Acupuncture at the auricular branch of the vagus nerve enhances heart rate variability in humans: An exploratory study

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BACKGROUND Recent animal and human studies have shown antiarrhythmic effects inhibiting inducibility of atrial fibrillation through low-level transcutaneous electrical stimulation at the auricular branch of the vagus nerve (ABVN).

OBJECTIVE The present study investigated effects of acupuncture at the ABVN on the autonomic cardiac nervous system in humans through analysis of heart rate and heart rate variability (HRV) parameters.

METHODS We enrolled 24 healthy male volunteers and compared acupuncture at the ABVN to placebo-acupuncture performed at the Ma-35 point (an acupuncture point used in traditional Chinese medicine to treat pain caused by gonarthrosis). An additional measurement without acupuncture served as control. We analyzed the following heart rate and HRV parameters: standard deviation of normal-to-normal intervals (SDNN), root mean square of successive R-R interval differences (RMSSD), high frequency (HF), low frequency (LF), LF/HF ratio.

RESULTS In comparison to placebo acupuncture, acupuncture at the ABVN led to a significant reduction in heart rate (approximately 4%–6%, $P < .05$) and an increase in overall HRV demonstrated by SDNN (approximately 19%, $P < .05$). RMSSD and power spectral density parameters (HF, LF, LF/HF) showed statistical trends ($P < .1$) induced by auricular acupuncture in favor of vagal tone. No relevant difference was shown between control and placebo group.

CONCLUSION Acupuncture of the region innervated by the ABVN may activate the parasympathetic nervous system, as suggested by reduction in heart rate and increase in SDNN. However, given the lack of clear significant changes in other HRV parameters, this effect seems modest and its evaluation requires further investigation.

KEYWORDS Atrial fibrillation; Acupuncture; Auricular branch of the vagus nerve; Autonomous cardiac nervous system; Heart rate variability; Vagus nerve

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Introduction

The autonomic cardiac nervous system (ACNS) is physiologically important and plays a major role in development and maintenance of atrial fibrillation (AF), which has been investigated accordingly in recent studies.[1,2] In particular, imbalance between the parasympathetic and sympathetic nervous system is likely to induce AF.[2,3]

Potential additional therapeutic approaches such as cardiac ganglionic ablation or denervation as well as noninvasive approaches via electroacupuncture have delivered promising results concerning a reduction of AF episodes.[4–7] In a canine model, low-level transcutaneous electrical stimulation—defined as stimulation at a voltage approximately 10% beneath the threshold of vagus nerve stimulation inducing *any slowing* of sinus rate or atrioventricular conduction—of the auricular branch of the vagus nerve (ABVN) showed antiarrhythmic effects by suppressing neural activity within the ganglionated plexi and thereby inhibiting inducibility of AF.[7] In patients with paroxysmal AF, low-level vagal stimulation recently demonstrated significant reduction in AF burden.[8]

Afferent vagus nerve fibers of the ABVN end at the nucleus tractus solitarii and respective stimulation leads to activation of the solitary nucleus,[9,10] which exerts direct effects on efferent nuclei of the vagus nerve and baroreflex.[11,12] Activation of both efferent vagal nerve and baroreflex leads to a parasympathetic response with a decrease in heart rate and blood pressure.

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KEY FINDINGS

- Acupuncture at the auricular branch of the vagus nerve reduces heart rate and increases total heart rate variability (standard deviation of normal-to-normal intervals).
- In young healthy men, auricular acupuncture may alter autonomic cardiac balance in favor of vagal tone, as indicated by low frequency / high frequency ratio.
- No difference between placebo acupuncture and control measurement without acupuncture was detected. This indicates that acupuncture alone has no effect on the autonomic cardiac nervous system.

To the best of our knowledge, there are no prior studies that analyzed the influence of acupuncture on human ACNS. Accordingly, the aim of this study was to investigate a possible role of acupuncture of the ABVN on the ACNS using heart rate and heart rate variability (HRV) analysis in healthy young male volunteers.

