



Brief Report

Cardiac Remodeling and Diastolic Dysfunction in Paroxysmal Atrial Fibrillation

Nathalie Noirclerc¹, Olivier Huttin^{1,*}, Christian de Chillou¹ , Christine Selton-Suty¹, Laura Fillipetti¹, Jean Marc Sellal¹ , Erwan Bozec², Erwan Donal³, Zohra Lamiral² , Masatake Kobayashi², João Pedro Ferreira², Patrick Rossignol² and Nicolas Girerd²

¹ Department of Cardiology, University Hospital of Nancy, 54000 Nancy, France; n.noirclerc@chru-nancy.fr (N.N.); c.dechillou@chru-nancy.fr (C.d.C.); c.seltontuty@chru-nancy.fr (C.S.-S.); l.Fillipetti@chru-nancy.fr (L.F.); jm.sellal@chru-nancy.fr (J.M.S.)

² Université de Lorraine, Inserm, Centre d'Investigations Cliniques-1433 and Inserm U1116, CHRU Nancy, F-CRIN INI-CRCT, 54000 Nancy, France; e.bozec@chru-nancy.fr (E.B.); z.lamiral@chru-nancy.fr (Z.L.); mkoba3858@gmail.com (M.K.); jp.ferreira@chru-nancy.fr (J.P.F.); p.rossignol@chru-nancy.fr (P.R.); n.girerd@chru-nancy.fr (N.G.)

³ Département de Cardiologie & CIC-IT U 804, Centre Hospitalier Universitaire de Rennes, 35033 Rennes, France; e.donal@chu-rennes.fr

* Correspondence: o.huttin@chru-nancy.fr; Tel.: +33-383-15-73-55; Fax: +33-383-15-38-24

Abstract: Background: Atrial fibrillation (AF) leads to the development of cardiac remodeling/diastolic dysfunction and vice versa. We intended to determine whether cardiac remodeling/diastolic dysfunction is present at early stages of AF. Methods: We studied 175 patients with paroxysmal AF, compared with 175 matched control subjects, who had available echocardiography data to investigate the association between echocardiographic variables and AF from the STANISLAS cohort. Results: In this study (mean age 55 years; 70.3% male), patients with paroxysmal AF had greater left ventricular mass compared to matched controls ($p < 0.05$). Patients with paroxysmal AF were also likely to have larger left atrial volume and a higher peak tricuspid regurgitation velocity, leading to higher prevalence (though $<10\%$ in the AF group) of diastolic dysfunction (all- $p < 0.05$). Multivariable conditional logistic regression models showed that paroxysmal AF was significantly associated with increased left ventricular mass and left atrial enlargement (all- $p < 0.001$), but not with e' and deceleration time of E wave (all- $p > 0.1$). Conclusions: Left ventricular mass and left atrial enlargement rather than diastolic dysfunction (as evaluated by echocardiography) were associated with paroxysmal AF irrespective of body mass index, blood pressure and renal function. These findings suggest that cardiac remodeling may occur very early in the natural history of AF.

Keywords: atrial fibrillation; diastolic dysfunction; left atrial remodeling; echocardiography; heart failure



Citation: Noirclerc, N.; Huttin, O.; de Chillou, C.; Selton-Suty, C.; Fillipetti, L.; Sellal, J.M.; Bozec, E.; Donal, E.; Lamiral, Z.; Kobayashi, M.; et al. Cardiac Remodeling and Diastolic Dysfunction in Paroxysmal Atrial Fibrillation. *J. Clin. Med.* **2021**, *10*, 3894. <https://doi.org/10.3390/jcm10173894>

Academic Editor: François Roubille

Received: 5 August 2021

Accepted: 25 August 2021

Published: 30 August 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia. It is associated with incident heart failure (HF), and with its progression [1]. It has been shown to have important risk-stratification properties in the setting of primary prevention and interacts with other important CV variables such as valvular calcifications [2].

