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Acupuncture in Severe, Stable Angina Pectoris: a Randomized Trial

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ABSTRACT. Ballegaard S, Jensen G, Pedersen F, Nissen VH (Medical Department P, Division of Gastroenterology, and Medical Department B, Division of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark). Acupuncture in severe, stable angina pectoris: a randomized trial. Acta Med Scand 1986; 220: 307–13.

Twenty-six patients with stable angina pectoris, resistant to medical treatment, were randomized to either active or sham acupuncture in a single-blind design. Sham acupuncture was defined as the insertion of needles in a point within the same spinal segments as the active acupuncture, but outside the Chinese meridian system. The effect was evaluated from anginal attack rate, nitroglycerin consumption and exercise tests. Compared to patients receiving sham acupuncture the patients receiving active acupuncture increased cardiac work capacity significantly, expressed as dPRP (difference in pressure-rate-product between rest and maximum exercise) and maximal PRP during exercise ($p<0.001$). None of the other variables showed any significant difference between the two groups. Concerning exercise tolerance the median difference was 138 Wmin (95% confidence limits −12.5 to 325 Wmin), concerning anginal attack rate the median difference was 29.5% (95% confidence limits 55% to −11%) and with regard to nitroglycerin consumption the median difference was 5% (95% confidence limits +67% to −44%). No significant effect of sham treatment was observed, no adverse effect was observed. We suggest that acupuncture may improve cardiac work capacity in patients with angina pectoris, refractory to medical treatment. *Key words: acupuncture and angina pectoris.*

Acupuncture is a treatment of disease by the insertion of needles through the skin on specific locations according to empirical Chinese methods (1). In recent years attention has focused on the pain-relieving effect of acupuncture. Both electro-acupuncture and transcutaneous electric nerve stimulation (TENS) have proven effective in alleviating various forms of pain in both animals (2) and humans (3–5) with the effect being mediated through release of neuropeptides in the central nervous system (6).

In recent years the use of acupuncture has increased considerably in the western countries. Open and unblinded studies have suggested a beneficial effect on angina pectoris by TENS (7, 8), electroacupuncture (9) and traditional Chinese acupuncture (10–12).

In the light of positive pilot studies, the aim of the present study was to examine the effect of acupuncture in severe angina pectoris in a randomized trial, which is the universally approved yardstick of effect in western medicine.

METHODS

Patients

Twenty-six patients with stable, medically resistant, exercise provoked angina pectoris (functional class III–IV NYHA) entered the trial. They were all waiting for aortocoronary bypass surgery, had no pre-

Abbreviations: dPRP = difference in pressure-rate-product between rest and maximum exercise, TENS = transcutaneous electric nerve stimulation.

vious heart surgery, no other known competing cause of chest pain, no previous myocardial infarction within the last six months, no valvular heart disease, no severe heart failure, no arterial hypertension WHO group II and III, and no previous acupuncture treatment. Patient characteristics are summarized in Table I.

The patients were selected among 56 consecutive patients with a positive evaluation with regard to aortocoronary bypass surgery. Eleven of these patients were excluded because of long travelling distance, seven refused participation, seven underwent acute operation, two had previous acupuncture treatment, one developed unstable angina pectoris, one severe heart failure and one died.

The diagnosis of exercise provoked angina pectoris was verified by the development of significant ST-depression ($\geq$1 mm in one or more leads) during exercise ECG and more than 50% stenosis of coronary arteries revealed by coronary arteriography. Ejection fraction was calculated from angiographies of the left ventricle, obtained in a right anterior oblique projection (35°).

The antianginal drug-treatment given the patient at the entry of the trial was regarded as optimal and remained unchanged during the study. The patients were told not to change habits concerning daily exercise and smoking. All patients gave informed consent before start of the study, which was approved by the local ethical committee.

Study design

The study period consisted of: 3 weeks of pretreatment control; after randomization 3 weeks of treatment, during which the patients received either active or sham acupuncture, and 3 weeks of posttreatment control. During the entire 9 weeks the patients filled in a diary. Exercise tests were performed immediately before and after the pretreatment control period and just after the treatment period. Due to the nature of the treatment a truly double-blind design was impossible, as the acupuncturist (S. B.) obviously was unblinded. The subjects and the doctor in charge of the exercise test were blinded. The global evaluation was carried out by the other authors on a blind basis as well.

