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Sinus Nodal Function and Risk for Atrial Fibrillation after Coronary Artery Bypass Graft Surgery

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Background: **Nonsurgical patients with sinus node dysfunction are at high risk for atrial tachyarrhythmias, but whether a similar relation exists for atrial fibrillation after coronary artery bypass graft surgery is not clear. The purpose of this study was to evaluate sinus nodal function before and after coronary artery bypass graft surgery and to evaluate its relation with the risk for postoperative atrial arrhythmias.**

Methods: **Sixty patients without complications having elective coronary artery bypass graft surgery underwent sinus nodal function testing by measurement of sinoatrial conduction time (SACT) and corrected sinus nodal recovery time (CSNRT). Patients were categorized based on whether postoperative atrial fibrillation developed.**

Results: **Twenty patients developed atrial fibrillation between postoperative days 1 through 3. For patients remaining in sinus rhythm (n = 40), sinoatrial conduction times were no different and corrected sinus nodal recovery times were shorter after surgery when compared with measurements obtained after anesthesia induction. Sinus node function test results before surgery were similar between the sinus rhythm and the atrial fibrillation groups. After surgery, patients who later developed atrial fibrillation had longer sinoatrial conduction times compared with the sinus rhythm group (P = 0.006), but corrected sinus nodal recover time was not different between these groups. A sinoatrial conduction time > 96 ms measured at this time point was associated with a 7.3-fold increased risk of postoperative atrial fibrillation (sensitivity, 62%; specificity, 81%; positive and negative predictive values, 56% and 85%, respectively; area under the receiver operator characteristic curve, 0.72).**

Conclusions: **These data show that sinus nodal function is not adversely affected by uncomplicated coronary artery bypass surgery. Patients who later developed atrial fibrillation, however, had prolonged sinoatrial conduction immediately after surgery compared with patients remaining in sinus rhythm. These results suggest that injury to atrial conduction tissue at the time of surgery predisposes to postoperative atrial fibrillation and that assessment of sinoatrial conduction times could provide a means of identifying patients at high risk for postoperative atrial fibrillation. (Key words: Arrhythmias cardiac; surgery.)**

DISORDERS of cardiac rate and rhythm are common after coronary artery bypass graft (CABG) surgery ranging in severity from transient abnormalities (*e.g.*, sinus bradycardia requiring temporary cardiac pacing) to more serious tachyarrhythmias that may lead to adverse patient outcomes. Atrial fibrillation, atrial flutter, or both are especially frequent complications that occur in as many as 40% of CABG surgical patients.[1–5] Although of little consequence in some patients, this arrhythmia may lead to hemodynamic compromise in others, and it is associated with longer hospitalization, threefold higher risk of cerebral thromboembolic complications, development of serious ventricular arrhythmias, need for permanent cardiac pacemaker insertion, and higher hospital costs.[1–3] Despite these important implications, the pathophysiologic mechanisms of postoperative atrial fibrillation are incompletely understood. In particular, it is unclear why patients undergoing similar surgical perturbations have varying susceptibility to the arrhythmia.

Autonomic nervous system imbalance is widely believed to contribute to the initiation and maintenance of postoperative atrial fibrillation.[4,5] We and others have evaluated autonomic responses to CABG surgery using analysis of heart rate variability which provides a method for evaluating sympathetic and vagal modulations of heart rate.[6–10] These data have shown that measures of heart rate variability are reduced nearly 50% after uncomplicated CABG surgery compared with patients having

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vascular surgery, and these reductions persist for at least 2 months postoperatively.[6–8] We have also shown in this same population of patients that atrial fibrillation is preceded by alterations in heart rate dynamics, and these changes identify patients susceptible to the arrhythmia.[11] The mechanisms for these findings are unknown, but they could be a manifestation of the autonomic conditions suggested to predispose to atrial fibrillation. Another explanation might be that sinus nodal function is impaired after CABG surgery, and this dysfunction leads to altered neuroregulation of heart rate and predisposition to atrial fibrillation. This hypothesis takes into account the pivotal role of the sinus node in determining atrial rate response to autonomic nervous system stimulation as well as the well-appreciated relation between sinus nodal dysfunction and risk for atrial fibrillation in nonsurgical patients.[12–16]

The effects of CABG surgery on the sinus node and whether there is a relation between sinus nodal dysfunction and postoperative atrial fibrillation have not been clearly established.[16] Accordingly, the purpose of this study was to determine the effects of CABG surgery on sinus nodal function and to evaluate whether preexisting or developing sinus nodal dysfunction is related to the risk for postoperative atrial arrhythmias.

