

Aortic Stiffness in Lone Atrial Fibrillation: A Novel Risk Factor for Arrhythmia Recurrence

Dennis H. Lau¹, Melissa E. Middeldorp¹, Anthony G. Brooks¹, Anand N. Ganesan¹, Kurt C. Roberts-Thomson¹, Martin K. Stiles¹, Darryl P. Leong¹, Hany S. Abed¹, Han S. Lim¹, Christopher X. Wong¹, Scott R. Willoughby¹, Glenn D. Young¹, Jonathan M. Kalman², Walter P. Abhayaratna³, Prashanthan Sanders^{1*}

1 Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia, **2** Department of Cardiology, Royal Melbourne Hospital and the Department of Medicine, University of Melbourne, Victoria, Australia, **3** Academic Unit of Internal Medicine, Canberra Hospital, Canberra, Australia

Abstract

Background: Recent community-based research has linked aortic stiffness to the development of atrial fibrillation. We posit that aortic stiffness contributes to adverse atrial remodeling leading to the persistence of atrial fibrillation following catheter ablation in lone atrial fibrillation patients, despite the absence of apparent structural heart disease. Here, we aim to evaluate aortic stiffness in lone atrial fibrillation patients and determine its association with arrhythmia recurrence following radio-frequency catheter ablation.

Methods: We studied 68 consecutive lone atrial fibrillation patients who underwent catheter ablation procedure for atrial fibrillation and 50 healthy age- and sex-matched community controls. We performed radial artery applanation tonometry to obtain central measures of aortic stiffness: pulse pressure, augmentation pressure and augmentation index. Following ablation, arrhythmia recurrence was monitored at months 3, 6, 9, 12 and 6 months thereafter.

Results: Compared to healthy controls, lone atrial fibrillation patients had significantly elevated peripheral pulse pressure, central pulse pressure, augmentation pressure and larger left atrial dimensions (all $P < 0.05$). During a mean follow-up of 2.9 ± 1.4 years, 38 of the 68 lone atrial fibrillation patients had atrial fibrillation recurrence after initial catheter ablation procedure. Neither blood pressure nor aortic stiffness indices differed between patients with and without atrial fibrillation recurrence. However, patients with highest levels ($\geq 75^{\text{th}}$ percentile) of peripheral pulse pressure, central pulse pressure and augmentation pressure had higher atrial fibrillation recurrence rates (all $P < 0.05$). Only central aortic stiffness indices were associated with lower survival free from atrial fibrillation using Kaplan-Meier analysis.

Conclusion: Aortic stiffness is an important risk factor in patients with lone atrial fibrillation and contributes to higher atrial fibrillation recurrence following catheter ablation procedure.

Citation: Lau DH, Middeldorp ME, Brooks AG, Ganesan AN, Roberts-Thomson KC, et al. (2013) Aortic Stiffness in Lone Atrial Fibrillation: A Novel Risk Factor for Arrhythmia Recurrence. PLoS ONE 8(10): e76776. doi:10.1371/journal.pone.0076776

Editor: John Calvert, Emory University, United States of America

Received: July 3, 2013; **Accepted:** September 2, 2013; **Published:** October 3, 2013

Copyright: © 2013 Lau et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: Drs. Lau and Leong are supported by a Postdoctoral Fellowship from the National Health and Medical Research Council of Australia (NHMRC). Drs. Brooks, Roberts-Thomson and Sanders are supported by the Heart Foundation of Australia (HFA). Dr. Ganesan is supported by a CVL grant from Pfizer Australia. Dr. Abed is supported by an Australian Postgraduate Award and an Earl Bakken Fellowship from the University of Adelaide. Dr. Lim is supported by a Postgraduate Scholarship from NHMRC. Dr. Wong is supported by the Rhodes scholarship. Dr. Willoughby is supported by the NHMRC. This work is supported by an equipment grant from Tom Simpson Trust Fund, HFA. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have the following interests. Drs. Kalman, Roberts-Thomson and Young report having served on the advisory board of and having received lecture fees from Medtronic and St Jude Medical. Dr Sanders reports having served on the advisory board of and having received lecture fees and research funding from Bard Electrophysiology, Biosense-Webster, Medtronic, Merck Sharp & Dohme, Sanofi-Aventis and St. Jude Medical. Dr A Ganesan has received grant funding from Pfizer Australia. This does not alter their adherence to all the PLOS ONE policies on sharing data and materials.

* E-mail: prash.sanders@adelaide.edu.au

Introduction

Atrial fibrillation (AF) has been recognized as an emerging epidemic. Increased focus on its prevention is thereby warranted given the limitations with current therapeutic options

[1]. Recently, aortic stiffness has been proposed as a novel modifiable risk marker for AF, with increased brachial pulse pressure found to be associated with AF development in the Framingham community-based observational cohort [2]. Importantly, this association was stronger than systolic blood

pressure alone and remained significant even after adjustment for established predictive factors such as left atrial enlargement and left ventricular hypertrophy [2].

