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Quantitative Electrocardiography for Predicting Postoperative Atrial Fibrillation after Cardiac Surgery

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Abstract

Background—Atrial fibrillation (AF) after cardiac surgery is a common marker of poor outcomes. Quantitative electrocardiographic (ECG) measurements may be valuable predictors of postoperative AF.

Methods—We evaluated clinical and ECG predictors of postoperative AF in 13,356 patients who underwent cardiac surgery in sinus rhythm.

Results—4,724 patients (35%) developed postoperative AF. P-wave amplitude in lead aVR and V1 were the strongest ECG predictors. A less negative P-wave amplitude in lead aVR was associated with increased risk for postoperative AF (OR 1.46, CI 1.32–1.61), as was a more positive or a more negative P-wave amplitude in lead V1 (OR 1.25, CI 1.16–1.36) after adjusting for clinical and procedural predictors of postoperative AF. Reclassification analysis showed a 7% discrimination improvement (p<0.0001).

Conclusions—P-wave amplitude in lead aVR and lead V1 are powerful predictors of postoperative AF and in combination with other clinical predictors can guide application of prophylactic interventions.

INTRODUCTION

Atrial fibrillation (AF) is the most common atrial arrhythmia after cardiac surgery occurring in about 35% of patients(1,2), who on average have worse outcomes compared to those who

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remain in sinus rhythm(3). Atrial conduction delay on preoperative electrocardiogram has been shown to be associated with postoperative AF(4,5). The objective of our study was (1) to conduct a comprehensive evaluation of quantitative measurements of P-wave duration and amplitude, PR interval, QRS duration, indices of left ventricular (LV) hypertrophy, and semi-quantitative ECG diagnosis of atrial enlargement in combination with clinical and procedural characteristics, to determine whether they could predict postoperative AF, so that high-risk patients, who benefit most from prophylaxis(6), can be identified preoperatively. Secondary objectives of this study were (2) to quantify the additional discriminative value of quantitative ECG measurements when combined with standard predictors of postoperative AF and (3) to explore clinical and structural cardiac correlates of these ECG predictors.

MATERIALS AND METHODS

Patients

From 1/1997 to 12/2002, 14,198 patients who were in sinus rhythm preoperatively underwent isolated coronary artery bypass grafting (CABG), isolated heart valve surgery, or both at Cleveland Clinic. We excluded patients with implanted pacemakers because of alterations of their electrocardiogram (ECG) tracings, leaving a study cohort of 13,356 patients. The study cohort was aged 30–93 years and mostly male (71%). More than half of patients underwent isolated CABG (58%), while 23% had isolated valve surgery, most commonly mitral valve repair followed by aortic valve replacement (Table 1).

ECG, Clinical, and Procedural Data

Quantitative ECG measurements were obtained from raw signal data of the last ECG before cardiac surgery with Magellan® 12 SL software (General Electric, Milwaukee, WI): P (and P') wave amplitude, P (and P') wave duration, P wave area in all 12 leads, PR interval, P-wave axis and QRS duration. P-wave amplitude and duration was measured from the first P-wave deflection (negative or positive). In a biphasic P wave, P' measurements described the second (terminal) deflection. The majority of patients had a biphasic P wave in lead V1 (84%) and therefore also had a P'. Rather than using the sum of P and P' amplitude, we considered P and P' wave as individual variables in patients with biphasic P waves. Indices for LV hypertrophy by Cornell and Sokolow-Lyon and P wave dispersion were calculated according to previously described criteria(7–9). To assess reproducibility of automated ECG variables we manually measured PR interval, QRS duration, P-wave amplitude in lead aVR and V1 in 100 random ECGs (Electronic Appendix A). Clinical and procedure-related patient data were retrieved from the Cleveland Clinic's Cardiovascular Information Registry, a prospective cardiac surgery database. LV ejection fraction, left atrial diameter, and left atrial volume were obtained from the Cleveland Clinic's Echocardiography Database. A total of 240 variables were analyzed, including demographic, clinical, coronary angiographic, quantitative electrocardiographic, echocardiographic, and procedural characteristics (Electronic Appendix B). The Institutional Review Board (IRB) approved use of all these data for research with requirement for written consent waived.

Endpoint

The primary endpoint was development of AF or atrial flutter after cardiac surgery and before hospital discharge requiring therapy (medical or electrical cardioversion or rate-controlling drugs) detected by continuous telemetry throughout the postoperative stay. This definition is consistent with that of the Society of Thoracic Surgeons national cardiac database, with the exception of allowing patients with a history of but free from atrial fibrillation at time of surgery into the study. (http://www.ctsnet.org/file/rptDataSpecifications252_1_ForVendorsPGS.pdf, page 125).

