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Sympathetic and Parasympathetic Coactivation Induces Perturbed Heart Rate Dynamics in Patients with Paroxysmal Atrial Fibrillation

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Recent evidence indicates that sympathetic/parasympathetic coactivation (CoA) is causally linked to changes in heart rate (HR) dynamics. Whether this is relevant for patients with atrial fibrillation (AF) is unknown.

Material/Methods: In patients with paroxysmal AF (n=26) and age-matched controls, (n=10) we investigated basal autonomic outflow and HR dynamics during separate sympathetic (cold hand immersion) and parasympathetic activation (O_2-inhalation), as well as during CoA (cold face test). In an additional cohort (n=7), HR response was assessed before and after catheter-based pulmonary vein isolation (PVI). Ultra-high-density endocardial mapping was performed in patients (n=6) before and after CoA.

Results: Sympathetic activation increased (control: 74±3 *vs.* 77±3 bpm, p=0.0098; AF: 60±2 *vs.* 64±2 bpm, p=0.0076) and parasympathetic activation decreased HR (control: 71±3 *vs.* 69±3 bpm, p=0.0547; AF: 60±1 *vs.* 58±2 bpm, p<0.0009), while CoA induced a paradoxical HR increase in patients with AF (control: 73±3 *vs.* 71±3 bpm, p=0.084; AF: 59±2 *vs.* 61±2 bpm, p=0.0006), which was abolished after PVI. Non-linear parameters of HR variability (SD1) were impaired during coactivation in patients with AF (control: 61±7 *vs.* 69±6 ms, p=0.042, AF: 44±32 *vs.* 32±5 ms, p=0.3929). CoA was associated with a shift of the earliest activation site (18±4 mm) of the sinoatrial nodal region, as documented by ultra-high-density mapping (3442±343 points per map).

Conclusions: CoA perturbs HR dynamics and shifts the site of earliest endocardial activation in patients with paroxysmal AF. This effect is abolished by PVI, supporting the value of emerging methods targeting the intrinsic cardiac autonomic nervous system to treat AF. CoA might be a valuable tool to assess cardiac autonomic function in a clinical setting.

MeSH Keywords: Atrial Fibrillation • Autonomic Nervous System • Catheter Ablation • Heart Rate

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Background

Atrial fibrillation (AF) is the most common symptomatic arrhythmia in adults, with an increasing incidence in the aging population [1–3]. Over the last decades, the autonomic nervous system has been identified as an integral part of the complex pathophysiology of AF [4–6]. In this context, the classical concept of "accentuated antagonism" of the 2 branches of the autonomic nervous system has recently been challenged [7–9]. Experimental evidence and Holter electrocardiography (ECG) studies indicate that sympathetic/parasympathetic coactivation alters atrial electrophysiology, resulting in a predisposition to AF [10–12]. It has also been demonstrated that cardiac autonomic coactivation is causally linked to changes in heart rate (HR) dynamics in healthy adults [13]. Whether this relationship is also valid for patients with AF has not been investigated so far. Using standardized physiological interventions [14–16], we show here that autonomic coactivation, in contrast to separate sympathetic or parasympathetic activation, perturbs HR dynamics in patients with paroxysmal AF.

Material and Methods

Subjects

Patients presenting to our department with a history of paroxysmal AF were screened for inclusion. The following exclusion criteria were applied: sick sinus syndrome, unstable anginal symptoms, history of myocardial infarction in the last 3 months, clinical signs of heart failure, left ventricular ejection fraction <30%, obstructive sleep apnea syndrome, chronic obstructive pulmonary disease, active inflammation (CRP >5 mg/l), hyperthyroidism, history of catheter ablation, or any direct neuromodulation therapy (e.g., spinal cord, vagus, or baroreceptor stimulation). Qualifying patients with a positive history of paroxysmal AF and documented sinus rhythm (≥24 h) in telemetry or Holter-ECG were assigned to the AF group, while patients without history of AF were part of the control group.

