ORIGINAL ARTICLE

Heart Rate Variability and Procedural Outcome in Catheter Ablation for Atrial Fibrillation

Geoffrey E.J. Seaborn, M.Sc., Keith Todd, M.D., Kevin A. Michael, M.B., C.h.B., Adrian Baranchuk, M.D., Hoshiair Abdollah, M.B., C.h.B., Christopher S. Simpson, M.D., Selim G. Akl, Ph.D., and Damian P. Redfearn, M.D.

From the Division of Cardiology (Arrhythmia Service), Kingston General Hospital, Queen's University, Kingston, Ontario, Canada

Introduction: In patients with normal hearts, increased vagal tone is associated with onset of paroxysmal atrial fibrillation (AF). Vagal denervation of the atria renders AF less inducible. Circumferential pulmonary vein isolation (CPVI) is effective for treating paroxysmal and persistent AF, and has been shown to impact heart rate variability (HRV) indices, in turn, reflecting vagal denervation. We examined the impact of CPVI on HRV indices, and evaluated the relationship between vagal modification and AF recurrence.

Methods: Electrocardiogram recordings were collected from 83 consecutive patients (63 male, 20 female, age 56.9 ± 9.3 years) undergoing CPVI for paroxysmal ($n = 56$) or persistent ($n = 27$) AF. Recordings were obtained over 10 minutes preprocedure, and at intervals up to 12 months. Antiarrhythmic medications were suspended prior to CPVI, and were resumed for 3 months following. Success was defined as no recurrence of atrial arrhythmia lasting longer than 30 seconds.

Results: In patients with successful procedures ($n = 56$, 42 paroxysmal, 14 persistent), HRV indices were significantly altered, with respect to preprocedure levels, over a sustained period. However, patients with recurrence ($n = 27$, 14 paroxysmal, 13 persistent) demonstrated similar HRV to their preprocedure levels over the follow-up period.

Conclusion: Our results suggest that patients experiencing recurrence after a single CPVI have HRV attenuated by the procedure only intermittently, whereas patients with one successful CPVI experience a sustained change. A short-term HRV recording is a convenient and potentially important marker for recurrence of atrial arrhythmia in a population undergoing CPVI.

Ann Noninvasive Electrocardiol 2014;19(1):23–33

catheter ablation; atrial fibrillation; autonomic nervous system; heart rate variability

Nomenclature

AA = Atrial arrhythmia
AF = Atrial fibrillation
AFL = Atrial flutter
AT = Atrial tachycardia
CPVI = Circumferential pulmonary vein isolation
DM = Diabetes mellitus
ECG = Electrocardiogram
GP = Ganglionated plexus
HF = High frequency

HR = Heart rate
HRV = Heart rate variability
Hz = Hertz
ISHNE = International Society for Holter and Noninvasive Electrocardiology
IHD = Ischemic heart disease
LA = Left atrium
LF = Low frequency
LF/HF = Low-frequency/high-frequency ratio
LVEF = Left ventricular ejection fraction
ms = milliseconds

Address for correspondence: Damian P. Redfearn, M.B., Ch.B., M.D., M.R.C.P.I., F.R.C.P.C., Director Arrhythmia Services, Associate Professor, Departments of Medicine, Biomedical and Molecular Sciences, and School of Computing, Queen's University, Kingston General Hospital, FAPC 3, 76 Stuart Street, Kingston, ON K7L 2V7, Canada. Fax: (613) 533-6084; E-mail: redfearn@queensu.ca

Conflicts of Interest: None

pNN50 = Proportion of normal-normal intervals differing from their neighbors by >50 ms