Methods

Study design

The study was randomized controlled (for sequence of acupuncture sites) and single-blinded (subjects were blinded concerning presumed effects of the different acupuncture sites). Since this particular issue has not been addressed so far and no comparable data are available, this study was conducted as a pilot study. Against this background, we enrolled 24 healthy male subjects aged between 18 and 25 years who provided written informed consent. All participants were free from structural cardiovascular disease (no history of syncope, myocardial infarction, or arrhythmia) or other possible confounders such as diabetes or autonomic disorders. None of the subjects was taking any medication. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the local ethics committee (FF 95/2015).

Acupuncture

All subjects underwent acupuncture of the ABVN located at the inferior concha of the ear and placebo-acupuncture (Ma35 point used to treat pain caused by gonarthrosis) (Figure 1). In addition, an analysis without acupuncture was performed to assess whether the placement of an acupuncture needle itself led to significant effects on heart rate or HRV.

Acupuncture was performed in cooperation with the Center for Traditional Chinese Medicine LuSHAN in Offenbach, Germany. Participants were randomly divided into 2 groups (each group: n = 12). For group 1 acupuncture of the ABVN was carried out first; for group 2 it was carried out second. Thus, each group acted as its own intrinsic control. In order to minimize possible influences of the first acupuncture session, procedures were performed with a minimum of 48 hours between interventions in an identical setting at the same time of the day. Measurement without acupuncture (CONTROL) was performed under the same conditions in 12 randomly selected subjects from the 24 subjects in the main analysis after completion of both acupuncture measurements.

Electrocardiographic (ECG) recordings were obtained with a 12-lead Holter ECG device (SpiderView; MicroPort CRM, Paris, France), corresponding memory cards, and

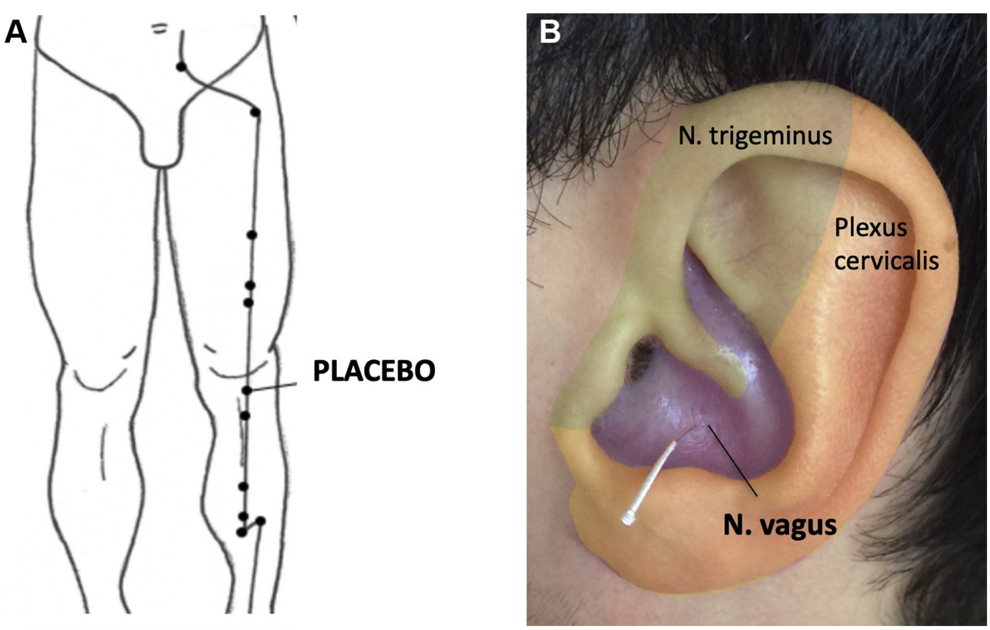

Figure 1 Acupuncture points used in this study. **A:** Ma35 (PLACEBO). **B:** Auricular branch of the vagus nerve; acupuncture needle in situ.

