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Relation of Functional Status to Risk of Development of Atrial Fibrillation

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ABSTRACT

Identifying patients at risk is now important as there are demonstrable ways to alter disease progression which could potentially prevent atrial fibrillation (AF) and its complications. We sought whether impaired functional capacity was associated with risk of AF, independent of myocardial dysfunction. In this community-based study, asymptomatic participants ≥ 65 years were recruited if they had ≥1 risk factor (eg. hypertension, diabetes mellitus and obesity). Participants underwent baseline echocardiography (including measurement of myocardial mechanics) and six minute walk test (SMWT). The CHARGE-AF score was used to calculate 5 year risk of developing AF. Receiver operator characteristics (ROC) curves were used to assess for independent risk factors for AF. A total of 607 patients (age 71±5 years, male 47%) were studied at baseline and followed for at least 6 months. Patients in the higher AF risk groups were older and had increased rates of hypertension, diabetes mellitus and ischemic heart disease ($p<0.05$). Higher AF risk was associated with lower exercise capacity, independent of lower mean global longitudinal strain (GLS), global circumferential strain (GCS), higher mean E/e’ ratio, indexed left atrial (LA) volume and LV mass. Multivariable linear regression confirmed association of LV and functional capacity parameters with AF risk. Although functional capacity is impaired in AF, this association precedes the onset of AF. In conclusion, poor functional status is associated with AF risk, independent of LV function.

Keywords: Atrial Fibrillation, risk, functional capacity

Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality,[1,2] including stroke, heart failure with impaired and preserved ejection fraction,[3] functional impairment,[4] and poor prognosis.[5] Although the prevalence of atrial fibrillation (AF) continues to increase in the aging population, there is currently not a proactive management approach in which patients at risk of AF are identified and treated before the onset of symptoms or complications. Earlier diagnosis of AF might have several benefits. The risk of AF increases following episodes of AF[6] and this likely contributes to atrial remodelling and altered mechanics.[7] Early diagnosis may allow prevention of complications such as stroke and heart failure, and prevention may avoid the symptoms, impaired quality of life and overall burden on the health care system associated with AF.[1,2] When implemented early, lifestyle interventions (eg. weight loss) have been associated with a reduction in symptom burden as well as improved cardiac remodelling.[8] Such an approach to prevention may be analogous to stage B heart failure,[9] the diagnosis of which in patients with risk factors permits the early implementation of pharmacological therapy and risk factor management to prevent or delay the onset of symptomatic heart failure. The risk factors for AF (hypertension, obesity and the metabolic syndrome) are common and not specific. We sought whether the detection of impaired functional capacity could better characterize risk of AF.

Methods.

This observational cohort study recruited patients from a large community based in Tasmania, which had the primary objective of early detection of heart failure. Asymptomatic participants ≥65 years were recruited if they had 1 or more risk factors, including hypertension (systolic blood pressure > 140mmHg or pre-existing use of anti-hypertensive medications), type 2 diabetes mellitus (based on self-report of diagnosis or the current use of diabetic medications), obesity (defined as a body mass index ≥ 30), previous chemotherapy, previous history of coronary artery disease or family history of heart failure. Exclusion criteria included: (1) Inability to provide written consent to participate in the study, (2) history of moderate or greater valvular disease, (3) known history of heart failure, (4) reduced left ventricular (LV) systolic function on baseline echocardiogram (LV ejection fraction <40%), (5) contraindications to beta blockers and angiotensin converting enzyme inhibitors, (6) expected life expectancy of less than one year or (7) inability to acquire interpretable images from baseline echocardiogram. All patients with a known history of AF or documented AF on baseline electrocardiography (ECG) were excluded from the study. All patients were provided written informed consent and ethics approval was obtained from the institution’s Human Research Ethics Committee.

All participants undertook a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, medical history, medication history as well as baseline examination data (height, weight, body mass index and blood pressure was recorded for all participants. Baseline ECG and echocardiography was conducted in all participants.