Materials and Methods

All procedures employed in this study were approved by the Washington University School of Medicine Human Studies Committee and individual informed consent was obtained from all participants. Sixty patients scheduled to undergo elective, primary CABG surgery at Barnes-Jewish Hospital (St. Louis, MO) were enrolled. Patients were excluded for digoxin use, preoperative use of antiarrhythmic therapy (*e.g.*, amiodarone), congestive heart failure, diabetes mellitus, renal failure requiring hemodialysis, preoperative atrial fibrillation, presence of a permanent cardiac pacemaker, or left ventricular ejection fraction $< 45\%$ determined at the time of cardiac catheterization.

Perioperative Care

All preoperative medications were continued until the time of surgery, including nitroglycerin, β-adrenergic receptors, and calcium channel-blocking drugs. Patients were premedicated with morphine 0.08–0.1 mg/kg intramuscularly and lorazepam 1 to 2 mg orally. Patient monitoring included a pulmonary artery catheter, direct radial artery blood pressure measurement, electrocardiographic leads II and V_5 with ST segment monitoring, and transesophageal echocardiography (TEE). Anesthesia was induced with midazolam 0.1 mg/kg and fentanyl 15–20 μg/kg intravenously, and vecuronium was given for skeletal muscle relaxation. Continuous intravenous infusions of fentanyl 0.1–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, midazolam 0.25–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and vecuronium were given for anesthesia maintenance. Volatile anesthetics were not administered at any time during surgery to avoid the potential confounding influences of these drugs on sinus nodal function test.[17] Centrifugal pumps (Biomedicus, Minneapolis, MN) and membrane oxygenators (Cobe, Denver, CO) were used for cardiopulmonary bypass. High potassium, intermittent, cold blood cardioplegia was administered after aortic cross-clamping under mild systemic hypothermia (venous temperature, 32°C). Perioperatively, potassium and magnesium were given intravenously to maintain normal serum concentrations. Patients were continuously monitored after surgery until the time of hospital discharge with telemetry ECG monitoring. The diagnosis of atrial fibrillation was based on clinical detection from the ECG telemetry monitors confirmed with 12-lead ECG. Atrial fibrillation was defined as a persistent arrhythmia with irregular, fluctuating baseline without well-defined P-waves and irregular RR intervals that required medical intervention.

Sinus Nodal Function Testing

Following tracheal intubation, a transesophageal atrial pacing–monitoring electrode (TAPCATH, Arzco Medical Systems, Tampa, FL) was inserted to 50 cm from the infraalveolar ridge and connected to the operating room ECG monitor *via* an esophageal pacing system (Model 7A pulse generator, Arzco Medical System). After placement of a TEE probe, the pacing electrode was withdrawn to a position that provided the largest atrial depolarization. The esophageal electrode was used only for monitoring the ECG to provide precise identification of the P-wave. After pericardiotomy, temporary atrial pacing leads were placed on the high right atrium by the surgeon. These pacing electrodes were used for overdrive atrial pacing when performing sinus nodal function testing before and after surgery (discussed below). Care was taken to place the electrodes in a position that would be used after surgery. During testing, the ECG was recorded on a strip recorder interfaced with the operating room monitoring system and running at a speed of 50 cm/s.