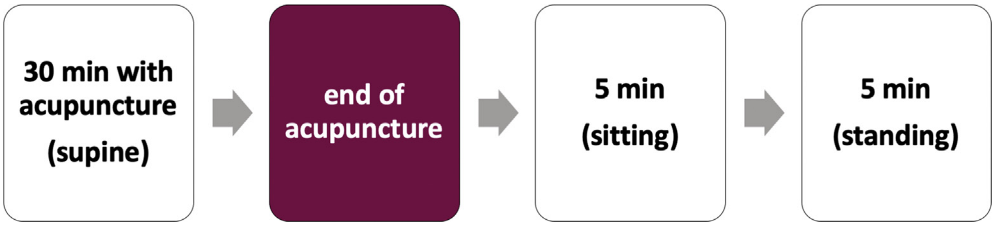

Figure 2 Schematic of test sequence.

BlueSensor VL ECG electrodes (Ambu, Bad Nauheim, Germany). The following acupuncture needles were utilized: 0.25 × 25 mm (diameter × length) for PLACEBO and 0.30 × 13 mm for ABVN (Maanshan Bond Medical Instruments Co, Ltd, Maanshan, China).

After the subject had been in a supine position for 5 minutes the acupuncture needle was placed, and after another 2 minutes the ECG recording was initiated and performed under the following conditions: 30 minutes in supine position with acupuncture, removal of the acupuncture needle, 5 minutes sitting, and 5 minutes standing. In order to minimize bias due to removal of the acupuncture needle, analysis of the ECG recording was paused for 5 minutes and subjects were left in a supine position during this time (Figure 2). Changes in body position were supposed to activate the ACNS.

Heart rate and HRV parameters

An individual evaluation of heart rate and HRV was carried out with help of SMARTlab (Ludwig-Maximilians University Hospital, Munich). We evaluated heart rate, standard deviation of normal-to-normal intervals (SDNN), root mean square of successive R-R interval differences (RMSSD), and power spectral density. For power spectral density absolute and normalized high-frequency spectrum (HF, corresponding to the parasympathetic portion of power spectral density at 0.15–0.4 Hz), low-frequency spectrum (LF, corresponding to the sympathetic portion of power spectral density at 0.04–0.15 Hz) and LF/HF ratio (corresponding to sympatho-parasympathetic balance) were analyzed.[13]

Statistical analysis

All variables were checked for normal distribution using the Kolmogorov-Smirnov-Lilliefors test. Subsequently, the variables were averaged for the corresponding time period and compared by paired *t* test. Significance level was set at 0.05 (5%) and values between 0.05 and 0.1 were considered as trend. Statistical analysis was performed with help of SPSS and Excel. The values are given as mean ± standard error of the mean.

Results

Study population

Age of the subjects was 23 ± 2 years. Average height and body weight were 185 ± 6 cm and 80 ± 6 kg, respectively, resulting in a mean body mass index of 24.4 ± 1.3 kg/m^2. A survey of the volunteers showed that they had been exercising for an average of 7 ± 3 hours per week in the last 12 months before acupuncture. Given the fact that there are large interindividual differences in ACNS,[14] a very homogeneous group was selected for this study in terms of age, body mass index, and fitness level. The intention was to provide the most representative result possible for healthy hearts with medium-to-high training load.

Comparison of PLACEBO acupuncture and CONTROL measurement without acupuncture

Twelve randomly selected subjects received an additional measurement without acupuncture. Statistical comparison between placebo acupuncture and measurement without acupuncture showed a reduction in heart rate during the sitting period for the control group (PLACEBO: 74 ± 2 beats per minute [bpm] vs CONTROL: 65 ± 1 bpm, $P = .02$). Since evidence for a sympathetic activation is given by higher LF normalized units (nu) and subsequently lower HFnu for this period (PLACEBO: 0.87 ± 0.02 [LFnu], 0.13 ± 0.02 [HFnu] vs CONTROL: 0.81 ± 0.03 [LFnu], 0.19 ± 0.03 [HFnu]; $P = .03$), it is conceivable that this effect may be attributed to the inconvenience of sitting up with a painful knee after removal of acupuncture needle. Therefore, it was considered unspecific. None of the other parameters showed any relevant difference at any time during the test sequence (Table 1). This applies in particular for the first 30 minutes of the test sequence, during which the acupuncture needle remained continuously in the subject's knees. It can therefore be assumed that the placement of an acupuncture needle alone did not lead to any relevant effect on ECG-based ACNS parameters. For this reason, only the differences between PLACEBO and ABVN were considered in the analysis.