RMSSD = Root mean square successive difference
RF = Radiofrequency

SDNN = Standard deviation of the normal-normal intervals

SR = Sinus rhythm

THEW = Telemetric and Holter ECG warehouse

ULF = Ultra low frequency

VLF = Very low frequency

INTRODUCTION

Circumferential pulmonary vein isolation (CPVI) is an effective strategy for treatment of paroxysmal and persistent atrial fibrillation (AF), yet its antiarrhythmic mechanisms remain controversial.¹ Increased vagal tone is thought to play a pathophysiological role in a subset of patients with AF.²⁻⁴ Numerous investigators have demonstrated that radiofrequency (RF) applications in the proximity of the pulmonary veins often induce vagal reflexes,^{1,5-9} yet there is insufficient evidence regarding the association between autonomic modification, by ablation of vagal nerve ganglia in the proximity of the pulmonary veins, and AF recurrence.^{1,10-17} Therefore, in a series of consecutive patients undergoing CPVI for paroxysmal or persistent AF, we assessed the impact of CPVI on heart rate variability (HRV) indices, in turn, reflecting the impact of this procedure on vagal denervation, and evaluated the relationship between autonomic modification and recurrence of atrial arrhythmia (AA: AF, atrial flutter (AFL), or atrial tachycardia (AT)) over a year follow-up.

METHODS

CPVI has been described previously.^{6-8,18,19} Digoxin and antiarrhythmic agents, including verapamil and diltiazem, were discontinued for a minimum of 5 half-lives prior to CPVI, with the exception of amiodarone due to its long half-life. The NavX electroanatomic system was used with an irrigated tip ablation catheter (Cool Path Duo, St. Jude Medical, MN, USA) with powers of 20-30 W. The endpoint of the procedure was electrical pulmonary vein isolation, by demonstration of

entrance and exit block when pacing within the veins and showing vein capture dissociated from the left atrium (LA), using CPVI with or without segmental lesions. No additional linear lesions were used unless typical atrial flutter (AFL) was observed, in which case a cavotricuspid isthmus ablation was performed. Following CPVI, patients received anticoagulation with warfarin. Patients were discharged with antiarrhythmic therapy, which was continued for a minimum of 3 months. Recurrence was defined as sustained atrial arrhythmia for a period greater than 30 seconds at any time within 1 year postprocedure. If AA occurred within 1 week following ablation, it was classified as early recurrence. Vagal response during ablation was defined as bradycardia (<40 bpm), asystole, or AV block. Patients were instructed to report any symptoms.

HRV analysis was used as an indicator of autonomic activity in accordance with guidelines for standardization.²⁰ Time-domain and frequency-domain indices were calculated from 10-minute high-resolution (1000 Hz) Holter electrocardiogram (ECG) signals obtained during sinus rhythm (SR) prior to CPVI, and at intervals of 1 hour, 24 hours, 6 weeks, 3 months, 6 months, and 12 months postprocedure using MATLAB (2012a, The MathWorks, Natick, MA, USA). In addition, one 10-minute ECG signal was collected from 46 healthy control subjects, although one was excluded due to the presence of excessive signal artifact. All nonsinus beats, such as ectopic events and pauses, were excluded from the analysis by manual inspection, and all R-wave detection errors were corrected. ECG recordings were collected using a SpiderView Holter monitor (ELA Medical Inc., Montrouge, Île-de-France, France). ECG files were imported using the THEW ISHNE software function for MATLAB.²¹ Automated R-wave detection was performed using the Myoelectric Control Development Toolbox for MATLAB.²² Written, informed consent was obtained from every patient in accordance with a protocol approved by the Queen's University Health Sciences Ethics Committee.

