

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

Arnt V Kristen,¹ Boris Schuhmacher,¹ Kathrin Strych,¹ Dirk Lossnitzer,¹ Hans-Christoph Friederich,² Thomas Hilbel,¹ Markus Haass,³ Hugo A Katus,¹ Antonius Schneider,⁴ Konrad M Streitberger,⁵ Johannes Backs¹

► Additional tables and figure are published online only. To view these files please visit the journal online (<http://heart.bmj.com>).

¹Department of Cardiology, University of Heidelberg, Heidelberg, Germany

²Department of Psychosomatic and General Internal Medicine, University of Heidelberg, Heidelberg, Germany

³Department of Cardiology, Theresienkrankenhaus Mannheim, Mannheim, Germany

⁴Institute of General Practice, Technische Universität München, München, Germany

⁵Department of Anaesthesiology and Pain Therapy, Inselspital, University of Bern, Bern, Switzerland

Correspondence to

Johannes Backs, University Hospital of Heidelberg, Im Neuenheimer Feld 410, Department of Cardiology, Heidelberg 69120, Germany; johannes.backs@med.uni-heidelberg.de

Boris Schuhmacher and Kathrin Strych contributed equally

Accepted 9 February 2010
Published Online First
15 June 2010

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 acupoints 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 delayed recovery.¹ In parallel with the severity of circulatory failure, peak oxygen consumption is decreased, the ventilatory threshold appears earlier and the slope of the increase in oxygen consumption versus time is reduced.¹ Remarkably, this exercise limitation is independent of the impairment of left ventricular ejection fraction (LVEF). Therefore, the 'muscle hypothesis' was proposed: raised levels of inflammatory cytokines are causing skeletal muscle fatigue and activation of muscle ergoreceptors, subsequently leading to an increase in ventilation, sensation of breathlessness, perception of fatigue and finally, autonomic dysbalance.² This is reflected by the current 'state-of-the-art' medical treatment of CHF with β blockers and ACE

inhibitors. Furthermore, novel approaches evaluate the clinical benefit of selective electric vagal nerve stimulation to normalise autonomic balance.³

As acupuncture has been shown to exert anti-sympathotonic, pro-vagotonic,⁴ and anti-inflammatory effects,⁵ it might be attractive and beneficial in addition to standard heart failure medication. Only one clinical study has evaluated the effects of acupuncture in patients with CHF so far.⁶ However, this study focused on acute effects on autonomic function and ventricular contractility or relaxation without placebo control, whereas long-term effects on the morbidity and exercise tolerance of patients with CHF were not explored. In general, many clinical acupuncture studies lacked adequate controls and a blinded design.

Here, we describe the first randomised placebo-controlled, single-blind study with a hypothesis-generating design that investigated the effects of acupuncture on cardiopulmonary function, exercise tolerance and quality of life of patients with CHF.

PATIENTS AND METHODS

Patients

This randomised prospective study included 17 patients (six female, 11 male, mean age 60.3±3.5 years) with stable CHF (New York Heart Association (NYHA) class II–III), referred to the Department of Cardiology at the University of Heidelberg. All patients had LVEF <40% caused by dilated or ischaemic cardiomyopathy. Diagnosis was established by coronary angiography and left ventricular catheterisation before study inclusion. All patients had sinus rhythm, were stable and compensated with individually optimised standard heart failure medication as well as oral anticoagulants for at least 3 months before inclusion in the study (including prophylactic defibrillator placement in 12 patients). Routine medication was continued during the study period. Patients were excluded if they had undergone acupuncture treatment within 6 months before the beginning of the study or if they presented with cutaneous eczema at potential acupoints.

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.⁷ The symptom-limited exercise test using a ramp protocol on a bicycle ergometer in a semisupine position⁸ consisted of a 5 min rest period and 2 min of free pedalling followed by 15 W increments in work load 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-Viasys 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.^{1,9}

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.¹⁰ It consists of 36 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 two summation scales—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 needling 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.¹¹ 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.^{11–13} 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 Lewith¹⁴ 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 (PA 31±9%; VA 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.