AF causes the progressive development of left atrial (LA) remodeling, particularly when AF is persistent. Patients with pre-existing structural cardiac abnormalities such as LA enlargement are likely to have a high incidence of AF, especially in subjects with cardiovascular risk factors or in patients with HF. Thus, AF and atrial enlargement are inter-related in a deleterious loop. Their common background and associated risk factors (i.e., aging, obesity, diabetes, and hypertension) suggest that they share etiologies [3]. However, which abnormalities, AF or LA enlargement, precede the other is yet to be studied. Precise cardiac phenotyping in paroxysmal AF might identify structural or functional abnormalities that precede the development of persistent AF.

2. Methods

We used echocardiographic data to investigate cardiac structure and diastolic function in 175 consecutive patients with paroxysmal AF, compared with 175 matched control subjects from the STANISLAS Cohort [4–6]. Patients with paroxysmal AF had no known or overt HF. They were enrolled in the current study after hospitalization to our center for a first AF ablation, when they were in sinus rhythm; their AF burden was not known. Controls were matched for age, sex and a history of hypertension. All subjects underwent echocardiography according to the current EAE/ASE recommendations, and diastolic dysfunction (DD) was diagnosed if ≥ 2 of 4 echocardiographic markers were abnormal [e' velocity, E/e' , LA volume index, and peak tricuspid regurgitation (TR) velocity] [4]. We also assessed the utility in this predominantly middle-aged population of the recently proposed LA volume index threshold of 25 mL/m² [7]. Statistical comparisons were performed using non-parametric tests. Associations of echocardiographic variables with paroxysmal AF were analyzed using conditional logistic regression models, taking account of the matched nature of the data, after adjustment for potential covariates including estimated glomerular filtration rate (eGFR) and body mass index (BMI).

3. Results

Patients with paroxysmal AF had higher BMI, poorer renal function, more severe dyspnea, a higher left ventricular (LV) mass, and a greater proportion of LA remodeling, compared with matched controls (Table 2). Patients with paroxysmal AF were also more likely to have DD (9.7% vs. 2.3%, $p = 0.0003$), although most Doppler diastolic parameters (lateral e' , E/e' and deceleration time) were not significantly different compared with controls. The difference in DD was associated with higher prevalence of LA volume index > 34 mL/m² and TR > 2.7 m/s in the patients with paroxysmal AF, at 40.8% and 29.3%, respectively, compared with $< 10\%$ in the controls (both, p -value < 0.05).

In multivariable analysis accounting for the matching and adjusted for BMI and eGFR, LV mass index (LVMI) [OR(95%CI) = 4.52 (2.05–9.97), $p < 0.0002$] and LA remodeling defined as LA volume index (LAVI) > 25 mL/m² [OR = 5.04 (2.55–9.99), $p < 0.0001$] were significantly associated with paroxysmal AF whereas e' and DT were not (Table 1). The current definition of DD was significantly associated with AF (Table 1) though it was present in less than 10% of patients with AF (Table 2).

Table 1. Association of diastolic dysfunction, diastolic functional parameters (e' or deceleration time) and cardiac remodeling variables (LVMI/LAVI) with paroxysmal atrial fibrillation status in multivariable conditional logistic regression models.

	OR (95% CI)	p -Value	P Interaction with Hypertension Status *
DD (Yes vs. No or indeterminate)	5.08 (1.34–19.17)	0.017	0.62
e' lateral < 10 cm/s	0.71 (0.35–1.41)	0.33	0.55
Deceleration time of E wave < 160 ms	1.18 (0.65–2.15)	0.58	0.73
LVMI > 88 (w) and > 102 g/m ² (m)	4.52 (2.05–9.97)	0.0002	0.59
LAVI > 25 mL/m ²	5.04 (2.55–9.99)	< 0.0001	0.02 **

Conditional logistic regression models were performed using the matching pairs as strata and adjusted for eGFR < 90 mL/min/1.73 m² and BMI used as a linear variable. * Interaction with hypertension could necessarily not be evaluated in conditional logistic regression as matching was partly based on hypertension status. Interaction models were consequently logistic models (i.e., not conditional models) adjusted for age, sex, hypertension status, eGFR and BMI. ** Association for LAVI > 25 mL/m² in patients with hypertension: 12.51 (4.82–32.44), $p < 0.0001$ and without hypertension: 3.05 (1.57–5.91), $p = 0.001$. Models using TR did not converge and were consequently not provided.