All patients were on optimal medical therapy according to current ESC guidelines [17]. Autonomic etiology of AF was assessed and classified as vagal, adrenergic, or mixed type [18,19]. Subjects were advised to refrain from exercise and alcohol (>24 h), as well as from intake of food, nicotine, and caffeine (>4 h) prior to testing [20,21]. Subjects rested in supine position in a quiet environment for at least 10 min prior to testing [13]. This study was approved by the local ethics committee (*ClinicalTrials.gov* identifier: NCT01262508), informed consent was obtained from each subject.

Autonomic function testing and measurement of physiological parameters

The study protocol for autonomic function testing consisted of an initial resting phase, after which baseline parameters were recorded over a period of 10 min. Standardized physiological interventions were then conducted in a randomized sequence, each followed by a resting period of 10 min.

Two-channel ECG, oscillographic measurements of blood pressure (BP) at intervals of 5 min, and beat-to-beat recognition of BP by plethysmography were continuously acquired (Task Force® Monitor, CNSystems AG, Graz, Austria) [22]. Photoplethysmographic measurement of pulse and respiratory frequency as well as peripheral O_2 saturation were recorded continuously (Philips IntelliVue® MP50 Monitor, Philips Healthcare, Eindhoven, The Netherlands) [23].

Three tests were used to assess basal autonomic outflow, according to international consensus [24–26]: 1) Deep breathing test with calculation of the expiratory-inspiratory HR difference (E-I difference) and the expiratory-inspiratory HR ratio (E/I ratio) [16,27,28]. 2) Active standing test with calculation of the HR response to postural change (ratio of cycle lengths at beats 15 and 30 after standing; 30/15 ratio) [29,30]. 3) Quantification of spontaneous baroreflex sensitivity by assessment of simultaneous changes in HR and BP during acquisition of baseline parameters, as described below. Selective stimulation of autonomic outflow was achieved using the 3 established protocols [13,15]: 1) Immersion of the right hand in ice water (–1°C to 0°C) for 2 min (sympathetic activation) [31]. 2) Inhalation of pure oxygen through a face mask at a rate of 5l/min for 5 minutes (parasympathetic activation) [32]. 3) Cold face test with refrigerated gel packs (–1 to 0°C) applied to the occipitofrontal and maxillary region for 2 min (sympathetic/parasympathetic coactivation) [13,33]. All tests were conducted under standardized surrounding conditions. Test results were rejected in case of poor signal quality, outside interference, or lack of patient compliance during maneuvers.

Analysis of heart rate variability

For analysis of HR variability (HRV), recorded ECG parameters were exported in 5-min intervals [34] and analyzed with the public domain Kubios HRV software 2.0 (Biosignal Analysis and Medical Imaging Group, Department of Physics and Mathematics, University of Eastern Finland) [35], following established guidelines [36]. The following parameters were used to investigate changes in HRV during the study protocol [7,37]: 1) Root mean square of successive R-R interval differences (RMSSD), as a measure of the time domain. 2) High frequency power of the HR spectrum (HF, 0.15–0.4 Hz), as a parameter of the frequency domain. 3) Short-term variability

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of R-R intervals in the Poincaré plot (SD1), as a non-linear parameter of HR dynamics.

Baroreflex sensitivity

Spontaneous baroreflex sensitivity was quantified using the sequence method during acquisition of baseline parameters and during stimulation of autonomic outflow [38,39]. In brief, this method evaluates simultaneous changes in HR and BP using standardized cut-off values. The resulting index (ms/mmHg) is a function of parasympathetic outflow [40].

Characterization of sinoatrial nodal functional topography by ultra-high-density mapping

To investigate the functional topography of the sinus node, we performed ultra-high-density mapping of the right atrium by using a specialized basket catheter (1.8-cm diameter) equipped with 8 octapolar electrode splines (2.5-mm spacing, Orion, Boston Scientific) during sinus rhythm [41]. Patients were kept under deep sedation and analgesia (i.v. propofol and fentanyl) during the procedure [42]. Acquisition and processing of ECG and positional data points occurred automatically by means of specialized software, using predefined acceptance criteria consisting of cycle length stability, relative timing of reference electrograms, electrode location stability, and respiratory gating (Rhythmia, Boston Scientific) [43]. Mapping was undertaken under baseline conditions, as well as during simultaneous $\beta_{1/2}$-adrenergic and m_2-muscarinergic receptor stimulation by concomitant administration of orciprenaline (10–30 µg/min) and high-flow oxygen insufflation (10 l/min) via a face mask.

