Clinical and echocardiographic parameters to characterize atrial fibrillation

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Clinical and echocardiographic parameters to
characterize atrial fibrillation

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PROEFSCHRIFT

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Voor mijn ouders

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Chapter 1

General introduction

General introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.¹ The estimated prevalence of AF is 0.4% to 1% in the general population. In people older than 80 years, the estimated prevalence of AF is more than 8%.² During the past 20 years, hospital admissions for AF have increased by 66%³ and AF has been recognized as a condition associated with chronic disabilities for which chronic disease management is needed.⁴⁻⁶ Due to aging of the “baby-boom generation” and the fact that people get older in general, it is expected that the number of patients with AF will increase tremendously within the next decades.

Impact of atrial fibrillation

AF results in contractile dysfunction of both atria of the heart. As a consequence the arrhythmia may produce hemodynamic impairment resulting in heart failure and thromboembolic events such as stroke, all of which lead to significant morbidity and mortality. The mortality rate is twice as high in patients with AF compared to patients in normal sinus rhythm. In addition, AF is associated with frequent hospitalizations, and impaired quality of life.⁷ Palpitations and dyspnea are the most common clinical symptoms in patients with AF. On the other hand about one third of the patients are asymptomatic. However, outcome between symptomatic AF patients and “silent” AF patients does not seem to differ.

Recent studies show that subclinical or silent AF is associated with a significantly increased risk of ischemic stroke.^{8,9} In 20-26% of all ischemic strokes patients appear to also have otherwise asymptomatic and heretofore undetected silent AF.¹⁰⁻¹² More intense rhythm monitoring results in better detection of silent AF.¹³ Also, as many as 30 to 45% of patients known with AF harbour asymptomatic attacks.¹⁴ Therefore, patients are not always aware of the arrhythmia and not triggered to visit a cardiologist and receive appropriate treatment. It must be noted that paroxysmal, persistent or permanent AF and silent or symptomatic AF all carry the same risk for stroke.¹⁵ The high morbidity rates of untreated - even silent - AF and as a consequence high costs urge adequate detection of patients at risk for the development of the arrhythmia and its major complications. “On-time” management of AF significantly reduces the complication-rate, i.e.: warfarin and aspirin reduce the occurrence of stroke by 60% and 20%, respectively.^{1,16} In addition, the newer direct thrombin inhibitors and factor Xa inhibitors are very effective drugs preventing thromboembolisms in patients with AF.¹⁷⁻¹⁹

The most recent update of the ESC guidelines for the management of AF stress the importance of screening for AF in patients of 65 years or older.²⁰ However, it remains to be seen whether efficient screening programs can be developed and if intervention in terms of stroke and vascular preventive therapy can be effective.

Screening for atrial fibrillation

As mentioned above, AF may result in lethal complications even before it has been diagnosed. Therefore, there is a need for primary prevention by screening to detect patients at risk for the development of AF. In addition, early diagnosis and treatment may prevent the progression of AF to sustained forms refractory to therapeutic interventions.²¹

Several screening methods to detect new-onset atrial fibrillation were studied in the past. The investigators of the SAFE study show that active screening for atrial fibrillation in a general population detects additional cases over current practice.²² They show that the preferred method of screening in patients aged 65 or over in primary care is opportunistic pulse taking with follow-up electrocardiography. However, opportunistic pulse checks are unlikely to identify paroxysmal AF and many strokes occur in people with paroxysmal AF.²³ Other investigators proposed a more intense intermittent rhythm monitoring in patients with high risk for AF and high risk for stroke.²⁴ More severe screening methods were described to detect AF in patients with stroke using long-term telemetry, pacemakers or implantable cardiac monitors. In patients with cryptogenic stroke, long term rhythm monitoring yielded short term incidences of new AF of 17-23% after screening the rhythm for 3 weeks to one year.^{12,13} Except for pacemakers and implantable cardiac monitors, the other screening approaches are not extremely yielding. Recently, Healey et al. have shown that subclinical atrial high rate events can be detected effectively by the atrial lead of an artificial pacemaker. Importantly, they showed that these subclinical arrhythmias increase the risk of stroke significantly (1.7% per year compared to 0.7% in patients without atrial high rate events).⁸ However, using these devices for primary prevention of AF in a general population is not feasible. In contrast to continuous monitoring using Holter in pacemaker, opportunistic screening reveals only 1.6% new AF per year whereas the “spontaneous” incidence is approximately 1% per year.²² Finding and optimizing the best technique for screening silent AF is a crucial clinical need and might require new tools.²⁵

To enhance its efficiency screening should target populations with the highest predicted short term incidence of AF. In other words targeted screening and its potential to steer upstream therapy as well as rhythm control should be studied.

How to improve screening for new-onset AF

Observational population studies such as the Framingham Heart study, the Manitoba Follow-up study and the Cardiovascular Health study reported several clinical and electrocardiographic and echocardiographic parameters that are associated with the development of new-onset AF.^{4,16,26-31} The clinical and electrocardiographic factors associated with new-onset AF are higher age, male sex, the presence of diabetes, hypertension, congestive heart failure, valve disease, obesity, coronary artery disease and p-wave duration. Left atrial enlargement, increased left ventricular wall thickness,

left ventricular diastolic dysfunction and a reduced left ventricular fractional shortening are predictive echocardiographic parameters for new-onset AF.^{32,33} However, these currently available risk stratification measures have limited predictive value in the individual patient.² More recently Schnabel and colleagues developed a risk score based on clinical, electrocardiographic and echocardiographic parameters with a good predicting ability regarding new-onset AF (C-statistic 0.78).³⁴ This scoring system could be used to identify those who could benefit from ECG monitoring and aggressive control of correctable predisposing factors. However, in a validation study, the predictive ability of the tool was slightly lower.³⁵

Besides the “classical” clinical, electrocardiographic, and echocardiographic parameters, there seems to be a link between serum based biomarkers (natriuretic peptides)^{36,37} and specific arrhythmia patterns on Holter recordings such as excessive supraventricular ectopic activity⁹ or after exercise testing³⁸, and the development new-onset AF and stroke.

Screening in high risk subsets of patients prone to develop AF and at the same time harboring a high stroke risk once AF has surfaced may be a strong strategy for combating stroke. High profile screening should then focus on populations which have an *a priori* chance of developing AF of at least 10% per year. Such an approach may help identify high risk patients in chronic sinus rhythm in whom - once AF is detected - timely initiated anticoagulation may prevent strokes. The notion that screening in high risk patients may discover AF frequently and lend a basis for prevention of (further) strokes is illustrated by several recent studies mentioned above.

Using AF prediction rules or parameters derived from scene of calamity imaging may help to steer screening toward arrhythmogenic subjects. In this respect, screening may be made more efficient by restricting it to patients with highly arrhythmogenic risk markers. Presumably, it is most efficient to combine several arrhythmogenic risk markers.

Since there is evidence that the remodeling of the atria initiating and maintaining the arrhythmia is already present before the first episode of AF occurs, patients demonstrating atrial remodeling - and therefore at risk for AF - could be selected for primary AF prevention (Figure 1.1).³⁹

The total atrial conduction time (TACT) - defined as the time interval between the initiation of the atrial activation in the sinus node to the last atrial depolarization from the same activation front - could be a valuable parameter to predict the onset of AF. Atrial dilatation and conduction slowing may both result in prolongation of the TACT. In this thesis, we evaluated PA-TDI an echocardiographic tool to determine the TACT.

Figure 1.1 Hypothetical representation of the time course of atrial substrate remodeling in relation to the clinical appearance of AF. (based on Cosio et al. Europace. 2008, modified by Prof. dr. IC van Gelder, UMCG, Groningen).

Prediction of AF progression

In clinical practice, one should distinguish between the clinical AF type (paroxysmal AF or more persistent forms of AF). This will affect the individual treatment strategy for each patient. Previous studies identified several parameters that were associated with AF progression: valvular disease, alcohol consumption, age, left atrial dimension and amount of atrial enlargement over time, stroke, and heart failure.^{15,40-42} However, correction for possible confounders was not always performed, and the currently available risk stratification parameters resulting from these studies have limited predictive value in individual patients. In this thesis we re-analysed clinical parameters of AF progression in a large cohort of patients with self-terminating arrhythmia. Progression of AF can be related to autonomic (dis)balance.^{43,44} This balance must be taken into consideration when choosing medication to treat the arrhythmia.¹⁰ In this thesis, we studied the effect of autonomic trigger patterns on AF progression, and the effects of medication.

One could hypothesize that aggressive treatment of reversible causes of AF progression may prevent the progression to sustained forms refractory to therapeutic interventions. Therefore, a better prediction of AF progression is essential.

Prediction of response to therapy

When AF occurs, there are several ways to treat the arrhythmia.¹⁰ When the patient is symptomatic, most patients undergo a pharmacological or electrical cardioversion to

restore normal sinus rhythm. To prevent recurrences, a large part of the patients is treated with oral anti-arrhythmic drugs, catheter ablation near the ostia of the pulmonary veins, or AF surgery. Unfortunately, therapy does not always result in lasting sinus rhythm and we do not know to which therapy the patient will have the best response. Therefore at present the physicians basically use a “trial and error” strategy to choose the appropriate rhythm control therapy for their AF patients. On the whole, this is unacceptable because therapy for AF can be perilous and result in complications.⁴⁵ Electrical cardioversion requires general anesthesia. Anti-arrhythmic drugs can cause pro-arrhythmia, heart failure and conduction disorders. Ablation surgery and catheter ablation near the ostia of the pulmonary veins are invasive procedures that may lead to infection, perforation, stroke, bleeding and death.

As we have to avoid unnecessary exposure of the patient to the risks of therapy, we require powerful tools to assist the physician in the choice of the best individual therapy for each patient with AF. In order to achieve better treatment of AF, we have to select patients for the therapy they are likely to respond to. The intracardiac electrogram may be used to estimate the amount of atrial remodeling by evaluating parameters such as its morphology and the atrial fibrillation cycle length (AFCL).⁴⁶ Assessment of these parameters may help predicting arrhythmia prognosis and response to therapy. However, this requires an invasive procedure. Recently, a strong correlation was found between the AFCL and the duration of the cyclic atrial fibrillatory wall motion determined with tissue Doppler imaging.⁴⁷ In this thesis, we studied the correlation between the **mechanical** atrial fibrillatory wall motion pattern using non-invasive tissue velocity echocardiography and the **electrical** intracardiac waveform.

Aims of this thesis

The main goals of this thesis are to provide novel clinical and echocardiographic tools to predict AF onset and its progression. Since autonomic AF is a clinical entity which has remained unexplored in larger patient populations, we focused on vagal and adrenergic trigger patterns and its implications for initiation and progression of AF. Also we studied large AF populations to see whether simple to obtain clinical scores could predict AF progression. In parallel we set out to look for heretofore unused or underused information from within the atrial wall. At present, nearly all non-invasive parameters known to predict onset and progression of AF as well as success of rhythm control therapy are only obliquely related to the *scene of calamity*. We reasoned that the scene of calamity, i.e. the very atrial wall itself, contains hidden information which may appear useful with respect to initiation and progression of AF. Based on previous observations from our lab we aimed to explore the clinical and electrophysiological correlates of new electro-echocardiographic parameters. The specific aim here was to in-depth characterize the atrial substrate in patients with AF. In addition, we set out to explore the potential clinical usefulness of our new electro-echocardiographic tools in patients with AF.

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Part I

Clinical parameters to characterize patients with atrial fibrillation

Chapter 2

Autonomic trigger patterns and anti-arrhythmic
treatment of paroxysmal atrial fibrillation:
data from the Euro Heart Survey

CB de Vos, R Nieuwlaat, HJGM Crijns, AJ Camm, JY LeHeuzey, CJ Kirchhof,
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Eur Heart J. 2008;29:632-639

Abstract

Aims

To investigate the clinical characteristics, management, and outcome of patients with paroxysmal atrial fibrillation (AF) associated with autonomic triggers.

Methods and results

One thousand five hundred and seventeen patients with paroxysmal AF participated in the Euro Heart Survey on AF. We categorized patients according to trigger pattern as reported by the physician: adrenergic (AF associated with exercise, emotion or during daytime only and absence of vagal triggers), vagal (postprandial or night time only, without presence of adrenergic triggers) and mixed (combination of vagal and adrenergic triggers). Vagal AF was found in 91 patients (6%), adrenergic in 229 patients (15%) and mixed in 175 (12%) patients. Underlying heart disease was equally prevalent in the three groups. Among patients with vagal AF, 73% were treated with non-recommended drugs according to the guidelines. In vagal AF, non-recommended treatment was associated with a shift to persistent or permanent AF in 19% of the patients, compared with none in the group receiving recommended treatment ($P=0.06$).

Conclusion

This study is the first to address the issue of autonomic trigger patterns and AF in a large population. Autonomic trigger patterns were seen frequently in paroxysmal AF patients. Autonomic influences should be taken into consideration since non-recommended treatment may result in aggravation of vagal AF.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The condition is frequently associated with structural heart disease, although a substantial number of patients have no underlying heart disease.¹ The autonomic nervous system is known to contribute to the initiation, perpetuation, ventricular response rate, and termination of AF, but its precise role remains controversial.

While the data are mainly empiric, there are two types of autonomic induced AF pointed out in the literature. Coumel and coworkers²⁻⁶ described adrenergic and vagal forms of AF. They reported that the adrenergic mediated episodes of AF are typically triggered by exercise and emotional stress, commonly associated with polyuria, and occur mainly during the day. Adrenergic AF is described to occur in the presence of heart disease.⁷ The vagal form is characterized by male predominance, younger age, minimal tendency to progress to permanent AF, and onset at rest or at night and after intake of food or alcohol. Episodes of vagal AF are typically preceded by progressive bradycardia. Studies using heart rate variability have confirmed vagal and adrenergic modes of onset of AF.⁸⁻¹¹ Furthermore, there is support for the notion that autonomic modulation influences early recurrences after electrical cardioversion.^{12,13}

Epidemiologic data on the prevalence or prognosis of autonomic AF are presently lacking. Furthermore, there is no controlled study examining the response to therapy in vagal or adrenergic AF. However, as in the previous guidelines, the 2006 ACC/AHA/ESC guidelines for the management of patients with AF contain specific recommendations regarding the medical treatment of patients with vagal or adrenergic AF.¹⁴ Beta-blocking drugs, sotalol, digitalis and propafenone are considered unsuitable since they may exacerbate the episodes of vagal induced AF, whereas in adrenergic AF drugs with beta-blocking properties are thought to be beneficial. These recommendations are primarily based on assumptions, since controlled studies on this subject are lacking.

The Euro Heart Survey on AF presents a unique overview of AF management in a large group of patients in several European countries.¹⁵ We identified the clinical characteristics and management of patients with paroxysmal AF associated with autonomic triggers among the patients in the Euro Heart Survey. To our knowledge, this study is the first to address the issue of AF triggers, autonomic trigger patterns, their clinical characteristics, management and outcome in a large population AF patients.

Methods

A detailed description of the methods, data collection, validation, and the first results of the Euro Heart Survey on AF have been presented by Nieuwlaet et al.¹⁵

In 2003 and 2004, 5333 AF patients were enrolled in this survey. These patients were enrolled in 182 hospitals among 35 different member countries of the European Society of Cardiology. Inclusion criteria were: age >18 years and AF on ECG or Holter recording in the previous 12 months or at the time of inclusion. Enrolment of consecutive patients took place at the outpatient clinic, cardiology ward, emergency department, electrical cardioversion department, electrophysiology laboratory, pacemaker and defibrillator implantation department, and cardiac surgery department.

AF was classified in five categories. The arrhythmia was first detected AF in 978 patients, paroxysmal AF in 1517 patients, persistent AF in 1167 patients, permanent AF in 1541 patients and unknown type of AF in 130 patients. In the present study, only the records from patients with paroxysmal AF were evaluated, leaving a study population of 1517 patients.

In the Euro Heart Survey, data were collected from medical records and medical information systems or entered by the attending physician.

The physicians were asked to report whether the following triggers for AF were present: caffeine intake, alcohol intake, inhalation of toxic gas or electrocution, electrolyte disturbances, acute myocardial infarction, exercise, emotion, postprandial occurrence, and sleep apnoea syndrome. Additionally, circadian rhythms were identified to determine whether the arrhythmia occurred during both day and night, during daytime mainly or started during the night (or was present at wake up).

Using the clinical characteristics of patients with autonomic predominance, we defined an adrenergic, a vagal, and a mixed trigger pattern. The adrenergic trigger pattern was defined as follows: initiated by exercise or emotion and/or present mainly during daytime without reported vagal triggers. We classified patients in the vagal group if AF occurred postprandially and/or was present during the night only without presence of any adrenergic triggers. Patients were classified in the mixed AF group when a combination of at least one adrenergic and one vagal trigger was present.

Patient management was performed consistent with common local practice.

The guidelines contest prescription of a beta-blocker, sotalol, digitalis or propafenone in patients with vagal AF. On the other hand, some drugs are recommended for adrenergic AF (i.e. treatment with a beta-blocker, sotalol, digitalis or amiodarone). In the present study, we evaluated the effect of guideline adherence (recommended treatment) and non-compliance with the guidelines (non-recommended treatment) regarding prescription of medication in autonomic AF.

To evaluate regional differences, we divided the patients into three geographical locations: Western, Central and Mediterranean Europe as defined previously.¹⁵

Statistical analysis

Data analysis was performed with SPSS statistical software (SPSS, Inc., release 12.0.1). Continuous variables are reported as mean±standard deviation and categorical

variables as observed number of patients (percentage). Whether there was a difference in characteristics, treatment or outcome between the three groups with vagal, adrenergic, and mixed trigger patterns was tested with ANOVA for continuous and χ^2 for categorical variables and these *P*-values are reported in the tables. Post hoc pairwise analysis was performed using Bonferroni and the corresponding *P*-values were reported in the text. When comparing two groups, differences for continuous variables were tested with an independent t-test and differences for categorical variables were tested with χ^2 . All tests performed were two-sided. Overall, a *P*-value of <0.05 was considered to be statistically significant.

Results

Atrial fibrillation triggers

One or more triggers were reported in 640 (42%) patients with paroxysmal AF. In 535 (35%) patients no triggers were found and in 342 (23%) patients the physician did not verify the presence of triggers. No differences regarding baseline characteristics, medical history, and previous interventions were found between the latter group and patients in whom the presence of triggers was verified by the physician (data not shown).

Exercise and emotion were the most frequently reported triggers of AF (Figure 2.1). Patients with triggers were somewhat younger compared with the patients in whom no trigger was found. Patients without triggers had less thyroid disease, more often sick sinus syndrome and an implanted pacemaker. No significant differences concerning other baseline characteristics were found (Table 2.1).

Figure 2.1 Percentages of triggers reported in patients with paroxysmal atrial fibrillation in the Euro Heart Survey.

Table 2.1 Characteristics of paroxysmal atrial fibrillation patients with vs. without triggers.

	Any trigger	No triggers found	P-value
n	640	535	
Age (years)	62±13	64±13	0.012
Female	258 (40%)	238 (45%)	0.149
Lone AF	102 (16%)	86 (16%)	0.870
Underlying heart disease			
Heart failure	156 (25%)	114 (21%)	0.222
Coronary artery disease	210 (33%)	162 (30%)	0.337
Valvular heart disease	118 (19%)	91 (17%)	0.575
Mitral stenosis	41 (6%)	26 (5%)	0.280
Hypertension	414 (65%)	325 (61%)	0.164
Other diseases			
Thyroid disease	36 (6%)	17 (3%)	0.047
Pulmonary disease	82 (13%)	66 (12%)	0.803
Sick sinus syndrome	31 (5%)	43 (8%)	0.023
Peripheral vascular disease	43 (7%)	30 (6%)	0.420
Renal failure	37 (6%)	33 (6%)	0.783
Malignancy	31 (5%)	19 (4%)	0.247
Stroke/TIA ^a	62 (10%)	46 (9%)	0.497
Previous interventions			
Pharmacological cardioversion	328 (51%)	283 (53%)	0.569
Electrical cardioversion	167 (26%)	127 (24%)	0.358
Catheter ablation	37 (6%)	28 (5%)	0.675
Pacemaker	26 (4%)	41 (8%)	0.008

Autonomic trigger patterns

Autonomic trigger pattern according to our definition could be identified in 495 of the patients with paroxysmal AF (33%): in 91 patients (6%) a vagal trigger pattern was present, 229 patients (15%) had an adrenergic trigger pattern, and 175 patients (12%) a mixed trigger pattern (Table 2.2). No differences regarding underlying heart disease, age or other baseline characteristics were found between patients with vagal, adrenergic, and mixed AF.

Vagal AF was not restricted to lone AF since hypertension (71%), coronary artery disease (29%) and heart failure (24%) were often present among the patients with a vagal trigger pattern. No differences regarding events during follow-up were found between the three autonomic trigger pattern groups (Table 2.3).

Autonomic trigger patterns and drug therapy

We compared therapy between patients with adrenergic and vagal triggers of AF to investigate the relationship between potential trigger patterns and clinical management. Patients with vagal AF were treated more often with Class Ic anti-arrhythmic drugs compared with patients with adrenergic AF ($P=0.007$), as suggested by the guidelines. Although not recommended, patients with a vagal trigger pattern were frequently treated with a beta-blocker, sotalol, digoxin or propafenone (Figure

2.2). No differences were found between the prescription of ACE (angiotensin converting enzyme)-inhibitors, AT(angiotensin)II receptor blockers, dihydropyridin calcium channel blockers, diuretics and statins between the vagal and adrenergic AF group. In total, 72% of the patients with vagal AF used non-recommended medication, especially betablockers. In the patients with vagal AF, beta-blockers (including sotalol) were prescribed in 51 patients (57%). On the other hand, 36% of the patients with adrenergic AF did not receive a beta-blocker.

Table 2.2 Characteristics of patients with an adrenergic, vagal and mixed trigger pattern.

	Adrenergic trigger pattern	Vagal trigger pattern	Mixed trigger pattern	<i>P-value</i>
N	229	91	175	
Age (years)	62 ± 13	62 ± 14	62 ± 13	0.609
Female	94 (41%)	38 (42%)	73 (42%)	0.988
Body Weight	81 ± 15	80 ± 19	80 ± 16	0.906
BMI	27 ± 5	28 ± 6	27 ± 5	0.484
Heart rate at inclusion (when SR) (BPM)	69 ± 13	66 ± 15	69 ± 17	0.533
Heart rate at inclusion (when AF) (BPM)	110 ± 32	109 ± 40	106 ± 29	0.390
Lone AF	35 (15%)	14 (16%)	37 (21%)	0.268
Underlying heart diseases				
Heart failure	58 (25%)	22 (24%)	34 (20%)	0.368
Coronary artery disease	69 (30%)	26 (29%)	55 (31%)	0.891
Valvular heart disease	43 (19%)	18 (20%)	28 (16%)	0.698
Mitral stenosis	16 (7%)	7 (8%)	8 (5%)	0.508
Hypertension	149 (65%)	65 (71%)	109 (62%)	0.331
Other diseases				
Thyroid disease	12 (6%)	5 (6%)	8 (5%)	0.906
Pulmonary disease	25 (11%)	6 (7%)	22 (13%)	0.322
Sick sinus syndrome	8 (3%)	7 (8%)	10 (6%)	0.261
Peripheral vascular disease	16 (7%)	2 (2%)	12 (7%)	0.220
Renal failure	12 (5%)	5 (6%)	7 (4%)	0.804
Malignancy	7 (3%)	5 (6%)	9 (6%)	0.429
Major bleeding	2 (1%)	1 (1%)	2 (1%)	0.960
Stroke / TIA	25 (11%)	8 (9%)	16 (9%)	0.796
Previous interventions				
Pharmacological cardioversion	125 (55%)	43 (47%)	98 (56%)	0.374
Electrical cardioversion	63 (28%)	22 (24%)	62 (35%)	0.107
Catheter ablation	12 (5%)	3 (3%)	17 (10%)	0.082
Pacemaker	8 (4%)	7 (5%)	0	0.542

BMI: Body Mass Index, SR: Sinus Rhythm, BPM: Beats Per Minute, TIA: Transient Ischemic Attack.

Table 2.3 Events during follow-up of patients with an adrenergic, vagal and mixed trigger pattern.

	Adrenergic trigger pattern	Vagal trigger pattern	Mixed trigger pattern	P-value
N	229	91	175	
Outcome at 1 year:				
Survival	170 (97%)	74 (96%)	142 (99%)	0.214
Pharmacological cardioversion	31 (22%)	17 (25%)	30 (23%)	0.847
Electrical cardioversion	19 (14%)	9 (13%)	18 (14%)	0.991
Catheter ablation	12 (8%)	8 (12%)	17 (13%)	0.278
Admission for AF	50 (41%)	25 (43 %)	55 (51%)	0.358
Cardiovascular Hospitalizations	65 (52%)	29 (50%)	65 (60%)	0.444
AF consultations during follow-up	115 (79%)	49 (77%)	106 (88%)	0.093
AF type worsening at 1 year (persistent or permanent)	22 (14%)	9 (14%)	18 (14%)	0.995
Symptoms at 1 year	60 (40%)	20 (31%)	59 (46%)	0.141

Figure 2.2 Prescription of medication in autonomic atrial fibrillation (AAD: anti-arrhythmic drugs).

In the Euro Heart Survey, physicians were also asked to report 1 year follow-up items regarding worsening of paroxysmal AF to persistent or permanent AF, number of pharmacological cardioversions, number of electrical cardioversions, number of ablations, and the frequency of admissions and consultations. Complete follow-up data were available for 53–70% of the patients with adrenergic AF and 62–73% of the patients having vagal AF depending on each item studied. To evaluate the effect of the choice of medical therapy, we looked at dissimilarities regarding baseline characteristics and outcome at 1-year follow-up among patients with autonomic trigger patterns receiving recommended and non-recommended treatment. As represented in Table 2.4, there were no significant differences in patient characteristics and medication in patients with vagal AF receiving recommended and non-recommended therapy. Nonrecommended treatment was associated with a clear trend towards aggravation of vagal AF. In the vagally mediated paroxysmal AF patients, non-recommended treatment was associated with a deterioration to persistent or

permanent AF in 19% of the patients during 1-year follow-up, compared with none in the group treated with recommended medication ($P=0.06$) (Figure 2.3).

Table 2.4 Characteristics and outcome of paroxysmal AF patients with a vagal or adrenergic trigger pattern who received recommended and non-recommended treatment.

	Adrenergic trigger pattern (n=221)			Vagal trigger pattern (n=91)		
	Non-recommended treatment group	Recommended treatment group	<i>P-value</i>	Non-recommended treatment group	Recommended treatment group	<i>P-value</i>
N	43	178		66	24	
Age, years (SD)	59 (15)	62 (12)	0.080	63 (14)	61 (14)	0.465
Female	18 (42%)	73 (41%)	0.919	31 (47%)	7 (30%)	0.130
<i>Underlying Heart Diseases:</i>						
Heart failure	6 (14%)	51 (29%)	0.046	18 (27%)	4 (17%)	0.301
Coronary disease	5 (12%)	64 (36%)	0.002	19 (29%)	7 (29%)	0.972
Valvular disease	7 (16%)	34 (19%)	0.669	14 (21%)	4 (17%)	0.634
Mitral stenosis	4 (9%)	11 (6%)	0.471	5 (8%)	2 (8%)	0.906
Hypertension	24 (56%)	123 (69%)	0.098	49 (74%)	16 (67%)	0.478
<i>Other diseases:</i>						
Thyroid disease	1 (2%)	11 (7%)	0.304	5 (8%)	0	0.194
COPD	4 (9%)	20 (11%)	0.706	4 (6%)	2 (9%)	0.664
<i>Medication :</i>						
ACE-inhibitor	20 (47%)	94 (53%)	0.458	31 (47%)	13 (54%)	0.546
ATII-receptor blocker	4 (9%)	17 (10%)	0.960	9 (14%)	2 (8%)	0.497
Statins	8 (19%)	48 (27%)	0.258	20 (30%)	5 (21%)	0.375
Diuretics	11 (26%)	67 (38%)	0.138	29 (44%)	9 (38%)	0.584
<i>Anti-arrhythmic drugs:</i>						
Amiodarone	0 (0%)	48 (27%)	<0.001	12 (18%)	8 (33%)	0.126
Disopyramide	1 (2%)	0 (0%)	0.041	0	0	-
Quinidine	1 (2%)	1 (1%)	0.273	0	0	-
Flecainide	6 (14%)	10 (6%)	0.058	6 (9%)	6 (25%)	0.05
Propafenone	12 (28%)	10 (6%)	<0.001	18 (27%)	0	0.004
<i>Outcome at 1 year:</i>						
Cardioversion	11 (38%)	30 (28%)	0.289	14 (29%)	7 (41%)	0.336
Catheter ablation	3 (10%)	9 (7%)	0.652	5 (10%)	2 (12%)	0.857
Admission for AF	10 (48%)	39 (41%)	0.556	19 (45%)	6 (40%)	0.726
Cardiovascular	12 (52%)	51 (53%)	0.972	22 (52%)	7 (47%)	0.704
<i>Hospitalizations</i>						
AF consultations during follow-up	20 (74%)	90 (79%)	0.582	38 (83%)	11 (65%)	0.129
AF type worsening at 1 year (persistent or permanent)	5 (16%)	16 (14%)	0.765	9 (19%)	0	0.062

COPD: Chronic Obstructive Pulmonary Disease; ACE: Angiotensin-Converting Enzyme; ATII: angiotensin II

In the adrenergic group, more heart failure and coronary artery disease were present in the patients receiving recommended therapy. No difference in progression to persistent or permanent AF was found in adrenergic AF between the groups treated with recommended and non-recommended medication. Concerning the other indicators of outcome such as AF interventions, hospitalizations and consultations, no

major differences were found between recommended and non-recommended treatment in both vagal and adrenergic AF.