The CHARGE-AF score[10] uses 12 clinical parameters (age, race, height, weight, systolic/diastolic blood pressure, current smoking, use of anti-hypertensives, history of diabetes mellitus/myocardial infarction, history of heart failure and ECG data (voltage criteria for left ventricular hypertrophy and PR interval) to assess 5 year risk of AF. Cardiovascular fitness was assessed using the six minute walk test (SMWT). This was conducted in marked corridors adjacent to the clinic where the total distance covered over six minutes was calculated to the nearest meter. All patients answered questionnaires to assess overall quality of life and function. These included the Duke Activity Status Index (DASI)[11], Minnesota Living with Heart Failure score (MLHF)[12], Charlson Index[13] and EuroQoL5D Visual Analog Scale (EQ-VAS).[14]

Echocardiograms were performed by qualified sonographers using the same equipment (Siemens ACUSON SC2000, Siemens Healthcare, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz). Two dimensional, M-Mode and Doppler measures were obtained using techniques outlined by the American Society of Echocardiography. LV dimensions were calculated in both diastole and systole in parasternal long axis views. LV hypertrophy was defined as LV mass index >115 g/m^2 in men and >95 g/m^2 in women. LV and left atrial (LA) volumes were indexed to body surface area and calculated by the Simpson biplane method. Abnormal LA volume index was defined as ≥34 ml/m^2.

Diastolic function was assessed by calculating mitral inflow peak early and late diastolic velocities (E and A wave), deceleration time and the E/A ratio (ratio <0.8 was used to define for impaired relaxation). The average of septal and lateral mitral annular early diastolic velocity (e’) was used to calculate the E/e’ ratio (> 13 was used to define raised LA filling pressures).

Global longitudinal strain (GLS) was calculated in apical 4 chamber views and global circumferential strain (GCS) was calculated in the mid-LV parasternal short axis view. Velocity vector imaging was used to assess ventricular strain. Manual tracing of the endocardial border of the LV was performed in end-systole and this was tracked during the cardiac cycle.

Patients were split into four groups based on AF risk (low 0-5%, medium 5-10%, high 10-15% and very high >15%). The primary outcome was to assess whether poor functional capacity was an independent risk factor for AF. All categorical variables are presented as frequencies/percentages and continuous variables presented as means/standard deviation (if normally distributed) or medians/IQR (if non-parametric). Statistical significance was performed using the chi square test for categorical data. Analysis of variance (ANOVA) was used to assess the interaction between groups. Associations between variables were assessed using linear regression. All variables with p<0.1 in univariable analyses were considered in multivariate models. ROC curves were generated to determine optimal cut-off values of continuous variables. Analyses were considered to be statistically significant if 2 tailed p values were <0.05. Statistical analysis was performed using SPSS v.22 (IBM, Chicago, Illinois).

Results

A total of 607 patients were included (mean±SD age 70.9±4.8 years, male 47%). The majority of patients had risk factors for heart failure and AF including type 2 diabetes mellitus (51%), obesity (43%), hypercholesterolemia (51%) and hypertension (79%). The median AF risk (CHARGE-AF) was 7.0% (IQR 3.5–10.5%). Baseline patient characteristics are summarized in Table 1.

Participants were split into 4 groups based on AF risk (low 0-5%, medium 5-10%, high 10-15% and very high risk >15%) (Table 2). Patients with higher AF risk were older, more likely to be male with higher systolic blood pressure and rates of diabetes mellitus, hypercholesterolemia and ischemic heart disease (p<0.05). Patients with low AF risk had a higher proportion who had previous chemotherapy. There was no statistically significant difference in smoking rates and body mass index between groups.

AF risk was associated with reduced functional capacity (Table 4). SMWT was lower in higher AF risk groups (496m in low risk vs. 432m in very high risk, $p<0.001$), and patients with higher AF risk had lower DASI scores ($p<0.001$), and had more medical co-morbidities ($p=0.04$).

