Acupuncture Inhibits Sympathetic Activation During Mental Stress in Advanced Heart Failure Patients

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ABSTRACT

Background: In heart failure (HF) patients, muscle sympathetic nerve activity is increased, and HF patients with the greatest sympathetic activation have the poorest prognosis. In animals, acupuncture is sympathoinhibitory, and the most profound sympathoinhibition occurs in animals with the highest resting sympathetic nerve activity. The purpose of this study was to test the hypothesis that acupuncture is sympathoinhibitory in humans with HF.
Methods and Results: Fifteen advanced HF patients underwent acute mental stress testing before and during (1) "real" acupuncture (n = 10), (2) non-acupoint acupuncture (n = 10), and (3) no-needle acupuncture control (n = 10). Muscle sympathetic nerve activity (MSNA) was recorded using peroneal microneurography. Resting MSNA was not different before and after acupuncture (52 ± 22 versus 50 ± 21 bursts/min, P = NS). During mental stress, SNA increased significantly. This increase was eliminated following real acupuncture (mean delta MSNA pre-acupuncture versus post-acupuncture: 149 ± 171 versus −169 ± 130, P = .03), but not after non-acupoint or no-needle acupuncture controls. The changes in blood pressure and heart rate during mental stress were not attenuated by real or control acupuncture.
Conclusion: Acute acupuncture attenuates sympathoexcitation during mental stress in advanced HF patients.
Key words: Autonomic nervous system, sympathetic nerve activity, cardiomyopathy, traditional Chinese medicine.

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Advanced heart failure is characterized by neurohumoral activation, including activation of the sympathetic nervous system. Patients with the greatest sympathetic activation have the poorest survival.[1] Pharmacologic therapies that have targeted this neurohumoral activation have markedly improved survival in patients with heart failure.[2–4] Although few investigations in humans have studied whether acupuncture modulates the autonomic nervous system, evidence in animals supports the concept that acupuncture has sympatholytic and depressor effects.[5,6]

In animal models, in which stimulation of somatic nerve afferents has been used as an acupuncture surrogate, blood pressure and cardiac ischemia are reduced.[5,6] In these models, somatic afferent stimulation has been shown to activate peripheral sensory neurons, leading to release of central nervous system opioids, which then mediate analgesic, sympatholytic, and depressor effects.[7,8] Interestingly, the decrease in sympathetic nerve activity and blood pressure is greatest in animal models of elevated sympathetic activity and hypertension.[8] The purpose of the present study was to test the hypothesis that acupuncture inhibits sympathetic nerve activation in patients with heart failure, in whom sympathetic nerve activity is markedly elevated. The effect of acupuncture during mental stress, a potent stimulus to the autonomic nervous system, was tested.

Methods

Human Subjects

After written informed consent was obtained, 15 patients with advanced heart failure were randomly assigned to two of the three study protocols outlined below. The study protocols were approved by the University of California—Los Angeles Investigational Review Board. Mean age of heart failure patients was 43 ± 11 years. All patients had chronic heart failure for greater than 3 months' duration and had been referred for heart transplantation evaluation. Patients were New York Heart Association functional class II and III. Mean ejection fraction was 0.23 ± 0.03. Because of the severity of heart failure, medications were not discontinued before the study, and included angiotensin-converting enzyme inhibitors, β-adrenergic blockers, diuretics, and digoxin. Patients abstained from caffeine on the day of the study, and were studied in the nonfasted state. Fourteen of 15 were acupuncture naïve; one had undergone acupuncture treatment for low back pain.