Figure 2.3 Effect of (non-)recommended treatment on worsening of atrial fibrillation (AF)-type (shift from paroxysmal AF at baseline to persistent or permanent AF at follow-up or from persistent AF at baseline to permanent AF at follow-up).

Regional disparity and (non-)recommended treatment

A few differences between European regions were observed. The largest number of patients in whom the physician did not verify the presence of triggers resided in Western Europe (54%) compared with only 21% in Central Europe and 25% in Mediterranean Europe. In case the presence of triggers was verified by the physician, the relative distribution of triggers and autonomic trigger patterns were similar across Europe (data not shown).

In the Mediterranean countries, a larger proportion of the population was treated in accordance with the ACC/AHA/ESC guidelines for the management of patients with vagal AF as 41% of the patients received recommended treatment according to the guidelines compared with 20% in Central Europe and 19% in Western Europe. In adrenergic AF, the percentage of patients receiving recommended medication was similar in Central, Mediterranean, and Western Europe.

Discussion

The Euro Heart Survey provides a unique insight into the characteristics of patients with triggers for AF and the way they are presently treated. To our knowledge, this is the first large observational study to provide an overall picture of autonomic trigger patterns for AF, its management and outcome. Physicians reported triggers in 42% of paroxysmal AF patients in the survey. An autonomic trigger pattern (adrenergic, vagal or mixed) was present in 33% of all patients. In contrast to the general opinion on

autonomic AF, there were no differences in patient characteristics and prevalence of concomitant heart disease in patients with vagal or adrenergic AF. In fact, we recorded heart failure, coronary artery disease, valvular heart disease and hypertension in as many patients having the vagal form of the arrhythmia as in patients with adrenergic AF. Also, both patient groups are of similar age. Despite the fact that physicians themselves reported the triggers in their patients, they presumably did not always correctly recognize the autonomic pattern, since 72% of the patients with vagal AF and 20% of the patients with adrenergic AF did not receive the recommended medication according to the ACC/AHA/ESC guidelines for the management of patients with AF.¹⁴ Although patients seem to respond well to what is considered non-recommended treatment, the present data suggest that especially in patients with vagal AF, this may be detrimental because of potential aggravation of the arrhythmia pattern. Among the patients with adrenergic AF, no significant differences in outcome (or trends) were found between the patients using recommended and non-recommended treatment. One could hypothesize that this would reduce the clinical relevance of adrenergic AF. On the other hand, adrenergic AF patients receiving recommended medication had more underlying heart disease such as coronary artery disease or heart failure (Table 2.4) making them more vulnerable for recurrent AF and the development of more sustained forms of the arrhythmia.

Patients with triggers for atrial fibrillation

The presence of paroxysmal AF is an interplay between initiating triggers and a perpetuating substrate. An arrhythmogenic substrate may develop with age or with prolonged exposure to underlying heart disease.¹⁶ Triggers may develop from high adrenergic tone, which may also increase the awareness of palpitations in case of an arrhythmia. In our study, patients in whom triggers were reported were somewhat younger and more often had thyroid disease. In contrast, patients with reported triggers of AF less often had sick sinus syndrome and pacemaker implantation, possibly because of their lower age. In case of pacemaker implantation, symptoms and therefore reported trigger-frequency may decrease.

At the time of the survey, physicians might have been less aware of the relation between obstructive sleep apnoea syndrome (OSAS) and AF, since the reported incidence is low. On the other hand, considering the relatively normal BMI (body mass index) of patients in this European survey, the prevalence of OSAS may have been truly low.

Clinical characteristics of patients with vagal or adrenergic atrial fibrillation

The precise role of the autonomic nervous system in the initiation, perpetuation, and termination of AF remains undefined.^{7-10,17} The clinical history is a consistent tool to

determine which type of autonomic predominance results in a destabilization of the arrhythmogenic substrate.³

The clinical characteristics of vagal and adrenergic AF have been described previously. According to Coumel et al.,⁴ the vagally induced form of AF would occur typically in middle aged males without demonstrable heart disease, and arises more frequently than adrenergic AF. Adrenergic AF would typically occur in the presence of heart disease and can be associated with disorders such as pheochromocytoma and hyperthyroidism.⁷ Our results reveal a different picture of these patients: vagal AF occurred in elderly men whose age did not differ from that in the general Euro Heart Survey population. In addition, many of the vagal AF patients had underlying heart disease. Furthermore, adrenergic AF was identified more frequently among the patients of the Euro Heart Survey than vagal AF (ratio 3:2).

Drug therapy and autonomic atrial fibrillation

As the initiation of AF can be related to autonomic balance, this balance must be taken into consideration in the choice of medication to treat the arrhythmia.⁵

The guidelines on AF treatment recommend a different approach concerning the choice of rate-control and antiarrhythmic drugs in patients with vagal or adrenergic AF.¹⁴ The recommendations seem to be based on empirical evidence since controlled studies on the effect of different drugs in autonomic induced AF are lacking. In the vagally mediated form of the arrhythmia, the guidelines advise to avoid treatment with beta-blocking drugs, sotalol, propafenone or digitalis, as they may worsen symptoms. Among the patients with adrenergic AF, the guidelines advise beta-blockers as first line treatment, followed by sotalol or amiodarone.

The results from the present study suggest that physicians do not seem to choose drug therapy based upon the autonomic pattern of induction of AF. Most remarkable was the finding that the frequency of beta-blocker administration was not altered by the presence of vagal triggers for AF (44% still received betablocker) or sympathetic triggers (36% did not receive a beta-blocker).

In general, physicians want to prevent high heart rates during recurrences of AF. Also, during treatment with Class Ic antiarrhythmic drugs, rate-control medication is advised to prevent 1:1 conduction in the case of Ic atrial flutter. Therefore, ratecontrolling drugs such as beta-blockers and digitalis are used frequently. However, non-dihydropyridine calcium channel blockers (i.e. verapamil and diltiazem) could be used as safe alternatives. Furthermore, the need for rate control in patients with paroxysmal vagal AF may be less, since the heart rate during vagal AF is usually not as high as in adrenergic AF.¹⁸ On the other hand, vagal AF patients also suffer frequently from underlying heart disease necessitating the application of a beta-blocker.

Among the patients with adrenergic AF, use of recommended treatment was particularly seen in patients suffering from chronic heart failure and coronary artery

disease. We assume that this is explained by the fact that a beta-blocker is indicated in both heart failure and coronary disease.

Although only borderline significant, there is a clear trend towards deterioration of the arrhythmia to persistent or even permanent AF in patients with vagal AF receiving non-recommended treatment. Clinical consumption (electrical or pharmacological cardioversions, catheter ablations, hospitalizations, consultations) was equal in both groups receiving recommended and nonrecommended medication.

Study limitations

In this non-randomized study, we performed a subgroup analysis of the Euro Heart Survey. As a result, our findings should be interpreted with care. An observed poor statistical significance in a subgroup may be a result of lack of power due to small numbers rather than absence of a relation. On the other hand, experimentwise type I error may be the result of multiple testing in this study.

Regrettably, there are no quantitative measures known to reproduce vagal or adrenergic predominance. The assessment of triggers in patients with AF is challenging. Adequate history taking is essential in the identification of trigger patterns as it might be difficult to discriminate between triggers that initiate the arrhythmia and factors that worsen the symptoms. In clinical practice, triggers such as exercise and emotion can be misinterpreted and wrongly recognized as triggers for AF. The physician has a crucial role in identifying this bias. Our report is based on this clinical judgement by the physician. Since data on triggers were not verified in 23% of the patients, the reported numbers on prevalence of triggers and autonomic trigger patterns are probably underestimated.

Conclusion

The Euro Heart Survey is the first large observational study to provide a description of the clinical characteristics of paroxysmal AF patients having triggers and autonomic trigger patterns, its management, and outcome. An autonomic trigger pattern (vagal or adrenergic) was found in almost one-third of the patients. Patients with vagal AF have similar characteristics to patients with adrenergic AF and much more frequently underlying heart disease than previously thought. Physicians do not seem to choose rhythm or rate control medication based upon autonomic trigger pattern of AF. However, the role of autonomic influences should be taken into consideration in order to achieve an optimal management of the disease as non-recommended treatment may result in aggravation of the arrhythmia.

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Chapter 3

Progression from paroxysmal to persistent atrial fibrillation

Clinical correlates and prognosis

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Abstract

Objectives

We investigated clinical correlates of atrial fibrillation (AF) progression and evaluated the prognosis of patients demonstrating AF progression in a large population.

Background

Progression of paroxysmal AF to more sustained forms is frequently seen. However, not all patients will progress to persistent AF.

Methods

We included 1,219 patients with paroxysmal AF who participated in the Euro Heart Survey on AF and had a known rhythm status at follow-up. Patients who experienced AF progression after 1 year of follow-up were identified.

Results

Progression of AF occurred in 178 (15%) patients. Multivariate analysis showed that heart failure, age, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, and hypertension were the only independent predictors of AF progression. Using the regression coefficient as a benchmark, we calculated the HATCH score. Nearly 50% of the patients with a HATCH score >5 progressed to persistent AF compared with only 6% of the patients with a HATCH score of 0. During follow-up, patients with AF progression were more often admitted to the hospital and had more major adverse cardiovascular events.

Conclusions

A substantial number of patients progress to sustained AF within 1 year. The clinical outcome of these patients regarding hospital admissions and major adverse cardiovascular events was worse compared with patients demonstrating no AF progression. Factors known to cause atrial structural remodeling (age and underlying heart disease) were independent predictors of AF progression. The HATCH score may help to identify patients who are likely to progress to sustained forms of AF in the near future.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. The arrhythmia is associated with increased morbidity and mortality, mainly as a result of 2 complications: stroke and heart failure.¹ In clinical practice, one should distinguish between the clinical AF type (paroxysmal AF, episodes of the arrhythmia that terminate spontaneously) and persistent AF (episodes that are sustained longer than 7 days and are not selfterminating).² The latter will affect the individual treatment strategy for each patient. Important differences were found between the clinical subsets of AF.³ Underlying heart disease occurs more frequently in patients with sustained AF. Patients with paroxysmal AF are more often treated with antiarrhythmic drugs, whereas patients with chronic AF receive more rate control therapy. In the CARAF (Canadian Registry of Atrial Fibrillation) study, investigators evaluated determinants of AF progression.⁴ The investigators found that underlying heart disease and age were independently associated with progression of AF. The Euro Heart Survey (EHS) on AF presents a unique overview of AF management in a large group of patients in several European countries. Nieuwlaat et al.⁵ previously reported the influence of underlying heart disease on the progression of AF in the EHS. However, in this univariate analysis, no correction for possible confounders was performed, and the contribution of each factor to AF progression was not studied.

The present study is the largest study to investigate the clinical correlates of arrhythmia progression in patients with paroxysmal AF. In addition, we evaluated the prognosis of patients with AF progression and validated a risk stratification rule to assess the probability of AF progression.

Methods

A detailed description of the methods, data collection, validation, and the first results of the EHS on AF were presented by Nieuwlaat et al.⁶ In 2003 and 2004, 5,333 AF patients were enrolled in this survey. These patients were enrolled at 182 hospitals in 35 different member countries of the European Society of Cardiology. Inclusion criteria were age older than 18 years and AF on an electrocardiogram or Holter recording in the previous 12 months or at the time of inclusion. Enrollment of consecutive patients took place at several sites within the cardiology departments.

AF was classified into 5 categories. The clinical AF type was first detected AF in 978 patients, paroxysmal AF in 1,517 patients, persistent AF in 1,167 patients, permanent AF in 1,541 patients, and unknown type of AF in 130 patients. In the present study, only the records for patients with paroxysmal AF and first detected AF in whom sinus rhythm restored spontaneously or after pharmacological treatment during admission were evaluated, leaving a study population of 1,219 patients with a known rhythm status at 1-year follow-up. We did not include patients who underwent

electrical cardioversion to sinus rhythm because one cannot be sure that those patients have self-terminating AF. In addition, we did not take persistent AF as a separate entity to evaluate progression to permanent AF because the classification permanent AF is physician driven and does not depend on the pathophysiology or clinical characteristics of the arrhythmia and therefore precludes proper assessment of progression.²

In the EHS on AF, data were collected from medical records and medical information systems or entered by the attending physician. Progression of AF was defined as follows: paroxysmal AF at baseline becoming persistent or permanent AF at 1-year follow-up or first detected AF at baseline with spontaneous conversion to sinus rhythm during admission becoming persistent or permanent AF at 1-year follow-up. We also determined the CHADS₂ score.⁷ This acronym stands for congestive heart failure, hypertension, age (75 years and older), diabetes mellitus, and a history of stroke/transient ischemic attack (TIA) (2 points). This scoring system allows instant classification of the relative thromboembolic risk in patients with AF and is incorporated in the latest guidelines on the management of AF.

Statistical analysis

Data analysis was performed with SPSS statistical software (version 15.0, SPSS Inc., Chicago, Illinois). Continuous variables are reported as mean $\pm$ SD and categorical variables as observed number of patients (percentage). When comparing patients with AF progression and no AF progression regarding baseline characteristics, treatment, or outcome, we used an independent *t* test for continuous variables and the Fisher exact test for categorical variables. The *P* values resulting from these analyses are reported in Tables 3.1, 3.2, and 3.3. All baseline characteristics showing a significant univariate relationship with AF progression at follow-up were included in a logistic regression model (heart failure in history, chronic obstructive pulmonary disease [COPD] in history, left atrial size on echocardiogram, age, regular physical activity, hypertension, coronary artery disease, valve disease, previous stroke or TIA, renal failure). We did not include the variables lone AF or CHADS₂ score in the model because they were derived from other variables included in the model. Model reduction was performed by stepwise excluding variables from the model with a *P* value <0.10 . All variables that were independently associated with AF progression were tested for interactions. To develop a convenient score, the regression coefficients of the final logistic regression model were used to estimate the contribution of each variable to the risk estimation of AF progression. This resulted in the attribution of 1 or 2 points for each variable included in the score.

The predictive accuracy of the known predictors of AF progression and the HATCH score was reported using a receiver-operator characteristic curve. To compare the discriminative power of the HATCH score (acronym stands for hypertension, age [75 years and older], transient ischemic attack or stroke (2 points), chronic obstructive

pulmonary disease and heart failure (2 points); this scoring system allows instant classification of the risk of progression to persistent or permanent AF in patients with paroxysmal AF) and the CHADS₂ score, we applied the DeLong, DeLong, Clarke-Pearson method using Analyse-it 2.20 statistical software (Leeds, United Kingdom). All tests performed were 2 sided. Overall, a P value of <0.05 was considered to be statistically significant.

Results

The age of the 1,219 patients included in the present study was 64 ± 13 years. Progression of AF to more sustained forms occurred in 178 patients (15%). Table 3.1 shows the baseline characteristics of patients with and without AF progression. Patients who experienced AF progression were older and performed less regular physical activity. In addition, these patients had more underlying heart disease.

Table 3.1 Baseline characteristics.

	All patients	No AF progression	AF progression	P-value
N	1219	1041 (85%)	178 (15%)	
Age (years)	64±13	63±13	68±11	<0.001
Female	524 (43%)	439 (42%)	85 (49%)	0.165
Body Mass Index (kg/m ²)	27±4	27±4	28±5	0.246
Symptoms (admission)	913 (75%)	773 (74%)	140 (79%)	0.261
Regular physical activity	415 (34%)	370 (36%)	45 (25%)	0.010
Echo and ECG characteristics				
Left atrial size on echo (mm)	43±8	43±8	45±8	<0.001
Ventricular rate (when sinus rhythm)	70±15	70±15	72±19	0.195
Ventricular rate (when AF)	109±30	109±31	110±30	0.712
AF-type				
1 st detected	165 (14%)	140 (13%)	25 (14%)	
Paroxysmal	1054 (86%)	901 (87%)	153 (86%)	
Underlying diseases				
Hypertension	752 (62%)	626 (60%)	126 (71%)	0.007
Coronary artery disease	392 (32%)	321 (31%)	71 (40%)	0.024
Diabetes mellitus	182 (15%)	148 (14%)	34 (19%)	0.110
Valve disease	233 (19%)	188 (18%)	45 (25%)	0.030
Heart failure	247 (21%)	181 (18%)	66 (38%)	<0.001
Chronic obstructive pulmonary disease	137 (11%)	104 (10%)	33 (19%)	0.002
Hyperthyroidism	60 (5%)	52 (5%)	8 (5%)	0.853
Stroke or TIA in history	105 (9%)	77 (8%)	28 (16%)	0.001
Malignancy	56 (5%)	47 (5%)	9 (5%)	0.699
Peripheral vascular disease	74 (6%)	58 (6%)	16 (9%)	0.089
Renal failure	56 (5%)	41 (4%)	15 (9%)	0.018
Lone AF	203 (17%)	189 (19%)	14 (8%)	<0.001
CHADS ₂ score	1,3±1,2	1,2±1,1	1,9±1,3	<0.001

ECG=electrocardiogram; TIA=transient ischemic attack

Hypertension, coronary artery disease, valve disease, heart failure, COPD, stroke or TIA, and renal failure occurred more frequently in patients with AF progression. This is reflected by the higher mean CHADS₂ score (1.9 ± 1.3 vs. 1.2 ± 1.1 , $P < 0.001$) and lower percentage of lone AF (8% vs. 19%, $P < 0.001$) in patients with AF progression compared with patients whose AF remained paroxysmal after 1 year. No significant difference was found between the percentage of patients with diabetes demonstrating AF progression and patients who remained in sinus rhythm. On the echocardiogram obtained at baseline, patients with AF progression had a larger left atrium.

Medication use at baseline is presented in Table 3.2. Understandably, all drugs associated with heart failure were used more frequently in patients with AF progression: digitalis, angiotensin-converting enzyme inhibitors, and diuretics. Furthermore, patients experiencing worsening of their AF used more oral anticoagulation, which likely is the result of a higher mean CHADS₂ score in this group. Patients with AF progression used angiotensin II receptor blockers (7% vs. 13%, $P = 0.023$) less frequently. Beta-blockers were prescribed in 56% of patients with heart failure and in 65% of patients with coronary artery disease.

Table 3.2 Medication use at baseline.

	All patients	No AF progression	AF progression	P-value
N	1219	1041 (85%)	178 (15%)	
Oral anticoagulation	594 (50%)	490 (49%)	104 (60%)	0.007
Aspirin	437 (37%)	376 (37%)	61 (35%)	0.611
Beta-blocker	495 (42%)	418 (41%)	77 (44%)	0.506
Diltiazem	36 (3%)	29 (3%)	7 (4%)	0.468
Verapamil	60 (5%)	48 (5%)	12 (7%)	0.257
Digitalis	136 (11%)	108 (11%)	28 (16%)	0.039
Any antiarrhythmic drug	627 (52%)	541 (52%)	86 (49%)	0.415
- Flecainide	89 (7%)	80 (8%)	9 (5%)	0.274
- Disopyramide	6 (1%)	6 (1%)	0	0.601
- Propafenone	111 (9%)	101 (10%)	10 (6%)	0.090
- Sotalol	145 (12%)	128 (12%)	17 (10%)	0.379
- Amiodarone	288 (24%)	237 (23%)	51 (29%)	0.086
Angiotensin-converting enzyme inhibitor	518 (44%)	411 (41%)	107 (62%)	<0.001
Angiotensin-II receptor blocker	142 (12%)	130 (13%)	12 (7%)	0.023
Diuretics	428 (36%)	339 (34%)	89 (51%)	<0.001

During follow-up, in patients with AF progression, either persistent (46%) or permanent (54%) AF developed (Table 3.3). The patients with progression were more often symptomatic compared with patients without AF progression. Patients without AF progression had either first detected AF (10%) or paroxysmal AF (83%), and nearly 7% of the patients were considered cured by their physician. Finally, patients who progressed to more sustained forms of AF underwent more electrical cardioversions, were more often admitted to the hospital for a cardiovascular problem, and had more often a stroke or TIA during the 1 year of follow-up. We found no significant differences in pharmacological cardioversions between both groups.

Table 3.3 Characteristics at one year follow-up.

	All patients	No AF progression	AF progression	P-value
N	1219	1041 (85%)	178 (15%)	
Symptoms	366 (32%)	280 (29%)	86 (52%)	<0.001
Death	22 (2%)	16 (2%)	6 (3%)	0.118
Type of AF				
-First detected	107 (9%)	107 (10%)	0	
-Paroxysmal	860 (71%)	860 (83%)	0	
-Persistent	81 (7%)	0	81 (46%)	
-Permanent	97 (8%)	0	97 (54%)	
-Considered cured	74 (5%)	74 (7%)	0	
Hospital admissions during 1 year				
Cardiovascular admissions	523 (53%)	419 (50%)	104 (71%)	<0.001
Pharmacological cardioversion	255 (23%)	217 (22%)	38 (24%)	0.534
Number of pharmacological cardioversions	0.4±1.3	0.4±1.3	0.5±1.0	0.847
Electrical cardioversion	161 (15%)	122 (13%)	39 (26%)	<0.001
Number of electrical cardioversions	0.2±0.7	0.2±0.7	0.4±0.8	0.009
Catheter ablation	61 (5%)	57 (6%)	4 (2%)	0.065
Major adverse Cardiovascular events				
Coronary artery disease	72 (6%)	57 (6%)	15 (8%)	0.168
- Myocardial Infarction	17 (1%)	12 (1%)	5 (3%)	0.091
- Unstable Angina	44 (4%)	34 (3%)	10 (6%)	0.130
Ischemic stroke or TIA	31 (3%)	20 (2%)	11 (6%)	0.003
- Ischemic stroke	20 (2%)	12 (1%)	8 (5%)	0.005
- TIA	11 (1%)	8 (1%)	3 (2%)	0.212
Combined survival/stroke	40 (3%)	27 (3%)	13 (7%)	0.005

The multivariate logistic regression regarding factors associated with AF progression after 1 year of follow-up is presented in Table 3.4. A history of heart failure, hypertension, COPD, and stroke or TIA and age older than 75 years were the only independent factors associated with AF progression. No significant interactions were found between these variables. Using the regression coefficient as a benchmark, we determined the relative contribution of each factor to the prediction of AF progression. This resulted in the HATCH score rule: 1 x (hypertension) + 1 x (age >75 years) + 2 x (stroke or TIA) + 1 x (COPD) + 2 x (heart failure).

Because of its plausible preventive effect on AF progression, we repeated the logistic regression including antiarrhythmic drugs. However, antiarrhythmic drugs were not present in the final logistic regression model resulting from this analysis. The final model contained the same variables as the initial analysis excluding antiarrhythmic drugs (data not shown). We also excluded first-detected AF patients who underwent a pharmacological cardioversion in a separate analysis (data not shown) because these patients could have a more advanced electrophysiological substrate than pure paroxysmal AF patients. However, this did not alter the results significantly.

Table 3.4 Independent predictors of AF progression resulting from multivariate logistic regression analysis.

	OR	OR 95%CI	Regression coefficient	P-value	Score
Heart Failure in history	2.22	1.54-3.22	0.80	<0.001	2
Hypertension	1.52	1.05-2.20	0.42	0.024	1
Chronic obstructive pulmonary disease	1.51	0.95-2.39	0.41	0.088	1
Stroke or TIA in history	2.02	1.24-3.31	0.71	0.007	2
Age > 75 years	1.57	1.07-2.30	0.45	0.024	1

OR=odds ratio; CI=confidence interval; TIA=transient ischemic attack

Nearly 50% of the patients with paroxysmal AF and a HATCH score of 6 or 7 had AF progression after 1 year compared with only 6% of the patients with a HATCH score of 0. The percentages of AF progression in patients with a HATCH score of 0 through 7 are presented in Figure 3.1. With increasing HATCH score, the proportion of patients with AF progression during follow-up increases.

Figure 3.1 Prevalence of the different HATCH scores and incidence of progression. The number of patients for each HATCH score is represented by the black bars. The percentage of atrial fibrillation (AF) progression after 1 year of follow-up per HATCH score is represented by the grey line.

The receiver-operator characteristic curve to discriminate individuals who will or will not have AF progression during follow-up based on their HATCH score is shown in Figure 3.2. The area under the curve (AUC) is 0.675 (95% confidence interval: 0.632 to 0.718, $P<0.001$). The predictive value of the HATCH score is higher than all other independent predictors of AF progression individually: heart failure (AUC=0.599), hypertension (AUC=0.564), COPD (AUC=0.542), stroke or TIA (AUC=0.545), and age (AUC=0.561). The AUC of the HATCH score was slightly higher compared with the CHADS₂ score (difference: 0.02 (95% confidence interval: 0.00 to 0.04); $P=0.0576$).

Figure 3.2 Predictive ability of the HATCH Score
The receiver-operator characteristic curve for the prediction of clinical atrial fibrillation type progression using the HATCH score.

We classified patients into 4 groups based on their HATCH score. The percentages of AF progression for each group are presented in Figure 3.3. This figure demonstrates that with increasing score, the percentage of AF progression during follow-up increases as well.

Figure 3.3 Incidence of AF progression.
The 1-year incidence of atrial fibrillation (AF) progression per HATCH score. The HATCH score is divided into 4 categories that could be clinically relevant.

Discussion

The present study is the largest study evaluating clinical correlates of AF progression. It provides a unique insight into the characteristics and prognosis of patients with progression from paroxysmal to more sustained forms of AF. Nearly 15% of the patients with paroxysmal AF included in this study progressed to persistent or permanent AF after 1 year of follow-up, despite the fact that more effort was made to obtain sinus rhythm in this group. In addition, patients with progression had more adverse cardiovascular events and were more often admitted in the hospital. Heart failure, previous stroke or TIA, COPD, hypertension, and age were independent predictors of AF progression. Considering the nature of these factors and in view of the fact that they are associated with future cardiovascular events, one may conjecture that structural rather than electrical remodeling of the atria is involved in AF progression. Underlying diseases might cause chronic stretch and atrial dilation, which seem to be important stimuli for chronic atrial structural remodeling (cellular hypertrophy, fibroblast proliferation, and tissue fibrosis), which enables maintenance of AF.⁸ It is likely that structural atrial remodeling leading to atrial pathology enables the development of cardiovascular events, which might explain the relatively high stroke rate among the patients with AF progression in our survey. In addition, recent studies showed that patients with a higher AF burden, which is the case in patients demonstrating AF progression, are more prone to have a stroke.⁹

Based on the predictors of AF progression, we developed a risk stratification rule to estimate the probability of AF progression in patients with paroxysmal AF: the HATCH score. This score enables the detection of patients in whom more sustained forms of AF are likely to develop in the near future. Previous studies showed that the presence of underlying heart disease is associated with poor outcome of rhythm control therapy.¹⁰ However, these patients are more likely to have AF progression. In the same way, our data suggest that the potential preventive effect of antiarrhythmic drugs on AF progression was outperformed by the promoting effect of underlying heart disease and age, as represented by the HATCH parameters. Therefore, it seems very important to identify patients that are likely to progress to persistent AF beforehand to avoid needless rhythm control therapy. This holds even more because AF progression may be associated with major events that are easily enhanced by rhythm control drugs known for their potential to induce proarrhythmia, heart failure, and atrioventricular block. In our study, relatively low numbers of beta-blockers were prescribed in patients with heart failure and coronary artery disease. We hypothesized that this is probably the result of the use antiarrhythmic drugs in our patients. Many antiarrhythmic drugs such as amiodarone, sotalol, and propafenone have beta-blocking properties. Bradycardia might result when these antiarrhythmic drugs are prescribed together with a beta-blocker. Our results suggest that if a high HATCH score is found, clinicians should focus on rate control and upstream therapy rather than rhythm control therapy. Several studies investigating AF progression have been published in the

past.^{5,11–13} The rate of AF progression described in these studies varied between 8%⁴ and 22%¹⁴ after 1 year of follow-up, depending on the rhythm-monitoring methods used. Various factors were associated with AF progression: valvular disease, alcohol consumption, age, left atrial dimension and amount of atrial enlargement over time, stroke, and heart failure. However, correction for possible confounders was not always performed, and the currently available risk stratification parameters resulting from these studies have limited predictive value in individual patients. Our findings suggest that combining several independent predictors of AF progression into a balanced rule outperforms all the previously known predictors for the development of sustained AF.

Clinical implications

The HATCH score in daily practice could guide the physician in the clinical decisionmaking process. First, patients with a high HATCH score should be monitored more frequently because they are prone to the development of cardiovascular events. In addition, one could hypothesize that the HATCH score may be used for early selection of patients for rhythm control therapy in an effort to prevent disease progression. Conversely, potentially harmful drugs and interventions including cardioversion and ablation may be avoided in patients with a high HATCH score. Obviously, further studies are needed to confirm these hypotheses and show the clinical value of the HATCH score when implemented in clinical practice.

Study limitations

We performed a subgroup analysis of the EHS. As a result, our data should be interpreted with care. Follow-up regarding rhythm status was unavailable for approximately 31% of the patients with first detected or paroxysmal AF at baseline. Patients with unknown rhythm status had more often underlying heart disease and a higher HATCH score (1.8 vs. 1.5) compared with patients with a known rhythm status at follow-up (additional data not shown). This may have led to an underestimation of the incidence of AF progression. Conversely, this does not, in our view, reduce the predictive capacity of the HATCH score.