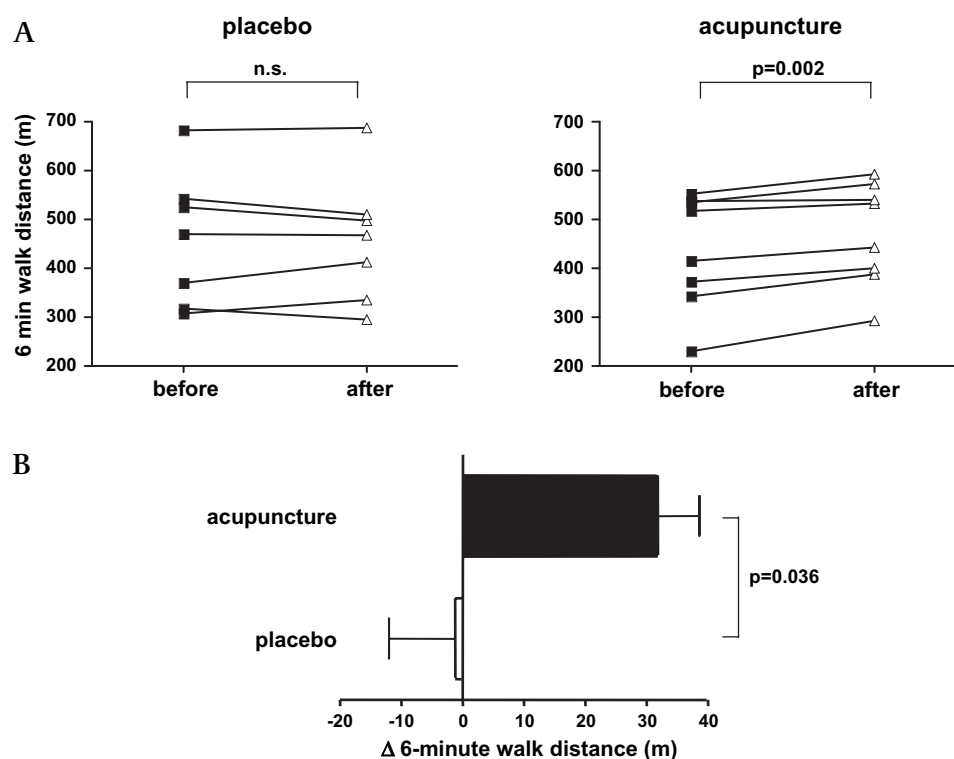
All patients completed the entire acupuncture protocol of 10 treatment sessions without any serious adverse events, such as rhythm disturbances, major bleedings, although almost all patients were receiving oral anticoagulants. Oral heart failure medication remained unchanged during the study period in 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 inefficiency during exercise, was improved after VA, but declined after PA as compared with study inclusion (figure 2B).

Heart failure

Figure 1 Absolute ambulated 6 min walking distance of patients with congestive heart failure (CHF) (n=8) before and after 10 sessions of placebo acupuncture in comparison with patients with CHF (n=9) before and after 10 sessions of verum acupuncture (A) as well as the absolute change of the 6 min walking distance after verum or placebo acupuncture (B).



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 (TNF α) 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 TNF α in all patients undergoing VA (median TNF α before VA 4.6 (3.3–9.4) pg/ml, after VA 1.3 (0.6–2.2) pg/ml but not of the patients undergoing PA (median TNF α before PA 4.3 (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 proinflammatory (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.⁷ Furthermore, the distance walked in 6 min was a better predictor of prognosis than the LVEF or the NYHA classification.¹⁵ The treatment-related increase in walking distance of 32 m seen in this study was comparable to observations with the use of ACE inhibitors,¹⁶ interval training,¹⁷ and cost-intensive cardiac resynchronisation therapy in patients with CHF.¹⁸ 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.¹⁹ Improvement in submaximal exercise capacity might also be related to neurohormonal dysbalance as a major characteristic of overt CHF² or metabolic factors that affect the efficacy of muscular gas exchange, ventilatory efficiency²⁰ and inflammatory mediators.²¹ 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 systolic²² or diastolic heart failure,⁸ and with pulmonary arterial hypertension.²³ Ventilatory inefficiency caused by respiratory muscle weakness is an indicator of systemic skeletal muscle myopathy resulting in exercise limitation.²

