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Cardiac autonomic regulation and PR interval determination for enhanced atrial fibrillation risk prediction after cardiac surgery

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ABSTRACT

Background: Changes in cardiac autonomic regulation and P-wave characteristics are associated with the occurrence of atrial fibrillation. The purpose of this study was to evaluate whether combined preoperative non-invasive determination of cardiac autonomic regulation and PR interval allows for the identification of patients at risk of new-onset atrial fibrillation after cardiac surgery.

Methods: RR, PR and QT intervals, and linear and non-linear heart rate variability parameters from 20 min high-resolution electrocardiographic recordings were determined one day before surgery in 150 patients on chronic beta blockers undergoing elective coronary artery bypass grafting, aortic valve replacement, or both, electively.

Results: Thirty-one patients (21%) developed postoperative atrial fibrillation. In the atrial fibrillation group, more arterial hypertension, a greater age, a higher EuroSCORE II, a higher heart rate variability index (pNN50: 9 ± 20 vs. 4 ± 10, $p = 0.050$), a short PR interval (156 ± 23 vs. 173 ± 31 ms; $p = 0.011$), and a reduced short-term scaling exponent of the detrended fluctuation analysis (DFA1, 0.96 ± 0.36 vs. 1.11 ± 0.30 ms; $p = 0.032$) were found compared to the sinus rhythm group. Logistic regression modeling confirmed PR interval, DFA1 and age as the strongest preoperative predictors of postoperative atrial fibrillation (area under the receiver operating characteristic curve = 0.804).

Conclusions: Patients developing atrial fibrillation after cardiac surgery presented with severe cardiac autonomic derangement and a short PR interval preoperatively. The observed state characterizes both altered heart rate regulation and arrhythmic substrate and is strongly related to an increased risk of postoperative atrial fibrillation.

1. Introduction

The first attempts to predict atrial fibrillation after cardiac surgery based on clinical characteristics date back almost 30 years [1]. Notwithstanding this, available prediction models still lack an appreciation of the underlying cause-related electrophysiological variables [2,3]. Several studies have contributed to the understanding of its multifactorial complex nature, paving the way to current preventive and therapeutic strategies [4–7]. Nevertheless, postoperative atrial fibrillation (POAF) not only represents the most frequent complication worsening outcomes in 10–65% of patients after cardiac surgery, but also significantly impacts on their long-term prognosis and mortality [5–8]. Recent studies utilizing parameters derived from non-invasive electrocardiography (ECG) revealed the association of P-wave characteristics during sinus rhythm (SR) with either paroxysmal atrial fibrillation or POAF [9,10]. The newest evidence emphasizes the dominant role of disturbed cardiac autonomic regulation (CAR) in the genesis, maintenance and suppression of atrial arrhythmias in different subgroups of patients, including POAF [11–15]. Similar to the autonomic perturbations detected at the initiation and termination of paroxysmal atrial fibrillation, the levels of intrinsic cardiac nerve activity also differ in SR vs. POAF patients after heart surgery [12,15]. Several patterns of CAR have been postulated as possible POAF triggers by assessing heart rate variability (HRV) [16–18], whereby a landmark study associated POAF with concomitant parasympathetic nervous system (PNS) withdrawal and sympathetic nervous system (SNS) activation [16]. Thus, the aim of the

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present study was to explore the patterns of CAR in patients developing POAF, and to assess the value of combined PR interval determination and HRV parameters in predicting the risk of POAF.

2. Methods

The present investigation was designed as a prospective observational study, comparing linear and non-linear HRV parameters and ECG intervals of the cardiac cycle in patients developing POAF or remaining in SR after cardiac surgery. The study complied with the Declaration of Helsinki, Finland, and the Oviedo Convention, Asturia, Spain. The State Ethics Committee of the Republic of Slovenia approved the study protocol (58/03/15), and informed consent was obtained from all the study participants prior to measurements.