Muscle Sympathetic Nerve Activity

Muscle sympathetic nerve activity (MSNA) was recorded directly from the peroneal nerve using the technique of microneurography.[4] Multiunit postganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode. Signals were amplified by a factor of 50,000 to 100,000 and band passed filtered (700 to 2000 Hz). Nerve activity was rectified and integrated (time constant 0.1 second) to obtain a mean voltage display of sympathetic nerve activity that was recorded on paper. All recordings of MSNA met previously established and described criteria.[9,10] Muscle sympathetic bursts were identified by visual inspection by a single investigator (H.R.M.) and expressed as burst frequency (bursts/min) and total activity (units/min). Total activity per minute was determined by the sum of the heights of individual bursts per minute. The interobserver and intraobserver variability in identifying bursts is <10% and <5%, respectively.[11]

Acupuncture

"Real" acupuncture. The skin was cleaned with alcohol. Acupuncture needles (4 cm, 0.25 mm diameter, Natural, Suzhou Guso Acupuncture and Moxibustion Appliance Co., Ltd., China) were inserted into right Li4 (Hegu, large intestine 4), right Liv3 (Taichong, liver 3), and left P6 (Neiguan, pericardium 6) points, and manually stimulated for approximately 15 seconds to achieve the De Qi sensation of heaviness, fullness, or soreness. Needles were left in place while volunteers rested for 15 minutes, and then needles were removed. These points were chosen because they associated with stress reduction[12] or have been used in the treatment of heart failure.[13,14]

Control Acupuncture

"Non-acupoint" acupuncture. The skin was cleaned with alcohol. Acupuncture needles were inserted bilaterally into a non-acupoint of the anterior deltoid muscle, and, similar to real acupuncture, were manually stimulated for 15 seconds until a sensation of De Qi was experienced. Patients rested for 15 minutes, and then needles were removed.

"No-needle" acupuncture. The skin was cleaned with alcohol. Patients were shown the acupuncture needles. An empty, plastic needle guide was then tapped, bilaterally, against the skin overlying the upper trapezius muscle, out of the patient's field of view. Patients rested for 15 minutes, and then the acupuncturist simulated needle removal.

All acupuncture was performed by the same licensed acupuncturist (J.L.Y.).

Mental Stress Tests Mental stress testing was performed for 4 minutes by either the Stroop color word test or mental arithmetic.[15,16] During Stroop color word test, patients were shown a series of names of colors printed in a different color ink from the color specified. Patients were instructed to identify the color, not read the printed word, as quickly as possible. During verbally administered mental arithmetic, patients were asked to subtract 1- or 2-digit numbers from 2- or 3-digit numbers as

quickly and accurately as possible, and answer out loud. Throughout the mental stress tests, patients were urged to work more quickly and more accurately. Because sympathetic responses to mental stress testing are strongly influenced by perception of task difficulty,[17] each patient was asked to assess task difficulty on completion of the protocol, using a standard 5-point scale of 0, not stressful; 1, somewhat stressful; 2, stressful, 3, very stressful; and 4, very, very stressful.

Blood Pressure and Heart Rate Blood pressure was monitored noninvasively with an automatic blood pressure cuff (Press-Mate 8800, Colin Medical Instrument Co., San Antonio TX). Systolic, diastolic, and mean blood pressure was measured every 30 seconds at baseline and during mental stress. Heart rate was monitored continuously through lead II of the electrocardiogram (ECG).

Experimental Protocol

Patients rested in the supine position. The ECG electrodes and blood pressure cuff were positioned, and the leg was positioned for microneurography. After an adequate nerve recording site was identified, patients rested for 10 minutes. Then blood pressure, heart rate, and MSNA were recorded for 5 minutes at baseline and during mental stress testing. After recovery, acupuncture was performed. Blood pressure, heart rate, and MSNA were again recorded at for 5 minutes at baseline and during repeat mental stress testing. Control acupuncture was always performed before real acupuncture.

Statistical Analysis Statistical analysis was performed using analysis of variance with repeated measures for two main effects: treatment (pre- and postacupuncture) and time (1, 2, 3, and 4 minutes). If significant main effects or a statistical interaction were noted, the simple effects were analyzed using paired Student *t* tests. Data were analyzed at baseline and during 4 minutes of mental stress testing. Within group, but not between group, analyses were performed. Probability values of $\leq .05$ were considered statistically significant.