Sinoatrial nodal function was evaluated by determina-

Table 1. Demographic and Other Patient Characteristics for Patients Remaining in Sinus Rhythm after Surgery and for Those with Postoperative Atrial Fibrillation

	Sinus Rhythm (n = 40)	Postoperative Atrial Fibrillation (n = 20)	*P*-Value
Age (mean ± SD)	63 ± 10	67 ± 9	0.17
Gender (male/female)	26/14	5/15	0.35
Hypertension	22	15	0.34
Current tobacco abuse	15	10	0.38
Preoperative medications			
β-receptor blockers	28 (70%)	12 (60%)	0.53
Ca^{++} channel blockers	13 (33%)	11 (53%)	0.22
ACE inhibitors	8 (21%)	3 (15%)	0.71
Nitroglycerin	27 (67%)	12 (60%)	0.75
Coronary artery stenosis			
Right >70%	30 (75%)	14 (70%)	0.75
Right 100%	15 (37%)	9 (45%)	0.65
Circumflex >70%	27 (67%)	12 (60%)	0.85
Circumflex 100%	9 (22%)	4 (20%)	0.85
LAD >70%	31 (77%)	15 (75%)	0.96
LAD 100%	9 (45%)	6 (30%)	0.41
Cardiopulmonary bypass duration (min)	124 ± 35	120 ± 37	0.69
Aortic clamp duration (min)	73 ± 29	67 ± 25	0.51
Number of bypass grafts	3.5 ± 1.0	3.5 ± 1.0	0.90

LAD = left anterior descending coronary artery.

tion of sinoatrial conduction time (SACT) and corrected sinus node recovery time (CSNRT). SACT was determined first by atrial pacing at a rate 20% greater than the patient's resting heart rate for 8–10 beats. Sinus nodal recovery time, or the PP interval between the last paced beat and the first sinus escape beat, was measured, and SACT was defined as one half the difference between the average PP interval from the last five sinus beats before atrial pacing and sinus nodal recovery time.[18] Following a rest period of 1 min, CSNRT was determined by atrial pacing at 120 beats/min for 20 s. CSNRT was defined as sinoatrial nodal recovery time minus the PP interval of the last sinus beat prior to onset of pacing.[19,20] The average of three measurements for SACT and CSNRT were determined. Postoperatively, SACT and CSNRT were repeated after chest closure immediately before transfer to the intensive care unit (≈ 1.5 h after discontinuing cardiopulmonary bypass).

The patients were monitored in real time for evidence of myocardial ischemia with seven-lead ECG and TEE. The TEE probe was positioned to image the left ventricle's short axis at the midpapillary level and its long axis in the longitudinal plane. Evaluation for myocardial ischemia was performed during and for 5 min after each testing period. A myocardial ischemic episode was defined as a > 1-mm shift in the ST segment at 60 ms after the J point or a new segmental wall motion abnormality detected with TEE.

Statistical Analysis

Patients were categorized based on whether they remained in sinus rhythm perioperatively or whether atrial fibrillation developed after surgery. Continuous data were analyzed with analysis of variance using Bonferroni *post hoc* test when appropriate and with Wilcoxon rank sum test when the data were nonparametrically distributed. Categorical data were analyzed using the Fisher exact test. Logistic regression analysis was used to evaluate the relation between the sinus nodal function test result and the development of postoperative atrial fibrillation. For this analysis, SACT and CSNRT were evaluated in 10-ms increments above the upper 95% confidence interval of the measurements made after anesthesia induction before surgery in the sinus rhythm group. Receiver operator characteristic curves were constructed to evaluate the predictive accuracy of the logistic models. All values are expressed as mean ± SD. A significant difference was considered to exist for $P \geq 0.05$.

Results

Postoperative atrial fibrillation developed between postoperative days 1 and 3 in 20 patients. Demographic data and other perioperative characteristics for the patients based on whether they remained in sinus rhythm or developed postoperative atrial fibrillation are listed in table 1. There were no significant differences between

Table 2. Hemodynamic Data for Each Period

	Sinus Rhythm	Postoperative Atrial Fibrillation	*P* Value
Before surgery			
Heart rate	67 ± 13	59 ± 14	0.04
Systolic pressure	116 ± 11	114 ± 10	0.43
Diastolic pressure	63 ± 9	64 ± 9	0.93
CVP	9 ± 3	9 ± 4	0.68
PCWP	11 ± 3	12 ± 3	0.28
After surgery			
Heart rate	80 ± 15*	75 ± 14*	0.25
Systolic pressure	120 ± 11	114 ± 6	0.03
Diastolic pressure	68 ± 9	60 ± 6	0.005
CVP	11 ± 4*	13 ± 3*	0.20
PCWP	13 ± 3*	13 ± 2	0.55

Heart rate (beats/min), arterial, central venous (CVP), and pulmonary capillary wedge pressures (PCWP) (mmHg) at each sinus nodal function testing period for patients remaining in sinus rhythm after surgery and for those developing postoperative atrial fibrillation. Data are presented as mean ± SD.

