RR Interval Dynamics Before Atrial Fibrillation in Patients After Coronary Artery Bypass Graft Surgery

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Background—Atrial fibrillation/flutter (AF) is a frequent complication of coronary artery bypass graft surgery (CABG) that leads to increased costs and morbidity. We hypothesized that heart rate variability (HRV), an indicator of cardiac sympathovagal balance, is altered before the onset of postoperative AF. Because nonlinear methods of HRV analysis provide information about heart rate dynamics not evident from usual HRV measures, we also hypothesized that approximate entropy (ApEn), a nonlinear measure of HRV, might have predictive value.

Methods and Results—Analysis of HRV was performed in 3 sequential 20-minute intervals preceding the onset of postoperative AF (24 episodes in 18 patients). These data were compared with corresponding intervals in 18 sex- and age-matched postoperative control subjects who did not develop AF. Patients had left ventricular ejection fractions >45% before surgery and were not receiving β-blockers during ambulatory ECG monitoring after surgery. Logistic regression demonstrated that on the basis of averaged values for the three 20-minute intervals, increased heart rate and decreased ApEn were independently associated with AF. Heart rate dynamics before AF was associated with either lower (n=19) or higher (n=5) RR interval variation by traditional measures of HRV or quantitative Poincaré analysis, suggesting the possibility of divergent autonomic conditions before AF onset.

Conclusions—In the hour before AF after CABG surgery, higher heart rate and lower heart rate complexity compared with values in control patients were independent predictors of AF. Decreased ApEn occurs in patients with either increased or decreased HRV by traditional measures and may provide a useful tool for risk stratification or investigation of mechanisms. (Circulation. 1998;98:429-434.)

Key Words: tachyarrhythmias • bypass • heart rate

Atrial fibrillation and flutter occur in 27% to 40% of patients after CABG, resulting in increased stroke risk and resource utilization.1-6 The strong association of postoperative AF with advancing age and the increasing proportion of cardiac surgical patients who are elderly suggest that the frequency of postoperative AF and associated complications is likely to increase.3,4,7 Electrophysiological mapping studies in patients indicate that the mechanism for AF is reentry, but the pathophysiology of AF after CABG surgery is not entirely clear and does not provide an explanation for why some individuals develop this arrhythmia while others exposed to similar surgery remain in sinus rhythm.3-10

Autonomic nervous system perturbations may enhance vulnerability to atrial arrhythmias.5,11-14 Analysis of HRV has been used to probe autonomic mechanisms of ventricular tachycardia and fibrillation and to identify patients at risk for ventricular arrhythmias.15-20 Preliminary investigations in primarily nonsurgical populations have suggested that risk for AF may be identified with measurement of HRV, but whether the onset of postoperative AF is preceded by autonomic dysfunction is not clear.13,14,21-23 Moreover, initial evaluations of HRV and AF risk have been limited to the usual time or frequency domain measures of HRV.13,14,21-23 Nonlinear methods of HRV analysis provide information about the dynamics of heart rate not evident with traditional methods of HRV measurement.18,20,24-26 Information about the dynamics of RR interval oscillations before AF could be useful in the understanding of its pathophysiology after CABG and in risk stratification of patients.

This study tested the hypothesis that heart rate dynamics are altered before the onset of AF in patients after CABG, and that ApEn, a nonlinear measure of HRV, might have predictive value in identifying patients at risk.

Methods

The study population consisted of 36 patients undergoing CABG surgery at Barnes-Jewish Hospital, St Louis, Mo, in whom ambulatory ECG monitoring was part of ongoing protocols.27 All procedures used in this study were approved by the Washington University School of Medicine Human Studies Committee, and individual informed consent was obtained. Patients were monitored with Marquette 8500 Holter recorders (leads CC5 and II, Marquette Electronics) for 2 to 3 days after surgery. In addition, all patients

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Selected Abbreviations and Acronyms