Considering the relatively low use of beta-blockers, ACE inhibitors, and angiotensin-receptor blockers, the patients included in the present analysis may have been undertreated, especially the patients concomitantly having coronary artery disease and heart failure.¹⁵ Future studies may show that progression factors other than the HATCH score are important in AF patients fully managed according to all the guidelines pertinent to their various underlying diseases. The definition of AF progression that we selected is arbitrary. In clinical practice, it is extremely difficult to robustly determine the progression from persistent to permanent AF because a firm end point is lacking. However, we believe that our definition reflects the pathophysiological stage of AF severity. This is supported by the direct or indirect relationship between AF

progression as defined and clinical outcomes such as hospital admissions and major adverse cardiovascular events.

The predictive value of the HATCH score was not flawless. In addition, the score should be validated in another population of patients with AF before it can be applied in clinical practice.

Conclusions

This is the largest study exploring the characteristics and outcome of patients with AF progression. A substantial number of patients progress to sustained AF within 1 year. The clinical outcome of these patients with regard to hospital admissions and major adverse cardiovascular events was worse compared with patients demonstrating no AF progression. Heart failure, previous stroke or TIA, COPD, hypertension, and age were independent predictors of AF progression. Based on these parameters, we developed the HATCH score, which enhances detection of patients in whom more sustained forms of AF are likely to develop in the near future.

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Editorial comment

Progression of Paroxysmal to Persistent Atrial Fibrillation

Factors Promoting the HATCH Score

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With a lifetime 1 in 4 risk of its development,¹ atrial fibrillation (AF) continues to be the most common cardiac arrhythmia that impairs quality of life and contributes to increased susceptibility to heart failure, hospitalization, stroke, and mortality, costing society more than \$15 billion annually.^{2,3} With the rapid increase in the number of elderly patients⁴ and cardiovascular comorbidities⁵, a 6-fold increase in the prevalence of AF (from 2.3 million to 15.9 million) is projected,⁶ highlighting the magnitude of the problem and the far-reaching implications that the epidemic of AF will have on the health and economics of the country. Thus, an urgent need exists to better understand clinical factors and the basic biology that predispose to AF and its progression and associated complications so that effective preventive strategies can be implemented to reduce the burden of AF on society. AF is a heterogeneous disorder with variable etiology, clinical profile, and natural history.² From a clinical perspective, AF has been broadly classified as paroxysmal, persistent (or long-lasting), and permanent, depending on the duration of symptoms and its propensity to terminate by itself, terminate with electrical or pharmacological intervention, or not terminate at all.^{2,7} The electrophysiological basis for the initiation and/or maintenance of AF varies depending on age, the presence of underlying heart disease, and other modulating factors. In the majority of patients, AF occurs in the setting of structural heart disease, with only a small percentage exhibiting AF as a primarily electrical disorder.^{2,8} Changes in hemodynamic, mechanical, neurohumoral, metabolic, and inflammatory factors that accompany aging or aging-associated diseases,⁹ such as heart failure, valvular heart disease, hypertension, myocardial infarction, pulmonary disease, and diabetes contribute to the development of AF, yet the common mechanistic link between these factors and the development of the substrate for AF or its progression is not fully understood.¹⁰

In this issue of the Journal, de Vos et al.¹¹ report the results of their investigation on the clinical correlates of AF progression and prognosis in patients enrolled in the Euro Heart Survey of AF. The Euro Heart Survey enrolled 5,333 adult patients between 2003 and 2004 in 182 hospitals among 35 different European countries and represents a unique overview of real-life AF management within cardiology practices across Europe.¹² Their report is on 1,219 patients with paroxysmal or first detected AF in whom sinus rhythm restored spontaneously or after pharmacological treatment during

admission and who had a known rhythm status at 1-year follow-up. Progression of AF to persistent or long-lasting forms occurred in 178 (15%) patients. These patients were older and had more underlying cardiovascular disease and other comorbidities. On multivariate analysis, HATCH (hypertension, age older than 75 years, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, and heart failure) were identified as independent predictors of AF progression. Using the regression coefficient as a benchmark, the investigators came up with the HATCH score to predict the probability of progression of AF. With an increasing HATCH score, the proportion of patients in whom AF progressed to longlasting forms was significantly higher with a greater number of hospital admissions and major adverse cardiovascular events compared with those with fewer of these risk factors.

The strength of this study is the provision of information about AF management and progression in patients in 35 European countries in real-life situations and the development of a risk prediction system for progression of paroxysmal or first detected AF. The major limitation is that information is provided only on <50% of patients (1,219 of 2,495) who were initially included in the survey with a first episode of AF or paroxysmal AF.¹² The patients who were not included could have gone either way (i.e. AF progressed or remained paroxysmal), and, hence, the reported results could under- or overestimate the true progression rate. In a population of AF patients referred to cardiology practices within university (majority of patients) and nonuniversity settings in 35 different (western, central, and Mediterranean) European countries with variable facilities and management left to the usual local institutional practices, the interpretation of the data and generalizability to AF patients in the community become difficult. This, combined with the short follow-up period and definition of paroxysmal AF used¹² diminishes the robustness of the conclusion. The authors included a significant number of patients with AF who required pharmacological cardioversion for restoration of sinus rhythm in paroxysmal AF, which, by standard definition, would have been classified as persistent AF.² These patients could have a different electrophysiological substrate or natural history from those who spontaneously converted to sinus rhythm and thus may have substantially influenced progression analysis. Differences in the definitions used and misclassification of AF subtype at enrollment, as previously reported,¹² also make comparison with other studies difficult. No information about the date of onset and duration of AF before enrollment is provided. A population with new-onset or recently diagnosed AF could have provided more useful information on progression to long-lasting AF. In addition, the use of beta-blockers and other cardiac medicines seems to be low, considering the substantial number of patients with coronary artery disease, hypertension, and heart failure who were included,¹³ raising the concern that these patients may have been undertreated, thus complicating the differentiation of atrial substrate progression due to coronary artery disease, heart failure, or remodeling solely caused by rhythm disturbance or uncontrolled ventricular rate response.

Although no new insights into the mechanisms of AF or risk predictions are reported, the proposed HATCH scheme for AF progression seems to be a useful scoring system and is the major strength of the article. The striking similarity to CHADS₂ (congestive heart failure, hypertension, age [75 years and older], diabetes mellitus, and a history of stroke or transient ischemic attack) score for risk of thromboembolic events¹⁴ is interesting. Both reflect the advanced age of the AF population and comorbidities, such as the presence of heart failure, hypertension, previous stroke/transient ischemic attack, chronic obstructive pulmonary disease (for progression vs. diabetes mellitus for thromboembolic risk), highlighting factors associated with an advanced substrate for AF progression and its complications. The HATCH score may help to identify patients who are at high risk of progression and hence may be followed more closely than they otherwise would be. The authors suggest that the HATCH score may also identify the population in which the rate versus rhythm control approach should be used, because antiarrhythmic agents were unable to prevent progression of AF in their population. In the absence of randomization to specific treatment strategies and treatment decisions left to the preference of the attending cardiologist,¹² the conclusion about the lack of effectiveness of antiarrhythmic agents in preventing progression needs to be made with caution. The HATCH score may help, but may not be the sole determinant of the decision for initiating antiarrhythmic therapy, as the treatment for paroxysmal AF needs to be individualized based on the presence of symptoms associated with frequent recurrences.² The findings of the study again reinforce previous recommendations regarding frequent monitoring¹⁵ for the development and treatment of comorbidities² that may accelerate AF progression and predispose to its complications.

In summary, this study validates the risk factors reported previously for AF progression² in a referral population of cardiology practices within a widely diverse geopolitical area in Europe. The HATCH score seems to be a useful tool to predict the progression of AF but should be validated in other populations with a longer follow-up period before it can be applied in clinical practice. The major challenge raised by this and other studies identifying risk factors for the development and progression of AF is to focus our efforts on identification of common mechanistic links between these factors and the molecular substrate that promotes the development of AF and its progression, so that effective strategies can be developed to prevent AF and its associated complications.

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Chapter 4

Progression of atrial fibrillation in the REgistry on
Cardiac rhythm disORDers assessing the control of
Atrial Fibrillation cohort: Clinical correlates and
the effect of rhythm-control therapy

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Abstract

Introduction

Paroxysmal atrial fibrillation (AF) may progress to persistent AF. We studied the clinical correlates and the effect of rhythm-control strategy on AF progression.

Methods

RecordAF was a worldwide prospective survey of AF management. Consecutive eligible patients with recent-onset AF were included and allocated to rate or rhythm control according to patient/physician choice. A total of 2,137 patients were followed up for 12 months. Atrial fibrillation progression was defined as a change from paroxysmal to persistent/permanent AF.

Results

Progression of AF occurred in 318 patients (15%) after 1 year. Patients with AF progression were older; had a higher diastolic blood pressure; and more often had a history of coronary artery disease, stroke or transient ischemic attack, hypertension, or heart failure. Patients treated with rhythm control were less likely to show progression than those treated only with rate control (164/1542 [11%] vs. 154/595 [26%], $P<0.001$). Multivariable analysis showed that history of heart failure (odds ratio [OR] 2.2, 95% CI 1.7-2.9, $P<0.0001$), history of hypertension (OR 1.5, 95% CI 1.1-2.0, $P=0.01$), and rate control rather than rhythm control (OR 3.2, 95% CI 2.5-4.1, $P<0.0001$) were independent predictors of AF progression. The propensity score-adjusted OR of AF progression in patients with rate rather than rhythm control was 3.3 (95% CI 2.4-4.6, $P<0.0001$).

Conclusions

Although heart failure and hypertension are associated with AF progression, rhythm control is associated with lower risk of AF progression.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.¹ Paroxysmal, that is, self-terminating, AF often progresses to persistent AF, which may complicate rhythm control.^{2,3} To determine the preferred treatment strategy in paroxysmal AF, it is appropriate to consider risk factors for AF progression.⁴ However, few data are available on the progression of paroxysmal AF to more sustained forms. Kerr et al.² evaluated determinants of AF progression in the Canadian Registry of Atrial Fibrillation (CARAF) study. They found that underlying heart disease and age are independently associated with progression of AF. More recently, de Vos et al.³ studied the clinical correlates of arrhythmia progression in patients with paroxysmal AF and evaluated the prognosis of patients with AF progression, introducing a risk stratification rule to assess the probability of AF progression. They found that heart failure, age, previous transient ischemic attack (TIA) or stroke, chronic obstructive pulmonary disease, and hypertension are independent predictors of AF progression. The clinical outcome of patients demonstrating AF progression regarding hospital admissions and major adverse cardiovascular events was worse compared with patients without progression. A recent report provides an overview of all established and emerging factors for incident AF and AF progression.⁵ The RecordAF is the first worldwide, 1-year observational, longitudinal study of the management of AF in recently diagnosed patients.⁶ In the present study, we evaluated AF progression in the RecordAF cohort.

Methods

RecordAF is an international (Europe, North and South America, and Asia), observational, prospective, 1-year longitudinal cohort study of patients with AF. A detailed description of the methods, data collection, and initial results of the RecordAF has been published previously.⁶ The study included 5,604 patients and was conducted at 532 sites in 21 countries. Institutional review board approval was obtained at all sites. Recruitment started in May 2007 and was completed in April 2008. The study was conducted in accordance with the Helsinki principles. Patients were included when aged ≥ 18 years with AF discovered at the inclusion visit or AF diagnosed ≤ 1 year from inclusion. Atrial fibrillation was diagnosed by electrocardiogram or Holter registration. Rate- or rhythm-control therapy was decided by the patient and the physician according to their standard practice. Exclusion criteria were AF resulting from a transient cause, post-cardiac surgery AF, life expectancy of < 1 year owing to a severe disease; mental disability; a pacemaker or an implantable cardioverter/defibrillator; scheduled pulmonary vein isolation, atrioventricular node/His bundle ablation, or pacemaker implantation; participation in an AF clinical trial in the previous 3 months; or pregnancy or breastfeeding. Eligible patients included those who met the inclusion

criteria regardless of the purpose of the visit to the cardiologist or the hospitalization. A total of 10 to 30 consecutive patients were enrolled at each site. The patients gave written informed consent to participate in the study. All patients were evaluated at baseline, after 6 months, and after 12 months during routine follow-up visits.

In the present study, only the records for patients with paroxysmal AF and first-detected AF in whom sinus rhythm restored spontaneously or after pharmacologic treatment during admission were evaluated, leaving a study population of 2,137. Atrial fibrillation progression was defined as a change from self-terminating or paroxysmal AF at baseline to non-selfterminating AF, that is, persistent or permanent AF after 1 year of follow-up. Atrial fibrillation type was determined according to the clinical judgment of the attending physician.

Statistical analysis

Data analysis was performed with SAS statistical software version 9.1 (SAS Institute, Cary, NC). Continuous variables are reported as mean $\pm$ SD, and categorical variables, as observed number of patients and percentage. When comparing patients with “AF progression” and “no AF progression” regarding baseline characteristics, treatment, or outcome, we used an independent t test for continuous variables and χ^2 or Fisher exact test for categorical variables. We calculated a derivate of the HATCH score (not including chronic obstructive pulmonary disease [COPD]). HATCH is an acronym for hypertension, age >75 years, TIA or stroke, COPD, and heart failure, which has been proposed as a simple prediction rule for AF progression.³ Unfortunately, we were unable to validate the HATCH score in the present study because a history of COPD was not included in the study case record form. We also calculated the CHADS₂ (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, stroke or, TIA) score, a scoring system allowing classification of the relative thromboembolic risk in patients with AF.⁷ All baseline characteristics with a *P* value >0.2 resulting from the univariate comparison between “no AF progression” and “AF progression at follow-up” and all variables having a plausible or historical association with AF progression were included in a logistic regression model to predict progression: age; family history of AF; gender; diabetes; dyslipidemia; hypertension; body mass index; family history of premature cardiovascular disease, coronary artery disease, heart failure, myocardial infarction, stroke, or TIA; valvular heart disease; smoking status; pulse pressure; and AF treatment strategy at baseline. Model construction was performed by a stepwise procedure, with a *P* value of 0.20 required for entering and of 0.05 for retaining the variable in the model. Odds ratios (ORs) and associated 95% CIs were calculated. To adjust for variables that could be associated with treatment strategy, we calculated a propensity score: a stepwise logistic regression was used to estimate the score for each patient based on a wide list of covariates that could possibly be associated with treatment strategy selection. In addition to the variables listed above, ethnicity, carotid stenosis, thyroid disease, renal disease, duration of AF, symptoms,

antithrombotic treatment, antihypertensive treatment, antidiabetic treatment, and country were included. All covariates associated with treatment strategy with a P value <0.5 were kept in the model. The patient population was divided into strata defined by the quintiles of propensity score. In each stratum, the main patient characteristics were comparable between rate-control and rhythm-control strategy. Effect of strategy on AF progression was tested across propensity score strata. Overall, $P<0.05$ was considered to be statistically significant.

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Results

We assessed 2,137 patients with paroxysmal AF at study entry and after 12 months of follow-up. The mean age in our population was 65 ± 12 years. Progression to persistent AF occurred in 318 patients (15%) after 1 year. Table 4.1 shows the baseline characteristics. In our population, patients with AF progression were older; had a higher diastolic blood pressure; and were more likely to have a history of coronary artery disease, stroke or TIA, hypertension, or heart failure. As a result, these patients less frequently had “lone AF.” Patients with a higher CHADS₂ score showed more AF progression: 19% progression when CHADS₂ >1 versus 14% progression when CHADS₂ is 1 and 9% progression when CHADS₂ is 0 ($P<0.0001$). Patients treated with rhythm control showed less progression than those treated with rate control: 11% versus 26%; $P<0.001$.

Atrial fibrillation-related medication used at baseline is presented in Figure 4.1. The use of class Ic antiarrhythmic drugs was associated with less AF progression, whereas the use of cardiac glycosides was associated with more AF progression at 1-year follow-up. Regarding non-AF-related medication, 46% used diuretics, 24% used dihydropyridine calcium-channel blockers, 83% used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 7% used nitrates, and 41% used lipidlowering drugs. No significant differences were found regarding prescription of these medications between patients with and without AF progression. Table 4.2 shows the electrocardiographic parameters of patients with versus without AF progression. The baseline characteristics of patients treated with a rate-control strategy versus those treated with a rhythm-control strategy are presented in Table 4.3. Patients receiving rhythm control were younger and had less valvular heart disease. On the other hand, they had more hypertension and heart failure. However, the left ventricular ejection fraction was nearly the same in both groups.

Table 4.1 Baseline characteristics.

Characteristic	Total	Progression	No progression	P value
N	2137	318	1819	
Age, years $\pm$ SD	65.1 $\pm$ 12	67.2 $\pm$ 11	64.7 $\pm$ 12	0.0011
Female sex, n (%)	1013 (47)	151 (47)	862 (47)	0.9749
Ethnicity (except in French arm of study)				0.2177
White	1818 (86)	268 (85)	1550 (87)	
Black	28 (1)	3 (1)	25 (1)	
Asian	170 (8)	34 (11)	136 (8)	
Other	88 (4)	10 (3)	78 (4)	
Body mass index, kg/m ²	28.2 $\pm$ 5	28.2 $\pm$ 5	28.2 $\pm$ 5	0.7581
Systolic BP, mm Hg	133.7 $\pm$ 19	134.8 $\pm$ 21	133.6 $\pm$ 19	0.3938
Diastolic BP, mm Hg	79.2 $\pm$ 11	80.5 $\pm$ 12	78.9 $\pm$ 11	0.0252
Pulse pressure, mm Hg	54.6 $\pm$ 15	54.3 $\pm$ 16	54.6 $\pm$ 15	0.4713
Family history of premature CVD, n (%)	402 (21)	46 (17)	356 (21)	0.0893
Family history of AF, n (%)	228 (11)	24 (8)	204 (11)	0.0527
Smoking status, n (%)				0.4014
Never	1189 (57)	186 (61)	1003 (57)	
Current	285 (14)	36 (12)	249 (14)	
Former	593 (29)	85 (28)	508 (29)	
Cardiovascular disease, n (%)				
Coronary artery disease	381 (19)	72 (24)	309 (18)	0.0213
Myocardial infarction	175 (8)	34 (11)	141 (8)	0.0770
Stroke or TIA	165 (8)	34 (11)	131 (7)	0.0283
Arterial hypertension	1499 (70)	247 (78)	1252 (69)	0.0015
Heart failure	437 (20)	103 (32)	334 (18)	<0.0001
Dyslipidemia	986 (46)	136 (43)	850 (47)	0.1954
Valvular heart disease	351 (17)	60 (19)	291 (16)	0.1932
Diabetes	321 (15)	54 (17)	267 (15)	0.2926
Arrhythmia other than AF	337 (16)	39 (12)	298 (17)	0.0571
Lone AF	436 (20)	35 (11)	401 (22)	<0.0001
Other disease, n (%)				
Thyroid disease	218 (10)	28 (9)	190 (11)	0.3909
Renal disease	124 (6)	23 (7)	101 (6)	0.2192
Strategy at baseline, n (%)				<0.0001
Rhythm control	1542 (72)	164 (52)	1378 (76)	
Rate control	595 (28)	154 (48)	441 (24)	

BP: blood pressure; CVD: cardiovascular disease; SD: standard deviation

At follow-up, 61% of the patients with AF progression had developed permanent AF and 39% persistent AF. Patients with progression more often underwent electrical and pharmacologic cardioversion (Table 4.4). In addition, they more often had a myocardial infarction, stroke, or TIA and were more frequently admitted for cardiovascular events during the year of observation.

Figure 4.1 Use of AF-related drugs at baseline according to AF status at 1 year.

Table 4.2 Electrocardiogram at baseline (when in sinus rhythm).

Characteristics	Total	Progression	No progression	P value
Number of patients	1445	131	1314	
PR (ms)	172.0 ± 33	175.0 ± 34	171.6 ± 33	0.4654
QT (ms)	395.6 ± 47	395.8 ± 48	395.6 ± 47	0.3710
QRS complex (ms)	92.9 ± 18	91.2 ± 18	93.1 ± 18	0.3701
T-wave abnormalities	275 (18)	41 (29)	234 (17)	0.0004

The multivariate logistic regression for factors associated with AF progression after 1-year follow-up showed that a history of heart failure (OR 2.2, 95% CI 1.7-2.9, $P < 0.0001$), history of hypertension (OR 1.5, 95% CI 1.1-2.0, $P = 0.0108$), and rate control rather than rhythm control (OR 3.2, 95% CI 2.5-4.1, $P < 0.0001$) were independent predictors of AF progression. The propensity score-adjusted OR of AF progression in patients with rate rather than rhythm control was 3.3, 95% CI 2.4 to 4.6, $P < 0.0001$. The progression rate according to the HATCH score (without COPD) is presented in Figure 4.2. In the subgroup of patients with a rate-control strategy, predictive factors for AF progression were heart failure (OR 2.9, 95% CI 1.8-4.5, $P < 0.0001$) and heart rate (OR 1.02 per beat/min, 95% CI 1.01-1.03, $P < 0.0001$). In the subgroup of patients with a rhythm-control strategy, predictive factors of AF progression were heart failure (OR 2.0, 95% CI 1.4-2.8, $P = 0.0002$), hypertension (OR 1.8, 95% CI 1.2-2.7, $P = 0.0064$), and heart rate (OR 1.01 per beat/min, 95% CI 1.02, $P = 0.0003$).

Table 4.3 Baseline characteristics according to strategy AF at baseline.

Characteristic	Rate-control strategy	Rhythm-control strategy	P value
N	595	1542	
Age, years $\pm$ SD	67.8 $\pm$ 11	64.0 $\pm$ 12	<0.0001
Female sex, n (%)	280 (47.1)	733 (47.5)	0.8431
Body mass index, kg/m ²	28.1 $\pm$ 6	28.2 $\pm$ 5	0.6925
Systolic BP, mm Hg	132.0 $\pm$ 20	134.4 $\pm$ 19	0.0112
Diastolic BP, mm Hg	78.0 $\pm$ 11	79.6 $\pm$ 11	0.0017
LVEF available, n (%)	476 (82.4)	1235 (82.2)	
LVEF by Classes, n (%)			0.1935
<30%	9 (1.9)	9 (0.7)	
30 to 35%	7 (1.5)	16 (1.3)	
36 to 40%	8 (1.7)	26 (2.1)	
41 to 50%	39 (8.2)	83 (6.7)	
>50%	412 (86.7)	1099 (89.1)	
Family history of premature CVD, n (%)	103 (19.7)	299 (21.3)	0.4569
Family history of AF, n (%)	60 (10.1)	168 (10.9)	0.5868
Cardiovascular disease, n (%)			
Coronary artery disease	112 (19.6)	269 (19.1)	0.7891
Myocardial infarction	50 (8.5)	125 (8.2)	0.8257
Stroke or TIA	49 (8.3)	116 (7.6)	0.5660
Arterial hypertension	411 (69.1)	1088 (70.6)	0.4890
Heart failure	104 (17.5)	333 (21.6)	0.0353
Dyslipidemia	279 (47)	707 (45.9)	0.6451
Valvular heart disease	124 (21.2)	227 (14.8)	0.0004
Diabetes	100 (16.8)	221 (14.4)	0.1546
Arrhythmia other than AF	94 (16.1)	243 (16.2)	0.9463
Lone AF	122 (20.6%)	314 (20.4%)	0.9357
Other disease, n (%)			
Thyroid disease	61 (10.4)	157 (10.4)	0.9707
Renal disease	38 (6.5)	86 (5.6)	0.4362

BP: blood pressure; CVD: cardiovascular disease; LVEF: left ventricular ejection fraction; SD: standard deviation.

Table 4.4 Characteristics at 1-year follow-up.

Characteristic	Total	Progression	No progression	P value
N	2137	318	1819	
Cardiovascular intervention, n (%)				
Pharmacologic conversion	243 (11)	47 (15)	196 (11)	0.0267
Electrical conversion	88 (4)	34 (11)	54 (3)	<0.0001
Catheter ablation	34 (2)	4 (1)	30 (2)	0.8086
Surgical AF therapy	7 (<1)	2 (1)	5 (<1)	0.2723
Cardiovascular event				
Myocardial infarction	13 (1)	6 (2)	7 (<1)	0.0065
Stroke/TIA	40 (2)	11 (3)	29 (2)	0.0204
Hospitalization for cardiovascular event	342 (16)	78 (25)	264 (15)	<0.0001
New arrhythmia	116 (6)	20 (7)	96 (5)	0.3802
Atrial flutter	29 (1)	8 (3)	21 (1)	0.0579
Other atrial arrhythmia	26 (1)	4 (1)	22 (1)	0.7826

Figure 4.2 Rate of AF progression by HATCH score (without COPD).

Discussion

The present investigation is a large observational study evaluating clinical correlates and outcome parameters of AF progression in patients with recently diagnosed AF. We found that 15% of the patients with paroxysmal AF showed AF progression within 1 year of follow-up. Previous studies showed that AF progression is associated with underlying heart disease and structural remodeling.^{2,3,8-13} Factors causing AF progression overlap largely with factors leading to the development of new-onset AF.⁵ Our findings are in line with these studies. A history of heart failure or hypertension and rate-control rather than rhythm-control strategy was independently associated with AF progression in our population. The first 2 factors (hypertension and heart failure) are known to induce structural remodeling of the atria. Both cause chronic stretch and atrial dilatation, which may activate signaling pathways leading to cellular hypertrophy, fibroblast proliferation, and tissue fibrosis. In addition, atrial fibrosis may lead to disruption of the electrical side-to-side junctions between muscle bundles,^{14,15} which may promote and sustain reentry. In addition, pacemaker studies revealed that patients with underlying disease are more prone to sustaining prolonged or multiple atrial tachycardias that result in AF.¹⁶ This is also reflected by an—on the whole—increased AF progression rate with increasing HATCH scores. Unfortunately, we were unable to validate the HATCH score in the present study because a history of COPD was not included in the study case record form. The third factor that we found to be associated with AF progression was rate control rather than rhythm control. This could suggest that rhythm control prevents AF progression. One could hypothesize that an aggressive rhythm-control strategy stops electrical remodeling. This is supported by

the goat studies performed by Wijffels et al.,¹⁷ who demonstrate that artificial maintenance of AF leads to a marked shortening of atrial refractory period, which enhances the inducibility and stability of AF. In addition, clinical data suggest that catheter ablation seems beneficial in reducing recurrences and delaying arrhythmia progression.¹⁸ On the other hand, “AF treatment strategy” was purely physician driven in the present study. It is possible that the treating physician only chose a rhythm-control strategy for the patients with less underlying disease, in whom the greatest probability of maintaining sinus rhythm was expected, and to avoid unnecessary exposure of patients to the adverse effects of rhythm-control drugs. Previous studies showed that a history of heart failure and valvular disease as well as advanced age was associated with a choice of rate control.⁶ Nevertheless, in the present study, univariate analysis showed that patients treated with rhythm control seem to have slightly more hypertension and heart failure. On the other hand, they were younger and had less valvular disease. We attempted to correct for the potential influence of these variables using propensity score models and found similar results. We identified some significant differences in the use of AF medication between patients with and without AF progression. Class Ic drugs could prevent electrical remodeling by reducing the number of AF recurrences. Then again, the physician chose which medication was administered to each patient. The use of class Ic drugs is contraindicated in many forms of underlying heart disease. Therefore, the patients using class Ic drugs probably have less underlying heart disease. In contrast, cardiac glycosides are often administered to patients with heart failure.

The 2 most important studies evaluating the outcome of treatment strategy in patients with AF (AFFIRM and RACE) did not study AF progression.^{19,20} AFFIRM classified “high risk AF patients” in first episode or recurrent AF, and RACE only studied patients with persistent AF. The study design did not enable to evaluate AF progression. More recently, the AF-CHF trial studied the effect of treatment strategy on mortality in patients with AF and systolic heart failure.²¹ All these studies demonstrate that a rhythm-control strategy is not associated with improved survival. Therefore, one could question the relevance of a rhythm-control strategy. On the other hand, knowing the factors that enhance (or prevent) AF progression might be very relevant in symptomatic AF patients.

A previous study showed a strong and graded link between body mass index and AF progression.²² However, in our study, there was no univariate nor multivariate association between obesity and AF progression. This could be explained by the difference in cohorts. In the study by Tsang et al.,²² only Olmsted County residents were included, whereas in our study, we included patients from 21 countries in different continents. One could hypothesize that the etiology of obesity and the unhealthy behavior associated with obesity might be different according to the local lifestyle.

Finally, patients demonstrating AF progression had a worse prognosis, with more cardiovascular events and admissions. It remains unclear whether achieving rhythm control would have prevented these events in our population.

Limitations

We performed a subgroup analysis of the RecordAF study. As a result, our findings should be interpreted with caution because there may be confounding factors that are beyond those tested here. Patients were not randomized into a rate- or rhythm-control strategy. Therefore, the choice between rhythm and rate control was per se influential regarding long-term outcome (and possibly not a consequence of the actual treatment). We want to stress that the observed association found in the present study between rate control and AF progression is hypothesis generating rather than conclusive evidence. Other studies show that P-wave dispersion might predict transition from paroxysmal to persistent AF.²³ We did not have data available in our cohort to verify this hypothesis. Unfortunately, we have no data on AF burden and left atrial size in the present cohort. Both were associated with AF progression in earlier publications.^{2,16} In our analyses, we corrected for many variables. The patient numbers of the cohorts that we compared (318 vs. 1819) were probably too low to adequately correct for that many variables. However, we believe that all these variables should be taken into account when trying to reduce the effect of potential confounders.