* $P < 0.001$ *versus* baseline measurement within the same group.

the two groups of patients for any of the variables listed. There were no episodes of myocardial ischemia after the sinus nodal function tests; inotropic medications were not given to any of the patients during or after surgery; and there were no perioperative deaths. Heart rate and hemodynamic data obtained immediately before sinus nodal function testing for each period are listed in table 2. Heart rate during the initial testing period after anesthesia induction was lower for patients who later developed atrial fibrillation compared with the sinus rhythm group. Compared with the initial measurements, heart rate was significantly higher after surgery in both groups.

Sinus nodal function testing results are listed in table 3. For patients remaining in sinus rhythm perioperatively, CSNRT measured immediately after surgery was significantly lower than the values measured after anesthesia induction but before surgery. There were no differences in the sinus nodal function test between the testing periods for patients developing postoperative atrial fibrillation. When comparing the test results between the patient groups, no differences were observed in either SACT or CSNRT after anesthesia induction but before surgery. Immediately after surgery, however, SACT was longer for patients who developed postoperative atrial arrhythmias compared with patients who did not develop this arrhythmia ($P = 0.006$). The CSNRT results obtained immediately after surgery were not different between patient groups with or without postoperative atrial fibrillation ($P = 0.26$).

Logistic regression analysis was performed to further evaluate the relation between sinus nodal function test results and susceptibility to postoperative atrial fibrillation. The best predictive cutoff for identifying patients at risk for postoperative atrial fibrillation was a SACT cutoff of 96 ms. Immediately after surgery, seven (17%) patients in the sinus rhythm group and 12 (60%) patients in the atrial fibrillation group had SACT values above this level ($P = 0.001$). The odds ratio for the development of postoperative atrial fibrillation for patients with a SACT > 96 ms at this time point was 7.3 (95% confidence intervals, 2.0–26.0; $P = 0.002$). The sensitivity of this SACT measurement for identifying risk for the arrhythmia was 62%, specificity was 81%, and the positive and negative predictive values were 56% and 85%, respectively. The area under the receiver operator characteristic curve was 0.72. There was no significant predictive model for identifying atrial fibrillation risk using similar analysis with the CSNRT results.

Discussion

The results of this study show that sinus nodal function is not adversely affected by CABG surgery for patients having an uncomplicated perioperative course. Although patients who developed atrial fibrillation did not have preexisting abnormalities of sinus nodal function before surgery, they did demonstrate prolonged SACT but not CSNRT, after surgery when compared with the sinus rhythm group. We found that a SACT of > 96 ms measured at the conclusion of surgery identified patients at risk for postoperative atrial fibrillation with high negative but moderate positive predictive accuracy.

In the present study we evaluated two fundamental

Table 3. Sinus Nodal Function Test Results

	Sinus Rhythm	Postoperative Atrial Fibrillation	*P* Value
Before surgery			
SACT	73 ± 40 (61–86)	83 ± 37 (64–103)	0.38
CSNRT	180 ± 95 (150–209)	181 ± 118 (118–244)	0.97
After surgery			
SACT	62 ± 39 (49–74)	98 ± 52 (70–125)	0.006
CSNRT	168 ± 82* (143–194)	216 ± 140 (141–291)	0.26

Results (mean ± SD ms, 95% confidence intervals) for patients remaining in sinus rhythm after surgery and for those developing postoperative atrial fibrillation.

* $P < 0.01$ *versus* baseline within the same group.