AF = atrial fibrillation/flutter
ApEn = approximate entropy
HRV = heart rate variability
pNN50 = percentage of successive RR intervals that deviated by >50% from the prior RR interval
rMSSD = root mean square of successive RR interval differences
SD1RR = average deviation of the plot data away from the long axis
SD2RR = average deviation of the plot data away from the axis perpendicular to the long axis
SDNN = SD of the mean RR interval

were continuously monitored after surgery with bedside ECG and telemetry. To eliminate confounding effects on HRV, patients were excluded for digoxin use, congestive heart failure, diabetes mellitus, renal failure requiring hemodialysis, preoperative AF, presence of a permanent cardiac pacemaker, or left ventricular ejection fraction <45% determined at the time of cardiac catheterization. All patients received routine postoperative care. Only patients who did not receive β-adrenergic receptor blocking drugs during the period of postoperative Holter monitoring were included in the study. No patient was withdrawn from β-blockers for the purpose of the study. The patients developing AF were matched on the basis of sex and similarity in age with patients remaining in sinus rhythm after surgery (control subjects).

Perioperative Management

All medications, including nitroglycerin, β-adrenergic receptor, and calcium channel blocking drugs, were continued until surgery. Patients received an opioid-based anesthetic supplemented with an intravenous anesthetic. Calcium channel blocking drugs, were continued until surgery. Patients received an opioid-based anesthetic supplemented with an intravenous anesthetic. Digoxin was used; ie, variables with the largest nonsignificant P values were eliminated until all values in the model were significant. Receiver operating characteristic curves were constructed to evaluate the predictive accuracy of the multivariate model. All values are expressed as mean±SE. A significant difference was considered to exist for P<0.05.

HRV Analysis

Holter tapes were analyzed with a Marquette SXP computerized scanner with version 5.8 software and standard QRS labeling techniques. Data files were transferred to a Sun workstation for secondary editing of QRS labeling and analysis of HRV. Heart rates were determined by use of all RR intervals. Time domain measures included the mean, standard deviation of the mean RR interval and its SD (SDNN), the percentage of successive RR intervals that deviated by >50% from the prior RR interval (pNN50), and the root mean square of successive RR interval differences (rMSSD). Frequency domain HRV analysis was performed by use of methods previously described.16,28 Fast Fourier power over a frequency range from 8.359×10−4 to 0.50 Hz. Power (ms²) in each component of the frequency spectrum was calculated by integration of the following bands: (1) total power (≤0.50 Hz); (2) very–low-frequency power (0.0033 to 0.04 Hz); (3) low-frequency power (0.04 to 0.15 Hz), reflecting modulation from the sympathetic and parasympathetic nervous systems; and (4) high-frequency power (0.15 to 0.40 Hz), reflecting modulation by the parasympathetic nervous system.29 The analysis was performed for the specified time period before the onset of AF but while the patient was still in sinus rhythm (ie, HRV analysis excluded all portions of the AF episode). Poincaré plots were constructed by plotting each RR interval from normal sinus beats against the previous RR interval. The methods used are similar to those previously described in which the y axis of the plot represented RRn+1; the x axis, RRn.20 A line of unity was then constructed from the origin with a slope=1. The center point of each Poincaré plot represents the average RR interval for that data segment. Quantitative analysis of the Poincaré plots was performed by first fitting an ellipse to the plot centered at the center point. The average deviation of the plot data away from the long axis (axis 1), termed SD1RR, reflects short-term beat-to-beat variability, and the average deviation of the plot data away from the axis perpendicular to the long axis (axis 2), termed SD2RR, reflects long-term variability over the epoch being analyzed.20 The ratio of SD1RR to SD2RR was determined.

ApEn was calculated by use of methods previously described.24–26 ApEn is a nonlinear measure of variability, expressing the logarithmic likelihood that data points that are of a certain deviation (r) over a defined number of observations (m) remain the same distance between incremental comparisons. More regularity is associated with small values of ApEn and greater irregularity with large values of ApEn. Approximate entropy was calculated for >1000 points sampled at 2 Hz from a detrended time series of RR intervals using values of m=2 and r=20% of the SD of the time series.