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

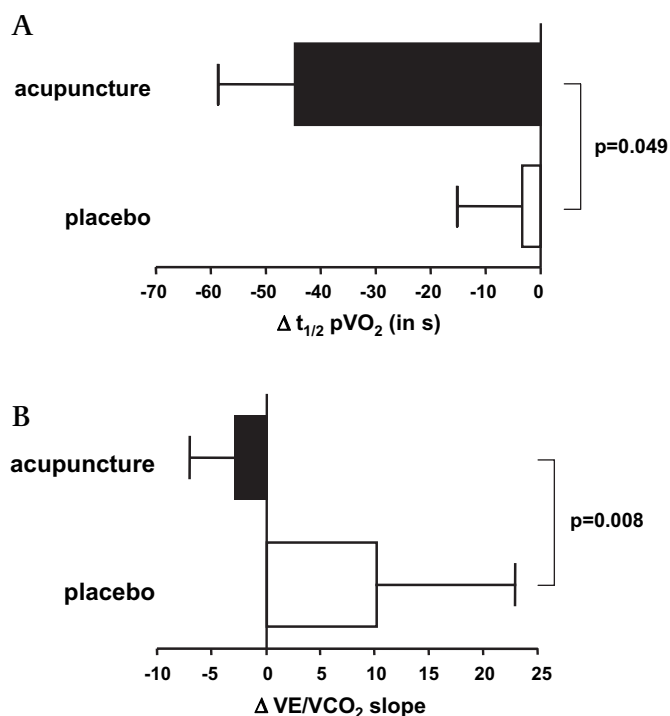


Figure 2 Relative change of (A) post-exercise pV_{O_2} recovery assessed by the half-life of peak oxygen uptake ($t_{1/2} pV_{O_2}$), and (B) VE/CO_2 slope, a marker of ventilatory inefficiency during exercise, after completion of the verum (n=9) or placebo (n=8) acupuncture protocol.

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 stimulation⁵; (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 effects²⁵ and is based on neuro-inflammatory reflexes.

These reflexes consist of an afferent arc of homeostatic autonomic reflexes activated by oxygen, glucose and other metabolites, finally resulting in activation of the efferent 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—for example, spleen, liver, gastrointestinal tract and the heart.²⁶ A feature of CHF is immune

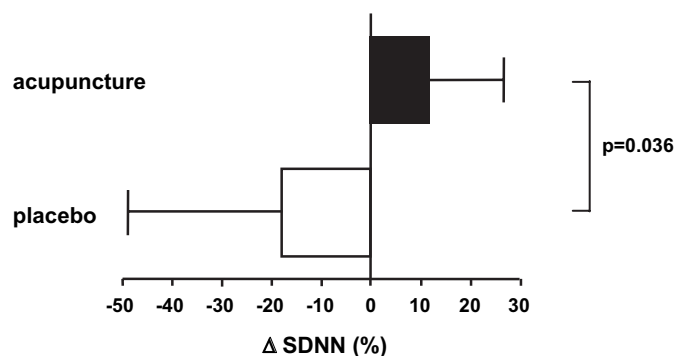


Figure 3 Relative change of the SD of all normal to normal R-R intervals during 24 h (SDNN) as a marker of overall heart rate variability and sympathetic tone after 10 treatment sessions of verum (n=9) in comparison with placebo (n=8) acupuncture in patients with congestive heart failure.

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 activation²⁸ 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,⁴ 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

Table 1 Baseline characteristics

Characteristics	Placebo	Acupuncture
Number of patients (n)	8	9
Male	6	5
Female	2	4
Age (years)	58±12	60±3
NYHA functional class	2.1±0.13	2.2±0.1
NYHA II (n)	7	7
NYHA III (n)	1	2
Heart failure medication		
ACE inhibitor (n)	8	9
β Blocker (n)	8	9
Diuretic (n)	8	7
Digitalis glycoside (n)	2	2
Oral anticoagulant (n)	7	7
Blood pressure (mm Hg)		
Systolic	112.1±2.7	118.2±3.6
Diastolic	78.2±3.8	72.4±2.3
Heart rate (bpm)	78±4	75±5

ACE: angiotensin converting enzyme; NYHA: New York Heart Association heart failure class.

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 anticoagulants 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.¹⁵ 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.

Acknowledgements We thank Robert Kell and Carsten Krüger for their helpful and stimulating discussions as well as Michaela Oestinger, Karin Hornig, and Maik Hornig for their excellent technical support.

Funding JB was supported by the Deutsche Forschungsgemeinschaft (BA-2258/2-1).