2.1. Study population

From April 2015 to October 2016, a total of 178 consecutive patients were enrolled. Eligibility criteria included aortic valve stenosis and/or regurgitation and/or ischemic heart disease scheduled for elective first cardiac surgery, with SR documented preoperatively from 20 min high-resolution ECG recordings, chronic beta-blocker medication with metoprolol or bisoprolol, left ventricular ejection fraction (LVEF) ˃40% with no heart failure medication. Patients underwent myocardial revascularization (coronary artery bypass grafting, CABG), aortic valve replacement (AVR), or both, electively. The exclusion criteria were a history or the presence of any atrial arrhythmia or atrioventricular conduction disorder, a permanent pacemaker, a contraindication to beta blockers or an incomplete beta blockade, defined as a preoperative resting heart rate out of the 60–80 bpm range, antiarrhythmic medication other than beta blockers, a history of previous cardiac operation, the need for a second run of cardiopulmonary bypass, and type 2 diabetes mellitus with late neurological complications.

2.2. Postoperative care and postoperative atrial fibrillation monitoring

The anesthetic technique and surgical strategies were standardized as previously described [18]. Postoperatively, heart rate and rhythm were projected onto a heart monitor with automatic arrhythmia detection (HP 1205A, Hewlett-Packard, Andover, MA, USA) until the fifth postoperative day. A standard 12-lead ECG was recorded daily thereafter, until the day of discharge and at any time in the case of a clinical suspicion of POAF. Beta blockade with target heart rates of 60–80 bpm was one of the prophylactic POAF strategy goals. Further measures included potassium substitution to maintain levels >4.5 mmol/L, magnesium supplementation, careful administration of diuretics to prevent excessive fluid shifts, keeping hemoglobin levels >8 mg/dL in asymptomatic patients and >10 mg/dL in symptomatic, multimorbid, or older patients (≥75 years).

If POAF occurred, electrolyte correction and fluid restitution were performed as appropriate, followed by additional beta blockers and finally amiodarone to allow for medical conversion. Patients with POAF persisting for >12 h and/or with hemodynamic instability received cardioversion.

In order to portray the physiologic mechanisms in the background but retaining clinical applicability, we described POAF by combining electrophysiologic and clinical criteria [5]. POAF was defined as any apparent self-sustaining irregular arrhythmia requiring medical intervention in the form of rhythm control agents and/or anticoagulation and/or cardioversion; sustained or repetitive enough to be detected by continuous monitoring or any clinically/electrocardiographically confirmed arrhythmia thereafter that was documented on the patient's chart by a member of the health-care team. Continuous monitoring/telemetry was used in 100% of the patients during the first 5 postoperative days.

2.3. Electrocardiography

ECG recordings were obtained on the day before surgery. Measurements were conducted in the afternoon to avoid the effects of circadian autonomic tone variations, 2 h after the last meal to avoid postprandial effects on the autonomic tone. Patients were in the supine position 15 min prior to recordings in a quiet, warm room, and were asked to relax, breathe normally, refrain from moving and talking, but to keep awake during the acquisition of the 20 min, high-resolution 12-channel ECG recording with a Cardiax device. The lengths of the PR, QRS and QT intervals were determined using Cardiax version 3.50 software (Mesa Medizintechnik GmbH, Benediktbeuern, Germany). RR intervals were determined using NevroEKG software (Jožef Stefan Institute, Ljubljana, Slovenia). The NN intervals (RR intervals with adjacent R-waves preceded by P-waves) were used in the spectral analysis. The RR intervals of the isolated premature beats were replaced by averages of the surrounding intervals, and recordings containing ectopy or edited segments exceeding ˃5% of the total recorded time were discarded. Time- and frequency-domain linear and non-linear HRV parameters were determined using PhysioToolkit software (PhysioNet http://www.physionet.org). Corrected QT intervals (QTc) were calculated using the Fridericia's and Hodges's correction formulas [19].

