

The influence of PC6 on cardiovascular disorders: a review of central neural mechanisms

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ABSTRACT

PC6 is a classic acupuncture point in traditional Chinese medicine. It is considered to be effective when treating cardiovascular disorders. In the present review the authors have focused on the neurophysiological bases of the effects of PC6 stimulation on cardiovascular mechanisms. Experimental studies have shown that the hypothalamic rostral ventrolateral medulla, arcuate nucleus and ventrolateral periaqueductal gray are involved in acupuncture attenuation of sympathoexcitatory cardiovascular reflex responses. This long-loop pathway also appears to contribute to the long-lasting, acupuncture-mediated attenuation of sympathetic premotor outflow and excitatory cardiovascular reflex responses. Acupuncture of PC6 modulates the activity in the cardiovascular system, an effect that may be attributed to attenuation of sympathoexcitatory cardiovascular reflex responses.

The theory of acupuncture developed from traditional Chinese medicine (TCM) techniques dates back to the second century BC.¹ Modern studies have extensively evaluated the beneficial effect of acupuncture on the cardiovascular system,² and it is increasingly clear that acupuncture is effective in treating cardiovascular disorders.³ Acupuncture is used to treat chronic ailments including cardiovascular disease and its symptoms, arrhythmias, palpitations, dyspnoea, vertigo, syncope, hypertension, hypotension and angina.⁴⁻⁸ It has been well documented that acupuncture at PC6 *Neiguan* effectively improves both symptoms and the underlying disease manifestation. In this review, we discuss the correlation between PC6 acupuncture and cardiac function on the basis of central neural mechanisms.

NEUROPHYSIOLOGICAL BASES

The long-loop pathway of the hypothalamic rostral ventrolateral medulla (RVLM), arcuate nucleus (ARC), ventrolateral periaqueductal gray (VLPAG) and medullary raphe are involved in the acupuncture-mediated attenuation of sympathoexcitatory cardiovascular reflex responses. The ARC provides excitatory projections to

the VLPAG, which inhibits premotor cardiovascular sympathoexcitatory activity. RVLM neurons modulate sympathoexcitatory reflexes evoked by visceral afferent stimulation.⁹⁻¹⁰ It is noteworthy that this long-loop pathway also appears to contribute to the long-lasting, acupuncture-mediated attenuation of sympathetic premotor outflow and excitatory cardiovascular reflex responses.¹¹

ROSTRAL VENTROLATERAL MEDULLA

Accumulating scientific evidence has recently shown that PC6 could modulate cardiovascular functions, possibly through the activation of the RVLM area.⁹⁻¹² The RVLM is an important area for cardiovascular activity where the neurons receive inputs from hypothalamic and midbrain defence areas and other cardiovascular centres, as well as baroreceptors, chemoreceptors, cardiopulmonary receptors, somatic and splanchnic nerves and acupoints. The RVLM sends outputs to the preganglionic sympathetic neurons in the intermediolateral column of the spinal cord, where afferent information that ultimately leads to cardiovascular regulation is integrated. The cardiovascular neurons in the RVLM are thus considered to be crucial for the control of peripheral sympathetic tone and cardiovascular activity.¹³ The targeting of a well-recognised set of acupoints, located along the pericardial meridian and positioned directly over the median nerve near the wrist by acupuncture stimulation with low current and low frequency in animals decreases the extent

of myocardial ischaemia by means of the reduction of myocardial oxygen demand, and it reduces sympathoexcitatory cardiovascular reflex responses, partly through an effect on the RVLM.¹⁴⁻¹⁵ Cardiac MRI data provide an accurate and reproducible measurement of stroke volume, ejection fraction, cardiac output, ventricular volumes and ventricular function,¹⁶ thereby providing a reliable method to monitor the effects of acupuncture on the cardiovascular system and to visualise the heart non-invasively with high spatial and temporal resolution. The correlation of time-varying functional MRI response with physiological parameters may provide insight into the relationship between the effects of acupuncture on the autonomic nervous system and neuroprocessing.¹⁷

HYPOTHALAMIC ARCULATE NUCLEUS

Li¹⁵ explained that acupuncture activates the ARC in the hypothalamus, which sends excitatory projections to VLPAG and then to the nucleus raphe obscurus. A recent examination of pathways involved in the inhibitory effect of acupuncture showed that excitation of the ARC, similar to that induced by acupuncture, inhibits RVLM neuronal activity, whereas the inactivation of neurons in the caudal VLPAG abolishes ARC-mediated inhibition (VLPAG panel). Furthermore, it has been shown that excitation of the ARC by electroacupuncture inhibits RVLM neuronal activity, whereas the inactivation of neurons in the caudal VLPAG abolishes this ARC-mediated inhibition (VLPAG panel).¹⁸

