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ATRIAL FIBRILLATION AND ITS ASSOCIATION TO CARDIAC FUNCTION AND STRUCTURE IN CARDIOVASCULAR DISEASE

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Stockholm MMXIV

Published by Karolinska Institutet.

ISBN 978-91-7549-608-5

Printed by
REPROPRINT AB
Stockholm 2014
www.reproprint.se
Gårdsvägen 4, 169 70 Solna

Karolinska Institutet

ATRIAL FIBRILLATION AND ITS ASSOCIATION TO CARDIAC FUNCTION AND STRUCTURE IN CARDIOVASCULAR DISEASE
AKADEMISK AVHANDLING

Som för avläggande av medicine licenciat examen vid Karolinska Institutet offentligen försvaras i Föreläsningssal 1 hus 18, plan 5, Danderyds sjukhus
Fredagen den 28 november kl 09.00

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STOCKHOLM 2014

ABSTRACT

Title: Atrial fibrillation and its association to cardiac function and structure in cardiovascular disease

Aim: To study associations between atrial fibrillation (AF) and echocardiographic measures of left atrial (LA) and left ventricular (LV) parameters in patients with underlying cardiovascular disease.

Hypothesis: LA and LV dysfunction can predict AF in heart failure (HF) or ischemic stroke.

Background: AF is a cardiac arrhythmia characterized by irregular ventricular rhythm caused by permanent or paroxysmal loss of normal sinus node function. AF is prevalent (3%) and rises sharply with age and with increasing severity of HF (40-60%).

Methods: Study I: Elderly patients with chronic HF (n=67) were retrospectively analysed for LV systolic and diastolic function: **Study II**: Patients with an ischemic stroke/TIA (n=174) without known AF were prospectively analysed by echocardiography including Tissue Doppler Imaging (TDI) for LA and LV function. Electrocardiographic screening was used during follow up to detect AF.

Results: Study I: AF was found in 41 patients (61%). Ejection fraction was higher ($p<0.01$), LV volume indices were smaller ($p<0.001$) and LV concentric hypertrophy was more common ($p<0.05$), transmitral early wave deceleration time was shorter ($p<0.05$) and pulmonary S/D ratio lower ($p<0.001$) in AF compared to SR patients. **Study II**: AF was found in 15 patients (8.6%) during 30 days follow up. The AF patients had higher LA volume index (LAVI, $p<0.05$), lower peak velocities during atrial contraction (A′, $p<0.05$), and higher ratio LAVI/A′ ($p<0.01$). LAVI and LAVI/A′ predicted AF by ROC analysis (AUC 0.71-0.78).

Conclusions: AF in chronic HF and ischemic stroke indicates a different patient population compared to normal rhythm with signs of diastolic dysfunction or abnormal LA function. Echocardiography using TDI can predict AF after ischemic stroke and gives an incremental value together with electrocardiographic methods to improve screening for AF.

LIST OF SCIENTIFIC PAPERS

The present thesis is bases on the following studies, which will be referred to by their Roman numerals

I. **Waldenhjort D**, Mejhert M, Edner M, Rosenqvist M, Persson H

   Congestive heart failure with and without atrial fibrillation- different patient populations?

   Scandinavian Cardiovascular Journal 2009; 43: 169-175

II. **Waldenhjort D**, Sobocinski Doliwa P, Alam M, Frykman-Kull, Engdahl J, Rosenqvist M, Persson H

   Echocardiography detects unknown atrial fibrillation in patients with a transient ischemic attack or stroke.

   Submitted

CONTENTS

LIST OF ABBREVIATIONS

A	Late ventricular filling peak velocity
A´	Cardiac velocity during late ventricular filling
ADHF	Acute Decompensated Heart Failure
AF	Atrial Fibrillation
AUC	Area Under the Curve
CCT	Cardiac Computed Tomography
CMR	Cardiac Magnetic Resonance
CRT	Cardiac Resynchronization Therapy
DC	Direct Current
DT	Deceleration Time
E	Early ventricular filling peak velocity
E'	Cardiac velocity during early ventricular filling
ECG	Electrocardiogram/Electrocardiograph
EF	Ejection Fraction
IVRT	Isovolumic Relaxation Time
LAVI	Left Atrial Volume Index
LA	Left Atrium
LV	Left Ventricle/Left Ventricular
MPI	Mycardial Performance Index
PAF	Paroxysmal Atrial Fibrillation
PVa	Peak Pulmonary Vein a-wave flow velocity
PVd	Peak Pulmonary Vein flow velocity during diastole
PVs	Peak Pulmonary Vein flow velocity during systole
ROC	Receiver Operating Characteristics
SR	Sinus Rhythm
TDI	Tissue Doppler Imaging
TIA	Transient Ischemic Attack
VCO_2	Carbon dioxide production

VCO_2/VO_2	Respiratory quotient
VE/VCO_2	Ventilatory equivalent for carbon dioxide
VE/VO_2	Ventilatory equivalent for oxygen
VO_2	Oxygen consumption
VO_2AT	Oxygen consumption at anaerobic threshold

1 INTRODUCTION

1.1 EPIDEMIOLOGY.

Atrial fibrillation, (AF) is the most common rhythm disorder in the population and the prevalence increases with age (1). The condition is sometimes easy to diagnose using a standard 12 lead electrocardiographic (ECG recording). However, there is a wide variation of symptoms, some of the patients are totally asymptomatic (silent AF) and are not aware about the presence of AF. Others have episodic AF (paroxysmal or persistent AF), with or without symptoms.

In Swedish studies, the prevalence is recently approximated to 3 % of the population (2). Because of the lack of symptoms in some cases, the current prevalence of AF is probably underestimated. The detection rate has been improved by screening of the elderly population with known risk factors for AF (3). Local information activities in the primary care setting makes people more aware about the AF condition and its intertwined high risk of 5-7% yearly risk of thromboembolic complications.