Pulmonary vein isolation for atrial fibrillation

In an additional cohort, we investigated whether HR characteristics during sympathetic/parasympathetic coactivation were influenced by pulmonary vein isolation (PVI). Cold face test was performed within 24 h before and after PVI. Deep sedation was achieved by continuous propofol infusion and additional fentanyl bolus administration throughout the procedure [42]. PVI was carried out as described before [44,45]. The procedures were guided by a 3-dimensional mapping of the left atrium using the Carto 3 system (Biosense Webster, Diamond Bar, CA, USA). The endpoint of PVI was documented entrance block confirmed by loss or dissociation of potentials in the circumferential mapping catheter for each pulmonary vein.

Statistical analysis

Continuous variables are presented as mean ± standard error of the mean; frequencies and percentages are given for categorical data. Changes in heart rate following autonomic interventions were examined by the Wilcoxon matched-pairs signed rank test within groups. For comparisons between groups, a 2-way repeated-measures analysis of variance with Sidak's multiple comparisons test was used for continuous data, and categorical data were compared using Fisher's exact test. $p<0.05$ was considered statistically significant. Statistical analysis was performed using GraphPad Prism 6.0® for Mac (GraphPad Inc., La Jolla, California, USA).

Results

Patient characteristics

Inclusion criteria were met by 26 patients (age 72±2 years, 13 males) presenting to our hospital. The AF etiology was vagal in 4 patients (15%), adrenergic in 2 (8%), and mixed in 1 patient (4%), and clear classification was not possible in 19 patients (73%) [46]. A detailed overview of clinical baseline characteristics is presented in Table 1. Notably, there was a relevant use of antiarrhythmic drugs in our collective. Those were primarily beta-blockers, with a comparable prevalence in both groups (control: n=7, 70% AF: n=22, 85%; p=0.3696). Specific antiarrhythmic drugs were used in 7 (32%) of the AF patients and in none of the controls. Amiodarone (n=3, 12%) and flecainide (n=2, 8%) were the most prevalent agents. Only single patients were treated with dronedarone and propafenone (n=1, 4%).

Sympathetic/parasympathetic coactivation induces paradoxical HR increase

Changes in HR during stimulation of autonomic outflow are shown in Figure 1. HR increased during sole sympathetic activation (control: 74±3 *vs.* 77±3 bpm, p=0.0098; AF: 60±2 *vs.* 64±2 bpm, p=0.0076) and decreased during separate parasympathetic activation (control: 71±3 *vs.* 69±3 bpm, p=0.0547; AF: 60±1 *vs.* 58±2 bpm, p<0.0009). In contrast, sympathetic/parasympathetic coactivation did not result in HR reduction, but rather a paradoxical HR increase in 17 out of 21 (81%) patients with AF (control: 73±3 *vs.* 71±3 bpm, p=0.084; AF: 59±2 *vs.* 61±2 bpm, p=0.0006) was observed. The increase of mean arterial blood pressure during sympathetic/parasympathetic coactivation was more pronounced in patients with AF (control: 95±5 *vs.* 100±6 mmHg, p=0.0213; AF: 97±4 *vs.* 106±4 mmHg, p<0.0001).

Impaired heart rate variability during parasympathetic activation

For HRV parameters in the time domain (RMSSD), frequency domain (HF: 0.15–0.4 Hz), or for non-linear parameters (SD1), no significant differences for sympathetic or parasympathetic stimulation were detected in controls or patients with AF. During sympathetic/parasympathetic coactivation, an increase

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Table 1. Patient characteristics.

