Journal of Clinical & Experimental Cardiology - Open Access

Research Article
OPEN ACCESS Freely available online
doi:10.4172/2155-9880.1000101

Left Atrial Enlargement Correlates with Inflammation and Oxidative Stress in Patients at High Risk for Atrial Fibrillation

Heather L. Bloom[1]*, Irfan Shukrullah[2], William Jang[3], Richard N. Vest III[4] and Samuel C. Dudley[2]

[1]Emory University School of Medicine, Department of Medicine, Division of Cardiology, Atlanta, Georgia, USA
[2]University of Illinois at Chicago, Section of Cardiology Chicago, IL, USA
[3]Virginia Mason Medical Center, Seattle WA, USA
[4]Medical University of South Carolina, Charleston, SC, USA

Abstract

Objective: To examine the relationship between enlarged left atrial volume and increased blood markers of oxidative stress in patients at high risk for atrial fibrillation.

Design: This is a retrospective study where a single blood draw was taken from a cohort of patients with internal cardioverter-defibrillators, cardiomyopathy and ejection fraction (EF) ≤ 30%, and sent for markers of oxidative stress and inflammation. Left atrial size was obtained from echocardiography.

Setting: Single center, multi-hospital, cohort of 191 patients who underwent subgroup analysis; these patients are a subgroup of those enrolled in a larger, prospective trial, multicenter trial.

Patients: See above

Interventions: Single blood draw, retrospective database/chart review

Outcome Measures: Levels of hsCRP, IL-6, TNF-α, nitrotyrosine, reduced to oxidized cysteine ratio, reduced to oxidized glutathione ratio, derivatives of reactive oxygen metabolites (DROMS)

Results: Under univariate analysis, BMI (ρ= 0.003, r= 0.211), IL-6 (ρ=0.03, r= 0.192) and cysteine ratio (ρ=0.004, r=0.242) all correlated with LA enlargement**.** Binary logistic regression demonstrated that the single factor that best classified normal vs. enlarged LA is cysteine (ρ=.001). The binary logistic model itself is significantly predictive, as indicated by an omnibus test of model coefficients (ρ<.001). When analyzed as a continuous variable, rather than using a cut point, increasing IL-6 levels correlated to increasing LA diameter.

Conclusions: These data suggest an association between IL-6, cysteine and left atrial enlargement (LAE). As LAE is associated with atrial fibrillation, reductions in inflammation and oxidative stress may lead to decreased risk of atrial fibrillation. Treatments to reduce oxidative stress may have potential to prevent development of atrial fibrillation.

Keywords: Atrial fibrillation; Inflammation; Oxidative stress; Arrhythmia

Abbreviations: AF: Atrial Fibrillation; DROM: Derivatives of Reactive Oxygen Metabolites; EF: Ejection Fraction; ICD: Implantable Cardioverter-Defibrillator; LA: Left Atrium; LAD: Left Atrial Diameter; RF: Radio-Frequency

Background

Atrial Fibrillation (AF) is an extremely common arrhythmia affecting more than 5% of the population over 65 years of age. It is an independent risk factor for death. AF progresses over time, increasing in prevalence with age and converts from paroxysmal AF to permanent AF. AF is considered to be responsible for approximately one-sixth of all ischemic strokes in people over age 60 years [1].

Large left atrial diameter (LAD) is associated with a high risk of AF in multiple patient populations. A case-control study comparing healthy volunteers to patient with idiopathic (lone) atrial fibrillation demonstrated that even patients with a first episode of AF had larger LA dimensions than those without AF [2]. Atrial size is an independent predictor of risk of arrhythmia recurrence after radiofrequency (RF) ablation of atrial flutter [3] and atrial fibrillation [4]. Surgical data also shows "moderate" LAD is the strongest predictor of success for the mini-maze procedure [5]. Inversely, reduction in atrial size predicts the post-operative success of sinus conversion with the RF maze procedure when used in conjunction with valvular surgery [6]. These data suggest increased LA size is a marker for the presence of an enhanced substrate for development of atrial fibrillation, due to atrial remodeling and that reversing this enlargement may decrease risk of atrial fibrillation. Conversely, atrial fibrillation leads to increase in left atrial size and decreasing rates of atrial fibrillation lead to reversed remodeling of the atrium.