1.2 DEFINITION OF ATRIAL FIBRILLATION

According to current guidelines (4, 5) AF is defined as: standard ECG shows irregular RR intervals, i.e RR intervals do not follow a repetitive pattern. There are no distinct P waves on the ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads most often lead V1. The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and >200 ms, corresponding to a heart rate of >300 atrial activations per minute. AF is considered to be paroxysmal (PAF) if the attacks are recurrent but terminate spontaneously within seven days. AF which do not terminate in seven days or need prior DC-cardioversion/ pharmacological agents is defined to be persistent. When no attempt is made to restore sinus rhythm, AF is defined as permanent.

1.3 COMORBIDITY AND ATRIAL FIBRILLATION

AF without structural changes in the heart is found predominantly in younger subjects and is termed lone AF, which is considered to be associated with a good prognosis (6). However, it is suggested that this entity is quite rare because of the emerging modern diagnostic imaging techniques which can detect early and subtle signs of abnormal cardiac function (7). In elderly subjects, AF is often accompanied with other diseases, such as hypertension, diabetes, congestive heart failure (CHF) and coronary artery disease. CHF in combination with AF is very common. In the large Swedish national registry RiksSvikt, AF is present in approximately 40-50 percent of the study population (8). In patients with CHF and preserved ejection fraction (HFPEF), there are indications suggesting the proportion of AF increases to over 60% with the concomitant diagnosis of AF (9). Further, the proportion of AF increases with severity of CHF (10).

It is important to identify and assess the risk profile including comorbidity for all individuals having AF. A substantial amount of data from the Framingham cohort study with a follow up time of more than 24 years have established a fivefold increase in risk for stroke for persons with chronic AF (11, 12) compared to no AF. In addition, more data are currently available describing the high risk for stroke with paroxysmal AF (PAF) which often is not fully treated with anticoagulants. This condition is often considered to be less harmful than chronic or permanent AF. A registry study from the largest hospitals of Scandinavia with a follow up time of six years confirms that the risk for stroke is twice in PAF compared to the general population and similar to the risk in permanent AF (13). It is thus very important to detect both symptomatic and silent AF because of the increased risk to develop thromboembolic complications, e.g. ischemic stroke. The prevalence of AF in patients with stroke is high, recent data says even higher than previously thought, 33% (14). Further, AF is shown to be an independent risk factor for myocardial infarction especially in women and in afroamerican cohorts (15).

1.4 HISTORICAL ASPECTS

In the ancient time in Greece, 2nd Century B.C., the Egyptian physicians were already aware about the heart and its function and structure. Symptoms and signs of illness were characterized and written down. In the early 19th Century the Egyptian papyrus was found by Egyptologists containing medical matters. Some of them were published by Georg Ebers in 1875 (the Ebers papyrus) Tachycardia and swelling of the limbs and dyspnoic symptoms were described already in the 2nd century B.C. This could, with our knowledge today, clearly illustrate some of the clinical pictures of CHF with or without possible concomitant AF.

The first ECG recordings were demonstrated in 1887 in London and later Willem Einthoven who was a professor of physiology from the Netherlands invented the string galvanometer and published his first article in 1903. In 1906 the first clinical ECG was transmitted from the laboratory to a nearby Academic hospital via transtelephonic technique.

The possibility to study the living and beating heart was an immediate diagnostic success when Inge Edler and Hellmuth Hertz in 1953 began to develop cardiac ultrasound and M-mode used to describe the mitral valve. Two-dimensional echocardiography was first demonstrated in the late 1950´s and with intracardiac probes in the 1960´s. Over time contrast echocardiography came in use in the 1960's which increased the clinical applications and later two dimensional transesophageal methods emerged. Development of the pulsed Doppler method in the late 1960s opened up a new era for diagnostic opportunities to measure intracardiac blood flow and pressure gradients. The Doppler techniques continued to evolve, to study motion and deformation in tissues which opened up for more accurate evaluation of the cardiac physiology when combined with 2-dimensional recordings. Today echocardiography with Doppler is the most commonly used non invasive method and is now considered as a routine in clinical practice.

1.5 SYMPTOMS AND DIAGNOSIS OF ATRIAL FIBRILLATION.

The most common symptoms of AF are palpitations, fatigue and dyspnoea and patients are often admitted to hospital because of a rapid and irregular heart rhythm. The diagnosis is confirmed by an ECG . However, many patients are not aware of the rhythm disorder (16). Some patients develop stroke as the presenting and even first symptom of AF at admission to hospital when the diagnosis of AF is confirmed by ECG. In these cases stroke is a complication of AF when a thrombus formed in the left atrium embolizes to the brain. The challenge is to find asymptomatic subjects with an increased risk for complications (CHA2DS-Vasc-score), in particular stroke. If the diagnosis of

AF is confirmed, the involved physicians have a responsibility to minimize risk for tromboembolic complications, using anticoagulant therapy (4).

The subjective symptoms might be difficult to interpret both for the patient and the physician. In the Classification list of symptoms adapted from the EHRA scoring system (European Heart Association), the severity of symptoms can be classified EHRA 1-5, and the higher score indicates more functional loss during everyday life (5). The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA HRQOL) is another method, trying to evaluate both physical and mental impairment of daily life activities in patients with arrhythmias in general. ASTA HRQOL has been found to be useful in the management and follow up of the medical or invasive treatment given to patients with AF (17).

AF is often confirmed by an ordinary 12-lead ECG. But 12-lead ECG requires equipment and staff to be performed, and the arrhythmia must also be present at the same time. Patients very often present with a normal ECG on having reported discomfort from the chest and a sense of palpitations and irregularity of the pulse. In PAF, patients need repeated recordings of ECG or Holter monitoring to confirm the diagnosis. A thumb led ECG (ZENICOR Medical systems) is also in use, where patients can use this recorder in outdoor settings, and in a standardized manner to collect ECG data for a prolonged time over weeks (18). There are also implantable devices (REVEAL) from which data can be obtained for months or even years. Similarly the patients who carry a standard or other pacemaker (e.g. heart failure pacemaker [CRT]), the device can be interrogated on a regular basis to evaluate episodes of AF.