VENTROLATERAL PERIAQUEDUCTAL GRAY

The VLPAG influences the acupuncture-associated inhibition of RVLM-mediated sympathetic premotor responses to visceral afferent stimulation. It was recently demonstrated that the extracellular concentration of γ -aminobutyric acid (GABA) in the VLPAG is decreased by acupuncture stimulation at PC5-6, which suggests that disinhibition of GABA in this area may promote the acupuncture-mediated inhibition of RVLM activity, as the projections from the VLPAG to the RVLM are mainly inhibitory.¹⁰ Studies of the role of GABA in the VLPAG have also shown that the endocannabinoid system disinhibits the GABAergic system.¹⁹⁻²⁰ In addition, stimulation at PC5-6 evoked more VLPAG action potentials than splanchnic nerve stimulation, which suggests that this nucleus is important mainly for processing somatic rather than visceral afferent



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information.¹⁸ Therefore, the midbrain VLPAG may be a significant transfer station between the ARC and the RVLM, which probably assists in the processing of somatic information during acupuncture. This pathway appears to contribute to the long-lasting, acupuncture-mediated attenuation of sympathetic premotor outflow and excitatory cardiovascular reflex responses.¹¹

Analyses of heart rate variability have revealed that acupuncture decreases the low frequency/high frequency ratio and increases the high frequency power, which indicates a shift to parasympathetic dominance. However, the observed correlations were weak, possibly because the prefrontal cortex activity induced by acupuncture is not closely linked with autonomic nervous system function.²¹ An investigation of the blood pressure and associated changes in human heart rate variability by manual stimulation of the PC6 indicated that the autonomic innervations of the heart are modified by acupuncture.²² Acupuncture at PC6 and ST36 *Zusanli* can improve ischaemic ECG findings in rats with acute myocardial ischaemia and the nucleus tractus solitarius – a centre that integrates cardiac functional activity.²³ Based on a study of demand-induced ischaemia in cats, Li¹⁴ suggested that stimulation of the median nerve to mimic electroacupuncture diminishes regional myocardial ischaemia triggered by a sympathetically mediated increase in the cardiac oxygen demand.²⁴

EFFECTS OF ACUPUNCTURE AT PC6 ON NEUROTRANSMITTERS

To determine the underlying mechanisms of the effect of acupuncture on the nervous system, the roles of several neurotransmitters in cardiovascular-related regions of the medulla have been examined. During and after acupuncture stimulation, neurotransmitters and neuromodulators such as nociceptin, GABA and opioids, including endorphins and enkephalins acting through μ and δ -opioid receptors in the RVLM, inhibit sympathetic outflow and the resulting cardiovascular sympathoexcitatory response.^{11 17 25} In addition, acetylcholine, endocannabinoids and glutamate appear to contribute to the effect of acupuncture on cardiovascular function in various regions of the hypothalamus, midbrain and medulla.^{26 27} Acupuncture thus probably modulates sympathoexcitatory responses by releasing neurotransmitters that inhibit the activity of bulbospinal presympathetic neurons, and it controls the peripheral

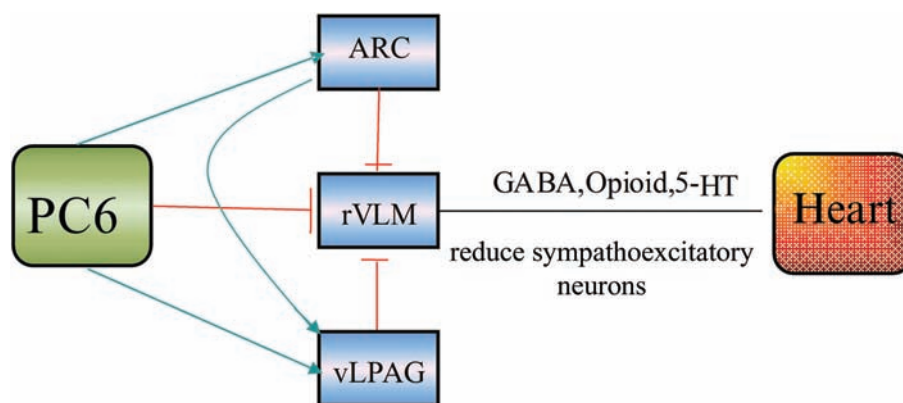


Figure 1 PC6 regulates cardiac function by the central nervous system. ARC, arcuate nucleus; 5-HT, 5-hydroxytryptamine; GABA, γ -aminobutyric acid; rVLM, rostral ventrolateral medulla; vLPAG, ventrolateral periaqueductal gray.

sympathetic tone and cardiovascular activities.

