



# Heart rate variability: a new tool to predict complications in adult cardiac surgery

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## Abstract

Heart rate variability (HRV) refers to the variations between consecutive heartbeats, which depend on the continuous modulation of the sympathetic and parasympathetic branches of the autonomic nervous system. HRV has been shown to be effective as a predictor of risk after myocardial infarction and an early warning sign of diabetic neuropathy, and in the cardiology setting is now recognized to be a useful tool for risk-stratification after hospital admission and after discharge. Recent evidences suggest that HRV analysis might predict complications even in patients undergoing cardiac surgery, and the present review summarizes the importance of HRV analysis in adult cardiac surgery and the perspectives for HRV use in current clinical practice. Although future larger studies are warranted before HRV can be included into daily clinical practice in adult cardiac surgery, HRV is a novel tool which might detect autonomic instability in the early postoperative phase and during hospital stay, thus predicting or prompt-diagnosing many of the post-operative complications.

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## 1 Introduction

The term heart rate variability (HRV) generally describes the variations between consecutive heartbeats, which is influenced by the continuous modulation of the sympathetic and parasympathetic branches of the autonomic nervous system. Sympathetic activity tends to increase heart rate and has a slower response compared to parasympathetic activity, which tends to decrease heart rate. The core for HRV analysis is the ECG recording from which the HRV time series can be extracted, and the heart beat period is commonly evaluated as the time difference between the QRS complexes, using commercially available software, to obtain a series of successive RR interval values.

HRV has been shown to be effective as a predictor of risk after myocardial infarction<sup>[1,2]</sup> and early warning sign of diabetic neuropathy,<sup>[3]</sup> and vagal modulation is regarded as

an important mechanism of sudden death.<sup>[4]</sup> Recent evidences suggest that HRV analysis might predict complications even in patients undergoing cardiac surgery and represent an important field of clinical research, and the present review summarizes the importance of HRV analysis in adult cardiac surgery and the perspectives for HRV use in current clinical practice.

## 2 Analysis methods

Based on the ECG recording, the series of consecutive RR intervals is therefore analyzed to produce quantitative outputs, which can be used as variables for clinical research. Briefly, HRV can be investigated using three different methods: time-domains, frequency-domain, and non-linear domains. The detailed mathematical description of each method exceed the scope of this review, and dedicated papers are available,<sup>[5]</sup> but it is important for clinicians and surgeons to understand the meaning of the main HRV parameters. Generally, time-domain measures require longer ECG recording than frequency-domain and non-linear domain measures and therefore is not suitable for real time analysis; on the other hand, artifacts might have detrimental effects in shorter recordings and clear signals are warranted

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for proper frequency-domain and non-linear analysis, which can be performed almost in real time with the most recent software.

### 2.1 Time-domain methods

The time-domain methods are the simplest and most intuitive to perform HRV analysis, since they represent direct mathematical operations to the series of successive RR interval values. These parameters include the mean value of RR intervals, the mean heart rate, their standard deviations (SDNN), and other features depending on the software used. Other measures include the number of successive intervals differing more than a defined time (such as 50 ms, NN50) or geometric measures calculated from the RR interval histogram. The HRV triangular index is the integral of the RR interval histogram divided by the height of the histogram, which depends on the selected bin width (generally 1/128), or derived parameters of these measures.<sup>[6]</sup>

### 2.2 Frequency-domain methods

In the frequency-domain methods, a power spectrum density (PSD) estimate is calculated for the RR interval series. The most important periodic component of HRV is the “respiratory sinus arrhythmia” which ranges from 0.15 Hz to 0.4 Hz and is considered an “high frequency” (HF) oscillation.<sup>[7]</sup> Those HF oscillations are related to the parasympathetic system. “Low frequency” (LF) oscillations are related to the sympathetic and parasympathetic nervous system, usually ranging from 0.04 Hz to 0.15 Hz. The fluctuations below 0.04 Hz are still under investigation, and are commonly divided into “very low frequency” (VLF, 0.003–0.04 Hz) and “ultra-low frequency” (ULF, < 0.003 Hz). The frequency-domain measures extracted from the PSD estimate include absolute and relative power for each frequency band, as well as the LF/HF power ratio and peak frequencies for each band.

### 2.3 Non-linear methods

In recent years, non-linear mechanism of autonomic control of the heart were gradually considered to be involved in the genesis of HRV. The non-linear features of HRV have been investigated using measured such as the Poincaré plot,<sup>[8,9]</sup> approximate and sample entropy analysis,<sup>[10]</sup> detrended fluctuation analysis,<sup>[11,12]</sup> correlation dimension<sup>[13]</sup> and recurrence plots.<sup>[14,15]</sup> Those methods intrinsically have a difficult interpretation of their physiological and pathological effect, but are becoming easily evaluated with the recent software of HRV analysis and are the most promising in the prediction of adverse events.