1.6 ATRIAL FIBRILLATION AND EFFECTS ON CARDIAC FUNCTION

During normal sinus rhythm the cardiac cycle consists of a period of relaxation and filling of the ventricles, named diastole, followed by a period of contraction, named systole. Approximately 70 per cent of blood flows passively directly from the atria to the ventricles. Additionally 20-30 per cent is contributed when the atria contract. During diastole the ventricular volume increases. When AF occurs the atrial contribution to the ventricular filling is impaired leading to impaired cardiac output. Rapid tachycardia shortens the diastolic phase and the filling of the ventricle becomes inadequate. Rapid AF can lower the systolic blood pressure due to reduced cardiac output. If the LV is already affected due to hypertrophy, dilation, valvular disease or chronic ischemic heart disease, the diastolic filling becomes complicated and the LV is more dependent on atrial contribution. An episode of rapid AF further impairs the hemodynamics leading to severe symptoms and acute decompensated heart failure (ADHF). The rate control is therefore one of the therapeutic options trying to stabilize the patient when restoration of sinus rhythm is not possible, especially in the elderly patients with CHF (19).

1.7 THE LEFT ATRIUM

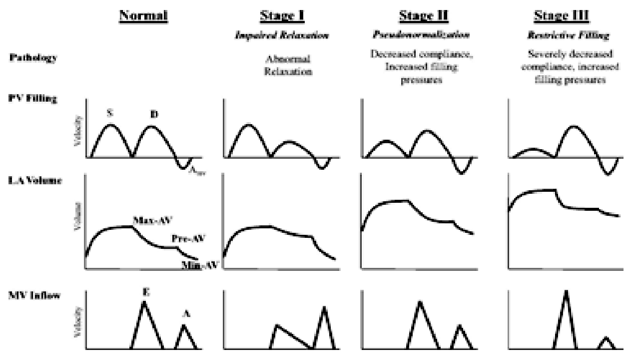
During ventricular systole the atrium accumulates blood because of the closed atrioventricular valves. When pressure is falling in the ventricle the rapid filling phase occurs in early diastole when the atrioventricular valves open shortly after the phase of isovolumic relaxation. The atrium enhances ventricular filling by its contraction in sinus rhythm (SR) after a short period of almost no filling (diastasis). AF alters the intraatrial pressure and longstanding AF affects the volume of the left atrium which becomes enlarged. This is called structural remodeling and is a complex and not yet fully understood process. The enlargement and changes in the atrium are also followed by electrical remodeling which can further initiate and maintain AF (20). Also, there is some evidence that fibrosis of the left atrium is a promoting mechanism for development of AF in patients with CHF (21). The enlargement and increased volume of the left atrium is, however complex. Concomitant valve diseases , i.e. mitral regurgitation and stenosis, hypertension and diastolic LV dysfunction all contribute to volume changes of the atrium. The measurements of the left atrium are therefore important and the anatomic variations and the outlining of the atria must be considered. The appendage, the pulmonary veins and sometimes elongation of the atria could be troublesome when measuring the volume and atrial function. The most current and clinically available method for measuring of cardiac structure and function is 2-dimensional echocardiography (2DE) for calculation of left atrial volume (LAV) and this could be indexed to body surface area (LAVI) according to present guidelines (22). Other modalities like cardiac computed tomography (CCT) and cardiac magnetic resonance (CMR) are feasible if accessible in the clinic (23).

1.8.1 LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

The diastolic phase of ventricular filling in the cardiac cycle consists of four components: ventricular isovolumetric relaxation, rapid filling phase of the ventricle, diastasis, and filling during atrial systole. The LV function during diastole is dependent on relaxation and compliance (24). The left atrium contracts during the atrial systole (late filling) and when AF occurs this active phase disappears and the contribution to ventricular filling is impaired. An enlarged left atrium or LAVI is considered to be an indication of reduced ability to fill the LV and a strong indicator of LV diastolic dysfunction (25). The progression from normal diastolic function to impaired relaxation of the LV is an early sign of mild diastolic dysfunction. This is followed by moderate diastolic dysfunction, named pseudonormalization, with increased filling pressures and a subsequent decreased compliance. The restrictive filling stage or severe diastolic dysfunction is categorized with severely decreased compliance and increased filling pressure. This process leads to an enlargement of the left atrium, and molecular changes in the calcium and contractile elements and possible atrial remodeling (26, 27). Diastolic functional assessment is complicated, but can be measured by 2DE, pulse-wave Doppler, tissue Doppler imaging (TDI) and speckle tracking.

There is no single measure to define diastolic function. An algorithm of several diastolic functional variables have to be used to categorize patients into one of the above categories of normal diastolic function, mild, moderate and severe diastolic dysfunction (24, 28, Figure below). Increase of end diastolic filling pressures is strongly associated with diastolic dysfunction and is also a hallmark of CHF. Filling pressure can be estimated noninvasively by Doppler echocardiography and TDI by using the E/E´ratio (29, 30). It is a particular challenge to measure diastolic function in patients with AF. However, LAVI, IVRT, DT, E/E´and pulmonary vein S/D ratio are possible to measure in AF.

Stages of diastolic dysfunction.



Rosenberg M A, and Manning W J Circulation. 2012;126:2353-2362.
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American Heart Association.