Heart rate

Compared to placebo, acupuncture of ABVN showed a significant reduction in heart rate in supine (ABVN: 60 ± 2 bpm vs PLACEBO: 64 ± 2 bpm, $P = .049$) and in sitting position (ABVN: 71 ± 2 bpm vs PLACEBO: 74 ± 2 bpm, $P = .026$). No difference was seen in standing position (ABVN: 84 ± 2 bpm vs PLACEBO: 84 ± 3 bpm, $P = .916$) (Figure 3, Table 2).

Table 1 Comparison between placebo (n = 24, acupuncture at Ma35) and control (n = 12, no acupuncture) group

Parameter	Position	Placebo	Control	*P* value
Heart Rate [beats/min]	supine	64 ± 2	60 ± 1	.79
	sitting	74 ± 2	65 ± 1	.02
	standing	84 ± 3	79 ± 1	.92
SDNN [ms]	supine	78 ± 5	86 ± 4	.83
	sitting	102 ± 8	115 ± 8	.73
	standing	79 ± 5	84 ± 4	.67
RMSSD [ms]	supine	46 ± 4	51 ± 5	.99
	sitting	37 ± 3	46 ± 3	.19
	standing	28 ± 2	29 ± 2	.98
HF [ms^2, nu]	supine	627 ± 105 [0.29]	593 ± 108 [0.22]	.053 [nu]
	sitting	443 ± 73 [0.13]	455 ± 82 [0.19]	.033 [nu]
	standing	231 ± 33 [0.07]	178 ± 30 [0.06]	.37 [nu]
LF [ms^2, nu]	supine	1614± 274 [0.72]	1929 ± 219 [0.78]	.053 [nu]
	sitting	3649 ± 695 [0.87]	2153 ± 312 [0.81]	.033 [nu]
	standing	3428 ± 497 [0.93]	2647 ± 394 [0.94]	.37 [nu]
LF/HF	supine	3,7 ± 1	6 ± 1	.12
	sitting	10 ± 1	9 ± 2	.16
	standing	19 ± 4	23 ± 3	.64

HF = high frequency; LF = low frequency; RMSSD = root mean square of successive R-R interval differences; SDNN = standard deviation of normal-to-normal intervals.

For power spectral density parameters, the *P* values given are for normalized units (nu).

HRV

SDNN and RMSSD

Acupuncture of ABVN resulted in a significantly higher SDNN compared to placebo for supine (ABVN: 93 ± 6 ms vs PLACEBO: 78 ± 5 ms, *P* = .012) and standing position (ABVN: 85 ± 5 ms vs PLACEBO: 79 ± 5 ms, *P* = .03). However, there was no difference in sitting position (ABVN: 108 ± 2 ms vs PLACEBO: 102 ± 8 ms, *P* = .33) (Figure 3, Table 2). Analysis of RMSSD showed a trend in favor of acupuncture at ABVN for supine (ABVN: 52 ± 4 ms vs PLACEBO: 46 ± 4 ms, *P* = .081) and sitting position (ABVN: 40 ± 3 ms vs PLACEBO: 37 ± 3 ms, *P* = .081).

Power spectral density (HF, LF, LF/HF)

Acupuncture of ABVN showed a trend for HFnu in supine position (ABVN: 743 ± 103 [0.33 nu] vs PLACEBO: 627 ± 105 [0.28 nu], *P* = .09 [nu]). Since statistical comparison was performed for normalized units, LFnu showed the same trend for ABVN in this position (ABVN: 1658 ± 224 [0.67 nu] vs PLACEBO: 1614 ± 274 [0.72 nu], *P* = .09 [nu]).

In order to relate these findings correctly, it is important to compare the LF/HF quotient. Comparison demonstrates a trend for ABVN (ABVN: 3 ± 1 vs PLACEBO: 3.7 ± 1, *P* = .08), indicating a shift of autonomic balance toward parasympathetic tone (Table 2).

