ORIGINAL ARTICLE

Celecoxib-Induced Change in Atrial Electrophysiologic Substrate in Arthritis Patients

Katerina Pizzuto, B.H.Sc.,* Henry L Averns, M.B., C.h.B.,*† Adrian Baranchuk, M.D.,*‡ Hoshiar Abdollah, M.B., Ch.B.,*‡ Kevin A. Michael, M.B., Ch.B.,*‡ Christopher Simpson, M.D.,*‡ and Damian P. Redfearn, M.D.*‡

*From the *Queen's University, Kingston, Ontario, Canada; †Department of Rheumatology, Kingston General Hospital, Kingston, Ontario, Canada; and ‡Heart Rhythm Service, Kingston General Hospital, Kingston, Ontario, Canada*

Background: Cyclooxygenase-2 inhibitors, the newest class of nonsteroidal antiinflammatories, pose an increased risk of adverse cardiovascular events, in particular atrial fibrillation (AF). We hypothesized that the COX-2 inhibitor celecoxib alters atrial electrophysiology, and thus promotes the development of AF.

Methods: Three prospective patient cohorts were created: Healthy patients (n = 35), inflammatory arthritis patients with no celecoxib use (n = 22), and inflammatory arthritis patients treated with celecoxib (n = 20). Patients were included in the arthritis cohorts if they were over the age of 18 and had a diagnosis of inflammatory arthritis. Patients in the celecoxib group must be actively treated with celecoxib for more than 2 months. Patients were excluded if they were taking antiarrhythmic mediation, had a diagnosis of AF, refractory hypertension, or congestive heart failure. High-resolution signal-averaged electrocardiogram was recorded and P-wave duration (PWD) was derived.

Results: PWD was significantly longer in inflammatory arthritis patients treated with celecoxib, compared to both healthy and inflammatory arthritis patients (P = 0.049, P = 0.036). There was no difference in the PWD of healthy patients as compared to inflammatory arthritis patients (P = 0.916). Mean PWD (standard error of the mean) of the inflammatory arthritis patients treated with celecoxib was 133.1 (2.7) ms as compared to 125.3 (1.6) ms in the healthy patients and 124.0 (2.9) ms in the inflammatory arthritis patients.

Conclusions: Given that PWD is a well-accepted noninvasive marker of atrial electrophysiology, our results suggest that these patients demonstrate adverse atrial remodeling predisposing to atrial arrhythmia.

Ann Noninvasive Electrocardiol 2013;00(0):1–7

atrial fibrillation; P-wave duration; inflammatory arthritis

Nonsteroidal antiinflammatories (NSAIDs) are a class of medication frequently used in the management of inflammatory conditions.[1] Cyclooxygenase-2 (COX-2) inhibitors are the newest class of NSAIDs, and were developed to offer equivalent efficacy and a safer gastrointestinal side effect profile compared to nonselective NSAIDs.[1] However, there is concern of a possible increase in cardiovascular events, and this risk was made public since the withdrawal of the potent

Address for correspondence: Dr Damian P. Redfearn, M.B., C.hB., M.D., M.R.C.P.I., F.R.C.P.C., Director of Heart Rhythm Service, FAPC 3, Kingston General Hospital, 76 Stuart Street, Kingston, ON, K7L 2V7, Canada. Fax: 613 548 1387; E-mail: redfeard@kgh.kari.net; Katerina Pizzuto, B.H.S.c., Queen's University, 99 University Avenue, Kingston, ON K7L 3N6, Canada. Fax: 613 548 1387; E-mail: kpizzuto@qmed.ca

Funding: This work was supported by the John F. Sparks Memorial Scholarship, which was awarded to K. Pizzuto by the Queen's University Undergraduate Medical Education Office.
Conflict of Interest: The authors declare no conflict of interest.