Assessment of LV diastolic function using transmitral pulse-wave Doppler (e.g. E/A ratio, E-wave DT and A wave velocity) has been in use for a long time but these variables are dependent on age, LV loading conditions (filling pressures) and medication. TDI is presently used more mandatory and predicts changes in the regional left atrial systolic function and changes correlating to normal ageing (31, 32). The progress of diastolic dysfunction, the remodeling and enlargement of left atrium and risk for developing AF is complex and not fully understood. Hypertension and ischemic heart disease promote diastolic dysfunction (24). Longstanding AF usually causes enlargement and remodeling of the left atrium. However the largest study examining the relationship between AF and diastolic dysfunction with 4480 participants in the Cardiovascular Health Study with a follow up for 12 years, stated that LA dimension, transmitral E- and A-wave velocity were independent risk factors for AF (33).

1.8.2 CARDIOPULMONARY EXERCISE TEST

During exercise, muscle cells need carbohydrates and fat and together with oxygen uptake to produce energy, i.e aerobic metabolism. Level of consumed oxygen at rest and during exercise (VO_2) is a measure of the amount of oxygen needed to produce the required energy during aerobic conditions. Carbon dioxide production (CO_2) is the end product of oxidative metabolism such as the production of exhaled (VCO_2) is measured to calculate energy use during aerobic and anaerobic conditions. The cardiopulmonary exercise test is used to evaluate CHF patients. It is known that peak or maximal or peak ventilatory parameters e.g. VO_2 and VCO_2 and derived cardiopulmonary indices like the ratio between amount of ventilation (VE) and VCO_2 (VE/VCO_2) are strong prognostic markers for mortality in young and elderly patients with CHF (34). These parameters are commonly used to assess objective evidence of functional capacity and prognosis in CHF and in particular before heart transplant surgery.

Recently published data showed that AF patients with HFPEF had lower peak VO2 during exercise compared to patients in sinus rhythm (35). AF was a marker of severity of HF with larger LA volumes, impaired diastolic function but also worse systolic function (within the context of preserved EF) compared to the sinus rhythm group. This illustrates the possible impact that AF itself reduces the physical capacity even when LV function is preserved and rate control is adequate. Further, in AF there is an obvious impact of lower stroke volume and cardiac index by the loss of atrial filling of the ventricles.

1.9 PROGNOSIS

AF is a complex disease that can be associated with an increased risk for thromboembolic events. It coexists with several other chronic and progressive disorders which further promote the burden of AF. Repeated episodes of AF itself stimulate the remodeling process and enlargement of left atrium and a vicious circle appears where the arrhythmogenic substrate maintains itself in the end. The independent impact of AF on prognosis in cardiovascular disesase is difficult to establish because the high mortality can be associated to the treatment of AF or to the underlying cardiovascular disease. AF is not a strong independent predictor of mortality in CHF (36). Some antiarrhythmic agents have sideffects, and severe bleeding complications with warfarin and the novel anticoagulants can be seen. Catheter ablation is not a completely harmless treatment option and even after a routine cardioversion (DC shock) thrombus can be formed and embolized.

The EURObservational Research programme- Atrial fibrillation General Registry Pilot phase collect data from 9 members of ESC countries and 3119 subjects, and the follow up time was one year. Despite oral anticoagulation the mortality was high 5.7% and the cause of death was cardiovascular in 70% of cases (37).

2 AIMS

1) To compare elderly hospitalized heart failure patients with or without AF with focus on echocardiographic and cardiopulmonary functional parameters.

2) To investigate if echocardiography including TDI can detect unknown AF in patients with an ischemic stroke/TIA

3 MATERIAL AND METHODS

3.1 SUBJECTS

Study I

The aim of this retrospective sub study was to compare elderly patients with CHF with or without AF regarding LV systolic and diastolic function.

Patients were derived from The Optimizing Congestive Heart Failure Outpatient Clinic Project (OPTIMAL), which was a randomized prospective study in patients hospitalized with HF between January 1996 and December 1999 at Danderyd University Hospital, a secondary referral center.

Sixty-seven elderly patients (Table 1) (age 60 years or more, mean age 74 years, female gender 34%) admitted to hospital due to CHF (NYHA class II-IV) and having an EF <45% or atrioventricular plane displacement (AVPD) less than 10 mm, were included. Subjects were divided into two subgroups, the sinus rhythm group (SR, n=26), and the atrial fibrillation group (AF, n=41).

Table 1 Demographic data at baseline

n = 67	Sinus rhythm n=26	Atrial fibrillation n=41
Age, mean (SD)	73 (7)	74 (6)
Females/males, n/n	8/18	15/26
Previous history n (%)		
Ischemic heart disease	21 (81)	23 (56)
Hypertension	8 (31)	11 (27)
Diabetes Mellitus	5 (19)	5 (12)
Idiopathic cardiomyopathy	3 (12)	6 (15)
Valvular disease	0 (0)	5 (12)
Prior heart failure	13 (50)	18 (44)
Medication n (%)		
Loop diuretics	24 (92)	39 (95)
ACE-inhibitors	22 (85)	33 (81)
Beta receptor blockade	12 (46)	28 (68)
Digitalis glycoside	7 (27)	28 (68)

n= number of patients.

Study II

The purpose of this sub study was to investigate if echocardiography including TDI at discharge, can predict unknown AF in patients after ischemic stroke.

Study population was derived from the PROPP-STOPP study conducted at Danderyds University Hospital, Södersjukhuset Stockholm and Hallands Hospital between 2007 and 2010 with focus on prevalence and detection of unknown AF in stroke patients.

This prospective echocardiographic study included 174 consecutive patients (mean age 74 years, female gender 40%) admitted to hospital with an ischemic stroke/TIA and sinus rhythm at admission. Patients were included within two weeks after the event. History of prior AF was an exclusion criterion (Table 2).