Results

All heart failure patients tolerated acupuncture without complications. No heart failure patient raised any suspicions about the authenticity of the control acupuncture. Results were unchanged when analyzed after the heart failure patient with prior acupuncture experience was eliminated.

Acupuncture Effects on Baseline Parameters

Real acupuncture did not change baseline heart rate, blood pressure, or MSNA (Table 1). After non-acupoint acupuncture, baseline mean arterial pressure (MAP) was slightly and significantly increased, but other parameters were unchanged. After no-needle acupuncture, baseline heart rate decreased slightly and significantly, but other parameters were unchanged.

Acupuncture Effects on Autonomic Responses to Mental Stress (n = 10)

An example of sympathetic neurograms before and after real acupuncture at rest and at peak mental stress is shown in Fig. 1. The increase in total activity of MSNA during mental stress was significantly attenuated after acupuncture (overall group effect $P = .03$, Table 2). Similarly, the percentage increase in total activity was significantly attenuated after acupuncture (overall group effect $P = .006$, Fig. 2A). The increase in bursts of MSNA, delta heart rate, and delta blood pressure were not different during mental stress after acupuncture (see Table 2). Perceived difficulty of mental stress testing was the same before and after acupuncture (1.8 ± 0.1 versus 1.8 ± 0.1, P = NS).

Control Acupuncture Effects on Autonomic Responses to Mental Stress

Non-Acupoint Acupuncture (n = 10) An example of sympathetic neurograms before and after non-

Table 1. Acupuncture Effects on Baseline Parameters

	Real		Non-Acupoint		No-Needle	
	Pre	Post	Pre	Post	Pre	Post
Heart rate (bpm)	73 ± 14	73 ± 15	77 ± 18	78 ± 18	76 ± 15	74 ± 13*
Mean arterial pressure (mm Hg)	74 ± 11	73 ± 10	71 ± 8	73 ± 7*	73 ± 9	73 ± 9
MSNA (bursts/min)	52 ± 22	50 ± 21	53 ± 21	51 ± 19	52 ± 21	51 ± 22
MSNA (total activity/min)	3,480 ± 2,562	3,288 ± 2,372	3,837 ± 3,528	2,679 ± 1,556	3,314 ± 1,681	3,675 ± 2,022

MSNA, muscle sympathetic nerve activity.
Values are means ± SD
*$P < .05$ pre versus post

