Mechanisms and Treatment of Atrial Fibrillation

Competing Autonomic Mechanisms Precede the Onset of Postoperative Atrial Fibrillation

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OBJECTIVES	This study was designed to evaluate autonomic changes preceding atrial fibrillation/flutter (AF) after thoracotomy.
BACKGROUND	Autonomic fluctuations before the onset of postoperative AF have been reported but with conflicting results.
METHODS	In 48 patients with postoperative AF, 2-h Holter recordings before the onset of AF were compared with corresponding data from 48 age- and gender-matched surgical controls without AF. Five-minute segments of heart rate variability (HRV) were studied using linear regression methods.
RESULTS	There was a near-significant trend for the RR interval among patients with AF to be lower than controls ($p = 0.06$), whereas the standard deviation of RRs ($p < 0.0001$), root mean square of successive RR differences ($p < 0.0001$), proportion of RRs >50 ms different ($p < 0.0001$), low-frequency power ($p = 0.0003$) and its log ($p < 0.0001$), and high-frequency-power ($p < 0.0001$) and its log ($p < 0.0001$) were all significantly greater in patients with AF, respectively. In comparison to controls, AF patients had a significant decrease in RR interval ($p = 0.02$) and significant increments in all time- and frequency-domain analyses studied.
CONCLUSIONS	In the period before the onset of postoperative AF, there are significant increases in HRV during a time when heart rate also increases. These novel findings are consistent with parasympathetic resurgence competing with increasing sympathetic activity as the triggering mechanism for postoperative AF. (J Am Coll Cardiol 2003;42:1262–8) © 2003 by the American College of Cardiology Foundation

Postoperative atrial arrhythmias, including specifically atrial fibrillation/flutter (AF), are seen in 6.1% of elderly patients undergoing non-cardiothoracic surgery and in 10% to 65% of patients after cardiothoracic operations (1–4). The clinical symptoms, time of AF onset, and natural course of the arrhythmia are similar whether a patient has had cardiac, thoracic, or other surgery (1–5). As in AF unrelated to

surgery, age >60 years is consistently the only independent preoperative risk factor most strongly associated with postoperative AF (1–6). It is well known that aging causes degenerative and inflammatory changes in atrial myocardium that lead to alterations in electrical properties of the atria (7,8). The utility of signal-averaged P-wave duration to predict postoperative AF remains controversial (9–12). We and others have observed that a greater preoperative heart rate (HR) was an independent predictor of AF after cardiothoracic surgery, suggesting that lower preoperative

vagal tone further stratifies those susceptible to AF among the elderly (4,6,13).

The mechanisms of postoperative AF, however, have not been well defined. Increased atrial ectopy can trigger postoperative AF (14). Although autonomic imbalance has also been implicated as a possible trigger of postoperative AF, there is some controversy as to whether this is primarily vagal or sympathetic in nature (15,16). Having a better understanding of the mechanisms of postoperative AF could lead to more targeted preventative or therapeutic interventions. To gain insight into autonomic influences preceding postoperative AF, we compared time and frequency domain parameters of heart rate variability (HRV) of patients who developed this arrhythmia with those of matched postoperative controls without AF.

METHODS

The data used in this study were obtained from an ongoing prospective database of 412 patients in sinus rhythm who had major thoracic surgery beginning in October 1990 to September 1999 at Memorial Sloan-Kettering Cancer Center and had Holter recordings postoperatively. With Institutional Review Board approval and written informed consent, patients participated in consecutive trials focused on the study of postoperative AF (2,17,18). All patients scheduled for thoracic surgery who met inclusion criteria were approached to enroll in the studies subject to the availability of research staff. Excluded from this study were 216 patients