Data Analysis

The time of AF onset was identified by visual inspection of the ECG. HRV analysis was performed on 20-minute segments of data beginning 60 minutes before AF onset. Each of these segments of HRV data was compared with HRV from the same time and postoperative day from control patients. Spectral analysis of HRV required >80% of normal RR intervals in the data set. Between-group comparisons of HRV and other continuous data were performed by use of ANOVA with Bonferroni post hoc test and Wilcoxon rank sum test. Categorical data were compared between groups with Fisher’s exact test. Regression analysis was performed to assess for relationships between time and frequency domain and nonlinear HRV measurements. Stepwise multivariate logistic regression analysis was performed by use of the average of three 20-minute values of all HRV measures from the 60 minutes before AF onset, SD1RR, SD2RR, SD1RR/SD2RR, ApEn, heart rate, and number of atrial ectopic beats. Because of their importance in identifying risk for postoperative AF in other reports, the duration of aortic cross clamping during surgery and preoperative use of β-adrenergic receptor blocking drugs were included in the multivariate analysis, along with the number of coronary bypass grafts performed, duration of cardiopulmonary bypass, preoperative hypertension, lung disease, and medication use.1–4 A backward, stepwise elimination process was used; ie, variables with the largest nonsignificant P values were eliminated until all values in the model were significant. Receiver operating characteristic curves were constructed to evaluate the predictive accuracy of the multivariate model. All values are expressed as mean±SE. A significant difference was considered to exist for P<0.05.

Results

There were 24 episodes of AF occurring in 18 patients on the 1st (n=9), 2nd (n=11), and 3rd (n=4) postoperative days. Patient demographic and other characteristics are shown in Table 1. Patients remaining in sinus rhythm postoperatively were more likely to have been receiving β-blockers before surgery, but there were no other demographic differences between patients with or without postoperative AF. All patients were weaned from ventilatory support. There were 24 episodes of AF occurring in 18 patients on the 1st (n=9), 2nd (n=11), and 3rd (n=4) postoperative days. Patient demographic and other characteristics are shown in Table 1. Patients remaining in sinus rhythm postoperatively were more likely to have been receiving β-blockers before surgery, but there were no other demographic differences between patients with or without postoperative AF. All patients were weaned from mechanical ventilation and had their tracheas extubated by the evening of surgery or early the next morning. There were no perioperative myocardial infarctions (new ECG Q wave or increases in MB isoenzymes of creatine kinase >50 IU), but there was 1 death on the evening of postoperative day 2 (after ambulatory ECG monitoring was completed) in a patient with AF who developed an acute neurological event after initial, uncomplicated recovery from surgery. No patient received inotropic drugs during the periods of ECG analysis.
TABLE 1. Clinical Characteristics of Patients with AF and Those Remaining in Sinus Rhythm After Surgery (Control Patients)

<table>
<thead>
<tr>
<th></th>
<th>Control Patients (n=18)</th>
<th>AF (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SE), y</td>
<td>67±2</td>
<td>69±2</td>
<td>0.50</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>12/6</td>
<td>12/6</td>
<td>1.00</td>
</tr>
<tr>
<td>History of MI (&gt;6 months before surgery), n</td>
<td>4</td>
<td>6</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>12</td>
<td>7</td>
<td>0.19</td>
</tr>
<tr>
<td>Mild COPD, n</td>
<td>1</td>
<td>2</td>
<td>0.72</td>
</tr>
<tr>
<td>Current tobacco use, n</td>
<td>3</td>
<td>2</td>
<td>0.43</td>
</tr>
<tr>
<td>Preoperative medication, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
<td>15</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>Ca²⁺ channel blockers</td>
<td>10</td>
<td>8</td>
<td>0.34</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1</td>
<td>4</td>
<td>0.36</td>
</tr>
<tr>
<td>Aspirin</td>
<td>13</td>
<td>14</td>
<td>0.57</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>11</td>
<td>12</td>
<td>0.60</td>
</tr>
<tr>
<td>Heparin</td>
<td>7</td>
<td>8</td>
<td>0.64</td>
</tr>
<tr>
<td>Bypass grafts (mean±SE), n</td>
<td>3.8±0.1</td>
<td>4.2±0.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min (mean±SE)</td>
<td>147±8</td>
<td>140±6</td>
<td>0.48</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min (mean±SE)</td>
<td>84±6</td>
<td>72±5</td>
<td>0.14</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; COPD, chronic obstructive pulmonary disease.