However, peripheral derived blood pressures are known to overestimate true central hemodynamic indices [3]. In particular, central pressures are important measures of subclinical organ damage with greater patho-physiological relevance than peripheral pressures and therefore, better at predicting disease progression and outcomes, including coronary stenosis and cardiovascular mortality [3-5]. Central pulse wave analysis is a clinically validated, non-invasive and reproducible method for assessment of aortic stiffness [5-7]. Radial artery waveform obtained by applanation tonometry can be used to derive the following surrogate measures of aortic stiffness: central systolic blood pressure, central pulse pressure, augmentation pressure and augmentation index. In individuals with aortic stiffness, increased pulse wave velocity results in merging of the incident and reflected arterial waves leading to increased augmentation pressure as well as central systolic and pulse pressures.

In this study, we aim to further investigate the role of aortic stiffness in AF by analyzing the central pulse wave of lone AF patients who have no apparent structural heart disease or conditions that predispose them to the arrhythmia. Recently, it has been demonstrated that lone AF patients have an abnormal atrial electrical and structural substrate [8-10]. We posit that aortic stiffness contributes to adverse atrial remodeling that result in the development and persistence of lone AF. The impact of such a consequence was studied by examining arrhythmia recurrence following catheter ablation in patients with lone AF.

Methods

Study Population

The Research Ethics Committee of the Royal Adelaide Hospital, Australia approved this study. From a total of 115 consecutive lone AF patients who underwent initial catheter ablation procedure at our institution for symptomatic AF between August 2005 and September 2010, 72 agreed to participate in this study. Due to the presence of AF during applanation tonometry in 4 patients, we only included data from the remaining 68 patients for analysis. Lone AF was defined as previously described by: absence of structural heart disease or stroke based on history, physical examination, chest X-ray, routine blood chemistry, and echocardiography; coronary artery disease was excluded by clinical, ECG or stress test criteria; pulmonary disease, hypertension, hyperthyroidism and diabetes were eliminated by appropriate tests [11]. An additional 50 age- and sex-matched control subjects with no echocardiographic evidence of structural heart disease or risk factors for AF were also recruited from the local community. All patients and control subjects gave informed written consent to the study protocol.

Blood Pressure and Radial Artery Pulse Wave Measurements

Measurements of blood pressure and radial artery applanation tonometry were performed in a quiet, temperature controlled room (22°C) with subjects in a recumbent position after 10 minutes of rest. All subjects were instructed to refrain from alcohol and caffeine consumption for 1 day prior to these measurements. Brachial blood pressure was the average of the last 2 readings (out of 3) measured in each subject at 5-minutes interval using a mercury sphygmomanometer and appropriately sized arm cuff.

Radial artery pressure waveform was acquired using a high fidelity applanation tonometer on the same arm (SphygmoCor Version 9, Atcor Medical, Itasca, IL, USA). The system has real-time monitoring of waveform quality (Figure 1A) allowing automatic capture once 11 seconds of acceptable data is obtained. The algorithm monitored each recording for pulse height, diastolic and shape variation. Quality of acquired data was also verified manually to ensure inclusion of only high quality recordings with operator index of >90%. Aortic pressure waveform was then derived using a validated generalized transfer equation [12]. Three measurements were performed on each subject to provide a mean value for each parameter: Central and peripheral pulse pressure – taken as the difference between their respective systolic and diastolic readings; Augmentation pressure – a measure of reflected pressure wave, taken as the difference between maximum central systolic pressure and the pressure at first peak (Figure 1B); and Augmentation index – taken as the percentage of augmentation pressure to pulse pressure ($AP/PP \times 100$).

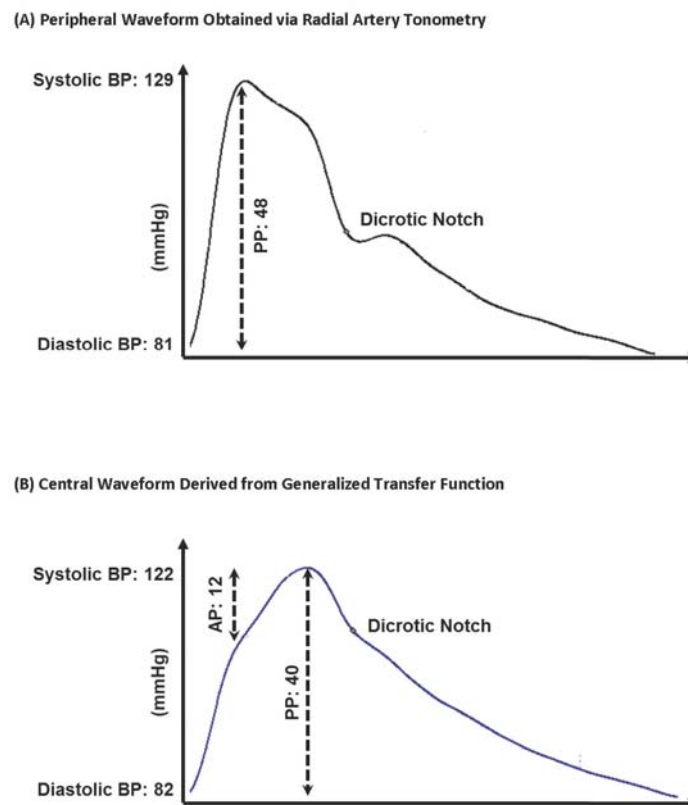
Definitions and Echocardiographic Measurements