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

- Cohen-Solal A, Laperche T, Morvan D, *et al*. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Analysis with gas exchange measurements and NMR spectroscopy. *Circulation* 1995;**91**:2924–32.
- Coats AJ. The "muscle hypothesis" of chronic heart failure. *J Mol Cell Cardiol* 1996;**28**:2255–62.
- Schwartz PJ, De Ferrari GM, Sanzo A, *et al*. Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail* 2008;**10**:884–91.
- Schneider A, Weiland C, Enck P, *et al*. Neuroendocrinological effects of acupuncture treatment in patients with irritable bowel syndrome. *Complement Ther Med* 2007;**15**:255–63.
- Zijlstra FJ, van den Berg-de Lange I, Huygen FJ, *et al*. Anti-inflammatory actions of acupuncture. *Mediators Inflamm* 2003;**12**:59–69.
- Middlekauff HR, Hui K, Yu JL, *et al*. Acupuncture inhibits sympathetic activation during mental stress in advanced heart failure patients. *J Card Fail* 2002;**8**:399–406.
- Zugck C, Krüger C, Dürr S, *et al*. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? *Eur Heart J* 2000;**21**:540–9.
- Kristen AV, Dengler TJ, Schonland SO, *et al*. Respiratory muscle weakness and inefficient ventilation in heart failure due to light-chain amyloidosis. *Amyloid* 2008;**15**:129–36.
- Cohen-Solal A, Czitrom D, Geneves M, *et al*. Delayed attainment of peak oxygen consumption after the end of exercise in patients with chronic heart failure. *Int J Cardiol* 1997;**60**:23–9.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.
- Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998;**352**:364–5.
- Schneider A, Enck P, Streitberger K, *et al*. Acupuncture treatment in irritable bowel syndrome. *Gut* 2006;**55**:649–54.
- Streitberger K, Friedrich-Rust M, Bardenheuer H, *et al*. Effect of acupuncture compared with placebo-acupuncture at P6 as additional antiemetic prophylaxis in high-dose chemotherapy and autologous peripheral blood stem cell transplantation: a randomized controlled single-blind trial. *Clin Cancer Res* 2003;**9**:2538–44.
- Vincent C, Lewith G. Placebo controls for acupuncture studies. *J R Soc Med* 1995;**88**:199–202.
- Bittner V, Weiner DH, Yusuf S, *et al*. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. *JAMA* 1993;**270**:1702–7.
- Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995;**273**:1450–6.
- Meyer K, Samek L, Schwaibold M, *et al*. Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. *Med Sci Sports Exerc* 1997;**29**:306–12.
- Cazeau S, Leclercq C, Lavergne T, *et al*. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–80.
- Keteyian SJ, Brawner CA, Schairer JR. Exercise testing and training of patients with heart failure due to left ventricular systolic dysfunction. *J Cardiopulm Rehabil* 1997;**17**:19–28.
- Coats AJ, Adamopoulos S, Radaelli A, *et al*. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation* 1992;**85**:2119–31.
- Gielen S, Adams V, Mobius-Winkler S, *et al*. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol* 2003;**42**:861–8.
- Arena R, Myers J, Aslam SS, *et al*. Influence of subject effort on the prognostic value of peak VO₂ and the VE/VCO₂ slope in patients with heart failure. *J Cardiopulm Rehabil* 2004;**24**:317–20.
- Meyer FJ, Lossnitzer D, Kristen AV, *et al*. Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2005;**25**:125–30.
- Massie BM, Conway M, Rajagopalan B, *et al*. Skeletal muscle metabolism during exercise under ischemic conditions in congestive heart failure. Evidence for abnormalities unrelated to blood flow. *Circulation* 1988;**78**:320–6.
- Zhang Y, Popovic ZB, Bibeovski S, *et al*. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ Heart Fail* 2009;**2**:692–9.
- Tracey KJ. Reflex control of immunity. *Nat Rev Immunol* 2009;**9**:418–28.
- Jankowska EA, Ponikowski P, Piepoli MF, *et al*. Autonomic imbalance and immune activation in chronic heart failure—pathophysiological links. *Cardiovasc Res* 2006;**70**:434–45.
- Coats AJ. Exercise training for heart failure: coming of age. *Circulation* 1999;**99**:1138–40.
- Ferrari R. The role of TNF in cardiovascular disease. *Pharmacol Res* 1999;**40**:97–105.
- Streitberger K, Steppan J, Maier C, *et al*. Effects of verum acupuncture compared to placebo acupuncture on quantitative EEG and heart rate variability in healthy volunteers. *J Altern Complement Med* 2008;**14**:505–13.
- Gentil D, Assumpcao J, Yamamura Y, *et al*. The effect of acupuncture and moxibustion on physical performance by sedentary subjects submitted to ergospirometric test on the treadmill. *J Sports Med Phys Fitness* 2005;**45**:134–40.

Heart

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

Arnt V Kristen, Boris Schuhmacher, Kathrin Strych, Dirk Lossnitzer, Hans-Christoph Friederich, Thomas Hilbel, Markus Haass, Hugo A Katus, Antonius Schneider, Konrad M Streitberger and Johannes Backs

Heart 2010 96: 1396-1400 originally published online June 15, 2010
doi: 10.1136/hrt.2009.187930

Updated information and services can be found at:
<http://heart.bmj.com/content/96/17/1396>

These include:

Supplementary Material

Supplementary material can be found at:
<http://heart.bmj.com/content/suppl/2010/06/21/hrt.2009.187930.DC1.html>

References

This article cites 31 articles, 11 of which you can access for free at:
<http://heart.bmj.com/content/96/17/1396#BIBL>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Drugs: cardiovascular system](#) (8747)
[Heart failure](#) (559)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>