Table 2. Clinical and echocardiographic characteristics of controls and patients with paroxysmal atrial fibrillation.

	Control Subjects <i>n</i> = 175	Paroxysmal AF Subjects <i>n</i> = 175	<i>p</i> -Value
CLINICAL CHARACTERISTICS	Mean ± SD	Mean ± SD	
Age (years)	55 ± 11	55 ± 11	matched
Male gender (%)	123 (70.3%)	123 (70.3%)	matched
Arterial hypertension self-reported by patient	68 (38.9%)	68 (38.9%)	matched
Systolic blood pressure (mmHg)	130 ± 16	130 ± 21	0.47
BMI (Kg/m ²)	26 ± 4	27 ± 5	0.049 *
Diabetes Mellitus	15 (8.6%)	15 (8.6%)	1.00
Heart rate (bpm)	63 ± 8	64 ± 13	0.12
eGFR (MDRD mL/min/1.73 m ²)	94 ± 15	78 ± 21	<0.0001 *
Dyspnea	29 (16.7%)	47 (29.9%)	0.005
ECHO CHARACTERISTICS			
LV mass index ASE Mean (g/m ²)	77.8 ± 18.2	93.5 ± 29.9	<0.0001
>88 in women and > 102 g/m ² in men	17 (10.8%)	62 (40.8%)	<0.0001
LVEF (%)	65.9 ± 5.9	62.7 ± 7.2	<0.0001
LV End-diastolic volume (mL/m ²)	48.3 ± 12.5	47.3 ± 12.2	0.60
Left atrial volume index Mean (mL/m ²)	22.3 ± 6.8	30.45 ± 11.94	<0.0001
>34 mL/m ²	11 (6.3%)	49 (29.3%)	<0.0001
>25 mL/m ²	50 (28.7%)	93 (62.4%)	<0.0001
E/A ratio	1.1 ± 0.3	1.23 ± 0.50	0.010
Deceleration time (DT) Mean (ms)	210.0 ± 51.5	201.5 ± 65.7	0.063
<160 (ms)	27 (15.4%)	40 (23.4%)	0.10
e' lateral Mean (cm/s)	11.5 ± 3.3	11.7 ± 3.6	0.68
<10 cm/s	51 (29.3%)	33 (23.1%)	0.46
Estimated pulmonary arterial pressure (mmHg)	18.8 ± 5.3	24.8 ± 6.5	<0.0001
TR > 2.7 m/sec	2 (2.7%)	14 (17.5%)	0.014
Average E/e' Mean	9.01 ± 2.42	9.15 ± 2.61	0.42
>14	2 (1.2%)	0	—
DIASTOLIC FUNCTION CLASSIFICATION			
Normal diastolic function <50%	166 (94.9%)	138 (78.9%)	
Indeterminate (50% positive)	5 (2.9%)	20 (11.4%)	0.0003
Diastolic Dysfunction (>50%)	4 (2.2%)	17 (9.7%)	

* Further adjustment for conditional logistic regression models.

4. Discussion

In this study, only 10% of patients with paroxysmal AF had DD as defined by the recent recommendations. The independent differences in echocardiographic variables between patients with paroxysmal AF and controls were related mainly to LV/LA remodeling and increased TR, rather than to e' velocities or E/e'. Since the groups had similar hypertension status and systolic blood pressures, we could disregard any influence of increased afterload. The much higher prevalence of atrial and ventricular remodeling, rather than DD, suggests that LV hypertrophy and LA enlargement may precede persisting AF rather than being the ultimate consequence of persisting AF. This finding may be the consequence of atrial

myopathy being both the substrate and the outcome of atrial fibrillation [8]; following this line of reasoning, stress-induced atrial myopathy would be the *primum movens* of structural and electrical atrial remodeling, resulting in AF. From a pathophysiological standpoint, growing evidence exists regarding the links between atrial fibrosis and AF. Wang et al. recently showed that a mutation targeting MFAP4 attenuates LA remodeling and susceptibility to AF [9]; This result suggests that common upstream pathways are involved in both atrial fibrosis/remodeling and AF.