Classification of AF was in accordance with expert consensus statement [13]. Paroxysmal AF was defined as recurrent AF that terminates spontaneously within 7 days. Persistent AF was defined as sustained AF lasting more than 7 days or between 2 and 7 days but requiring cardioversion. All echocardiographic measures were performed according to the American Society of Echocardiography guidelines [14]. In brief, left atrial measurements were taken using M-mode in the standard parasternal long axis view; and in 2-D apical 2- and 4-chamber views for measurements of left atrial area. Left atrial volume was calculated using the bi-plane area-length method and indexed for body surface area to derive left atrial volume index. Inter-ventricular septum was measured using both M-mode and 2-D from the parasternal long axis window. Left ventricular ejection fraction was calculated using the modified Simpson's rule.

Electrophysiology Study and Ablation

Electrophysiological procedures were performed with patients in the fasting state and under conscious sedation using midazolam and fentanyl. The ablation technique utilized at our institution has been previously described [8]. In brief, a single trans-septal puncture was performed under fluoroscopic guidance for left atrial access (BRK-1 needle, St Jude Medical, St Paul, MN, USA). The following catheters were used: Decapolar in the coronary sinus (Live wire Steerable, St Jude

Figure 1: Peripheral and Central Pulse Waveforms



25

Figure 1. Peripheral and Central Pulse Waveforms. (A) This figure depicts a peripheral waveform obtained via radial artery tonometry. In this sample from a lone AF patient, peripheral blood pressure is 129/81 with a pulse pressure of 48 mmHg. (B) Aortic waveform can then be derived from peripheral waveform shown in (A) with the SphygmoCor software's generalized transfer function. The central blood pressure is 122/82 with a pulse pressure of 40 mmHg. Augmentation pressure is a measure of reflected pressure wave, which is the difference between aortic systolic pressure and the first peak of the waveform. Augmentation index in this example is $12/40 \times 100 = 30\%$.

doi: 10.1371/journal.pone.0076776.g001

Medical); Circular for pulmonary vein mapping (Lasso Variable, Biosense-Webster, Diamond Bar, CA, USA); and 3.5 mm tip externally irrigated for ablation (Navistar or Celsius Thermocool, Biosense-Webster). Electroanatomic mapping system (CARTO, Biosense-Webster or Ensite NavX, St. Jude Medical) was used routinely for non-fluoroscopic navigation. Unfractionated heparin was administered in repeated boluses to maintain an activated clotting time of 300–350 seconds.

The ablation strategy included wide-encircling pulmonary vein ablation with an endpoint of pulmonary vein isolation in all patients. Further substrate modification was performed for patients with AF episodes lasting longer than 48 hours. This included linear ablation at the left atrial roof with endpoint of conduction block and/or electrogram-guided ablation at highly

fractionated sites with abolition of fractionated signals as endpoint. Typically, radiofrequency power of 30W was used for pulmonary vein ablation and up to 35W for substrate modification while irrigation rate was fixed at 30 ml/min.

Follow-Up

Patients were reviewed 3 monthly for the first year after ablation and 6 monthly thereafter. At each review, AF recurrence was ascertained from ambulatory 7-day Holter monitoring, 12-lead ECG and patients' symptoms. All patients were treated with flecainide or sotalol for the first 6 weeks following the ablation procedure. Ongoing anti-arrhythmic drug use was at the discretion of the treating physician. Warfarin anti-coagulation was routine in all patients for a period of 3

Table 1. Baseline Characteristics.

	Control (n=50)	Lone AF (n=68)	P
Age (yr)	58.6±11.3	59.3±10.5	0.6
Male sex (%)	74.0	73.5	1.0
Body mass index (kg/m ²)	26.9±4.4	27.5±4.5	0.5
Duration of AF (months)	-	60 (IQR 43-120)	-
Longest AF episodes (days)	-	2 (IQR 0.5-30)	-
Echocardiography			
Left atrial parasternal size (cm)	3.4±0.5	3.9±0.7	0.004
Left atrial volume (ml)	52.7±15.5	66.0±23.1	0.002
Left atrial volume index (ml/m ²)	26.8±6.8	32.3±10.8	0.005
Left atrial area (cm ²)	18.5±3.5	21.6±5.0	<0.001
Inter-ventricular septum (mm)	9.8±1.5	10.1±1.5	0.4
Left ventricular ejection fraction (%)	64±5	64±7	0.7

IQR: Inter-quartile range.

doi: 10.1371/journal.pone.0076776.t001

months following ablation and continued in those with a CHADS₂ score ≥2. Procedural success was determined as the absence of any atrial arrhythmia longer than 30 seconds without anti-arrhythmic drug use after a blanking period of 6 weeks.