We calculated the AVNN (average NN interval), SDNN (SD of all NN intervals), RMSSD (root mean square of successive differences) and pNN50 (percentage of pairs of adjacent NN intervals differing by >50 ms) in the time domain. Spectral power was analysed with a discrete Fourier transform on linearly detrended segments comprising 1200 data points. The frequency-domain measures included total power (0.01–0.40 Hz), very-low frequency power (0.01–0.04 Hz), low-frequency (LF) power (0.04–0.15 Hz) indicating modulated SNS activity, and high-frequency (HF) power (0.15–0.40 Hz) indicating PNS modulation [20] and LF/HF ratio. In the non-linear HRV domain, a detrended fluctuation analysis (DFA) was applied to explore the fractal-like properties of the heart rhythm. DFA is a modified root-mean-square analysis of a random walk used to quantify the fractal-like correlation properties of RR intervals. The correlation properties were determined for both short-term (≤11 beats, DFA1) and long-term (>11 beats, DFA2) fluctuations of RR intervals. The DFA1 scaling exponent is >1 when the cardiac sympatho-parasympathetic autonomic interplay is altered in a reciprocal fashion and <1 during the concomitant activation of both PNS and SNS [20–22].

2.4. Statistical analysis

The demographic, perioperative (Table 1) and ECG-derived data of the two study groups (Tables 2 and 3) were compared with the independent samples *t*-test for normally distributed variables, the Mann-Whitney *U* test for non-normally distributed variables, and the χ^2 test for categorical variables, whereby the Kolmogorov-Smirnov test served as a normality check. The ECG variables that significantly differed with respect to POAF, were further fed into univariate and multivariate versions of logistic regression. The multivariate logistic regression model was built using the forward likelihood ratio approach. Evaluation of regression models was performed by computing the area under the receiver operating characteristic curve (AUC) in a leave-one-out cross validation. In this way, POAF prediction for each particular patient was derived from the logistic regression model, having been estimated from the rest of the patients to make certain that the logistic regression models were trained on one data set and validated on another. In addition, a nomogram of

Table 1
Clinical characteristics of the study patients.

	POAF group (n = 31)	SR group (n = 119)	p-Value
Demographic characteristics			
Age (years)	74.3 ± 7.4	67.1 ± 11.7	**≤0.001**
Male sex	16 (53%)	80 (67%)	0.107
BMI (kg/m^2)	27.6 ± 5.2	28.5 ± 4.1	0.323
EuroSCORE II[a]	2.2 ± 1.4	1.6 ± 1.1	**0.034**
Preoperative characteristics			
Diabetes mellitus type 2 (no/oral/insulin)	23 (74%)/7 (23%)/1 (3%)	86 (72%)/23 (19%)/10 (8%)	0.594
Arterial hypertension	29 (94%)	93 (78%)	**0.050**
Hypercholesterolemia	11 (35%)	32 (27%)	0.346
History of AMI	5 (16%)	18 (15%)	0.890
Left ventricular ejection fraction ≤55%	7 (23%)	15 (13%)	0.229
NYHA class (0/I/II/III/IV)	0/3/20/8/0	2/15/63/36/3	0.820
Preoperative creatinine (μmol/l)[a]	80 ± 23	82 ± 22	0.385
Chronic obstructive pulmonary disease	4 (13%)	6 (5%)	0.248
Beta blockers	31 (100%)	119 (100%)	–
Angiotensin-converting enzyme inhibitors	24 (78%)	95 (80%)	0.768
Statins	18 (58%)	64 (54%)	0.670
Perioperative characteristics			
Surgery type			
AVR/CABG/AVR + CABG	13 (42%)/8 (26%)/10 (32%)	55 (46%)/37 (31%)/27 (23%)	0.538
CABG (off pump/on pump)	4 (50%)/4 (50%)	23 (62%)/14 (38%)	0.862
Cardiopulmonary bypass time (min)	102 ± 36	92 ± 35	0.174
Cross-clamp time (min)	78 ± 31	70 ± 30	0.146
RBC transfusion (packs)[a]	1.9 ± 2.6	1.0 ± 1.6	**0.039**
Respiratory support (h)[a]	7.5 ± 9.4	5.9 ± 7.5	0.385
Fresh frozen plasma (packs)[a]	2.6 ± 2.5	1.6 ± 1.9	0.051
Inotropes (h)[a]	16.2 ± 27.3	14.6 ± 20.1	0.721
ICU stay (h)[a]	111.3 ± 123.9	51.7 ± 57.1	0.004
Hospital stay (days)[a]	9.9 ± 10.2	6.2 ± 3.8	0.001
Postoperative medication			
Beta blockers	24 (78%)	98 (83%)	0.530
Angiotensin-converting enzyme inhibitors	22 (72%)	83 (70%)	0.895
Statins	15 (48%)	59 (50%)	0.906