Data Analysis

Variable Selection—To create stable and reproducible parsimonious prediction models for development of postoperative AF, automated bootstrap aggregation (bagging) with cluster analysis of highly correlated variables(10) selected from 74 quantitative ECG and 86 clinical variables (see Electronic Appendix B for variable list and Appendix C for detailed description).

Missing data was handled by 5-fold multiple imputation(11).

Model Comparison—The additional predictive value of quantitative ECG variables was compared to prediction models (1) with clinical predictors only, (2) clinical predictors and semi-quantitative ECG diagnosis of atrial enlargement, and (3) clinical predictors and quantitative ECG measurements in two ways: First, integrated discrimination improvement of reclassification analysis (IDI) and relative IDI(12). Second, change of C-statistic, a measure of improved fit of the model to the data (see Electronic Appendix C for detailed description of analytical technique).

Evaluation of Clinical Correlates of P-wave amplitude in Lead aVR—We evaluated echocardiographic and clinical variables associated with P-wave amplitude in lead aVR by linear regression with stepwise variable selection.

Presentation—Continuous variables are summarized by means and standard deviations or median and 25th and 75th percentile, if skewed and compared with two-tailed Student's t-test or Mann Whitney U-test, respectively. Categorical variables are summarized by frequencies and percentages and compared with χ^2 statistics.

RESULTS

Occurrence of Postoperative AF

Of the 13,356 patients, 4,724 (35%) developed postoperative AF before discharge. Occurrence was highest on postoperative day 2 and in mitral valve replacement and combined procedures (e.g. CABG plus aortic valve replacement, mitral and aortic valve replacement). Many characteristics of patients who developed AF postoperatively differed from characteristics of patients who did not (Table 1).

Prediction of Postoperative AF

Fourteen predictors of postoperative AF were identified: P-wave amplitude in lead aVR and P-wave amplitude in lead V1, and 12 clinical predictors (Table 2 and 3). The model had a C-statistic of 0.74, showed goodness-of-fit (Hosmer-Lemeshow: $p=0.5$) and was well calibrated.

ECG Predictors of Postoperative AF—Preoperative P-wave amplitude was reliably associated with occurrence of postoperative AF. The variables best representing this were P-wave amplitudes in lead aVR and V1 (Table 2).

Less negative P-wave amplitude in lead aVR was associated with greater risk of postoperative AF. Larger positive P-wave amplitude in lead V1 was associated with greater risk of postoperative AF, as was more negative initial deflection of P-wave amplitude in lead V1 (Figure 1). The majority of patients had biphasic P waves in lead V1, however in those cases P' did not add to the prediction of postoperative AF. Figure 2 shows patients stratified according to 50- μ V increments of P-wave amplitude in lead aVR and their associated multivariable-adjusted odds ratios of developing postoperative AF. There was a “dose-

effect” relationship, with more negative P-wave amplitude being protective and less negative P-wave amplitude predisposing patients to postoperative AF.

Clinical Predictors of Postoperative AF—Clinical risk factors for postoperative AF were older age, higher body mass index, history of atrial arrhythmia (although patients were in sinus rhythm at time of surgery), larger left atrial volume, preoperative beta blocker use, and higher preoperative hematocrit. Risk was lower in African-American patients and those with hypothyroidism. Patients who underwent valve surgery had a higher occurrence of postoperative AF, as did those with more perioperative red blood cell transfusions (Table 2).

Nomogram—A representative graph nomogram of the relationship of preoperative predictors to development of postoperative AF is shown in Figure 3. For a 70 year-old (78 points) Caucasian patient (18 points) without prior AF (0 points) or hypothyroidism (5 points), left atrial volume of 30cc (3 points), a preoperative hematocrit of 47% (transformed=1.38, 7 points), BMI of 30kg/m² (3 points), a P-wave amplitude in lead aVR of -100μV (10 points) and a P-wave amplitude in lead V1 of 100μV (5 points) undergoing aortic valve replacement (8 points). The patient’s score is 137, which translates into an estimated probability of postoperative AF of 45%.

Comparison of prediction models

When we compared the prediction model derived from (1) standard clinical variables alone, with (2) standard variables plus semi-quantitative ECG diagnosis of left, right or bi-atrial enlargement or (3) standard variables plus quantitative ECG predictors, we found an increase of integrated discrimination improvement (IDI) by 7% only with addition of quantitative ECG predictors, not with semi-quantitative ECG diagnosis of atrial enlargement to standard clinical predictors (IDI= 0.0103, P<0.0001, Table 3).