Heart Rate Dynamics

Sixty-minute averaged results for patients with and without AF from the hour before arrhythmia onset are shown in Table 2. Of the 72 total 20-minute analysis periods before AF, spectral HRV data were unavailable before 22 episodes of AF owing to the predefined criteria requiring <20% ectopic beats for inclusion. Because of the number of episodes with missing spectral data and because frequency domain analysis provided no additional information about AF risk, only the time domain HRV, Poincaré analysis, and ApEn results are listed in Table 2. The results indicate that traditional HRV measures did not distinguish between patients developing AF and control patients. Moreover, examination of the pattern of HRV during each 20-minute period approaching AF did not reveal differences in heart rate dynamics between periods, suggesting the absence of acute modulation of these measures immediately before the onset of the arrhythmia.

The association between the variables listed in Table 2 and susceptibility to AF was calculated by use of multivariate logistic regression analysis. On the basis of this analysis, which included preoperative β-adrenergic receptor blocker use and aortic cross-clamp time, only ApEn (OR 0.02; 95% CI, 0.001 to 0.450; P=0.013) and heart rate (OR 1.11; 95% CI, 1.030 to 1.202; P=0.007) were independently associated with susceptibility to postoperative AF (area under receiver operating characteristic curve, 0.80).

There was no significant correlation between ApEn and time or frequency domain HRV measures or between ApEn and SD1RR, SD2RR, and SD1RR/SD2RR in the hour before AF onset. Weak relationships were observed between ApEn and the number of atrial ectopic beats (r²=0.08, P=0.03) and average heart rate (r²=0.09, P=0.02).

Further examination of the Poincaré analysis results in patients with AF revealed in some patients a pattern of high RR interval variation consistent with sinus alternans (the Figure), although this rhythm was not present immediately before AF onset. HRV associated with episodes of AF thus appeared to fit into 2 distinct patterns, either low or high RR interval variations. To further explore the dynamics of heart rate in patients susceptible to AF, HRV for the hour before AF was categorized as being associated with high (n=5) RR interval variations if SD1RR was >20 ms and/or SD2RR >40 ms. The remaining patients with AF (n=19) were categorized as having low RR interval variations. ApEn, Poincaré analysis, and time domain HRV results for the hour before arrhythmia onset for patients with AF, separated for the low and high RR interval variation groups, are compared in Table 3. Although these data suggest that divergent autonomic conditions existed before AF, the ranges for many of the HRV variables for AF and control patients overlapped. This suggested that the categorization as either “low” are “high” does not distinguish AF susceptibility.

Discussion

These results show that patients who developed AF after CABG have reduced heart rate complexity, higher heart rates, and more frequent atrial ectopy before the onset of the arrhythmia than those who did not develop the arrhythmia. Standard measures of HRV did not distinguish between these 2 groups. Logistic regression analysis indicated that only lower ApEn and higher heart rate were independently associated with AF.

Higher heart rates are associated with increased activity of the sympathetic and/or decreased activity of the parasympathetic nervous system. Thus, our findings of higher heart rates in patients developing AF support the hypothesis of a relationship between AF after CABG and excessive adrenergic activation. The association between increased atrial
ectopy and postoperative AF has previously been observed, but in this study, the number of atrial premature beats was not independently associated with AF susceptibility. It must be noted that some patients developing AF had little prior atrial ectopy and some patients remaining in sinus rhythm had very frequent atrial premature beats, suggesting that the presence of atrial ectopy itself, in at least some patients, may not be causally related to the substrate for AF.