Values are expressed as mean ± standard deviation, or frequency (%). AMI = acute myocardial infarction; AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass grafting; ICU = intensive care unit; NYHA = New York Heart Association; POAF = postoperative atrial fibrillation; RBC = red blood cell; SR = sinus rhythm.
Bold values indicates significance at P-value ≤ 0.05.
[a] Non-normally distributed data.

Table 2
Comparison of preoperative ECG intervals, linear and non-linear heart rate variability parameters between patients who developed postoperative atrial fibrillation and patients who remained in sinus rhythm.

	POAF group (n = 31)	SR group (n = 119)	p-Value
ECG intervals			
RR interval (ms)	875 ± 72	905 ± 138	0.432
PR interval (ms)[a]	156 ± 23	173 ± 31	**0.011**
QRS complex (ms)[a]	102 ± 20	102 ± 17	0.998
QT interval (ms)	418 ± 32	417 ± 32	0.895
QTc interval – Fridericia (ms)	434 ± 24	429 ± 25	0.303
QTc interval – Hodge (ms)	433 ± 23	428 ± 25	0.253
Linear HRV parameters			
AVNN (ms)	906 ± 151	925 ± 131	0.489
SDNN (ms)[a]	36 ± 21	33 ± 16	0.218
RMSSD (ms)[a]	29 ± 37	21 ± 16	0.302
pNN50 (%)[a]	9 ± 20	4 ± 10	0.050
TP (ms^2)[a]	1275 ± 1197	1389 ± 1547	0.998
VLF (ms^2)[a]	507 ± 590	580 ± 689	0.389
LF (ms^2)[a]	199 ± 328	248 ± 386	0.210
HF (ms^2)[a]	190 ± 309	209 ± 389	0.833
LF/HF[a]	1.83 ± 1.44	2.22 ± 1.73	0.265
Non-linear HRV parameters			
DFA1	0.95 ± 0.36	1.11 ± 0.30	**0.032**
DFA2[a]	0.92 ± 0.22	0.96 ± 0.14	0.624

Values are expressed as mean ± standard deviation. AVNN = average NN interval; DFA1 and DFA2 = detrended fluctuation analysis short- and long-term scaling exponent; HF = high frequency power; HRV = heart rate variability; LF = low frequency power; LF/HF = ratio of low to high frequency power; pNN50 = percentage of pairs of adjacent NN intervals differing >50 ms; POAF = postoperative atrial fibrillation; QTc = corrected QT interval; RMSSD = root mean square of successive differences; SDNN = standard deviation of all NN intervals; SR = sinus rhythm; TP = total power; VLF = very-low frequency.
Bold values indicates significance at P-value ≤ 0.05.
[a] Non-normally distributed data.

the final multivariate logistic regression model was produced to associate risk factors with the development of POAF. All statistical analyses were performed using the SPSS software package (IBM SPSS Statistics, version 20); the logistic regression modeling and evaluation were done with the KNIME Analytic Platform (KNIME GmbH, Konstanz, Germany, version 3.3.1), whereby a p-value <0.05 was considered as being statistically significant.

3. Results

3.1. Patient characteristics

Of the 178 patients that were initially enrolled, 8 patients were excluded because of non-compliance with the aforementioned criteria, 3 died in the early postoperative course (from pneumonia-associated sepsis, cerebrovascular infarction, and mesenteric ischemia), and 17 had ectopic activity that was not amenable to advanced ECG analyses. In the final sample of 150 patients, 31 patients (21%) developed POAF (POAF group) and 119 did not (SR group). Patients experienced episodes of POAF after a median of 2 days (range 1–6 days) after surgery.