Several recent studies have linked increased oxidative stress with atrial fibrillation. In a pig model of atrial fibrillation, superoxide anions are up-regulated by a factor of 3.0, and nitric oxide is down-regulation by a factor of 3.7 [7]. In a recent project, we compared serum markers of inflammation and oxidative stress in a cross-sectional, case-control designed study of 22 subjects with persistent or permanent AF and controls. Multivariate models produced strong and significant associations between oxidative markers and atrial fibrillation [8], with inter-quartile odds ratios as high as 13.6. Several other trials

***Corresponding author:** Heather L Bloom, MD, Atlanta VAMC, Suite 111B, 1670 Clairmont Dr, Decatur GA 30033, Tel: 404.321.6111 ex 6391; Fax: 404.329.2211; E-mail: hbloom@emory.edu

Received August 03, 2010; **Accepted** August 29, 2010; **Published** August 29, 2010

Citation: Bloom HL, Shukrullah I, Jang W, Vest RN III, Dudley SC (2010) Left Atrial Enlargement Correlates with Inflammation and Oxidative Stress in Patients at High Risk for Atrial Fibrillation. J Clinic Experiment Cardiol 1:101 doi:10.4172/2155-9880.1000101

have shown that administration of antioxidant medications, statins, decrease canine atrial ERP [9] and in humans decrease recurrence of paroxysmal atrial fibrillation following cardioversion [10], and rates of atrial fibrillation both post-operatively [11] and in heart failure patients [12]. Another study identified atrial NADPH oxidase activity as the strongest independent predictor of post-operative AF, suggesting that this oxidase may be a key mediator of atrial oxidative stress [13].

Based on the above discussion, we hypothesized that LA enlargement would be associated with increased blood markers of oxidative stress, in patients at high risk of AF.

Methods

This is an unfunded retrospective study approved by the Emory University Internal Review Board. At the time of enrollment in another trial, the Genetic Risk Assessment for Defibrillator Events (GRADE) trial, a single blood draw was performed on 191 subjects. All of these patients had internal cardioverter-defibrillators (ICDs), placed for primary prevention for cardiomyopathy, with ejection fraction (EF) ≤ 30%. The rational for performing this study in these patients is that their underlying cardiac disease placed them at high risk for arrhythmias and we had the resources available due to the primary study requirements. LA size was obtained from echocardiography, with an anterior posterior diameter greater than 5.0 cm defined as moderately enlarged. This value was selected based on the cut off value for the highest tertile; multiple different studies have used different values for left atrial enlargement. Although a standard definition of left atrial "enlargement" is 4.2 cm, several studies have suggested that a "moderate" enlargement of the left atrium correlates with AF recurrence risk, without giving specific values to define [14-16] Serum levels of oxidative stress markers were obtained in 181 patients.

Demographic and medical information obtained on enrollment included: age, gender, race, history of smoking, medications, New York Heart Association (NYHA) class, etiology of heart disease, hypercholesterolemia, history of myocardial infarction (MI) history of coronary artery bypass (CABG) surgery, family history of heart disease, history of arrhythmias, history of syncope, echocardiogram results, cardiac catheterization results, nuclear imaging results, electrocardiograms, blood pressure, heart rate, electrolytes, and date of ICD implantation surgery and any ICD generator exchanges.