DOI:10.1111/anec.12097

COX-2 inhibitor rofecoxib in 2004.[2] The Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial reported an increased risk of adverse cardiovascular events including myocardial infarction, stroke, and congestive heart failure.[3,4] Since then, much work has been done to elucidate other adverse cardiovascular events and the mechanism by which they are caused. It currently remains unclear as to whether this potential cardiovascular toxicity is specific to the COX-2 inhibitors or if the risk is shared among all nonselective NSAIDs.[5]

A large Danish-population-based case-control study reported an association between NSAIDS and the development of atrial arrhythmias such as atrial fibrillation (AF) and flutter.[1] Patients at highest risk of AF development were taking a selective COX-2 inhibitor. We sought to investigate the hypothesis that potent COX-2 inhibition alters atrial electrophysiologic substrate compared with nonselective NSAID use and thus provides a substrate for the observed increased incidence of this arrhythmia.

METHODS

The study complies with the Declaration of Helsinki and The Queen's University Health Sciences Research Ethics Board approved the study design and protocol. Prior to any of the study procedures being performed, written informed consent was acquired from each patient. This was a prospective study with 3 cohort groups. The first cohort was a group of historically collected controls who were patients recruited from the Kingston General Hospital (KGH) Emergency Room. Patients were excluded if they were taking celecoxib, had conduction abnormalities on surface electrocardiogram (ECG) or signs or symptom of cardiac disease. The second and third cohorts were collected from the KGH Outpatient Rheumatology clinics and were included if they were over the age of 18 and had a diagnosis of an inflammatory arthritis. Patients included in the third cohort must also be actively treated with celecoxib for more than 2 months duration. Patients were excluded from the study if they were taking antiarrhythmic medication, had a diagnosis of AF, had hypertension that was unresponsive to more than 3 antihypertensive medications, or had a history of congestive heart failure.

Patients' demographics were collected including, age, gender, height, weight, and rheumatologic diagnosis and disease duration. Patients also provided a list of medications including NSAIDs, disease modifying antirheumatic drugs (DMARDs), oral steroids, and biologics.

Signal-Averaged P-Wave Recording and Analysis

Patients' skin was prepared and cleaned prior to the orthogonal positioning of the silver–silver chloride electrodes. Patients were laying supine and a high-resolution signal-averaged ECG was then recorded at 1000 Hz for 10 minutes. Recordings were collected using a digital SpiderView Holter monitor (ELA Medical Inc., Montrouge, Île-de-France, France). The investigator was blinded to the patient identification and cohort prior to P-wave analysis. The ECG signals were then amplified 10,000 times and put through a band-pass filter between 1 and 300 Hz. The lead with the most obvious P wave and the least background noise was then further band-pass–filtered between 20 and 50 Hz. This filtered lead was the trigger channel, which was used to select and align P waves for signal averaging. The most common P-wave morphology with at least 100 beats was analyzed and the P-wave duration (PWD) was derived using automated calipers.

STATISTICAL ANALYSIS

Data were tested for normality using the D'Agostino and Pearson omnibus normality test. Normally, distributed data were compared using a one-way ANOVA and nonnormally distributed data were compared with the Kruskal–Wallis test. Equal variances were assumed and posthoc analysis was carried out using Tukey's range test. Categorical data were compared using the Chi-squared test or the Fisher's exact test, if any category had less than 5 subjects. A 2-tailed P-value of <0.05 will be considered statistically significant.

RESULTS

Sixty-one patients were screened. Of those, 8 patients refused to participate in the study owing to time constraints, 8 patients did not show for their clinic appointment, and 45 patients agreed to

Table 1. Clinical and Demographic Characteristics of Patients Included in the Study