Conclusions

In this large AF population, 15% of patients who were recently diagnosed with AF progressed to persistent or permanent AF within 1 year. Heart failure, hypertension, and rate-control rather than rhythm-control strategy were independently associated with AF progression. The clinical outcome of patients demonstrating AF progression is worse compared with patients demonstrating no AF progression. The observed associations found in the present study are hypothesis generating rather than conclusive evidence. Further studies are needed to evaluate the hypothesis that a rhythm-control strategy prevents AF progression.

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Part II

Echo-electrocardiography to identify the substrate for atrial fibrillation during sinus rhythm

Chapter 5

Atrial activation time determined by transthoracic Doppler tissue imaging can be used as an estimate of the total duration of atrial electrical activation

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Abstract

Background

Currently, the total atrial activation time, as indicated by the P-wave duration using signal-averaged (SA) electrocardiogram (ECG) (SAECG), is the most powerful predictor of atrial fibrillation. However, because of practical limitations, this technique is not used in clinical routine. In this study we evaluated several alternative techniques to measure the total atrial activation time, including a new parameter that uses atrial Doppler tissue imaging (TDI).

Methods

For 30 patients who were in sinus rhythm and underwent a transthoracic echocardiogram, we determined the P-wave duration on surface ECG and SA-ECG, and the interval from the onset of the P wave (lead II) until the onset of the echocardiographic flow Doppler A wave over the mitral valve. In addition, using pulsed wave TDI in the 4-chamber view, we measured the interval of time from initiation of the ECG P wave (lead II) until the peak of the local lateral left atrial (LA) TDI signal. Correlation between the SA-ECG, surface ECG, and echocardiographic parameters were evaluated by Spearman correlation tests.

Results

All parameters that were used to estimate total atrial activation time showed a significant correlation with the SA-ECG P-wave duration. Although the interval of time from initiation of the ECG P wave until the peak of the local lateral LA TDI signal was significantly longer than the SA-ECG P-wave duration (151.12 ± 19.4 vs. 128.4 ± 15.8 milliseconds, respectively, $P < 0.01$), it showed the highest correlation ($R = 0.91$, $P < 0.001$). There was no significant correlation between the SA-ECG and routine echocardiographic parameters such as LA, right atrial, or total atrial size. Measurement of the interval of time from initiation of the ECG P wave until the peak of the local lateral LA TDI signal added 1 ± 0.5 minutes to a routine echocardiographic evaluation, whereas measurement of the SA-ECG P-wave duration took 20 ± 5 minutes ($P < 0.01$).

Conclusions

LA TDI is an easy, fast, and reliable method to estimate the total atrial electrical activation time, and may be useful in the identification of those prone to develop atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.¹ With increasing age of the population, the numbers of patients with AF will grow tremendously, creating the need for primary prevention.² To enable prevention, we need a better way to predict who will develop AF in the future. Currently, risk stratification for AF is based on clinical and echocardiographic parameters that are derived from population-based observational studies such as the Framingham Heart Study and the Manitoba Follow-up Study.³⁻⁶ For the individual patient, the currently available risk stratification parameters are of limited value for prediction of AF.⁷

Factors that facilitate AF are atrial dilatation and depressed intra-atrial conduction. Together, they determine the total time required for atrial electrical activation, the total atrial conduction time (TACT), with the maximal P-wave duration as an equivalent on the 12-lead surface electrocardiogram (ECG). The gold standard for determination of the P-wave duration is the signal-averaged (SA) ECG (SA-ECG) technique. This has been used to determine the total duration of atrial activation and has a reasonable predictive power for the development of AF.⁸⁻¹¹ However, P-wave determination by SA-ECG has not found its way into clinical practice, possibly because it requires special hardware and is a time-consuming technique.

Recently, Fuenmayor et al.¹² described an alternative technique to estimate TACT. They measured the time from the onset of the ECG P wave (lead II) until the onset of the A wave as determined by flow Doppler echocardiography over the mitral valve (PA-mv). They demonstrated a significant correlation with invasively determined TACT. However, this technique is not able to detect left atrial (LA) late activation and, thereby, theoretically underestimates TACT.

We hypothesized that the duration of atrial electrical activation can be estimated more accurately by a novel echocardiographic technique using Doppler tissue imaging (TDI) of the local LA wall motion. Therefore, we compared transthoracic pulsed wave TDI of the local lateral LA wall motion with current techniques to estimate TACT.

Methods

We included 30 consecutive patients in normal sinus rhythm who were referred to our department of cardiology for a routine transthoracic echocardiogram. The examination consisted of a standard 2-dimensional echocardiogram, including M-mode and Doppler echocardiography (Sonos 5500, Philips Medical Systems, Andover, Mass). To estimate TACT, we determined PA-mv interval (average of 3 cycles). In addition, in the 4-chamber apical view, the time from initiation of the ECG P wave (lead II) to the onset or the peak of the local lateral LA TDI signal (PA-TDI) was measured using pulsed wave TDI, with the sample placed at the lateral wall of the LA just above the mitral valve (average of 3 cycles) (Figure 5.1).

Figure 5.1 Example of measurement of time from initiation of electrocardiographic P wave (lead II) to peak of local lateral left atrial Doppler tissue signal.

After echocardiography, a 12-lead surface ECG was recorded in each patient using an ECG system (MAC 5000, Marquette Medical Systems, Milwaukee, Wis). All 12-lead ECGs were obtained in the supine position. The measurement of the maximum P wave was done manually by an independent observer who was unaware of the results from the other tests. To improve accuracy, measurements were performed with calipers and magnifying glass. The onset of the P wave was defined as the junction between the isoelectric line and the beginning of the P-wave deflection and the offset of the P wave as the junction between the end of the P-wave deflection and the isoelectric line.^{13,14}

Finally, P-wave SA-ECG was recorded from X-, Y-, and Z-lead system using the ECG system (MAC 5000, Marquette Medical Systems). All recordings were performed in a quiet atmosphere to reduce ambient noise. P waves were recorded until a target noise level of less than 0.3 μV was achieved in the TP segment of the ECG, and until at least 500 beats were analyzed. Before SA, a P-wave template was created and measured P waves were correlated with that template. Unless a match of more than 95% was present, P waves were rejected to exclude atrial premature beats. P-wave filtering with a bandwidth of 40 to 250 Hz was applied to the averaged P wave.

The times needed for recording and analysis of the PA-mv and PA-TDI intervals, and measurement of the P-wave duration on either surface ECG or using SA-ECG, were recorded.

Patient characteristics, including arrhythmia history, were derived from the chart and the electronic ECG database, which consists of all ECGs that are made in our hospital.

Statistical analysis

Results are expressed as the mean $\pm$ SD. Correlation between the echocardiographic and ECG variables was evaluated by the Spearman correlation test. Alpha value was set at 0.05 and confidence intervals at 95%. All analyses were performed using statistical software (SPSS 11.0, SPSS Inc, Chicago, Ill).

Results

Table 5.1 shows the characteristics of the patients included in this validation study. Figure 5.2, A, demonstrates that there was a significant, but poor correlation between the SA-ECG P-wave duration and the P-wave duration from the surface ECG ($R=0.60$, $P=0.001$). The average value of the PA-mv interval (128.9 ± 20.1 milliseconds) closely resembled the average value of the SA-ECG P-wave duration (128.4 ± 25.8 milliseconds), and the correlation between the two parameters ($R=0.76$, $P=0.001$) (Figure 5.2, B) was better than between SA-ECG and surface ECG P-wave duration. TACT as estimated by TDI (PA-TDI) (151.1 ± 19.4 milliseconds) was significantly longer than the SA-ECG P-wave duration. However, the PA-TDI interval showed the highest correlation with the SA-ECG. ($R=0.91$, $P=0.001$) (Figure 5.2, C). This was true only for the PA-TDI interval until the peak of the atrial velocity curve, not for the interval until the onset of the atrial tissue velocity deflection ($R=0.54$, $P=0.002$). The correlation was similar for patients with or without a history of AF (Figure 5.2). In this study, there was no difference in atrial activation time between patients with or without a history of AF, as indicated by SA-ECG (156.2 ± 20.5 vs. 148.8 ± 18.9 milliseconds, respectively, $P=\text{not significant}$) or PA-TDI (131.4 ± 18.1 vs. 126.9 ± 14.8 milliseconds, respectively, $P=\text{not significant}$). However, the current study was not designed for this purpose and the number of included patients may have been too low to reveal a significant difference.

There was no significant correlation between the SA-ECG and other echocardiographic parameters, such as LA, right atrial, or total atrial size. Measurement of the PA-mv and PA-TDI intervals both prolonged a routine echocardiographic examination by 1 ± 0.5 minutes, which was significantly shorter than measurement of TACT by SA-ECG, which took 20 ± 5 minutes ($P<0.01$). Determination of the maximum P-wave duration took 2 ± 1 minutes.

Table 5.1 Patient characteristics.

N	30
Age	60
Men	16
Cardiovascular disease	
Hypertension	5 (17%)
Coronary artery disease	15 (50%)
Congestive heart failure	5 (16.7%)
Medication	
Nitrates	10 (33%)
Beta-blockers	12 (40%)
Calcium-channel blocker	3 (10%)
AAD	
Sotalol	3 (10%)
Flecainide	2 (6.7%)
Amiodarone	2 (6.7%)
Diuretics	5 (16.7%)
ACE inhibitors	10 (33%)
Echocardiographic parameters	
LA size, mm	40.4 ± 7
LVEDD, mm	50.4 ± 6.4
LVESD, mm	35.1 ± 7.3
IVSEDWT, mm	8.7 ± 1.8
PWEDWT, mm	8.4 ± 1.2
LVEF, %	55.4 ± 13.4
PA-mv, ms	128.9 ± 20.1
PA-TDI start, ms	91.4 ± 26.6
PA-TDI peak, ms	151.2 ± 19.4
Electrocardiographic parameters	
HR, beats/min	64 ± 3
Maximum P-wave duration, ms	113 ± 14
PQ, ms	172 ± 26
QRS, ms	98 ± 17
QTc, ms	419 ± 24
SA-ECG P-wave duration, ms	128.4 ± 15.8

AAD: Antiarrhythmic drugs; ACE: angiotensin-converting enzyme; HR: heart rate; IVSEDWT: interventricular septum end-diastolic wall thickness; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; PA-TDI: onset or peak of the local lateral LA TDI; PA-mv: onset of the A wave as determined by flow Doppler Echocardiography over the mitral valve; PWEDWT: posterior wall end-diastolic wall thickness; SA-ECG: signal averaged ECG.

Figure 5.2 Correlation between signal-averaged electrocardiogram (ECG) and P-wave duration on surface ECG (A), time from onset of ECG P wave (lead II) until onset of A wave as determined by flow Doppler echocardiography over mitral valve (B), and time from initiation of ECG P wave (lead II) to peak of local lateral left atrial Doppler tissue signal (C). Open circles, Patients with history of atrial fibrillation.

Discussion

Mechanisms of AF

In their multiple wavelet theory, Moe¹⁵ postulated the existence of independent wandering wavelets as the basis for AF. Many studies have supported the hypothesis that AF results from multiple re-entrant circuits, with areas of delayed conduction to initiate and maintain the arrhythmia.¹⁵⁻¹⁸ It has been demonstrated that the atria should be able to harbor a critical number of wavelets to develop and sustain AF.¹⁷ The number of wavelets that fit into the atria depends on the atrial mass, the conduction velocity, and the atrial refractory period.

Characterization of AF vulnerability

The vulnerability for AF development could be evaluated by means of an electrophysiologic study by programmed electrical stimulation or burst pacing. However, this is impractical for the evaluation of large patient groups. A noninvasive alternative is measurement of TACT, which is the time elapsed between the initiation of atrial depolarization (usually in the region of the sinus node) and the last depolarization (usually in the lateral LA wall) of the same activation front. TACT prolongs in case of increased atrial size or decreased conduction velocity. Therefore, theoretically, a prolonged TACT should correlate with vulnerability for AF.

Determination of TACT

The simplest way to determine TACT is by measuring P-wave duration on the 12-lead surface ECG. A prolonged P-wave duration may reflect slow intra-atrial conduction or an increase in atrial size. A prolonged P-wave duration predicts postoperative AF.¹⁹

Based on the same principle, the improved method of measuring P-wave duration by SA-ECG was shown to be of superior value for the prediction of AF.⁹ Although it allows more precise measurement of the P-wave duration, it requires special (SA-ECG) hardware and software that is only available in a limited number of hospitals.

An alternative approach to determine TACT is invasive measurement of the time elapsed between activation at the high right atrium (near the superior vena cava) and the inferior and lateral aspect of the LA at the coronary sinus during an electrophysiologic study. Recently, Fuenmayor et al.¹² proposed a new noninvasive way to estimate the TACT by measuring the PA-mv interval. They demonstrated a significant correlation between the PA-mv interval and TACT as determined by invasive electrophysiology. Although this is an easy, inexpensive, and fast technique, theoretically it gives an underestimation of the TACT because transmitral blood flow starts well before activation and contraction of the LA is completed. A further improvement of this technique, based on the same principle, was put forward by Kinay

et al,²⁰ who measured the time from the start of the P wave (lead II) to the onset of the LA appendage ejection flow by means of transesophageal echocardiography. It was demonstrated that this is an effective predictor of recurrent AF. Major disadvantages of this method are that TEE is an unpleasant examination for the patient and it requires special skills of the examiner, which makes this technique impractical for examination of large patient groups, as is required during risk stratification to perform primary prevention of AF.

The current study examined the value of a new technique to estimate TACT by pulsed wave TDI. The principle is similar to the technique used by Kinay et al.²⁰ but now transthoracic pulsed wave TDI reveals the local movement of the LA wall, which is usually activated last during in sinus rhythm.²¹

We were able to demonstrate that this noninvasive technique had the best correlation with the gold standard P-wave duration as determined by SA-ECG, in comparison with surface ECG P-wave duration and PA-mv interval. The PA-TDI interval using the onset of the a wave was significantly shorter than the P wave until the peak of the TDI time velocity curve. Also, the correlation between SA-ECG P-wave duration and PA-TDI peak was much better than with the PA-TDI onset, which may be significantly affected by neighboring LA cells, thus, representing overall LA activation.

The obvious advantage of the PA-TDI (peak) method is that it does not require special skills or devices, other than standard echocardiography machines that are used for routine echocardiograms. Furthermore, measuring the PA-TDI interval is fast and easy to perform.

Conclusion

The results of our study demonstrate that LA TDI is an easy, fast, and reliable method to estimate the total atrial activation time, and may be of value for the identification of patients with an atrial substrate vulnerable for AF.

Study limitations

Total atrial activation time is defined as the time elapsed between the initiation of atrial depolarization (usually in the region of the sinus node) and the last depolarization of the same activation front. It should be kept in mind that the PA-TDI interval includes both the time required for the propagation of impulses from the sinus node to the LA, and the time required for the electromechanical coupling in the LA. Therefore, the PA-TDI interval overestimates the total atrial activation time. Fortunately, the time required for excitation-contraction coupling appears to be rather constant. The PA-TDI interval prolonged the SA-ECG interval by 22.8 ± 8.2 milliseconds. This resulted in a high correlation with the SA-ECG P-wave duration, which may make the PA-TDI a suitable parameter for the identification of an atrial substrate vulnerable for (future development of) AF.

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Chapter 6

Clinical and echocardiographic correlates of intra-atrial conduction delay

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Abstract

Aims

The total atrial conduction time (TACT) is an important electrophysiological parameter. We developed a new transthoracic echocardiographic tool (PA-TDI). The PA-TDI interval is a reflection of the TACT. In the present study, we evaluated the clinical and echocardiographic correlates of intra-atrial conduction delay.

Methods and results

We studied 427 patients without class I anti-arrhythmic agents or amiodarone. All patients underwent an echocardiogram and the PA-TDI interval was measured. Patient characteristics were recorded. The mean PA-TDI was 157 ± 22 ms. Multivariate linear regression analysis revealed that atrial fibrillation (AF) in history ($B=9.7$; 95%CI 5.7–13.8; $P<0.001$), hypertension ($B=5.5$; 95%CI 1.4–9.8; $P=0.01$), clinically relevant valve disease ($B=5.7$; 95%CI 0.5–10.8; $P=0.03$), age ($B=5$; 95%CI 3.3–6.6; $P<0.001$), and body mass index (BMI; $B=2.6$; 95%CI 0.3–4.9; $P=0.026$) were independently associated with the PA-TDI interval. On the echocardiogram: the aortic diameter ($B=0.7$; 95%CI 0.2–1.2; $P=0.009$), left atrial dimension ($B=0.9$; 95%CI 0.5–1.3; $P<0.001$), mitral valve E-wave deceleration time ($B=0.1$; 95%CI 0.1–0.1; $P<0.001$), aortic incompetence ($B=13$; 95%CI 3.3–22.6; $P=0.008$), and mitral incompetence ($B=11$; 95%CI 3.6–17.5; $P<0.003$) were independently associated with the PA-TDI interval.

Conclusions

This study is the largest to investigate the relation between the atrial conduction time, underlying heart diseases, and echocardiographic parameters. We found that the PA-TDI was independently prolonged in patients with a history of AF, hypertension, valve disease, higher age, and a higher BMI. Signs of diastolic dysfunction, valve incompetence, and enlarged atrium or aortic root on the echocardiogram were associated with a prolonged PA-TDI. This suggests that early and aggressive treatment of hypertension, diastolic dysfunction, and obesity could prevent intra-atrial conduction delay.

Introduction

The total atrial conduction time (TACT) is an important electrophysiological parameter that can be determined during an electrophysiological study.¹ A delay of atrial conduction is strongly associated with underlying diseases affecting the atria directly or indirectly.^{2–5} Delayed conduction is one of the requirements for the initiation of reentry and the development of atrial fibrillation (AF).⁶ This implies that prevention or amelioration of atrial conduction delay may prevent the development of atrial arrhythmias such as AF. Indeed, previous studies suggest that the TACT may be a useful target of therapy.^{7–10} We validated a novel noninvasive echocardiographic technique using atrial tissue Doppler imaging (PA-TDI or atrial electromechanical interval) that strongly correlates with TACT.¹¹ In previous studies, we showed that a prolonged PA-TDI is the most important predictor of new-onset AF.^{11,12} Other investigators confirmed our findings in different populations.^{13,14} A prolonged PA-TDI interval is also associated with recurrence of AF after catheter ablation.¹⁵ Knowing the conditions that prolong the TACT is essential in order to develop therapies or strategies for prevention of AF. However, the clinical determinants of a prolonged TACT were never studied before in a large population. In this report, we used the echocardiographic PA-TDI to study the clinical and echocardiographic correlates of intra-atrial conduction delay in a large group of patients.

Methods

Study population

We studied 522 outpatient clinic patients referred to the Maastricht University Medical Centre for a standard transthoracic echocardiographic examination for various medical conditions (including AF in 273 patients). Patients were included between January 2003 and February 2007. Patients were enrolled if they were 18 years or older and had sinus rhythm during the echocardiogram. Exclusion criteria were previous pacemaker implantation, an implantable cardioverter–defibrillator and the use of class I anti-arrhythmic agents or amiodarone. The 249 patients without previous AF have been reported in a separate paper on the role of PA-TDI in the prediction of AF.¹²

Echocardiographic examination

The echocardiographic examination consisted of a standard twodimensional echocardiogram, including M-mode and Doppler echocardiography (Sonos 5500, Philips Medical Systems, Andover, MA, USA) during continuous electrocardiogram (ECG) monitoring according to the recommendations as described in the American Society of Echocardiography guidelines. Left atrial volume was obtained from the

singleplane area-length of the apical four-chamber view, just prior to mitral valve opening, and with the patient in the left-lateral decubitus position. Additionally, we determined the PA-TDI interval.¹¹ In the apical fourchamber view, the pulsed-wave tissue Doppler sample was placed on the lateral wall of the left atrium just above the mitral annulus. The PA-TDI interval, defined as the time-interval from initiation of the electrocardiographic P-wave recorded by the echo machine (lead II) to the peak of the A'-wave of the atrial tissue Doppler tracing (Figure 6.1), was measured in three cardiac cycles and averaged.

The investigator who performed the echocardiographic measurements (including PA-TDI interval) was an independent observer blinded for other patient characteristics.

Figure 6.1 Example of PA-TDI measurement. PA-TDI is defined as the time interval between the onset of electrocardiographic P wave in lead II and the top of the A'-wave on the atrial tissue Doppler velocity curve from the left atrial wall.

Data collection

Patient characteristics, including medication, (arrhythmia) history, and ECGs at the time of echocardiography were collected. Data were derived from the patient charts and electronic medical records. A diagnosis of AF in history was defined as a documented episode of AF lasting 30 s or more. 'Valve disease' was defined as clinically relevant valve disease at discretion of the treating physician. The study complies with the Declaration of Helsinki. Patient informed consent was obtained and the Institutional Review Board approved the study.

Statistical analysis

Continuous variables are presented as mean and standard deviation, categorical variables as observed number of patients and percentages. We used an independent t-test after performing Levene's test for equality of variances to compare all continuous variables. Categorical variables were tested with Fisher's exact test. Tables 6.1 and 6.2 show the *P*-values resulting from multiple uncorrected t-tests for continuous variables and Fisher's exact tests for categorical variables. This allowed us to identify parameters to feed into the linear regression analysis. Therefore, these tables are not presenting the ultimate results of the analysis. All parameters with a *P* value <0.1 resulting from the univariate comparisons in Tables 6.1 and 6.2 were included in the linear regression models presented in Table 6.3. We did not include medication in the multivariate analysis presented in Table 6.3 since it is a reflection of the underlying diseases already included in the model. Model reduction was performed by stepwise exclusion of variables from the model with a *P*-value <0.1. For all continuous variables in the final regression analysis model, we determined their correlation with PA-TDI using Pearson's correlation test. Statistical analysis was performed with SPSS statistical software (SPSS Inc. release 16.0) and statistical significance was assumed for *P*<0.05. All tests performed were two sided.

Results

From the initial population of 522 patients, 95 patients were excluded because of use of conduction slowing class I antiarrhythmic agents or amiodarone leaving a final study population of 427. The mean PA-TDI was 157±22 ms. The shortest PA-TDI interval we measured was 103 ms and longest was 230 ms. Baseline characteristics of all patients in relation to the mean PA-TDI interval in our population are shown in Table 6.1. Patients with a prolonged PA-TDI duration (≥157 ms) were older and more often suffered from AF, hypertension, coronary artery disease, clinically relevant valve disease, and more often used oral anticoagulation, beta-blockers, nitrates, angiotensin converting enzyme (ACE)-inhibitors and diuretics. Patients with a shorter PA-TDI interval used more aspirin. Figure 6.2 shows the mean PA-TDI interval according to age in tertiles and hypertension in patients with and without AF.

Table 6.1 Baseline characteristics in relation to the mean PA-TDI duration in our population - univariate analysis.

	PA-TDI<157 ms (n=222)	PA-TDI≥157 ms (n=205)	P-value
Age (years)*	60±13	67±11	<0.001
Female, n (%)	121 (45)	97 (47)	0.147
Body mass index (kg/m ²)*	27±4	28 ±4	0.081
Underlying Risk Factors and Cardiovascular Disease			
AF in history, n (%)	74 (33)	114 (55)	<0.001
Hypertension, n (%)	122 (55)	132 (64)	0.049
Coronary artery disease, n (%)	22 (10)	34 (17)	0.045
Diabetes mellitus, n (%)	29 (13)	22 (11)	0.551
Valve disease, n (%)	30 (14)	50 (24)	0.004
Heart failure, n (%)	14 (6)	20 (10)	0.213
Thyroid disease, n (%)	15 (7)	12 (6)	0.843
Chronic obstructive pulmonary disease, n (%)	14 (6)	15 (7)	0.704
Medication			
Oral anticoagulation, n (%)	39 (18)	85 (42)	<0.001
Aspirin, n (%)	70 (32)	42 (21)	0.011
Beta-blocker, n (%)	63 (28)	104 (51)	<0.001
Sotalolol, n (%)	28 (13)	40 (20)	0.064
Verapamil, n (%)	18 (8)	19 (9)	0.732
Digitalis, n (%)	10 (5)	14 (7)	0.401
Nitrates, n (%)	8 (4)	22 (11)	0.004
Angiotensin-converting enzyme inhibitor, n (%)	37 (17)	61 (30)	0.002
Angiotensin-II receptor blocker, n (%)	49 (22)	44 (22)	0.907
Diuretics, n (%)	33 (15)	56 (27)	0.002
Statins, n (%)	64 (29)	54 (26)	0.589
Alpha-blocker, n (%)	7 (3)	5 (3)	0.774
Dihydropyridin calcium channel blocker, n (%)	27 (12)	36 (18)	0.133

* average (standard deviation)

Figure 6.2 Clinical parameters affecting the PA-TDI interval.

Mean PA-TDI interval $\pm$ standard deviation according to age in tertiles and hypertensive patients (grey bars) versus nonhypertensive patients (dark grey bars). The upper panel shows patients without a history of atrial fibrillation and the lower panel patients with a history of atrial fibrillation.

A history of AF was present in 188 (44%) patients. Atrial fibrillation was paroxysmal and self-terminating in 165 (88%) patients and persistent and previously terminated by electrical or chemical cardioversion in 23 (12%) patients.

Echocardiographic differences according to PA-TDI duration are shown in Table 6.2. Patients with a longer PA-TDI interval have an increased aortic width, increased atrial dimensions, and a larger and thicker left ventricle. The E-wave deceleration slope is decreased and the E-wave deceleration time is increased in the patients with a longer PA-TDI interval. Patients with a prolonged PA-TDI interval had more aortic valve incompetence and mitral valve incompetence. Figure 6.3 shows the mean PA-TDI interval according to mitral valve E-wave deceleration time and left atrial dimension.

Table 6.2 Echocardiographic parameters in relation to the mean PA-TDI duration in our population - univariate analysis.

	PA-TDI<157 ms (n=222)	PA-TDI≥157 ms (n=205)	P-value
Dimensions:			
Ao Diameter (mm)	33.6 ± 4	35.1 ± 4	<0.001
Left atrial dimension (mm)	39 ± 5	42 ± 5	<0.001
Left atrial volume (cc)	51 ± 20	57 ± 25	0.012
Right atrial volume (cc)	42 ± 14	46 ± 16	0.049
Left ventricular end diastolic dimension (mm)	48 ± 5	50 ± 5	<0.001
Left ventricular end systolic dimension (mm)	32 ± 6	34 ± 6	0.002
Interventricular septum width (mm)	9.1 ± 1.1	9.9 ± 5.8	0.025
Posterior wall width (mm)	8.7 ± 0.9	9.1 ± 1.1	0.002
Left ventricular mass (g)	185 ± 44	209 ± 54	<0.001
Left ventricular end diastolic volume (cc)	109 ± 28	120 ± 35	0.001
Left ventricular end systolic volume (cc)	42 ± 21	49 ± 27	0.006
Caval vein (mm)	17 ± 4	17 ± 4	0.256
Right ventricular systolic pressure (mmHg)	30 ± 6	32 ± 8	0.182
Left ventricular function:			
Left ventricular ejection fraction (%)	61 ± 9	60 ± 9	0.072
Mitral valve Doppler:			
Maximal E-wave velocity (cm/sec)	75 ± 17	73 ± 20	0.292
E-wave deceleration slope (m/sec ²)	396 ± 145	355 ± 157	0.006
E-wave deceleration time (ms)	196 ± 44	218 ± 62	<0.001
Maximal A-wave velocity (cm/sec)	76 ± 20	75 ± 21	0.462
E/A ratio	1.04 ± 0.4	1.06 ± 0.6	0.603
Valve disease:			
Aortic incompetence (>grade 1)	4 (2%)	18 (9%)	0.002
Mitral incompetence (>grade 1)	9 (4%)	28 (14%)	<0.001
Tricuspid incompetence (>grade 1)	14 (6%)	17 (8%)	0.460
Mitral valve stenosis	0	2 (1%)	0.230
Aortic stenosis	8 (4%)	8 (4%)	1.000
Systolic right ventricular pressure (mm Hg)	30 ± 6	32 ± 8	0.182

Figure 6.3 Echocardiographic parameters affecting the PA-TDI interval. Mean PA-TDI interval and 95% confidence intervals according to mitral valve E-wave deceleration time and left atrial dimension, both in tertiles.

Multivariable linear regression analysis revealed that AF in history, hypertension, clinically relevant valve disease, age, and BMI were independently associated with the PA-TDI interval (Table 6.3). When excluding patients with AF in history, hypertension ($B=10$, $P<0.001$), age ($B=5$ per 10 years increase of age, $P<0.001$), and BMI ($B=4$ per 5 points increase of BMI, $P=0.011$) remained significantly associated with a prolonged PA-TDI interval.

Table 6.3 Multivariate linear regression analysis: clinical and echocardiographic parameters that independently prolong the PA-TDI interval and correlation coefficients of all continuous variables resulting from the correlation with PA-TDI.

	B (ms)	95%CI for (B)	P-value	R ²	P-value
Demographic and clinical parameters					
AF in history	9.7	5.7-13.8	<0.001		
Hypertension	5.5	1.4-9.8	0.010		
Valve disease	5.7	0.5-10.8	0.030		
Age (per 10 years)	5	3.3-6.6	<0.001	0.34	<0.001
BMI (per 5 kg/m ²)	2.6	0.3-4.9	0.026	0.13	0.008
Echocardiographic parameters					
Aorta diameter (per mm)	0.7	0.2-1.2	0.009	0.22	<0.001
Left atrial dimension (per mm)	0.9	0.5-1.3	<0.001	0.34	<0.001
Aortic incompetence (>grade 1)	13	3.3-22.6	0.008		
Mitral incompetence (>grade 1)	11	3.6-17.5	0.003		
Mitral valve E-wave deceleration time (per ms)	0.076	0.039-0.113	<0.001	0.25	<0.001

Regarding the echocardiographic parameters: the aortic diameter, left atrial dimension, mitral valve E-wave deceleration time, aortic incompetence, and mitral incompetence were independently associated with the PA-TDI interval in our population (Table 6.3). When excluding patients with a history of AF, the clinical parameters hypertension, age and BMI remained independently associated with the PA-TDI interval. The echocardiographic parameters aorta diameter, left atrial dimension, aortic incompetence, and mitral valve E-wave deceleration time remained independently associated with PA-TDI interval when performing multivariate linear regression analysis in patients without a history of AF.