All patients were receiving the beta blocker metoprolol or bisoprolol preoperatively and as soon as possible after surgery, provided they were free of inotropic agents and were hemodynamically stable. Of the 31 patients with POAF, 27 were treated with beta blockers with the addition of amiodarone in 18. Four patients that did not convert to SR medically underwent cardioversion, whereby two unsuccessfully cardioverted patients were discharged on anticoagulation. Finally, one patient received a permanent pacemaker due to prolonged bradycardia. The pre- and perioperative characteristics of the study patients are reported in Table 1.

3.2. ECG intervals and RR interval dynamics

As shown in Table 2, the POAF group presented with significantly shorter PR intervals compared to the SR group. Among HRV parameters, the time-domain parameter pNN50 was significantly higher in the POAF group. The non-linear HRV parameter DFA1 was lower in the POAF group.

3.3. Type of operation with respect to the underlying structural heart disease

No differences were observed in ECG intervals, and linear and non-linear HRV parameters among the three different types of operation (Supplemental Table). Patients undergoing AVR and CABG had significantly lower LVEF and longer cardiopulmonary bypass times.

3.4. Atrial fibrillation prediction modeling

Logistic regression modeling was performed to ascertain the effects of the significant variables (i.e. age, arterial hypertension, EuroSCORE II, PR interval, pNN50, and DFA1) on the likelihood of POAF occurrence. The forward-stepwise logistic regression revealed an advanced age, a shorter PR interval and a lower DFA1 to be associated with an increased risk of developing POAF (Table 3). The logistic regression model with age alone predicted POAF with an AUC of 71.3%, the model with added PR interval increased the AUC to 78.8%, and the final model with all three variables (age, PR interval and DFA1) yielded a final AUC of 80.4%.

Furthermore, a nomogram of the final logistic regression model was generated to show how the parameters age, PR interval and DFA1 predict POAF (Fig. 1) and can be interpreted in the following way. If an 83-year-old patient (blue spot in the Age scale) has a PR interval of 140 ms (blue spot in the PR interval scale) and has an estimated DFA1 of 0.7 (blue spot in the DFA alpha1 scale), then there is a 70% chance that he/she will develop POAF. Also, note that the most important predictor according to the nomogram is PR interval, which has 100 points, while Age has a maximum of 85.3 points, and DFA1 has 30.6 points in the nomogram scale.

4. Discussion

Contrary to traditional time- and frequency-domain linear HRV analyses, non-linear DFA-derived HRV parameters could discriminate POAF from normal SR also preoperatively. The novel finding of this study is that both a preoperative reduction of DFA1 and a short PR interval are associated with an increased risk of POAF. The latter was accompanied by a doubled HRV time-domain parameter pNN50, suggesting concurrently increased PNS activity. Of note, DFA1 and PR interval

Table 3
Significant clinical and heart rate variability parameters for the prediction of postoperative atrial fibrillation by applying univariate and multivariate logistic regression modeling.

Variable	Univariate				Multivariate			
	OR	95% CI	p-Value	AUC (%)[b]	OR	95% CI	p-Value	AUC (%)[b]
Age[a]	1.098	1.042–1.158	<0.001	71.3	1.113	1.048–1.181	<0.001	
PR interval	0.976	0.958–0.995	0.011	61.5	0.973	0.953–0.993	<0.001	80.4
DFA1	0.099	0.024–0.414	0.001	64.4	0.163	0.032–0.838	0.030	

AUC = area under the receiver operating characteristic (ROC) curve; CI = confidence interval; DFA1 = short-term scaling exponent of detrended fluctuation analysis; OR = odds ratio.
[a] Age is modeled as per year older.
[b] AUCs were computed from the ROC analyses following leave-one-out cross-validation principle.