Discussion

Main findings

The present study demonstrated a reduction in heart rate of approximately 4%–6% by acupuncture of the ABVN compared to placebo acupuncture in healthy young males. Moreover, auricular acupuncture showed significant higher values for SDNN (approximately 20% higher) and trends concerning RMSSD increase as well as HF (LF) increase and LF/HF reduction, respectively.

Reduction in heart rate; enhanced total HRV as demonstrated by SDNN in supine, sitting, and standing position; and the trends observed for RMSSD and LF/HF are suggestive for parasympathetic activation of cardiac autonomous nervous system.

Irrespective of this hypothesis, in this specific cohort of subjects auricular acupuncture did not show clear significant changes in power spectral density parameters, leaving its exact mechanism of action and influence on the ACNS speculative. In addition to the small number of subjects studied, one reason for the lack of clearer, trendsetting results could be the high interindividual variance of ACNS, which might lead to a heterogeneous effect of acupuncture treatment on HRV. Furthermore, it is well known that even moderate physical exercise exerts a major influence on parasympathetic cardiac tone, as demonstrated by increased HRV.[15] Since subjects reported an average training time of 7 hours per week, it is conceivable that in physically trained, young, healthy subjects acupuncture treatment only shows mild effect on the already high vagal tone.

The present results are consistent with the recent finding of De Couck and colleagues,[16] who performed electrical transcutaneous vagus nerve stimulation at the ABVN in 30 healthy subjects and found a significant increase in SDNN but not in power spectral density compared to baseline measurement.

Hypothesis on neural arcs and previous work on transcutaneous auricular vagus nerve stimulation

Linz and colleagues[3] suggest that cardiac parasympathetic innervation begins in the medulla oblongata, where