Correlates of P-wave amplitude in aVR

Changes of P-wave amplitude in lead aVR in presence of structural cardiac abnormalities or other clinical patient comorbidities have not been well defined. The strongest predictors of less negative P-wave amplitude in lead aVR were older age, white race, male gender, larger left atrial volume and prior cardiac surgery, while P-wave amplitude in lead V1 was only weakly correlated (Electronic Figure 1). The linear regression model only accounted for 10% of the variance of P-wave amplitude in lead aVR in this patient cohort and therefore did not explain clinical characteristics underlying P-wave amplitude in lead aVR well.

DISCUSSION

Principal Findings

Quantitative measurements of P-wave amplitude obtained from preoperative 12-lead ECG are powerful risk predictors of AF after cardiac surgery (Table 2). We present a prediction rule of postoperative AF from a comprehensive evaluation of clinical and electrocardiographic patient characteristics using bagging techniques for stable and accurate prediction. Automated measurements of P-wave amplitude were independent predictors of postoperative AF, but P-wave duration, P-wave dispersion, PR interval, QRS duration, ECG indices of LV hypertrophy and semi-quantitative ECG diagnosis of atrial enlargement were not. The predictive value of P-wave amplitude in lead aVR can partially be explained by its correlation to older age, white race and left atrial enlargement and deserves further studies. Accurate prediction of postoperative AF is important because it can identify subgroups of patients most likely to benefit from prophylactic interventions, which currently are not used routinely despite their proven efficacy(13–15).

ECG Predictors of Postoperative AF

Of 74 measured ECG variables, P-wave amplitude in lead aVR and V1 were the most reliable predictors of postoperative AF. The bimodal distribution of occurrence of postoperative AF with changes in P-wave amplitude in lead V1 are consistent with current knowledge of more positive P-wave deflection suggesting right atrial enlargement and more negative P-wave deflection suggesting left atrial enlargement. Although it is difficult to grasp why larger positive P-wave amplitude is associated with postoperative AF, elevated pulmonary pressure (as seen with left systolic or diastolic ventricular failure, COPD, sleep apnea or valve disease) should be considered. Interestingly, although the majority of patients had a biphasic P wave in lead V1, P' amplitude was not independently predictive of postoperative AF. Lead -aVR corresponds to 30 degrees in the frontal plane, which is close to the mean P-wave axis (Table 1) and may provide an explanation for the predictive power of P-wave amplitude in lead aVR in our study. However, we are not aware of data describing the structural substrate of P-wave amplitude changes in lead aVR. This gap of knowledge triggered our exploratory analysis of echocardiographic and clinical variables, which are most predictive of P-wave amplitude in lead aVR. Age, prior cardiac surgery and alterations of left atrial size were associated with changes in atrial signal on ECG. Gender and race as determinants of P-wave amplitude may be related to body impedance or genetic factors. Interestingly, body mass index or chronic obstructive pulmonary disease, both known to affect body impedance, was not independently associated with P-wave amplitude in aVR. The relationship of left ventricular ejection fraction to P-wave amplitude was non-linear: An ejection fraction beyond 50% (higher or lower) was associated with more negative P-wave amplitude in aVR. This indicates that left ventricular function as well as volume status (hyperdynamic ventricular function) may impact atrial depolarization on ECG. P-wave amplitude in V1 was not correlated with P-wave amplitude in aVR (E-Figure 2).

Semi-quantitative diagnoses of left, right or bi-atrial enlargement, available from standard 12-lead ECG did not improve prediction of postoperative AF, while quantitative assessment of the P wave did.

Clinical Predictors of Postoperative AF

Consistent with prior studies(2), older age and prior episodes of AF were associated with increased risk of postoperative AF. Patients with paroxysmal and chronic AF have elevated hematocrit levels(16,17), which may explain the independent predictive power of preoperative levels in our study. Chronic lung disease or obstructive sleep apnea causing intermittent hypoxemia with erythropoietin-mediated erythrocytosis may also explain our observation. We confirmed the previously reported association of body mass index with postoperative AF(18). Perioperative transfusions of red blood cells have been described to be associated with postoperative AF(19), possibly via an inflammatory response to blood products(20). We hypothesize that the protective role of hypothyroidism in our study is linked to lower endogenous thyroxine hormone levels in this group of patients, although we did not measure thyroid-stimulating hormone levels as an indicator of thyroid function. Interestingly, it has been reported that exogenous thyroxine supplementation in the perioperative period decreases the occurrence of postoperative AF(21), which is an alternative explanation for its decreased occurrence in patients with hypothyroidism. African-Americans patients had markedly lower occurrence of postoperative AF. Alonso and colleagues reported in a recent study that patients of African-American descent have a 41% lower age- and gender- adjusted cumulative risk of developing AF in the non-surgical setting, despite a higher prevalence of hypertension(22). Although it has been argued that this difference observed in the outpatient setting is attributed to detection bias secondary to poor healthcare access for some African-American patients(23), the diagnosis of

postoperative AF should not be affected by such bias. Therefore, a genetic basis for observed low occurrence of postoperative AF seems plausible.