Statistical Analysis

All results are expressed as mean $\pm$ standard deviation. The power of each frequency band is reported as its percentage contribution to the total frequency power observed in each individual. The

Table 1. Patient Demographics

	All Patients (n = 83)	Success (n = 56)	Failure (n = 27)	P
Age (Years)	56.9 ± 9.3	57.0 ± 10.2	56.7 ± 7.1	0.5
Gender	63 m, 20 f	41 m, 15 f	22 m, 5 f	0.4
Atrial fibrillation duration (months)	80.4 ± 74.3	74.9 ± 70.1	91.0 ± 74.3	0.2
Left atrium diameter (mm)	40.9 ± 6.4	39.7 ± 6.0	44.0 ± 6.6	0.2
Left atrium volume (mL/m ²)	37.2 ± 11.8	36.6 ± 11.1	38.3 ± 13.4	0.8
Paroxysmal AF (n)	56	42	14	0.04
Persistent AF (n)	27	14	13	0.04
Vagal response (n)	19	14	5	0.5
	All Patients (n = 83)	Success (n = 56)	Failure (n = 27)	P
Ischemic heart disease (n)	13	9	4	0.9
Diabetes mellitus (n)	12	10	2	0.2
LVEF < 30% (n)	5	5	0	0.1
Thyroid dysfunction (n)	2	0	2	0.04
Pericarditis (n)	1	1	0	0.5
Lupus (n)	1	0	1	0.5
Renal failure (n)	3	3	0	0.2
Valvular heart disease (n)	2	2	0	0.3

very-low-frequency (VLF) and ultra-low-frequency (ULF) power-spectral components are absent due to their measurement not being appropriate for the relatively short-term recordings used in our analysis. For comparison, low-frequency (LF) and high-frequency (HF) power-spectral components are normalized to their percentage contribution to the total frequency power in each patient due to the sensitivity of frequency-domain measurements. In order to compare patient groups, results were tested for normality using one-sample Kolmogorov-Smirnov tests, and, depending on the outcome, were then subjected either to unpaired t-tests or Wilcoxon rank-sum tests with a minimum significant probability value of $P < 0.05$. All statistical analysis was performed using MATLAB (2010a, The MathWorks).

RESULTS

Of the 89 consecutive patients with paroxysmal or persistent AF undergoing their first CPVI between March 2007 and September 2010, 83 were included in the present analysis (56 paroxysmal, 27 persistent). The remaining 6 patients were excluded due to errors in ECG collection, excessive signal artifact in the ECG preventing accurate R-wave detection, or permanent pacing. Population characteristics are presented in Table 1. Procedure duration was 276.0 ± 73.4 minutes, and RF ablation time was 50.4 ± 18.0 minutes.

During the procedure, 19 (22.9%) patients exhibited a vagal response. Ablation was continued following vagal response with ventricular pacing via the right ventricular apex. In the week following CPVI, 3 patients experienced early recurrence. During the 12-month follow-up, 27 patients experienced recurrence, 20 of whom required repeat ablation. Groups were comparable in age, gender, AF duration, LA diameter, vagal response, and LA volume, although the proportion of patients with persistent AF was significantly larger in the group experiencing recurrence (48.1% vs 25.0%, $P = 0.04$).

Time Domain

In the group with successful CPVI, the mean RR interval duration was significantly decreased from preprocedure levels at 1 hour and 24 hours ($P < 0.01$), while there was no significant change over the follow-up period in the group with arrhythmia recurrence. At the 1-hour interval, the group with successful CPVI exhibited an SDNN (standard deviation of the normal-normal RR interval durations) significantly lower than the group with AF recurrence (23.88 ± 13.31 vs 36.56 ± 18.81 , $P = 0.02$). By 24 hours, both groups exhibited a marked change compared with preprocedure levels (Table 2). In the 57 (67.5%) patients free from recurrence, time-domain indices, root mean square successive difference (RMSSD), and pNN50 (proportion of intervals differing from their neighbors by more than 50 milliseconds) were