Statistical Analysis

Continuous variables were expressed as means ±SD or median with inter-quartile range accordingly using the Shapiro-Wilks test of normality. Data were compared using the unpaired Student's t-test or Wilcoxon rank-sum test as appropriate. Categorical data were expressed as numbers and percentages, and compared using Fisher's exact test. Kaplan-Meier survival analysis with log-rank testing was applied to compare post ablation AF recurrence. Statistical significance was established with two-tailed P value less than 0.05.

Results

Baseline Characteristics

Patient characteristics are presented in Table 1. Of the 68 lone AF patients, 43 had paroxysmal AF and 25 had persistent AF. Body mass index was similar between the two groups. Lone AF patients had significantly larger left atrial dimensions even though these were still within reference range for normal adults.

Peripheral and Central Pressures

The various peripheral and central blood pressure parameters are detailed in Table 2. Specifically, there was no significant difference in either peripheral or central systolic, diastolic & mean blood pressures. However, lone AF patients had significantly elevated measures of aortic stiffness: peripheral pulse pressure, central pulse pressure and augmentation pressure. Examples of peripheral and central pulse waveforms of the two groups are shown in Figure 2.

Table 2. Peripheral and Central Blood Pressures.

	Control (n=50)	Lone AF (n=68)	P
Peripheral Pressures (mmHg)			
Systolic	125±8	129±14	0.06
Diastolic	80±7	79±10	0.7
Mean	95±6	95±10	0.9
Pulse Pressure	45±8	50±12	0.009
Central Pressures (mmHg)			
Systolic	114±8	117±14	0.08
Diastolic	81±7	79±10	0.4
Mean	95±7	95±11	0.7
Pulse Pressure	33±6	38±11	0.02
Augmentation Pressure	6±3	9±7	0.04
Augmentation index (%)	21±10	22±13	0.5

doi: 10.1371/journal.pone.0076776.t002

Aortic Stiffness and Atrial Fibrillation Recurrence

During a mean (±SD) follow-up of 2.9±1.4 years, 38 of the 68 lone AF patients had recurrence of AF at 31±27 weeks after single ablation procedure. As shown in Table 3, there was no significant difference in patient characteristics, AF type and echocardiographic parameters between cases and controls. Specifically, there was no difference in anti-hypertensive medication use including beta-blockers, renin-angiotensin system inhibitors, calcium channel blockers and diuretic agents.

Even though no differences were seen in both mean peripheral and central pressures, patients with highest levels of aortic stiffness (≥75th percentile) had higher AF recurrence rates when compared to those with values less than the 75th percentile (Peripheral pulse pressure ≥57mmHg: 82% vs. 47%, P=0.01; Central pulse pressure ≥45mmHg: 87% vs. 47%, P=0.008; Augmentation pressure ≥12mmHg: 76% vs. 48%, P=0.04; Augmentation index ≥33%: 76% vs. 49%, P=0.055). Importantly, corresponding analysis of those with highest levels of central or peripheral systolic, diastolic and mean blood pressure (≥75th percentile) showed no relationship to higher AF recurrence rates. Likewise, left atrial dimensions (parasternal area & volume ≥75th percentile) and inter-ventricular septal thickness (≥75th percentile) were not significantly associated with higher AF recurrence (all P>0.7). In addition, only central aortic stiffness indices were associated with lower survival free from AF using Kaplan-Meier statistics (Central pulse pressure ≥75th percentile, P=0.02 – Figure 3A; Augmentation pressure ≥75th percentile, P=0.04 – Figure 3B; Augmentation index ≥75th percentile, P=0.053 & Peripheral pulse pressure ≥75th percentile, P=0.06 – both not illustrated).