	AF patients (n=26)	Controls (n=10)	p-Value
Patient characteristics			
Age (years)	72±2	68±5	0.6233
Sex (male)	13 (50)	6 (60)	0.714
Height (cm)	170±2	172±4	0.9293
BMI (kg/m^2)	29±1	30±2	0.9901
CHA_2DS_2-VASc–Score 0/1/≥2, n	1/1/24	1/1/8	1.0/1.0/0.3048
EHRA Score I/II/III/IV, n	13/6/1/10	–/–/–/–	0.0058/0.1567/1.0/0.0345
Comorbidities			
CAD	19 (73)	6 (60)	0.5439
CHF	10 (39)	5 (50)	0.7086
NYHA class I/II/III/IV, n	0/7/4/0	1/2/2/0	0.2778/1.0/ 1.0/1.0
Hypertension	21 (81)	8 (80)	1.0
Diabetes mellitus	4 (15)	1 (10)	1.0
CKD (GFR <60 ml/min/1.73 m^2)	6 (23)	3 (30)	0.6856
Medication prior to PVI			
Beta-blocker	22 (85)	7 (70)	0.3696
ACE inhibitor/AT-II antagonist	14 (54)	6 (60)	1.0
Statin	20 (77)	5 (50)	0.224
Flecainide	2 (8)	0 (0)	1.0
Propafenone	1 (4)	0 (0)	1.0
Amiodarone	3 (12)	0 (0)	0.5448
Dronedarone	1 (4)	0 (0)	1.0

Values are mean ± standard error of the mean or n (%). AF – atrial fibrillation; BMI – body mass index; CAD – coronary artery disease; CHF – congestive heart failure; CKD – chronic kidney disease.

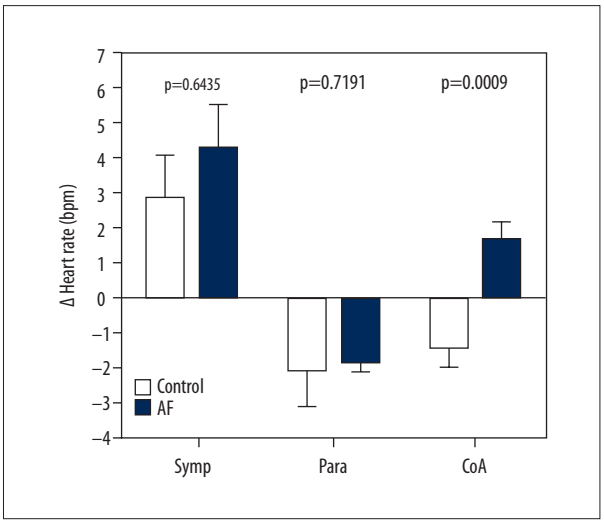

Figure 1. Paradoxical heart rate (HR) increase during sympathetic/parasympathetic coactivation (CoA). During separate sympathetic (Symp) and parasympathetic activation (Para), patients in the control group (white columns) and patients with atrial fibrillation (AF, blue columns) exhibited physiological and associated changes in HR. Differences in HR regulation in patients with AF only become apparent during sympathetic/parasympathetic coactivation, as indicated by a paradoxical increase in HR, compared to patients in the control group.

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Table 2. Basal parasympathetic outflow in patients with atrial fibrillation (AF) and age-matched controls. Data from standardized tests of autonomic function including the deep breathing test, the active standing test, and baroreflex sensitivity (BRS) are shown.

	Patients with AF	Controls	p-value
Deep breathing test	(n=21)	(n=8)	
E-I difference [min^{-1}] (norm: ≥5)	5.7±0.9	10.8±2.2	0.02
<5 min^{-1} [n, (%)]	8 (38)	2 (25)	0.6749
E-I ratio (norm: ≥1.10)	1.11±0.09	1.16±0.04	1.0
<1.10 [n, (%)]	8 (38)	2 (25)	0.6749
Active standing test	(n=17)	(n=8)	
30/15 ratio (norm: ≥1.09)	1.16±0.03	1.22±0.08	1.0
<1.09 [n, (%)]	8 (47)	2 (25)	0.4018
Baroreflex sensitivity	(n=19)	(n=8)	
BRS [ms/mmHg] (norm: ≥9.3)	10.5±1.6	11.2±2.6	0.9918
<9.3 [n, (%)]	11 (58)	4 (50)	1.0