Discussion

The present study is the largest to investigate the relationship between PA-TDI, underlying cardiovascular diseases and echocardiographic parameters. We used the PA-TDI interval—a relatively new echocardiographic parameter¹¹—to estimate the TACT.

Clinical correlates of intra-atrial conduction delay

In this study, PA-TDI was independently prolonged in patients with a history of AF, hypertension, clinically relevant valve disease, higher age, and a higher BMI. We found that after correcting for possible confounders, a history of AF increases PA-TDI by +/- 10 ms, a history of hypertension by 5 ms and clinically relevant valve disease by 6 ms. Each additional 10 years of age increases PA-TDI with +/- 5 ms and each additional 5 kg/m² of BMI increases PA-TDI with 3 ms. The strong association between prolonged atrial conduction time and AF is not surprising since on one hand long conduction times are a prerequisite for the development of AF and on the other hand, AF itself may induce remodelling and hence contribute to lengthening of conduction through the atria.^{6,16} As has been suggested previously, prevention of AF may ameliorate atrial structural remodelling and prevent further AF episodes. Since it is unlikely that available therapies reduce atrial conduction time, preventive therapy might focus especially on suppression of AF in the subset with still normal conduction. Ageing is a recognized determinant of atrial size and fibrosis but unfortunately non-modifiable with respect to prevention of conduction abnormalities. Hypertension and valve disease are associated with diastolic dysfunction inducing intermittent pressure rises and dilatation of the atria and hence atrial fibrosis.^{17,18} In turn, this prolongs the TACT because of 'detour conduction' in larger atria. Although BMI relates to hypertension we showed an independent impact on TACT. From our data we cannot tell whether high BMI effected an increase in TACT through obstructive sleep apnea which was recently described as being associated with atrial conduction slowing.² On the other hand, the pericardial fat that overlies the cardiac surface including the inter- and intra-

atrial conduction system might be responsible for atrial conduction delays. Recent studies demonstrate a relation between pericardial fat and atrial conduction delay.¹⁹ Reducing body weight may ameliorate the atrial conduction time. Indeed, the effect of a high BMI on atrial conduction is likely to be reversible since obesity studies demonstrate that substantial weight loss is associated with improvement in atrial repolarization abnormalities on the ECG in obese subjects.²⁰ Patients with a prolonged PA-TDI interval more often used oral anticoagulation, beta-blockers, nitrates, ACE-inhibitors, and diuretics. It is difficult to interpret the relation between PA-TDI and the use of medication in the present study. The univariate analysis showed that in patients with a long PA-TDI interval AF, hypertension, and coronary artery disease occurred more frequently. Oral anticoagulation is typically prescribed in patients with AF, beta-blockers in patients with coronary artery but also in patients with hypertension and AF, nitrates are frequently applied in patients with coronary artery disease, and ACE-inhibitors and diuretics are usually prescribed in patients with hypertension. Therefore, one could hypothesize that the differences found in medication use according to the length of the PA-TDI interval are the result of underlying heart disease. On the other hand, one could imagine that some medication directly influences the PA-TDI interval. Unfortunately, the present study does not provide an answer to this question.

Echocardiographic correlates of intra-atrial conduction delay

We also investigated echocardiographic parameters that were associated with PA-TDI. We found that increased left atrium (LA) dimension, increased aortic diameter, aortic, and mitral valve incompetence and a longer E-wave deceleration time are independently associated with a prolonged PA-TDI interval. The latter probably reflects mild diastolic dysfunction since it might be a sign of an impaired relaxation of the left ventricle. However, other parameters necessary to confirm this finding such as the pulmonary vein flow and E/e' were not available in all patients. However, smaller studies using the signal averaged ECG to assess atrial conduction also demonstrate increased left atrial pressure and impaired LV relaxation in patients with delayed atrial conduction.²¹ The increased aortic diameter could be a reflection of the presence of aortic incompetence. However, our data show an independent relation between aortic diameter and PA-TDI. Another explanation could be inadequate management of hypertension. Since hypertension in history is also one of the clinical parameters, which was independently associated with a delay of the PA-TDI interval in this study, lowering the blood pressure is probably crucial to prevent prolongation of the TACT. An increased LA dimension could be the reflection of intermittent left atrial pressure rises typically seen in diastolic left ventricular dysfunction.²²

Future perspectives

Since recent studies suggest that a prolonged PA-TDI is associated with the development of new-onset AF and poor outcome of rhythm control,^{10,12–15} one could

hypothesize that reducing the duration of PA-TDI (or preventing its lengthening) improves primary and secondary prevention of AF. Our study suggests that early and aggressive treatment of hypertension, diastolic dysfunction, and obesity could prevent an increased PA-TDI. This was also suggested in smaller clinical studies.²³ In addition, recent laboratory studies affirm that upstream therapy might enhance atrial conduction by reducing atrial fibrosis.^{7,23} PA-TDI could be used to select appropriate candidates for upstream therapy and evaluating its effect.

Limitations

The PA-TDI interval overestimates the total atrial activation time since it includes both the time required for the propagation of impulses from the sinus node area to the left atrium and the time required for the electromechanical coupling in the left atrium. Furthermore, there seems to be a minor delay in ECG processing on all echo machines. In our study, this delay amounts to a maximum of 5 ms (unpublished technical information by Philips Medical Systems, Andover, MA, USA). Fortunately, this delay is consistent and therefore unlikely to have affected our results.

Some of the parameters in Table 6.2 showed only a small difference but still a significant univariate P value, which may relate to the large sample size. Obviously, these differences may be of limited clinical relevance because they were at times smaller than the error in individual measurements. However, it should be noted that Tables 6.1 and 6.2 concerned univariate analyses used to identify parameters to feed the regression analysis. All our patients were included in a cardiology outpatient clinic. As a result, the population we studied may not be representative of the general population. On the other hand, PA-TDI is intended for patients with cardiovascular diseases. The investigator who included the patients (R.G.T.) is a general cardiologist with a special interest in electrophysiology. For that reason, many patients included in the present study had a history of AF. However, we verified our main findings in a group of patients excluding those with a history of AF and found similar results.

Conclusions

The present study is the largest clinical study to investigate the relation between the atrial conduction times, underlying heart diseases, and echocardiographic parameters. We found that PA-TDI was prolonged in patients with a history of AF, hypertension, clinically relevant valve disease, higher age, and a higher BMI. On the echocardiogram, a larger left atrium, a larger aortic diameter, a longer E-wave deceleration time, and aortic and mitral incompetence were also associated with a prolonged PA-TDI interval. Since recent studies suggest that atrial conduction delay is associated with the development of new-onset AF and poor outcome of rhythm control, one could hypothesize that reducing atrial conduction time (or preventing its lengthening) improves primary and secondary prevention of AF. Based on our results, one could

hypothesize that early and aggressive treatment of hypertension, diastolic dysfunction, and obesity could prevent atrial conduction delay.

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Editorial comment

Atrial electromechanical function

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As one of the four cardiac pumps, the left atrium abides by the natural properties of myocardial function, i.e. electrical stimulation, irrespective of the conduction pattern, followed by mechanical muscle contraction then stroke volume ejection. While failure of native ventricular electrical stimulation is not compatible with life, that of the atrium is tolerable and many patients may live a completely normal life in atrial fibrillation. In fact, recent evidence supports the notion that rate-controlled atrial fibrillation has a clinical outcome similar to the rhythm-controlled one.¹ Patients with severe left ventricular disease, however, may respond differently and develop fast worsening symptoms with atrial fibrillation, because of the loss of the component of stroke volume pumped by the left atrium.

Full understanding of left atrial function requires critical appreciation of its detailed anatomy as well as myocardial fibre architecture. Anatomically, the left atrium is the functional opponent to the left ventricle, with reciprocal shortening and lengthening relationship between the two. The dominant myocardial fibres of the left atrium are longitudinally orientated, originating from the back of the atrium and inserting around the circumference of the mitral annulus. A smaller group of fibres run transversely around the base of the left atrium, although not covering its full circumference.² Thus, the main axis of the left atrial cavity shortening is longitudinal with the mitral annulus moving back towards the rear of the atrium after the P-wave and during the PR interval and returning to its resting position at the time of the first heart sound, marking end-diastole. It is worth mentioning that not only does this pattern of function mirror that of the left ventricle, although in the opposite direction, but the atrium also does not function in isolation of the ventricle. Myocardial development studies have shown close relationship between age-related changes in the function of the atrium and the ventricle which themselves are closely related. As left ventricular lengthening velocities reduce with age, those of left atrial shortening reciprocally increase in order to secure normal stroke volume entering the left ventricle.³ Conventional measurements of the left atrial size rely on longitudinal and transverse diameters as well as its area measurements. Segmental left atrial myocardial function is easily assessed from the longitudinal motion amplitude and velocity of the lateral, septal, and posterior segments as shown by the mitral annulus excursion during atrial systole. This is easily achieved using tissue Doppler or speckle tracking techniques. The amplitude of left atrial longitudinal motion is also assessed by the same techniques or by conventional M-mode.

Similar to the left ventricle, the main determinant of left atrial contractile function is its intrinsic myocardial function, which has its well-established maturation course, between foetal life and adolescence.⁴ As the atrium gets large in size due to various pathologies, with the commonest secondary to left ventricular and valve diseases, its overall contractile function falls and eventually pump failure and atrial fibrillation. Even in patients with paroxysmal atrial fibrillation and only small increase in atrial size we have shown significant reduction in segmental left atrial function particularly in areas adjacent to the pulmonary veins.⁵ Critical investigation of atrial function shows that such pathophysiological course is not that simple. We and others have previously shown that atrial flutter and fibrillation are commonly preceded by progressive prolongation of P-wave duration which itself proved a good predictor for the occurrence of atrial arrhythmias.^{6,7} This is explained on the basis of progressive atrial enlargement and myocardial stretching, which increase its surface area and hence the prolonged depolarization time. Such behaviour is similar to that occurring in dilated left ventricles with prolonged depolarization time and broad QRS duration.

Another important component of left atrial function is its electromechanical delay, similar to that seen in the left ventricle. This can easily be studied by the same Doppler echocardiographic techniques mentioned above and left atrial motion measured with reference to the onset of its electrical depolarization, the P-wave. Studies have used the onset of segmental left atrial shortening (excursion) or peak shortening velocity as two possible landmarks for electromechanical delay. Normal values for the two measurements have been determined and well documented. Normally, the three left atrial segments shorten in a synchronous fashion with no more than few milliseconds time difference between them, again a finding similar to that seen in the left ventricle. We have previously shown that such measurement is significantly abnormal and its relationship with that of the right atrium is disturbed in patients who develop atrial flutter.⁸ Furthermore, within the same atrium there is emerging evidence suggesting the presence of segmental left atrial dyssynchrony in patients with right heart disease, with some segments contracting significantly later than the others (unpublished data from Umea University) in response to the increase in right atrial pressures. Although left atrial contractile contribution to the stroke volume is relative to its wall thickness, it remains functioning as a pump with a need to behave in a satisfactory synchronous manner.

In this issue Weijs B et al.⁹ report an interesting measure of delayed atrial contraction as shown by the time interval between the onset of the P-wave and peak atrial systolic velocity. Interestingly, the authors report a number of clinical findings predicted by such measure, namely history of atrial fibrillation, hypertension, relevant valve disease, age, and body mass index. In addition, echocardiographic evidence of dilated aortic diameter, left atrial dimension, E-wave deceleration time, and aortic and mitral regurgitation were also independently associated with prolonged intra-atrial conduction. It seems that most of those conditions and functional disturbances result in various degrees of raised left atrial pressure. Age and long-standing hypertension

are associated with the development of stiff left ventricle and raised left atrial pressure, a known substrate for atrial fibrillation. This can clearly be manifested in the form of short E-wave deceleration time, which reflects raised left ventricular end-diastolic pressure. Significant mitral and aortic valve disease, as mentioned above increase the overload on the left ventricle, again resulting into a similar pattern of pathophysiology, and increased left atrial pressure. Finally, aortic dilatation seems to represent an external left atrial wall stress which destabilizes its function and hence atrial arrhythmia, although this finding is not well documented in the literature. The reported index seems to reflect atrial electromechanical delay in a very simple and feasible way. The onset of the P-wave is easily measured on the superimposed electrocardiogram and the peak atrial shortening velocity should adequately be obtained by tissue Doppler or speckle tracking techniques, making such measure highly reproducible. Finally, to the clear scientific mind such an index of atrial electromechanical delay should be seen to encompass the prolonged P-wave as a reflection of delayed atrial depolarization in addition to the pure delay in the atrial mechanical function, if it exists.

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Chapter 7

Atrial tissue Doppler imaging for prediction of new-onset atrial fibrillation

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Abstract

Background

The total atrial conduction time (TACT) is an independent predictor of atrial fibrillation (AF). A new transthoracic echocardiographic tool to determine TACT by tissue Doppler imaging (PA-TDI (the time from the initiation of the P wave on the ECG (lead II) to the A' wave on the lateral left atrial tissue Doppler tracing)) has been developed recently.

Objective

To test the hypothesis that measurement of PA-TDI enables prediction of new-onset AF.

Methods

249 Patients without a history of AF were studied. All patients underwent an echocardiogram and the PA-TDI interval was measured. Patient characteristics and rhythm at follow-up were recorded.

Results

During a mean (SD) follow-up of 680 (290) days, 15 patients (6%) developed new-onset AF. These patients had a longer PA-TDI interval than patients who remained in sinus rhythm (172 (25) ms vs. 150 (20) ms, $P=0.001$). Furthermore, the patients developing AF were older, more often had a history of heart failure or chronic obstructive pulmonary disease, more often used α blockers, had enlarged left atria and more frequently mitral incompetence on the echocardiogram. After adjusting for potential confounders, Cox regression showed that PA-TDI was independently associated with new-onset AF (OR=1.375; 95%CI 1.037 to 1.823; $P=0.027$). The 2-year incidence of AF was 33% in patients with a PA-TDI interval >190 ms versus 0% in patients with a PA-TDI interval <130 ms ($P=0.002$).

Conclusions

A prolonged PA-TDI interval may predict the development of new-onset AF. This measure may be used to identify patients at risk in future strategies to prevent the development or complications of AF.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and may result in life-threatening complications such as stroke and heart failure.¹ Unfortunately, treatment often comes too late—for example, when stroke is the first manifestation of AF.² Therefore, prediction and prevention of AF and its complications is essential. There has been an increase in the number of admissions to hospital for AF in recent years, demonstrating the need for primary prevention of new-onset AF.³ To enable primary prevention strategies, we have to identify which patients are at increased risk for the development of AF. Observational population studies resulted in the discovery of clinical and echocardiographic parameters that are associated with the development of AF.^{4–7} However, the currently available risk stratification parameters have limited predictive value in the individual patient.⁸

Age or underlying heart disease may result in atrial dilatation or a depressed intra-atrial conduction.^{9–11} This will lead to an increased total atrial conduction time (TACT) and facilitate AF. Recently, we validated a new non-invasive echocardiographic method to determine the TACT, using transthoracic tissue Doppler imaging of the atria (the PA-TDI interval).¹² We demonstrated that PA-TDI is an easy, fast and reliable method to estimate the TACT. This study was designed to test the hypothesis that non-invasive measurement of the TACT facilitates the identification of subjects at risk for development of AF in patients with no prior history of atrial arrhythmias.

Methods

We prospectively studied a total of 249 consecutive patients in sinus rhythm. We included all consecutive patients from the outpatient clinic of one of our cardiologists (RGT) who were referred for a standard echocardiographic examination for various cardiovascular diseases. Patient-informed consent was obtained and the study was approved by our institutional review board. Exclusion criteria were a history of AF, atrial flutter, atrial tachycardia, age <18 years, previous pacemaker implantation or an implantable cardioverter-defibrillator.

The echocardiogram

An independent observer blinded for the history of the patients performed the echocardiogram while subjects were lying in the left lateral decubitus position. All patients underwent standard twodimensional transthoracic echocardiography, including M mode, and Doppler echocardiography (Sonos 5500, Philips Medical Systems, Andover, Massachusetts, USA). Recordings were made in the standard projections (subcostal, parasternal long-axis, parasternal short-axis, four-chamber apical long-axis and two-chamber apical long-axis views). Aortic diameter, atrial

volumes, ventricular wall thickness, left ventricular dimensions, left ventricular mass, left ventricular ejection fraction, caval vein width and collapse index, valve disorders, wall motion disorders and Doppler flow patterns of the mitral valve (E wave, A wave) were determined in all patients according to the recommendations of the American Society of Echocardiography.

Additionally, we determined the TACT with tissue Doppler imaging as described previously.¹² In the apical four-chamber view, the pulsed-wave tissue Doppler sample was placed on the lateral wall of the left atrium just above the mitral annulus. The PA-TDI interval, defined as the time-interval from initiation of the electrocardiographic P wave recorded by the echo machine (lead II) to the peak of the A' wave of the atrial tissue Doppler tracing (Figure 7.1), was measured in three cardiac cycles and averaged.

Figure 7.1 Example measurement of the PA-TDI interval.

The electrocardiogram

At the time of inclusion, all patients underwent 12-lead ECG recording obtained in the supine position using an ECG system (MAC 5000, Marquette Medical Systems, Milwaukee, Wisconsin, USA). Previous studies have shown that the surface ECG P-wave duration, also an estimate of the TACT, is a predictor for new-onset AF after cardiac surgery.¹³ Therefore, an independent observer who was unaware of the results from the other examinations or the patients' history did a manual P-wave duration measurement. The onset of the P wave was defined as the junction between the isoelectric line and the beginning of the P-wave deflection, and the offset of the P-wave as the junction between the end of the P-wave deflection and the isoelectric line. To improve accuracy, a digital calliper and magnifying glass were used to perform the measurements.

Data collection

Patient characteristics, medical history and medication at the time of echocardiography were collected. Furthermore, we verified the absence of atrial arrhythmias by examining the patient charts and our electronic medical records and an electronic ECG database which stores all ECGs and Holter recordings performed in our hospital. In all patients a virtual CHADS2 score was calculated. This acronym stands for Congestive heart failure, Hypertension, Age (75 years and older), Diabetes mellitus and a history of Stroke/transient ischaemic attack (2 points). This scoring system allows instant classification of the relative thromboembolic risk in patients with AF, and is incorporated in the latest guidelines on the management of AF.¹⁴ During follow-up, patients were seen at 6-month intervals in our outpatient department. During every visit, symptoms of AF were thoroughly verified and an ECG was obtained. When in doubt about the rhythm status of the patient, a Holter recording was performed. As soon as patients were admitted to the first aid department with cardiac complaints, the rhythm was verified by one of our cardiologists and the presence of AF was recorded in the digital charts of our cardiology department. Since the University Hospital Maastricht has a strong regional community care function, none of the patients were lost to follow-up.

Statistical analysis

Data analysis was performed with SPSS statistical software V.15.0. Continuous variables are reported as mean (SD) and categorical variables as observed number of patients (percentage). Since our survival data were partly censored, we performed a Cox regression univariate analysis when comparing patients who developed AF during follow-up with patients who did not. When comparing 2-year incidences of AF we used χ^2 to evaluate three or more groups and Fisher's exact test when comparing two groups. Given the limited number of events, we first determined an odds ratio (OR) for PA-TDI alone to predict AF during follow-up using Cox regression analysis. Later, we adjusted the OR for potential confounders. All parameters showing a significant univariate relation with the occurrence of new-onset AF during follow-up were included in a Cox regression model (heart failure in history, mitral incompetence on echo, chronic obstructive pulmonary disease in history, α -blocker use, left atrial size on echocardiogram and age). We did not include the CHADS2 score in the model since it was derived from other variables included in the model (age and history of heart failure). The predictive accuracy of PA-TDI was reported using a receiver operating characteristic (ROC) curve. All tests performed were two sided. Overall, a *P*-value of <0.05 was considered to be significant.

Results

We included 249 patients in our study. The PA-TDI interval ranged between 103 ms and 223 ms. The mean (SD) age of our cohort was 62 (13) years. Many patients had underlying cardiovascular disease. The most common disease was hypertension which occurred in 61% of our patients. Table 7.1 presents the other baseline and electrocardiographic characteristics of our cohort. The body mass index and underlying heart disease of our cohort were in line with previous large cohort studies evaluating echocardiographic predictors of AF.^{7,15} Therefore, we believe that our population is representative of general cardiac outpatient clinics.

During a mean (SD) follow-up of 680 (290) days, 15 (6%) patients developed new-onset AF. Of all patients developing AF, two (13%) had one episode of paroxysmal AF, 12 (80%) had recurrent episodes of paroxysmal AF and one (7%) had permanent AF. The patients who developed AF during follow-up were older (70 (13) years vs. 61 (13) years, $P=0.01$) and more often had a history of heart failure and chronic obstructive pulmonary disease. α Blockers were used more frequently in the patients who developed AF during the follow-up period. As a result, the mean CHADS2 score was higher in these patients. No other differences were seen in baseline characteristics between the patients who demonstrated AF during follow-up and those who did not.

The echocardiogram of the patients who developed AF showed a longer mean (SD) PA-TDI interval at baseline than patients who remained in sinus rhythm (172 (25) ms vs. 150 (20) ms, $P=0.001$). The standard echocardiographic examination demonstrated enlarged left atrial size and more mitral incompetence in the patient with new-onset AF during followup (Table 7.1).

Table 7.1 Patient characteristics.

	All patients	No AF during FU*	AF during FU*	P-value†
N	249	234	15	
Age (years)	62 ± 13	61±13	70 ± 13	0.009
Female	135 (54%)	127 (54%)	8 (53%)	0.987
Body Mass Index (kg/m ²)	27 ± 4	27 ± 4	27 ± 4	0.755
Underlying Heart Disease:				
Hypertension	153 (61%)	142 (61%)	11 (73%)	0.643
Coronary artery disease	26 (10%)	24 (10%)	2 (13%)	0.527
Diabetes mellitus	29 (12%)	27 (12%)	2 (13%)	0.686
Thromboembolic events	9 (4%)	9 (4%)	0	0.633
Valve disease	49 (20%)	44 (19%)	5 (33%)	0.091
Heart failure	22 (9%)	17 (7%)	5 (33%)	0.007
Stroke or transient ischemic attack	47 (19%)	44 (19%)	3 (20%)	0.534
Electrophysiology study/ablation	11 (4%)	10 (4%)	1 (7%)	0.670
Chronic obstructive pulmonary disease	17 (7%)	13 (6%)	4 (27%)	0.014
Thyroid disease	12 (5%)	11 (5%)	1 (7%)	0.662
Virtual CHADS2 score (mean)	1,37 ± 1,23	1,32 ± 1,17	2,21 ± 1,72	0.007
Virtual CHADS2 score (median, range)	1 (6)	1 (5)	2 (6)	0.007

Table 7.1 Patients characteristics (continued).

	All Patients	No AF during FU*	AF during FU*	P-value‡
N	249	234	15	
Medication:				
Oral anticoagulation	18 (7%)	16 (7%)	2 (13%)	0.279
Aspirin	63 (25%)	58 (25%)	5 (33%)	0.551
Sotalol	9 (4%)	8 (3%)	1 (7%)	0.562
Beta-blocker	90 (36%)	82 (36%)	8 (53%)	0.204
Verapamil	14 (6%)	13 (6%)	1 (7%)	0.776
Digitalis	5 (2%)	4 (2%)	1 (7%)	0.115
Nitrates	18 (7%)	18 (8%)	0	0.520
Angiotensin-converting enzyme inhibitor	57 (23%)	52 (23%)	5 (33%)	0.902
Angiotensin-II receptor blocker	53 (21%)	51 (22%)	2 (13%)	0.487
Diuretics	58 (23%)	52 (23%)	6 (40%)	0.256
Statins	69 (28%)	64 (28%)	5 (33%)	0.637
Dihydropyridin calcium channel blocker	48 (19%)	44 (19%)	4 (27%)	0.827
Alpha-blocker	6 (2%)	4 (2%)	2 (13%)	0.004
Number of cardiovascular drugs (mean):	1,96 ± 1,94	1,92 ± 1,69	2,60 ± 2,29	0.272
Number of cardiovascular drugs (median, range):	2 (7)	2 (7)	2 (7)	0.272
Electrocardiogram:				
Heart rate (bpm†)	71 ± 13	71 ± 14	71 ± 11	0.977
P-wave duration (ms)	89 ± 22	89 ± 21	97 ± 33	0.669
PQ-interval (ms)	158 ± 29	157 ± 27	170 ± 53	0.066
QRS duration (ms)	93 ± 17	93 ± 17	99 ± 22	0.112
Tissue Doppler imaging:				
PA-TDI duration (ms)	152 ± 21	150 ± 20	172 ± 25	0.001
Maximal A'-wave velocity (cm/sec)	16 ± 5	16 ± 5	14 ± 4	0.215
Dimensions:				
Aorta diameter (mm)	34 ± 4	34 ± 4	34 ± 4	0.806
Left atrial dimension (mm)	40 ± 5	40 ± 5	43 ± 7	0.018
Left ventricular end-diastolic diameter (mm)	49 ± 6	49 ± 6	49 ± 7	0.775
Left ventricular end-systolic diameter (mm)	33 ± 7	33 ± 7	35 ± 10	0.223
Interventricular septum width (mm)	9 ± 1	9 ± 1	10 ± 2	0.689
Posterior wall width (mm)	9 ± 1	9 ± 1	9 ± 2	0.894
Left ventricular mass (g)	197 ± 52	196 ± 51	203 ± 64	0.586
End diastolic volume (cc)	112 ± 34	112 ± 35	103 ± 19	0.282
End systolic volume (cc)	45 ± 29	45 ± 29	39 ± 9	0.370
Caval vein (mm)	17 ± 4	17 ± 4	18 ± 5	0.985
Left ventricular function:				
Left ventricular ejection fraction (%)	60 ± 10	61 ± 9	56 ± 14	0.095
Hypokinesia	42 (17%)	38 (16%)	4 (27%)	0.480
Mitral valve Doppler assessments:				
Maximal E-wave velocity (cm/sec)	74 ± 18	74 ± 18	78 ± 15	0.410
E-wave deceleration slope (m/sec ²)	383 ± 155	379 ± 150	453 ± 216	0.301
E-wave deceleration time (ms)	203 ± 51	204 ± 50	185 ± 60	0.524
Maximal A-wave velocity (cm/sec)	82 ± 42	82 ± 43	77 ± 19	0.882
E/A ratio	0.98 ± 0.32	0.97 ± 0.33	1.03 ± 0.22	0.870
Valvular disorders:				
Aortic incompetence	13 (5%)	12 (5%)	1 (7%)	0.749
Mitral incompetence	17 (7%)	13 (6%)	4 (27%)	0.009
Tricuspid incompetence	14 (6%)	12 (5%)	2 (13%)	0.118
Aortic stenosis	10 (4%)	9 (4%)	1 (7%)	0.421
Mitral valve stenosis	1 (1%)	1 (1%)	0	0.868
Systolic right ventricular pressure (mmHg)	31 ± 7	30 ± 6	33 ± 11	0.126

*Follow-up; †Beats per minute; ‡P-value resulting from comparison "no AF during FU" versus "AF during FU"

Prediction of atrial fibrillation during follow-up

Cox regression analysis showed that the echocardiographic PA-TDI interval was associated with the development of AF during follow-up (per 10 ms; OR=1.520; 95%CI 1.195 to 1.933; $P=0.001$). When adjusting for possible confounders as defined in the statistical section, we found an OR of 1.375 (95%CI 1.037 to 1.823; $P=0.027$) (Table 7.2).

Table 7.2 Cox regression analysis: risk of new-onset AF during follow-up in patients without a history of AF corrected for possible confounders.

	OR (95%CI)	<i>P</i> -value
PA-TDI (per 10 ms increase)	1.375 (1.037-1.823)	0.027
Heart failure in history	1.929 (0.400-9.307)	0.413
Mitral incompetence on echo	2.866 (0.666-12.342)	0.158
Chronic obstructive pulmonary disease in history	3.383 (0.827-13.848)	0.090
Alpha-blocker use	6.800 (0.933-49.568)	0.059
Left atrial size on echocardiogram (per mm)	0.991 (0.880-1.115)	0.875
Age (per year)	1.016 (0.956-1.081)	0.606

Figure 7.2 shows the ROC curve to discriminate between people who will or will not develop new-onset AF during follow-up based on the PA-TDI. The area under the curve was 0.740 (95%CI 0.608 to 0.871; $P=0.002$). Using the ROC curve of PA-TDI, we determined the optimal cut-off value for PA-TDI to predict the occurrence of atrial fibrillation: 165 ms (sensitivity 67%; specificity 77%). A lower cut-off point (i.e. 150 ms) would result in a higher sensitivity (80%) and a lower specificity (50%), implying that many patients would be wrongly identified as patients developing new-onset AF.

Figure 7.2 ROC curve of PA-TDI to predict the development of atrial fibrillation.

The Kaplan–Meier 2-year cumulative risk for the development of AF was significantly increased for patients with a baseline PA-TDI interval >165 ms (Figure 7.3).