Discussion

Major Findings

This study utilized well-validated, non-invasive central pulse wave analysis technique to examine central pressures and aortic stiffness in patients with lone AF who had no apparent

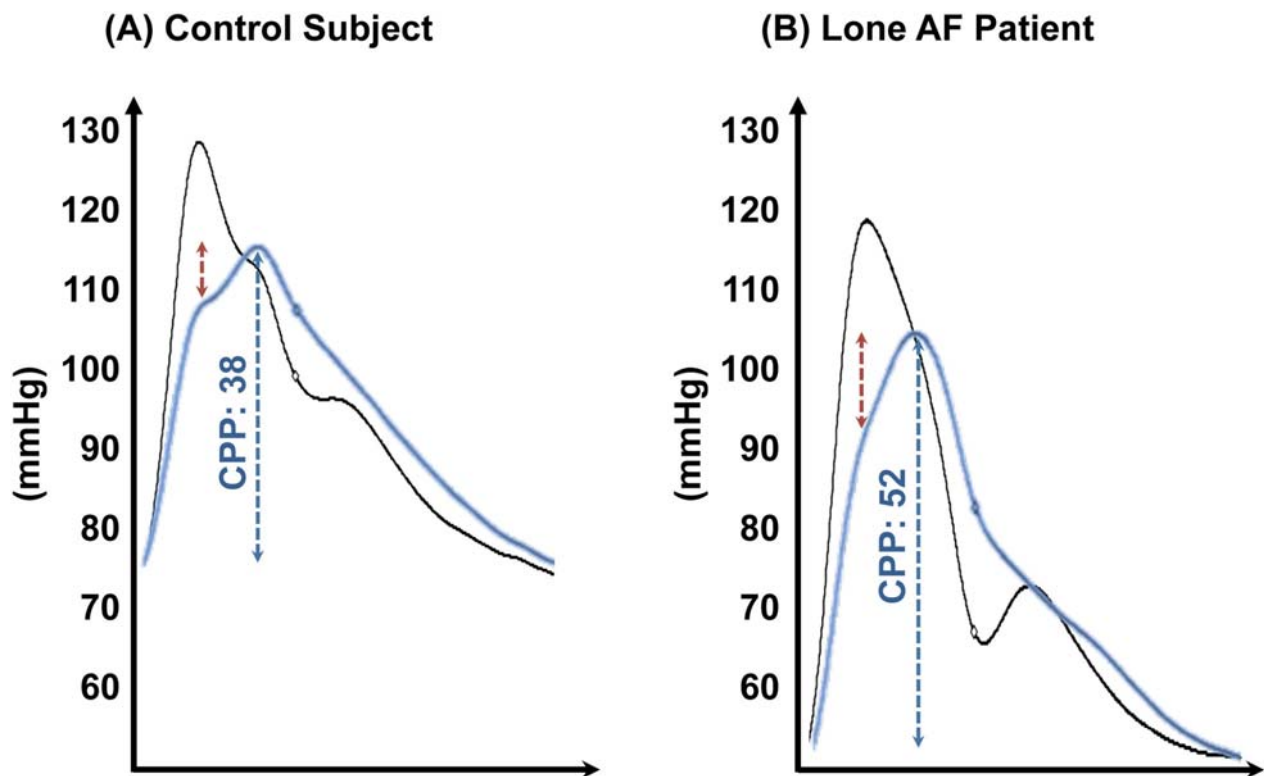


Figure 2. Examples of Peripheral and Central Pulse Waveforms. (A) Waveforms from a control subject showing peripheral pressures (black) of 128/76 with a pulse pressure of 52 mmHg and central pressures of 115/77 (blue) with a pulse pressure of 38 mmHg. Central augmentation pressure (red, *dotted*) is 7 mmHg. (B) Waveforms from a patient with lone AF showing peripheral pressures (black) of 120/54 with a pulse pressure of 66 mmHg and central pressures of 106/54 (blue) with a pulse pressure of 52 mmHg. Central augmentation pressure (red, *dotted*) is 12 mmHg.

doi: 10.1371/journal.pone.0076776.g002

structural heart disease and risk factors for AF. The major findings are as follows:

- 1 Increased aortic stiffness (higher pulse pressure and augmentation pressure) was evident in lone AF patients as compared to controls;
- 2 Measures of aortic stiffness demonstrated stronger association with AF recurrence following catheter ablation than standard brachial blood pressure measures and conventional echocardiographic parameters;
- 3 Lone AF patients had larger left atrial dimensions than controls.

Therefore, this study implicates aortic stiffness as a silent contributing factor in the development of lone AF. Elevated aortic stiffness, by leading to abnormal atrial remodeling, creates a path to development of the substrate that develops apparently "lone" AF.

Aortic Stiffness: A Silent Factor Leading to Remodeling and Atrial Fibrillation

Studies in lone AF patients have alluded to several underlying atrial abnormalities thereby pointing to the possibility

of as yet unrecognized risk factors. These abnormalities include: increased inflammation, diastolic dysfunction, increased fibrosis and microvascular dysfunction [15–18]. More recently, our group has demonstrated further evidence of significant electrical and structural changes in lone AF atria [8,9]. This included structural abnormalities evidenced by loss of myocardial voltage, conduction slowing, sinus node dysfunction and prolonged atrial refractoriness. Non-invasive delayed enhancement magnetic resonance imaging has also demonstrated this abnormal atrial substrate [10]. As such, lone AF patients are ideal candidates for studies aiming to uncover novel AF risk factors in the absence of structural heart disease [4,5]. As seen in this study, both peripheral and central measures of aortic stiffness were higher in lone AF patients and associated with higher arrhythmia recurrence following catheter ablation. Aortic stiffness may signify an 'atrial-myopathy' in patients who have apparent normal left atrial dimensions, ventricular thickness and brachial systolic blood pressure. The present study also affirms the findings of the Framingham study linking aortic stiffness to the development of AF [2]. We believe aortic stiffness is an unrecognized silent

Table 3. Characteristics and Hemodynamics by Atrial Fibrillation Recurrence.