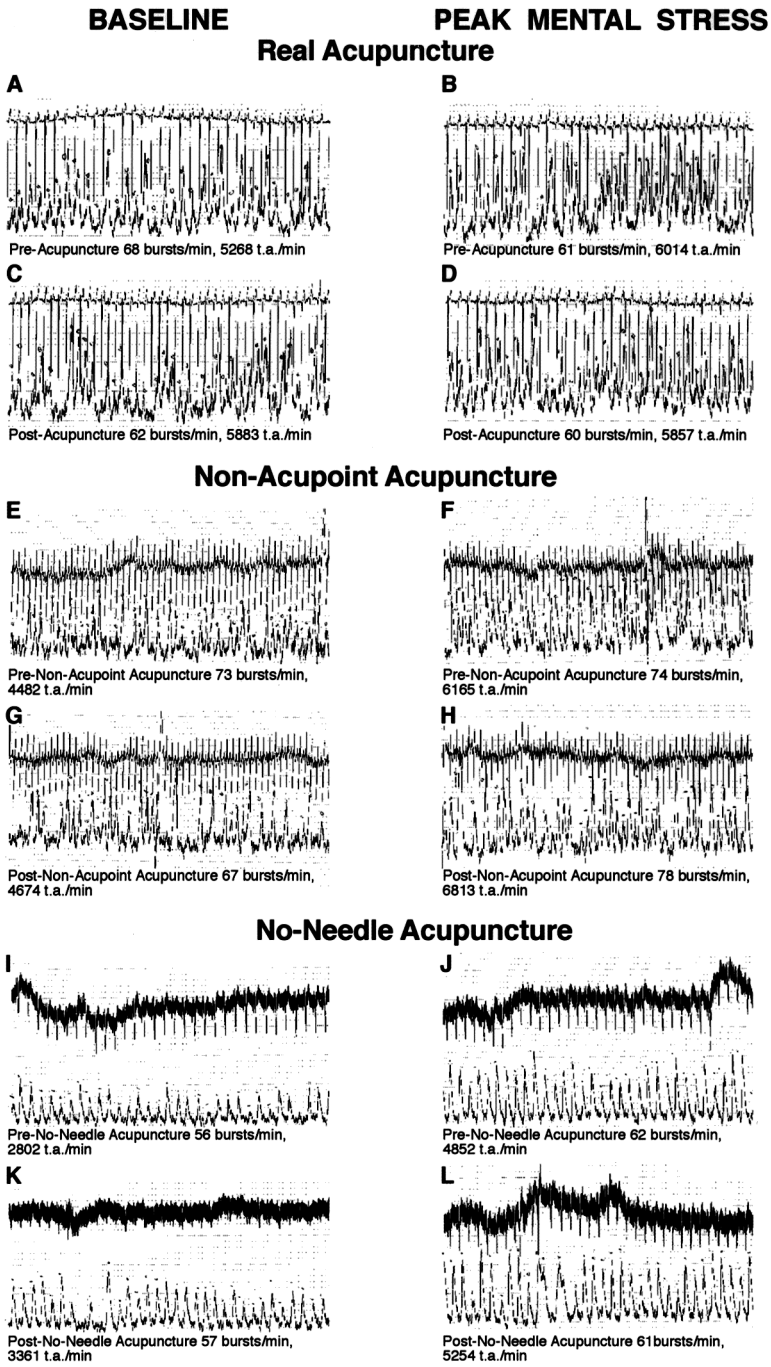

Fig. 1. Nerve recordings at rest and during mental stress from 3 different patients with heart failure. The duration of each neurogram recording is 20 seconds. For panels A-L, top tracing is the electrocardiogram and bottom tracing is the simultaneous neurogram. At rest, each heart beat is followed by a burst of MSNA. Panels A-D. In the absence of acupuncture, the height of the sympathetic bursts increases further during mental stress. Following acupuncture, resting MSNA is not different from resting MSNA recorded before acupuncture. Following acupuncture, MSNA does not increase during mental stress. Panels E-H. Following acupuncture, resting MSNA is not different from resting MSNA recorded before acupuncture. In the absence *and in the presence of* non-acupoint acupuncture, the height of the sympathetic bursts increases further during mental stress. Panels I-L. Following acupuncture, resting MSNA is not different from resting MSNA recorded before acupuncture. In the absence *and in the presence of* no-needle acupuncture, the height of the sympathetic bursts increases further during mental stress.