Table 2. Demographic data

	All	non AF	AF	P
Number of patients	174	159	15	
Age years mean (range)	74 (48 - 91)	74 (48 - 91)	75 (65 - 84)	0.68
Gender male	104 (60%)	98 (62%)	6 (40%)	0.10
Smokers	19 (11%)	18 (11%)	1 (7%)	0.58
Diabetes Mellitus	29 (17%)	28 (18%)	1 (7%)	0.28
Congestive Heart Failure	7 (4%)	7 (4%)	0 (0%)	0.41
Previous Stroke / TIA	39 (22%)	35 (22%)	4 (27%)	0.68
Ischemic Heart Disease	41 (24%)	39 (25%)	2 (13%)	0.33
Hypertension	112 (64%)	103 (65%)	9 (60%)	0.71
Previous Palpitations	26 (15%)	22 (14%)	4 (27%)	0.18

3.2 METHODS

Study I

All patients in this substudy were elderly patient with HF. After medical stabilization, echocardiography was performed and eligible patients with systolic dysfunction were enrolled. All echocardiographic measurements were calculated according to the American Society of Echocardiography using Acuson 128 XP/10 software.

AF was detected in 41 subjects at ECG, Holter monitoring or during exercise test and was considered as AF group. The SR-group consisted of patients with no visible AF during hospital stay. A cardiopulmonary exercise test was performed with sampling of peak VO_2, peak respiratory equivalents for oxygen VE/VO_2, carbon dioxide, VE/VCO_2, VCO_2/VO_2) were calculated. Anaerobic threshold was estimated by the V-slope method.

Blood sample for assessment of brain natriuretic peptide (BNP) was obtained after 30 min of supine rest. The blood sample was immediately centrifuged and the plasma was frozen until analysis.

To asses the Quality of life in the HF patients, The Nottingham Health Profile (NHP) was used containing measurements of six different dimensions in this non disease specific questionnaire.

The follow up data and outcomes of all cause mortality were determined from death certificates. Data regarding hospitalization rates were collected from the National board of Health and Welfare.

Study II

The second study is an echocardiograpic substudy including patients from the three participating centers in the PROPP-STOPP study.

According to inclusion criteria all patients with prior known AF were excluded. 2D echocardiography including TDI measurements was performed. Left atrial volume was indexed to body surface area (LAVI) and was measured according to the biplane Area-Length method. Atrial functional parameters, i.e. myocardial velocities during atrial contraction and during p-wave of the ECG (A´) in ventricular septum and atrial septum were recorded by colour coded TDI. The A´ in atrial septum was measured by placing the cursor on interatrial septum near the atrioventricular plane. The A´ at ventricular septum was recorded by placing the sample volume near the mitral annulus. Indices of LAVI divided by atrial and septal A´ (atrial and septal LAVI/A´) were calculated. Some other diastolic parameters were also measured, e.g. the ratio of early transmitral velocity to TDI mitral annular early diastolic velocity (E/E´) measured in basal septal and lateral walls and calculated as mean E/E´, transmitral E/A ratio, isovolumic relaxation time, and transmitral E-wave deceleration time (DT). In addition myocardial performance index (MPI), an expression of combined diastolic and systolic LV function was measured from

TDI based different time intervals of the cardiac cycle. LV mass and LV ejection fraction (LVEF) were also calculated.

A compact disc with the full examination was sent from the centers to the core lab at Danderyd hospital. The echocardiographers were blinded for the ECG recordings until all data was collected and the study inclusion was stopped. A random control of 30 echocardiographic protocols were blindly reviewed to repeat echocardiographic accuracy of measurements.

Finally echocardiographic data was evaluated to compare functional parameters in subjects who developed AF, during follow up participating the main study protocol, versus sinus rhythm. The primary hypothesis was that measures of diastolic function would be able to predict patients with later detected AF.

Episodes of AF were detected with 24-hour -Holter monitoring and a previously validated thumb held-ECG monitoring (Zenicor Medical Systems AB) in a standardized manner, twice daily and additional recordings if there were symptoms of palpitations. The observational time was 30 days after discharge. An episode of at least 10 seconds with irregular ventricular rhythm without p-waves was defined as AF.

3.3 STATISTICS

Study I

Data are presented as frequencies, median or mean values (SD), as appropriate. Pearson´s correlation coefficients were used when needed. Student´s t-test was used for comparison between two groups after checking for normally distributed data, if necessary log-transformation was performed before the test. The chi square two test with Yates correction was used for comparison of proportions. Mann-Whitney U-test was used to compare paired data if the material was not normally distributed. A power calculation showed that the present study sample size would be sufficient to detect a 20 % difference between the groups in peak VO2 and a 33% difference in EDVI with alpha =0.05 two-sided, and beta= 80%. A conservative approach with p-value < 0.001 was considered statistically significant to correct for multiple testing and the exploratory character of the study. The p-values shown in the tables are uncorrected.

Study II

The results for continuous data are presented as mean and one standard deviation or median and range as appropriate. Nominal data is presented as number and percentage of cases. For comparison between AF and non-AF groups, Students` t-test or Mann-Whitney U tests were used as appropriate. Chi square test was used to test differences in proportions. Receiver Operating Characteristics (ROC) analyses was performed for variables of interest to access the predictive ability to detect later occurrence of AF. All analyses were performed with Statistica (data analysis software system) version 10, StatSoft, Inc (2011), USA. No formal power calculation regarding echocardiographic measurements was performed in the original study protocol, the power analysis was performed for the primary endpoint detection of silent AF (14).

3.4 ETHICS

Both studies were performed in accordance with the Helsinki declaration and was approved by the regional ethical committee (95-207 and 2007/386-31/12;). Each patient gave written informed consent to participate in the studies.

4 RESULTS

4.1 STUDY I. DO ELDERLY HEART FAILURE PATIENTS WITH ATRIAL FIBRILLATION COMPARED TO SINUS RHYTHM HAVE SIGNS OF MORE OR LESS DETERIORATION IN CARDIAC FUNCTION AND CARDIOPULMONARY CAPACITY.

Sixty-seven elderly patients with HF participated in this study. The demographic data at baseline showed no significant differences in previous history, medication or age. There were numerically more male participants in the AF group (63% vs 56%) and more patients with ischemic heart disease in the SR group (81% vs 56%). AF patients tended to have more treatment with digitalis (68% vs 27%).

