with the development of a depressor

response after cessation of the sciatic nerve stimulation. The post-stimulation reduction of the splanchnic sympathetic outflow paralleled the fall in blood pressure. This implies that the post-stimulation depressor response is attributed to the sympathetic inhibition.

Yao et al.<sup>19)</sup> showed that when the post-stimulation depressor response had fully developed in SHR, naloxone (10–15 mg/kg, i.v.) almost fully reversed the depressor response for 15–30 minutes. If a bolus dose of naloxone was given 5–10 minutes before sciatic nerve stimulation, followed by a continuous intravenous infusion of naloxone in the following 2 hours, the post-stimulation depressor response was attenuated in a dose-dependent manner, whereas the pressor response and tachycardia were unaffected. The dose of naloxone used here is much higher than that used to reverse the analgesic effect of EA, which is only 1 mg/kg in the tail flick experiments on rats. The mechanism of the difference needs further investigation.

In order to analyze whether the other neurotransmitters were involved in this long-lasting depressor response, the following experiments were done<sup>19)</sup>. Parachlorophenylalanine methylester-HCl (PCPA), a tryptophan hydroxylase inhibitor that reduces the synthesis of serotonin, was used to pretreat the SHR. The acupuncture-like sciatic nerve stimulation produces only a pressor response during the stimulation period, but no post-stimulation depressor response appeared. This indicates the possible participation of serotonin in the mechanism of the depressor response. If the rats were pretreated with benzerazid and peripheral decarboxylase inhibitors and 5-HTP, the precursor of serotonin, were given 30 minutes later, the acupuncture-like sciatic nerve stimulation was followed by a more marked post-stimulation depressor response. The magnitude of the was greater than that of the response induced by either

5-HTP alone or sciatic nerve stimulation alone, showing an additive effect. The effect of 5-HTP was attributable to an increase in the central serotonin, since the peripheral decarboxylase was inhibited by benzerazid. If the serotonin reuptake inhibitor zimelidine was admitted before the sciatic nerve stimulation, the post-stimulation depressor response was also enhanced. Therefore, there is much evidence to show that serotonin is also involved in the post-stimulation depressor response.

## CLINICAL APPLICATION

In clinic, when doctors or acupuncturists treat hypertensive patients, they will not only use Zusanli or Neiguan, but also like to use more acupoints in one treatment, such as Quchi, Sanyinjiao etc. Underneath these acupoints are deep somatic nerves, which have more myelinated fibres. So to stimulate these points could release more endorphins, gaining a better depressor effect. However, if acupoints are stimulated too much, including acupoints innervated by superficial nerves and unmyelinated fibres, the patient will be overexcited, and no depressor effect can be obtained.

Since the depressor is long lasting (up to 12 hours) doctors treat hypertensive patients once a day or every other day. After treating them for a course (about 10 treatment) stable results are usual, especially in stages I and II.

It should be mentioned that the depressor effect of acupuncture is related to the release of endorphin, 5-HT etc. and activation of their receptors in the brain. Any medicine or chemicals that interfere with the neurotransmitters or receptors in the brain will affect the effect of acupuncture. Of course any medicine or chemicals that help the release of endorphin and activation of opiate receptors etc. will increase the effectiveness of EA.

## CONCLUSION

In summary, western scientists and clinicians have always been skeptical about acupuncture despite its long history since the mechanisms underlying acupuncture's action still remain unclear. Thus, a better understanding, particularly a mechanistic understanding, in addition to rigorous randomized well controlled clinical trials will aid substantially in increasing acceptance of this

promising integrative medical modality by the western medical and scientific communities. In the future, a combination of Traditional Chinese Medicine and Western Medicine will not only promote the development of integrative physiology and neuroscience, but will enhance the effectiveness and reduce the cost of treating disease.

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