t.a. = total activity

Table 2. Acupuncture Effects on Autonomic Response to Mental Stress

		Min-1	Min-2	Min-3	Min-4	Overall *P* value
Real Acupuncture						
Heart rate (bpm)	pre	2.6 ± .4	3.7 ± .5	5.2 ± .5	5 ± .5	NS
	post	3.6 ± .8	4.5 ± .8	4.6 ± .9	3.2 ± .5	
MAP (mm Hg)	pre	–1.6 ± .8	1.7 ± .6	2.1 ± .8	1.8 ± .9	NS
	post	2.1 ± .5	4.6 ± .7	3.5 ± .6	2.9 ± .7	
MSNA (bursts/min)	pre	2.3 ± .5	1.7 ± .4	2.5 ± .3	–1.3 ± .6	NS
	post	0.6 ± .5	1.2 ± .4	–1.3 ± .4	1.1 ± .5	
MSNA (TA/min)	pre	–10 ± 54	122 ± 65	447 ± 57*	37 ± 85	0.03
	post	–63 ± 37	–54 ± 34	–289 ± 67	–271 ± 85	
Non-Acupoint Acupuncture						
Heart rate (bpm)	pre	1.2 ± .2	1.7 ± .2	3.0 ± .3	2.3 ± .4	NS
	post	2.3 ± .4	1.0 ± .4	3.1 ± .3	2.4 ± .4	
MAP (mm Hg)	pre	–.2 ± .4	1.0 ± .4	2.0 ± .4	2.7 ± .6	NS
	post	–1.0 ± .3	1 ± .4	1 ± .5	1.1 ± .6	
MSNA (bursts/min)	pre	3.9 ± .4	2.4 ± .3	1.4 ± .4	1.6 ± .5	NS
	post	–10 ± 5	.3 ± .6	.3 ± .5	1.1 ± .6	
MSNA (TA/min)	pre	229 ± 71	327 ± 66	215 ± 95	370 ± 86	NS
	post	341 ± 51	471 ± 86	0.1 ± 121	150 ± 126	
No Needle Acupuncture						
Heart rate (bpm)	pre	1.7 ± .2	3.2 ± .3	4.8 ± .5	4.5 ± .5	NS
	post	4.3 ± .4	5.0 ± .4	4.7 ± .3	5.7 ± .3	
MAP (mm Hg)	pre	1.0 ± .4	3.5 ± 6	3.5 ± .7	3.9 ± .7	NS
	post	2.0 ± .5	1.9 ± .6	2.2 ± .5	1.4 ± .6	
MSNA (bursts/min)	pre	2.4 ± .4	5.0 ± .7	3.1 ± .5	4.2 ± .6	NS
	post	2.2 ± .2	5.6 ± .5	4.6 ± .6	2.3 ± .8	
MSNA (TA/min)	pre	441± 55	813 ± 83	911 ± 95	1061 ± 103	NS
	post	323 ± 44	586 ± 71	857 ± 70	630 ± 79	

MAP, mean arterial pressure; MSNA, muscle sympathetic nerve activity; TA, total activity.
Values are means ± SEM.
*$P \leq .05$ pre versus post acupuncture, point-wise comparisons.

acupoint acupuncture at rest and at peak mental stress is shown in Fig. 1. The increase in total activity of MSNA (see Table 2), percentage increase in total activity (Fig. 2B), and the increase in bursts of MSNA (see Table 2) were unchanged during mental stress after non-acupoint acupuncture. The increase in heart rate and blood pressure were not different during mental stress after non-acupoint acupuncture (see Table 2). Perceived difficulty of mental stress testing was the same before and after non-acupoint acupuncture (2.1 ± 0.1 versus 2.4 ± 0.1, P = NS).

No-Needle Acupuncture (n = 10) An example of sympathetic neurograms before and after no-needle acupuncture at rest and at peak mental stress is shown in Fig. 1. The increase in total activity of MSNA (see Table 2), percentage increase in total activity (Fig. 2C), and the increase in bursts of MSNA (see Table 2) were unchanged during mental stress after no-needle acupuncture. The increase in heart rate and blood pressure were not different during mental stress after no-needle acupuncture (see Table 2). Perceived difficulty of mental stress testing was the same before and after acupuncture (1.7 ± 0.1 versus 1.9 ± 0.1, P = NS).

Discussion

The major findings of our study are: that (1) sympathetic activation during mental stress is virtually eliminated after acupuncture at Li4, P6, and Liv3; (2) this sympathomodulatory effect of acupuncture is not a placebo effect and is not due to accommodation to mental stress testing because during control studies consisting of non-acupoint acupuncture and no-needle acupuncture, sympathetic activation was not attenuated; and (3) a single session of acupuncture does not lower resting