Abbreviations and Acronyms

AF	=	atrial fibrillation/flutter
CABG	=	coronary artery bypass grafting
HF	=	high-frequency power
HR	=	heart rate
HRV	=	heart rate variability
LF	=	low-frequency power
pNN50	=	proportion of adjacent RRs >50 ms different
RMSSD	=	root mean square of difference of successive RRs
SD	=	standard deviation

receiving drugs such as prophylactic intravenous diltiazem or class I and III antiarrhythmic drugs that may reduce the frequency of AF episodes. Preoperative beta-blockers were continued postoperatively to avoid withdrawal. Patients who were taking calcium channel blockers for hypertension or coronary artery disease resumed taking these medications on the first postoperative day. The primary end point of this study was the new onset of sustained (>30 s) AF defined by an irregularly irregular cardiac rhythm other than sinus within 96 h after surgery and detected by Holter recordings. We examined the first episode in every patient because at that time no prior antiarrhythmic medications were given that might interfere with our results of subsequent episodes. Of the remaining 196 patients, 48 patients who developed postoperative AF and met the inclusion criteria were compared with 48 age- and gender-matched controls who underwent the same operation but did not develop AF. The operations were performed using standard thoracotomy approaches. Postoperative pain relief was provided to all patients by continuous administration of either an epidural opioid (usually fentanyl) (n = 49) or an intravenous opioid (usually morphine) patient-controlled analgesia (n = 47). Patient-controlled analgesia pumps were used in all patients with the goal of achieving a visual analog pain score of 3 or less.

Ambulatory electrocardiography and HRV analysis. Dual-lead electrocardiographic recordings (leads CM_2 and CM_1 or CM_5) were made on Marquette 8500 Holter recorders. Recordings were made continuously beginning upon arrival in the post-anesthesia care unit for 72 to 96 h. The Holter tapes were digitized on a Marquette series 8000 scanner. The signal was sampled at 128 Hz. The decisions made automatically by the computer were reviewed and corrected by an experienced technician and then by a cardiologist. When calculating the HRV parameters only normal-to-normal (NN) intervals were used. Thus, both ectopic coupling intervals and post-ectopic pauses were excluded. For frequency-domain analysis, each interval that was to be excluded because of ectopic beats or artifact was replaced by holding the previous coupling interval level throughout the time interval to the next valid coupling interval. The HRV analysis was done during the 2 h preceding AF onset and in a corresponding time window in

controls. The HRV indices measured were: mean RR interval (ms) and its standard deviation (SD; ms); root mean square of difference of successive RRs (rMSSD; ms); proportion of adjacent RRs >50 ms different (pNN50; %); low (LF; 0.04 to 0.15 Hz) and high frequency (HF; 0.15 to 0.40 Hz) power (ms^2) (19). Fast Fourier transformation was used to compute the power within the defined frequency limits for each 5-min interval. The LF/HF ratio has been proposed by some to be an index of sympathovagal balance (20).

Continuous data are presented as mean value $\pm$ SD. Patient and operative characteristics between patients with and without AF were compared using the Student *t* test for normally distributed variables; the Mann-Whitney *U* test was used for comparisons of supraventricular and ventricular ectopy. Categorical variables were compared using the Fisher exact test. Time and frequency domain parameters in the two hours period preceding AF were assessed using mixed effects linear regression models in which the non-independence of data from the same patient is taken into account. The difference in the slope coefficient over time between patients with and without AF for HRV variables was assessed for statistical significance. Each HRV variable was of interest and tested a priori. Analysis of LF and HF is presented with and without log transformation. To provide additional information on HRV between the groups, a secondary analysis of data selected from four time points before AF onset was done using paired *t* tests with Bonferroni correction for multiple comparisons. All statistical tests were two-tailed, and $p < 0.05$ was regarded as statistically significant.

RESULTS

Characteristics and surgical data of patients who did (n = 48) or did not (n = 48) develop AF are presented in Table 1. The mean sinus rate 5 min before AF onset was 93 ± 16 versus 86 ± 15 beats/min in controls, p = 0.04. The mean number of atrial premature beats during the 2 h preceding AF was significantly greater among patients with AF than controls, 392 ± 561 versus 28 ± 58, p < 0.0001, as was the number of supraventricular runs (3 or more beats), 1.8 ± 3.8 versus 0.02 ± 0.14, p < 0.0001, and premature ventricular beats 30 ± 67 versus 7 ± 23, p < 0.0001, respectively. ST-segment changes (up- or downsloping) occurred in 6/48 patients with AF compared to 10/48 patients without AF, p = 0.41. When patients who had evidence of pericarditis were excluded, regional ST-segment changes were present in 5/48 patients with AF compared to 6/48 patients without AF, p = 0.99. None of the patients studied developed a myocardial infarction postoperatively.