Figure 7.3 Kaplan–Meier cumulative incidence of the first occurrence of atrial fibrillation (AF).

We divided the patients into four groups according to the PA-TDI interval measured at baseline (for each 30 ms increase). The 2-year incidence of AF was 33% in patients with a PA-TDI interval >190 ms vs. 0% in patients with a PA-TDI interval <130 ms ($P=0.002$) (Figure 7.4).

Figure 7.4 2-Year incidence of new-onset atrial fibrillation (AF) in patients classified according to the PA-TDI interval measured at baseline.

Discussion

This study demonstrates that the TACT as determined by tissue Doppler imaging may help to identify patients with a substrate vulnerable for AF. After correcting for possible confounders, the PA-TDI interval remains the most important predictor of new-onset AF. The longer the PA-TDI interval, the higher the incidence of new-onset AF. In fact, each 10 ms increase of PA-TDI is associated with an increased risk of developing AF of 37–52% in the next 2 years. Therefore, the PA-TDI interval may become a useful measure for risk stratification to improve efficiency of primary prevention of AF.

Importance of predicting atrial fibrillation

AF can result in life-threatening complications such as stroke and heart failure. Therefore, the application of adequate individual treatment is essential.^{16,17} Unfortunately, many patients have silent AF.¹⁸ As a result, treatment may come too late. In this study, the virtual CHADS2 score in the group of patients who developed AF indicates that most of our patients do have an indication for oral anticoagulation once they develop AF. Adequate administration of oral anticoagulation will reduce the risk of thromboembolic complications by 60%.¹⁹ Therefore, one could imagine that prophylactic anticoagulation could be applied in patients with a high CHADS2 score and a long PA-TDI interval. However, this hypothesis needs to be confirmed in prospective randomised trials. Recent studies demonstrated that new-onset AF and associated stroke were significantly reduced by losartan.^{20,21} In our study, these “upstream” drugs did not prevent AF. However, drug treatment was not randomised, and the trend towards an increased number of cardiovascular drugs may in fact reflect the presence of more severe underlying heart disease.

In our study, we demonstrate that a short PA-TDI interval (<130 ms) seems to prevent patients from developing AF. Therefore, one could hypothesise that these patients are not candidates for primary prevention. Patients with a PA-TDI interval >165 ms have a reasonable chance of developing AF and could be candidates for primary prevention using “upstream” cardiovascular drugs. A PA-TDI interval >190 ms makes patients very vulnerable for the development of AF. These patients could be treated with prophylactic anticoagulation, especially when they have a high CHADS2 score.

In summary, the use of a simple echocardiographic measure enhances identification of patients at increased risk for AF, which may make primary prevention more cost effective by reducing the numbers needed to treat.

Classic predictors of atrial fibrillation

Observational population studies such as the Framingham Heart study, the Manitoba Follow-up study and the Cardiovascular Health study reported several clinical and

echocardiographic parameters that are associated with the development of new-onset AF.^{4-7,22,23} The clinical factors associated with new-onset AF are higher age, male sex, the presence of diabetes, hypertension, congestive heart failure, valve disease and coronary artery disease. Left atrial enlargement, increased left ventricular wall thickness, left ventricular diastolic dysfunction and a reduced left ventricular fractional shortening are predictive echocardiographic parameters for new-onset AF.^{15,24}

However, these currently available risk stratification measures have limited predictive value in the individual patient.⁸ This study showed that the PA-TDI interval outperformed all the previously known predictors of AF. This is possibly because the pathophysiological mechanisms by which ageing and the above-mentioned conditions leading to AF have a final common pathway, which result in prolongation of the TACT.⁹

Role of the total atrial conduction time in the prediction of atrial fibrillation

The multiple wavelet re-entry theory postulated the existence of multiple spatially discrete activation fronts (wavelets) resulting in re-entry at changing locations as the basis for AF.^{25,26} A decreased conduction velocity, leads to a shorter wavelength of the re-entrant wave fronts. An increased atrial size can harbour more wave fronts of a certain size at the same time. Both will favour AF. An increased TACT, which is the time elapsed between the initiation of atrial depolarisation and the last depolarisation of the same activation front,²⁷ incorporates both conduction slowing and atrial dilatation, and may therefore reflect the existence of a substrate vulnerable for AF. Determination of the TACT may therefore be better than the classical predictors of AF since it might not only demonstrate the presence of underlying disease but also its severity. P-wave duration on the 12-lead ECG and PA-mv using the mitral Doppler flow signal^{28,29} provide estimates of the TACT. However, PA-TDI determined by transthoracic tissue Doppler imaging had the best correlation with the “gold standard” (SA-ECG P-wave duration).¹² Previous studies presented a similar parameter measuring the interval between the onset of the P wave on the ECG till the onset of the A' wave of the left atrial lateral wall instead of the peak of the A' wave (atrial electromechanical interval or AEMI).^{30,31} Post hoc analysis of our data showed similar results using both methods (data not shown).

Study limitations

The PA-TDI interval overestimates the total atrial activation time since it includes both the time required for the propagation of impulses from the sinus node area to the left atrium, and the time required for the electromechanical coupling in the left atrium. However, in a recent validation study, this electromechanical coupling appeared to be constant.¹² Furthermore, there seems to be a minor delay in ECG processing on all echo machines. In our study, this delay amounts to a maximum of 5 ms (unpublished

technical information by Philips Medical Systems, Andover, Massachusetts, USA). Fortunately, this delay is consistent and therefore unlikely to affect our results.

This study was of limited size. As a result, the exact cut-off values need to be confirmed in a larger study with a longer follow-up. This would allow a study of the contribution of PA-TDI to a prediction model including “classical” predictors of new-onset AF. Nevertheless, it seems reasonable to state that a larger PA-TDI interval is related to an increased incidence of AF.

All our patients were included in a cardiology outpatient clinic. As a result, the population we studied may not be representative of the general population. On the other hand, PA-TDI is intended for patients with cardiovascular diseases. The investigator who included the patients (RGT) is a general cardiologist with a special interest in electrophysiology. For that reason, one might hypothesise that this led to a selection bias. On the other hand, all patients with a history of atrial arrhythmias, a pacemaker or an implantable cardioverter-defibrillator were excluded from our study and the patient characteristics of our population are representative of a general cardiac outpatient clinic.

Finally, AF incidence was derived from partly symptom-driven ECG and Holter recordings. This may have led to an underestimation of the AF incidence, since a large number of AF episodes are known to be asymptomatic.

Conclusion

The total atrial conduction time as determined by tissue Doppler imaging is a feasible, non-invasive tool for the identification of patients with a substrate vulnerable for AF. A long PA-TDI interval is associated with the development of new-onset AF. Therefore, PA-TDI has the potential to become a valuable measure for risk stratification to enable primary prevention of AF and its complications.

The exact cut-off values found in this study need to be confirmed in a second study. Studying the role of PA-TDI to predict new-onset AF in a general population would require a large number of patients and a long follow-up owing to the relatively low incidence of AF in this group. Alternative study designs (a selected study group) should result in a more feasible study.

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Part III

Echo-electrocardiography to characterize the atrial substrate during atrial fibrillation

Chapter 8

The fibrillating atrial myocardium visualized:
An unexploited source of information

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.¹ The arrhythmia results in contractile dysfunction of both atria of the heart. In the past, physicians assumed that the atria were immobile during AF. However, during cardiothoracic surgery, one observed that the atria were actually fibrillating. This interesting finding has remained unexploited in clinical practice.

Tissue velocity imaging (TVI) is a relatively new echocardiographic technique used for noninvasive quantification and timing of local myocardial wall motion.² It may be used to observe atrial myocardial movement during AF at multiple sites in the atria, providing evidence of general and regional contraction disturbances that may relate to stroke and hemodynamic atrial failure. In addition, TVI of the atrial wall may uncover electrophysiological information. Recent studies found a strong temporal correlation between atrial mechanical contraction assessed by tissue Doppler imaging (TDI) and the electrical fibrillatory cycle length assessed by the intracardiac electrogram.³ However, no attention has been paid to the amplitude or velocity information in the TDI recordings.

We performed TVI echocardiography in two patients with AF undergoing a His bundle ablation. The first patient had a nonremodeled left atrium (paroxysmal AF, electrophysiological type 1 AF,⁴ left atrial volume normalized for body surface area 36 ml/m²). The other patient had a remodeled atrium (permanent AF, electrophysiological type 2 AF,⁴ left atrial volume normalized for body surface area 74 ml/m², and a history of heart failure).

After the ablation, TVI images were recorded in the apical four-chamber view. The sample volume was obtained in the lateral left atrium just superior to the mitral annulus. The TVI tracings of the atrial wall revealed the fibrillating myocardium as a substitute of the atrial contraction (A') observed during sinus rhythm (Figure 8.1A). These direct recordings of the AF wall movements showed a 4 times lower velocity in the remodeled compared with the nonremodeled left atrium, which may relate to atrial contractile failure and/or higher atrial afterload (Figure 8.1B and 8.1C). Furthermore, the frequency of the fibrillating myocardium (f) was higher in the remodeled atrium, which reflects a shorter atrial refractory period, and therefore this atrium may well harbor permanent AF.³

We believe that TVI of the fibrillating atrial myocardium itself provides essential information on atrial cardiomyopathy, stroke risk, and electrical remodeling. The recordings presented herein illustrate that the fibrillating atrial myocardium may harbor heretofore largely unexploited information that deserves further study.

Figure 8.1

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Chapter 9

Atrial fibrillatory wall motion and degree of atrial remodeling in patients with atrial fibrillation:
A tissue velocity imaging study

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Abstract

Introduction

The atrial fibrillation cycle length (AFCL) and the intracardiac atrial electrogram morphology may be used to characterize atrial fibrillation (AF). However, assessment of these parameters requires an invasive electrophysiological study. We assessed clinical and electrophysiological correlates of noninvasive tissue velocity imaging (TVI) of the right and left atrial myocardial fibrillatory wall motion.

Methods and results

We performed an electrophysiological study in 12 patients with AF referred for His bundle ablation. Using atrial electrograms, we determined the AFCL (AFCL-egm) and electro-physiological AF type. Simultaneously, transthoracic echocardiography was performed. We used the TVI traces to determine the cycle length of the atrial fibrillatory wall motion (AFCL-tvi) and atrial fibrillatory wall velocities (AFV-tvi). AFCL-tvi matched very well with AFCL-egm ($r^2=0.98$; $P<0.001$), both in the left and right atrium. Patients with permanent AF had shorter AFCL-tvi (155 ± 15 ms vs. 216 ± 23 ms; $P<0.001$), higher AFCL-tvi variability, and lower AFV-tvi compared to patients with paroxysmal AF. Three electrophysiological AF types were found based on the morphology of the electrograms and these related to specific TVI patterns.

Conclusion

TVI of the atrial fibrillatory wall motion may enhance noninvasive characterization of atrial remodeling in patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.¹ The arrhythmia is associated with shortening of atrial refractoriness² as represented by a reduced atrial fibrillation cycle length (AFCL).^{3,4} In addition, AF is linked with increased dispersion of refractoriness⁵ as well as heterogeneity of conduction, prolonged conduction times, and fractionation of intracardiac atrial electrograms.^{6,7} Evaluation of these parameters, which represent atrial remodeling, may help predict arrhythmia prognosis and response to therapy. However, this requires an invasive procedure. Noninvasive assessment of these parameters may appear useful in clinical practice. Recently, we demonstrated that there is a correlation between the mechanical atrial fibrillatory wall motion and the electrophysiological AFCL in the left atrium.⁸ In addition, there is evidence that tissue velocity imaging (TVI) of the fibrillating atrial myocardium enables visualization of atrial remodeling.⁹ In this study, we assessed clinical and electrophysiological correlates of noninvasive TVI of the right and left atrial myocardial fibrillatory wall motion.

Methods

We studied 12 consecutive patients with symptomatic paroxysmal or permanent AF who were referred to our electrophysiology laboratory for His bundle ablation. The only exclusion criterion was age <18 years. All patients were implanted with a VVIR or DDDR (depending on the clinical AF type) pacemaker at least 2 weeks before the procedure. The study was approved by the Institutional Review Board and all patients gave informed consent for participation in the study.

Data acquisition

Patients were instrumented with an RF-ablation catheter (Celsius™ DS electrophysiology catheter, Biosense Webster, Johnson&Johnson, bipolar, interelectrode spacing 0.5 cm) and an electrophysiology catheter (Supreme electrophysiology catheter, St. Jude Medical, bipolar, interelectrode spacing 0.5 cm). Filter settings were high pass 30 Hz and low pass 400 Hz. All patients underwent successful His bundle ablation. After ablation the implanted pacemaker was temporarily programmed at 40 bpm. We recorded local atrial activation at the lateral wall of the right atrium and the coronary sinus in close proximity of the mitral valve annulus in order to establish the right and left AFCL from the intracardiac electrogram (AFCL-egm). When patients were in sinus rhythm during the procedure, AF was induced by pacing in the coronary sinus for 10 seconds at a short cycle length (<300 ms), resulting in 1:1 atrial capture. When AF was induced, the electro-physiological and echocardiographic measurements were performed at least 3 minutes after induction of the arrhythmia.^{10,11}

During the electrophysiological procedure, transthoracic echocardiography (apical 4-chamber view) was performed using a Vivid 7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) with 3.5 MHz cardiac transducer. Patients were in supine position and the TVI images were made in the apical 4-chamber view during the end-expiratory phase in order to avoid respiratory artifacts. The narrowest image sector angle possible enabling imaging of both atrial lateral walls was used to attain the maximum frame rate possible (>100 Hz).

Before the procedure, left ventricular end diastolic diameter, left ventricular end systolic diameter, interventricular end diastolic width, posterior wall end diastolic width, left ventricular ejection fraction and systolic right ventricular pressure were determined according to the recommendations of the American Society of Echocardiography. Atrial volumes were measured using the biplane Simpson rule. The investigational clocks on the echo-machine and electrophysiology system were synchronized and the start of the echocardiographic measurement was labeled on the electrophysiology recording.

Data analysis

Two independent observers (RT and LP) unaware of clinical type of AF classified the electrograms into 3 categories according to their morphology as previously described by the group of Waldo (Figure 9.1).¹² Type I: discrete atrial complexes separated by an isoelectric line free of perturbations; Type II: discrete atrial complexes separated by an isoelectric line with perturbations; Type III: discrete atrial complexes are mostly absent and the isoelectric line contains perturbations. When 2 electrophysiological AF types were present in the same tracing, the observers were asked to report the dominant type. Subsequently, AFCLs were measured manually using Bard Electrophysiology (Lowell, MA, USA) software (AFCL-egm). To have acceptable rates of error, we studied electrograms of a sufficiently long duration.¹³ Approximately 100 AFCLs were measured in both left and right atrium (LA, RA). We also evaluated the mean AFCL of the 5% shortest (P5) and 5% longest (P95) fibrillation intervals. The variability was then calculated by subtracting the P5 from the P95.

Using commercially available software (Q-analysis, GE Healthcare) we evaluated TVI traces during the late diastole (between the end of E' wave and start of S' wave). Care was taken to obtain the TVI sample from the electrode catheter recording sites. However, in some patients the catheters could not be visualized in the 4-chamber view. In that case, we used standardized locations to obtain our tracings. Regarding the left atrial data: the distal ablation catheter was placed in the CS in close proximity to the point where it crosses the mitral valve annulus. This location corresponds to the lateral wall of the left atrium near the mitral valve annulus in the apical 4-chamber view and is easy to identify. Regarding the right atrial data, the electrophysiology catheter was placed against the mid right atrial wall. This location corresponds to the midlateral wall of the right atrium in the apical 4-chamber view.

Figure 9.1 Examples of intracardiac electrograms in for each electrophysiological AF type and measurement of the AFCL-egm. Type I: patient number 3, left atrial location; Type 2: patient number 10, right atrial location; Type III: patient number 11, right atrial location. (speed 25 mm/sec).

One hundred cycle lengths of the atrial fibrillatory wall motion (AFCL-tvi) were measured at both atrial sites from the TVI traces. AFCL-tvi was defined as the time interval between 2 consecutive deflections of the late diastolic atrial tissue velocity curve (Figure 9.2). We evaluated the P5 and P95 of the AFCL-tvi and its variability as indicated above. AF wall motion velocity (AFV-tvi) was defined as the mean amplitude of 100 atrial fibrillatory deflections.

Figure 9.2 Examples of atrial TVI tracings for each electrophysiological AF type Type 1: patient number 1, left atrial location; Type 2: patient number 10, right atrial location; Type 3: patient number 6, left atrial location. (speed 40 mm/sec).

Statistical analysis

Data analysis was performed with SPSS statistical software (SPSS, Inc., release 15.0, Chicago, Illinois, USA). Continuous variables are reported as mean $\pm$ standard deviation or median with interquartile range and categorical variables as observed number of patients (percentage). We performed Levene's test for equality of variances in all continuous variables before testing differences with an independent *t*-test when comparing 2 groups or with ANOVA when comparing 3 or more groups. Categorical variables were tested with Fisher's exact test. Correlations were evaluated by Spearman correlation tests. Additionally, the relationship between mean AFCL-egm and mean AFCL-tvi was evaluated using Bland-Altman bias analysis. The difference between the measurements was plotted against their average. Two standard deviations around the mean difference represented the upper and lower limits of agreement. All tests performed were 2-sided. Overall, a *P*-value of <0.05 was considered to be statistically significant.

Results

Patient characteristics

Five patients (42%) had paroxysmal AF and 7 patients (58%) had permanent AF. The mean total duration of the AF history among our patients was 9 ± 6 years and the median duration of the last episode was 123 days (interquartile range: 2–444). The majority of patients had some form of underlying heart disease (hypertension; coronary artery disease; diabetes mellitus; heart failure; clinically significant valvular heart disease). Nearly all patients were treated with rate-control and 3 patients received antiarrhythmic drugs (sotalol or flecainide). Table 9.1 shows other baseline characteristics. Typical electrophysiological findings included shortest AFCL-egm in permanent AF. In addition, paroxysmal AF patients mostly showed electrophysiological AF type I (70% of all recordings in paroxysmal AF patients) and no type III AF, whereas type I occurred in only 23% and type III in 46% in permanent AF patients.

Correlation Between AFCL-tvi and AFCL-egm

AFCL-tvi could be identified in all patients on the echocardiographic TVI tracings at both left and right atrial locations. In 1 patient, we did not obtain an intracardiac electrogram of the left atrium since the coronary sinus was inaccessible (Table 9.1). A significant correlation was found between the mean AFCL-tvi and AFCL-egm in the LA ($r^2 = 0.99$; $P < 0.001$) and RA ($r^2 = 0.97$; $P < 0.001$). The overall correlation between the mean AFCL-tvi and AFCL-egm measured at the 2 atrial locations is presented in Figure 9.3A ($r^2 = 0.98$; $P < 0.001$). The mean AFCL-egm and mean AFCL-tvi for all patients

measured at both atrial sites were compared in a Bland-Altman plot. The mean difference (AFCL-egm–AFCL-tvi) was 0.99 ms, and the 95% limit of agreement (± 1.96 SD) was ± 7.07 ms. We also found a significant correlation between P5 of the AFCL-egm and AFCL-tvi ($r^2=0.67$; $P=0.003$) and the P95 of both measurements ($r^2=0.77$; $P<0.001$) (Figure 9.3B and 9.3C, respectively). Figure 9.4 shows the distribution of 100 AFCL-egm and 100 AFCL-tvi in patient number 10 in the LA and RA. No significant correlations were found between LA volume as determined by echocardiography and AFCL-tvi measured in the LA ($r^2=0.182$; $P=0.59$) and between RA volume and AFCL-tvi measured in the RA ($r^2=0.48$; $P=0.12$).

Relation between the clinical AF type, AFCL-tvi, and AFV-tvi

Patients with paroxysmal AF had a significantly longer AFCL-tvi than patients with permanent AF (216 ± 23 ms vs. 155 ± 15 ms; $P<0.001$). The P5 and P95 of the AFCL-tvi were also longer in patients with paroxysmal AF compared to permanent AF (Table 9.2). Furthermore, the AFV-tvi was higher in patients with paroxysmal AF compared to permanent AF.

Relation between electrophysiological AF type, AFCL-tvi, and AFV-tvi

The mean AFCL-tvi and the mean AFV-tvi were highest in electrophysiological type I AF, intermediate in type II and lowest in type III (Figures 9.2 and 9.5). In addition, a significant difference of AFCL-tvi variability was found between type I (lowest) and type III AF (highest). Table 9.3 presents TVI parameters according to electrophysiological AF type.

Table 9.1 Characteristics of the 12 study patients.

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Characteristics												
Sex	f	m	m	f	m	m	m	m	f	m	f	m
Age (years)	83	77	88	61	63	71	61	68	65	59	70	61
Total AF duration (years)	13	19	4	6	13	6	2	19	5	6	6	4
Clinical AF type	PAF	PAF	PAF	PAF	PAF	Perm	Perm	Perm	Perm	Perm	Perm	Perm
Underlying cardiovascular disease	Ht	Ht	CAD, VHD	HF	Ht, Stroke	Ht, CAD, HF	CAD	CAD	Ht, CAD	DM,	Ht, CAD, HF	Ht, HF
Antiarrhythmic drugs	BB, Vpm	BB, Vpm	Sot, Vpm	BB, Vpm	Flec, Vpm	BB, Dig	BB, Dig	BB, Dig	BB, Dig		BB	Sot, Dig
Electrophysiology												
- EP-type LA	II	I	I	II	II	III	I	I	III	II	NA	II
- EP-type RA	I	I	I	I	I	III	III	I	III	II	III	II
AFCL-egm LA												
- Mean (ms)	200	245	185	206	235	-	145	171	-	165	NA	142
- P5 (ms)	180	238	172	120	210	-	130	158	-	147	NA	106
- P95 (ms)	220	255	200	265	261	-	192	187	-	186	NA	171
AFCL-egm RA												
- Mean (ms)	201	245	190	215	241	-	-	172	-	171	-	150
- P5 (ms)	172	238	163	186	220	-	-	143	-	124	-	122
- P95 (ms)	222	252	223	249	268	-	-	201	-	202	-	175
Echocardiography												
- LA volume (ml)	60	68	80	112	121	44	47	50	72	97	107	143
- RA volume (ml)	50	97	41	87	56	39	38	40	85	44	46	58
- LVEDD (mm)	50	47	48	37	50	45	57	40	49	45	40	40
- LVESD (mm)	32	26	38	27	33	31	43	30	41	35	29	29
- IVSDD (mm)	8	9	12	11	9	10	9	8	9	14	9	9
- PWEDWD (mm)	8	9	12	11	9	10	9	8	8	10	10	9
- LVEF (%)	65	75	50	54	50	55	48	65	40	50	54	54
- SRVP (mmHg)	<30	<30	<30	30	<30	<30	<30	<30	40	<30	40	30

Table 9.1 Characteristics of the 12 study patients (continued).

Patient	1	2	3	4	5	6	7	8	9	10	11	12
AFCL-tvi LA												
- Mean (ms)	202	244	182	207	238	148	150	170	164	162	NA	141
- P5 (ms)	170	230	160	153	210	90	120	140	120	114	NA	120
- P95 (ms)	240	260	200	250	260	198	179	200	210	197	NA	173
AFV-tvi (cm/sec)	4.3	10.15	3.46	4.83	4.29	0.58	0.42	1.20	0.42	1.94	NA	1.51
AFCL-tvi RA												
- Mean (ms)	203	243	188	212	235	156	150	172	165	173	122	139
- P5 (ms)	180	210	160	173	200	99	120	130	110	140	80	110
- P95 (ms)	230	270	220	250	260	200	170	216	210	210	201	160
AFV-tvi (cm/sec)	5.44	10.06	3.53	1.81	9.16	0.27	1.53	3.62	0.26	3.32	0.19	2.2

Patients ordered according to clinical type of AF and increasing LA volume. m: male; f: female; EP: Electrophysiological; PAF: paroxysmal AF; Perm: permanent AF; LA: Left atrium; RA: Right atrium; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; IVSEDD: Interventricular end diastolic width; PWEDWD: Posterior wall end diastolic width; LVEF: Left ventricular ejection fraction; SRVP: systolic right ventricular pressure; P5: 5th percentile; P95: 95th percentile; Ht: Hypertension; CAD: Coronary artery disease; DM: Diabetes mellitus; HF: Heart failure; VHD: clinically significant valvular heart disease; Sot: sotalol; Flec: flecainide; BB: Beta-blocker; Vpm: Verapamil; Dig: Digoxin; NA: not available

Figure 9.3 Correlation between AFCL-tvi and AFCL-egm measured at left (black dots) and right atrial (open dots) locations. (A): Correlation between mean AFCL-tvi and mean AFCL-egm; (B): Correlation between P5 AFCL-tvi and P5 AFCL-egm; (C): Correlation between P95 AFCL-tvi and P95 AFCL-egm.

Figure 9.4 Example of the distribution of 100 AFCLs in patient number 10 with permanent AF using both the intracardiac electrogram and TVI at two atrial locations. (A) Distribution of AFCL-tvi measured in the left atrium; (B) Distribution of AFCL-tvi measured in the right atrium; (C) Distribution of AFCL-egm measured in the left atrium; (D) Distribution of AFCL-egm measured in the right atrium.

Table 9.2 Local atrial TVI characteristics according to clinical AF type.

	Clinical AF type		
	Paroxysmal	Permanent	P-value
N	10	13	
Mean AFCL-tvi (ms)	216±23	155±15	<0.001
P5 AFCL-tvi (ms)	185±26	115±18	<0.001
P95 AFCL-tvi (ms)	244±22	194±18	<0.001
Difference P95-P5 (ms)	59±19	79±24	0.044
AFV-tvi (cm/sec)	5.7±3.0	1.3±1.2	<0.001

Table 9.3 Local atrial TVI characteristics according to electrophysiological AF type.

	Electrophysiological AF type			P-value
	Type I	Type II	Type III	
N	10	7	6	
Mean AFCL-tvi (ms)	200±33	180±37	151±16	0.021
P5 AFCL-tvi (ms)	170±36	145±36	103±16	0.002
P95 AFCL-tvi (ms)	228±31	213±39	198±15	0.176
Difference P95-P5 AFCL-tvi (ms)	58±16	68±18	95±24	0.004
AFV-tvi (cm/sec)	4.9±3.7	3.2±1.3	0.5±0.5	0.014

Figure 9.5 Atrial TVI parameters according to electrophysiological AF type. (P5: fifth percentile; P95: ninety-fifth percentile).

Discussion

This study shows that echocardiographic TVI of the left and right atrial fibrillatory wall motion may correspond to several electrophysiological parameters during AF. First, a strong correlation was found between the mean AFCL-tvi and the mean AFCL-egm. In addition, there was a significant correlation between the electrophysiological and echocardiographic P5 and P95 of the AFCL. The former relationship suggests that AFCL-tvi may reflect the functional atrial refractory period, the latter relationship denotes that AFCL-tvi may indicate temporal dispersion of conduction. These notions are further supported by the finding that electrophysiological AF type was associated with

specific TVI patterns. With increasing electrophysiological complexity, the AFCL-tvi shortened, the AFCL-tvi variability increased and the AFV-tvi decreased. Finally, atrial TVI findings correlated with the clinical type of AF since patients with permanent AF had shorter mean AFCL-tvi and higher AFCL-tvi variability compared to patients with paroxysmal AF. In addition, AFV-tvi was lower in permanent AF suggesting more advanced structural remodeling and compromised atrial contractile function in these patients. Taken together, our findings suggest that TVI of the atrial fibrillatory wall motion may be used to noninvasively characterize remodeling in AF.

Relation between the clinical AF type and the atrial fibrillatory wall motion determined with TVI

The functional atrial refractory period is represented by the AFCL as measured during AF.^{4,5} Atrial refractoriness and its spatial dispersion play an important role in the development and maintenance of AF. Prolongation of refractoriness enhances self termination of AF whereas shortening is associated with persistence of AF. In our study, we found that patients with paroxysmal—self-terminating—AF had longer AFCL-tvi compared to patients with permanent AF. These findings are in line with previous electrophysiological studies.¹⁴ Increased variability of cycle length has been reported before in patients with induced AF and seems to relate to complex patterns of atrial conduction suggesting advanced remodeling.¹⁵ In this respect it is noteworthy that the largest variability was seen in patients with permanent AF. Furthermore, permanent AF was linked to low atrial wall velocities on TVI, again suggesting advanced structural remodeling as expected in these patients.

Relation between electrophysiological AF type and the atrial fibrillatory wall motion determined with TVI

Paroxysmal AF was associated with noncomplex electrophysiological AF types (types I and II)¹² with long average AFCL, whereas the complex type III electrograms with short AFCL, high AFCL variability and electrogram fragmentation were mainly seen in permanent AF patients. Not only the higher AF burden in permanent AF but also the higher accumulated number of associated cardiac conditions may have caused electrogram fragmentation in permanent rather than paroxysmal AF. Fragmentation represents structural and electrical remodeling and is associated with fibrosis, cellular and myofibril uncoupling and disarray and local detour conduction.¹⁶ The association of fragmentation and low atrial fibrillatory velocities seems obvious since the same pathologic factors causing fragmentation mentioned above may cause decreased atrial contractility.^{17,18} In addition, atrial motility results from the sum of contractions from the individual atrial cells. In case of type III AF, the disorganized atrial activation, as represented by fragmented electrograms, results in disorganized contractions, with a reduced overall velocity of atrial motion, if any at all.

There was no clear relation between right or left atrial volume and type of AF. Usually, larger atria harbor structural pathology of the atrial wall. Absence of a relationship suggests that the other factors like AF burden are more important. Alternatively, the low number of observations may have precluded a firm conclusion in this respect.