	Healthy Controls	Inflammatory Arthritis Controls	Celecoxib Treated	
Number of patients	35	22	20	
Age(years), mean ± SD	51.6±11.3	50.3±17.6	53.7±17.6	P = 0.764
Sex M/F n (%)	27/8 (77/23)	4/18(18/82)	6/14(30/70)	**P < 0.0001**
Medical History:				
Hypertension	9	9	5	P = 0.408
Previous MI	0	1	0	P = 0.298
Sleep apnea	3	3	1	P = 0.617
Thyroid disease	2	2	5	P = 0.091
Hyperlipidemia	7	2	7	P = 0.120
Diabetes	4	2	1	P = 0.727
Smoker	11	13	9	P = 0.118
Medication Use:				
NSAID use	11	13	20	**P < 0.0001**
Beta blockers	1	3	1	P = 0.261
ACE inhibitors	5	3	3	P = 0.992
Diuretics	2	4	1	P = 0.214

participate. After data collection, 2 patients were removed from the study owing to poor-quality recordings. One patient was excluded due to a history of AF and refractory hypertension. Thus, 22 patients were recruited to the inflammatory arthritis controls and 20 inflammatory arthritis patients taking celecoxib were enrolled.

Demographic data for the patients in the 3 groups are presented in Table 1. There is a statistically significant difference between the gender distributions of the 3 groups, as the healthy controls have a higher proportion of men than women. This is likely attributable to the higher prevalence of inflammatory arthritic conditions, like rheumatoid arthritis, in females. There is also a statistically significant difference in NSAID use between the groups, as all patients in the third cohort were taking celecoxib. NSAID use in the healthy or inflammatory control group included the use of diclofenac, naproxen, ibuprofen, or aspirin, but not celecoxib. There was no combination NSAID use in the celecoxib-treated group. There was no significant difference in the past medical history or cardiovascular medication use between the groups. While there was no statistically significant difference in the proportion of patients with thyroid disease (P = 0.091), it is worthwhile to note that 6% (n = 2) of patients had thyroid disease in the healthy controls and 9% (n = 2) in the inflammatory arthritis controls, as compared to 25% (n = 5) in the celecoxib cohort.

The rheumatologic characteristics of patients in the inflammatory arthritis control group and the celecoxib treated group are presented in Table 2. There is no statistically significant difference in the rheumatologic serology, rheumatologic diagnosis of patients, or disease duration. The classification of "seronegative spondyloarthropathy" includes patients diagnosed with ankylosing spondylitis, psoriatic arthritis, and reactive arthritis. Diagnoses included in the "other inflammatory arthritis" category include juvenile idiopathic arthritis and erosive osteoarthritis.

SAPW Analysis

There was a statistically significant difference between the PWD of the groups (P = 0.025). Posthoc analysis showed that the mean PWD of the healthy control and inflammatory arthritis groups was similar, with a mean PWD (standard error of the mean) of 125.3(1.6) ms and 124.0(2.9) ms, respectively (P = 0.916). Figure 1 shows the marked lengthening of PWD in the celecoxib-treated groups with a mean PWD of 133.1(2.7) as compared to healthy controls and inflammatory arthritis controls (P = 0.049, P = 0.036). These results are depicted in Tables 3 and 4.

DISCUSSION

AF is the most common heart rhythm disorder in which disorganized electrical impulses within the atrium lead to deterioration of the mechanical function of the atria. The prevalence of AF increases with age and has a significant impact on

Table 2. Clinical Characteristics of Arthritis Patients Included in the Study

	Inflammatory Arthritis Controls	Celecoxib Treated	
Number of patients	22	20	
Sex M/F n (%)	4/18(18/82)	6/14(30/70)	P = 0.477
BMI(kg/m2), mean ± SD	28.7±7.5	29.1±6.4	P = 0.877
Diagnosis:			
			P = 0.302
Rheumatoid arthritis	16	12	
Seronegative spondyloarthropathy	5	4	
Other inflammatory arthritis	1	4	
Disease duration (years), mean ± SD	8.2±7.9	6.2±8.8	P = 0.156
NSAID use	9	20	**P < 0.0001**
Number of Disease Modifying Antirheumatic Drugs Used:			
			P = 0.064
0	4	10	
1	1	12	
2	4	0	
3	2	1	
Biologic use	2	1	P = 0.607
Steroid use	5	3	P = 0.699
Serology:			
			P = 0.426
Rheumatoid factor +	10	6	
Rheumatoid factor −	10	11	
Rheumatoid factor unknown	2	3	