Time-domain HRV parameters. There was a near-significant trend for the RR-interval among AF patients to be lower than controls (p = 0.06, Fig. 1A), whereas SD (p < 0.0001, Fig. 1B), rMSSD (p < 0.0001, Fig. 1C), and pNN50 (p < 0.0001, Fig. 1D) were all significantly greater

Table 1. Patient Characteristics

	AF (n = 48)	Controls (n = 48)	p
Preoperative			
Age, yrs	70 ± 8	70 ± 8	0.99
Weight, kg	76 ± 16	72 ± 14	0.27
Male (%)	32 (67)	32 (67)	0.99
Heart rate, beats/min	73 ± 13	74 ± 14	0.88
Smoking (%)	35 (73)	35 (73)	0.99
Hypertension (%)	20 (42)	15 (31)	0.29
Coronary artery disease (%)	7 (15)	4 (8)	0.52
Diabetes mellitus (%)	4 (8)	6 (13)	0.74
Chemotherapy (%)	7 (15)	11 (23)	0.30
Medication			
ACE-inhibitors (%)	5 (10)	6 (13)	0.68
Beta-blockers (%)	6 (13)	6 (13)	0.99
Ca-channel blockers (%)	7 (15)	6 (13)	0.77
Pulmonary function			
FEV_1, % predicted	80 ± 29	84 ± 23	0.53
FVC, % predicted	90 ± 27	97 ± 22	0.17
DCO, % predicted	78 ± 20	79 ± 17	0.77
Intraoperative			
Lobectomy (%)	32 (67)	39 (81)	0.16
Pneumonectomy (%)	9 (19)	7 (15)	
Extrapleural pneumonectomy	7 (15)	2 (4)	
Estimated blood loss, l	0.5 ± 0.6	0.4 ± 0.4	0.20
Fluid replacement, l	2.8 ± 3.2	2.6 ± 2.1	0.62
Postoperative			
Epidural analgesia (%)	25 (52)	24 (50)	0.84
Pericarditis (%)	5 (10)	5 (10)	0.99
Pneumonia or acute respiratory failure (%)	4 (8)	3 (6)	0.99

ACE = angiotensin-converting enzyme; AF = atrial fibrillation/flutter; DCO = diffusion capacity of carbon monoxide; FEV_1 = forced expiratory volume; FVC = forced vital capacity.

in patients with AF, respectively (Table 2). When all patients were considered together, there were no significant changes in time-domain parameters of HRV over the 2 h study window (Table 2). However, in comparison to controls patients with AF had significant changes in HRV parameters over time: RR decreased while SD, rMSSD, and pNN50 all increased (Figs. 1A to 1D, Table 2). To provide additional information on HRV between the groups, a secondary analysis of data selected from four time points before AF onset was done (Table 3). For example, in comparison to controls time-domain parameters of HRV studied were significantly different 5 min before AF onset: mean RR interval was 657 ± 112 versus 717 ± 134 ms, p = 0.05; SD was 73 ± 42 versus 40 ± 33 ms, p < 0.005; rMSSD was 108 ± 70 versus 46 ± 56 ms, p < 0.005; and pNN50 was 12.8 ± 11.9 versus 2.7 ± 6.9%, p < 0.005, respectively (Table 3).