Univariable regression showed clinical AF risk was associated with impaired functional capacity (assessed by SMWT and DASI), as well as quality of life (EQ-VAS), Charlson Index and male gender. In a multivariable linear regression model, SMWT (β = -0.188, $p<0.001$) was independently associated with clinical AF risk. Using ROC curves, the optimal cutoff for SMWT was 500m (AUC 0.60, 95% C.I 0.56 to 0.65, $p<0.001$), for DASI was 42.7 (AUC 0.64, 95% C.I 0.59 to 0.69, $p<0.001$) and for MLHF was 24 (AUC 0.59, 95% C.I 0.51 to 0.68, $p=0.02$) (see Figure 1).

The association between AF risk and atrial and LV parameters is shown in Table 3. Higher clinical AF risk was associated with lower ejection fraction (60±5.9 vs. 62±4.8% in lowest risk, $p=0.001$), worse GLS (-17.6±2.6% vs -19.1±2.4% in lowest risk, $p<0.001$) and GCS (-29.7±4.9 vs -31.0±5.7%, $p=0.002$). Indexed LV mass was noted to be higher in patients with higher AF risk (99.4±24.8 g/m^2 vs 84.5±21.4 g/m^2, $p<0.001$). AF risk was associated with GLS (β = 0.19, $p< 0.001$), E/e' (β = 0.16, $p<0.001$) and male gender (β = 0.26, $p< 0.001$). Using ROC curves, the optimal cutoff for GLS was -18% (AUC 0.598, 95% C.I 0.552 to 0.643, $p<0.001$), and that for indexed LA volume was 35 ml/m^2 (AUC 0.586, 95% C.I 0.537 to 0.635, p = 0.001).

Discussion

This study suggests that AF risk is associated with impaired functional capacity as assessed with the SMWT and less activity (assessed by the DASI), independent of LV function and LV mass. SMWT <500m as well as DASI <42.7 and MLHF >24 were associated with AF risk.

A number of clinical features are associated with AF, including the metabolic syndrome, hypertension and type 2 diabetes mellitus. The CHARGE-AF score was developed from a total of 18,556 patients with a wide age range (46–94 years) and ethnic diversity (19% African-Americans) based on pooled data from the Framingham Heart Study[15], the ARIC[16] and the Cardiovascular Health Study (CHS)[17]. The bedside clinical score gives a 5 year risk of developing AF using clinical variables including age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive therapy, history of diabetes mellitus/myocardial infarction and heart failure with overall good model discrimination (C-statistic 0.765, 95% C.I 0.748 – 0.781). The CHARGE-AF score has been validated in multiple cohorts, is easy to implement in clinical practice, and can be calculated in the absence of ECG data.[10]

A deficiency in clinical risk scores is that they do not incorporate atrial or LV mechanics or LA size, all of which are implicated in the pathogenesis of AF.[7,18-20] AF risk is associated with reduced atrial reservoir, conduit and pump strain[21] which is likely a marker of progressive atrial fibrosis and can be used to predict recurrence following catheter ablation[22] or cardioversion.[23] The use of LV strain analysis to predict AF risk is poorly understood. LV regional deformation allows for objective assessment of systolic function.[24] LV strain analysis has important applications for the assessment for cardiomyopathy, myocardial ischemia[24,25] and assessment for LV dyssynchrony post cardiac resynchronization therapy.[24] Changes to atrial size and fibrosis in the absence of mitral valve disease is often due to progressive changes to the LV including increase in LV mass, higher filling pressures and concentric remodelling which are commonly associated with age and hypertension and give rise to poor exercise capacity.[26]

We have found in this study that altered myocardial mechanics are independently associated with AF risk. This has several implications for clinical practice. Echocardiography and deformation analysis is non-invasive, easily accessible and cost effective and can be utilised in screening programs. This can potentially lead to early diagnosis of AF prior to the onset of complications such as stroke. The relationship between AF and LV mechanics also raises the possibility of AF risk in patients with underling structural heart disease or a known history of heart failure. AF in these patients is associated with a poorer prognosis, thus early diagnosis would impact prognosis.[5]

AF is associated with impaired quality of life and poor functional capacity.[2] Restoration of sinus rhythm following pharmacological therapy or catheter ablation is associated with improvement in New York Heart Association functional class, improvement in quality of life and modest improvement in exercise capacity.[27] Whilst the link between AF and quality of life is well understood, it is unclear if poor functional capacity can contribute to AF risk. Common risk factors for AF such as obesity, hypertension and type 2 diabetes mellitus are associated with impaired quality of life and reduced exercise capacity.[8,28] Poor exercise capacity could offer a surrogate risk assessment tool in clinical practice to identify patients at risk of AF.