Yet, we did also identify LV hypertrophy as being more frequent in paroxysmal AF, which suggests that pathophysiological processes going beyond the atria are involved in a number of patients. This finding is in line with the report of Seko et al., reporting an increased prevalence of AF appears with increasingly abnormal LV remodeling patterns [10].

Our study could also support the concept that paroxysmal AF precedes the development of DD in most patients with paroxysmal AF, at least when DD is defined using the cut-points for e' velocities and E/e' proposed in the 2016 recommendations. Indeed, a minority of patients with AF had DD (<10%), which suggests that DD (as defined by the current echocardiographic definition) is hardly present in this population. The e' velocity was abnormal in only 23.1% of the patients with paroxysmal AF, and none had an abnormal E/e' index.

Although the prevalence of DD, LA remodeling and LV remodeling were different in our cohort, the associations of all three parameters with AF in the multivariable model were similar (OR ~5). Another intriguing point is the greater difference in TR velocity than in mitral flow or myocardial velocities between paroxysmal AF and controls, suggesting that an increased TR velocity might be clinically useful, albeit infrequent, and may constitute an early sign of disease rather than just a late consequence of chronically elevated LV filling pressures. A growing body of evidence suggests that, not infrequently, isolated functional TR is concomitant to AF and right atrial remodeling [11]. This further supports the early involvement of TR in the natural history of AF.

5. Strengths and Limitations

The main strengths of our study are the use of research-quality echocardiography in a community-based cohort (STANISLAS), and the refined methods (matching and adjustment) used to evaluate the association of echocardiographic variables with paroxysmal AF. However, it is a single-center study of patients referred for ablation of paroxysmal AF, who are not representative of the much broader population of all patients with AF. In addition, TR and DD could not be included in the multivariable analysis because the number of subjects with these parameters was small. We applied the most recent definition of DD, but have emphasized how changing definitions strongly influences the proportion of patients who are diagnosed as abnormal [4]. Other definitions of DD may have yield different results and further analysis should be conducted with future definition of DD. In addition, as DD goes beyond its echocardiographic definition, our results do not formally ascertain that DD is not involved in early stages of AF.

6. Conclusions

In the current study, LA enlargement and LV hypertrophy, rather than LV diastolic dysfunction, are associated with paroxysmal AF, irrespective of hypertension history, blood pressure, eGFR and BMI. We found also that very few patients with AF fulfill the current criteria for DD. These results suggest that cardiac remodeling occurs very early in the natural history of AF, before it progresses from paroxysmal to persistent AF and before the development of DD.

Author Contributions: For research articles with several authors, the following statements should be used “Conceptualization, O.H. and N.G.; methodology, N.G. and Z.L.; writing—original draft preparation, N.N.; writing—review and editing, all coauthors; supervision, O.H. and N.G. All authors have read and agreed to the published version of the manuscript.”

Funding: This study was sponsored by the Nancy CHRU and funded by the Programme Hospitalier de Recherche Clinique (PHRC), a public grant overseen by the French National Research Agency (ANR) as part of the second “Investissements d’Avenir” programme (reference: ANR-15-RHU-0004), and Contrat de Plan Etat Région Lorraine and FEDER, La Région Lorraine, and la Fondation de Recherche en Hypertension Artérielle. The authors deeply thank the entire Clinical Investigation Centre staff and collaborators all of whom are involved in the daily management of the STANISLAS cohort.

Institutional Review Board Statement: The STANISLAS study protocol were reviewed and approved by the Local Ethics Committee of CPP-Est 3, France.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the STANISLAS study.

Data Availability Statement: The data can be made available upon reasonable request to the principal investigator of the study (P.R.).

Conflicts of Interest: Rossignol reports grants and personal fees from AstraZeneca, Bayer, CVRx, Fresenius, and Novartis, personal fees from Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa, and is the cofounder of CardioRenal, a company developing a telemonitoring loop in heart failure (including potassium measurements). Girerd reports grants and personal fees from AstraZeneca, Bayer, Boehringer, Lilly, Novartis and Vifor.