The Poincaré plot is a graphical representation of the

correlation between successive RR intervals expressed in milliseconds, such as the plot of  $RR^{\text{time}+1}$  as a function of  $RR^{\text{time}}$ , and the shape of the plot is therefore evaluated. The normal representation is an ellipse, oriented per the line of the bisector. The standard deviation of the points perpendicular to the bisector is denoted SD1 and describes the short-term variability (mainly caused by respiratory sinus arrhythmia), while the standard deviation of the points along the bisector is denoted SD2 and describes the long-term variability.

Approximate entropy (ApEn) measured the complexity of the signal, and higher values indicate high irregularity of the signal. Sample entropy (SampEn) and Multiscale entropy (MSE) differ in terms of the mathematical calculations, and were designed to reduce the calculation bias of ApEn.

Detrended fluctuation analysis (DFA) measures the correlation within the signal, and is represented as a double log plot of the index  $F(n)$  as a function of segment length  $n$ . The slope of the regression line relating  $\log[F(n)]$  to  $\log(n)$  is described as a scaling exponent “alfa”. Alfa-1 and alfa-2 are short term and long term fluctuation slopes, respectively.

Correlation dimension (D2) is another method for measuring the complexity of the time series, and is expected to give information on the minimum number of variables needed to model the underlying system. This value is approximated by the slope of a regression curve calculated from a log-log plot, and is generally expressed as a peak point (pPD2).

Recurrence plot analysis uses vectors to represent the RR interval time series as a trajectory in a spatial matrix. Quantitative measures arising from this analysis are recurrence rate, determinism of time series, and Shannon entropy.

### 2.4 From cardiology

Risk stratification of patients who survived an acute myocardial infarction (AMI) is extremely relevant in managing post-AMI care, such as choosing the optimal medical therapy or indicating the implantation of a cardioverter-defibrillator device. Currently, left ventricular function measured as the left ventricular ejection fraction (EF) is the most commonly used method.<sup>[16,17]</sup> However, after AMI and revascularization many patients have a preserved EF, thus impairing the ability to stratify accurately patients based exclusively on EF. Wolf, *et al.*<sup>[18]</sup> in the late ‘70s were the first to describe the association of simple parameters of HRV and increased post-infarction mortality. One-minute ECG analysis after admission and diagnosis of AMI revealed that patients with greater sinus arrhythmia had lower mortality rate compared to patients with less pronounced variability of sinus impulses. In 1987, Kleiger, *et al.*<sup>[19]</sup>

proved that patients with a history of myocardial infarction and a higher risk of sudden cardiac death could be identified by the use of HRV. Patients with SDNN < 50 ms had 5-fold greater relative risk of death compared to patients with longer SDNN. Kurths, *et al.*<sup>[20]</sup> more than 20 years ago decided to take into account the HRV in the post-infarction risk stratification, detecting abnormalities among patients originally classified in the low risk group by traditional methods. Those studies were confirmed over the years and the scientific community started to consider the reduced HRV as a strong marker of arrhythmogenic death.<sup>[21–23]</sup> The decreased HRV was recognized to be a marker of cardiac autonomic nervous system dysfunction associated with high risk for severe ventricular arrhythmias and mortality in the post-AMI population. Noncontractile and necrotic left ventricular wall are known to enhance sympathetic activity, which is documented as HRV reduction. Increased adrenergic activity increases the myocardial vulnerability and electrical instability, mainly considered as the risk of malignant arrhythmias.

Changes in HRV have been investigated among patients with chronic heart failure, which is characterized by sympathetic hyperactivation, and recent studies found associations between HRV parameters and the severity of disease.<sup>[24–28]</sup> A low LF/HF ratio is a predictor of adverse events and reduction of LF component is associated to right ventricular dysfunction.<sup>[29]</sup>

Over the years treatment strategies improved, while conventional methods to analyze HRV, such as time domains, were found to have an insufficient accuracy for predicting outcomes.<sup>[30,31]</sup> In parallel, frequency domain and non-linear methods to evaluate HRV improved, and risk stratification with the most recent HRV measures is a challenging opportunity, as shown in the DIAMOND-MI, CARISMA, RE-FINE and DYNAMIT studies.<sup>[32]</sup> HRV is now considered a strong prognostic tool in the cardiology scenario and many studies are evaluating the HRV as primary outcome.