The value of AFCL and electrophysiological AF type in clinical practice

The morphology of the atrial electrograms and duration of the AFCL provides valuable information in patients with AF.¹⁹ The distribution and the duration of the AFCL can be useful to identify sites of high-frequency activity during AF. These sites play an important role in the maintenance of AF since ablation targeting these sites may result in prolongation of the AFCL and termination of AF.²⁰⁻²⁵ Moreover, measurement of the atrial fibrillatory frequency might predict short- and long-term success of catheter ablation.^{26,27} In addition, heterogeneity of AFCL is associated with recurrence of AF after electrical cardioversion.²⁸ Antiarrhythmic drugs could restore homogeneity of the AFCL²⁹ and increase the AFCL,³⁰ which is associated with termination of AF.³¹

Considering the above, AFCL and electrophysiological AF type may play an important role in clinical management of patients with AF. However, up till now the invasive nature of electrophysiology studies precludes a wide scale use in clinical practice. We strongly believe that TVI of the atrial fibrillatory wall movement will encourage the use of AFCL in clinical practice. Better selection of patients for drug prophylaxis, cardioversion, and catheter ablation are among the possibilities in addition to monitoring of those treatments and predicting their outcome. This avoids unnecessary exposure of patients to the risks of therapy and enhances “tailored treatment.”

Alternative noninvasive methods to determine the AFCL

The local AFCL is presently measured during an electrophysiological study. This procedure is invasive and timeconsuming and therefore not extensively used in clinical practice. Husser *et al.* described electrocardiographic methods to estimate the AFCL.³² Although this technique provides valuable information, it requires special software and it only provides global estimation of the right atrial AFCL. Therefore, this technique is less suitable to evaluate the homogeneity of the AFCL distribution at several atrial sites. Recently, our research group developed a noninvasive way to determine the AFCL by means of pulsed wave tissue Doppler echocardiography (AFCL-tdi).⁸ In contrast, TVI has the advantage of simultaneous multisite imaging, which theoretically enables fast assessment of homogeneity of AFCL distribution. Furthermore, the information on mean atrial fibrillatory wall motion velocity as determined by TVI (AFV-tvi) gives an extra dimension to the electrical measurements. Future development of automated analysis software will improve the clinical application of this technique.

Limitations

We included patients who were referred for a His bundle ablation. These patients probably did not respond to the conventional therapies of AF. As a result, our findings need to be confirmed in a more “healthy” AF population. We determined the AFCL at 2 atrial sites. Lower tissue velocities were observed at the atrial site that is firmly attached to the rest of the body (the pulmonary vein area) implying that analysis of the atrial fibrillatory wall motion at these locations could be challenging. Furthermore, the echocardiographic examination was performed in supine position due to the risk of catheter dislocation that might have resulted in lower image quality. The current method needs a long diastole to avoid artifacts by interference with ventricular motion that occurs during the first phase of diastole. Currently, we are developing a method allowing TVI measurements during higher heart rates in patients with AF. This study was of limited size. Therefore, our results and its clinical impact need to be confirmed in a larger study aiming at the relation between the fibrillatory wall motion and outcome parameters. Manual measurement of AFCL-tvi and AFV-tvi is rather time-consuming. Future development of automated analysis software will improve the clinical application of this technique. As a final point, the usual limitations inherent to TVI regarding the angle of insonation and loading conditions of the heart also apply in this study. To limit the influence of these potential confounders, we selected patients who were hemodynamically stable and care was taken to align the ultrasound beam with the direction of the myocardium studied.

Conclusions

We found a strong correlation between the velocity and cycle length of the local atrial fibrillatory wall motion on TVI and the local AFCL and AF type determined during electrophysiology studies. Therefore, TVI of the fibrillating atrial myocardium may enhance noninvasive characterization of remodeling in patients with atrial fibrillation. Nevertheless, more studies are needed to confirm our findings and establish its clinical impact.

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Chapter 10

The mechanical fibrillation pattern of the atrial myocardium is associated with acute and long-term success of electrical cardioversion in patients with persistent atrial fibrillation

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Abstract

Background

Electrophysiological studies demonstrate that a short atrial fibrillation cycle length (AFCL) is related with poor outcome of electrical cardioversion (ECV) of atrial fibrillation (AF). We found previously that the mechanical AFCL (AFCL-tvi) and atrial fibrillatory velocity (AFV-tvi) may be determined non-invasively using color tissue velocity imaging and closely relates to the electrophysiological AFCL.

Objective

In the present study, we evaluated the relation between AFCL-tvi, AFV-tvi and success of ECV in patients with AF.

Methods

We prospectively studied 133 patients with persistent AF by performing an echocardiogram before ECV and measured the AFCL-tvi and AFV-tvi in the right atrium (RA) and left atrium (LA). Recurrent AF was monitored.

Results

Nineteen patients had failure of ECV, 42 remained in sinus rhythm after one year follow-up and 72 had a recurrence of persistent AF. Patients with immediate ECV failure had a lower median right atrial AFV-tvi compared to patients with a successful ECV: 0.7 (0.2-1.0) versus 1.7 (0.9-2.8) cm/sec, $P=0.008$. Patients with maintenance of sinus rhythm after one year had a longer AFCL-tvi measured in the left atrium compared to patients with recurrence of AF (150 versus 137 ms; $P=0.017$) and higher AFV-tvi in both atria (1.4 versus 0.9 cm/sec in LA; $P=0.013$ and 2.2 versus 1.4 cm/sec in RA; $P=0.011$). Multivariate analyses showed that all atrial TVI parameters were independently associated with maintenance of sinus rhythm after one year.

Conclusions

Higher atrial fibrillatory wall velocities and longer AFCLs determined by echocardiography are associated with acute and long-term success of ECV.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.¹ Most symptomatic patients undergo pharmacological or electrical cardioversion (ECV) to restore normal sinus rhythm. Unfortunately, ECV is not always successful.² In addition, 40-70% of the patients have recurrence of AF within 2 years after a successful ECV.³ Identification of patients in whom ECV is likely to be successful will avoid unnecessary exposure of expected non-responders to complications of ECV. Factors that facilitate AF are depressed intra-atrial conduction as well as shortening of the atrial refractory period. The former factor relates to atrial structural remodeling, the latter is represented by the atrial fibrillation cycle length (AFCL).⁴ Electrophysiological studies demonstrated that AFCL is associated with maintenance of sinus rhythm.⁵⁻⁷ In previous studies we showed that, as an alternative to the invasive electrophysiological studies, color tissue velocity imaging (TVI) is a reliable non-invasive tool to assess the mechanical atrial fibrillatory frequency which is closely related to the electrophysiological AFCL and hence atrial refractoriness.⁸⁻¹¹ In addition, the velocity of the atrial fibrillatory wall motion as assessed by TVI (AFV-tvi) is inversely associated with the extent of arrhythmogenic structural atrial remodeling.^{10,11} In the present study we evaluate the relation between these electrophysiology-based echocardiographic tools and success of ECV and recurrences of persistent AF after ECV.

Methods

This study was approved by the Institutional Review Board for human research. We studied 133 consecutive patients referred for an ECV with symptomatic persistent AF. All patients were included in our outpatient clinic and had AF lasting >1 month which was verified by serial ECGs. Informed consent was obtained from all patients. Patients using class I or III anti-arrhythmic drugs were excluded. Other exclusion criteria were age <18 years, atrial flutter, and secondary AF. The decision of ECV referral and pretreatment with anti-arrhythmic drugs was made by the treating physician.

Echocardiogram

Before ECV (<1 hour), trans-thoracic echocardiography including color TVI in the apical 4-chamber view was performed with a Vivid 7 ultrasound system (GE Healthcare). Patients were in supine position and the color TVI images were made during the end-expiratory phase in order to avoid respiratory artifacts. The frame rate was set above 100 Hz. Offline, we studied TVI curves obtained from late diastole from the lateral wall of the left atrium just above the mitral annulus and from the lateral wall of the right atrium just above the tricuspid valve. At these specific atrial locations, the intrinsic motility of the myocardium is generally the highest. Moreover, these anatomical spots

near the atrioventricular annulus are easy to identify which enhances the reproducibility of the measurements. We tried to avoid ventricular artifacts as much as possible by performing our measurements in the late diastolic phase when the ventricular contraction and relaxation are completed. Finally, the atrial sites where we measured AFCL were previously validated by comparing the AFCL-TVI with the electrophysiological AFCL on the electrogram.¹¹

The atrial fibrillatory cycle length (AFCL-tvi) and atrial fibrillatory velocity (AFV-tvi) were measured at both atrial sites using the color TVI curves (Figure 10.1). AFCL-tvi was defined as the mean time interval between two consecutive negative deflections of the late diastolic atrial tissue velocity curve and AFV-tvi was defined as the mean difference in velocity of negative and positive deflections of the late diastolic atrial tissue velocity curve. From at least 3 cycles, AFCL-tvi and AFV-tvi were measured and averaged by one of the investigators (CDV) who was blinded for the result of the ECV. In order to evaluate the inter-observer variability of the TVI measurements, a second investigator (IL) repeated these measurements in 14 randomly selected patients. According to the recommendations of the American Society of Echocardiography the left ventricular global systolic function was evaluated by LV ejection fraction, mitral flow velocity was assessed by pulsed-wave Doppler from the apical 4-chamber view and left atrial volumes were measured using the biplane Simpson rule.

Figure 10.1 Example of a Tissue Velocity Imaging (TVI) tracing of the left atrial lateral wall in a patient with atrial fibrillation and measurement of Atrial Fibrillation Cycle Length (AFCL-tvi) and velocity of the atrial fibrillatory wall motion (AFV-tvi).

Electrical cardioversion

Using a biphasic Lifepak® defibrillator (Medtronic) electrical cardioversion was performed with paddles placed in an antero-lateral position using 100 Joules followed by 200, and 360 Joules until sinus rhythm was obtained or until failure to convert with 360 Joules. Continuous ECG monitoring was performed during 3 hours after the procedure. Failure of ECV was defined as total shock failure or immediate recurrence of AF (recurrence within 2 minutes after ECV). We did not perform a separate analysis of total shock failure patients. This would have been interesting from a pathophysiological point of view. However, the patient numbers in the “failure of ECV” group were too low to split this group.

Follow-up

All our patients were seen within one month after ECV at our outpatient clinic, and subsequently at regular intervals. Within the first year of follow-up most patients were seen at least at three moments in time depending on the treating physician and symptoms of the patients. All patients were followed-up for at least one year. During every visit, symptoms of AF were evaluated and a 12-lead ECG was made. When in doubt about the rhythm status of the patient, a Holter recording was performed. If patients were admitted to the emergency department with cardiac complaints, the rhythm was verified by one of our cardiologists and the presence of AF was recorded in the digital charts of our cardiology department. None of the patients were lost to follow-up. Recurrence of persistent AF was defined as AF on a follow-up 12-lead ECG and subsequently documented as continuous AF on 24 hour Holter.

Statistical analysis

Data analysis was performed with SPSS statistical software (SPSS, Inc., release 20.0). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Since most of these variables were not normally distributed, we reported continuous variables as “median (25th percentile – 75th percentile)”. Categorical variables were reported as “observed number of patients (percentage)”. Differences between variables that were not normally distributed were tested with the Mann-Whitney U test when comparing two groups and the Kruskal-Wallis test when comparing three groups. Categorical variables were tested with Fisher’s exact test when comparing two groups and Chi-square when comparing three groups. The predictive accuracy of our new tissue velocity parameters were reported using Receiver-operator characteristics (ROC). Differences in AF-free survival were determined using Kaplan-Meier curves (log-rank test). The interobserver variability of AFCL-tvi and AFV-tvi was evaluated using Spearman correlation tests. All baseline characteristics showing a significant univariate relationship with persistent AF recurrence at follow-up and all variables known to be associated with outcome of ECV

were included in a logistic regression model (hypertension, heart failure, left atrial dimensions, age, AF duration). Because of the risk of interaction, all TVI parameters were included separately to the model. Model reduction was performed by stepwise excluding variables from the model with a P value >0.10 . We evaluated model accuracy and discrimination by integrated discrimination improvement (IDI).¹² The clinical model includes age, duration of AF episode and LA diameter. We included all consecutive patients in the univariate analysis which might give a better representation of the variables associated with success of ECV. The multivariate analyses and Kaplan-Meier analyses were limited only to patients in whom the TVI parameters were obtained. All tests performed were two-sided. Overall, a P -value of <0.05 was considered to be statistically significant.

Results

We included 133 consecutive patients before ECV. In nineteen patients (14%) ECV failed to restore sinus rhythm and 114 (86%) had a successful ECV. Of all patients in whom sinus rhythm was obtained, 42 (37%) remained in sinus rhythm and 72 (63%) had a recurrence of AF during one year follow-up.

The median AFCL-tvi was 140 (129-156) ms when measured in the left atrium and 155 (140-170) ms when measured in the right atrium. The median AFV-tvi was 1.0 (0.6-1.7) cm/sec measured in the left atrium and 1.5 (0.8-2.6) cm/sec in the right atrium. The clinical and echocardiographic baseline characteristics of the study population according to immediate success of ECV are presented in Table 10.1. Except for the TVI parameters, no significant differences were found. Table 10.2 shows the characteristics of our population according to overall maintenance of sinus rhythm during one year follow up. Significant differences were only found for the TVI parameters. In addition, there was a trend for longer AF duration and less hypertension in patients with AF recurrence during follow-up. The medication used by the patients is presented in Table 10.3.

Measurement of the AFCL-tvi was feasible in 91 (68%) patients in the left atrium and in 85 (64%) patients in the right atrium. The AFV-tvi could be determined for 101 (76%) patients in the left atrium and for 94 (71%) patients in the right atrium. We compared the characteristics in patients in whom the TVI parameters could be obtained with the patients in whom they could not be obtained as an attempt to exclude any forms of bias and found no significant differences.

Table 10.1 Clinical and echocardiographic characteristics of the study population according to immediate success of electrical cardioversion.

	All patients	Failure of electrical cardioversion	Success of electrical cardioversion	P-value*
N	133	19 (14%)	114 (86%)	
Age (years)	67 (59-74)	66 (52-73)	67 (59-74)	0.792
Female	39 (29%)	8 (42%)	31 (27%)	0.275
Total AF duration (months)	7 (3-40)	8 (3-29)	6 (3-40)	0.615
AF duration current episode (days)	101 (57-84)	107 (64-231)	97 (56-172)	0.357
Ventricular rate (bpm)	82 (73-96)	82 (69-100)	82 (73-96)	0.872
Underlying diseases				
Hypertension	75 (56%)	11 (58%)	64 (56%)	1.000
Coronary artery disease	35 (26%)	3 (16%)	32 (28%)	0.399
Valvular heart disease	24 (18%)	2 (11%)	22 (19%)	0.524
Heart failure	38 (29%)	7 (37%)	31 (27%)	0.417
Echography				
Left atrial size (mm)	46 (42-50)	44 (42-51)	46 (42-50)	0.927
Left Atrial volume (ml)	87 (66-109)	101 (75-115)	84 (66-108)	0.190
Right atrial volume (ml)	74 (55-96)	81 (62-104)	74 (54-96)	0.270
Ejection fraction (%)	52 (43-60)	55 (43-62)	51 (44-60)	0.465
TVI echography				
AFCL-tvi LA (ms) n=91	140 (129-156)	133 (105-148)	140 (130-160)	0.072
AFCL-tvi RA (ms) n=85	155 (140-170)	130 (115-169)	155 (140-170)	0.081
AFV-tvi LA (cm/sec) n=101	1.0 (0.6-1.7)	0.8 (0.1-1.6)	1.0 (0.6-1.7)	0.174
AFV-tvi RA (cm/sec) n=88	1.5 (0.8-2.6)	0.7 (0.2-1.0)	1.7 (0.9-2.8)	0.008

* P-value resulting from the comparison "failure of electrical cardioversion" versus "success of electrical cardioversion". AF: atrial fibrillation; FU: follow-up; AFCL: atrial fibrillation cycle length; AFV: atrial fibrillation velocity; LA: left atrium; RA: right atrium.

Immediate failure of ECV

We found a trend towards a shorter median AFCL-tvi in patients with a failed ECV compared to patients with a successful ECV: 133 versus 140 ms in the left atrium and 130 ms versus 155 ms in the right atrium. See Table 10.1 for details. The atrial fibrillatory wall velocity in the left atrium did not significantly differ between ECV failure and ECV success. However, in the right atrium, a significant difference of AFV-tvi was found between patients with a successful ECV (1.7 cm/sec) versus patients with a failed ECV (0.7 cm/sec).

Next, we studied the predictive ability of AFCL-tvi and AFV-tvi regarding acute success of ECV by creating ROC-curves. AFV-tvi measured in the right atrium significantly predicted immediate success of ECV: AUC 0.74, $P=0.018$. AFV-tvi measured in the left atrium (AUC 0.62; $P=0.174$) and AFCL-tvi measured in the left (AUC 0.69; $P=0.073$) or right atrium (AUC 0.68; $P=0.081$) did not significantly predict immediate success of ECV. We calculated the IDI by comparing the clinical model for prediction of successful cardioversion with the new model (clinical model + AFV-tvi of the right atrium). The IDI showed that the discrimination slope of the new model was 14% higher than the clinical model itself.

Table 10.2 Clinical and echocardiographic characteristics of the study population according to overall maintenance of sinus rhythm during follow-up.

	All patients	Failure of ECV or recurrence of AF during FU	Overall maintenance of sinus rhythm	P-value*
N	133	91 (68%)	42 (32%)	
Age (years)	67 (59-74)	68 (59-73)	67 (59-75)	0.697
Female	39 (29%)	29 (32%)	10 (24%)	0.415
Total AF duration (months)	7 (3-40)	7 (3-41)	5 (3-35)	0.144
AF duration current episode (days)	101 (57-84)	108 (64-199)	80 (46-152)	0.076
Ventricular rate (bpm)	82 (73-96)	82 (73-96)	84 (73-97)	0.875
Underlying diseases				
Hypertension	75 (56%)	46 (51%)	29 (69%)	0.060
Coronary artery disease	35 (26%)	22 (24%)	13 (31%)	0.407
Valvular heart disease	24 (18%)	19 (21%)	5 (12%)	0.237
Heart failure	38 (29%)	30 (33%)	8 (19%)	0.148
Echography				
Left atrial size (mm)	46 (42-50)	45 (42-50)	47 (44-51)	0.292
Left Atrial volume (ml)	87 (66-109)	86 (66-109)	91 (67-109)	0.815
Right atrial volume (ml)	74 (55-96)	74 (58-100)	75 (52-95)	0.479
Ejection fraction (%)	52 (43-60)	52 (41-60)	54 (48-60)	0.185
TVI echography				
AFCL-tvi LA (ms) n=91	140 (129-156)	137 (123-151)	150 (134-170)	0.017
AFCL-tvi RA (ms) n=85	155 (140-170)	150 (135-170)	156 (144-177)	0.216
AFV-tvi LA (cm/sec) n=101	1.0 (0.6-1.7)	0.9 (0.5-1.6)	1.4 (0.8-2.4)	0.013
AFV-tvi RA (cm/sec) n=88	1.5 (0.8-2.6)	1.3 (0.7-2.3)	2.2 (1.4-3.1)	0.011

* P-value resulting from the comparison "Failure of ECV or recurrence of AF during FU" versus "Overall maintenance of sinus rhythm". AF: atrial fibrillation; FU: follow-up; AFCL: atrial fibrillation cycle length; AFV: atrial fibrillation velocity; LA: left atrium; RA: right atrium.

Overall recurrence of persistent AF within one year after ECV

Left atrial AFCL-tvi was longer in patients who remained in sinus rhythm during follow-up compared to patients with recurrent AF: 150 ms versus 137; $P=0.017$. See Table 10.2 for details. In the right atrium, AFCL-tvi did not differ between patients with long term sinus rhythm and those with recurrent AF. However, for both atria AFV-tvi was higher in the patients that maintained sinus rhythm: 1.4 cm/sec versus 0.9 cm/sec in the left atrium; $P=0.013$ and 2.2 cm/sec versus 1.3 cm/sec in the right atrium; $P=0.011$. Next we performed ROC analyses to study the predictive ability of AFCL-tvi and AFV-tvi regarding recurrence of AF within one year after ECV. AFV-tvi measured in the right atrium (AUC 0.67, $P=0.01$), AFV-tvi of the left atrium (AUC 0.66, $P=0.01$) and AFCL-tvi measured in the left atrium (AUC 0.66, $P=0.02$) were significant predictors of AF recurrence.

Table 10.3 Medication used at baseline.

	All patients	Failure of electrical cardioversion	Recurrence of AF during FU	Maintenance of sinus rhythm	P-value*
N	133	19 (14%)	72 (54%)	42 (32%)	
Rate-control drugs					
Beta-blockers	96 (71%)	14 (74%)	48 (67%)	33 (79%)	0.39
Digoxine	35 (26%)	4 (21%)	21 (67%)	10 (24%)	0.70
Non-dihydropyridine calcium channel blockers	16 (12%)	4 (21%)	6 (8%)	6 (14%)	0.27
Other medication					
Diuretics	47 (35%)	7 (37%)	23 (32%)	17 (41%)	0.65
Angiotensin converting enzyme inhibitors	48 (36%)	8 (42%)	30 (42%)	10 (24%)	0.13
Angiotensin receptor blockers	48 (36%)	8 (42%)	20 (28%)	20 (48%)	0.09
Statins	60 (45%)	8 (42%)	27 (38%)	25 (60%)	0.07
Calcium channel blockers	11 (8%)	1 (5%)	7 (10%)	6 (14%)	0.78
Nitrates	14 (11%)	1 (5%)	7 (10%)	6 (14%)	0.52

* P-value resulting from the comparison “failure of electrical cardioversion” versus “recurrence of AF during FU” versus “maintenance of sinus rhythm”. AF: atrial fibrillation; FU: follow-up.

Multivariable analyses show that absence of hypertension, AFCL-tvi measured in the left atrium, AFCL-tvi measured in the right atrium, AFV-tvi measured in the left atrium and AFV-tvi of the right atrium were all independently associated with recurrence of AF within one year after ECV (Table 10.4). We calculated the IDI by comparing the clinical model for prediction of maintenance of sinus rhythm after 1 year with the new model (clinical model + AFV-tvi in the right atrium). The IDI showed that the discrimination slope of the new model was 4% higher than the clinical model itself. Finally, we created an AF-tvi score combining TVI parameters to determine the Kaplan-Meier 1-year AF-free survival. (Figure 10.2).

Table 10.4 Independent predictors of persistent AF at one year resulting from the multivariable analysis (each TVI parameter added to the model separately).

	OR	CI	P-value*
Model including AFCL-tvi LA			
AFCL-tvi LA (per ms)	0.97	0.96-0.99	0.01
Hypertension	0.30	0.11-0.84	0.01
Model including AFCL-tvi RA			
AFCL-tvi RA (per ms)	0.98	0.97-0.99	0.03
Hypertension	0.29	0.09-0.85	0.02
Model including AFV-tvi LA			
AFV-tvi LA (per cm/sec)	0.62	0.39-1.00	0.04
Hypertension	0.39	0.15-1.02	0.05
Model including AFV-tvi RA			
AFV-tvi RA (per cm/sec)	0.74	0.55-1.00	0.04

AFCL: atrial fibrillation cycle length; AFV: atrial fibrillatory velocity; LA: left atrium; RA: right atrium; CI: confidence interval; OR: odds ratio

Figure 10.2 Kaplan–Meier one-year AF-free survival according to the AF-tvi score.

Interobserver variability

Twenty-eight repeated measurements were performed (left and right atrium in 14 patients). We evaluated the correlation between the measurements performed by two independent observers. For the measurement of AFCL-tvi, the correlation coefficient was 0.830 ($P < 0.001$) and for the measurement of AFV-tvi, the correlation was 0.813 ($P < 0.001$).

Discussion

New TVI parameters to characterize patients with AF

In the presence of a short excitable gap (as present during AF with functional reentry), the duration of the atrial refractory period is related to the AFCL as measured during AF.⁴ Duytschaever et al. found a strong correlation between atrial mechanical fibrillatory wall motion assessed by tissue Doppler imaging (TDI) and the electrical

fibrillatory cycle length assessed by the intracardiac electrogram.⁸ The AFCL is inversely associated with the number of wavelets participating in AF maintenance.¹³ Conversion to sinus rhythm may be hampered by a short AFCL. In addition, a short refractory period sets the stage for a supervulnerable phase immediately after applying a DC countershock to convert persistent AF.¹⁴ Considering the above, it is plausible that AFCL-tvi is associated with maintenance of sinus rhythm after ECV.

Atrial contractile dysfunction is strongly related to electrical remodeling.¹⁵ In addition, atrial dilatation due to heart disease results in loss of atrial contractility. Besides, structural heart disease results in atrial tissue fibrosis which is an important hallmark of atrial arrhythmogenicity. In our study, lower atrial fibrillatory wall velocity signals were associated with worse outcome. TVI echocardiography may demonstrate differences in contractile and, hence, structural remodeling and arrhythmogenicity among persistent AF patients.^{10,11}

Although, we found in the present study that AFV-tvi measured in the left atrium was longer in patients with immediate success of ECV compared to immediate failure of ECV, this difference was not statistically significant. AFV-tvi was significantly longer in patients with successful cardioversion when measured in the right atrium. We found that the overall AFV-tvi was lower in the left atrium compared to the right atrium. In addition to that, the variation of AFV-tvi was much smaller in the left compared to the right atrium. Therefore, we believe that AFV-tvi measured in the right atrium has the highest intrinsic predictive power regarding immediate success of ECV.

Predicting success of electrical cardioversion in patients with AF

The most consistent clinical predictors of successful ECV were a short duration of the AF episode, younger age, a small atrial size and the use of anti-arrhythmic drugs or beta-blockers.¹⁶⁻²⁰ There is increasing evidence that AF is associated with inflammation which might be reduced by statins.²¹ Inhibition of the RAAS can possibly reduce atrial structural remodeling by decreasing fibrosis which can result in a decrease in the incidence of AF.²² The predictive value of valvular disease is less evident.^{19,23} Other clinical parameters associated with unsuccessful ECV are a history of coronary artery disease, female sex, weight, hypertension, and sleep apnea syndrome.^{20,24,25} However, the predictive value of the parameters evaluated is low.²⁶ Echocardiographic parameters predicting ECV success were left atrial appendage (LAA) peak bloodflow velocity, pulmonary vein blood flow patterns and mitral Doppler peak A-wave velocity.²⁷⁻²⁹ P-wave duration during sinus rhythm and global right atrial fibrillatory frequency during AF are electrocardiographic parameters that are associated with maintenance of sinus rhythm after ECV.³⁰

Basically, all clinical and echocardiographic “predictors” described above, primarily relate to structural remodeling whereas the electrocardiographic predictors described previously also seem to reflect the global amount of electrical remodeling.

Limitations

The current TVI method needs a long diastole to avoid artifacts by interference with ventricular motion. As a result, measurement of AFCL-tvi and AFV-tvi was not feasible in patients with a too high ventricular rate. In some patients we could not measure AFCL-tvi despite a long diastole because the velocity of the signal was too low. However, these signals could be a manifestation of advanced structural remodeling and may identify patients with potential ECV failure as reflected by the low AFV-tvi. In addition to that, we do not have data regarding the temporal intra-patient variability since we only performed one echocardiographic recording in each patient. However, a previous publication studying longer recordings shows little temporal intra-patient variability.¹¹ The predictive power of our technique is too low to categorically exclude patients from an ECV attempt. This might be the result of a somewhat underpowered sample size. On the other hand, we found a strong and independent relation between AFCL-TVI, AFV-TVI and outcome of ECV in persistent AF patients. We believe that this might guide the physician in the management of patients with AF. Taken together, patients with a short AFCL-TVI and/or low AFV-TVI could be candidates for pre-treatment with anti-arrhythmic drugs to enhance the short- and long-term success rate of ECV. In addition, we believe that further developments in echocardiography (especially regarding temporal and spatial resolution) may improve the accuracy of our measurements. Not all co-variables described in the past which could influence the success of ECV were included in the present analysis. However all patients in whom AF was thought to be secondary to underlying disease were not included in our study. We did not change the paddle position in case of ECV failure, which could have increased immediate success of ECV. However, our ECV protocol represent standard practice and therefore we feel our results are valid for such practice. Finally, the usual limitations inherent to TVI regarding the angle of insonation and loading conditions of the heart also apply in this study.

Conclusions

In the present study, we evaluated the relation between the mechanical fibrillatory wall motion during AF and outcome of ECV. Two echocardiographic TVI parameters, AFCL-tvi and AFV-tvi, closely reflecting electrical and structural remodeling of the atrial walls, appear to be independently associated with success or failure of rhythm control by electrical cardioversion in persistent AF. Long AFCL-tvi and high AFV-tvi are associated with long term maintenance of sinus rhythm in patients undergoing cardioversion for persistent AF. We believe that non-invasive imaging of local electrophysiological and structural atrial changes may trigger a shift of paradigm in diagnosis and management of AF patients. Obviously, more and larger studies are needed to show that these conclusions remain true in different populations such as patients on anti-arrhythmic drugs or ablated patients.

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Chapter 11

General discussion

General discussion

Atrial fibrillation (AF) may lead to significant morbidity and mortality.¹ It is expected that the number of patients with AF will increase tremendously within the next decades which will have an important socioeconomic impact.^{2,3} This thesis aims to contribute to a better identification of patients at risk for the development of the arrhythmia and prediction of response to therapy. We evaluated the role of clinical parameters and explored new electrophysiology-derived echocardiographic parameters to characterize the atrial substrate in patients with AF.