Frequency-domain HRV parameters. Patients with AF had significantly greater values in LF (p = 0.0003, Fig. 2A), Ln LF (p < 0.0001, not shown), HF (p < 0.0001, Fig. 2B), Ln HF (p < 0.0001, not shown), but lower LF/HF ratio (p = 0.006, Fig. 2C) than controls (Table 2). When all patients were considered together, there were no significant changes in frequency-domain parameters of HRV over the 2 h study window (Table 2). However, in comparison to

controls, patients with AF had significant increments in LF, Ln LF, HF, and Ln HF, but not in LF/HF ratio (Figs. 2A to 2C, Table 2). Table 3 shows HRV data selected from four time points before AF onset. In comparison to controls, all frequency-domain parameters of HRV studied were significantly different 5 min before AF onset: LF was 2,529 ± 3,799 versus 705 ± 1,452 ms², p = 0.02; Ln LF was 6.9 ± 1.5 versus 5.5 ± 1.4 (ms²), p < 0.005; HF was 7,325 ± 7,049 versus 2,282 ± 8,433 ms², p = 0.01; and Ln HF was 8.1 ± 1.6 versus 5.7 ± 1.8 (ms²), p < 0.005; and LF/HF ratio was 0.5 ± 0.7 versus 2.0 ± 2.8, p = 0.004, respectively (Table 3).

DISCUSSION

The main findings of this study are that patients who develop postoperative AF have a significant elevation of HR that is accompanied by a consistent and significant rise in time- and frequency-domain parameters of HRV during the 2 h preceding the onset of AF in comparison to age- and gender-matched controls undergoing major noncardiac thoracic surgery. These data suggest that vagal activation in the setting of sympathetic predominance contribute strongly to postoperative AF.

Dissecting sympathetic and parasympathetic influences on the sinus node using HRV measures has been extensively utilized despite some well-defined limitations (20,21). Time domain indices represent respiratory modulation of vagal activity. Frequency domain indices are more complex to interpret, but in general the HF component has been thought to reflect primarily vagal activity whereas LF reflects both sympathetic and vagal activity (20). The impressive elevations in time-domain indices of HRV we observed simultaneously with an increasing HR suggest vagal resurgence in a background of increasing sympathetic activity immediately before AF onset. These findings are in contrast to classic examples as described by Coumel of adrenergically or vagally mediated AF characterized by an increasing or decreasing HR before arrhythmia onset, respectively (22). The independence of neural modulation of RR cycle length from HRV has been described in nonsurgical patients and may be interpreted differently in postoperative patients in whom changing respiratory patterns and varying systemic opioid concentrations occur (23).