Echocardiographic measurements (Table 3) showed generally higher EF in the AF group. Volumes indices of the LV were significantly smaller and the mitral E-Point septal separation (EPSS) was lower compared to the sinus group. Left atrial diameter and AVPD were similar in the two groups. LV mass index was high in both groups but diastolic parameters tended towards a shorter E-wave deceleration time and significantly lower ratio of pulmonary venous S-wave/D-wave in the AF group. Further LV concentric remodeling was more frequent with AF.

There were no differences in ventilatory parameters (Table 4) between the two groups. Peak oxygen consumption, ventilatory equivalents, anaerobic threshold and physical capacity were severely reduced in both groups. In the AF group resting and peak exercise heart rates were slightly higher. There were no differences in Quality of Life, NYHA functional class and BNP between the two groups.

Table 3 Echocardiographic variables

	Units	Sinus rhythm n=26	Atrial fibrillation n=41	p-values
Left atrium	cm	4.7 (0.7)	4.6 (0.9)	ns
Septum	cm	1.1 (0.3)	1.3 (0.4)	<0.05
Posterior wall	cm	1.0 (0.3)	1.1 (0.2)	ns
LVEDD	cm	6.2 (1.1)	5.4 (0.9)	<0.05
LVESD	cm	5.3 (1.3)	4.3 (1.2)	<0.01
EDVI	ml/ m^2	83 (29)	56 (24)	<0.001
ESVI	ml/ m^2	59 (25)	35 (19)	<0.0001
EPSS	Cm	2.0 (0.9)	1.2 (0.6)	<0.0001
EF	%	31 (10)	39 (10)	<0.01
AV-mean	Cm	7.2 (2.0)	6.7 (2.0)	ns
AV-RV	Mm	14.7 (4.9)	13.6 (4.7)	ns
LVMI	g/m^2	144 (39)	139 (36)	ns
LVH >125 g/m^2	%	63%	59%	ns
RWT >0.45	%	21%	50%	<0.05
E deceleration time	ms	207 (83)	170 (41)	<0.05
S/D ratio	-	0.98 (0.48)	0.55 (0.44)	<0.001

Values are mean (SD), or proportions (%) as indicated.

Abbreviations

AV-mean	Atrioventricular displacement in mm
AV-RV	Atrioventricular displacement right ventricle in mm
EDVI	Enddiastolic volume index (ml/m^2 BSA)
ESVI	Endsystolic volume (ml/m^2 BSA)
EPSS	E-point septal separation

EF	Ejection fraction
FS	Fractional shortening
LVEDD	Left ventricular enddiastolic diameter
LVESD	Left ventricular endsystolic diameter
LVMI	Left ventricular mass index
LVH	Left ventricular hypertrophy
RWT	Relative wall thickness
S/D ratio	Ratio pulmonary venous S-wave/D-wave

Table 4 Cardiopulmonary exercise test parameters

	Units	Sinus rhythm n=26	Atrial fibrillation n=41	p-value
VO_2 AT	ml/kg/min	8.4 (3.0)	7.2 (2.2)	ns
Peak VO_2	ml/kg/min	12 (4.3)	11 (3.2)	ns
Peak VCO_2/VO_2	-	1.1 (0.1)	1.1 (0.1)	ns
Peak VE/VO_2	-	44 (11)	47 (11)	ns
Peak VE/VCO_2	-	42 (8.5)	44 (8.5)	ns
Exercise tolerance	Watt	74 (29)	72 (29)	ns
Heart rate, rest	Bpm	70 (17)	83 (22)	<0.01
Heart rate, peak	Bpm	111 (18)	124 (30)	ns

Values are mean (SD).

Abbreviations

Bpm	Beats per minute
VO_2	Oxygen consumption
VCO_2	Carbondioxide production
VO_2AT	Oxygen consumption at anaerobic threshold
VCO_2/VO_2	Respiratory quotient
VE/VO_2	Ventilatory equivalent for oxygen
VE/VCO_2	Ventilatory equivalent for carbondioxide

4.2 STUDY II. CAN ECHOCARDIOGRAPHY DETECT UNKNOWN ATRIAL FIBRILLATION IN PATIENTS WITH STROKE/TIA?

From the Proppstopp study cohort, 174 consecutive enrolled patients underwent extensive echocardiographic evaluation with TDI measurements of atrial functional parameters. From the ECG recordings, 15 patients (8.6 %) were found to have AF during follow up.

Demographic data at baseline showed no significant differences between the AF and the SR group regarding previous history, age, or smoking habits. There was a weak trend for more women in the AF group (62% vs 40%, p=0.10).

Echocardiography (Table 5) showed significantly larger LAVI, higher LAVI/A´ and lower A´ velocities in ventricular and atrial septum in the AF group. No significant differences were found between the groups regarding to LV, EF, LV-mass index, E/E´, other diastolic function variables and MPI.

Receiver Operating Characteristics (ROC) for detection of paroxysmal AF (PAF) showed AUC for LAVI/A´ in atrial septum 0.78, 0.76 in ventricular septum and for LAVI 0.71. LAVI was possible to measure in 95% of the patients, LAVI/A´in ventricular septum in 93% and in atrial septum in 87% of the patients.