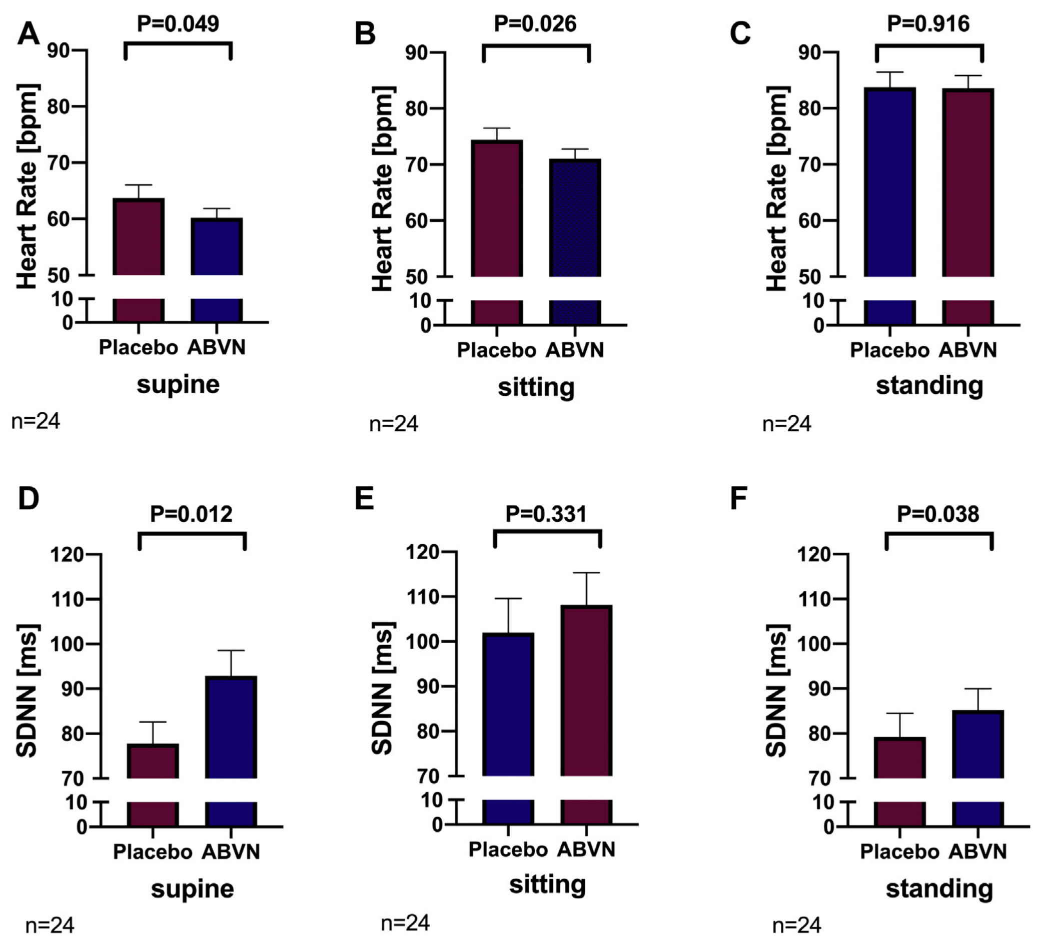

Figure 3 Comparison of heart rate (**A:** supine; **B:** sitting; **C:** standing) and standard deviation of normal-to-normal intervals (SDNN) (**D:** supine; **E:** sitting; **F:** standing) between auricular branch of the vagus nerve (ABVN) and Placebo.

preganglionic fibers of the vagus nerve originate from the nucleus ambiguus (AMB), nucleus tractus solitarii (NTS), and dorsal motor nucleus (DMN) and synapse onto postganglionic neurons of the intrinsic ganglia of the heart. Acetylcholine released by these preganglionic fibers binds to nicotinic receptors of the postganglionic neurons.[3] The NTS plays a major role in baroreflex by detecting changes in baroreceptor firing rate and accordingly adjusting autonomic cardiac function.[11] In an animal model, baroreflex neural arc was reset by afferent vagus nerve stimulation.[17] Gao and colleagues[18] recently showed that acupuncture of the ABVN of the rat activates baroreceptor-sensitive neurons in the NTS to a similar extent as baroreflex itself, leading to reduction in heart rate and systolic blood pressure. This effect was inhibited by atropine.[18]

In addition to baroreflex control, the NTS provides direct synaptic fibers to the AMB and DMN, which control parasympathetic outflow.[12] Several studies have provided evidence for central projection of the ABVN onto the solitary nucleus.[9,10] In this context, a human functional magnetic resonance imaging study demonstrated an increase in NTS activity by electrical ABVN stimulation.[10] Besides its effect on cardiovascular system, ABVN stimulation has demonstrated the ability of suppressing epileptiform activity.[19]

In summary of the previous research, we suggest that acupuncture of ABVN leads to an activation of the NTS and thus to an indirect parasympathetic effect on cardiac function. Furthermore, a baroreflex-like effect is conceivable (Figure 4).

Acupuncture at the ABVN increases the activity of the solitary nucleus (NTS) projecting to the vagal efferent neurons of the AMB and DMN and thus resulting in enhanced parasympathetic activation. Furthermore, activation of the solitary nucleus indirectly leads to sympathetic inhibition via a baroreflex-like effect.

Potential clinical implication

Given that low-level vagus nerve stimulation has shown antiarrhythmic effects,[4,6] the possibility to reduce AF recurrence by parasympathetic stimulation using acupuncture in addition to antiarrhythmic drug therapy or ablation is a promising approach.

Lomuscio and colleagues[17] demonstrated the efficacy of acupuncture in maintaining sinus rhythm after electrical cardioversion in 80 patients with persistent AF by acupuncture, including the Neiguan point located on the ventral forearm. Acupuncture showed comparable recurrence rates to

Table 2 Comparison between auricular branch of the vagus nerve (n = 24, acupuncture at ABVN) and placebo (n=24, acupuncture at Ma35)