Table 2. Time-Domain Heart Rate Variability Indices

RR Mean (ms)	Pre	1 Hour	24 Hours	6 Weeks	3 Months	6 Months	12 Months
Success	1001.44 ± 165.30	828.19 ± 113.95	830.05 ± 113.03	964.51 ± 150.05	953.25 ± 165.89	943.46 ± 172.23	960.31 ± 169.55
P (vs baseline)	N/A	<0.01	<0.01	0.29	0.17	0.13	0.29
Failure	1056.77 ± 210.55	890.86 ± 169.46	823.12 ± 127.78	1055.10 ± 182.93	920.95 ± 189.66	1077.78 ± 123.18	1211.80 ± 0
P (vs baseline)	N/A	0.13	0.02	1	0.21	0.88	0.75
P (success vs failure)	0.52	0.24	0.62	0.13	0.93	0.11	0.21
Control				904.18 ± 158.84			
SDNN (ms)	Pre	1 Hour	24 Hours	6 Weeks	3 Months	6 Months	12 Months
Success	46.58 ± 24.18	23.88 ± 13.31	22.58 ± 12.63	29.97 ± 21.91	27.44 ± 17.83	28.14 ± 15.44	36.42 ± 16.06
P (vs baseline)	N/A	<0.01	<0.01	<0.01	<0.01	<0.01	0.20
Failure	41.66 ± 11.49	36.56 ± 18.81	23.89 ± 13.10	28.55 ± 19.58	25.92 ± 12.06	41.65 ± 38.83	14.97 ± 0
P (vs baseline)	N/A	0.62	<0.01	0.047	0.02	0.27	0.25
P (success vs failure)	0.91	0.02	0.83	0.64	0.75	0.62	0.21
Control				52.63 ± 23.07			
RMSSD (ms)	Pre	1 Hour	24 Hours	6 Weeks	3 Months	6 Months	12 Months
Success	43.82 ± 27.38	27.74 ± 17.34	27.72 ± 18.52	34.35 ± 35.06	29.51 ± 19.67	27.01 ± 16.18	34.96 ± 30.36
P (vs baseline)	N/A	<0.01	<0.01	0.01	<0.01	<0.01	0.08
Failure	35.82 ± 14.10	37.19 ± 20.16	29.04 ± 20.27	26.61 ± 25.36	23.03 ± 9.50	45.87 ± 54.27	10.08 ± 0
P (vs baseline)	N/A	0.88	0.21	0.03	0.07	0.27	0.25
P (success vs failure)	0.55	0.08	0.92	0.29	0.70	0.77	0.27
Control				46.62 ± 25.57			
pNN50 (%)	Pre	1 Hour	24 Hours	6 Weeks	3 Months	6 Months	12 Months
Success	15.44 ± 14.91	6.99 ± 11.55	5.67 ± 9.14	6.57 ± 10.44	8.70 ± 13.88	5.88 ± 8.61	13.17 ± 20.95
P (vs baseline)	N/A	<0.01	<0.01	<0.01	0.01	<0.01	0.23
Failure	16.32 ± 17.50	14.32 ± 15.41	7.10 ± 8.93	6.92 ± 13.39	4.14 ± 2.96	14.64 ± 23.20	0.21 ± 0
P (vs baseline)	N/A	0.57	0.08	0.03	0.07	0.53	0.25
P (success vs failure)	0.94	0.04	0.41	0.79	0.99	0.70	0.27
Control				18.38 ± 15.14

Figure 1. Time-domain HRV analysis over time. The indices of patients with successful procedures, patients with unsuccessful procedures, and control subjects, are presented in green (circles), red (inverted triangles), and blue (dotted lines), respectively. Results are listed as mean $\pm$ standard deviation.

significantly reduced with respect to preprocedure levels at all follow-up intervals with the exception of 12 months (Table 2, Figure 1). There was also a significant difference between patients with

successful procedures and patients with recurrence at the 1 hour follow-up interval for the pNN50 index (6.99 ± 11.55 vs 14.32 ± 15.41 , $P = 0.04$). In these data, if a reduction of ≥ 10 in SDNN is

Figure 1. continued

exhibited by a patient at the 1 hour follow-up interval with respect to their preprocedure level, there would be a sensitivity of 96%, specificity of 63%, positive predictive value of 89%, and negative predictive value of 83% for freedom from AA recurrence.