CSNRT = corrected sinus nodal recovery time; SACT = sinoatrial conduction time.

properties of sinus nodal function, impulse generation and conduction, by testing CSNRT and SACT, respectively.[14,15,18–20] With both tests, the time to the first atrial escape beat after overdrive pacing is measured and the calculated results assume that there is constant distance between the site of atrial electrogenesis and the recording electrode. To minimize variation among measurements obtained at different time points, the site of monitoring of the ECG P-wave was kept constant (*i.e.*, an esophageal electrode), and care was taken to place the epicardial atrial pacing electrodes in the same location before and after surgery. Detailed electrophysiologic investigations in both animals and humans have demonstrated that the site of atrial impulse initiation is widely distributed to atrial sites in addition to the sinus node (subsidiary pacemakers).[21–23] Different sites of the "pacemaker complex" become dominant depending on autonomic tone, with superior pacemakers dominating during tachycardia and inferior atrial sites becoming active during bradycardia.[21–23] Thus, the atrial pacemaker location responsible for the first atrial escape beat after cessation of pacing may have varying distances from the recording electrode depending on prevailing autonomic tone. This consideration may explain our finding that sinus nodal test results were lower after surgery in the normal sinus rhythm group when adrenergic tone is higher than during general anesthesia before surgical stimulation.

In this study, CSNRT after surgery was not different between the sinus rhythm and atrial fibrillation groups, suggesting that impulse generation in the sinus nodal complex was not impaired in the latter group of patients. Patients developing atrial fibrillation, however, did have a significantly longer SACT after surgery compared with the sinus rhythm group, indicating an abnormality in conducting impulses out of the sinus node. It is possible that the latter findings may be related in some way to broader abnormalities in atrial conduction previously shown by other investigators in patients at risk for postoperative atrial fibrillation.[24–28] Prolonged conduction along with dispersion of atrial refractoriness developing after surgery confer the electrophysiologic substrate to support the multiple reentry pathways of atrial fibrillation.[29–31] Atrial ischemic injury resulting from aortic cross-clamping during cardioplegic arrest has been suggested to be a factor predisposing to atrial fibrillation after CABG surgery.[32,33] Perhaps our findings of a prolonged SACT at the conclusion of surgery represents evidence of atrial ischemic or other injury to specialized atrial conduction tissue during surgery and serves as a marker for the actual pathophysiologic process predisposing to atrial fibrillation.

Sinus nodal function testing was performed only at one time point after surgery, but we did not determine if sinus nodal dysfunction was present several days after surgery, when most episodes of atrial fibrillation develop.[1–3] Further investigations of whether sinus node dysfunction is present before the onset of atrial fibrillation could support therapeutic interventions using cardiac pacing. In this regard, studies of patients with sick sinus syndrome suggest that atrial pacing lowers the incidence of atrial fibrillation and thromboembolism.[34–36] Pacing both atria (dual-site pacing) has been shown to have added benefit in reducing the frequency of atrial fibrillation and flutter in similar populations.[37,38] It is hypothesized that by simultaneously pacing each atrium, intra-atrial conduction delay is reduced, thereby overcoming a component of the electrophysiologic substrate of the arrhythmia.[37–39]

Identifying individuals at risk for postoperative atrial fibrillation would allow for appropriate targeting of therapy to patients likely to benefit the most from treatment while avoiding exposing lower-risk patients to proarrhythmic effects and other side-effects of pharmacologic treatment. With the exception of age, risk stratification based on demographic or operative variables has often resulted in inconsistent findings among studies regarding which clinical variables are independent predictors of postoperative atrial fibrillation.[1–3] Prolonged atrial conduction as assessed by measuring P-wave duration from the scalar or signal-averaged ECG has been proposed as a method of prospectively identifying individuals at risk for atrial arrhythmias.[24–28] Signal-averaging methods allow for the detection of even low-amplitude electrical activity to precisely measure P-wave duration. This latter method has been shown to identify risk for postoperative atrial fibrillation with positive predictive values of 37–65% and negative predictive values of 82–87%.[26,28] This predictive accuracy is similar to what we found to be associated with a prolonged SACT immediately after surgery (positive predictive value, 56%; negative predictive value, 85%). Insofar as many patients have temporary atrial pacing electrodes placed after CABG surgery, our methodology is easier than the more complex methods involving special ECG acquisition systems and computer software needed to measure the signal-averaged ECG.