Biomarker data

A single blood draw was perform at the time of enrollment and analyzed for markers of oxidative stress and inflammation in the Emory Biomarkers Core Laboratory. Inflammatory markers measured were hsCRP, IL-6, TNF-α and nitrotyrosine. Markers for oxidative stress were: ratios of oxidized to reduced glutathione (Glu) and cystiene (Cys) in plasma (thiol ratios), and derivatives of reactive oxygen species (DROMs) [17,18]. Thorough methods to prevent rapid oxidation of samples have been defined previously [19]. Blood was collected from an antecubital vein and transferred immediately to a micro centrifuge tube containing 0.5 mL of a preservation solution of 100 mM serine·borate (pH 8.5) containing (per mL) 0.5 mg sodium heparin, 1 mg bathophenanthroline disulfonate sodium salt, and 2 mg iodoacetic acid. This procedure minimizes auto-oxidation and hemolysis [20]. All blood was drawn between 7:30 am and 3:00 pm in non-fasting patients. Following centrifugation to remove blood cells, aliquots (200 μL) were transferred to tubes containing 200 μL of 10% (w/v) perchloric acid containing 0.2 M boric acid and 10-μM γ-Glu-Glu as an internal standard. Samples were stored at -80°C (< 2 months) prior to further processing to form N-dansyl derivatives and analysis by HPLC with fluorescence detection. Reduced glutathione, cystiene, and cystiene levels in plasma were greater than 1000 times the level of detection (~1 nM). Oxidized glutathione levels were approximately10 times this limit. Previous data have shown stable measurements with this length of storage [21]. Metabolites were identified by co-elution with standards, and quantification was obtained by integration relative to the internal standard. Samples from control and AF patients were performed identically.

The redox states (E_h) of the thiol/disulfide pools were calculated with the Nernst equation, $E_h = E_o + RT/nF \ln [\text{disulfide}]/[\text{thiol}]^2$, where E_o is the standard potential for the redox couple, R is the gas constant, T is the absolute temperature, n is 2 for the number of electrons transferred, and F is Faraday's constant. The standard potential E_o used for the glutathione and cystiene redox couples was -264 mV and -250 mV, respectively. Less negative E_h numbers imply a more oxidized state. DROMs were measured in Carr units with higher values indicating higher levels of oxidative stress. DROMs (Diacron International, Grosseto, Italy) and inflammatory markers, high sensitivity C-reactive protein (hsCRP; Life Diagnostics, West Chester, PA), interleukin-6 (IL-6; R&D Systems), and tumor necrosis factorα (TNFα; R&D Systems), were measured using commercially available kits.

Data analysis

Statistical analysis was performed using SPSS software version 14.0 (SPSS Inc. Headquarters, Chicago, Illinois 60606). Univariate and multivariate analysis were performed to examine the relationship between LA enlargement and these markers of oxidative stress.

Results

Demographic data is presented in Table 1 Average age is 67±10 years, average ejection fraction (EF) 19.4%±6.6%, 81% are male, 36% are diabetic, 59% hypertensive, 67% smokers, 56% on statins, 82% are on angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB) and 38% have a body mass index (BMI) greater than 30. One third of the patients, 67 (%) had LA enlargement (Table 1). Comparisons between the moderate LAD group and the rest of the group revealed no statistical significance (Table 2). Under univariate analysis, BMI ($\rho = 0.003$, $r = 0.211$), IL-6 ($\rho = 0.03$, $r = 0.192$) and cysteine ($\rho = 0.004$, $r = 0.242$) all correlated with LA enlargement (Table 3).

To evaluate which factors were best able to distinguish the presence or absence of LA enlargement, we employed a binary logistic regression involving both categorical variables (Age, DM, HTN, smoking, statin, ACE, or ARB) as well as continuous variables (BMI, CRP, IL6, TNFα, Nitrotyrosine, Cys, Glu). This demonstrated

	N=171
Average Age	67 ± 10 years
Average EF	19.4% ± 6.6%
Male	81% (141)
Diabetic	36% (62)
Hypertensive	59% (103)
Smoker	67% (117)
Statins	56% (97)
ACE or ARB	82% (143)
BMI > 30	38% (66)

Abbreviations: EF=Ejection Fraction; ACE=Angiotension Converting Enzyme Inhibitor ARB=Angiotensin Receptor Blocker; BMI=body-mass index

Table 1: Demographic data for all patients.