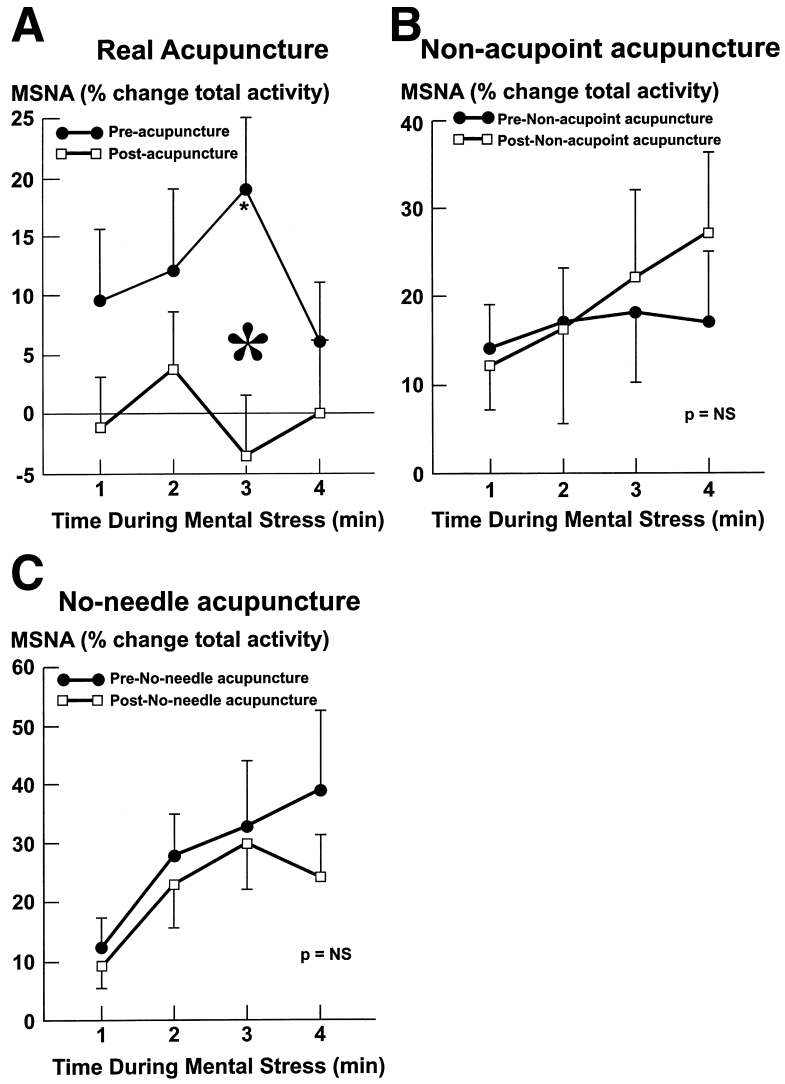

Fig. 2. Acupuncture effect on percentage change in total nerve activity during mental stress. Panel A. Acupuncture at known acupoints significantly attenuates the increase MSNA during mental stress(overall group effect, *p = 0.006). Point-wise comparisons revealed greater attenuation of MSNA at minute 3 (*p<0.001) of mental stress. Panel B. Non-acupoint acupuncture does not attenuate the increase in MSNA during mental stress. Panel C. No-needle acupuncture does not attenuate the increase in MSNA during mental stress. In all panels, pre-acupuncture is illustrated by solid lines and solid symbols, and post-acupuncture is illustrated by dashed lines and open symbols.

sympathetic nerve activity in heart failure. Further studies are necessary to determine the effects of a longer course of acupuncture.

Microneurography enables the direct recording of sympathetic nerve activity to the vasculature of skeletal muscle. Nerve activity is quantifiable and is typically reported either as the number of bursts per minute or as total nerve activity that takes into account the height of the bursts and the number.[9,10] In the present study, we report the MSNA level in both types of units, but draw our conclusions only from the total activity data. Why is this scientifically acceptable? Bursts of sympathetic nerve activity are entrained by the heart rhythm, and a maximum of 1 burst is present per heart beat. Whereas in resting healthy humans, a burst of sympathetic activity may typically follow about one fourth of the heart beats, in heart failure patients, it is not uncommon to find a burst of sympathetic activity following almost every heart beat.[20] Thus in sympathoexcitatory states such as heart failure, the most sensitive way to detect a change in MSNA is to calculate the total activity by measuring both the height and frequency of the bursts. In fact, during mental stress, the maximum increase in burst number was only 9%, compared with increases up to 40% in total

activity. Thus the reliance on total activity is appropriate to detect changes in MSNA in this study.