Although experimental models have shown that increased vagal tone alone may produce AF, vagally mediated AF is uncommon, and it may be the heightened background sympathetic tone that helps promote AF with increased vagal activity. It is conceivable that vagal rebound promotes ectopy by shortening refractoriness in a heterogeneous matter and that the increased background sympathetic activity may then promote AF (24). The LF/HF ratio may represent sympathovagal balance, but the utility of this index has been challenged (20,21). Recent work in volunteers studied under conditions of autonomic blockade or stimulation showed that HR but not LF/HF ratio is a
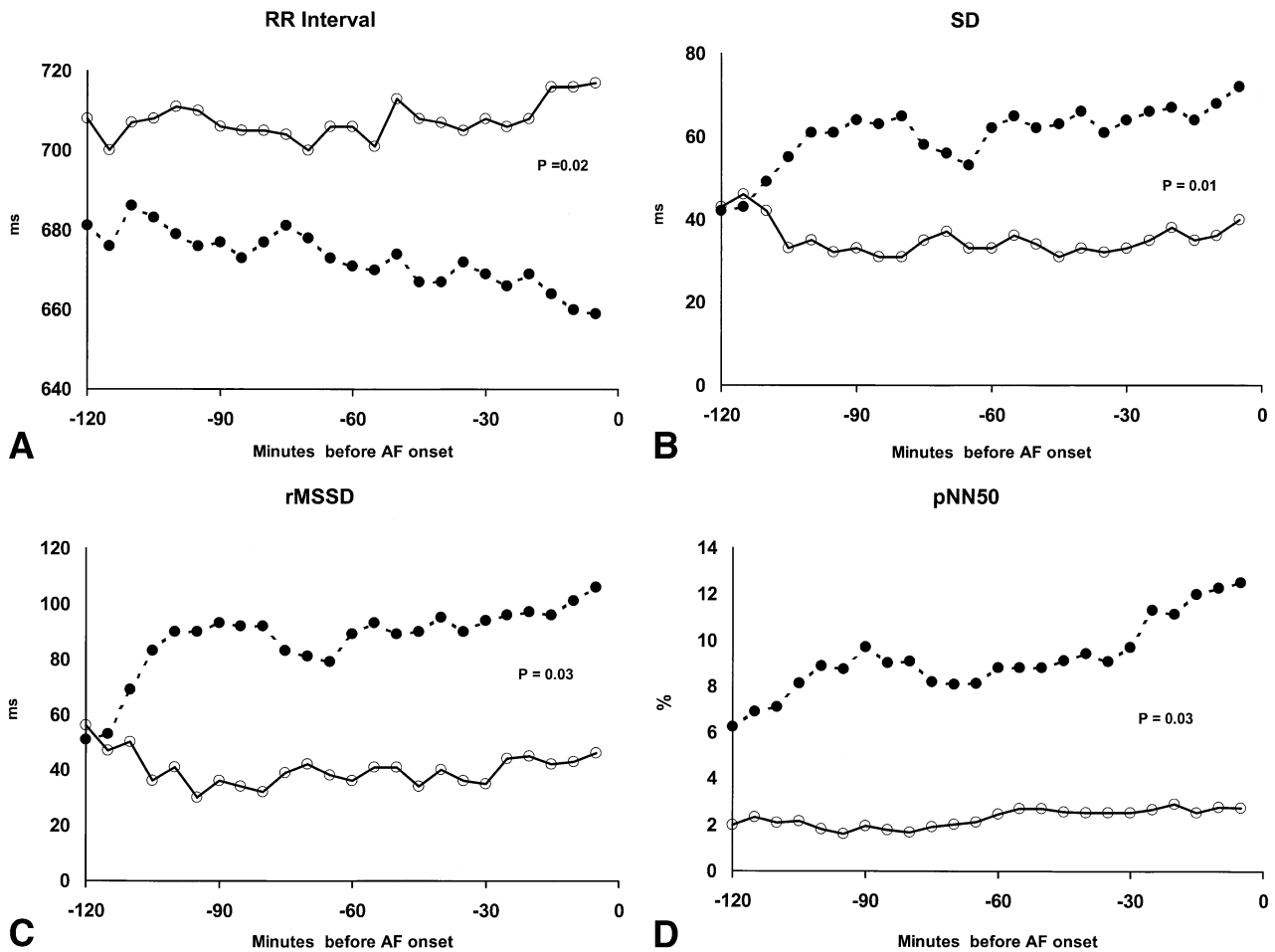
Figure 1. Continuous 5-min data of time-domain parameters of heart rate variability (HRV) during the 2 h preceding the onset of atrial fibrillation/flutter (AF) **(filled circles)** or in the corresponding study window in controls **(unfilled circles)**. **A** = RR interval; **B** = SD; **C** = rMSSD; **D** = pNN50. See text for abbreviations. P values in the figures represent the group by time interaction results.

reliable and practical index of sympathovagal balance (21). Nevertheless, in the current study the LF/HF ratio was significantly lower among patients with AF in comparison to controls, which is consistent with vagal resurgence but showed no significant change over time in either group since both components increased in parallel. The mechanism responsible for AF in our patients is not entirely clear but

Table 2. p Values Representing Heart Rate Variability Differences

	Time (5 Min Intervals)	Group (AF vs. Controls)	Interaction (Time and Group)
RR, ms	0.53	0.06	0.02
SD, ms	0.59	< 0.0001	0.01
rMSSD, ms	0.94	< 0.0001	0.03
pNN50, %	0.40	< 0.001	0.03
LF, ms^2	0.94	0.0003	0.05
Ln LF, ms^2	0.42	< 0.0001	0.0008
HF, ms^2	0.74	< 0.0001	0.009
Ln HF, ms^2	0.87	< 0.0001	0.007
LF/HF ratio	0.57	0.006	0.24