References

1. Ferreira, J.P.; Santos, M. Heart failure and atrial fibrillation: From basic science to clinical practice. *Int. J. Mol. Sci.* **2015**, *16*, 3133–3147. [[CrossRef](#)] [[PubMed](#)]
2. Mazzone, C.; Cioffi, G.; Di Nora, C.; Barbati, G.; Guidetti, F.; Faggiano, P.; Gaibazzi, N.; Faganello, G.; Borca, E.C.; Di Lenarda, A. Prognostic role of cardiac calcifications in primary prevention: A powerful marker of adverse outcome highly dependent on underlying cardiac rhythm. *Int. J. Cardiol.* **2018**, *258*, 262–268. [[CrossRef](#)] [[PubMed](#)]
3. Santhanakrishnan, R.; Wang, N.; Larson, M.G.; Magnani, J.W.; McManus, D.D.; Lubitz, S.A.; Ellinor, P.T.; Cheng, S.; Vasan, R.S.; Lee, D.S.; et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. *Circulation* **2016**, *133*, 484–492. [[CrossRef](#)] [[PubMed](#)]
4. Huttin, O.; Fraser, A.G.; Coiro, S.; Bozec, E.; Selton-Suty, C.; Lamiral, Z.; Frikha, Z.; Rossignol, P.; Zannad, F.; Girerd, N. Impact of Changes in Consensus Diagnostic Recommendations on the Echocardiographic Prevalence of Diastolic Dysfunction. *J. Am. Coll. Cardiol.* **2017**, *69*, 3119–3121. [[CrossRef](#)] [[PubMed](#)]
5. Verdugo-Marchese, M.; Coiro, S.; Selton-Suty, C.; Kobayashi, M.; Bozec, E.; Lamiral, Z.; Venner, C.; Zannad, F.; Rossignol, P.; Girerd, N.; et al. Left ventricular myocardial deformation pattern, mechanical dispersion, and their relation with electrocardiogram markers in the large population-based STANISLAS cohort: Insights into electromechanical coupling. *Eur. Heart J. Cardiovasc. Imaging* **2020**, *21*, 1237–1245. [[CrossRef](#)] [[PubMed](#)]
6. Frikha, Z.; Girerd, N.; Huttin, O.; Courand, P.Y.; Bozec, E.; Olivier, A.; Lamiral, Z.; Zannad, F.; Rossignol, P. Reproducibility in echocardiographic assessment of diastolic function in a population based study (the STANISLAS Cohort study). *PLoS ONE* **2015**, *10*, e0122336. [[CrossRef](#)] [[PubMed](#)]
7. Kou, S.; Caballero, L.; Dulgheru, R.; Voilliot, D.; De Sousa, C.; Kacharava, G.; Athanassopoulos, G.D.; Barone, D.; Baroni, M.; Cardim, N.; et al. Echocardiographic reference ranges for normal cardiac chamber size: Results from the NORRE study. *Eur. Heart J. Cardiovasc. Imaging* **2014**, *15*, 680–690. [[CrossRef](#)] [[PubMed](#)]
8. Dilaveris, P.; Antoniou, C.K.; Manolakou, P.; Tsiamis, E.; Gatzoulis, K.; Tousoulis, D. Biomarkers Associated with Atrial Fibrosis and Remodeling. *Curr. Med. Chem.* **2019**, *26*, 780–802. [[CrossRef](#)] [[PubMed](#)]
9. Wang, H.; Liu, M.; Wang, X.; Shuai, W.; Fu, H. MFAP4 deletion attenuates the progression of angiotensin II-induced atrial fibrosis and atrial fibrillation. *Europace* **2021**.
10. Seko, Y.; Kato, T.; Haruna, T.; Izumi, T.; Miyamoto, S.; Nakane, E.; Inoko, M. Association between atrial fibrillation, atrial enlargement, and left ventricular geometric remodeling. *Sci. Rep.* **2018**, *8*, 6366. [[CrossRef](#)] [[PubMed](#)]
11. Utsunomiya, H.; Itabashi, Y.; Mihara, H.; Berdejo, J.; Kobayashi, S.; Siegel, R.J.; Shiota, T. Functional Tricuspid Regurgitation Caused by Chronic Atrial Fibrillation: A Real-Time 3-Dimensional Transesophageal Echocardiography Study. *Circ. Cardiovasc. Imaging* **2017**, *10*, e004897. [[CrossRef](#)] [[PubMed](#)]