While the link between AF and quality of life is well understood, previous work has not shown whether poor functional capacity can contribute to AF risk. The results of our study suggest that poor exercise capacity is an independent risk factor for AF. Exercise and weight loss programs have recently been shown to improve AF symptom burden and atrial remodelling.[29] The reasons why poor exercise capacity contributes to AF risk is unclear. Improvement in cardiovascular fitness may have a protective role in AF possibly by preventing atrial remodelling. The strong association between immobility and obesity may lead to altered atrial mechanics and increased atrial size which can create a substrate for arrhythmia. Patients with poor functional capacity are more likely to have associated co-morbidities such as hypertension and diabetes mellitus which are known risk factors for AF. Poor exercise capacity could offer a surrogate risk assessment tool in clinical practice to identify patients at risk of AF.

The limitations of our study include potential for population selection bias as patients were recruited with newspaper and radio advertising. Our study is an observational study and our primary outcome measure was to assess AF risk using a validated risk score. A potential weakness is that we did not follow up patients to assess the true incidence of AF in the cohort. Hence although we are able to attribute higher AF risk, we are unable to demonstrate a higher incidence of AF in patients with reduced functional capacity.

AF places a huge burden on the health care system and screening programs to identify patients at risk of AF will be important in the future, as there are demonstrable ways to alter disease progression which could potentially prevent AF and its complications. Mass screening has the potential to be expensive so assessment should begin with a clinical risk assessment tool. The association of reduced exercise capacity and functional status with AF risk has two implications. It may be a marker of treatable risk, similar to obesity, as well as identifying a patient subgroup appropriate for close monitoring for AF.

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Figure legends:

Figure 1. Receiver Operator Characteristic (ROC) Curves comparing functional capacity parameters to AF risk. Abbreviations: DASI – Duke Activity Status Index, MLHF – Minnesota Living with Heart Failure Score, SMWT – Six minute walk test. A) ROC curve comparing male gender to CHARGE-AF. B) ROC curve comparing six minute walk test cutoff 500m to CHARGE-AF. C) ROC curve comparing Duke Activity Status Index cutoff 42.7 to CHARGE-AF. D) ROC curve comparing Minnesota Living with Heart failure Score cutoff 24 to CHARGE-AF.

Tables:

Table 1 – Baseline characteristics of cohort

Table 2 – Clinical characteristics of participants in relation to AF risk. There are significant differences in relation to age, sex, blood pressure, diabetes, hypertension, ischemic heart disease, past chemotherapy and current medical therapy.

Table 3 - Association between AF risk with atrial and left ventricular dysfunction

Table 4 – Association between AF and functional capacity

Table 1 – Baseline characteristics of cohort

Baseline Characteristic	Total Cohort (n = 607)
Age (years) (SD)	70.9 ± 4.8
Men	282 (47%)
Systolic BP (mmHg) (SD)	140.0 ± 16.8
Diastolic BP (mmHg) (SD)	81.8 ± 10.4
BMI (kg/m^2) (SD)	29.4 ± 5.3
Current Smoking	14 (2%)
Diabetes Mellitus	311 (51%)
Obesity	263 (43%)
Hypercholesterolemia	307 (51%)
Hypertension	481 (79%)
Previous history of IHD	47 (8%)
Previous chemotherapy	74 (12%)
Baseline Medications	
Beta blockers	40 (7%)
ACE-I/ARB	405 (67%)
Calcium blockers	129 (21%)
Lipid Lowering drugs	306 (50%)
Anti-platelet agents (aspirin/clopidogrel/ticagrelor/prasugrel)	209 (34%)

Obesity – defined as Body Mass Index ≥ 30 kg/m^2

Table 2 – Clinical characteristics of participants in relation to AF risk. There are significant differences in relation to age, sex, blood pressure, diabetes, hypertension, ischemic heart disease, past chemotherapy and current medical therapy.

