# Stratifying the Risk of Developing Atrial Fibrillation after Coronary Artery Bypass Graft Surgery Using Heart Rate Asymmetry Indexes

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**Abstract**

*Heart period (HP) asymmetry (HPA) is a peculiar pattern detectable over short-term HP variability recordings suggesting that cardiac deceleration runs are shorter than acceleration ones in healthy subjects. We tested the hypothesis that two traditional HPA indexes, namely the Porta's index (PI) and Guzik's index (GI), can distinguish patients scheduled for coronary artery bypass graft (CABG) surgery developing atrial fibrillation (AF) after surgery from the ones who do not (noAF). HP was derived from the electrocardiogram in 130 patients scheduled for CABG before (PRE) and after (POST) the induction of general anesthesia. PI assesses the percentage of positive HP changes, while GI quantifies the percent sum of the squared positive variations. Positive departures from 50 suggest that a series exhibits HPA. Surrogate analysis was exploited to assess the significant presence of HPA patterns. The likelihood of detecting HPA patters was higher in AF subjects and this result held during PRE. GI featured a greater statistical power than PI. Neither HP mean nor variance distinguished the two groups. HPA indexes can be exploited to improve stratification of the risk for post-surgery AF.*

## 1. Introduction

Heart period (HP) asymmetry (HPA) is a particular kind of nonlinear pattern detected over short-term HP variability recordings indicating that heart decelerates faster than it accelerates in healthy subjects (i.e. periods featuring HP augmentation last less than epochs of HP shortening) [1,2]. The HPA analysis was helpful to translate the concept of nonlinear dynamics into a comprehensible notion useful in pathophysiology given that the nonlinear feature was robustly defined, easily recognized even in short HP variability series [2] and the presence of HPA patterns was directly related to the autonomic nervous system (ANS) state [3].

Patients undergoing coronary artery bypass graft (CABG) surgery are likely to develop postoperative atrial fibrillation (AF) and this adverse event occurs in a significant percentage of individuals (i.e. 25%) [4]. AF causes a longer hospitalization duration, and, if prolonged over time, it increases the patient's long-term risk for stroke and heart failure [5]. We hypothesize that HPA analysis could be helpful to better discriminate subjects who develop AF after CABG from the ones who do not (noAF). This hypothesis is supported by the observation that this peculiar type of nonlinearity depends on the ANS state [3] and ANS plays an important role in the AF development [6].

Therefore, the aim of this study is to test the association between HPA indexes and the likelihood of developing AF in CABG patients. This association was checked before (PRE) and after (POST) the induction of general anesthesia [6-8]. Two indexes, widely utilized for the assessment of HPA, were utilized [1,2].

## 2. Experimental protocol and data analysis

### 2.1. Experimental protocol

At the Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, 130 patients (66.4±9.8 years, mean±standard deviation, min-max age range: 43-86 years, 116 males) scheduled for CABG surgery were enrolled. The study adhered to the principles of the declaration of Helsinki for studies involving human subjects and was approved by the local Ethics Committee. All subjects gave their written informed consent. Surface electrocardiogram was acquired ahead of surgery during PRE and POST periods.

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Details about the population, inclusion and exclusion criteria and induction of general anesthesia can be found in [6-8]. The development of AF was checked from the patient's admission in intensive care unit after surgery till the hospital discharge. CABG patients were classified as AF (n=38) or noAF (n=92) depending on whether they developed or did not post-surgery AF.

## 2.2. Beat-to-beat series extraction

HP was assessed as the time distance between two consecutive R-wave peaks derived from the surface electrocardiogram. Parabolic interpolation was applied to minimize the jitters of detection of the R-wave apex. HP series were accurately checked to avoid missing beats and values affected by isolated ectopic beats were corrected by means of cubic spline interpolation between the closest values unaffected by the non-sinus beat. A maximum of 5% of beats with respect of the total length of the series was corrected. Sequences of 256 consecutive values were randomly selected within PRE and POST periods. In presence of evident nonstationarities the random selection was repeated. HP mean and variance were computed as well.

## 2.3. HPA analysis

HPA analysis was performed via two well-established indexes, namely the Posta's index (PI) and Guzik's index (GI). PI was calculated as percentage of positive HP changes with respect to the overall amount of variations [2,3], while GI was computed as the percent sum of the squared positive variations with respect to the overall sum of squared changes. Variations were assessed as difference between the current HP and the previous one. Both PI and GI are bounded between 0 and 100. PI larger than 50 implies that the number of HP augmentations (i.e. cardiac decelerations) is higher than the number of HP reductions (i.e. cardiac accelerations). The reverse situation is observed with PI smaller than 50. GI larger than 50 implies that the average magnitude of squared positive variations indicating the total cardiac deceleration is larger than that of squared negative variations indicating total cardiac accelerations. The reverse situation is observed with GI smaller than 50.

