Amplitude Symbolic Analysis Identifies Patients at Risk of Developing Atrial Fibrillation after Cardiac Surgery

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Abstract

Atrial fibrillation (AF) is one of the most common complications after cardiac surgery, characterizing about 20-40% of patients. Autonomic control impairment, usually studied via heart rate variability, has been suggested as one of the possible leading factors. We here suggest the use of symbolic analysis (SA) and amplitude SA (ASA) markers as derived from the heart period (HP) beat-to-beat series to predict the risk of post-surgery AF. HP was derived from 76 patients in sinus rhythm undergoing cardiac surgery, studied before (BASAL) and after (ANESTH) propofol general anesthesia induction. Patients were labeled as AF (n=21) or noAF (n=55) whether they did or did not develop AF episodes after surgery. Markers of traditional symbolic analysis (SA) and ASA were extracted. Results show that ASA markers were able to detect the expected depression of autonomic control during ANESTH and discriminated noAF and AF, with AF showing a reduced cardiac autonomic control in BASAL. SA indexes were less powerful in this regard. Remarkably, ASA markers showed the best association with the AF outcome with respect to traditional time domain and clinical variables, reporting an area under the ROC curve of 0.72, a sensitivity of 0.74 and specificity of 0.67. We suggest the computation of ASA markers in cardiac surgery patients to improve risk stratification for post-surgery AF.

1. Introduction

Subjects undergoing cardiac surgery are at risk of developing several postoperative complications as atrial fibrillation (AF). This adverse event occurs in about 20-40% of subjects and leads to a prolonging of operative stay, increases burden for the health care system and features serious consequences including cognitive decline and ischemic stroke [1], [2]. Although several studies have attempted to understand mechanisms and causes related to the occurrence of postoperative AF, all the reasons are still to be clarified. It is believed that autonomic nervous system (ANS) can play a relevant role in triggering AF. ANS can be studied by means of heart period (HP) variability tools. Previous studies have tried to link HP variability markers to the development of post-surgery AF, with different results [3], [4], [5], [6]. It was suggested that markers of baroreflex sensitivity can be very powerful in predicting postoperative AF episodes, however baroreflex sensitivity analysis requires the recording of arterial pressure and the application of tools for bivariate analysis [3], [6].

Symbolic analysis (SA) approaches are model-free tools exploiting a coarse-graining approach to characterize HP fluctuations and filtering out irrelevant features [7], [8], [9]. In practice, HP variability is decomposed in a sequence of patterns of easy interpretability, directly linked to HP complexity [10], [11]. Recently, amplitude SA (ASA) has been proposed to prevent the limitation of SA that focuses on the probability of finding pattern families without accounting for the information associated with their amplitude [12]. Combining information about classification of patterns with that of the amplitude of variations, the ability of symbolization techniques to discriminate clinical states and pathologies could be enhanced [8], [13].

In this study we hypothesize that ASA markers of HP spontaneous variability can be used to predict post-cardiac surgery AF. To do so, SA and ASA markers were here computed in cardiac surgery patients the day of surgery before the induction of propofol general anesthesia in basal condition (BASAL) and after general anesthesia induction (ANESTH) , checking whether they were associated with the development of post-surgery AF.

2. Experimental Protocol and Data

Analysis

2.1. Experimental Protocol

As part of a larger ongoing study, 76 patients (age: 63±11 yrs, 28 females, 48 males) scheduled for major cardiac surgery with cardiopulmonary bypass were enrolled at the Department of Cardiac Surgery of IRCCS Policlinico San Donato, San Donato Milanese, Milan Italy. The study was approved by San Raffaele Hospital ethical committee (approval number: 06/int/2023; approval date: 15/02/2023; authorization date: 01/03/2023; ClinicalTrials registration: NCT05786274). Patients signed an informed consent prior to participating. Inclusion criteria were cardiac sinus rhythm, age≥18 yrs, first intervention, and no ongoing pregnancy. Electrocardiogram (ECG) from modified lead II was continuously recorded for 5 minutes from the patient's monitor via an analog-to-digital board (National Instruments, USA) connected to a laptop and a custom-made LabVIEW application (National Instruments, USA). Acquisitions took place in BASAL and ANESTH with patients in supine position. Sixty-five patients were acquired in BASAL and 62 in ANESTH. The entire protocol was previously described in [14], [15]. Sampling rate was 400 Hz. Beat-to-beat series of HP were extracted in BASAL and ANESTH and stationary sequences of 256 consecutive HPs were selected within these two experimental sessions. Mean and variance of HP were assessed, labeled as μ_{HP} and σ^2_{HP} and expressed in ms and ms^2 respectively. After surgery, the occurrence of AF was checked until hospital discharge. Among the group acquired in BASAL, 19 out of 65 patients develop post-surgery AF episodes and were labeled as AF, while 47 did not and were labeled as noAF. Analogously, in the group acquired in ANESTH 17 patients were AF and 46 noAF.