To increase the patients' confidence that they were receiving the correct acupuncture treatment, the acupuncturist employed an electrically resistant measurement device (APF 700 Biometer, Odense, Denmark), which was adjusted to beep over both active and sham acupoints. He then explained to the patient that the beep indicated the exact location of the acupoint and would then confirm the accuracy required for correct needling technique.

Treatment

During the treatment period all patients received seven treatments in the supine position. Active treatment: Acupuncture was given at points Pericardium 6 (Neiguan), Stomach 36 (Zusanli) and Urinary Bladder 14 (Jueyinshu) bilaterally (designed by O. Dahl, M.D., according to traditional Chinese acupuncture theory). The acupoints were identified according to traditional anatomical locations (1). The needles used were Chinese of stainless steel, 30 gauge and 1.5 inches long. After obtaining needle sensation (or the arrival of "Qi") the needles were left in place for 20 min. The arrival of "Qi" is described as the reaction the patient feels when the needle is inserted to a certain depth in the acupoint. The sensation is variously described as sore, aching, numb, heavy, distended or swollen and is not to be confused with the pain a needle might produce when it pricks the skin (13). No electrical or mechan-

Table I. *General characteristics of study groups*

	Active group	Sham group
No. of patients completing treatment	13	13
Male : female	12 : 1	11 : 2
Median age (y.) (range)	54 (40–70)	58 (38–66)
Extension of atherosclerosis 1 : 2 : 3 vessel disease	1 : 7 : 5	0 : 2 : 11
Prior myocardial infarction	8	9
Left ventricular function		
Ejection fraction $\leq$40 %	1	2
Ejection fraction >40%	12	11
Medical treatment		
β Blockage	9	9
Calcium-antagonist	11	12

ical stimulation of the needles was given. Sham treatment: The needles were inserted through the skin in points within the same spinal segments as the acupoints, but outside the Chinese meridian system and were not triggerpoints. In all other respects the treatments were identical. The treatment was carried out in the hospital on an outpatient basis.

Effect evaluation

Effect was evaluated from: Diaries, exercise tests, and subjective global evaluation by the patient at the end of the trial.

The patients were instructed to fill in their diaries daily, stating the number of anginal attacks, activity at the time of the pain attack and nitroglycerin consumption. The diaries were collected after each period, and final evaluation was made at the end of the entire trial.

Three exercise tests were performed for each patient. Exercise tests were carried out on a bicycle ergometer. Workload was increased incrementally by 50 W, exercising 4 min at each step. A 12 lead ECG was recorded continually on paper before, during and for 10 min after the test. Blood pressure was measured by cuff every 2 min in the sitting position and after the test in the supine position. The patients were encouraged to exercise to their maximum limit and to express their symptoms. Exercise variables used in the evaluation were: Exercise tolerance (cumulative work during bicycle exercise test), difference in pressure-rate-product between rest and maximum exercise (dPRP), maximal PRP during exercise, maximum ST-depression and length of time until maximum ST-depression.

After the trial the patients were asked for their global evaluation of the effect of the treatment on an ordinal scale: Improvement of general well-being after treatment/no improvement of general well-being after treament.

Statistics

Between-group differences were evaluated by rank-sum tests for unpaired data (Mann-Whitney). The patients' global evaluation was analysed by Fisher's exact test. Five per cent was chosen as significance level.

RESULTS

No significant difference was detected between the two groups with regard to age, sex, prior myocardial infarction, extension of coronary artery disease, left ventricular function (ejection fraction of ventriculography, medical treatment (Table I), exercise test variables (Table II), anginal attack rate and nitroglycerin consumption (Table IV) at randomization.

All patients completed the trial. No complications or adverse effects were observed.