	No AF Recurrence (n=38)	AF Recurrence (n=30)	P
Age (yr)	59.1±11.9	59.6±9.4	0.8
Male sex (%)	76.7	71.1	0.8
Body Mass Index (kg/m ²)	27.2±4.2	27.7±4.8	0.7
Paroxysmal/Persistent AF (%)	63.3/36.7	63.2/36.8	1.0
Echocardiography			
Left atrial parasternal size (cm)	3.8±0.5	3.9±0.8	0.7
Left atrial volume (ml)	62.5±17.5	68.9±27.0	0.4
Left atrial volume index (ml/m ²)	30.3±8.5	34.2±12.4	0.2
Left atrial area (cm ²)	20.8±4.1	22.3±5.6	0.3
Inter-ventricular septum (mm)	10.1±1.9	10.9±1.7	0.09
Left ventricular ejection fraction (%)	65.2±7.4	63.5±7.0	0.3
Peripheral Pressures (mmHg)			
Systolic	127±14	130±14	0.3
Diastolic	80±10	78±10	0.8
Mean	95±10	95±10	1.0
Pulse Pressure	47±9	52±14	0.3
Central Pressures (mmHg)			
Systolic	116±13	119±14	0.4
Diastolic	81±10	78±10	0.4
Mean	95±11	95±11	1.0
Pulse Pressure	35±8	40±13	0.3
Augmentation Pressure	7±4	10±8	0.2
Augmentation index (%)	21±10	23±14	0.6

doi: 10.1371/journal.pone.0076776.t003

factor in lone AF contributing to occult abnormal atrial remodeling.

Causes of Aortic Stiffness: Implications in Atrial Fibrillation

The causes of aortic stiffness remain incompletely understood. The lack of association between aortic stiffness and conventional cardiac risk factors other than hypertension and aging has been well documented [19–21]. Other possible contributing factors include inflammation and mechanical stress [20,22,23]. Interestingly, recent reports had also found increased arterial stiffness and P-wave duration in subjects with pre-hypertension [24,25]. Indeed, systolic blood pressure in the pre-hypertensive range has been shown to be independently associated with incident AF in a large prospective study [26]. Furthermore, pre-clinical work has shown a relationship between short-term hypertension and increased atrial inflammation leading to a substrate for AF [27]. The atrial remodeling process in the same hypertensive model was progressive, highlighting the potential benefits of early treatment to prevent formation of an arrhythmogenic substrate [28]. Taken together, aortic stiffness may identify a subset of at-risk patients in the pre-hypertensive spectrum. Recognition

and targeting of aortic stiffness in patients with or at risk of AF may be important in our bid to reduce the burden of this emerging epidemic.

Aortic Stiffness: Central versus Peripheral Measures

Theoretically, central pressure is more patho-physiologically relevant to the heart than their peripheral counterparts as its proximity will exert greater strain leading to increased afterload and impaired relaxation [5]. A recent systematic review and meta-analysis highlighted the value of central hemodynamic indices in predicting cardiovascular outcomes [3]. Central pulse wave analysis from applanation tonometry of the radial artery has been accepted as a valid measure of subclinical target organ damage. Central estimates of aortic stiffness as used in this study provided additional information that may also be useful for monitoring of therapeutic effects. Recently, the CAFÉ investigators have shown that different anti-hypertensive agents can have significantly different effects on central aortic pressures despite similar brachial readings [29]. Specifically, amlodipine±perindopril combination had greater effects on central pressures than atenolol±thiazide. While heart rate reduction with beta-blockade is thought to be responsible for the less effective central pressure reduction, whether the difference in central aortic pressures could explain the different clinical outcomes in these 2 groups remains unknown [30]. Nevertheless, further evaluation is required to assess central aortic stiffness in AF.

Clinical Implications

This study affirms aortic stiffness as a novel modifiable risk factor for AF. It can be used to identify “high-risk” pre-hypertensive patients with subclinical atrio-myopathy. Further studies are necessary to determine whether targeting of aortic stiffness with anti-hypertensive medications may modify the burden or progression of AF. Of note, agents with central blood pressure effects such as inhibitors of the renin angiotensin system have also been shown to reduce the occurrence of AF in various patient groups including normotensive lone AF patients [31,32].