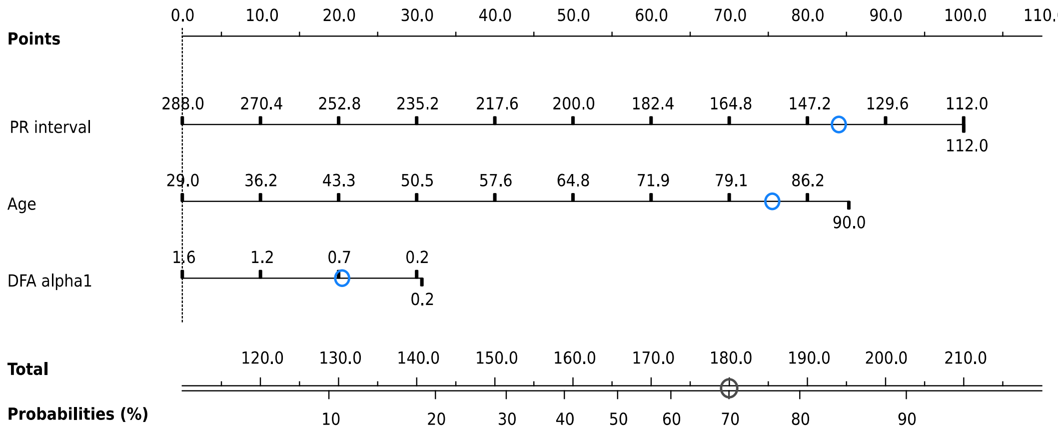

Fig. 1. Nomogram of the final logistic regression model for prediction of postoperative atrial fibrillation with age, PR interval and short-term scaling exponent of detrended fluctuation analysis (DFA alpha1).

remained independent predictors of POAF even after adjusting for age, demonstrating that a disturbed CAR and altered P-wave characteristics play a prominent role in the degeneration of SR to POAF after cardiac surgery. In agreement with previous data, advanced age, arterial hypertension and increased transfusion rates potentiate the likelihood of POAF also in our study. The observed peak POAF incidences on the second postoperative day again correlate closely with data from similar studies [3,5,6].

4.1. PR interval and postoperative atrial fibrillation

Several studies have shown that prolonged, but also short PR intervals carry an increased risk of spontaneous atrial fibrillation in the general population [23–25]. In our study, patients developing POAF presented with short PR intervals preoperatively. This is a new finding, suggesting that similarly to the general population prolonged, but also shortened PR intervals might carry an increased risk of POAF after cardiac surgery. A short PR interval has been described in the presence of concomitant SNS activation due to faster atrial and atrioventricular nodal conduction, as well as an accelerated atrial firing rate [26]. Unlike suspected degenerative alterations of the myocardium and the conduction system causing prolongation of PR interval [23,24], the association of a short PR interval with atrial fibrillation might be attributed to genetics, as both the genetic loci responsible for either shortening or prolonging the PR interval were associated with an increased risk of atrial fibrillation [27,28]. Nevertheless, the observed combination of a shortened PR interval and an altered CAR in our POAF group, most likely mirroring the concurrent activation of both PNS and SNS, is consistent with the suggested concept of competing sympathetic and parasympathetic coactivation preceding the onset of POAF [17]. Interestingly, this observation is consistent with the very recent evidence of increased intrinsic cardiac neural activity in patients developing POAF [12,15], supporting our finding that competing sympathetic and parasympathetic coactivation enhances the likelihood of POAF occurrence after cardiac surgery even under expected antiarrhythmic effects of chronic beta blocker therapy.

4.2. Linear heart rate variability and postoperative atrial fibrillation

Several studies have documented reduced linear HRV in the time and frequency domains with further depression of HRV and an abrupt rise in heart rate, corresponding to excessive adrenergic activation after surgery [29,30]. Enigmatically, studies on postoperative HRV showed an increase in time- and frequency-domain HRV parameters prior to the onset of POAF, consistent not only with expressed adrenergic modulation but also showing pronounced PNS activation [17]. Nevertheless, Hogue et al. suggested that two different patterns of CAR might underlie POAF after CABG, i.e. PNS activation and SNS predominance [16]. Kinoshita et al. further showed that reduced preoperative HRV parameters after isolated CABG, mirroring lesser PNS activation, resulted in a lower incidence of POAF [31]. Although several aspects remain to be clearly elucidated, the present study importantly supports the association between POAF, increased preoperative PNS modulation superimposed on pronounced, excessive SNS and humoral adrenergic modulation [17,30]. As such, it describes another predisposing condition to POAF, including not only reciprocal sympathetic activation and parasympathetic withdrawal as reported in earlier studies but also the competing coactivation of sympathetic and parasympathetic systems, albeit under the expected beneficial effects of long-term beta blockade. Similarly to Bari et al. [14], parameters from the linear HRV domain proved useless for atrial fibrillation risk prediction as opposed to parameters from the non-linear HRV domain. As in the Bari's study [14], the reason may lie in the fact that the comparable observed means of highly dispersed parameters result in weak statistical power, pointing to excessively high inter-subject variability.