AF = atrial fibrillation/flutter; HF = high frequency (0.15–0.40 Hz); LF = low frequency (0.04–0.15 Hz); rMSSD = root mean square of difference of successive RRs; pNN50 = proportion of adjacent RRs > 50 ms different; SD = standard deviation of RRs.

may represent a combination of the effects of altered sympathovagal balance, intraoperative trauma to autonomic fibers, and inflammatory changes that occur in response to major pulmonary resection (25). Observations made in patients with focal ectopy originating from the pulmonary veins have suggested a primary increase in adrenergic drive followed by marked modulation toward vagal predominance before the onset of paroxysmal AF unrelated to surgery (26). Whether ectopic atrial activity from the pulmonary veins contributes to the genesis of postoperative AF remains unknown.

In the present study, patients with AF had more frequent atrial and ventricular ectopy than controls. Atrial fibrillation is often initiated by an atrial premature contraction (8,14). Once initiated, AF can cause further alterations in atrial electrical and structural properties (remodeling), which promote the maintenance of the arrhythmia and facilitate its re-initiation should it terminate (8). The use of temporary bi-atrial overdrive pacing was shown to be effective to prevent AF after coronary artery bypass grafting (CABG) (27,28). The proposed mechanism for this beneficial effect was that overdrive pacing primarily decreased the incidence

Table 3. HRV Preceding the Onset of AF

	AF	Controls	p value
RR, ms			
120 min	672 ± 109	708 ± 130	0.55
60 min	685 ± 109	709 ± 130	0.99
30 min	670 ± 119	705 ± 130	0.56
5 min	657 ± 112	717 ± 134	0.05
SD, ms			
120 min	60 ± 37	35 ± 28	0.004
60 min	50 ± 37	33 ± 37	0.12
30 min	62 ± 43	32 ± 31	< 0.005
5 min	73 ± 42	40 ± 33	< 0.005
rMSSD, ms			
120 min	87 ± 63	40 ± 48	< 0.005
60 min	69 ± 61	38 ± 58	0.08
30 min	89 ± 70	36 ± 53	< 0.005
5 min	108 ± 70	46 ± 56	< 0.005
pNN50%			
120 min	9.1 ± 9.8	2.3 ± 5.5	< 0.005
60 min	7.3 ± 10.1	2.2 ± 5.6	0.004
30 min	9.3 ± 10.4	2.5 ± 6.7	< 0.005
5 min	12.8 ± 11.9	2.7 ± 6.6	< 0.005
LF, ms^2			
120 min	2,217 ± 2,543	657 ± 812	< 0.005
60 min	1,060 ± 1,389	743 ± 2,136	0.99
30 min	2,647 ± 3,802	523 ± 919	0.004
5 min	2,529 ± 3,799	705 ± 1,452	0.02
Ln LF, ms^2			
120 min	7.1 ± 1.2	5.8 ± 1.3	< 0.005
60 min	6.1 ± 1.5	5.5 ± 1.5	0.26
30 min	6.7 ± 1.9	5.2 ± 1.5	< 0.005
5 min	6.9 ± 1.5	5.5 ± 1.4	< 0.005
HF, ms^2			
120 min	7,522 ± 9,640	1,625 ± 2,806	< 0.005
60 min	3,412 ± 4,601	1,400 ± 2,624	0.03
30 min	8,995 ± 14,665	2,430 ± 10,682	0.09
5 min	7,325 ± 7,049	2,282 ± 8,433	0.01
Ln HF, ms^2			
120 min	8.1 ± 1.5	6.2 ± 1.6	< 0.005
60 min	6.8 ± 2.0	5.6 ± 1.9	0.03
30 min	7.6 ± 2.2	5.5 ± 1.8	< 0.005
5 min	8.1 ± 1.6	5.7 ± 1.8	< 0.005
LF/HF ratio			
120 min	0.6 ± 0.7	1.3 ± 1.7	0.04
60 min	1.0 ± 1.2	2.2 ± 3.1	0.09
30 min	1.0 ± 2.0	3.0 ± 7.5	0.36
5 min	0.5 ± 0.7	2.0 ± 2.8	0.004