Frequency Domain

In the frequency-domain HRV indices, we observed a significant reduction in HF power at all follow-up intervals for patients with successful procedures, consistent with sustained vagal

Figure 2. Frequency-domain HRV analysis over time. The indices of patients with successful procedures, patients with unsuccessful procedures, and control subjects, are presented in green (circles), red (inverted triangles), and blue (dotted lines), respectively. Results are listed as mean $\pm$ standard deviation.

withdrawal (Table 3, Figure 2). In contrast, patients with recurrence showed no change from preprocedure levels. In LF power, we observed a significant reduction up to 6 months in patients with successful procedures, and a significant reduction at the 24 hour and 6 week intervals in patients with re-

currence. In the LF/HF measure, we observed a reduction up to 3 months in patients with successful procedures, and a reduction only at 24 hours in patients with recurrence. There was also a significant difference between patients with successful procedures and patients with recurrence at the 1

Figure 2. continued

hour follow-up interval for the LF index (124.60 ± 216.49 vs 212.46 ± 243.54 , $P = 0.01$) and HF index (171.41 ± 309.24 vs 356.27 ± 414.18 , $P = 0.03$)

DISCUSSION

Our results suggest that significant alteration of autonomic control over heart rate (HR), by CPVI for paroxysmal or persistent AF, is associated with freedom from recurrence of atrial arrhythmia over a year follow-up. Following CPVI, patients free of recurrent AF were characterized by sustained HRV changes consistent with vagal withdrawal. In contrast, particularly in the time-domain indices, patients experiencing AF recurrence exhibited a delayed HRV response at 24 hours that was not sustained over follow-up. The difference in HRV indices 1 hour postprocedure is marked between the two groups. The current results emphasize the role of vagal denervation and autonomic modification in the success of CPVI, these changes often being absent in patients with recurrent AF. Therefore, evidence of extensive ganglionated plexus (GP) ablation, as indicated by change in HRV, appears to be an important factor in successful outcome.²³

Our principal goal was to investigate the long-term effect of catheter ablation on HRV and

correlate with recurrence. We observed significant and marked differences between cohorts. Importantly, patients with a favorable outcome had sustained and significant reductions in the HRV variables from baseline and compared with patients demonstrating recurrence. This is the first study to demonstrate the utility of short-term HRV analysis as a measure of procedural efficacy during follow-up visits. Very recent data suggest the role of GP as sources for focal rotors in AF, would that be the case, abolition of rotors would markedly affect HRV. The temporary changes observed in the recurrence group may merely reflect inflammatory edema postprocedure rather than true ablation. In addition, clinical research on HRV and procedural outcome following CPVI is needed, particularly as the procedure extends toward the heart failure population where reductions in HRV have been associated with worse outcomes.²⁴ Combined approaches to risk stratification, such as P-wave duration and P-wave dispersion, may prove beneficial.^{25,26}

Whether the change in the autonomic nervous system is desirable remains to be determined but either as an intentional or indirect consequence of ablation, reductions in HRV appear to be a factor associated with better outcome and the effect is sustained to a year or more.