## 2.5 To cardiac surgery

In cardiac surgery, preoperative, intraoperative and postoperative management modify the autonomic nervous system, and it is known that many drugs might induce alterations in HRV, such as propofol.<sup>[33]</sup> After the induction of the anesthesia, the reduced sympathetic nervous activity results in a decrease of peripheral vascular resistance through an increase of vascular compliance.<sup>[34]</sup> Also, HRV spectral powers decrease after the anesthetic induction.<sup>[35]</sup> Sternotomy increases the adrenergic catecholamine release and increase mean heart rate<sup>[36]</sup> and this results in an increase of the LF and VLF power.<sup>[35]</sup> Cardiopulmonary by-

pass and cardioplegic arrest during the central phase of cardiac procedure minimize the influence of HRV. However, the restoration of cardiac activity is generally associated with an unstable heart rhythm; depending on the cardioplegia technique and a plethora of other confounding factors, DC shock might be required to restore an adequate rhythm.

Thereafter, HRV might assume an important role as a potential detector of autonomic system instability in the early postoperative phase in intensive care unit and during hospital stay. As many of the postoperative complications after cardiac surgery are related or associated to autonomic instability, HRV analysis might help physicians in preventing those complications and improve the standards of care in primary and secondary hospitals. HRV has been investigated in cardiac surgery only in recent years, and therefore there are no specific recommendations about its clinical use and implications. However, future researches will help in clarifying HRV role in the postoperative management of patients who underwent cardiac surgery.

## 2.6 Coronary artery surgery

Coronary artery bypass graft (CABG) surgery leads to significant HRV reduction, which is even more pronounced that after myocardial infarction. Unlike myocardial infarction where myocyte necrosis occurs, the probable reasons for HRV fluctuations after CABG might be related to a combined effect of surgical manipulation on the heart, prolonged anesthesia, and cardioplegia. The effect of extracorporeal circulation “in se” can be considered trivial. Off-pump CABG is followed by extensive adrenergic activation that is similar to on-pump CABG with similar HRV time domains and frequency domains, both in the early postoperative phase and a few months after surgery.<sup>[37,38]</sup>

The prognostic importance of HRV after CABG is an actual topic and extremely debated. There are reports from the cardiac arrhythmia suppression trial (CAST) indicating that the reduced HRV after CABG is not relevant in predicting mortality, unlike the strong prognostic potential of HRV in case of post-AMI patients. This finding might be explained by the greater benefit related to the revascularization of the ischemic myocardium compared to the post-ischemic autonomic dysfunction.<sup>[39,40]</sup> On the other hand, other groups reported that postoperative HRV decrease influenced mortality rate in patients after CABG. During the follow up, the majority of adverse coronary events occurred in patients with decreased postoperative HRV.<sup>[41]</sup> Patients were divided in two groups depending on the SDNN (93 ms as cutoff) and impaired postoperative HRV clearly affected mortality rate. The measurement of non-linear HRV parameters after CABG identified patients at higher risk of

complicated post-operative course. Alfa-1 parameter of DFA was the most significant independent predictor of long intensive care unit stay,<sup>[44]</sup> and preoperative non-linear behavior was able to predict morbidity and mortality in a small study.<sup>[45]</sup> Those non-linear analyses are extremely promising and might be included in clinical research scenarios in the next years.

HRV values decrease soon after CABG and returned to the preoperative level within two months; however, even 6 months after surgery, HRV did not exceed the preoperative level.<sup>[42]</sup> However, reduced HRV persisting for months after CABG should be carefully considered especially if accompanied by a reduced ejection fraction, both indicating greater arrhythmogenic risk,<sup>[43]</sup> and eventually requiring anti-arrhythmic treatment. In any case, patients with decreased HRV months after CABG require careful monitoring for potential complications.

## 2.7 Valvular heart surgery

HRV reduction after cardiac surgery has also been recorded among patients undergoing valve surgery.<sup>[46]</sup> Several months after cardiac surgery, almost half of the patients with an implanted artificial aortic or mitral valve have decreased HRV. Patients with an implanted artificial mitral valve had a shorter RR interval and lower values of total power compared to patients with an implanted artificial aortic valve. However, postoperative decreased HRV in those patients have no importance in long-term prediction of mortality rate.

Recent percutaneous procedure (TAVI) were also investigated in terms of HRV variations,<sup>[47]</sup> comparing surgical to trans-femoral or trans-apical valve replacement. All HRV parameters were significantly depressed in surgical patients, while they were almost completely preserved in case of trans-femoral access; trans-apical cases showed an intermediate behaviour. Authors concluded that surgical aortic valve replacement leads to profound depression of some cardiac autonomic parameters, while less invasive procedures allow better preservation of HRV. In particular, trans-femoral TAVI does not induce any significant deterioration of HRV parameters and seems to be the strategy with less impact on the cardiovascular autonomic system. Considering the early and late requirement for permanent pacemaker implantation after TAVI, HRV analysis might help in stratifying patients and identifying those at higher risk for significant arrhythmic events.

