Acupuncture improves exercise tolerance of patients with heart failure: a placebo-controlled pilot study

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ABSTRACT

Background Congestive heart failure (CHF) is a complex clinical syndrome with autonomic dysbalance and increased plasma levels of inflammatory cytokines, which further worsen the syndrome. Experimental data have shown that stimulation of certain acupuncture points decreases autonomic dysbalance.

Objective To test the therapeutic potential of acupuncture for life-threatening diseases such as CHF.

Methods 17 stable patients with CHF (New York Heart Association class II–III, ejection fraction <40%) receiving optimised heart failure medication were randomised into a verum acupuncture (VA) and placebo acupuncture (PA) group. Cardiopulmonary function, heart rate variability and quality of life were explored.

Results No improvements of the cardiac ejection fraction or peak oxygen uptake were observed, but the ambulated 6 min walk distance was remarkably increased in the VA group (+32 ±7 m) but not the PA group (−1 ±11 m; p<0.01). Accordingly, post-exercise recovery after maximal exercise and the VE/VCO2 slope, a marker of ventilatory efficiency, were improved after VA but not PA. Furthermore, heart rate variability increased after VA, but decreased after PA. The ‘general health’ score and ‘body pain’ score of the quality-of-life questionnaire SF-36 tended to be improved after VA.

Conclusion Acupuncture may become an additional therapeutic strategy to improve the exercise tolerance of patients with CHF, potentially by improving skeletal muscle function.

INTRODUCTION

Chronic heart failure (CHF) is one of the most serious medical and health economic problems in civilised countries affecting millions of people. The prognosis is dismal despite optimised heart failure medication. During exercise the majority of patients with CHF are limited by dyspnoea and fatigue with medications. During exercise the majority of patients with CHF are limited by dyspnoea and fatigue with medications. Additionally, autonomic dysbalance, including the use of penetrating and non-penetrating needles, and the possible risks of acupuncture treatment (haematoma, infection and fainting). The study was approved by the institutional ethics committee of the University of Heidelberg. Patients were informed about the study design, including the use of penetrating and non-penetrating needles, and the possible risks of acupuncture treatment (haematoma, infection and fainting).

Cardiopulmonary performance and autonomic balance of the patients were assessed before beginning of the acupuncture protocol and 4 weeks after the last acupuncture sessions. This assessment consists of echocardiography, 6 min walk test,
cardiopulmonary exercise test, 24 h Holter monitoring, quality-of-life assessment by a validated/standardised questionnaire (SF-36).

**Echocardiography**

All transthoracic echocardiograms were obtained by experienced investigators unaware of the study. Left ventricular dimensions were measured at the end of diastole on M-mode echocardiograms derived mainly from the parasternal long-axis plane. LVEF was calculated using the biplane Simpson’s method.

**Exercise tolerance**

All patients were familiar with the 6 min walk test for assessment of submaximal exercise capacity as previously described in detail. The symptom-limited exercise test using a ramp protocol on a bicycle ergometer in a semisupine position consisted of a 5 min rest period and 2 min of free pedalling followed by 15 W increments in workload every 2 min at a pedal speed of 55–60 rpm. Minute ventilation (VE), oxygen uptake, carbon dioxide production (VCO₂) were continuously analysed and averaged from eight consecutive breaths (Oxycon Alpha, Jaeger-Vaays Healthcare, Würzburg, Germany). Peak oxygen uptake (pVO₂) was defined as the highest oxygen consumption measured during the last 30 s of symptom-limited exercise. Ventilatory efficiency was calculated from the slope of VE versus VCO₂ over the linear part. For evaluation of post-exercise recovery pVO₂ 1 min after cessation of exercise was determined.

**Holter recording**

From the time series of R–R intervals, SDNN (SD of all normal to normal R–R intervals during 24 h as a marker of overall heart rate variability) was calculated over consecutive 5 min segments, excluding segments with >15 noise or ectopic beats.

**Quality-of-life assessment**

Health-related quality of life was assessed with the SF-36 that was described earlier. It consists of 56 items representing eight subscales that cover the domains of physical functioning, role functioning physical, bodily pain, general health perception, vitality, social functioning, role functioning, emotional as well as mental health. The eight subscales range from 0 to 100 (higher scores indicating better quality of life) and are summarised by the physical component scale and the mental component scale. The completed questionnaire at baseline was compared with the results after 10 acupuncture sessions by an investigator who was blinded to all clinical data.