Opioid release from the central nervous system^{11 28} and cardiovascular reflex changes²⁹ are assumed to have physiological roles in eliciting the effects of acupuncture at PC6. The beneficial effect of acupuncture at PC6 on hypertension, cardiac ischaemia and arrhythmias is achieved by reduced sympathetic outflow mediated by the excitation of nucleus raphe obscurus neurons, which inhibit cardiovascular neurons in the RVLM that, in turn, activate opioid,³⁰ GABA²⁰ and 5-hydroxytryptamine (5-HT) receptors.³¹ The midline medulla oblongata, which includes the raphe obscurus, raphe magnus and raphe pallidus, is involved in the regulation of cardiovascular responses. Opioids and 5-HT are regarded as important neurotransmitters in this region. It is therefore likely that the medullary raphe nuclei, particularly the nucleus raphe pallidus, process somatic signals during acupuncture and participate in acupuncture-mediated modulation effects on cardiovascular function by an opioid or serotonergic mechanism.^{25 32} The midline medulla oblongata modulates sympathetic outflow and cardiovascular responses by means of the RVLM,³³⁻³⁵ and the raphe nuclei directly project to the RVLM.³⁶ Opioids and 5-HT function as important neurotransmitters in this region,^{37 38} and during electroacupuncture, serotonergic neurons mediate the input from the nucleus raphe pallidus to the RVLM to inhibit the sympathetic outflow.³¹

EFFECTS OF ACUPUNCTURE AT PC6 ON NEUROMODULATORS NO AND NOS

Nitric oxide (NO) is an essential molecule for signal transmission in the central nervous system, and it is widely distributed

in the cardiovascular centres, including the RVLM.³⁹ NO can reduce the afferent activity of the sympathetic nervous system to provide vasodilation, reduced blood pressure and reduced heart rate variability. These effects may occur at multiple levels, including the hypothalamus, medulla oblongata, sympathetic nervous system of the spinal cord and peripheral sympathetic nerves. NO in the RVLM has been shown to inhibit sympathetic efflux, which reduces cardiac oxygen consumption and is beneficial for cardiac functions.⁴⁰ Many reports have described the distribution of nitric oxide synthase (NOS) in the ventrolateral medulla, which is involved in cardiovascular regulation.^{41 42} Stimulation of PC6 has been shown to upregulate myocardial NO and NOS and decrease the myocardial intracellular calcium level in myocardial ischaemic reperfusion injury rats, which may contribute to its effect in relieving myocardial injury.⁴³ The hypothalamic ARC and its opiate receptors participate in the inhibitory effects of acupuncture on electrostimulation-induced heart ventricular extrasystole in rabbits.⁴⁴

Our conclusions are summarised in figure 1. Acupuncture at PC6 elicits its cardiac effects by reducing the activity of sympathetic neurons. This effect is primarily achieved by adjusting the brain to secrete inhibitory neurotransmitters such as GABA, opioid and 5-HT.

PERSPECTIVES

Acupuncture is a therapeutic modality that is anchored in TCM. The nature of its effect creates unique methodological challenges and controversies, including the choice of a placebo and different forms of treatment based on a non-western system of diagnosis. Nonetheless, standards have

evolved to address these issues.⁴⁵ The usefulness of acupuncture as a complementary and/or alternative therapy in animals is well established, but more research on its clinical efficacy relative to conventional therapy, as well as the underlying mechanisms of its effects, is warranted. When evaluating the effects of acupuncture at PC6 on cardiac function, we should carefully combine modern scientific research methods with classic theory and clinical methods, and we should focus on the development of clinical efficacy.

In summary, an increasing amount of evidence suggests a correlation between acupuncture at PC6 and effects on the heart. Acupuncture at PC6 can stimulate the long-loop pathway to activate the ARC, VLPAG and nucleus raphe pallidus, which inhibit the RVLM to reduce the cardiovascular sympathoexcitatory reflex response through the upregulation of GABA, opioids, 5-HT, NO and NOS. Some clarity remains lacking because of the insufficiency of systematic research. According to TCM theory, which focuses on bidirectional channel conduction, nerves serve a two-way transmission function. Recent studies⁴⁶⁻⁴⁷ have revealed that the magnetic stimulation of the heart meridian on the human body affects brain and spinal cord activity, and this activity is associated with the direction of the magnetic pole. Therefore, the direction of the magnetic pole should be carefully considered when using magnetic therapy. In this review, we only focus on the relationship of PC6 with the heart; future studies should address potential correlations between the meridian and various systematic components.

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