in the frequency domain and non-linear analysis was observed after PVI in controls (HF: 182±60 *vs.* 249±86 ms^2, p=0.0273; SD1: 61±7 *vs.* 69±6 ms, p=0.042), while in patients with AF, an increase in the frequency domain (HF: 133±36 *vs.* 414±126 ms^2, p=0.0098) but not in non-linear parameters (SD1: 44±32 *vs.* 32±5 ms, p=0.3929) was obvious.

Basal autonomic outflow in patients with and without AF

There was no difference in basal autonomic outflow, as determined by baroreflex sensitivity (p=0.9918) and the active standing test (p=1.0). In the deep breathing test, the E-I difference was lower in the AF group (AF: 5.7±0.9, control: 10.8±2.2, p=0.02), while the E-I ratio did not differ between groups (AF: 1.11±0.09, control: 1.16±0.04, p=0.6749). However, all 3 tests indicated no difference between groups in the proportion of individuals with pathological autonomic outflow (Table 2).

Catheter ablation abolishes paradoxical HR response

In patients undergoing PVI (n=7), a paradoxical HR increase was observed during autonomic coactivation prior to the procedure (57±2 *vs.* 64±3 bpm, p=0.038). Following PVI, a trend towards elevation in mean resting HR was observed (57±2 *vs.* 64±3 bpm, p=0.081). Autonomic coactivation after PVI did not change HR (64±3 *vs.* 65±3 bpm, p=0.3046).

Impact of coactivation on the functional topography of the sinoatrial node

To investigate the impact of autonomic coactivation on the functional topography of the sinoatrial node, high-density mapping of the right atrium was performed (n=6, 5 males, mean age 65±4 years) (Figure 2). At baseline, the area of earliest activation was located at the medial level of the lateral aspect of the right atrium. Under extrinsic autonomic coactivation a decrease of sinus cycle length (976±18 *vs.* 734±30 ms, p=0.0014), a decrease of mean blood pressure (79±6 *vs.* 64±8 mmHg, p=0.0385), and a rise in SpO_2 (95±0.6 *vs.* 97±0.7%, p=0.0349) were observed. The location of the area of earliest activation shifted towards an anterior and superior position in all but 1 case, where it shifted lateral and inferior. The mean distance between the sites of earliest activation at baseline and during extrinsic coactivation was 18±4 mm. An average of 3442±343 points per map were acquired, with a consistent point number between maps (baseline: 3199±482, coactivation: 3686±511, p=0.2030).

Discussion

There are 3 main findings of this study: 1) In patients with paroxysmal AF, sympathetic/parasympathetic coactivation results in perturbed HR dynamics, indicated by a paradoxical HR increase and impaired HRV indices. 2) The paradoxical HR increase during autonomic coactivation was abolished after PVI. 3) The observed effects appear to be independent of the autonomic etiology of AF and basal parasympathetic outflow.

Role of the sinus node function in AF

Previous studies have established a direct pathophysiological link between changes in sinus node function and AF, beyond its role as a gauge of autonomic outflow. Changes in autonomic