Cardiac surgery results in multiple perturbations of the autonomic nervous system that may be related to the development of postoperative atrial fibrillation.[4–8,40,41] Functional uncoupling of atrial β-adrenergic receptor

signal transduction pathways occurs in patients after CABG and valvular surgery, and perhaps these alterations account for the previously observed impairment of autonomic heart rate control after surgery.[42–44] Similar β-adrenergic receptor changes measured from peripheral lymphocytes after noncardiac surgery were found to be correlated with reduced heart rate variability postoperatively.[45] Nonetheless, altered β-adrenergic receptor function perioperatively would not explain abnormalities in heart rate variability that persist for up to 2 months after CABG surgery.[7,8] The results of the current study showing that sinus nodal function was unaffected by CABG surgery in patients without atrial arrhythmias suggests that alterations in β-adrenergic receptors does not lead to functional impairment of atrial rate responsiveness in most patients undergoing surgical coronary artery revascularization. Additionally, these data support the hypothesis that sites proximal to the sinus node are responsible for the reduction in heart rate variability observed in even uncomplicated patients postoperatively.[6–8] Cold cardioplegic arrest and aortic cross-clamping results in reduced sympathetic nerve conduction experimentally, and similar injury after CABG surgery may contribute to reduced heart rate variability postoperatively.[41]

Limitations

Our data suggest that, compared with patients remaining in sinus rhythm, conduction out of the sinus node, but not sinus nodal impulse generation, is impaired after CABG surgery in patients developing atrial fibrillation postoperatively. We can not totally exclude the possibility that abnormalities of CSNRT could be found in the latter patients in studies that include a larger sample size. The sinus nodal tests used in this study have been shown to have relatively low sensitivity but high specificity in identifying sinus nodal dysfunction in symptomatic patients with sick sinus syndrome.[15] Consequently, the possibility that sinus nodal dysfunction might have gone undetected in some patients can not be totally excluded. This study did not include patients with reduced left ventricular function, diabetes, and other conditions, and whether our findings apply to other higher-risk patients can not be ascertained from this data. Additionally, the small sample size of this study precludes evaluating the predictive accuracy of sinus nodal function testing in comparison with other patient variables previously recognized to identify risk for postoperative atrial fibrillation, especially patient age.[1–3]

Our results show that sinus nodal function is not adversely affected by CABG surgery in patients remaining in sinus rhythm postoperatively. Compared with patients remaining in sinus rhythm, however, patients developing postoperative atrial fibrillation had evidence of sinus nodal dysfunction immediately after surgery. Our findings are consistent with prior investigations that suggest that injury to atrial conduction tissue at the time of surgery predisposes to the later development of postoperative atrial fibrillation. Assessment of SACT after surgery could potentially provide a means of identifying patients at high risk for atrial arrhythmias.

References

1. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL: Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 1993; 56:539–49

2. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, Browner WS, for the Multicenter Study of Perioperative Ischemia Research Group: Atrial fibrillation following coronary artery bypass graft surgery. JAMA 1996; 276:300–6

3. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, Collins JJ Jr, Cohn LH, Burstin HR: Predictors of atrial fibrillation after coronary artery surgery: Current trends and impact on hospital resources. Circulation 1996; 94:390–7

4. Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G, Tonkin AM: Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. Ann Thorac Surg 1995; 60:1709–15

5. Andrews TC, Reimold SC, Berlin JA, Antman EM: Prevention of supraventricular arrhythmias after coronary artery bypass surgery. Circulation 1991; 84(suppl 3):III-236–44

6. Hogue CW, Stein PK, Apostolidou I, Lappas DG, Kleiger RE: Alterations in temporal patterns of heart rate variability after coronary bypass surgery. ANESTHESIOLOGY 1994; 81:1356–64

7. Niemelä MJ, Airaksinen KE, Tahvanainen KU, Linnaluoto MK, Takkunen JT: Effect of coronary artery bypass grafting on cardiac parasympathetic nervous function. Eur Heart J 1992; 13:932–5

8. Kuo CD, Chen GY, Lai ST, Wang YY, Shih CC, Want JH: Sequential changes in heart rate variability after coronary artery bypass grafting. Am J Cardiol 1999; 83:776–9

9. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ: Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. Science 1981; 213:220–2

10. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H: Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985; 248:H151–3

11. Hogue CW Jr, Domitrovich PP, Stein PK, Despotis GD, Re L, Schuessler RB, Kleiger RE, Rottman JN: RR interval dynamics before atrial fibrillation in patients after coronary artery bypass graft surgery. Circulation 1998; 98:429–34

12. Berger RD, Saul JP, Cohen RJ: Transfer function analysis of autonomic regulation. I. The canine atrial rate response. Am J Physiol 1989; 256:H142–52

13. Sosnowski M, Petelenz T: Heart rate variability: Is it influenced by disturbed sinoatrial node function? J Electrocardiog 1995;28:245–51

14. Bigger JT Jr, Reiffel JA: Sick sinus syndrome. Annu Rev Med 1979; 30:91–118

15. Crossen KJ, Cain ME: Assessment and management of sinus node dysfunction, Modern Concepts of Cardiovascular Disease. Dallas, American Heart Association, 1986, pp 43–8

16. Pagè PL: Sinus node during atrial fibrillation: To beat or not to beat? Circulation 1992;86:334–6

17. Bosnjak ZJ, Kampine JP: Effects of halothane, enflurane and isoflurane on the SA node. ANESTHESIOLOGY 1983; 58:314–21

18. Narula OS, Shantha N, Vasquez M, Towne WD, Linhart JW: A new method for measurement of sinoatrial conduction time. Circulation 1978; 58:706–14

19. Ward DE, Camm AJ: Clinical Electrophysiology of the Heart. Baltimore, Edward Arnold, 1987, pp 63–93

20. Josephson ME, Seides SF: Clinical Cardiac Electrophysiology: Techniques and Interpretations. Philadelphia, Lea & Febiger, 1979, pp 51–78

21. Boineau JP, Schuessler RB, Mooney CR, Wylds AC, Miller CB, Hudson RD, Borremans JM, Brockus CW: Multicentric origin of the atrial depolarization wave: The pacemaker complex. Circulation 1978; 58:1036–48

22. Boineau JP, Schuessler RB, Hackel DB, Miller CB, Brockus CW, Wylds AC: Widespread distribution and rate differentiation of the atrial pacemaker complex. Am J Physiol 1980; 239:H406–15

23. Boineau JP, Canavan TE, Schuessler RB, Cain ME, Corr PB, Cox JL: Demonstration of a widely distributed atrial pacemaker complex in the human heart. Circulation 1988; 77:1221–37

24. Buxton AE, Josephson ME: The role of P-wave duration as a predictor of postoperative atrial arrhythmia. Chest 1981; 80:68–73

25. Weber UK, Osswald S, Huber M, Buser P, Skarvan K, Stulz P, Schmidhauser C, Pfistere M: Selective versus non-selective antiarrhythmic approach for prevention of atrial fibrillation after coronary surgery: Is there a need for pre-operative risk stratification? Eur Heart J 1998;19:794–800

26. Steinberg JS, Zelenkofske S, Wong S-C, Gelernt M, Sciacca R, Menchavez E: Value of the P-wave signal-averaged ECG for predicting atrial fibrillation after cardiac surgery. Circulation 1993; 88:2618–22

27. Klein M, Evans SJL, Blumberg S, Cataldo L, Bodenheimer MM: Use of P-wave-triggered, P-wave signal-averaged electrocardiogram to predict atrial fibrillation after coronary artery bypass surgery. Am Heart J 1995; 129:895–901

28. Stafford PJ, Kolvekar S, Cooper J, Fothergill J, Schlindwein F, deBono DP, Spyt TJ, Garratt CJ: Signal average P-wave compared with standard electrocardiography or echocardiography for prediction of atrial fibrillation after coronary after coronary bypass grafting. Heart 1997; 77:417–22

29. Moe GK: On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn Ther 1980; 95:140.:183–8

30. Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, Smith PK, Corr PB, Boineau JP: The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. J Thorac Cardiovasc Surg 1991; 101:406–26

31. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA: High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994; 89:1665–80