**Acupuncture treatment**

To achieve comparability, all patients in the verum acupuncture (VA) group were treated according to a fixed selection of six bilateral acupoints and one medial point (see online supplementary table 1 and online supplementary figure 1) through band aid and plastic ring with a 0.30×30-mm stainless steel needle (Asia Med, Munich, Germany). Care was taken that with needle insertion at each VA point, a dull needle sensation (called de qi) occurred, that usually vanished during the course of a session. Acupoints were chosen (a) according to a concept of traditional Chinese medicine (TCM) in CHF-like syndromes (see online supplementary table 1) and (b) if known to alter autonomic function as well. The placebo acupuncture (PA) group received 10 sessions at identical acupoints with a blunted, telescopic placebo needle (Asia Med), as we have described in detail previously. This placebo needle simulates an acupuncture procedure without penetrating the skin. Each PA procedure was performed 2 cm from, but adjacent to, the real acupoint to avoid acupressure effects.

Each patient was scheduled for a total of 10 standardised VA/PA sessions twice a week, over 5 weeks. In both cases, the needle remained for 30 min without additional stimulation. Acupuncture treatment was performed as a standardised VA in a quiet, dimly lit room at a comfortable temperature. Although the rules of TCM would have been best met if individual therapeutic schemes had been used, this was avoided to allow statistical comparison between groups and to keep the placebo effect as small as possible, as individualised treatment would amplify patient–doctor interactions. Both interventions were performed by trained acupuncturists.

**Randomisation and blinding**

After receiving written informed consent from the patients for participating in this study, the acupuncturists obtained randomisation allocation either to a VA or a PA by phone from a member of the Department of Medical Biometry, University of Heidelberg, who had no contact with the study patients. Thus, an adequate concealment was assured and balance between groups ensured. Only the acupuncturists knew the randomisation profile. The patients and the staff doctors were not informed of the allocation. Blinding of the patients was ensured by using the placebo needle in the same therapeutic setting, which has proved to be successful previously. The acupuncturists answered questions about acupuncture using an identical answer catalogue. To assess blinding, questions about the credibility of the treatment according to Vincent and Lewith were posed to each patient after treatment.

**Statistical analysis**

All results are expressed as median and range. Continuous variables of the two groups at baseline were compared using Mann–Whitney test, categorical variables by Fisher’s exact test. The effect of treatment was analysed by comparison of baseline data with data after 10 sessions of PA/VA treatment by Wilcoxon match paired test. A level of p<0.05 was accepted as statistically significant.

**RESULTS**

**Baseline characteristics**

Patients of the VA and PA groups did not differ in clinical baseline characteristics or in the severity and oral treatment of CHF (table 1). In particular, the LVEF (VA 31±9%; PA 29±12%) and maximal exercise capacity (pVO₂ PA 15.2±1.2 ml·min⁻¹·kg⁻¹; VA 14.6±1.9 ml·min⁻¹·kg⁻¹) did not differ from the values for patients of the PA group at study inclusion.

All patients completed the entire acupuncture protocol of 10 treatment sessions without any serious adverse events, such as rhythm disturbances, major bleedings, although almost all patients were receiving oral anticoagulants. Oral heart failure medication remained unchanged during the study period in all patients.

**Effects of acupuncture on exercise tolerance**

Although LVEF remained unchanged after completion of the study protocol in both groups (PA 32±9%; VA 31±1%), patients receiving VA treatment achieved a longer 6 min walk distance than patients of the PA group (figure 1). No differences were seen for maximal exercise capacity indicated by pVO₂ (PA 15.3±1.1 ml·min⁻¹·kg⁻¹; VA 14.6±1.2 ml·min⁻¹·kg⁻¹). Nevertheless, post-exercise pVO₂ recovery as assessed by the half-life of pVO₂ was improved after completion of the VA protocol as compared with PA (figure 2A) and VE/VCO₂ slope, a marker of ventilatory insufficiency during exercise, was improved after VA, but declined after PA as compared with study inclusion (figure 2B).
Effects of acupuncture on autonomic balance
After 10 treatment sessions, patients with CHF receiving VA treatment presented an improved SDNN, whereas heart rate variability in patients receiving PA was decreased (figure 3).