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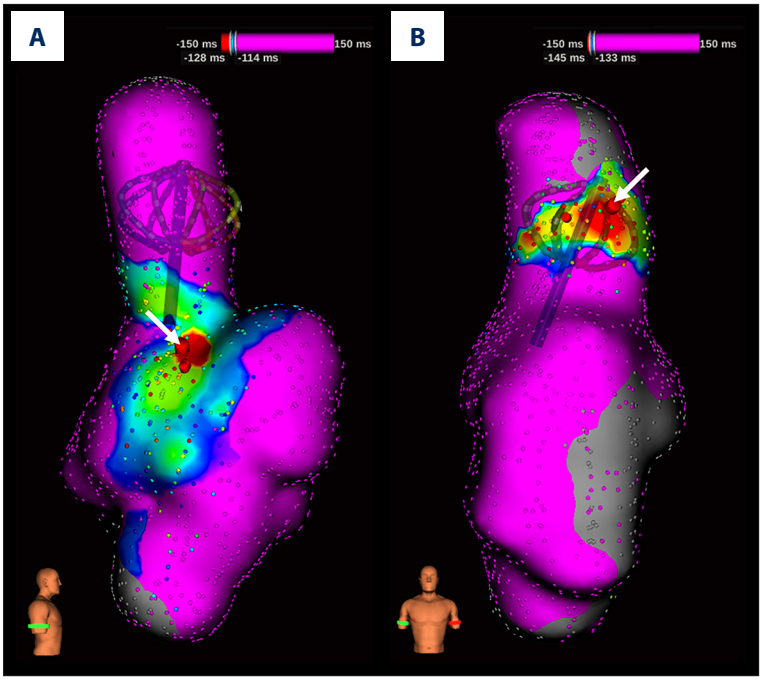

Figure 2. High-density activation mapping of (**A**) the right atrium at rest and (**B**) during extrinsic autonomic coactivation (n=6). Coactivation was achieved by simultaneous $\beta_{1/2}$-adrenergic (i.v. orciprenaline) and m_2-muscarinergic (high-flow oxygen insufflation) receptor stimulation. At baseline, the area of earliest activation was located at the medial level of the lateral aspect of the right atrium. Under extrinsic sympathetic and parasympathetic coactivation, the location of the area of earliest activation (red marker indicated by white arrow) shifted anterior and superior. Surface distance between sites of earliest activation at baseline and during extrinsic autonomic coactivation was 25.7 mm.

activation and balance elicit changes in local automaticity, conduction velocity, and refractory periods [47]. Due to the structural and functional heterogeneity of the sinus node region, this results in changes of pacemaker activity and altered conduction to the surrounding atrial tissue, introducing premature atrial depolarizations, multiple exit sites, and local conduction blocks [48]. These factors contribute to the induction and maintenance of AF.

Autonomic coactivation induces a paradoxical HR increase

Experimental evidence indicates that sympathetic/parasympathetic coactivation results in alterations of atrial electrophysiology that predispose to AF. We here demonstrate that autonomic coactivation in patients with paroxysmal AF goes along with perturbed HR dynamics, including an HR increase, when physiologically a decrease would be expected [17]. This was accompanied by a shift of the earliest endocardial activation site during simultaneous extrinsic adrenergic/muscarinergic stimulation, as demonstrated by ultra-high-density mapping.

Our findings are consistent with recent data from retrospective Holter-ECG studies in patients with AF that are not explained by the classical concept of "accentuated antagonism" of sympathetic and parasympathetic activity [7]. In this study a primary increase in sympathetic tone followed by an abrupt increase in parasympathetic activation was observed.

Importantly, there are several factors which might influence this findings in patients with AF. First, a reduced HR decrease with increasing age has been described [49]. However, this is not sufficient to explain the phenomenon found in our study, because age-matched controls have been investigated. Second, beta-blockers are widely used in patients with AF and their impact cannot be fully determined. While this was also the case in our collective, the no prevalence was similar between individuals with AF and controls. Furthermore, previous studies have not reported a pronounced decrease in HR during sympathetic/parasympathetic coactivation under beta-blocker therapy [50]. Blockade of beta-1 receptors would be expected to dampen the observed HR increase. In summary, this indicates that beta-blockers might not be sufficient to target the neural substrate of AF in the vast majority of patients. This is supported by the progressive nature and high burden of AF found in large clinical trials, as well as data from real-world registries which have investigated patients with AF treated with beta-blockers [51,52]. Third, the previous also holds true for the specific antiarrhythmic drugs, used in only one-third of our AF patients. While there is limited data on the effect of antiarrhythmic drugs on HR variability, the present evidence [53,54] suggests only an insignificant impact of propafenone and amiodarone, which might also be assumed to be true for dronedarone. Flecainide appears to have a more pronounced effect [55], but was only used in 2 individuals. Concerning their influence on HR, those antiarrhythmics exert a negative chronotropic effect, somewhat dampening the observed HR increase, and were not used in the control group, where they could have masked a possible HR increase. Fourth, congestive heart failure, hypertension, and chronic kidney disease are accompanied by increased sympathetic activity [56–58]; therefore, the impact of comorbidity cannot be excluded.