	Large LAD N=58	N=113	ρ value
Average Age	64 ± 9 years	67 ± 10 years	0.06
Average EF	18.5% ± 5.5	19.4% ± 6.6%	0.30
Male	86% (49)	81% (91)	0.67
Diabetic	36% (21)	36% (41)	1.0
Hypertensive	60% (35)	59% (67)	0.6
Smoker	72% (41)	67% (76)	0.7
Statins	61 %(35)	56% (63)	0.26
ACE or ARB	83% (48)	82% (93)	0.99
BMI > 30	45% (26)	40% (45)	0.6

Abbreviations: EF=Ejection Fraction; ACE=Angiotensin Converting Enzyme Inhibitor ARB=Angiotensin Receptor Blocker; BMI=body-mass index

Table 2: Demographics compared between LAD and non-LAD patients.

	ρ=	r =
BMI	0.003	0.211
IL-6	0033	0.192
Cys	0.000	0.304

Table 3: Factors significant by Univariate Analysis (ρ values and linear correlation coefficients).

that the single factor that best classified normal vs. enlarged LA is Cys (ρ=.001). The binary logistic model itself is significantly predictive, as indicated by an omnibus test of model coefficients (ρ<.001), and the Hosmer and Lemeshow "goodness of fit" test (ρ=.02).

However, left atrial enlargement is not a binary state, but rather the size of the left atrium is a continuous value. So to better assess the relationship of left atrial size with our biomarkers, we used a linear regression to examine our patients with all atrial sizes. In this regression model, IL-6 (ρ=.043) was the dominant predictors of LA size, though BMI once more trended towards significance (ρ=.076). The regression model itself fit well, with a significance of ρ=.006.

Limitations

This is a single center, retrospective study. The time between the single blood draw and the echocardiogram documentation of left atrial size was often months to years apart.

Conclusions

These data suggest an association between IL-6, Cysteine and LA enlargement.

Discussion

These data demonstrate the importance and utility of oxidative stress markers in left atrial enlargement. Of all the factors recorded, the model that best predicted LA enlargement required only a single measure of oxidative stress, cysteine ratios. In those patients who did not yet exhibit left atrial enlargement, the marker most predictive of LAD was IL-6, establishing these biomarkers as reliable indicators of increasing LAD.

Our data suggest that an enlarged left atrium is associated with high inflammatory marker IL-6. This marker also correlates linearly with increasing LA size in patients who do not yet meet criteria for enlarged left atrium. The oxidative stress marker cysteine best predicts the presence or absence of left atrial enlargement. This may help to explain the association between left atrial size and atrial fibrillation. Increased oxidant stress may also explain in part the association of AF with atherosclerosis, hypertension, diabetes, older age, obesity, and male sex. Failure to address increased oxidative stress may partially explain the difficulties with rhythm management strategies for these patients.

A recent study shows that decrease in LA area occurring 30 days following CV favors long term sinus rhythm maintenance [22]. In a cohort study, LA diameter independently predicted cardiovascular events (nonfatal stroke, coronary heart disease, congestive heart failure, and fatal cardiovascular disease) after adjustment for established clinical, echocardiographic, and inflammatory risk factors [23]. Thus, LA dilatation identifies individuals at heightened risk who warrant aggressive risk factor modification. Treatments to decrease oxidative stress may provide a target for such risk factor modification. Additionally, serial documentation of LA size may provide an objective measurement for the efficacy for such treatments.

Several lines of evidence link oxidative stress with arrhythmias [24,25]. Atrial fibrillation has been well correlated with increased oxidative stress [26] Moreover, available data suggests that oxidative stress may mediate acute and chronic electrophysiological changes and the electrical remodeling that contribute both to the initiation and maintenance of AF. These electrical changes include the down-regulation of L-type calcium channels and thereby the inward calcium current [27], and also structural changes in atrial tissue ("structural remodeling") as mentioned briefly above. Proteases and phosphatases such as calpain and calcineurin induce calcium dependent tissue alterations; oxidative stress may mediate these alterations. As is well known, atrial fibrillation begeats atrial fibrillation; data suggests that atrial fibrillation in turn could lead to increase in oxidative stress also. Either way, tailoring therapies to treat oxidative stress may significantly impact risk of atrial fibrillation.