Table 5. Echocardiographic data

	All	non AF	AF	p
LAVI, ml/m^2	32.0 (8.6)	31.6 (8.6)	37.2 (6.7)	0.018
A mitral inflow, cm/s	80.9 (26.2)	81.4 (25.3)	76.2 (35.3)	0.500
A´ ventricular septum, cm/s	7.1 (1.7)	7.2 (1.6)	5.9 (2.2)	0.010
A´atrial septum, cm/s	5.8 (1.4)	5.9 (1.4)	4.8 (1.4)	0.013
LAVI/A´, ventricular septum	4.3 (3.2-5.8)	4.2 (3.2-5.5)	6.7 (5.0-8.7)	0.001
LAVI/A´, atrial septum	5.3 (4.1-7.0)	5.1 (4.1-6.8)	8.5 (5.9-11.0)	0.003
LV E/E´, mean	11.2 (3.8)	11.2 (3.9)	11.5 (2.9)	0.842
E/A, ratio	0.85 (0.73-1.09)	0.84 (0.72-1.08)	0.92 (0.81-1.37)	0.054
LV IVRT, ms	91 (25)	91 (25)	91 (25)	0.889
LV DT, ms	247 (24)	247 (25)	252 (24)	0.435
PVs/PVd	1.51 (0.41)	1.51 (0.42)	1.39 (0.35)	0.614
PVa, cm/s	32.0 (28.0-38.0)	32.0 (28.0-39.0)	30.5 (29.0-33.0)	0.483
LV mass index, g/m^2	107 (22)	108 (23)	105 (22)	0.735
LV EF, %	62.7 (8.9)	62.5 (9.1)	64.5 (6.8)	0.473
LV MPI	0.51 (0.19)	0.51 (0.19)	0.54 (0.15)	0.553

5 GENERAL DISCUSSION

For the individual patient AF is sometimes devastating due to the well known tromboembolic complications, i.e. stroke which can create a lifelong handicap and suffering for the patient and high rehabilitation costs for the society. The most important task today is to find patients with an increased risk for such an event. This would enable us to find and treat patients at risk for tromboembolic stroke because of silent or symptomatic AF. The risk factors are also well known from different studies (11, 13) and thus the CHA2DS2-VASC- score has been implemented for guidance in the every day clinical practice. The new era of novel oral anticoagulants as a complement to Warfarin should make it more convenient with medical treatments that suit more patients because of less need for therapy control. However, the challenge is to find all these patients who have silent or asymptomatic AF. Finding new tools and diagnostic procedures might help in decision making for individuals with severe risk for developing AF.

5.1 ATRIAL FIBRILLATION, THE VICIOUS CIRCLE

Left atrium is a very complex thin walled structure with contractile elements and excitable cells which initiate and conduct electrical impulses. It contributes to the cardiac output and can be an embolic source for formation of thrombus. Electrophysiologically the complexity about the triggers, the arrythmogenic substrate, the pulmonary veins and the electrical and structural remodeling is not fully understood. Today catheter ablation is used successfully in many patients to reduce AF burden and symptoms. However longterm results of efficacy are not available and information on outcome of ablation in CHF is lacking.

However, from another point of view, one might consider the complex mechanism of structural remodeling and the comorbidities of AF to improve methods of screening and detection of AF. Hypertension and CHF enhances diastolic dysfunction (24, 25) and diastolic dysfunction is linked to increased LA size and volume (25, 28). AF is more than 10 times more frequent in CHF compared to the population and it seems likely that the triggering mechanism for AF could be influenced by alterations in LV function and cardiac structure (33). As earlier stated the risk for developing AF is associated to both structural and electrical remodeling. In study I we compared elderly patients hospitalized with CHF. Heart failure patients with AF had a better EF, and smaller LV volumes indicating less deterioration of systolic function. Better EF by 6% was found with AF in a large registry study with unselected CHF patients to support our findings (38). In our study, peak VO_2 was severely reduced in both SR and AF groups implying that AF is not only a finding of end stage CHF disease and AF itself may have an impact on cardiac function and functional capacity. The left atrial diameter was in our limited study not significantly larger with AF but the diastolic parameters such as shorter E-wave DT and lower pulmonary S/D-ratio support possible connections between AF and diastolic dysfunction as an important mechanism for evolution of AF (24, 33). Low S/D ratio has been found to predict elevated filling pressures in AF (39). These findings are further supported by the high proportion of AF found in HFpEF (9). In patients with HFpEF there is also a link between AF and increased risk of stroke (40). HFpEF is broadly defined as a preclinical state of diastolic dysfunction and remodeling of left atrium plays an important role in the pathophysiology and is associated with risk factors as diabetes, hyperlipidemia and peripheral vascular disease (41). Treatment of those risk factors is considered to stop the progression to diastolic dysfunction and CHF, AF and stroke. A single episode of AF should be treated according to the guidelines. Question might arise whether early treatment of AF can stop the remodeling process of the atrium and reduce AF burden. Secondly, whether catheter ablation should be combined with medical treatment. These considerations warrant further studies on this topic.

5.2 IS ECHOCARDIOGRAPHY IMPORTANT FOR DECISION MAKING IN PATIENTS WITH STROKE?

In study II we used standard echocardiography and TDI for prospectively measuring left atrial functional parameters and volume in patients admitted to hospital with stroke or TIA. We found larger LA volumes and lower intrinsic velocities in subjects developing AF under the follow up period using Holter monitoring and thumb held ECG-device. The combined indexed volume/ velocities LAVI/A´ for both ventricular and atrial septum were also significantly higher. Our results are strongly supported by similar recent results from two other investigators (42, 43). Echocardiographic evaluation in our study was performed prior to discharge and it is unlikely that an episode of PAF with atrial stunning prior to echocardiographic examination could explain any change in velocities in the atrial wall. In patients with a high CHA2DS-VASc-score and subjective episodes of palpitations or possible undiagnosed asymptomatic AF, this method could be of additional value for ruling out patients with low risk for tromboembolic complications, in accordance with ESC guidelines (4). This could facilitate the further evaluation of patients in the high risk group with abnormal LAVI or LAVI/A´indices to perform long term monitoring of ECG by available methods like Holter monitoring, telemetry at hospital or methods like thumb-ECG.

6 CONCLUSIONS

Elderly hospitalized patients with CHF and AF, had more preserved systolic function and less dilated LV volumes but signs of more diastolic dysfunction compared to patients with CHF without AF. Exercise capacity is however reduced equally in both groups. Our results support the theory that AF is more a contributing factor to CHF than the mere consequence of end stage CHF disease. Secondly, we suggest that diastolic dysfunction or concentric remodeling may serve as important factors for the development of AF and further remodeling in patients with CHF.