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Effects on HR regulation are independent of basal parasympathetic outflow

The mechanisms underlying our observations appear to be independent of tonic parasympathetic outflow, as demonstrated by the congruent results in basal autonomic outflow testing. Determining whether it is possible to increase parasympathetic activity is therefore mandatory for characterization of neural cardiac control in patients with AF. This is also important because it is often impossible to unequivocally classify the autonomic etiology of AF according to current guidelines. The tests applied here have been available for decades and might be useful for patient selection in light of emerging pharmacological and/or interventional neuromodulation therapies [59,60]. Pre-interventional characterization of phasic neural control may have significant implications for the design, performance, and outcome of future interventional studies.

Possible mechanism of perturbed HR dynamics

HRV analysis did not demonstrate an increase in parasympathetic parameters in the time and frequency domain or in non-linear parameters during O_2 inhalation and revealed a heterogeneous response during sympathetic/parasympathetic coactivation. The observed physiological response of BP to sympathetic and parasympathetic stimulation, as well as to autonomic coactivation, implies an effective preganglionic stimulation during those maneuvers [33]. This suggests a disruption of postganglionic parasympathetic sinus node modulation as a possible underlying mechanism, since facial cooling would be expected to increase parasympathetic activity and result in increased HRV parameters [31].

Several investigators have studied the abnormal modulation of the sinus node in AF patients, with divergent results. Initial experimental approaches demonstrated the importance of sympathetic/parasympathetic interactions for the induction of AF in animal models [61,62]. Previous observational studies in humans reported predominant sympathetic activity with reduced parasympathetic outflow [63], as well as autonomic coactivation with initial increase in sympathetic drive followed by parasympathetic predominance before the onset of AF [7]. While providing valuable insights into the complex sympathetic/parasympathetic interplay during the induction of paroxysmal AF using indirect indices of autonomic control or clinical endpoints, application of these data to the clinical reality of AF is limited. Our study, using physiological stimuli in patients with AF, demonstrates for the first time a perturbation of HR dynamics during autonomic coactivation.

Implications for clinical autonomic modulation

As discussed above, our data implies a postganglionic parasympathetic deficit, resulting in a paradoxical HR increase under CoA. Also, data from the small subgroup of patients examined after PVI indicates a post-procedural attenuation of this effect. These observations support the value of emerging clinical methods to modify the intrinsic cardiac autonomic neuronal system in AF patients [9]. While those concepts have been tested in an experimental setting and hold great promise, they cannot at present be translated into broad clinical application [64]. There remain a variety of questions that warrant further exploration of those methods. CoA, as a simple but meaningful test, might be a valuable tool for assessment of cardiac autonomic function in this setting.

Study limitations

Due to the extensive testing protocol and the strict application of exclusion criteria, the number of examined subjects was limited. Nevertheless, the resulting data allowed the identification of significant differences in physiological responses. It can be argued that the inclusion of more individuals might have rendered some borderline results significant, thus adding some further aspects to the observation.

The effects observed in our study, especially concerning heart rate, may appear slight at first sight, but those effects were observed consistently and reproducibly and achieved robust significance in the statistical analysis. It should be kept in mind that heart rate is a tightly regulated parameter; therefore, slight variations are the result of complex underlying physiological interactions.

Conclusions

Sympathetic/parasympathetic coactivation perturbs HR dynamics and shifts the site of earliest endocardial activation in patients with paroxysmal AF. This effect is abolished by PVI, supporting the value of emerging methods targeting the intrinsic cardiac autonomic nervous system to treat AF. CoA might be a valuable tool for clinical assessment of cardiac autonomic function.

Statement

Philips Inc. had no role in the design, conduct, or analysis of the study.

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