Finally, heart valve surgery was a strong predictor of postoperative AF in our study, likely due to pressure or volume overload of left atria from valve disease with associated remodeling of ion channels(24), preoperative stretch and fibrosis(25), and inflammation caused by direct manipulation during surgery. Off-pump CABG as a protective factor did not reach statistical significance after multivariable adjustment.

Clinical Implications

Current guidelines(15) recommend using perioperative beta blockers (class I), amiodarone (class IIA), and sotalol (class IIB) to prevent postoperative AF. Many clinicians have valid concerns about potential adverse events from these medications given perioperatively to prevent postoperative AF, although they appeared safe in randomized trials(13). The impact on healthcare resources may not outweigh physicians' and patients' safety concerns, hence preventing routine application of effective medical prophylaxis. Quantitative measurements of the P-wave are strong predictors of postoperative AF that can be easily obtained from preoperative ECG with commercially available software. Our proposed prediction model was created with statistical techniques that increase model stability and generalizability and thus could change current practice by increasing the use of prophylactic medications, with a better risk to-benefit ratio in high-risk patients. Because previous clinical trials have shown a residual risk of postoperative AF of about 20% in treated patients(6,13), medical prophylaxis in patients with an estimated risk less than 20% may not be useful. Therefore, our risk assessment tool (Figure 4) can help clinicians and patients make informed decisions about prophylactic medication use.

Limitations

We used bootstrap aggregation to stabilize our prediction model and increase generalizability of our results. However, all data were obtained from a single tertiary referral center. Therefore, our prediction model should be tested in other patient populations. According to STS definitions, postoperative AF and atrial flutter were recorded as one outcome variable. However, we evaluated patients undergoing CABG and/or valve surgery between 2005 through 2009 when we differentiated between postoperative AF and atrial flutter. Out of 10,265 patients 1789 patients developed postoperative AF, while only 97 developed postoperative atrial flutter, equaling 5% of atrial arrhythmic events. We were not able to adjust for postoperative medication use. To obtain quantitative ECG measurements, commercially available software is required, and although compatible with the most commonly used electronic ECG storage system (MUSE, General Electric, Milwaukee, WI), some ECG systems do not provide comparable detailed ECG measurements. The effect of noise has to be considered in automated ECG measurements, but is unlikely to introduce informative bias. Comparison of manual and automated ECG measurements correlated well. While automated measurements give more detailed information, it is unknown which of the two is more accurate, because a golden standard for such measurements has not been established (Appendix A).

Conclusions

P-wave amplitudes in lead aVR and V1 are novel, powerful predictors of postoperative AF, which in combination with clinical characteristics can identify patients at high risk for developing such adverse event. Our risk score can guide the application of prophylactic medications, because high-risk patients may receive more net benefit from such therapies. Adequate preoperative risk assessment with application of prophylactic interventions in

high-risk patients should improve surgical outcomes and reduce burden on healthcare resources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Adjusted probability of postoperative atrial fibrillation (AF) according to P-wave amplitude in leads aVR and V1. Less negative P-wave amplitude in lead aVR and more negative or more positive P-wave amplitude in lead V1 (bimodal distribution) was linked to greater risk of postoperative AF. Positive and negative P-wave amplitude in V1 are mutually exclusive on an individual patient level. Dashed lines represent 95% confidence intervals.

Figure 2.
P-wave amplitude in lead aVR: Strata with patient number and their associated risk of postoperative AF. OR indicates odds ratio.