Table III shows posttreatment exercise variables in the two groups. Patients receiving active treatment had a significantly higher dPRP ($p<0.005$) than the patients receiving sham treatment. The median difference between values on active and on sham treatment was

Table II. *Pretreatment exercise test variables*

Delta PRP is expressed as median, other values as median and range. Delta indicates difference between exercise and rest values

	Active acupuncture	Sham acupuncture
Exercise tolerance (Wmin)	550 (250–975)	368 (88–1 725)
Time to maximal ST-depression (min)	2 (0–4.5)	2 (0–7)
Size of maximal ST-depression (mm)	1 (0–3)	1 (0–3)
Maximal PRP ($mmHgmin^{-1}$)	21.090	18.280
Interquartile range	16.698–23.612	14.300–20.480
Delta PRP ($mmHgmin^{-1}$)	9.690	11.655
Interquartile range	7.528–12.878	6.328–14.177
Delta blood pressure (mmHg)	40 (10–70)	30 (0–50)
Delta pulse	40 (24–60)	32 (19–68)

Table III. *Posttreatment exercise variables*

Delta PRP is expressed as median, other values as median and range. Delta indicates difference between exercise and rest values

	Active acupuncture	Sham acupuncture
Exercise tolerance (Wmin)	550 (150–1 300)	256 (100–1 700)
Time to maximal ST-depression (min)	2 (0–7.5)	2 (0–4.5)
Size of maximal ST-depression (mm)	1 (0–3)	1 (0–2)
Maximal PRP ($mmHgmin^{-1}$)	24.640	13.530*
Interquartile range	15.540–27.540	12.263–17.640
Delta PRP ($mmHgmin^{-1}$)	12.580	6.592*
Interquartile range	7.295–15.440	4.360–9.730
Delta blood pressure (mmHg)	45 (10–157)	17.5 (0–50)
Delta pulse	42 (10–70)	31.5 (20–66)

* $p<0.005$.

6320 $mmHgmin^{-1}$ (95% confidence limits 1 910–10 870 $mmHgmin^{-1}$) (1 mmHg=0.133 kPa). Maximal PRP was significantly higher in the active treatment group as well ($p<0.005$). The median difference between values on active and on sham treatment was 11 650 $mmHgmin^{-1}$ (95% confidence limits 6 020–15 820 $mmHgmin^{-1}$). No significant difference was detected concerning the other exercise test variables, anginal attack rate or nitroglycerin consumption (Table IV). When compared to pretreatment values, there was a significant difference between values on active and on sham treatment, concerning dPRP ($p<0.001$) and maximal PRP ($p<0.001$) but not concerning other variables. Concerning dPRP the median difference between values on active and on sham treatment was 51% (95% confidence limits 16–88%), concerning maximal PRP, the median difference was 28% (95% confidence limits 10–55%), concerning exercise tolerance, the median difference was 138 Wmin (95% confidence limits −12.5 to 325 Wmin), concerning anginal attack rate the median difference was 29.5% (95% confidence limits −11 to 55%) and concerning nitroglycerin consumption the median difference was 5% (95% confidence limits −44 to 67%). With regard to exercise tolerance the improvement is expressed in Wmin instead of per cent as for some patients a comparison between the two pretreatment exercise tests showed a difference of more than 100%, with only a little difference, when the difference was expressed in exact numbers as the subjects were

Table IV. *Comparison of anti-anginal effects of active and sham acupuncture evaluated from patient's diary (median and range)*

	Treatment phase		
	Pretreatment	Treatment	Posttreatment
No. of anginal attacks per 3 weeks			
Active acupuncture	58 (10–167)	51 (4–194)	55 (8–168)
Sham acupuncture	81 (15–155)	74 (1–167)	66 (41–149)
Nitroglycerin consumption (0.25 mg tablets per 3 weeks)			
Active acupuncture	28 (0–190)	27 (0–182)	39 (1–193)
Sham acupuncture	42 (0–108)	28 (0–161)	30 (0–152)

only able to exercise a few minutes on the lowest exercise level. Some of these patients had changes in exercise tolerance after treatment close to 100%, even though there was no improvement with regard to other variables, indicating effect of the treatment. The use of exact numbers in Wmin eliminates this "noise". Concerning missing data the values of the third exercise test are compared either with the average between first and second exercise test or with the existing one, as a comparison between first and second exercise test did not reveal any training effect of other systemic variation. Comparing periods of individual weeks of treatment and posttreatment did not reveal any significant difference between values on active and on sham treatment.