Standard echocardiography and TDI at discharge can be useful in decision making to follow up patients with high risk for tromboembolic events. LA volume and functional diastolic parameters LAVI/A´ in septal walls of LV and atrium may be used to rule out patients who need prolonged screening for AF.

7 FUTURE PERSPECTIVES

AF is a complex disease with not yet fully understood links to electrical and structural changes of the heart and the left atrium. The connection between diastolic dysfunction and progression of heart failure and onset of AF is still unclear. The medical treatment of the arrhythmia itself and intensive treatment of other risk factors should be beneficial to improve prognosis. The screening of AF in the elderly population with increased risk is important and after a stroke or tromboembolic event, efforts must be made to rule out AF. Echocardiography with TDI can have an incremental value together with electrocardiographic methods to detect AF. More patients may be treated with the newer oral anticoagulants and the incidence of stroke may be decreased.

8 ACKNOWLEDGEMENTS

I would like to thank all of you who helped and supported me working with this thesis. And to all the patients participated in the studies, without you nothing would have been possible. But some of you I would like to thank in particular:

Hans Persson: My supervisor for your excellent guidance, patience and for sharing a small piece of your great knowledge with me.

Mahbubul Alam: My Co-supervisor for your kind support and expert skills in echocardiography and imaging.

Märit Mejhert: My mentor ,colleague and Co-author in study I. For your support and useful advises during this journey**.** And for enlightening me about scientific work.

Peter Sobocinski Doliwa: My Co-author in study II. For your support with the endless work in our database and all the datasheets we tried to interpret.

Mårten Rosenqvist: My Co-author in stydy I and II..Thank you for all your adwice concerning starting up with AURICULA at Ersta Hospital and your expert opinions of Atrial fibrillation.

Viveka Frykman-Kull: My Co-author in study II. Thank you for trying to teach me the concept of Cardiac pacing.

Magnus Edner: You introduced me into the most challenging world of Cardiology.

Johan Engdahl: My Co-author in study II. For your contribution with patients from your centre and for interesting discussions about atrial fibrillation.

Håkan Wallén: For your interest in my research and for our amusing discussions about hemostasis, thrombus formation and fear of flying.

Magnus von Arbin: Thank you for your contribution to my knowledge of how to handle the stroke patient, during my internship at Danderyds Hospital.

Jenny Rasck: Thank you for teaching me how to measure Doppler curves and for your great humour and skills.

Margatetha Ring: Thank you for all your work with the patients enrolled in the study**.**

Eva Linder-Klingsell in memorian for all your effort in the OPTIMAL-study.

Monica Rydell- Karlsson: For your sense of humour and our laughs together in the core lab when we interpreted my statistical files.

Staffan Hederoth: My current chief at Ersta Hospital for providing time for my research projekt.

Patrik Hjalmarsson: For being a nice friend and a very good doctor**.**

Lena Lindgren: For our friendship and for your enthusiasm that always makes me smile**.**

Håkan Andersson: My oldest friend from childhood, for your once every twenty-four hours, help with my old computer that never works.

And to all of my other friends, relatives and collegues, for your encouragement and love that makes this thesis worth while.

These studies received economic support from:

The regional agreement on medical training and clinical research (ALF) between Stockholm County Council (SLL) and Karolinska Institutet. The Swedish Heart and Lung Foundation, Klebergska stiftelsen, Stiftelsen Tornspiran, Konung Gustaf V:s och Drottning Victorias Frimurarstiftelse, Zenicor Medical Systems AB.

9 SVENSK SAMMANFATTNING

Förmaksflimmer (FF) är en vanlig sjukdom i befolkningen som uppskattningsvis drabbar cirka 3%. Sjukdomen har ett brett panorama av symtom från ett helt asymptomatiskt stadium till svåra besvär med attacker med hjärtklappning, andfåddhet och nedsatt ork. I de högre åldersgrupperna ses förmaksflimmer vanligen tillsammans med andra sjukdomar som t ex. högt blodtryck, diabetes och hjärtsvikt. Med ökande ålder och andra samtidigt existerande sjukdomar ökar också risken för komplikationer där den vanligast kända är stroke. Detta innebär en cirkulationsrubbning i hjärnan som ofta orsakas av att det bildas proppar i hjärtats vänstra förmak som tranporteras till hjärnan via blodströmmen. Förmaksflimmer diagnostiseras vanligen genom att registera hjärtrytmen via vanligt vilo-EKG eller med olika typer av bandspelar EKG där hjärtrytmen registeras under en längre tid.

Syftet med den första studien har varit att jämföra äldre patienter med hjärtsvikt som lagts in på sjukhus. Patienter med eller utan FF har jämförts med avseende på hjärtfunktion, strukturella skillnader i hjärtats förmak och kammare samt förmågan till fysisk ansträngning kan påverkas vid flimmersjukdom.

Den andra studien utfördes på patienter som insjuknat med stroke eller cirkulationstörning i hjärnan utan någon känd flimmersjukdom. Patienterna har följts upp med omfattande ekg registeringar under 24 timmar samt en långtidsregistering under 30 dagar för att påvisa flimmersjukdom. En omfattande ultraljudsundersökning av hjärtat med sk vävnadsdoppler (TDI) utfördes vid utskrivning för att kunna påvisa strukturella skillnader och hahstigheter i hjärtats förmak och kammare.

Sammanfattningvis kan man säga att metoderna har påvisat skillnader i hjärtats struktur och funktion hos äldre patienter med hjärtsvikt och förmaksflimmer. Ultraljudsundersökning av hjärtat hos patienter med stroke kan komma att användas för att användas i screeningen av patienter där man ännu inte kunnat hitta förmaksflimmersjukdomen.

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