Table 3. Frequency-Domain Heart Rate Variability Indices

LF (ms²)	Pre	1 Hour	24 Hours	6 Weeks	3 Months	6 Months	12 Months
Success	706.95 ± 1057.57	124.60 ± 216.49	101.92 ± 257.14	215.29 ± 381.95	175.99 ± 398.85	223.93 ± 390.45	236.72 ± 224.71
P (vs baseline)	N/A	<0.01	<0.01	<0.01	<0.01	<0.01	0.06
Failure	384.82 ± 369.88	212.46 ± 243.54	85.45 ± 132.82	169.55 ± 394.06	100.59 ± 93.73	903.05 ± 1862.30	51.74 ± 0
P (vs baseline)	N/A	0.24	<0.01	0.01	0.05	0.34	0.25
P (success vs failure)	0.62	0.01	0.70	0.29	0.80	0.68	0.34
Control				733.31 ± 710.60			
HF (ms²)	Pre	1 Hour	24 Hours	6 Weeks	3 Months	6 Months	12 Months
Success	760.66 ± 1366.24	171.41 ± 309.24	171.72 ± 324.30	397.12 ± 894.74	269.85 ± 455.62	215.35 ± 327.28	248.50 ± 306.85
P (vs baseline)	N/A	<0.01	<0.01	<0.01	<0.01	<0.01	0.02
Failure	318.97 ± 381.26	356.27 ± 414.18	213.40 ± 300.58	315.63 ± 804.33	132.00 ± 82.06	1159.23 ± 2311.61	27.14 ± 0
P (vs baseline)	N/A	0.81	0.11	0.07	0.29	0.76	0.25
P (success vs failure)	0.43	0.03	0.75	0.46	0.99	0.57	0.34
Control				740.92 ± 875.23			
LF/HF	Pre	1 Hour	24 Hours	6 Weeks	3 Months	6 Months	12 Months
Success	1.26 ± 1.05	0.89 ± 1.05	0.56 ± 0.58	0.85 ± 1.06	0.63 ± 0.54	1.11 ± 1.27	1.80 ± 1.38
P (vs baseline)	N/A	0.02	<0.01	<0.01	<0.01	0.13	0.14
Failure	1.66 ± 1.70	1.16 ± 1.24	0.58 ± 0.64	0.77 ± 0.99	0.93 ± 0.72	0.55 ± 0.38	1.91 ± 0
P (vs baseline)	N/A	0.24	0.01	0.06	0.38	0.07	0.5
P (success vs failure)	0.57	0.40	0.84	0.66	0.27	0.40	0.87
Control				1.88 ± 3.07			

Limitations

When performing HRV analysis, it is ideal to exclude patients taking medications that influence autonomic control of heart rate. However, this was not feasible in the current analysis due to the importance of beta-blockers in this population. Screening for asymptomatic AF over the year follow-up is a limiting factor for many AF studies.²⁷ We did not employ long-term recordings or implanted devices, and it is therefore likely that episodes of asymptomatic AF were missed.²⁸ However, we believe that patients destined for symptomatic recurrence would have presented during the relatively long 12-month follow-up period.

Considering that patients are removed from the analysis following any recurrence of atrial arrhythmia, the patient group with unsuccessful CPVI becomes smaller over the year follow-up, while the patient group with successful CPVI is stable in size over time. At 12 months, only one patient remained in the group with unsuccessful CPVI. Although it would be ideal to continue to monitor patients with recurrence as planned, this was not feasible due to these individuals typically receiving a repeat procedure or other therapeutic intervention. Additionally, no blanking period was used to allow for full disclosure of events within the 3 months following ablation. However, patients that demonstrated symptomatic recurrence within this time were not followed further. This is a potential limitation of the study, but only 3 patients had recurrence within the 3 months following CPVI; thus, the impact on the data is modest.

CONCLUSION

Autonomic modification assessed by a short-term HRV recording is a convenient and potentially important marker associated with recurrence outcome in a population undergoing CPVI. In addition, prospective studies appear warranted to identify the association between HRV and GP ablation and ultimate procedural success.

Acknowledgments: Financial support to the first author from the Queen's University Faculty of Arts and Science is gratefully acknowledged.