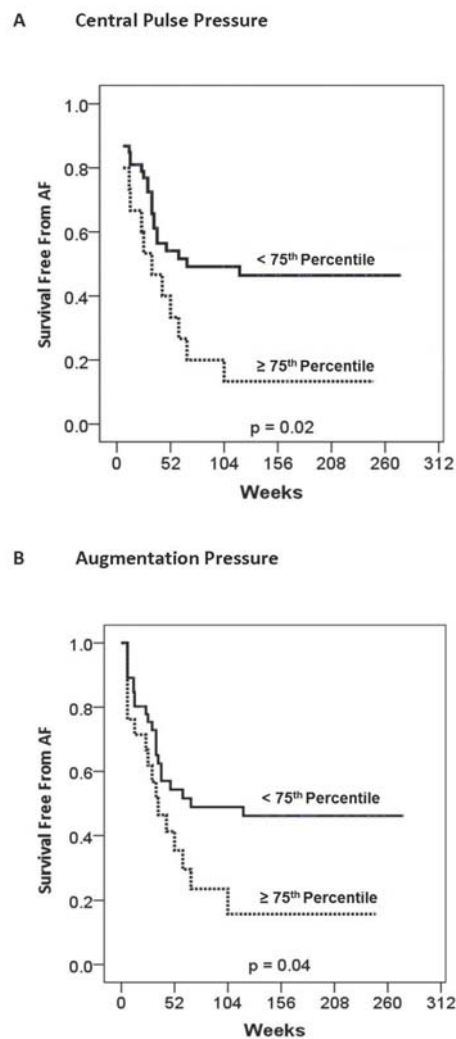
Study Limitations

We did not have longitudinal measures of central pulse wave analysis. Inclusion of pulse wave velocity measurements would have strengthened our findings. Pulse wave analysis ideally requires stable artery waveforms, which is difficult when a subject is in AF.

Conclusions

Lone AF is associated with greater aortic stiffness; which contributes to higher AF recurrence following catheter ablation procedures. Active monitoring and targeting of this novel risk factor may improve outcomes in patients with AF.

Figure 3: Kaplan-Meier Survival Curves



1

Figure 3. Kaplan-Meier Survival Curves. (A) Lone AF patients with central pulse pressure $\geq 75^{\text{th}}$ percentile had lower survival free from AF following catheter ablation. (B) Similarly, lone AF patients with augmentation pressure $\geq 75^{\text{th}}$ percentile had poorer outcome following catheter ablation.

doi: 10.1371/journal.pone.0076776.g003

Author Contributions

Conceived and designed the experiments: DHL MEM AGB ANG KCR WPA JMK PS. Performed the experiments: DHL MEM AGB SRW KCR ANG MKS DPL HSL HSA CXW.

Analyzed the data: DHL MEM AGB SRW DPL HSA HSL CXW MKS ANG. Contributed reagents/materials/analysis tools: KCR PS WPA GDY JMK. Wrote the manuscript: DHL WPA JMK PS KCR GDY AGB. NA.