Clinical parameters to characterize patients with atrial fibrillation

In the first part of this thesis, we evaluated the role of clinical parameters to characterize AF. A better characterization of AF using clinical parameters may improve treatment of the arrhythmia.

In **chapter 2**, we studied the clinical characteristics and management of patients with paroxysmal AF associated with autonomic triggers among the patients in the Euro Heart Survey.⁴ Coumel *et al.* were the first to describe an autonomic origin of atrial fibrillation.⁵ Electrophysiology studies show that activation of the cardiac autonomic nervous system – mostly by vagal stimulation – enhance inducibility of AF by pulmonary vein ectopy and may cause shortening of the atrial effective refractory period and atrial fibrillation cycle length (AFCL), regional conduction delays, heterogeneous changes in the atrial fibrillatory cycle length and complex fractionated electrograms that may maintain the arrhythmia.⁶⁻⁹ Ablation of ganglionated plexi can suppress pulmonary vein potentials and reduce complex fractionated atrial electrograms, and thereby control atrial fibrillation.¹⁰ We found that an autonomic trigger pattern (adrenergic, vagal or mixed) was present in 33% of all patients with paroxysmal AF in the Euro Heart Survey. It is important to classify these patients correctly since successful management of autonomic AF may depend on its recognition.¹¹ Beta-blocking drugs, sotalol, digitalis and propafenone are considered unsuitable in vagal AF since they may exacerbate the episodes of vagal induced AF, whereas in adrenergic AF drugs with beta-blocking properties are thought to be beneficial. However, these guidelines derived recommendations are based on empirical evidence and expert opinion since controlled studies on the effect of different drugs in autonomic induced AF are lacking.⁵ Our observations are among the first to add information to the knowledge base concerning the broad management of autonomic AF. Our data suggest that autonomic AF may be recognized using straightforward history taking. Further, we found that in patients with vagal AF, prescription of non-recommended treatment may be detrimental because of aggravation of the arrhythmia pattern. Our observational data are not underpinned by physiologic measurements of autonomic function in the various patient profiles as

found by simple history taking. Nevertheless, considering the above the autonomic patterns identified appeared clinically meaningful. Further studies may lead to a refinement of the clinical assessment especially if supported by autonomic function testing. This may contribute to a better treatment of atrial fibrillation.

In **Chapters 3 and 4** we characterized patients with AF progression in two cohorts: the Euro Heart Survey population¹² and the RecordAF population¹³ respectively. In clinical practice, one can discriminate three clinical AF types: paroxysmal AF (the episodes of the arrhythmia terminate spontaneously), persistent AF (the episodes are not self-terminating), and permanent AF (the physician decides that further attempts to restore normal sinus rhythm are useless).¹¹ Several previous studies investigated AF progression.¹⁴⁻¹⁸ We explored the possibility to predict AF progression using clinical parameters and found that heart failure, previous stroke or TIA, COPD, hypertension and age were independent predictors of AF progression in the Euro Heart survey.¹⁹ We developed a new simple prediction rule to estimate the probability of AF progression in patients with paroxysmal AF: the HATCH score.

Why is the HATCH score so important for clinicians? First, factors united in HATCH are known to induce structural remodeling of the atria causing chronic stretch and atrial dilatation leading to atrial fibrosis. This may lead to disturbance of the electrical junctions between muscle bundles inducing reentry.^{20,21} This explains why the potential preventive effect of antiarrhythmic drugs was annulled by the promoting effect of underlying heart disease and age as represented by HATCH. Secondly, HATCH represents not only arrhythmia progression but is also associated with cardiovascular events during follow-up. Since antiarrhythmic drugs may result in lethal complications and AF progression is associated with more adverse cardiovascular events that could be enhanced by antiarrhythmic drugs, we believe prediction of AF progression could contribute to a safer and more rational treatment by avoiding antiarrhythmic therapy in patients with a high risk of AF progression. As pointed out by Drs Jahangir and Murarka in their editorial comment accompanying our JACC paper on progression, the similarity of the HATCH score to the CHADS₂ score is striking.²² This suggests that the same parameters leading to AF progression, also induce thromboembolic complications in patients with AF. In their editorial, the authors deplore that no information about the duration of AF before enrollment is provided. Obviously all patients included had paroxysmal forms of AF. Unfortunately, information regarding the total AF duration was not available in all patients in this cohort. However, in the RecordAF cohort AF duration was not an independent predictor of AF progression. In addition, the same authors noticed that the fact that antiarrhythmic drugs were not preventing AF progression in the Euro Heart Survey population might be due to the absence of randomization to specific treatment strategies. Despite the fact that no randomization was performed, in the RecordAF population, we studied AF progression in a slightly different population of patients with recent-onset AF only. In this study the decision whether patients were treated with rate or rhythm control was made at

inclusion which enabled us to study the effect of treatment strategy more consistently. However, we could not appraise all confounders related to the physician's choice for either rate or rhythm control therapy. In RecordAF the same AF progression rate at one year follow-up was found as in the Euro Heart Survey (15%). Besides heart failure and hypertension, treatment strategy (rate- versus rhythm-control) was found to be an independent predictor of AF progression in the RecordAF population. This suggests that rhythm control prevents electrical remodeling and maybe also structural remodeling. These notions are supported by the goat studies that demonstrate that artificial maintenance of AF shortens the atrial refractory period which promotes inducibility and maintenance of AF.²³ Furthermore, this notion is supported by the observation in the ATHENA trial showing that dronedarone is associated with less AF progression and at the same time with fewer major adverse events.²⁴ Unfortunately, we were unable to validate the HATCH score in RecordAF because a history of chronic obstructive pulmonary disease was not included in the RecordAF case record form.

Echo-electrocardiography to identify the substrate for atrial fibrillation during sinus rhythm

In the second part of this thesis we studied new, non-invasive, electrophysiology-derived echocardiographic parameters to identify patients vulnerable for the development of AF. AF is associated with complications such as stroke and heart failure resulting in considerable morbidity and mortality.^{25,26} Unfortunately, preventive treatment comes too late when stroke is the first manifestation of AF. We believe that prediction of new-onset AF enables to start adequate therapy on time reducing the development of AF-related complications.

The total atrial conduction time or TACT (the total time required for atrial electrical activation) is an important electrophysiological parameter.²⁷ The longer TACT is, the higher the risk of developing AF. This relates to the fact that conduction slowing is an important determinant of reentry and at the same time an expression of atrial remodeling including fibrosis, amyloidosis, fat accumulation and other changes related to an arrhythmogenic atrial substrate. TACT can be determined using the signal-averaged ECG p-wave or the maximal p-wave duration on the 12-lead surface ECG.²⁸ However, p-wave measurement on the 12-lead ECG has a lower predictive value compared to the other techniques and p-wave analysis by signal averaged ECG has not found its way into clinical practice, possibly because it requires special hardware whilst it is rather time-consuming. In **chapter 5** we validated a new echocardiographic technique to estimate the TACT using pulsed-wave tissue Doppler echocardiography, namely PA-TDI.²⁹ Echocardiography is the diagnostic working horse of cardiology and therefore measurement of PA-TDI may find its way much more easily into clinical practice compared to signal-averaged p-wave duration. We found that PA-TDI was highly correlated with the signal averaged p-wave duration and was easy to perform.

In **chapter 6**, we studied the clinical determinants of a prolonged TACT using PA-TDI.³⁰ Multivariate linear regression analysis revealed that AF in history, hypertension, clinically relevant valve disease, age, and body mass were independently associated with the PA-TDI interval. The independent association between a prolonged TACT and AF could be explained by the fact that long conduction times are a condition for the development of AF and - on the other hand - AF itself may induce electrical remodeling.^{23,31} A decreased conduction velocity, leads to a shorter wavelength of the reentrant wave fronts. An increased atrial size can harbour more wave fronts of a certain size at the same time. Both will favor AF.^{32,33} Age, valve disease and hypertension are known to induce atrial fibrosis which prolongs the TACT because of “detour conduction”. Regarding the independent relation between TACT and body mass index, we hypothesized that this might be the result of obstructive sleep apnea which frequently occurs in obese patients or pericardial fat that alters inter- and intra-atrial conduction.^{34,35} The aortic diameter, left atrial dimension, mitral valve E-wave deceleration time, aortic incompetence, and mitral incompetence were the echocardiographic parameters that were independently associated with the PA-TDI interval. We theorized that this might be a reflection of (insufficiently treated) hypertension, raised left atrial pressure and diastolic left ventricular dysfunction. In the editorial comment accompanying our paper, Dr Henein is in favour of such interpretation by suggesting that the common denominator of a prolonged TACT seems to be a raised left atrial pressure.³⁶

In **chapter 7** we evaluated the role of PA-TDI to identify subjects at risk for development of new-onset AF.³⁷ We found that patients who will develop AF in the future have a longer PA-TDI interval at baseline compared to patients who remain in sinus rhythm. After adjusting for other clinical and echocardiographic parameters - known predictors of AF - PA-TDI was the strongest predictor of new-onset AF in the studied population. The longer the PA-TDI interval, the higher the incidence of new-onset AF. Table 11.1 shows a possible clinical application of the PA-TDI tool for primary prevention of AF. We found that patients with a PA-TDI interval <130 ms are unlikely to develop AF. Therefore, we hypothesized that these patients are not candidates for primary prevention. If PA-TDI <130 ms and associated cardiovascular disease is mostly absent, further management could consist of repeating PA-TDI measurement in 5 years. However, if associated cardiovascular disease is present, the risk of developing AF is moderate and upstream therapy is warranted focusing on the underlying cardiovascular disease. Typically, treatment would include angiotensin receptor blocker and if coronary or other vascular disease plays a role, also aspirin and a statin. One may in addition, consider repeating PA-TDI measurement in 2 years. Patients with a PA-TDI interval between 130-160 ms have a reasonable chance of developing AF and could benefit from primary prevention using “upstream” cardiovascular drugs irrespective of the presence of underlying heart disease. In this group PA-TDI should be monitored more frequently. In patients with very long PA-TDI (>190 ms), the risk of developing AF is very high and since such long PA-TDI usually is a harbinger of

advanced associated cardiovascular disease, one should in addition to optimizing upstream therapy also consider installing prophylactic antithrombotic treatment certainly if the virtual CHADS₂ score is 2 or higher. Post-hoc analyses showed that PA-TDI significantly increased with increasing CHA₂DS₂-VASc score. However, in the Cox regression analysis, PA-TDI outperformed CHA₂DS₂-VASc score to predict new-onset AF. For patients 'in the middle' (PA-TDI 160-190 ms) a midstream management is advocated. Obviously, future studies should evaluate the cost-benefit and cost-effectiveness of such an approach.

Table 11.1 Hypothetical clinical application of PA-TDI for primary prevention of AF.

PA-TDI	UHD*	Risk of AF	Strategy
<130 ms	No	Low	- Re-measure PA-TDI in 5 years
	Yes	Moderate	- Re-measure PA-TDI in 2 years - Start upstream therapy [#]
130–160 ms	Yes*	Moderate	- Re-measure PA-TDI in 1 year - Start upstream therapy
160–190 ms	Yes*	High	- Start upstream therapy - OAC if virtual CHADS ₂ >3 - Frequent ECG and Holter monitoring
>190 ms	Yes*	Very High	- Start upstream therapy - OAC if virtual CHADS ₂ >2 or consider subcutaneous loop recorder - Frequent ECG and Holter monitoring

UHD=underlying heart disease; [#] start, continue or intensify upstream therapy; * if PA-TDI>130 ms, underlying CV disease unavoidable; OAC=oral anticoagulation

Other investigators confirmed our findings regarding the ability of PA-TDI to predict the development of AF in different populations.³⁸⁻⁴⁰ Several studies showed that a prolonged PA-TDI interval is also associated with recurrence of AF after catheter ablation.^{41,42}

Since all these recent studies suggest that a prolonged PA-TDI is associated with the development of new-onset AF and poor outcome of rhythm control, one could hypothesize that reducing the duration of PA-TDI (or preventing its lengthening) improves primary and secondary prevention of AF. Our findings in chapter 6 suggest that early and aggressive treatment of hypertension, diastolic dysfunction, and obesity could prevent an increased PA-TDI. This hypothesis is plausible since previous studies showed that aggressive treatment of hypertension results in a reduction of the TACT. (Figure 11.1)^{43,44}

Figure 11.1 The effect of aggressive treatment of hypertension on the inter-atrial conduction time measured using the mitral Doppler signal. (based on Fuenmayor *et al.* International Journal of Cardiology. 2005, modified by Cees de Vos).

Echo-electrocardiography to characterize the substrate for atrial fibrillation during atrial fibrillation

In the third part of this thesis we studied new, non-invasive, electrophysiology-derived echocardiographic parameters to characterize patients during AF. Characterization of AF could lead to prediction of arrhythmia prognosis and response to therapy. To prevent recurrences, a large part of AF patients is treated with oral anti-arrhythmic drugs, catheter ablation near the ostia of the pulmonary veins, or AF surgery. Unfortunately, therapy does not always result in lasting sinus rhythm and we do not know to which therapy the patient will have the best response. In addition, therapy for AF can be perilous and result in complications.¹¹ Electrical cardioversion requires general anesthesia. Anti-arrhythmic drugs can cause pro-arrhythmia, heart failure and conduction disorders. AF surgery and catheter ablation near the ostia of the pulmonary veins are invasive procedures that may lead to infection, perforation, stroke, bleeding and death. As we have to avoid unnecessary exposure of the patient to the risks of therapy, we require powerful tools to assist the physician in the choice of the best individual therapy for each patient with AF.

Electrophysiology studies show that the arrhythmia is associated with shortening of atrial refractoriness as represented by a reduced atrial fibrillation cycle length (AFCL).^{23,45,46} In addition, increased dispersion of refractoriness as well as heterogeneity of conduction, prolonged conduction times, and fractionation of intracardiac atrial electrograms are common findings in patients with AF.⁴⁷⁻⁴⁹ We

believe that these parameters representing atrial remodeling, may help to predict arrhythmia prognosis and response to therapy. Recent studies found a strong temporal correlation between atrial mechanical contraction assessed by tissue Doppler imaging (TDI) and the electrical fibrillatory cycle length assessed by the intracardiac electrogram.⁵⁰

In **chapter 8** we present the concept of atrial fibrillatory wall motion as determined by tissue velocity echocardiography. Tissue velocity imaging (TVI) is a relatively new echocardiographic technique employed for non-invasive quantification and timing of local myocardial wall motion.⁵¹ The technique is derived from tissue Doppler imaging and yet the basic principles are similar. However TVI enables to record myocardial wall motion patterns at several myocardial locations simultaneously.

We performed TVI echocardiography in two patients: the first patient had a non-remodeled left atrium and the other patient had a remodeled atrium. The recordings of the atrial fibrillatory wall movements showed a 4 times lower velocity in the remodeled compared to the non-remodeled left atrium. We hypothesized that this may relate to atrial contractile failure or higher atrial afterload. In addition to that, the frequency of the fibrillating myocardium was higher in the remodeled atrium, which possibly reflects a shorter atrial refractory period. **Chapter 9** develops these notions further. The study presented therein shows that echocardiographic TVI of the left and right atrial fibrillatory wall motion closely correlates to electrophysiological parameters during AF. We found a strong correlation between the mechanical fibrillation cycle length determined with tissue velocity echocardiography (AFCL-tvi) and the electrical atrial fibrillation cycle length determined during electrophysiology study (AFCL-egm). In addition, electrophysiological AF type was associated with specific TVI patterns. With increasing electrophysiological complexity, the AFCL-tvi shortened, the AFCL-tvi variability increased and the AFV-tvi decreased. The morphology of the atrial electrograms and duration of the AFCL-egm provides valuable information in patients with AF regarding prognosis and response to therapy.⁵²⁻⁵⁵ Therefore, we strongly believe that TVI of the atrial fibrillatory wall movement may enable prediction of prognosis and response to therapy in patients with AF. In **Chapter 10** we prospectively evaluated the relation between AFCL-tvi, AFV-tvi and success of ECV in patients with AF. We found that higher atrial fibrillatory wall velocities and longer AFCLs determined by echocardiography are associated with acute success of ECV and long term maintenance of sinus rhythm. We hypothesized that to improve outcome, prophylactic antiarrhythmic drugs may be considered including pretreatment before ECV in patients with shorter AFCL-tvi or lower AFV-tvi. Taken together, our data suggest that non-invasive assessment of electrophysiological, functional and structural atrial characteristics using TVI echocardiography may be used to predict success of ECV and long term maintenance of sinus rhythm in patients with persistent AF. However, further studies are needed to show that refining our AF diagnostics using TVI will indeed enhance efficiency of rhythm control in persistent AF.

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Summary
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Summary

The general introduction of this thesis (**chapter 1**) describes the background of atrial fibrillation (AF), explains why it is important to screen patients for atrial fibrillation, pictures the potential benefits of predicting AF progression to more sustained forms and predicting response to therapy in patients who already have the arrhythmia.

AF is the most common cardiac arrhythmia in the world. Its prevalence increases considerably with advancing age. In people older than 80 years, almost 1 out of 10 has AF. Due to aging of the “baby-boom generation” and the fact that people get older in general, it is expected that the number of patients with AF will increase tremendously within the next decades. AF may result in life-threatening complications such as ischemic stroke and heart failure. Therefore, there is a need for primary prevention by screening to detect patients at risk for the development of AF. In patients who already developed AF, knowing the factors causing progression of AF from paroxysmal to more persistent forms is essential. Treating reversible causes of AF progression may prevent the progression to sustained forms refractory to therapeutic interventions. In addition to that, we require powerful tools to predict individual response to therapy, as we have to avoid unnecessary exposure of the patient to the risks of therapy.

In the first part of this thesis, we evaluated the role of clinical parameters to characterize AF. A better characterization of AF using clinical parameters may improve treatment of the arrhythmia. In **chapter 2**, we studied the clinical characteristics and management of patients with paroxysmal AF associated with autonomic triggers. We found an autonomic trigger pattern in 33% of all patients with paroxysmal AF in the Euro Heart Survey. It is important to classify these patients correctly since successful management of autonomic AF may depend on its recognition. Our data suggest that beta-blocking drugs, sotalol, digitalis and propafenone should be avoided in vagal AF since they may exacerbate the episodes of AF. In **Chapters 3 and 4** we studied AF progression in two different cohorts. Approximately 15% of the patients had AF progression in one year. In clinical practice, one can discriminate three clinical AF types: paroxysmal AF (the episodes of the arrhythmia terminate spontaneously), persistent AF (the episodes are not self-terminating), and permanent AF (the physician decides that further attempts to restore normal sinus rhythm are useless). We found that heart failure, previous stroke or TIA, COPD, hypertension, and age were independent predictors of AF progression. We developed a new simple prediction rule to estimate the probability of AF progression in patients with paroxysmal AF: the HATCH score. Besides heart failure and hypertension, treatment strategy (rate- versus rhythm-control) was found to be an independent predictor of AF progression in the RecordAF population.

In the second part of this thesis we studied new, non-invasive, electrophysiology-derived echocardiographic parameters to identify patients vulnerable for the

development of AF. We believe that prediction of new-onset AF enables to start adequate therapy on time reducing the development of AF-related complications. The total atrial conduction time or TACT (the total time required for atrial electrical activation) is an important electrophysiological parameter. The longer TACT is, the higher the risk of developing AF. In **chapter 5** we validated a new echocardiographic technique to estimate the TACT using pulsed-wave tissue Doppler echocardiography, namely PA-TDI. In **chapter 6**, we studied the clinical and echocardiographic determinants of a prolonged TACT using PA-TDI in a large population. AF in history, hypertension, valve disease, age, body mass, diastolic dysfunction and enlarged left atrium and aortic root dimensions were independently associated with the PA-TDI interval. In **chapter 7** we evaluated the role of PA-TDI to identify subjects at risk for development of new-onset AF. PA-TDI was the strongest predictor of new-onset AF in the studied population. The longer the PA-TDI interval, the higher the incidence of new-onset AF. One could hypothesize that reducing the duration of PA-TDI (or preventing its lengthening) might improve primary and secondary prevention of AF.

In the third part of this thesis we studied new, non-invasive, electrophysiology-derived echocardiographic parameters to characterize patients during AF. As we have to avoid unnecessary exposure of the patient to the risks of therapy, we require powerful tools to determine to which therapy the patient is most likely to respond. Electrophysiology studies show that AF is associated with shortening of atrial refractoriness as represented by a reduced atrial fibrillation cycle length (AFCL). We believe that these parameters representing atrial remodeling, may help to predict arrhythmia prognosis and response to therapy. In **chapter 8** we present the concept of atrial fibrillatory wall motion as determined by tissue velocity echocardiography. Tissue velocity imaging (TVI) is a relatively new echocardiographic technique employed for non-invasive quantification and timing of local myocardial wall motion. **Chapter 9** develops these notions further. We show that the atrial fibrillatory wall motion detected with echocardiographic TVI of the left and right atrial fibrillatory wall motion closely correlates to electrophysiological parameters during AF such as AFCL. In **Chapter 10** we prospectively evaluated the relation between the atrial fibrillatory wall motion detected with echocardiographic TVI and success of electrical cardioversion (ECV) in patients with AF. We found that higher atrial fibrillatory wall velocities and longer AFCLs determined by echocardiography are associated with acute success of ECV and long term maintenance of sinus rhythm. Our data suggest that non-invasive assessment of electrophysiological, functional, and structural atrial characteristics using TVI echocardiography may be used to predict success of ECV and long term maintenance of sinus rhythm in patients with persistent AF.

Samenvatting

Boezemfibrilleren of atriumfibrilleren (AF) is de meest voorkomende hartritmestoornis ter wereld. De ritmestoornis ontstaat door een soort elektrische storing in de boezems van het hart, waardoor deze niet meer normaal kunnen samentrekken maar fibrilleren. Hoe ouder men is, hoe groter de kans op het ontwikkelen van AF. Bij patiënten boven de 80 jaar oud heeft zelfs 1 op de 10 AF. De ritmestoornis kan tot levensbedreigende complicaties leiden zoals een beroerte of hartfalen. Daarom is het essentieel om te kunnen voorspellen wie AF zal gaan ontwikkelen in de toekomst zodat behandeling vroegtijdig gestart kan worden. Als een patiënt eenmaal AF heeft ontwikkeld, is het belangrijk om te weten bij welke patiënt een “verergering” van de ritmestoornis te verwachten valt en of een behandeling zal aanslaan of niet.

In dit proefschrift wordt een nieuwe hartecho meting beschreven (PA-TDI) die bij cardiologische patiënten duidelijk gerelateerd is aan het ontwikkelen van AF. Hoe langer PA-TDI, hoe groter de kans dat een patiënt AF zal ontwikkelen. Ook is gekeken welke aandoeningen er voor zorgen dat deze PA-TDI meting langer wordt. Wellicht dat het agressief behandelen van deze aandoeningen, verlenging van PA-TDI kan voorkomen en daarmee ook het ontwikkelen van AF in de toekomst zou kunnen voorkomen.

We hebben factoren onderzocht die een aanval van AF kunnen uitlokken en zogenaamde autonome patronen hierin herkend. Deze autonome patronen kunnen ontstaan wanneer een bepaald deel van het zenuwstelsel uit balans raakt. We laten in dit proefschrift zien dat het belangrijk is om deze patronen te herkennen, omdat bepaalde min of meer standaard behandelingen bij AF dan beter vermeden kunnen worden om verergering van AF type te voorkomen. Er zijn 3 verschillende klinische AF typen: paroxysmaal (enkel korte aanvallen van de ritmestoornis die spontaan over gaan), persisterend (aanvallen duren langer en gaan niet vanzelf over) en permanent (de arts beslist dat pogingen om normaal sinus ritme te herstellen geen zin meer hebben en de ritmestoornis wordt geaccepteerd). We hebben in dit proefschrift gekeken naar factoren die aan progressie (of verergering) van het AF type gerelateerd zijn. Op basis hiervan is een score ontwikkeld (de HATCH score) die kan voorspellen hoe groot de kans is dat een patiënt met paroxysmaal AF een verergering van AF type ondergaat.

Daarnaast is het van belang om de beste individuele behandelstrategie te kiezen. Immers, alle verschillende behandelingen die kunnen worden toegepast, kunnen weer bijwerkingen en complicaties geven. Het is daarom belangrijk om patiënten zo adequaat mogelijk te behandelen zonder ze bloot te stellen aan de gevaren van zinloze behandelingen. In het laatste deel van het proefschrift, worden enkele hartecho metingen beschreven die kijken naar de frequentie en snelheid van het bewegen van

de boezems. We hebben gevonden dat deze echo metingen sterk gerelateerd zijn aan de mate van elektrische storing in de boezems en daardoor zou kunnen aangeven hoe ver gevorderd de ritmestoornis is en of een bepaalde behandeling kans van slagen heeft.

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Ik ben dankbaar dat ik tijdens mijn promotietraject kennis heb mogen maken met de verschillende aspecten van wetenschappelijk onderzoek. Ik heb in deze periode uiteraard veel geleerd maar ook zeker veel plezier gehad. Er zijn vele mensen die mij in de afgelopen jaren hierbij hebben geholpen. Het is onmogelijk om iedereen hier afzonderlijk te noemen. Ik dank alle patiënten die hebben deelgenomen aan mijn projecten, mijn begeleiders voor hun inspirerende rol en alle mogelijkheden die zij voor mij hebben gecreëerd, collega-onderzoekers voor de fijne samenwerking en de afleiding waarvoor zij hebben gezorgd, mijn lieve vrienden en familie voor hun support en natuurlijk in het bijzonder mijn vrouw Judith, de allerleukste vrouw die er bestaat.

Curriculum Vitae

Cees de Vos was born the 20th of October 1980 in Liempde, the Netherlands. After completing secondary school at Lycée Saint Adrien in Villeneuve d'ascq (France) in 1999, he started his medical training at Maastricht University. As a medical student, he became involved in professor Crijns's research group at the department of Cardiology in Maastricht University Medical Center in 2003. After obtaining his medical degree in 2005, he became a PhD fellow under supervision of Prof. dr. HJGM Crijns and dr. RG Tieleman focussing on the clinical management of patients with atrial fibrillation and new echocardiographic parameters to characterize patients with atrial fibrillation. He was allowed to present his work on many occasions at large international congresses. His cardiology training at Maastricht University Medical Center, guided by Prof. dr. HJGM Crijns and dr. EC Cheriex, started in 2009 with 2 years of Internal Medicine at the Orbis Medical Center in Sittard under supervision of dr. BJ Looij. In 2012 followed one year of training at Viecuri Medical Center in Venlo under supervision of dr. JG Meeder. Presently, he is completing his Cardiology training in Maastricht University Medical Center.

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Valorisatie

Relevantie

Gezien de dubbele vergrijzing zal het aantal patiënten met atriumfibrilleren (AF) enorm toenemen de komende jaren. De meest beruchte complicaties van AF, herseninfarct en hartfalen, zijn aandoeningen die afschuwelijke gevolgen hebben voor de patiënt maar ook resulteren in hoge kosten binnen de gezondheidszorg. In dit proefschrift zijn een aantal klinische en echocardiografische parameters beschreven die er voor kunnen zorgen dat het optreden van AF beter kan worden voorspeld en AF gerichter kan worden behandeld. Dit zou het aantal complicaties die voorvallen bij AF kunnen reduceren. Daarnaast kunnen deze “tools” helpen bij het selecteren van de juiste behandeling voor de individuele patiënt. Beiden kunnen tot een kostenbesparing leiden.

Doelgroepen

De onderzoeksresultaten die gerapporteerd zijn in dit proefschrift kunnen van betekenis zijn voor patiënten en behandelend artsen (cardiologen en huisartsen). Wat de patiënten betreft zijn de beschreven resultaten met name toepasbaar bij patiënten die zich presenteren op een polikliniek of afdeling Cardiologie. Daarnaast zouden patiënten in de huisartsenpraktijk met een reeds wat verhoogde a priori kans voor het ontwikkelen van AF (bijvoorbeeld vanaf de leeftijd van 65 jaar of bij bepaalde onderliggende aandoeningen) kunnen profiteren van de bevindingen beschreven in dit proefschrift.

Activiteiten/Producten

Een aantal klinische en echocardiografische parameters beschreven in dit proefschrift zouden kunnen worden opgenomen in een screeningsproces, bijvoorbeeld screening om patiënten die in de toekomst AF zullen ontwikkelen vroegtijdig te detecteren, screening naar progressie van AF indien de ritmestoornis reeds aanwezig is en screening voor de optimale therapie voor de individuele patiënt.

Innovatie, Planning & Realisatie

Op dit moment is de screening voor AF nog niet toereikend. AF wordt vaak te laat herkend. Een herseninfarct of hartfalen zijn dan de eerste uiting van de ritmestoornis. Daarnaast is de behandeling van de individuele patiënt met AF nog te vaak het resultaat van “trial and error”. De klinische en echocardiografische parameters beschreven in dit proefschrift zouden kunnen bijdragen aan een adequatere screening en “tailored therapy”. Deze “tools” zouden eventueel kunnen worden opgenomen in huidige screening methoden in de huisartspraktijk of een centrum voor 1,5 lijnszorg.

In het ziekenhuis zou men het standaard echo protocol kunnen uitbreiden aangezien alle patiënten met AF ten minste 1 maar vaak meerdere echocardiogrammen ondergaan. De progressie score, het autonome patroon herkenning en echo metingen zouden kunnen worden opgenomen in het ziekenhuis EPD en bij elke bezoek worden geëvalueerd. De behandelend arts kan dan deze parameters consulteren om een optimaal behandelplan te maken voor de patiënt.