Effects of acupuncture on quality of life
Quality of life as assessed by the SF-36 questionnaire tended to be improved as indicated by the subscale concerning ‘general health perception’ and ‘body pain’ in patients of the VA group, but not in patients of the PA group. Other domains were unaffected (see online supplementary table 2).

Effects of acupuncture on inflammatory cytokines
The data obtained suggested to us that the beneficial effects of VA were mediated by an improved oxygen metabolism and skeletal muscle function rather than an improvement of the cardiac output. In a search for the underlying mode of VA action, plasma levels of tumour necrosis factor α (TNFα) were retrospectively measured (R&D Systems, Wiesbaden, Germany), which was not part of the initial study design. Unfortunately, we did not store plasma samples of all included patients but only of five patients treated with VA and three with PA; these showed an excessive reduction of TNFα in all patients undergoing VA (median TNFα before VA 4.6 (3.5–9.4) pg/ml, after VA 1.3 (0.6–2.2) pg/ml but not of the patients undergoing PA (median TNFα before PA 4.5 (2.7–6.8) pg/ml, after PA 4.6 (4.2–6.1) pg/ml).

**DISCUSSION**
As far as we know, this study is the first prospective, randomised controlled trial investigating the effect of acupuncture, in addition to optimised heart failure medication, in patients with stable CHF. After 10 sessions of VA an increase in submaximal exercise capacity was seen. This was accompanied by improved ventilatory efficacy and recovery after exercise and was associated with provagotonic (and in a subgroup of patients anti-inflammatory) effects. As no serious adverse events occurred, this acupuncture treatment protocol might become a safe and beneficial adjunctive treatment in CHF.

**Exercise intolerance in CHF and skeletal muscle fatigue**
Submaximal exercise tolerance (6 min walk distance) was improved after VA but not PA. This test has been used as the primary end point in numerous clinical CHF trials, as it is easy to use, of low cost and correlates well with the peak oxygen consumption. Furthermore, the distance walked in 6 min was a better predictor of prognosis than the LVEF or the NYHA classification. The treatment-related increase in walking distance of 52 m seen in this study was comparable to observations with the use of ACE inhibitors, interval training, and cost-intensive cardiac resynchronisation therapy in patients with CHF. In this regard, it will be interesting to evaluate, whether acupuncture can improve the prognosis of patients with CHF. Remarkably, each of the patients in the VA group showed an increase in 6 min walking distance without changing further treatment modalities. As LVEF did not improve after VA, the question arises how the improved submaximal exercise tolerance is mediated. It is now well known that in CHF there is no relationship between LVEF and exercise capacity. Improvement in submaximal exercise capacity might also be related to neurohormonal dysbalance as a major characteristic of overt CHF or metabolic factors that affect the efficacy of muscular gas exchange, ventilatory efficiency, and inflammatory mediators. In this study VA, but not PA, treatment resulted in more efficient ventilation (decrease of VE/VCO2 slope), which has been reported to be a strong prognostic marker for adverse events in patients with systolic or diastolic heart failure, and with pulmonary arterial hypertension. Ventilatory inefficiency caused by respiratory muscle weakness is an indicator of systemic skeletal muscle myopathy resulting in exercise limitation. It is well known that patients with CHF were inadequately characterised by their peak oxygen consumption as maximal exercise is required by patients who are rarely used to strenuous activity and may therefore lack sensitivity to detect subtle
improvement in exercise capacity. Thus, special interest has been focused on the post-exercise phase. The recovery period is largely unaffected by exercise level and does not depend on the intensity of the exercise test.\(^1\) In healthy subjects, oxygen consumption declines rapidly after exercise, whereas in patients with CHF the recovery phase is delayed in parallel with the severity of the disease. The kinetics of this recovery are related to the recovery of skeletal muscle energy storage in active muscles that are depleted and are replenished slowly in CHF.\(^24\) Thus, our finding that acupuncture improves both ventilatory efficiency and post-exercise recovery suggests that acupuncture may prevent skeletal muscle fatigue.