Abbreviations as in Table 2.

of atrial ectopy after surgery by reducing rate-dependent electrophysiologic changes and helped reduce atrial dispersion of refractoriness (27–29). The observation that prophylactic atrial pacing prevents AF after CABG does not exclude the possibility that the autonomic changes we observed may promote AF. For example, fixed rate atrial pacing may suppress ectopy in making refractoriness more homogenous, thus decreasing the susceptibility of atrial myocardium to autonomic changes. Furthermore, vagal rebound may explain why the efficacy of beta-adrenergic blockers to reduce the incidence of postoperative AF is controversial (3,4).

Little work has been done using HRV to understand autonomic mechanisms before postoperative AF (15,16,30).
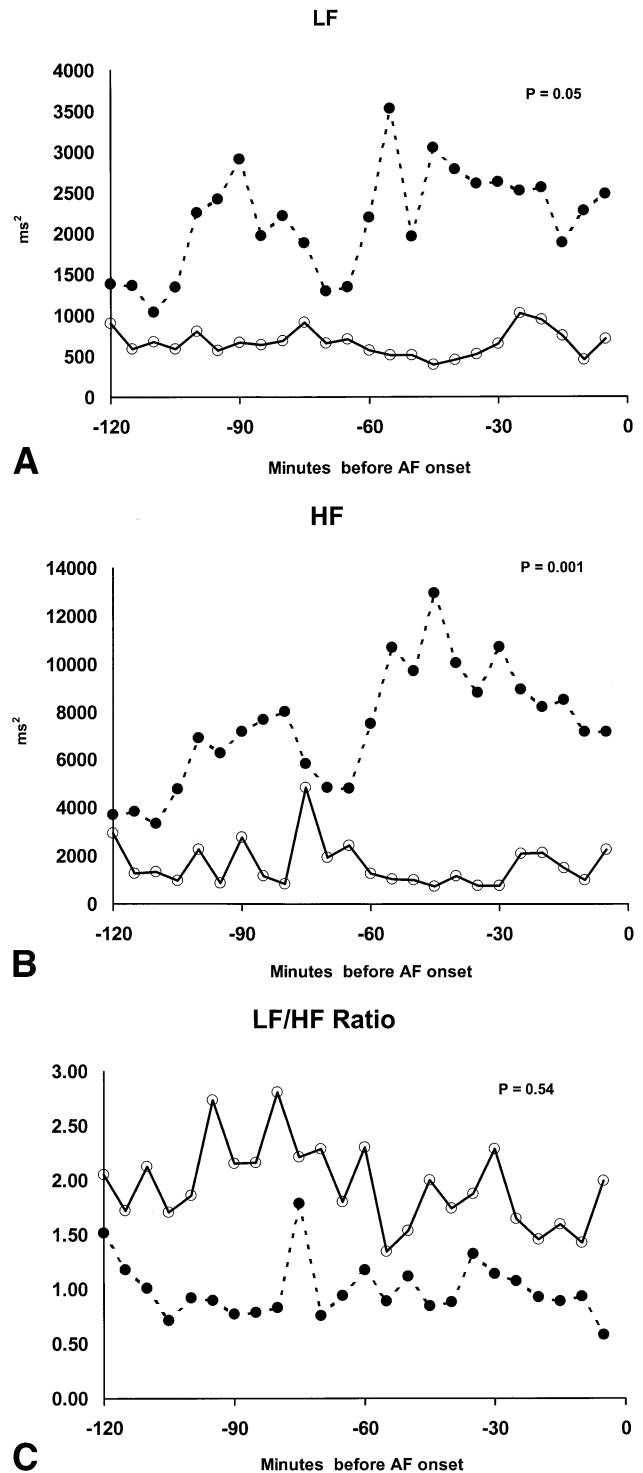

Figure 2. Continuous 5-min data of frequency-domain parameters of HRV during the 2 h preceding the onset of AF **(filled circles)** or in the corresponding study window in controls **(unfilled circles)**. **A** = LF; **B** = HF; **C** = LF/HF ratio. See text for abbreviations. P values in the figures represent the group by time interaction results.