One anti-oxidant therapy is statin medications. Statins reduce reactive oxygen species and have anti –inflammatory properties [28]. One prospective study has shown that atorvastatin decreased the recurrence rate of AF after elective cardioversion [29]. The mechanism is unknown, but could be via reduction in oxidative stress. Statins have also been shown to decrease rates of ventricular arrhythmias [30,31]; other work at our institution suggests there is a relationship between oxidative stress and ventricular arrhythmias [32].

This study leaves us with several interesting clinical questions that need to be addressed. Are there effective treatments for oxidative stress? Do clinical decreases in levels of oxidative stress correlate with decreases in LA size, as our model predicts? If so, does this decrease in turn lessen risk of AF? The linear association of CRP and IL-6 with increasing LA size also gives us a marker of increasing risk not previously established. The clinical impact could be significant.

References

1. Wolf PA, Abbott RD, Kannel WB (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 22: 983-988.
2. Sitges M, Teijeira VA, Scalise A, Vidal B, Tamborero D, et al. (2007) Is there an anatomical substrate for idiopathic paroxysmal atrial fibrillation? A case-control echocardiographic study. Europace 9: 294-298.
3. Ellis K, Wazni O, Marrouche N, Martin D, Gillinov M, et al. (2007) Incidence of Atrial Fibrillation Post-Cavotricuspid Isthmus Ablation in Patients with Typical Atrial Flutter: Left-Atrial Size as an Independent Predictor of Atrial Fibrillation Recurrence. J Cardiovasc Electrophysiol 18: 799-802.
4. Scherer M, Therapidis P, Wittlinger T, Miskovic A, Moritz A (2007) Impact of left atrial size reduction and endocardial radiofrequency ablation on continuous atrial fibrillation in patients undergoing concomitant cardiac surgery: three-year results. J Heart Valve Dis16: 126-131.
5. Szalay ZA, Skwara W, Klövekorn WP, Brunner-La Rocca HP, Knez I, et al. (2004) Predictors of failure to cure atrial fibrillation with the mini-maze operation. J Card Surg 19: 1-6.
6. Chen MC, Chang JP, Guo GB, Chang HW (2001) Atrial size reduction as a predictor of the success of radiofrequency maze procedure for chronic atrial fibrillation in patients undergoing concomitant valvular surgery. J Cardiovasc Electrophysiol 12: 867-874.
7. Dudley SC Jr, Hoch NE, McCann LA, Honeycutt C, Diamandopoulos L, et al.

(2005) Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage: role of the NADPH and xanthine oxidases. Circulation 112: 1266-1273.