Nonlinear methods of HRV analysis have been shown to provide information about the dynamics of heart rate and ventricular arrhythmia risk not evident with conventional methods of HRV analysis. Reduced complexity of heart rate dynamics has been shown to occur with normal aging, congestive heart failure, and postoperative left ventricular dysfunction after noncardiac surgery. On the basis of these findings, one might suppose that reduced ApEn would be associated with impaired cardiac function, but others have also shown ApEn to be higher in patients with prior myocardial infarction. The physiological determinants of ApEn have not been well defined. In this study, ApEn did not correlate with other HRV variables, so our data provide little evidence for a direct relationship between the magnitude of ApEn and the level of autonomic modulation of heart rate. This implies that ApEn provides unique information about heart rate dynamics not available from other standard HRV measures and that this information may be potentially useful for stratification of arrhythmic risk.

In this study, we noted that AF could be preceded by either depressed or elevated normal-to-normal RR interval variability. In the latter patients, sinus alternans (the Figure) was observed, an ECG rhythm also described in patients before spontaneous ventricular arrhythmias. It has been suggested

TABLE 3. HRV, Including Poincaré Analysis and ApEn Results for Average of 3 20-Minute Periods in the Hour Before AF for Patients With Low or High RR Interval Variations

<table>
<thead>
<tr>
<th></th>
<th>AF Low RR Group (n=19)</th>
<th>AF High RR Group (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>102±3</td>
<td>92±5</td>
</tr>
<tr>
<td>Mean NN</td>
<td>604±17</td>
<td>674±38</td>
</tr>
<tr>
<td>SDNN</td>
<td>15±1</td>
<td>37±5*</td>
</tr>
<tr>
<td>pNN50</td>
<td>0.5±0.2</td>
<td>10.7±6.2*</td>
</tr>
<tr>
<td>rMSSD</td>
<td>13±1</td>
<td>38±18*</td>
</tr>
<tr>
<td>SD1RR</td>
<td>8.9±0.4</td>
<td>26.8±7.2*</td>
</tr>
<tr>
<td>SD2RR</td>
<td>18.5±0.9</td>
<td>42.0±7.2*</td>
</tr>
<tr>
<td>SD1RR/SD2RR</td>
<td>0.53±0.03</td>
<td>0.72±0.21</td>
</tr>
<tr>
<td>ApEn</td>
<td>0.97±0.06</td>
<td>0.78±0.07</td>
</tr>
<tr>
<td>APBs</td>
<td>60±29</td>
<td>117±43</td>
</tr>
</tbody>
</table>

APB indicates atrial premature beats. Values are mean±SE.

*P<0.05 vs AF low RR group.
that fluctuations in cardiac cycle length and ventricular repolarization phenomenon increase susceptibility to ventricular arrhythmias by altering myocardial conduction and repolarization, as has been shown experimentally.\textsuperscript{20,23,30} Perhaps markedly varying RR intervals also result in alterations in atrial repolarization, contributing to the electrophysiological substrate of AF after CABG in some patients. Beat-to-beat sinus alternans, however, was not directly related to the onset of the arrhythmia and thus may result from a common neuroelectrophysiological precursor of AF. The possibility that marked fluctuations of RR intervals could lead to electrophysiological remodeling, as has been described after even brief periods of AF, is intriguing.\textsuperscript{37} If so, the resultant altered atrial refractoriness might progress to the point where enough myocardial tissue is affected to support AF.

Our findings that patients developing AF had patterns of either higher or lower normal-to-normal RR interval variations may indicate that the arrhythmia is an end point associated with divergent autonomic substrates. It can be argued that in the low RR interval variability group, reduced HRV, which has been associated with risk of life-threatening ventricular arrhythmias and with atrial arrhythmias in nonsurgical patients, represents high cardiac sympathetic and/or reduced vagal tone.\textsuperscript{15–22} Thus, HRV indexes in the low RR variability group are consistent with sustained sympathetic activation and/or reduced vagal tone or reduced responsiveness of the heart to autonomic efferent stimulation.