**Does acupuncture target neuroimmunomodulation?**
Reduction of LVEF causes skeletal muscle myopathy that in turn results in ergoreflex activation and subsequently sympathoexcitation and increased ventilation that further worsen CHF. This vicious cycle links the symptoms of breathlessness and fatigue.\(^2\) Thus, therapeutic strategies focusing on a decrease of sympathetic activity and an increase of parasympathetic activity may further reduce the morbidity and mortality of patients with CHF. This concept is currently also under investigation using electrical vagal nerve stimulation; (ClinicalTrials.gov #NCT00461019: ‘CardioFiT for Heart Failure—Safety and Efficacy Study Protocol’). This therapeutic benefit of vagal nerve stimulation has been demonstrated in an experimental model of CHF and was associated with pronounced anti-inflammatory effects\(^25\) and is based on neuroinflammatory reflexes.

These reflexes consist of an afferent arc of homoeostatic autonomic reflexes activated by oxygen, glucose and other metabolites, finally resulting in activation of the effenter motor neural arc that transmits the signal to modulate immune responses. Direct stimulation of the vagus nerve inhibits cytokine production by innate immune cells in different organs—e.g. spleen, liver, gastrointestinal tract and the heart.\(^26\) A feature of CHF is immune activation, with proinflammatory cytokines overexpressed both in the systemic circulation and locally in the failing myocardium.\(^27\) TNF\(~\alpha~\) has several properties that lead to metaboreceptor activation\(^28\) and are particularly detrimental in CHF, such as negatively inotropic effects, the promotion of left ventricular remodelling and the induction of dilated cardiomyopathy. Furthermore, TNF\(~\alpha~\) can cause skeletal muscle wasting and apoptosis, and, therefore, may be important in the development of cardiac cachexia and exercise limitation.\(^29\)

We have recently demonstrated an increase of parasympathetic tone after acupuncture treatment,\(^3\) therefore it appears to be promising in addition to standard CHF treatment as it is less invasive and is less expensive than device implantation.\(^30\) This is supported by a decrease of heart rate during exercise after acupuncture and moxibustion (warming of acupoints using mugwort) sessions in sedentary patients, indicating vagal activation.\(^31\) In this study parasympathetic activation was demonstrated by measurement of heart rate variability. Furthermore, very interesting preliminary data supporting the interaction of acupuncture and neuroinflammatory reflexes in patients with CHF are demonstrated in a subgroup of the study patients by an excessive reduction of TNF\(~\alpha~\) in all patients receiving VA but not in those receiving PA.

**Quality of life**
The effect of acupuncture on exercise capacity, ventilatory efficiency, post-exercise recovery and autonomous balance was
associated with a trend towards an improvement in quality of life according to ‘general health perception’ and ‘body pain’, as measured by the SF-36 questionnaire. These factors may reflect in part the impaired quality of life in CHF due to dyspnoea and functional limitations.

Safety

Although we included patients with CHF requiring treatment with oral antiocoagulants with warfarin (or aspirin), no major adverse effects or complications, such as major bleeding, occurred. Nevertheless, we cannot exclude the possibility that serious adverse effects due to acupuncture may be seen in a larger patient cohort using warfarin.

Limitations

This is a pilot study investigating the supplementary effects of acupuncture in addition to optimised heart failure medication on exercise capacity in patients with stable CHF. Owing to the small patient number, statistical power is limited. Although the cause of CHF in the VA and PA groups was not homogeneous, we observed a significant improvement in exercise tolerance in all patients of the VA group. Owing to the design of a controlled study, we ignored individual treatment concepts according to the paradigms of TCM. The acupuncture concept used in this study was chosen based on our own previous studies, on acupoints known to alter autonomic function and inflammation and on a TCM concept that is used to treat CHF-like syndromes. Nevertheless, we cannot exclude the possibility that effects might have been obtained using other acupuncture points.

CONCLUSIONS

This randomised controlled single-blind pilot study gives the first indication that acupuncture may improve submaximal exercise tolerance of patients with CHF when given in addition to optimised standard heart failure medication. This improvement was associated with an optimised ventilatory efficacy, post-exercise recovery, autonomous balance and reduction of inflammatory cytokines. Further investigations are warranted to confirm the acupuncture effects on exercise tolerance and safety in a larger CHF population and to test the potential of acupuncture to reduce the mortality of patients with CHF, since an increase in 6 min walk distance correlates with the prognosis of patients with CHF.13 Furthermore, more research is needed to understand the beneficial mechanisms of acupuncture in CHF—in particular, its effect on neurohormonal balance and the production of inflammatory cytokines.

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Competing interests

None.

Ethics approval

This study was conducted with the approval of the University of Heidelberg.

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES


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