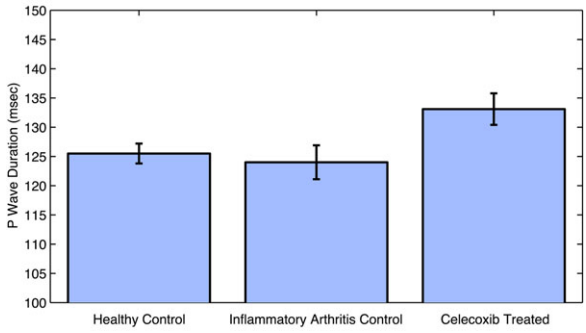

Figure 1. P-Wave duration analysis. The mean PWD is reported in milliseconds (ms). The error bars represent standard error of the mean.

overall population health, as complications from AF include heart failure, thromboembolism, and stroke. AF accounts for about one-third of all cardiac rhythm–related hospitalizations.[1,7] Importantly, the onset of AF mandates consideration of anticoagulants such as warfarin to mitigate the risk of stroke; however, the concomitant use of NSAIDs increases the risk of serious adverse events such as gastrointestinal bleeding.[8] To date, the epidemiological data relating COX-2 inhibitor use to AF explore only the association between the two, but little work has explored the etiology of this association or potential risk markers. This study investigated the effect of celecoxib on atrial electrophysiology using PWD, a surrogate noninvasive marker.

A case-control study of patients diagnosed with chronic or paroxysmal AF found that use of traditional NSAIDs was associated with an increased risk of chronic AF development, with an incidence rate ratio of 1.44. However, NSAIDs were not stratified based on potency of COX-2 inhibition.[6] A large Danish population–based case-control study reported an association between nonselective NSAIDs, COX-2 inhibitors, and the development of atrial arrhythmias.[1] The study reported an incidence rate ratio of 1.50 of AF or atrial flutter with current COX-2 inhibitor use as compared to no use[1] and an incidence rate ratio of 1.33 in nonselective NSAID users as compared to no use.[1] In addition, patients taking the COX-2 inhibitor celecoxib have a much higher incidence rate ratio of developing AF compared to those taking rofecoxib.[1] The incidence rate ratio of developing AF in new users of the COX-2 inhibitor celecoxib was 2.29, as compared to a much lower incidence rate ratio 1.93 in rofecoxib users.[1]

Our results show a longer PWD in the celecoxib-treated patients, as compared to the

Table 3. P-Wave Duration Measurements

	Healthy Controls	Inflammatory Arthritis Controls	Celecoxib Treated	
Mean PWD (ms±SEM)	125.3±1.6	124.0±2.9	133.1±2.7	**P = 0.025**

Table 4. Posthoc Analysis of P-Wave Duration

	Healthy Controls vs Inflammatory Arthritis Controls	Inflammatory Arthritis Controls vs Celecoxib	Healthy Controls vs Celecoxib
Difference in Mean PWD	Not Significant (P = 0.916)	Significant (**P = 0.036**)	Significant (**P = 0.049**)

inflammatory arthritis and healthy cohorts, see Table 4. However, there was no difference in mean PWD between the healthy controls and the inflammatory arthritis cohort. The signal-averaged PWD is a well-validated method that can be used to predict AF development.[10–14] In patients diagnosed with paroxysmal AF, PWD is significantly longer as compared to healthy control patients, and is a marker of the adverse electromechanical remodeling within the atria of AF patients, with marked changes in PWD yielding high risk of AF development.[9] In addition, the measurement of PWD has a coefficient of reproducibility of 10% and thus is able to reproduce PWD measurement with 95% accuracy to within 14 ms of original reading and 68% accuracy to within 7 ms of the original reading.[10] Thus, our results show that patients on celecoxib have a lengthened PWD as compared to patients not taking the medication, but would otherwise be deemed similar in terms of cardiovascular risk and rheumatologic disease severity. This is the first study to demonstrate a significant change in cardiac markers directly associated with celecoxib use and this change in atrial substrate correlates with the observed increased risk of atrial arrhythmia in patients taking celecoxib.