Parameter	Position	ABVN	Placebo	*P* value
Heart Rate [beats/min]	supine	60 ± 2	64 ± 2	.049
	sitting	71 ± 2	74 ± 2	.026
	standing	84 ± 2	84 ± 3	.916
SDNN [ms]	supine	93 ± 6	78 ± 5	.012
	sitting	108 ± 2	102 ± 8	.331
	standing	85 ± 5	79 ± 5	.038
RMSSD [ms]	supine	52 ± 4	46 ± 4	.081
	sitting	40 ± 3	37 ± 3	.081
	standing	28 ± 1	28 ± 2	.85
HF [ms^2, nu]	supine	743 ± 103 [0.33]	627 ± 105 [0.29]	.09 [nu]
	sitting	529 ± 97 [0.15]	443 ± 73 [0.13]	.39 [nu]
	standing	249 ± 40 [0.08]	231 ± 33 [0.07]	.6 [nu]
LF [ms^2, nu]	supine	1658 ± 224 [0.67]	1614± 274 [0.72]	.09 [nu]
	sitting	3635 ± 589 [0.85]	3649 ± 695 [0.87]	.39 [nu]
	standing	3631 ± 597 [0.92]	3428 ± 497 [0.93]	.6 [nu]
LF/HF	supine	3 ± 1	3,7 ± 1	.08
	sitting	11 ± 2	10 ± 1	.82
	standing	19 ± 3	19 ± 4	.93

HF = high frequency; LF = low frequency; RMSSD = root mean square of successive R-R interval differences; SDNN = standard deviation of normal-to-normal intervals.

For power spectral density parameters, the *P* values given are for normalized units (nu).

amiodarone therapy and was superior to sham acupuncture and control group, with neither acupuncture nor antiarrhythmic therapy (27% vs 35% vs 69% vs 54%, *P* = .0075).[17] However, acupuncture at this point is difficult to reconcile with the anatomical understanding of the vagal nerve fibers.

It can be assumed that the antiarrhythmic effect of acupuncture is based on the stabilization of autonomic balance. Modulation of parasympathetic tone by additional acupuncture treatment could reduce AF recurrence rate and improve the outcome of catheter ablation or antiarrhythmic drug therapy. This may be particularly important in the first weeks after sinus rhythm restoration, since increased sympathetic and reduced vagal modulation characterizes patients with early AF relapse.[20] A future trial with patients suffering from AF would be of interest to determine to what extent acupuncture influences patients with pre-existing cardiac conditions.

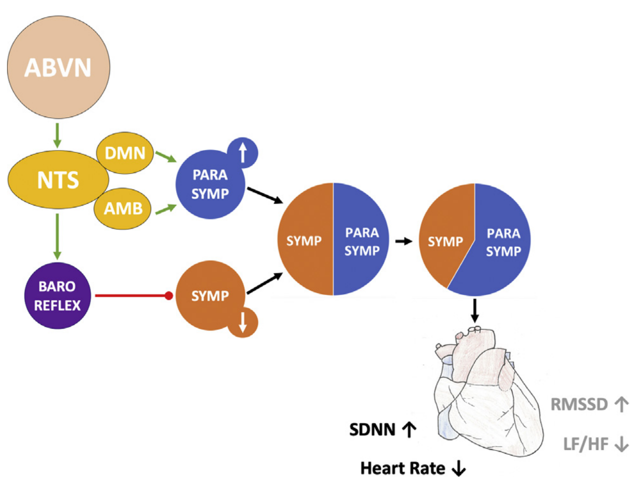

Figure 4 Schematic diagram of the hypothesized neural arc induced by acupuncture at the auricular branch of the vagus nerve (ABVN). Acupuncture at the ABVN increases the activity of the solitary nucleus (NTS) projecting to the vagal efferent neurons of the nucleus ambiguus (AMB) and dorsal motor nucleus (DMN) and thus resulting in enhanced parasympathetic (PARA SYMP) activation. Furthermore, activation of the solitary nucleus indirectly leads to sympathetic inhibition (SYMP) via a baroreflex-like effect.

Limitations

Since studies have shown that the ACNS is subject to a high interindividual variance,[14] this study aimed to obtain a high reliability through its homogeneous population and was therefore performed in male subjects, leaving unclear if the results found can be applied in both sexes. Moreover, since it was designed as a pilot study, the study population was small, and a significantly larger number of subjects could have provided more information and more accurate results. Several significant results and trends suggest a possible parasympathetic activation of acupuncture at ABVN, but it must be considered that any kind of exploratory analysis is—to a certain extent—affected by false-positive results owing to multiple testing.

Lastly, HRV represents an indirect estimate of cardiac autonomic function with significant limitations driven by the influence of respiration and changes in heart rate.

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