Unlike in the ventricle, in which sympathetic activation is believed to promote and vagal stimulation to protect against the development of arrhythmias, both sympathetic and parasympathetic activation may alter atrial refractoriness and promote AF.\textsuperscript{1,13–14,38} Vagal modulation manifests as rapid oscillation in heart rate, especially as quantified by pNN50 and rMSSD.\textsuperscript{29} Thus, the high RR interval variations observed in the high RR interval variability group are consistent with heightened vagal tone, perhaps reflex in origin, as a result of sustained perioperative sympathetic activation and/or reduced vagal tone or reduced responsiveness of the heart to autonomic efferent stimulation.

In this study, HRV results from patients with AF and the control group overlapped, suggesting that the low and high RR interval variations and associated autonomic conditions are not unique to patients susceptible to AF. The development of AF requires an electrophysiological substrate to sustain the arrhythmia.\textsuperscript{8,13–30} It is reasonable to speculate that in the presence of the substrate for AF, cardiac autonomic alterations could promote the arrhythmia, whereas other patients who lack the substrate tolerate similar autonomic conditions without AF. Because there appears to be a relationship between reduced heart rate complexity and arrhythmia susceptibility, further understanding of the physiological correlates of ApEn could provide insights into the mechanisms that promote postoperative AF.

**Study Limitations and Clinical Implications**

Although higher heart rates and decreased ApEn were independent determinants of AF susceptibility in post-CABG patients, the temporal sequence of abnormalities in RR interval dynamics before AF onset was not determined. The question of whether HRV indexes can identify risk for AF in a clinically useful time frame, allowing the institution of abortive therapeutic measures, remains to be answered in larger studies. The finding of a very broad range and apparent bimodal distribution of HRV in patients with AF will also require confirmation in larger studies. These differences in HRV patterns (ie, low or high RR interval variations) may have existed before surgery. However, in the 8 patients in whom preoperative ambulatory ECG data were available, the higher or lower patterns of HRV were not evident. Although the possibility cannot be excluded, HRV before surgery does not appear to be an explanation for our findings.

HRV may be influenced by multiple factors, including ventricular dysfunction and cardioactive drugs such as β-adrenergic receptor agonists and antagonists.\textsuperscript{31,42} To eliminate these potentially confounding influences, we excluded patients for left ventricular dysfunction or use of β-blockers during ambulatory ECG monitoring after surgery. Whether our findings apply to patients with reduced left ventricular function remains to be defined. Administration of β-blocking drugs has been suggested to reduce the frequency of postoperative AF, but the relationship between the acute withdrawal of these drugs after surgery and susceptibility to the arrhythmia has not been consistently demonstrated.\textsuperscript{1,13,30} We have previously shown that preoperative β-blocker use does not influence HRV results after uncomplicated CABG.\textsuperscript{21} In the present study, compared with the patients later developing AF, significantly more control patients were receiving β-blockers before surgery. However, adjusting for preoperative β-blocker use in the multivariate model did not influence our results, suggesting minimal effects of these drugs on our results. Nonetheless, heart rate dynamics before AF in patients taking β-blockers remains to be explored.

We conclude that the analysis of HRV from the ensemble of patients susceptible to AF after CABG misses important characteristics of HRV in this population because of both depressed or elevated normal-to-normal RR variations. The finding of 2 different HRV patterns in patients after CABG suggests that either the underlying autonomic balance alone is not related to the development of AF or that AF is the final common end point for divergent autonomic or other causes. The possibility of heightened vagal tone in some patients before AF indicates that measures aimed only at reducing adrenergic activation, such as β-adrenergic blocking drugs, would not be effective AF prophylaxis for all patients.\textsuperscript{36} The strong association of ApEn and AF for the entire group of patients suggests that ApEn may provide a clinically useful tool for risk stratification or investigation of the mechanism underlying AF.
References


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