32. Smith PK, Buhrman WC, Levett JM, Ferguson TB Jr, Holman WL, Cox JL: Supraventricular conduction abnormalities following cardiac operations: A complication of inadequate atrial preservation. J Thorac Cardiovasc Surg 1983; 85:105–15

33. Mullen JC, Khan N, Weisel RD, Christakis GT, Teoh KH, Madonik MM, Mickle DA, Ivanov J: Atrial activity during cardioplegia and postoperative arrhythmias. J Thorac Cardiovasc Surg 1987; 94: 558–65

34. Sasaki Y, Shimotori M, Akahane K, Yonekura H, Hirono K, Endoh R, Koike S, Kawa S, Furuta S, Homma T: Long-term follow-up of patients with sick sinus syndrome: A comparison of clinical aspects among unpaced, ventricular inhibited paced, and physiologically paced groups. Pacing Clin Electrophysiol 1988; 11:1575–83

35. Alt E, Völker R, Wirtzfeld A, Ulm K: Survival and follow-up after pacemaker implantation: A comparison of patients with sick sinus syndrome, complete heart block, and atrial fibrillation. Pacing Clin Electrophysiol 1985; 8:849–55

36. Santini M, Alexidou G, Ansalone G, Cacciatore G, Cini R, Turitto G: Relation of prognosis in sick sinus syndrome to age, conduction defects and modes of permanent cardiac pacing. Am J Cardiol 1990; 65:729–35

37. Saksena S, Prakash A, Hill M, Krol RB, Munsif AN, Mathew PP, Mehra R: Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. J Am Coll Cardiol 1996; 28:687–94

38. Prakash A, Saksena S, Hill M, Krol RB, Munsif AN, Giorgberidze I, Mathew P, Mehra R: Acute effects of dual-site right atrial pacing in patients with spontaneous and inducible atrial flutter and fibrillation. J Am Coll Cardiol 1997; 29:1007–14

39. Yu WC, Chen SA, Tai CT, Feng AN, Chang MS: Effects of different atrial pacing modes on atrial electrophysiology: Implications for the mechanism of biatrial pacing in prevention of atrial fibrillation. Circulation 1997; 96:2992–6

40. Marin-Neto JA, Carneiro JJ, Maciel BC, Secches AL, Gallo L, Terra-Filho J, Manco JC, Lima-Filho EC, Vincente WVA, Sader AA, Amorim DS: Impairment of baroreflex control of the sinoatrial node after cardiac operations with extracorporeal circulation in man. J Thorac Cardiovasc Surg 1983; 86:718–26

41. Murphy DA, Armour JA: Influences of cardiopulmonary bypass temperature, cardioplegia, and topical hypothermia on cardiac innervation. J Thorac Cardiovasc Surg 1992; 103:1192–9

42. Booth JV, Landolfo KP, Chesnut LC, Bennett-Guerrero E, Gerhardt MA, Atwell DM, El-Moalem HE, Smith MS, Funk BL, Kuhn CM, Kwatra MM, Schwinn DA for the Duke Heart Center Perioperative Desensitization Group: Acute depression of myocardial β-adrenergic receptor signaling during cardiopulmonary bypass. ANESTHESIOLOGY 1998; 89:602–11

43. Gerhardt MA, Booth JV, Chesnut LC, Funk BL, El-Moalem HE, Kwatra MM, Schwinn DA, the Duke Heart Center Perioperative Desensitization Group: Acute myocardial β-adrenergic receptor dysfunction after cardiopulmonary bypass in patients with cardiac valve disease. Circulation 1998; 98:II-275–81

44. Schranz D, Droege A, Broede A, Brodermann G, Schafer E, Oelert H, Brodde OE: Uncoupling of human cardiac beta-adrenoceptors during cardiopulmonary bypass with cardioplegic cardiac arrest. Circulation 1993; 87:422–6

45. Amar D, Fleisher M, Pantuck CB, Shamoon H, Zhang H, Roistacher N, Leung DHY, Ginsburg I, Smiley RM: Persistent alterations of the autonomic nervous system after non-cardiac surgery. ANESTHESIOLOGY 1998; 89:30–42