There are a number of risk factors that contribute to the pathophysiology of AF. One of the proposed risk factors is systemic inflammation. In patients with AF, there is a structural remodeling of the atrium that has an increase in inflammatory infiltrates, necrosis of myocytes, and fibrosis of the musculature.[18–20] In addition, increased C-reactive protein (CRP), an inflammatory marker, is a significant predictor of future AF onset.[18] In patients with inflammatory arthritis, inflammatory markers such as CRP and erythrocyte sedimentation rate (ESR) are often elevated. In previous work investigating P-wave dispersion, another measure that has been used to predict AF development, unselected patients with rheumatoid arthritis had an elevated P-wave dispersion and maximum PWD as compared to healthy controls.[21,22] Our study supports this and refines this to the population taking the COX-2 inhibitor celecoxib, rather than nonselective NSAIDs, where PWD between the inflammatory arthritis group and the healthy controls was not different.

While fibrosis is an important contributor to AF pathophysiology, electrical alterations to the action potential duration, conduction velocity, and refractory period in the atria play a key role in the initiation and maintenance of AF.[20] Once initiated, AF can be maintained by either an irregular ectopic firing, a single localized reentrant circuit or by multiple reentrant circuits.[6,20] Ectopic beat release can be a direct result of an alteration to the potassium currents that allow for atrial repolarization and maintain the normal atrial resting potential. If the action potential duration of the atria is prolonged, it can allow for early after depolarizations due to recovery of the L-type calcium current, initiating an early depolarization phase.[20,23] Celecoxib's activity as an antiinflammatory selectively targets the COX-2 enzyme; however, it also acts on other cellular targets, including ion channels, independent of its COX-2 activity.[24] At clinically relevant concentrations of celecoxib, the drug binds to several voltage-gated potassium channels within the myocardium including Kv1.5, Kv4.3 +KChIP2, and Kv7.1 +KCNE1, and inactivates them in vitro.[24] In the human myocardium, several voltage-gated potassium channels regulate the duration of the action potential, and Kv1.5 channels are specifically located in the atrium.[23]

In addition, mutations of the KCNA5 gene that encodes the Kv1.5 potassium channel has been associated with familial cases of AF.[24,25] Thus, celecoxib's ability to bind to this atrial-specific potassium channel may be of clinical relevance and we hypothesize that the observed increased incidence of AF in patients taking celecoxib is linked to its Kv1.5 binding capacity. In addition, study is needed to elucidate the effect of this blockade on in vivo human atrial action potential, repolarization, and conduction.

Taken together, the present study revealed that PWD was increased in patients with inflammatory arthritis treated with celecoxib. Given that PWD is a well-accepted noninvasive marker of atrial electrophysiology, our results suggest that these patients exhibit changes in atrial electrophysiologic substrate that would link to an increased risk of AF; moreover, this change was readily appreciated and may represent a future marker for risk stratification of patients.

LIMITATIONS

A limitation of the study was its cross-sectional-type design. It would be ideal to randomize patients to celecoxib treatment and record patients' PWD both before and after treatment initiation. The study selected patients with an inflammatory arthritis, and did not include patients with degenerative osteoarthritis, in which NSAID use is very prevalent; however, this group has not reported an increased risk of atrial arrhythmia. The study was underpowered to evaluate PWD with thyroid disease patients excluded from all cohorts. The difference in proportion of males within the healthy cohort may have contributed to a longer PWD.[26]

Acknowledgments: *We wish to thank Dr. Mala Joneja for allowing us to recruit patients from her clinic. We also wish to thank Geoff Seaborn, Sharlene Hammond, and Gwen Ewart of the Arrythmia Research Office for their helpful discussions and support.*