4.3. Non-linear heart rate variability and postoperative atrial fibrillation

Recently, two studies provided evidence of an association between non-linear HRV and the occurrence of POAF, showing profound DFA1 reductions before on- or off-pump CABG [32,33]. Similarly to Tarkiainen et al. [32] and Ksela et al. [33], in a previous study from our group, we found reduced fractal correlation properties of the RR interval dynamics [18], though we failed to show significant differences in DFA1 that remained in the normal range in both POAF and SR patients, likely due to the smaller sample size. However, we demonstrated that reduced DFA2 highly correlated with DFA1 [18]. The present study, utilizing data from a two-fold larger cohort, shows more consistently reduced DFA1 in the POAF group, while SR patients retained levels comparable to the normal population. Remarkably, our DFA1 values in the POAF vs. SR group are in line with the reported DFA1 relationships in atrial fibrillation vs. non-atrial fibrillation group in a very recent study associating long-term risk of atrial fibrillation with CAR in coronary artery disease [11].

4.4. Prediction of postoperative atrial fibrillation

Recent studies demonstrated a significant improvement of POAF prediction by adding the ECG and HRV variables to age, race, arterial hypertension, LVEF, and history of previous atrial fibrillation [10,31,32]. Adding the PR interval and the occurrence of atrial premature contractions increased the AUC of the predictive model from 0.71 to 0.78 [10]. Kinoshita et al. showed that POAF risk diminishes with descending levels of preoperative PNS modulation [31]. Tarkiainen et al. demonstrated that a higher DFA1 reduced the risk of POAF independently of age and other clinical risk factors, with the AUC of the predictive model being 0.70 [32]. Reassuringly, in the present study, predictive models are highly consistent with the aforementioned ones [10,31,32] with improved AUC of our model reaching 0.804.

4.5. Study limitations

Several limitations should be acknowledged. First, the observed incidence of POAF could indicate that our patients presented with less extensive structural heart disease and fewer comorbidities, representing patients at low risk of POAF. With regard to beta blockade, we deliberately enrolled patients that were predominantly prescribed metoprolol and bisoprolol to minimize the potential bias deriving from the antiarrhythmic effects of different beta blocking agents [34]. In contrast to Tarkiainen et al. [32], we excluded only diabetic patients with late neurological complications with arguably differential CAR [20], and patients with less severe forms of diabetes mellitus were equally distributed in the POAF and SR groups without affecting the results of our study significantly. Second, advanced ECG analyses could not yield meaningful results in patients with short paroxysms of POAF or (supra)ventricular ectopy exceeding 5% of the recordings. The reported low POAF incidences could potentially reflect a minor portion of patients missed from arrhythmia surveillance after the fifth postoperative day. Nonetheless, we intend to overcome the aforementioned shortcomings by introducing a novel wireless ECG sensor capable of 7-day continuous ECG monitoring, automated POAF detection and advanced HRV analyses, into routine POAF surveillance in our departments [35] (Supplemental Figure).

5. Conclusion

Increased pNN50, reduced DFA1 and shortened PR interval mirror a breakdown in fractal RR interval dynamics, an altered arrhythmic substrate and a CAR suggestive of PNS coactivation rather than withdrawal. The parameters age, DFA1 and PR interval are associated with an increased risk of POAF, with the AUC of the model in the good-to-excellent range. The combination of high-resolution ECG-based RR interval dynamics and P-wave analysis might offer valuable additional information for enhanced risk stratification of POAF, paving a more robust way to targeted prophylactic therapies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.070.

Conflict of interest

The authors report no conflicts of interest.

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