2.2. Computation of SA and ASA Markers

According to SA approach [16] the series $HP = \{HP_n, n = 1, \dots, N\}$, where n is the progressive beat counter and N the total length of the series, is coarse-grained into ξ equal-amplitude bins. The original values are then substituted with an integer ranging from 0 to ξ-*1*, hence creating a series of symbols $HP^{\xi} = \{HP_n^{\xi}, n = 1, \dots, N\}$. Exploiting a delayed-embedded procedure, *m*-dimensional patterns $HP_{m,i}^{\xi} = [HP_i^{\xi}\ HP_{i-1}^{\xi} \dots HP_{i-m+1}^{\xi}]$ are created from the series. Like in [16] we set $\xi = 6$ and $m = 3$ and N=256. Each pattern $HP_{m=3,i}^{\xi=6}$ was classified into four classes: i) no variation (0V) if all the symbols were found in the same bin, i.e. were equal; ii) one variation (1V) if two adjacent symbol were equal and the third different; iii) two like variations (2LV) if the symbols featured two variations of the same signs, i.e. formed an ascending or descending pattern; iv) two unlike variations (2UV) if the symbols featured two variations of different signs, i.e. formed a peak or a valley. The rate of occurrence of each class in the time series was computed as the number of patterns within a singles class divided by the total number of patterns, *i.e.* $N–m+1$ multiplied by 100, thus labeling SA markers as 0V%, 1V%, 2LV%, 2UV%.

ASA approach allows to account also for the information about the amplitude of the pattern [12]. We choose the global approach described in [12] that is based on the computation of the fractional contribution of each symbolic class to the total sum of squared deviations of each HP from the global mean μ_{HP}. Defined as σ^2_{HP} the variance of HP global ASA markers are obtained by multiplying σ^2_{HP} by the fractional contribution of each symbolic class to the total sum of squared deviations. ASA markers were labeled as a0V, a1V, a2LV, a2UV and expressed in ms^2.

2.4. Statistical Analysis

All indexes were compared between noAF and AF groups within the same experimental condition (i.e., BASAL and ANESTH) and between experimental conditions within the same group via a two-way analysis of variance (Holm-Sidak test for multiple comparisons). A $p<0.05$ with appropriate post-hoc correction was deemed at significant. The indexes separating AF from noAF with a $p<0.05$ were entered in a logistic regression model whose regression coefficient, odds ratio and 95% confidence interval were computed. The area under the ROC curve (AUC) of the most powerful index was computed and its sensitivity, specificity and negative (NPV) and positive predictive value (PPV) according to the Youden index criterion were assessed.

3. Results

Table 1 describes time domain, SA and ASA makers computed over HP series in noAF and AF patients at BASAL and during ANESTH. μ_{HP} increased in ANESTH with respect to BASAL but the increase was significant only in noAF. Similarly, σ^2_{HP} decreased in ANESTH, only in noAF and, in BASAL, it was lower in AF than in noAF. During ANESTH, 0V% was significantly lower in AF than noAF subjects. 2UV% decreased during ANESTH compared to BASAL in both noAF and AF groups. a0V, a1V, a2LV and a2UV decreased in ANESTH compared to BASAL and these changes were significant only in noAF. During BASAL, a0V, a1V, a2LV and a2UV were lower in AF than in noAF. 1V% and 2LV% did not differ between populations or experimental conditions.

All the indexes were also compared at a univariate level between noAF and AF groups (i.e. separately during BASAL and ANESTH). σ^2_{HP}, a0V, a1V, a2LV and a2UV in BASAL, were significantly lower in AF than noAF and

Table 1. HP variability, SA and ASA markers in noAF and AF during BASAL and ANESTH.

Parameter	BASAL		ANESTH	
	noAF	AF	noAF	AF
μ_{HP}	858±323	834±243	978±342*	940±293
σ^2_{HP}	1645±1650	725±834#	398±643*	348±620
0V%	40±20	37±16	35±19	26±18#
1V%	43±16	44±12	43±15	43±13
2LV%	6±5	7±5	6±6	9±9
2UV%	11±7	12±8	16±8*	21±12*
a0V [ms^2]	593±645	278±321#	184±422*	109±279
a1V [ms^2]	708±708	309±379#	144±196.78*	139±248
a2LV [ms^2]	161±255	68±94#	23±39*	32±43
a2UV [ms^2]	183±237	69±90#	47±66*	68±92