REFERENCES

1. Schmidt M, Christiansen C, Mehnert F, et al. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: Population based case-control study. BMJ 2011;343:3450.
2. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296(13):1633–1644.
3. Mitchell J, Warner T. COX isoforms in the cardiovascular system: Understanding the activities of non-steroidal anti-inflammatory drugs. Nat Rev Drug Discov 2006;5: 75–86.
4. Solomon S, McMurray J, Pfeffer M, et al. Cardiovascular risk associated with celecoxib in clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352(11):1071–1080.
5. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296(13):1633–t1644.
6. DeCaterina R, Ruigomez A, Rodriguez LAG. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. Arch Intern Med 2010;170(16):1450–1455.
7. Fuster V, Ryden LA, Cannom DS, et al. 2011 ACCD/AHA/HRS Focused Updates Incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123:e269–367.
8. Pisters R, Lane DA, Nieuwlaat R, et al. A novl-user friendly score (HAS-BLED) to assess 1 year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest 2010;138:1093–1100.
9. Stafford P, Robinson D, Vincent R. Optimal analysis of the signal averaged P wave in patients with paroxysmal atrial fibrillation. Br Heart J 1995;74:413–418.
10. Stafford P, Cooper J, Fothergill J, et al. Reproducibility of the signal averaged P wave time and frequency domain analysis. Heart 1997;77:412–416.
11. Dixen U, Vang Larsen M, Ravn L, et al. Signal-averaged P wave duration and the long-term risk of permanent atrial fibrillation. Scan Cardiovasc J 2008;42:31–37.
12. Baciarello G, Bella R, Di Maio F, et al. Analysis of high resolution atrial activation: Report on 403 cases. Am Heart J 1987;113(2):307–315.
13. Fukunami M, Yamada T, Ohmori M, et al. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by p wave-triggered signal-averaged electrocardiogram. Circulation 1991;83(1):162–169.
14. Opolski G, Stanislawska J, Slomka K, et al. Value of the atrial signal-averaged electrocardiogram in identifying patients with paroxysmal atrial fibrillation. Int J Cardiol 1991;20:315–319.
15. Gen R, Akbay E, Camsari A, et al. P-wave dispersion in endogenous and exogenous subclinical hyperthyroidism. J Endocrinol Invest 2010;33(2):88–91.
16. Katircibasi MT, Deniz F, Pamukcu B, et al. Effects of short-term propylthiouracil treatment on p wave duration and p wave dispersion in patients with overt hyperthyroidism. Exp Clin Endocrinol Diabetes 2007;115(6):376–379.
17. Selmer C, Olesen JB, Hansen ML, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: A large population cohort study. BMJ 2012;345:7895.
18. Aviles RK, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation.Circulation 2003;108:3006–3010.
19. Frustaci A, Chimenti C, Bellocci F, et al. Histological substrate of atrial biopsies in patients with lone atrial fibrillation.Circulation 1997;96:1180–1184.
20. Iwasaki Y, Nishida K, Kato T, et al. Atrial fibrillation pathophysiology: Implications for management.Circulation 2011;124:2264–2274.

21. Yavuzkir M, Ozturk A, Dagli N, et al. Effect of ongoing inflammation in rheumatoid arthritis on P-wave dispersion. J Int Med Res 2007;35:796–802.
22. Dilaveris P, Gialafos J. P-wave dispersion: A novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 2001;6(2):159–165.
23. Johnson JN, Tester DJ, Perry J, et al. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. Heart Rhythm 2008;5:704–709.
24. Macias A, Moreno C, Moral-Sanz J, et al. Celecoxib blocks cardiac Kv1.5, Kv4.3 and Kv7.1 (KCNQ1) channels: Effects on cardiac action potentials.J Mol Cell Cardiol 2010;49:984–992.
25. Olson T, Alekseev A, Liu X, et al. (2006). A Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation.Hum Mol Genet2006;15(14):2185–2191.
26. Dhala A, Underwood D, Leman R, et al. Signal-averaged P-wave analysis of normal controls and patients with paroxysmal atrial fibrillation: A study in gender differences, age dependence, and reproducibility. Clin Cardiol 2002;25(11):525–531.