Although we have detected a sympathomodulatory effect of acupuncture in patients with advanced heart failure, the mechanisms underlying this effect remain speculative. Recent scientific studies in acupuncture analgesia support the concept that the sympathomodulatory effects of acupuncture are mediated by endogenous opioids in the central nervous system.[19,20] Experimental evidence supports the concept that opioids in the central nervous system, in addition to modulating acupuncture analgesia, may also play a role in sympathetic neural regulation of the cardiovascular system. Thoren and colleagues[8] used acupuncture-like stimulation of the sciatic nerve in Wistar-Kyoto normotensive rats (WKR). After 30 minutes of acupuncture, blood pressure and heart rate fell significantly, and remained depressed for 12 hours. Recordings of efferent splanchnic nerve efferent discharge demonstrated a simultaneous fall in sympathetic activity, consistent with the hypothesis that the depressor response was mediated through attenuation of the sympathetic nervous system. This sympathomodulatory effect is abolished by intravenous naloxone.[8] Similarly, Li and colleagues[6] studied a feline model of electroacupuncture in which the median nerve was stimulated with low frequency (5 Hz) to mimic electroacupuncture. Myocardial ischemia induced by reflex activation of the cardiovascular system was improved after 30 minutes of electroacupuncture. This anti-ischemic effect is abolished by naloxone administered intravenously or microinjected into the rostral ventrolateral medulla (rVLM).[7] The rVLM, where opioid receptors have been localized, is an important cardiovascular center as well[20,21] and may mediate the sympatholytic effects of acupuncture in heart failure.

Acupuncture has it greatest effects in animal models of disease compared to healthy animals.[8,21] For example, somatic nerve stimulation decreases splanchnic nerve activity and blood pressure in WKR rats, but these effects are significantly greater in spontaneously hypertensive rats in which resting blood pressure and sympathetic nerve activity are elevated.[8] Similarly, in Dahl salt-sensitive, prehypertensive rats, sciatic nerve stimulation resulted in suppression of renal sympathetic nerve activity, whereas in Dahl salt-resistant, normotensive rats, it did not.[21] In humans with heart failure, an increase in resting MSNA is the rule. Sympathetic nerve activation present at rest may render heart failure patients more susceptible to the sympathomodulatory effect of acupuncture, which was not seen in healthy humans.[22]

Criticism of prior acupuncture studies include a lack of objective endpoints and inadequate or absent controls.[23] In this study, acupuncture effects on quantifiable endpoints, such as MSNA, blood pressure, and heart rate, were measured, addressing the first concern. To address the second concern, we included two different control paradigms. Although non-acupoint acupuncture has been shown to have analgesic effects in up to 50% of study patients,[24] we did not see an effect of non-acupoint acupuncture on the autonomic responses during mental stress in this study. The no-needle acupuncture paradigm served both as a time control to ensure that repeated mental stress testing was not associated with a decrease autonomic response and a placebo control in which skin penetration with its potential physiologic effects was avoided.

Limitations

We studied the effects of a single session of acupuncture on the autonomic responses to mental stress. These findings cannot be extrapolated to chronic acupuncture and do not imply an ongoing sympathomodulatory response. Our study does not address the potential mechanisms of the sympathomodulatory effect of acupuncture in patients with heart failure. Although data in humans and animals support central nervous system opioid release as a critical step in acupuncture efficacy, the mechanisms underlying the sympathomodulatory effect of acupuncture in heart failure are beyond the scope of the current study and remain unknown. The results of this small study require confirmation in a larger heart failure population.

In summary, a single session of acupuncture does not change the resting level of sympathetic nerve activity directed to muscle in patients with chronic heart failure, but eliminates the surges in sympathetic activation during mental stress.

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