8. Neuman RB, Bloom HL, Shukrullah I, Darrow LA, Kleinbaum D, et al. (2007) Oxidative stress markers are associated with persistent atrial fibrillation. Clin Chem 53: 1652-1657.
9. Shiroshita-Takeshita A, Schram G, Lavoie J, Nattel S (2004) Effect of simvastatin and antioxidant vitamins on atrial fibrillation promotion by atrial-tachycardia remodeling in dogs. Circulation 110: 2313-2319.
10. Siu CW, Lau CP, Tse HF (2003) Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. Am J Cardiol 92: 1343-1345.
11. Marin F, Pascual DA, Roldan V, Arribas JM, Ahumada M, et al. (2006) Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. Am J Cardiol 97: 55-60.
12. Bardy G, Dickinson M, Hellkamp J, Anderson J, Johnson G, et al. (2008) Statin therapy was associated with reduced atrial fibrillation and flutter in heart failure patients in SCD-HeFT. Heart Rhythm 3: s49.
13. Kim YM, Kattach H, Ratnatunga C, Pillai R, Channon KM, et al. (2008) Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 51: 68-74.
14. Mattioli AV, Sansoni S, Lucchi GR, Mattioli G (2000) Serial evaluation of left atrial dimension after cardioversion for atrial fibrillation and relation to atrial function. Am J Cardiol 85: 832-836.
15. Tsang TS, Manolio TA, Gottdiener JS, Gardin JM, Cardiovascular Health Study Collaborative Research Group (2002) Left atrial dimensions determined by M-mode echocardiography in black and white older (> or =65 years) adults (The Cardiovascular Health Study). Am J Cardiol 90: 983-987.
16. Parkash R, Green MS, Kerr CR, Connolly SJ, Klein G, et al. (2004) The association of left atrial size and occurrence of atrial fibrillation: a prospective cohort study from the Canadian Registry of Atrial Fibrillation. Am Heart J 148: 649-54
17. Cesarone MR, Belcaro G, Carratelli M, Cornelli U, De Sanctis MT, et al. (1999) A simple test to monitor oxidative stress. Int Angiol 18: 127-130.
18. Abramson JL, Hooper WC, Jones DP, Ashfaq S, Rhodes SD, et al. (2005) Association between novel oxidative stress markers and C-reactive protein among adults without clinical coronary heart disease. Atherosclerosis 178: 115-121.
19. Jones DP, Carlson JL, Samiec PS, Sternberg P Jr, Mody VC Jr, et al. (1998) Glutathione measurement in human plasma. Evaluation of sample collection, storage and derivatization conditions for analysis of dansyl derivatives by HPLC. Clin Chim Acta 275: 175-184.
20. Kosior DA, Szulc M, Torbicki A, Opolski G, Rabczenko D (2005) A decrease of enlarged left atrium following cardioversion of atrial fibrillation predicts the long-term maintenance of sinus rhythm. Kardiol Pol 62: 428-437.
21. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, et al. (2006) Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). Am Heart J 151: 412-418.
22. Kim YH, Lim dS, Lee JH, Shim WJ, Ro YM, et al. (2003) Gene expression profiling of oxidative stress on atrial fibrillation in humans. Exp Mol Med 35: 336-349.
23. Korantzopoulos P, Kolettis TM, Kountouris E, Dimitroula V, Karanikis P, et al. (2005) Oral vitamin C administration reduces early recurrence rates after electrical cardioversion of persistent atrial fibrillation and attenuates associated inflammation. Int J Cardiol 102: 321-326.
24. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, et al. (2002) A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 347: 1834-1840.
25. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, et al. (2002) A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 347: 1825-1833.
26. Zarauza J, Rodriguez Lera MJ, Farinas AC, Hernando JP, Ceballos B, et al. (2006) Relationship Between C-Reactive Protein Level and Early Recurrence of Atrial Fibrillation After Electrical Cardioversion. Rev Esp Cardiol 59: 125-129.
27. Tsai CT, Wang DL, Chen WP, Hwang JJ, Hsieh CS, et al. (2007) Angiotensin II increases expression of alpha1C subunit of L-type calcium channel through a reactive oxygen species and cAMP response element-binding protein-dependent pathway in HL-1 myocytes. Circ Res 100: 1476-1485.
28. Lefer DJ (2002) Statins as potent antiinflammatory drugs. Circulation 106: 2041-2042.
29. Ozaydin M, Varol E, Aslan SM, Kucuktepe Z, Dogan A, et al. (2006) Effect of atorvastatin on the recurrence rates of atrial fibrillation after electrical cardioversion. Am J Cardiol 97: 1490-1493.
30. Goldberger JJ, Subacius H, Schaechter A, Howard A, Berger R, et al. (2006) Effects of statin therapy on arrhythmic events and survival in patients with nonischemic dilated cardiomyopathy. J Am Coll Cardiol 48: 1228-1233.
31. Vyas AK, Guo H, Moss AJ, Olshansky B, McNitt SA, et al. (2006) Reduction in ventricular tachyarrhythmias with statins in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. J Am Coll Cardiol 47: 769-773.
32. Bloom HL, Shukrullah I, Veledar E, Gutmann R, London B, et al. (2010) Statins Decrease Oxidative Stress and ICD Therapies. Cardiol Res Pract 2010.