Whereas Jidéus et al. (30) found that patients who developed postoperative AF did not differ from controls in HRV measures after CABG, Dimmer et al. (15) showed that patients with AF had a modest increase in HR, SD, and

LF/HF ratio before AF onset. The latter results were interpreted to suggest that vagal withdrawal and increase in sympathetic tone were the primary triggers of postoperative AF (15). Hogue et al. (16) used linear and nonlinear measures of HRV in 18 patients who developed AF after cardiac surgery and found that patients with AF had a greater HR and lower approximate entropy 1 h before AF onset in comparison to controls. These investigators also found that among the patients with AF there were 19 AF episodes that were preceded by low HRV and 5 AF episodes by high HRV (16). They suggested that their preliminary findings may represent two different autonomic patterns underlying AF after CABG: one of heightened vagal tone and one of adrenergic predominance. Our results in a much larger group of noncardiac thoracic surgical patients support one autonomic mechanism for the trigger of postoperative AF. However, our data differ from Hogue et al. (16) in that the two patient populations studied differ in severity of cardiac disease, lower use of beta-blockers, and in surgery that does not involve cardiopulmonary bypass.

There have been conflicting reports on the meaning of HRV changes before paroxysmal AF unrelated to surgery (31–33). The most recent study showed that the increases in HRV were preceded by a decreasing RR interval (33). These data in nonsurgical patients are comparable to ours, where RR decreased and frequency domain parameters of HRV increased before AF onset. In addition, time domain parameters of HRV also increased in our patients, providing consistent data to suggest that vagal rebound or resurgence was occurring in addition to an elevation in sympathetic tone before the trigger of postoperative AF.

Study limitations. Our patient population consists of prospectively collected data in an ongoing database of consecutive trials, but not necessarily of all consecutive patients who had surgery at our institution during the study period. Nevertheless, this population of patients represents one of the more comprehensive and large prospective databases of patients undergoing major noncardiac thoracic surgery focused on the problem of postoperative AF with Holter data. Our results may not apply to patients with illnesses that might affect autonomic state and regulation. We chose to study 5-min HRV over a 2-h period preceding AF instead of 24-h periods, as this represented a critical time where short-term autonomic changes influencing the trigger of this arrhythmia were likely to occur (15,16). Heart rate variability is only an indirect measure of autonomic influences on the sinus node, and therefore interpretation concerning the exact mechanism of postoperative AF should be made with caution (23). Linear methods of HRV analysis (Fast Fourier) may be influenced by several important conditions, including age, posture, respiratory rate, circadian rhythms, disease states, and medications. Posture and respiratory rate could not be controlled, and we uniformly treated our patients with opioids postoperatively according to a standard protocol. Patients with AF had significantly more supraventricular and ventricular ectopy than controls, and

this could have artifactually increased HRV in the AF group. On the contrary, because ectopic and post-ectopic intervals were excluded from the time domain analysis and constant RR intervals were substituted for these intervals in the frequency domain analysis, increased ectopy would actually tend to decrease HRV in the AF group because the intervals were otherwise assumed to be constant.

Conclusions and clinical implications. In comparison to matched controls, patients who developed AF after major noncardiac thoracic surgery demonstrated significant changes in HRV that are consistent with vagal resurgence competing in a background of increasing sympathetic activity as the primary autonomic mechanism responsible for the trigger of postoperative AF. To the best of our knowledge, these novel results represent the largest study using HRV to understand autonomic influences preceding postoperative AF, and suggest that interventions that modulate both the sympathetic and parasympathetic nervous systems may be beneficial in suppressing postoperative AF.

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