Six of 12 patients in the active treatment group and one of 12 patients in the sham treatment group reported improvement of general well-being after treatment (p=0.10).

DISCUSSION

The present study demonstrated that those who received the active acupuncture treatment had a significant improvement in exercise test variables concerning dPRP and maximal PRP. This may be interpreted as an increase in cardiac function capacity (14). Such an increase would be easily understandable if the patient's pain had been reduced. However, the fact that there has been no significant pain reduction in this trial, brings up the question of other mechanisms, responsible for the improvement in myocardial function. Decreased afterload due to systemic vasodilation is described after treatment of angina pectoris by TENS (8) and increased cardiac output after acupuncture (9, 10) as well as vasodilation in ischemic limbs (15), supposedly mediated through serotonergic pathways, leading to sympatho-inhibition (16). The fact that we could not show a significant improvement of exercise tolerance in the patients might be due to a difference in exercise test methodology, as the workload in this study was increased by 50 W every 4 min, while others use increments of 5 to 10 W/min (8). We did not study haemodynamic variables.

An important question was the selection of the control treatment in an acupuncture trial. If the control group were to receive no treatment, the results of the active treatment could be due to a placebo effect of an unspecific needle effect. If the control group were to receive needles in points in spinal segments, other than those of the active treatment group, it might be concluded that needles inserted in points in different spinal segments cause different effect. We therefore decided that the sham group should have needles inserted in points within the same spinal segment as the active group, to evaluate whether or not a treatment with acupuncture in acupoints had greater therapeutical effect than points chosen at random within the same spinal segment.

The fact that the present study shows that different points within the same spinal segment have different therapeutic qualities might support previous observations that acupoints are sites on the skin with a higher concentration of nerves (17), or support a hypothesis of a correlation between trigger points and acupoints for visceral pain (18).

The present acupoint prescription in the active treatment group consisted both of points with neural relationship to the heart, being within the same spinal segments and of some with no apparent relation. It is impossible to conclude that some points are more important for the achieved effect than others. However, a question arises regarding the selected acupoints that have no apparent neural relationship to the heart. This implies, according to traditional Chinese medicine, the existence of a unique energy system, which is governed by properties, not explained by western medicine. Our findings may in this context support a hypothesis of a synergistic relationship between mechanisms implied by the theory of traditional Chinese medicine and western neurophysiology.

Traditional Chinese medicine employs a method and vocabulary different from western

medicine for describing disease. A symptomatic manifestation, which in western medicine is considered to characterize one disease entity, may according to traditional Chinese medicine be part of different diseases and may therefore lead to different acupoint prescriptions. This, more individually suited treatment plan, should therefore, in theory, more efficiently ameliorate the patient's condition (1, 13). The possibility that another choice of treatment would have produced a different result cannot be excluded. In this trial we selected one of the more commonly used point prescriptions in order to examine the effect of a general treatment.

A large part of the population (30–70%) responds poorly to acupuncture and TENS in general (19–21). Moreover, possibly 5% of the population are hyper-strong reactors, i.e. patients that might respond to a sham treatment (20). Inclusion of general non-responders and hyper-reactive subjects inevitably weakens the statistical power of any clinical trial of acupuncture and TENS. At the present we are examining methods for detecting general non-responders.

In this study there was no significant clinical effect in severe, stable angina pectoris. However, the patients were at an advanced stage of the disease, characterized by symptoms, refractory to medical treatment and coronary arteriograms showing multi-vessel disease in the majority of the patients. In less severely ill patients a clinical effect might have been observed.

Although only one of several variables was significantly improved, we consider the problem of mass significance to be limited as there were other tendencies in the favour of active treatment and in addition the criteria are mutually correlated. This finding of both significant and insignificant results shows that in this trial the number of patients has been too small or the variance of data too great to give rise to parallel findings concerning the different variables. One could go into details about this question through type II-risk analysis. We have expressed the statistical power of the study by calculating the 95% confidence limits of the observed differences between values on active and on sham treatment.

The present study suggests that acupuncture might have a beneficial effect on angina pectoris, additional to that of pharmacological treatment. The results suggest several lines of further study: the effect of acupuncture on cardiac physiology and the effect of acupuncture in patients with angina pectoris, due to less advanced coronary artery disease.

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