REFERENCES

1. Pappone C, Santinelli V, Manguso F, et al. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. *Circulation* 2004;109:327-334.
2. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation* 2002;105:2753-2759.
3. Schauerte P, Sherlag BJ, Pitha J, et al. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. 2000;28:2774-2780.
4. Klöngheben T, Grönefeld G, Yi-Gang L, et al. Heart rate variability to assess changes in cardiac vagal modulation prior to the onset of paroxysmal atrial fibrillation in patients with and without structural heart disease. *Ann Noninvasive Electrocardiol* 2006;4(1):19-26.
5. Hsieh M, Chiou C, Wen Z, et al. Alterations of heart rate variability after radiofrequency catheter ablation of focal atrial fibrillation originating from pulmonary veins. *Circulation* 1999;100:2237-2243.
6. Pappone C, Rosanio S, Oreto G, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. *Circulation* 2000;102:2619-2628.
7. Pappone C, Oreto G, Rosanio S, et al. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: Efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation* 2001;104:2539-2544.
8. Pappone C, Rosanio S, Augello G, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: Outcomes from a controlled nonrandomized long-term study. *J Am College Cardiol* 2003;42(2):185-197.
9. Nakagawa H, Jackman WM, Sherlag BJ, et al. Pulmonary vein isolation during atrial fibrillation: Insight into the mechanism of pulmonary vein firing. *J Cardiovasc Electrophysiol* 2003;14:261-262.
10. Edgerton JR, Edgerton ZJ, Weaver T, et al. Minimally invasive pulmonary vein isolation and partial autonomic denervation for surgical treatment of atrial fibrillation. *Ann Thorac Surg* 2008;86(1):35-38.
11. Scanavacca M, Pisani CF, Hachul D, et al. Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal atrial fibrillation. *Circulation* 2006;114:876-885.
12. Spector P, Reynolds MR, Calkins H, et al. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol* 2009;104(5):671-677.
13. Bauer A, Deisenhofer I, Schneider R, et al. Effects of circumferential or segmental pulmonary vein ablation for paroxysmal atrial fibrillation on cardiac autonomic function. *Heart Rhythm* 2006;3(12):1428-1435.
14. Hsieh MH, Chiou CW, Wen ZC, et al. Alterations of heart rate variability after radiofrequency catheter ablation of focal atrial fibrillation originating from pulmonary veins. *Circulation* 1999;100:2237-2243.
15. Miyazawa S, Yamane T, Date T, et al. Impact of pulmonary vein isolation on the autonomic modulation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses. *Europace* 2009;11:576-581.
16. Pokushalov E, Romanov A, Artyomenko S, et al. Left atrial ablation at the anatomic areas of ganglionated plexi for paroxysmal atrial fibrillation. *PACE* 2010;33:1231-1238.
17. Yoshida N, Yamada T, Murakami Y, et al. Vagal modification can also help prevent late recurrence of atrial fibrillation after segmental pulmonary vein isolation. *Circulation* 2009;73:632-638.

18. Haïssaguerre M, Jaïs P, Shah D, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339(10):659–666.
19. Oral H, Scharf C, Chugh A, et al. Catheter ablation for paroxysmal atrial fibrillation: Segmental pulmonary vein ostial ablation versus left atrial ablation. *Circulation* 2003;108(19):2355–2360.
20. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurements, physiological interpretation, and clinical use. *J Am Heart Assoc* 1996;93:1043–1065.
21. ECG FILE FORMAT AND READING PROCEDURES FROM THE THEW [Internet]. Available from: <http://thew-project.org/THEWFileFormat.html>. Accessed June 27, 2012.
22. Chan ADC, Green GC. Myoelectric control development toolbox. Proceedings of 30th Conference of the Canadian Medical & Biological Engineering Society 2007:M0100.
23. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovas Electro-physiol* 2012;23(5):447–454.
24. Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997;79(12):1645–1650.
25. Platonov PG. P-wave morphology: Underlying mechanisms and clinical implications. *Ann Noninvasive Electrocardiol* 2012;17(3):161–169.
26. Tükek T, Yildiz P, Akkaya V, et al. Factors associated with the development of atrial fibrillation in COPD patients: The role of P-wave dispersion. *Ann Noninvasive Electrocardiol* 2002;7(3):222–227.
27. Arya A, Hindricks G, Piorowski C, et al. Clinical implications of various follow up strategies after catheter ablation of atrial fibrillation. *PACE* 2006;30(4):458–462.
28. Verma A, Champagne J, Sapp J, et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF). *JAMA Intern Med* 2013;173(2):149–156.