## 2.8 Atrial fibrillation

Atrial fibrillation (AF) is the most common complication after cardiac surgery, with an incidence ranging from 15%

to 50% of cases after CABG or valvular surgery.<sup>[48]</sup> Pre-existing electrophysiological features of the conduction system, ischemia-reperfusion injury, impairment of sino-atrial node function, atrial stretch, postoperative metabolic changes, pericardial effusion and inflammation are all contributing factors to early postoperative AF, usually manifesting in the 2<sup>nd</sup> or 3<sup>rd</sup> postoperative day. Autonomic oscillations have been shown to precede and follow the development of postoperative AF.<sup>[49,50]</sup> In the period before the onset of postoperative AF, there are significant increases in time-domain and frequency-domain of HRV, consistent with parasympathetic resurgence competing with increasing sympathetic activity as the triggering mechanism for postoperative AF. The importance of autonomic modulation is also suggested by the fact that postoperative AF is uncommon in heart transplant recipients, since the complete cardiac autonomic denervation plays a protective role.<sup>[51,52]</sup> Chamchad, *et al.*<sup>[53]</sup> using non-linear analysis showed that elevated pPD2 values were associated to increased risk of postoperative AF after elective CABG. However, the limitation of those small observational studies lies in the fact that many confounding factors are not adequately evaluated and the generalization of results is not possible. Future researches, using non-linear analysis in large cohort of patients, might confirm those findings.

## 2.9 Bridging the gap: from research to clinical practice

The comprehension of the behavior of biological signals is a pivotal step toward a tailored patient's care. The main advantage of HRV signals lies in the fact that all parameters can be collected using non-invasive tools, and calculated almost in real time with newer software. Although HRV indexes are appealing, future research might help in bridging the gap towards a widespread clinical use.

Nonlinear parameters are not standardized in terms of data acquisition methodology, such as the minimum number of RR intervals required to have a reliable measure. Also, as HRV represents the final outcome of the autonomic system, it can be affected by comorbidities such as diabetes or advanced age. Sensitivity, specificity and predictive values of HRV values are dependent on the chosen cutoff, which vary between the studies. The characteristics of each study population, such as age, diabetes, preoperative risk factors, depression,<sup>[54]</sup> heart failure, recent or previous AMI, or medications, greatly influence HRV measures. Therefore, at present there is no universal definition or algorithm to determine the ideal cutoff for each HRV measure. The analysis of non-linear domains has been introduced in clinical research in the last years and appears very promising, but the "cut-off limitation" is still present and will be overcome by

larger studies.

HRV methods can capture many aspects of autonomic heart rate modulation, but individual HRV indexes might have limited predictive capacity as they do not reflect the global effects of the autonomic nervous system dysfunction among patients who underwent cardiac surgery. The integrated features of HRV might predict better the outcomes than the individual measures of HRV, and based on this consideration Song, *et al.*<sup>[55]</sup> developed a support vector machine algorithm to predict cardiac death. A 5-dimension HRV feature vector was obtained by the combination of five time-domain measures of HRV and was shown to be the best classifier for predicting cardiac death after AMI, compared to left ventricular ejection fraction (LVEF), SDNN, deceleration capacity and more complex indexes. This result was confirmed by another study which showed that combined surrogate markers of HRV were correlated with the risk of aortic valve replacement surgery.<sup>[56]</sup> This “integrated strategy” in HRV analysis might provide clinically reliable variables through a combination of single HRV features or with the implementation of known relevant parameters, such as ejection fraction.

HRV has been recently introduced in preclinical studies involving chronic heart failure and mesenchymal stem cells (MSC). Endovenous MSC treatment one week after ligation of the left coronary artery resulted in a late increase of HRV parameters which paralleled the decrease of myocardial infarction size and myocardial interstitial fibrosis.<sup>[57]</sup> Therefore, HRV might be used in the near future as a surrogate parameter to evaluate the effect of stem cell treatment in regenerative medicine.

### 3 Conclusions

Although future larger studies are warranted before HRV can be included into daily clinical practice in adult cardiac surgery, HRV is a novel tool which might detect autonomic instability in the early postoperative phase and during hospital stay, thus allowing to predict or prompt-diagnose postoperative complications. HRV analysis methods are relatively easy-to-use and economic, and this wide availability will help in providing additional evidences to tailor patient’s care.

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