## 2.4. Surrogate data approach

We used a surrogate data approach to check the significance of HPA. Surrogates were built by destroying HPA while preserving static HP distribution and dynamical linear properties of HP series (i.e. the power spectrum). Surrogate series preserving HP power spectrum and histogram were generated via iteratively-refined amplitude-adjusted Fourier transform (IRAAFT) method [9]. In order to achieve the best approximation of power spectrum in presence of an unmodified HP

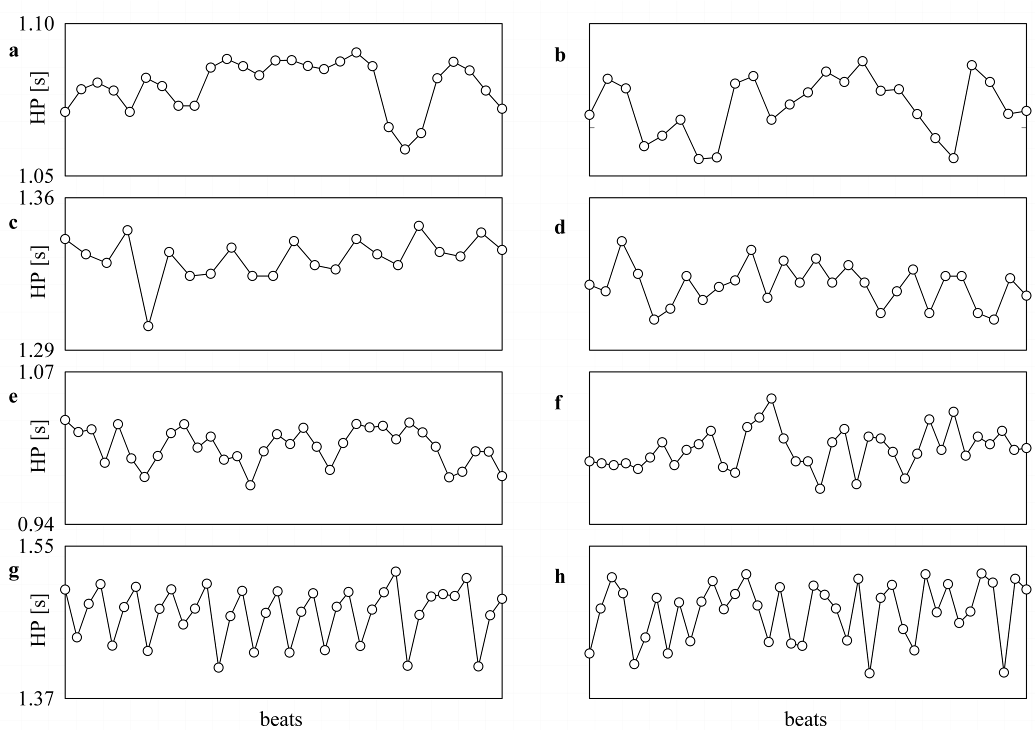


Figure 1. Line plots show the short HP sequences derived from a noAF patient during PRE (a), an AF patient during PRE (c), a noAF patient during POST (e), an AF patient during POST (g). The examples exemplifies the two types of HPA patterns in (c,g). Short sequences of the relevant IRAAFT surrogates are shown in (b,d,f,h) respectively.

distribution, the procedure for generating IRAAFT surrogates was iterated up to 1000 times for each surrogate. When computed over IRAAFT surrogates PI and GI were about 50 given that the HPA was destroyed. For each original series we generated a set of 200 IRAAFT surrogates and we implemented a two-sided nonparametric test. The null hypothesis of linear dynamics was rejected whether PI, or GI, computed over the original data was smaller than the 2.5th percentile or larger than the 97.5th percentile of the distribution of PI or GI calculated over the surrogates. In both these cases a significant presence of HPA patterns was found. No distinction was made about the type of HPA pattern. Otherwise, the original series was consistent with the null hypothesis. The percentage of rejection of the null hypothesis with respect to the total number of subjects was computed in both AF and noAF groups during PRE and POST and taken as an indication of the percentage of nonlinear dynamics (NL%).

## 2.5. Statistical analysis

Two way repeated measures analysis of variance (Holm-Sidak test for multiple comparisons, one factor repetition) was applied to check whether the differences between experimental conditions (i.e. PRE and POST) assigned the post-surgery outcomes (i.e. AF or noAF) and between post-surgery outcomes assigned the experimental conditions in relation to HPA markers (i.e. PI and GI). $\chi^2$ test for unpaired comparisons and McNemar test for paired comparisons was used to check whether the differences between post-surgery outcomes (i.e. AF versus noAF) and between experimental conditions (i.e. PRE versus POST) were significant in relation to NL%. A $p<0.05$ was always considered as significant.

## 3. Results

Figure 1 shows original sequences derived from PRE and POST conditions in Figs.1a,c,e,g and the relevant IRAAFT surrogates in Figs.1b,d,f,h. Sequences are fragments of the full original and surrogate series utilized to computed HPA indexes. Series relevant to a noAF subject are depicted in Figs.1a,b,e,f, while those relevant to an AF individual in Figs.1c,d,g,h. The AF subject has evident asymmetric patterns with shorter raises and longer drops in Fig.1c (PI=57.6 and GI=65.26). The opposite asymmetric pattern was observed in Fig.1g featuring longer raises and shorter drops (PI=35.5 and GI=37.42). GI and PI relevant to the sequences derived from a noAF individual were 47.3 and 50.2 respectively (Fig.1a) and 49.6 and 50.8 respectively (Fig.1e). Surrogate series (Figs.1b,d,f,h) did not exhibit a prevalent type of asymmetric patterns and HPA indexes were about 50.