Variable	**Low Risk (0-5%) n = 185**	**Moderate Risk (5-10%) n = 228**	**High Risk (10-15%) n = 103**	**Very High Risk (> 15%) n = 91**	**P Value**
Age (years (SD)	68.1 (2.9)	68.9 (3.5)	72.7 (4.0)	76.9 (5.0)	< 0.001
Men	44/185 (24%)	118/228 (52%)	66/103 (64%)	54/91 (59%)	< 0.001
Systolic BP (mmHg) (SD)	136.0 (15.1)	138.8 (14.6)	140.7 (16.4)	150.5 (21.1)	< 0.001
Diastolic BP (mmHg) (SD)	81.0 (10.4)	81.5 (9.8)	82.7 (10.3)	83.2 (12.0)	0.324
BMI (kg/m^2) (SD)	28.9 (4.9)	29.4 (5.4)	30.7 (6.1)	29.3 (4.9)	0.064
Current Smoking	1/185 (0.5%)	5/228 (0.2%)	3/103 (3%)	5/91 (5.4%)	0.077
Diabetes Mellitus n/total	68/185 (37%)	118/228 (52%)	69/103 (67%)	56/91 (62%)	< 0.001
Obesity n/total	75/185 (41%)	96/228 (42%)	51/103 (49.5%)	41/91 (45%)	0.486
Hypercholesterolemia n/total	83/183 (45%)	115/209 (55%)	58/96 (60%)	51/85 (60%)	0.039
Hypertension n/total	126/185 (68%)	181/228 (79%)	88/103 (85%)	86/91 (95%)	< 0.001
Previous history of IHD n/total	3/185 (2%)	15/228 (7%)	14/103 (14%)	15/91 (16%)	< 0.001
Previous chemotherapy n/total	32/185 (17%)	26/228 (11%)	12/103 (12%)	4/91 (4%)	0.020
Baseline Medications					
Beta blockers n/total	8/185 (4%)	15/228 (7%)	9/103 (9%)	8/91 (9%)	0.387
ACE-I/ARB n/total	111/185 (60%)	157/228 (69%)	74/103 (72%)	63/91 (69%)	0.127
Calcium blockers n/total	25/182 (14%)	49/199 (25%)	27/95 (28%)	28/79 (35%)	0.001
Lipid Lowering drugs n/total	85/182 (47%)	111/202 (55%)	59/95 (62%)	51/79 (65%)	0.019
Anti-platelet agents (aspirin.clopidogrel/ticagrelor.prasugrel) n/total	49/182 (27%)	78/200 (39%)	41/93 (44%)	41/79 (52%)	0.001

Table 3 - Association between AF risk with atrial and left ventricular dysfunction