References

- Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM et al. (2009) Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. *Circulation* 119: 606-618. doi:10.1161/CIRCULATIONAHA.109.192590. PubMed: 19188521.
- Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ et al. (2007) Pulse pressure and risk of new-onset atrial fibrillation. *JAMA* 297: 709-715. doi:10.1001/jama.297.7.709. PubMed: 17312290.
- Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K et al. (2010) Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 31: 1865-1871. doi:10.1093/eurheartj/ehq024. PubMed: 20197424.
- Guidelines Committee (2003) 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 21: 1011-1053. doi:10.1097/00004872-200306000-00001. PubMed: 12777938.
- Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME et al. (2007) Central blood pressure measurements and antihypertensive therapy: a consensus document. *Hypertension* 50: 154-160. doi:10.1161/HYPERTENSIONAHA.107.090068. PubMed: 17562972.
- Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C et al. (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 27: 2588-2605. doi:10.1093/eurheartj/ehl254. PubMed: 17000623.
- Sakuragi S, Abhayaratna WP (2010) Arterial stiffness: methods of measurement, physiologic determinants and prediction of cardiovascular outcomes. *Int J Cardiol* 138: 112-118. doi:10.1016/j.ijcard.2009.04.027. PubMed: 19473713.
- Stiles MK, John B, Wong CX, Kuklik P, Brooks AG et al. (2009) Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the "second factor". *J Am Coll Cardiol* 53: 1182-1191. doi:10.1016/j.jacc.2008.11.054. PubMed: 19341858.
- Wong CX, Stiles MK, John B, Brooks AG, Lau DH et al. (2010) Direction-dependent conduction in lone atrial fibrillation. *Heart Rhythm* 7: 1192-1199. doi:10.1016/j.hrthm.2010.05.037. PubMed: 20639109.
- Mahnkopf C, Badger TJ, Burgon NS, Daccarett M, Haslam TS et al. (2010) Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: implications for disease progression and response to catheter ablation. *Heart Rhythm* 7: 1475-1481. doi:10.1016/j.hrthm.2010.06.030. PubMed: 20601148.
- Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR Jr et al. (1987) The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med* 317: 669-674. doi:10.1056/NEJM198709103171104. PubMed: 3627174.
- Chen CH, Nevo E, Fetis B, Pak PH, Yin FC et al. (1997) Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 95: 1827-1836. doi:10.1161/01.CIR.95.7.1827. PubMed: 9107170.
- Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ et al. (2012) 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. *Heart Rhythm* 9: 632-696. doi:10.1016/j.hrthm.2011.12.016. PubMed: 22386883.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E et al. (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18: 1440-1463. doi:10.1016/j.echo.2005.10.005. PubMed: 16376782.
- Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA et al. (1997) Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 96: 1180-1184. doi:10.1161/01.CIR.96.4.1180. PubMed: 9286947.
- Jais P, Peng JT, Shah DC, Garrigue S, Hocini M et al. (2000) Left ventricular diastolic dysfunction in patients with so-called lone atrial fibrillation. *J Cardiovasc Electrophysiol* 11: 623-625. doi:10.1111/j.1540-8167.2000.tb00023.x. PubMed: 10868734.
- Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A et al. (2001) C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 104: 2886-2891. doi:10.1161/hc4901.101760. PubMed: 11739301.
- Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE et al. (2008) Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. *J Am Coll Cardiol* 51: 2053-2057. doi:10.1016/j.jacc.2008.01.055. PubMed: 18498961.
- Cecelja M, Chowienicz P (2009) Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension* 54: 1328-1336. doi:10.1161/HYPERTENSIONAHA.109.137653. PubMed: 19884567.
- McEniery CM, Spratt M, Munnelly M, Yarnell J, Lowe GD et al. (2010) An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly prospective study. *Hypertension* 56: 36-43. doi:10.1161/HYPERTENSIONAHA.110.150896. PubMed: 20530296.
- McEniery CM, Yasmin, Maki-Petaja KM, McDonnell BJ, Munnelly M et al. (2010) The impact of cardiovascular risk factors on aortic stiffness and wave reflections depends on age: the Anglo-Cardiff Collaborative Trial (ACCT III). *Hypertension* 56: 591-597. doi:10.1161/HYPERTENSIONAHA.110.156950. PubMed: 20696989.
- Schnabel R, Larson MG, Dupuis J, Lunetta KL, Lipinska I et al. (2008) Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection. *Hypertension* 51: 1651-1657. doi:10.1161/HYPERTENSIONAHA.107.105668. PubMed: 18426996.
- Yasmin, McEniery CM, Wallace S, Mackenzie IS, Cockcroft JR et al. (2004) C-reactive protein is associated with arterial stiffness in apparently healthy individuals. *Arterioscler Thromb Vasc Biol* 24: 969-974. doi:10.1161/01.ATV.24.9.969. PubMed: 15001456.
- Celik T, Yuksek UC, Bugan B, Celik M, Fici F et al. (2009) P-wave dispersion and its relationship to aortic elasticity in young prehypertensive patients. *Am J Hypertens* 22: 1270-1275. doi:10.1038/ajh.2009.157. PubMed: 19779469.
- Gedikli O, Kiris A, Ozturk S, Baltaci D, Karaman K et al. (2010) Effects of prehypertension on arterial stiffness and wave reflections. *Clin Exp Hypertens* 32: 84-89. doi:10.3109/10641960902993103. PubMed: 20374190.
- Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE et al. (2009) Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 119: 2146-2152. doi:10.1161/CIRCULATIONAHA.108.830042. PubMed: 19364977.
- Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Worthington M et al. (2010) Short-term hypertension is associated with the development of atrial fibrillation substrate: a study in an ovine hypertensive model. *Heart Rhythm* 7: 396-404. doi:10.1016/j.hrthm.2009.11.031. PubMed: 20185115.
- Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG et al. (2010) Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. *Heart Rhythm* 7: 1282-1290. doi:10.1016/j.hrthm.2010.05.010. PubMed: 20466075.
- Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A et al. (2006) Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 113: 1213-1225. doi:10.1161/CIRCULATIONAHA.105.595496. PubMed: 16476843.
- Williams B, Lacy PS (2009) Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. *J Am Coll Cardiol* 54: 705-713. doi:10.1016/j.jacc.2009.02.088. PubMed: 19679248.
- Schneider MP, Hua TA, Böhm M, Wachtell K, Kjeldsen SE et al. (2010) Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol* 55: 2299-2307. doi:10.1016/j.jacc.2010.01.043. PubMed: 20488299.

32. Belluzzi F, Sernesi L, Preti P, Salinaro F, Fonte ML et al. (2009) Prevention of recurrent lone atrial fibrillation by the angiotensin-II

converting enzyme inhibitor ramipril in normotensive patients. *J Am Coll Cardiol* 53: 24-29. doi:10.1016/j.jacc.2008.08.071. PubMed: 19118720.