Figure 3. Nomogram for risk of developing postoperative atrial fibrillation (AF) with *preoperative variables* only: Find for each patient variable the associated score in the first line and add them to get “Total Points.” Total point score can then be extrapolated to determine the probability of developing postoperative AF after cardiac surgery (e.g., 0.5 indicates a 50% risk)

Table 1

Clinical, Procedural and Quantitative Electrocardiographic Patient Characteristics

Variable	All patients (n=13,356)	No Postoperative AF (n=8,632)	Postoperative AF (n=4,724)	P value
	No. (%) or Mean $\pm$ SD	No. (%) or Mean $\pm$ SD	No. (%) or Mean $\pm$ SD	(AF vs. No AF)
<i>Clinical and Procedural Characteristics</i>				
Age (years)	64 $\pm$ 12	61 $\pm$ 12	68 $\pm$ 10	<.0001
Female	3,843 (29)	2,452 (28)	1,391 (29)	.18
Race				
Caucasian	11,427 (86)	7,189 (83)	4,238 (90)	<.0001
African-American	683 (5.1)	529 (6.1)	154 (3.3)	
History of atrial arrhythmia	1,333 (10)	468 (5.4)	865 (18)	<.0001
LV ejection fraction (%)	50 $\pm$ 13	50 $\pm$ 13	50 $\pm$ 13	.3
Left atrial volume (cc)	45 $\pm$ 27	42 $\pm$ 24	50 $\pm$ 30	<.0001
CABG	10,261 (77)	6,715 (78)	3,546 (75)	.0003
Aortic valve replacement	2,588 (19)	1,446 (17)	1,142 (24)	<.0001
Mitral valve replacement	584 (4.4)	245 (2.8)	339 (7.2)	<.0001
Mitral valve repair	2,536 (19)	1,451 (17)	1,085 (23)	<.0001
>2 units RBC transfusion	3072 (23)	1,075 (12)	1,026 (22)	<.0001
<i>Quantitative ECG measurements^a</i>				
P-wave amplitude aVR (μ V)	-87 $\pm$ 34	-91 $\pm$ 32	-80 $\pm$ 33	<.0001
P-wave amplitude V1 (μ V) ^b	34 (19, 53)	34 (19, 53)	39 (19, 58)	<.0001
P-wave area, aVR (mV*ms)	-4.8 $\pm$ 1.9	-5.1 $\pm$ 1.9	-4.6 $\pm$ 2.1	<.0001
PR interval (ms)	170 $\pm$ 40	170 $\pm$ 36	180 $\pm$ 45	<.0001
P-wave axis (degrees)	44 $\pm$ 25	44 $\pm$ 24	44 $\pm$ 28	0.6

^aRepresentative sample; see electronic appendix for full list of evaluated variables^bSkewed data distribution shown as 50th (25th, 75th) percentile.

KEY: AF indicates atrial fibrillation; CABG, coronary artery bypass grafting; ECG, electrocardiographic; LV, left ventricular; RBC, red blood cell; SD, standard deviation.

Table 2

Electrocardiographic and Clinical Multivariable-Adjusted Risk Factors for Postoperative Atrial Fibrillation

Variable	Odds Ratio ^a	95% CI	Reliability (%) ^b
<i>ECG predictors of AF</i>			
Less negative P-wave amplitude in aVR ^c	1.46	1.32–1.61	100
Higher P-wave amplitude in V1 ^c	1.25	1.16–1.36	100
<i>Clinical predictors of AF</i>			
Older age	2.16	1.93–2.41	100
African-American	0.44	0.32–0.60	100
Higher body mass index per kg•m ⁻²	1.06	1.01–1.11	60 ^d
History of atrial arrhythmia	2.70	2.37–3.07	100
Hypothyroidism	0.79	0.69–0.91	75
Larger left atrial volume ^c	1.26	1.20–1.33	100
Preoperative beta blocker use	1.08	1.01–1.18	81
Higher preoperative hematocrit ^c	1.12	1.07–1.18	80 ^d
More RBC transfusions ^c	1.21	1.17–1.25	100
Aortic valve replacement	1.43	1.30–1.59	91
Mitral valve repair	1.81	1.62–2.01	89
Mitral valve replacement	2.28	1.87–2.79	88

^aOdds ratio compares 25th with 75th percentiles of continuous predictors.^bPercent of times variable appeared in 500 bootstrap samples.^cRestricted cubic spline or squared transformation.^dCluster reliability.

KEY: CI indicates confidence interval; RBC, red blood cell.

Table 3

Prediction model comparison

Predictors	C-statistic	IDI	Relative IDI
Prediction model with standard predictors ^a	0.726		
plus semi-quantitative diagnosis of atrial enlargement ^b	0.726	0.0005	0.3%
plus quantitative ECG variables ^c	0.735	0.0103	7.1%

^aModel includes clinical, procedural and echocardiographic patient variables listed in Table 3.

^bDiagnostic codes for right, left and bi-atrial enlargement.

^cP-wave amplitude in lead aVR and V1.

KEY: ECG indicates electrocardiogram; IDI, integrated discrimination improvement.