	Clinical AF risk (CHARGE-AF)						**Univariate**		**Multivariate**	
Independent Variables	**Low Risk (0-5%) Mean (SD)**	**Medium Risk (5-10%) Mean (SD)**	**High Risk (10-15%) Mean (SD)**	**Very High Risk (> 15%) Mean (SD)**	**P value**	**R^2**	**Standardized Coefficient (β)**	**ANOVA F statistic (P value)**	**β**	**P Value**
Male	44/185 (24%)	118/228 (52%)	66/103 (64)	54/91 (59)	< 0.001	0.068	0.260	F(1, 605) = 44.0 (< 0.001)	0.263	<0.001
Ejection Fraction (%)	62.2 (4.8)	60.7 (5.6)	60.2 (6.0)	59.6 (5.9)	0.001	0.018	-0.134	F(1, 599) = 11.0 (0.001)		
Global Longitudinal Strain (%)	-19.1 (2.4)	-18.4 (2.6)	-18.4 (2.5)	-17.6 (2.6)	< 0.001	0.035	0.186	F(1, 605) = 21.6 (< 0.001)	0.125	0.002
Global Longitudinal Strain Rate (s^{-1})	-1.38 (0.24)	-1.33 (0.18)	-1.35 (0.18)	-1.31 (0.20)	0.21	0.009	0.094	F(1, 604) = 5.4 (0.02)		
Global Circumferential Strain (%)	-31.0 (5.7)	-29.5 (5.4)	-28.6 (6.0)	-29.7 (4.9)	0.002	0.004	0.066	F(1, 603) = 2.6 (0.11)		
Global Circumferential Strain Rate (s^{-1})	-2.7 (0.71)	-2.5 (0.62)	-2.5 (0.65)	-2.6 (0.56)	0.263	0.001	0.028	F(1, 603) = 0.47 (0.50)		
E′ Average (m/s)	0.076 (0.02)	0.078 (0.02)	0.076 (0.02)	0.070 (0.02)	0.003	0.017	-0.131	F(1, 605) = 10.6 (0.001)		
E/e' (Average septal and lateral)	8.71 (2.4)	8.60 (2.4)	8.98 (2.5)	10.0 (3.1)	< 0.001	0.026	0.162	F(1, 605) = 16.3 (< 0.001)	0.202	<0.001
Left atrial volume (ml/m^2) - indexed	30.1 (9.2)	31.4 (10.0)	32.6 (7.6)	34.7 (10.5)	0.001	0.029	0.170	F(1, 604) = 18.1 (<0.001)		
Left Ventricular mass (g/m^2) – indexed	84.5 (21.4)	92.1 (21.2)	96.1 (23.1)	99.4 (24.8)	< 0.001	0.053	0.230	F(1, 604) = 33.6 (<0.001)		
Multivariate Regression Model						0.124				F (3,603) = 28.5 (<0.001)

Table 4 – Association between AF and functional capacity

	Clinical AF risk (CHARGE-AF					**Univariate**			**Multivariate**	
Independent Variables	**Low Risk (0-5%) Mean (SD) n = 185**	**Medium Risk (5-10%) Mean (SD) n = 228**	**High Risk (10-15%) Mean (SD) n = 103**	**Very High Risk (> 15%) Mean (SD) n = 91**	**P value**	**R^2**	**Standardized Coefficient (β)**	**ANOVA F statistic (P value)**	**β**	**P Value**
Male	44/185 (24)	118/228 (52)	66/103 (64)	54/91 (59)	< 0.001	0.068	0.260	F(1, 605) = 44.0 (< 0.001)	0.306	< 0.001
Six Minute Walk Test (m)	495.8 (89.4)	484.9 (93.7)	438.9 (110.6)	431.8 (117.2)	< 0.001	0.064	-0.253	F(1, 571) = 39.1 (<0.001)	-0.188	< 0.001
Duke Activity Status Index	46.8 (10.5)	44.2 (11.6)	40.2 (13.3)	38.6 (13.5)	< 0.001	0.078	-0.279	F(1, 592) = 50.0 (< 0.001)		
Minnestoa Living with Heart Failure Score	4.7 (10.4)	6.0 (12.1)	9.7 (12.9)	10.8 (16.2)	< 0.001	0.040	0.199	F(1, 590) = 24.3 (<0.001)		
EuroQoL EQ-5D Visual Analogue Score	82.2 (13.8)	80.5 (15.4)	79.8 (15.2)	78.9 (14.8)	0.308	0.007	-0.084	F(1, 590) = 4.21 (0.041)		
Charlson Index	1.8 (2.4)	1.6 (2.0)	2.3 (2.8)	2.2 (2.6)	0.043	0.008	0.087	F(1, 605) = 4.59 (0.033)		
Multivariate Regression Model						0.184				F (6, 562) = 21.2 (<0.001)