BASAL: before anesthesia induction; ANESTH: after propofol general anesthesia induction; noAF: no atrial fibrillation group; AF: atrial fibrillation group; HP: heart period; μ=mean; σ^2= variance; 0V%: percentage of patterns with no variation; 1V%: percentage of patterns with one variation; 2LV%: percentage of patterns with two like variations; 2UV%: percentage of patterns with two unlike variations; a0V: amplitude of no variation patterns; a1V: amplitude of one variation patterns; a2LV: amplitude of two-like variations patterns; a2UV: amplitude of two-unlike variations patterns. The symbol * indicates $p<0.05$ vs BASAL within the same group, while the symbol # indicates $p<0.05$ vs noAF within the same experimental condition.

were tested via a univariate logistic regression model of association with the outcome together with the markers resulting associated with AF in a previous work on a similar population, namely age and hematocrit [6]. Remarkably, age, sex, hematocrit and other clinical variables as ejection fraction did not significantly differ between the two populations and were not significantly associated with the outcome. During BASAL, a1V was the index featuring the best association with AF (odds ratio of the logistic regression: 0.998; 95% confidence interval: 0.997-1.000; p =0.042). A ROC curve of the association of a1V with AF occurrence was built and shown in Figure 1, reporting an AUC of 0.72. According to Youden index criterion, sensitivity and specificity were, respectively 0.74 and 0.67, PPV was 47.7% and NPV 86.4%.

4. Discussion

The main findings of this work can be summarized as: i) ASA markers allowed the detection of the expected autonomic depression during ANESTH in cardiac surgery patients; ii) ASA indexes assessed in BASAL were able to differentiate noAF and AF patients, while SA indexes were less powerful; iii) among ASA markers the a1V showed the best association with postoperative AF.

All the ASA indexes decreased as expected in ANESTH, thus pointing towards a reduction in the autonomic function. Since the decrease was evident regardless of the type of ASA markers, it can be concluded that both sympathetic and vagal branches of the autonomic control are affected by ANESTH [17], [18]. Remarkably, the decline of the autonomic function during ANESTH was much more evident in the noAF group than in the AF one, likely because the magnitude of HP variations during BASAL in noAF patients was much higher.

A depressed autonomic control was suggested as a trigger of postoperative AF [3]. As a matter of fact, during BASAL σ^2_{HP} was smaller in the AF group than in the noAF one. However, σ^2_{HP} exhibited a limited power when associated with more traditional markers that have been found useful to predict AF. Since SA indexes demonstrated remarkable ability in separating experimental conditions and/or groups [8], we tested their ability in predicting AF in our cohort of patients undergoing cardiac surgery. However, in this study SA markers exhibited limited ability in separating AF from noAF subjects. Conversely, ASA indexes were found to be much more powerful, thus confirming the complementary role of ASA with respect to SA markers [12]. Indeed, ASA markers allowed the

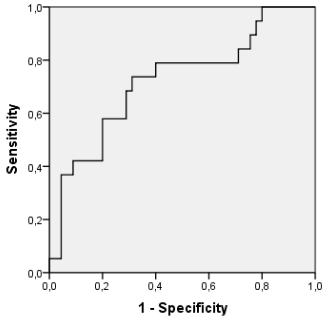

Figure 1. ROC curve of the association of a1V in BASAL with AF. The AUC was 0.72.

differentiation of noAF and AF groups, being generally lower in AF than noAF patients. This result would point to a depressed autonomic control in patients prone to develop post-surgery AF. A preserved autonomic function could thus protect patients from the risk of arrhythmias, while a reduced autonomic control, probably both on sympathetic and vagal branches, would not allow the system to counteract the onset of AF. This finding is in line with previous works suggesting a depressed baroreflex and vagal control in AF patients [3], [5], [6]. Remarkably, one ASA marker such as the a1V was the index with the strongest association with the outcome, resulting more powerful of the other HP variability, SA and clinical markers in predicting the AF onset. If results were confirmed on a larger scale, a short recording of preoperative ECG and the assessment of efficient and time-saving ASA indexes could be suggested in clinical practice to improve arrhythmic risk stratification in cardiac surgery, helping clinicians in tailoring treatments and reducing the costs for the healthcare system.

5. Conclusions

This work originally proposes the use of SA and ASA markers to discriminate patients at risk of developing AF after cardiac surgery. Patients were assessed before and after the induction of propofol general anesthesia. ASA markers indicated that patients who will develop post-surgery AF feature a depressed autonomic control already before the intervention with a specific ASA index remaining associated with the outcome according to a logistic regression model. We suggest that ASA could provide markers useful to predict the onset of AF after cardiac surgery, improving arrhythmic risk stratification.

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