The results of the HPA analysis in noAF (black bars) and AF (white bars) subjects during PRE and POST conditions are summarized in Fig.2. Grouped error bar graphs report PI (Fig.2a) and GI (Fig.2b) (mean plus standard deviation), while grouped bar graphs summarize findings relevant to NL% when the discriminant statistic in the surrogate test was PI (Fig.2c) and GI (Fig.2d). GI distinguished AF from noAF during PRE (Fig.2b) and this differentiation was evident from the percentage of rejection of the null hypothesis of linear dynamics as well (Fig.2d) indicating that HPA was more likely detected in AF just before the administration of general anesthesia. Moreover, GI detected the effect of anesthesia in noAF individuals (Fig.2b) even though this effect did not lead to an increased likelihood of observing nonlinear dynamics (Fig.2d). PI exhibited trends similar to GI even though with a weaker statistical power (Figs.2a,c).

## 4. Discussion

The main finding of the study is the association between HPA indexes and the risk of developing AF. Remarkably, as already reported in [8] neither HP mean nor variance distinguished AF from noAF groups.

An increased presence of HPA patterns is associated with a greater risk of developing AF after CABG as detected by GI and confirmed by surrogate analysis. Remarkably, this observation was based on the results of HPA analysis during PRE, thus suggesting that HPA indexes can be fruitfully exploited in risk stratification before CABG surgery. The lower level of HPA associated with a smaller probability to develop AF after CABG surgery is in disagreement with the paradigm that a cardiac regulation featuring more important nonlinearities and greater time irreversibility should be more functional, flexible and fault tolerant than a much linear cardiac control [10,11]. Conversely, in this study the loss of

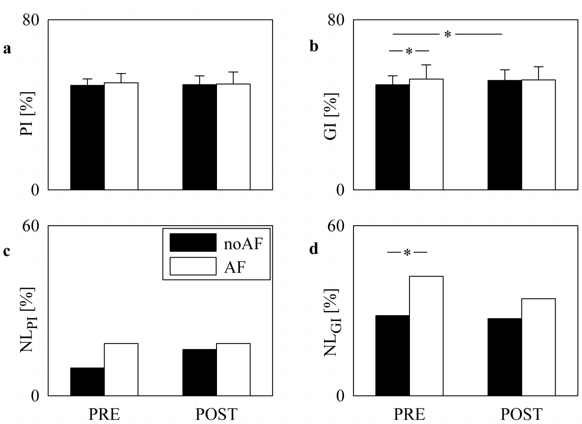


Figure 2. Grouped error bar graphs show PI (a) and GI (b) as a function of the experimental condition (i.e. PRE and POST) in both noAF (black bars) and AF (white bars) subjects. Grouped bar graphs show NL% as detected via the surrogate test over PI (c) and GI (d) indexes.

linearity as detected from HPA analysis might suggest the loss of integration among multiple regulatory mechanisms. The nonlinear intrinsic nature of the physiological mechanisms might appear more evident when the linearizing effect of a higher level integration reflex is lost [12]. We suggest that subjects more at risk of developing AF have an impaired ability to integrate several control mechanisms that makes them less fault tolerant and more susceptible to arrhythmias. This observation is supported by the increased percentage of HPA patterns as detected by GI during POST. Indeed, general anesthesia is a condition reducing the cardiac control ability by depressing autonomic nervous system activity [7]. This depression might limit the ability to integrate several control mechanisms, thus unveiling lower level nonlinear mechanisms. This effect of general anesthesia was more evident in noAF likely because the loss of capability to integrate control mechanisms was already lost by AF group in PRE condition. Analyses carried out over PI confirmed conclusions mainly based on GI even though the statistical power of PI was weaker. It worth noting that HPA is just one of many nonlinear components contributing to the overall complexity of the HP variability signal [3,11] and this particular feature makes difficult the generalization of these findings to the overall class of nonlinear patterns.

## 5. Conclusions

The present study showed that patients with different risk to develop post-surgery AF were characterized by a dissimilar level of HPA, thus suggesting that these peculiar nonlinear components of the HP series might be fruitfully exploited in risk stratification. Given that this differentiation was found before the induction of anesthesia, this analysis could be exploited well before cardiac surgery to identify CABG individuals more susceptible to arrhythmias. This study linked for the first time a precise nonlinear feature detected in short-term HP variability to the concept of risk stratification of post-surgery adverse events. Therefore, we recommend the inclusion of HPA parameters in clinical scores of risk to test their incremental value. Future studies should investigate the origin of HPA patterns and link their presence to specific physiological mechanisms [13].

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