

TO THE EDITOR:

Key role of long-duration cardiac rhythm monitoring in patients with sickle cell disease with atrial hyperexcitability

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Atrial arrhythmias (AAs) are frequent in adult patients with sickle cell disease (SCD) and represent an increasingly reported cause of stroke.¹⁻⁴ In line with this, a recent large-scale study underlined that stroke incidence markedly increased with age in patients with SCD in the modern era, pointing out an unmet need to develop adapted guidelines addressing aging and cardiovascular risk burden evolution in this very specific population.⁵ Previous study conducted by our team unmasked the key role of 24-hour electrocardiogram monitoring (24-hour Holter) to identify atrial hyperexcitability (AH) in patients with SCD.¹ However, the association between AH and sustained AA occurrence remains unknown. Leveraging data from Drepacoeur registry,^{1,6} this preliminary study aims to report the utility of long-duration cardiac rhythm monitoring (LDRM) in detecting sustained AAs in patients with SCD showing AH on 24-hour Holter. Early detection of sustained AAs and more specifically atrial fibrillation (AF) appears crucial for implementing therapeutic strategies to further prevent cerebrovascular complications.⁷

Between 2019 and 2023, adults with SCD were prospectively included in Drepacoeur registry for suspected cardiac involvement, as previously described.^{1,6} All patients underwent comprehensive cardiovascular evaluation in a day hospital, including clinical examination, echocardiography, 24-hour Holter, and biology workup. Only patients with homozygous SCD (sickle cell anemia [SCA]) who underwent LDRM after 24-hour Holter results were included in this preliminary report. AH on 24-hour Holter was defined by the presence of excessive supraventricular ectopic activity (≥ 720 premature atrial complexes [PACs] per 24 hours or any episodic runs of ≥ 20 PACs, according to European Heart Rhythm Association [EHRA] consensus⁸). Patients were then classified depending on LDRM indications: AH exploration or control group. The control group included patients with SCA who underwent LDRM for other reasons (eg, ventricular arrhythmias), without AH on 24-hour Holter.⁶ Written informed consent was collected, and the database was declared to the Commission Nationale de l'Informatique et des Libertés (n°7830264) and approved by the ethics committee (protocol 2013/NICB).

Regarding LDRM evaluation, external 14-day monitoring (Spiderflash; MicroPort, Shanghai, China) or internal loop recorder (ILC; Medtronic Reveal LINQ, Dublin, Ireland) was scheduled after multidisciplinary decision. AF was identified as an irregular heart rhythm without P waves lasting at least 30 seconds, according to current guidelines.⁹

The primary outcome of the study was to evaluate the incidence of AF using LDRM in patients with SCA with AH. Secondary objective was to identify factors associated with the onset of AF.

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Study data are available upon reasonable request from the corresponding author, Thomas d'Humières (thomas.dhumieres@aphp.fr).

The full-text version of this article contains a data supplement.

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Table 1. Study population description

24-h study population description							
	Participants (n = 23)		AH group (n = 13)		Control group (n = 10)		P value
Demographic and clinical data							
Age, y	53	(49- 61)	57	(51-63)	53	(49- 54)	.67
Male, n (%)	11	(48)	7	(54)	4	(40)	.51
Body mass index, kg/m ²	23.6	(19.5- 26.5)	23.0	(19.6- 24.3)	24.8	(21.9- 27.0)	.51
Systolic blood pressure, mm Hg	133	(124- 145)	131	(11- 146)	133	(127- 138)	.37
Diastolic blood pressure, mm Hg	73	(67- 86)	71	(67- 80)	78	(70- 89)	.17
Cardiovascular history, n (%)							
Heart failure	11	(48)	7	(54)	4	(40)	.51
Thromboembolic history	9	(39)	6	(46)	3	(30)	.43
Pulmonary hypertension	3	(13)	2	(15)	1	(10)	.91
Ischemic stroke or TIA history	0	(0)	0	(0.0)	0	(0)	-
Chronic kidney disease	11	(48)	6	(46)	5	(50)	.81
Treatments, n (%)							
Antithrombotic treatment	8	(35)	7	(54)	1	(10)	.03
Anticoagulation	5	(22)	4	(31)	1	(10)	
Antiplatelet therapy	3	(13)	3	(23)	0	(0)	
Beta-blockers	10	(44)	6	(46)	4	(40)	.77
Hydroxyurea	17	(74)	9	(69)	8	(80)	.56
RBC exchange transfusion	4	(17)	2	(15)	2	(20)	.77
Laboratory test							
Hemoglobin, g/dL	9.0	(8.4- 9.7)	9.0	(8.5- 9.7)	9.0	(8.4- 9.5)	.79
Leukocytes, ×10 ⁹ /L	6.9	(5.3- 9.4)	7.7	(5.3- 9.4)	6.1	(5.4- 8.9)	.54
Platelets, ×10 ⁹ /L	277	(188- 442)	318	(199- 483)	269.5	(163- 305)	.17
GFR, mL/min per 1.73 m ²	88.5	(64.5- 108.5)	92.0	(67.0- 107.0)	95.0	(74.5- 112.5)	.92
Total bilirubin, μmol/L	26.0	(20.1- 41.0)	25.8	(10.0- 46.3)	26.4	(20.2- 37.3)	.68
LDH, IU/L	363	(315- 653)	427	(315- 6;53)	358	(339- 568)	.74
TSH, mIU/L	2.4	(1.5- 3.5)	2.4	(1.6- 3.3)	2.4	(1.6- 3.4)	.88
Echocardiography data							
Indexed LV volume, mL/m ²	64.2	(48.6- 99.8)	57.5	(45.2- 99.8)	67.2	(62.3- 90.9)	.65
Indexed LV mass, mg/m ²	89.1	(80.2- 156.6)	89.1	(80.2- 127.3)	94.4	(83.2- 148.0)	.89
Cardiac output, L/min	7.2	(5.2- 8.9)	5.7	(5.0- 8.7)	7.2	(6.7- 8.6)	.38
LVEF in Simpson biplane, %	61	(55- 63)	61	(56- 63)	59	(54- 62)	.85
GLS, %	−18.5	(−21.0- −16.1)	−18.0	(−20.5- −16.8)	−18.9	(−21.5- −16.5)	.53
Indexed LA volume, mL/m ²	57	(48-69)	56	(48- 60)	60	(54- 68)	.83
TRV, m/s	2.9	(2.4- 3.2)	2.7	(2.3- 3.0)	2.9	(2.6- 3.5)	.18
24-h Holter results							
PAC, per 24 h	-		3500	(1070- 5000)	29	(17- 171)	.004
PVC, per 24 h	-		143	(45- 411)	1039	(115-2880)	.05
ESVEA, n (%)	-		13	(100)	0	(0)	<.001
LDMR data, n (%)							
14-d Holter	21	(91)	11	(85)	10	(100)	
ICM	2	(8)	2	(15)	0	(0)	
Evaluation criteria, AF detection, n (%)	6	(26)	6	(46)	0	(0)	.01

boldface values means statistically significant

ESVEA, excessive supraventricular ectopic activity; GFR, glomerular filtration rate; GLS, global longitudinal strain; ICM, insertable cardiac monitoring; LDH, lactate dehydrogenase; LV, left ventricular; LVEF, left ventricular ejection fraction; PVC, premature ventricular complex; RBC, red blood cell; TIA, transient ischemic attack; TRV, tricuspid regurgitation velocity; TSH, thyroid-stimulating hormone.

Based on Chronic Kidney Disease - Epidemiology Collaboration formula.

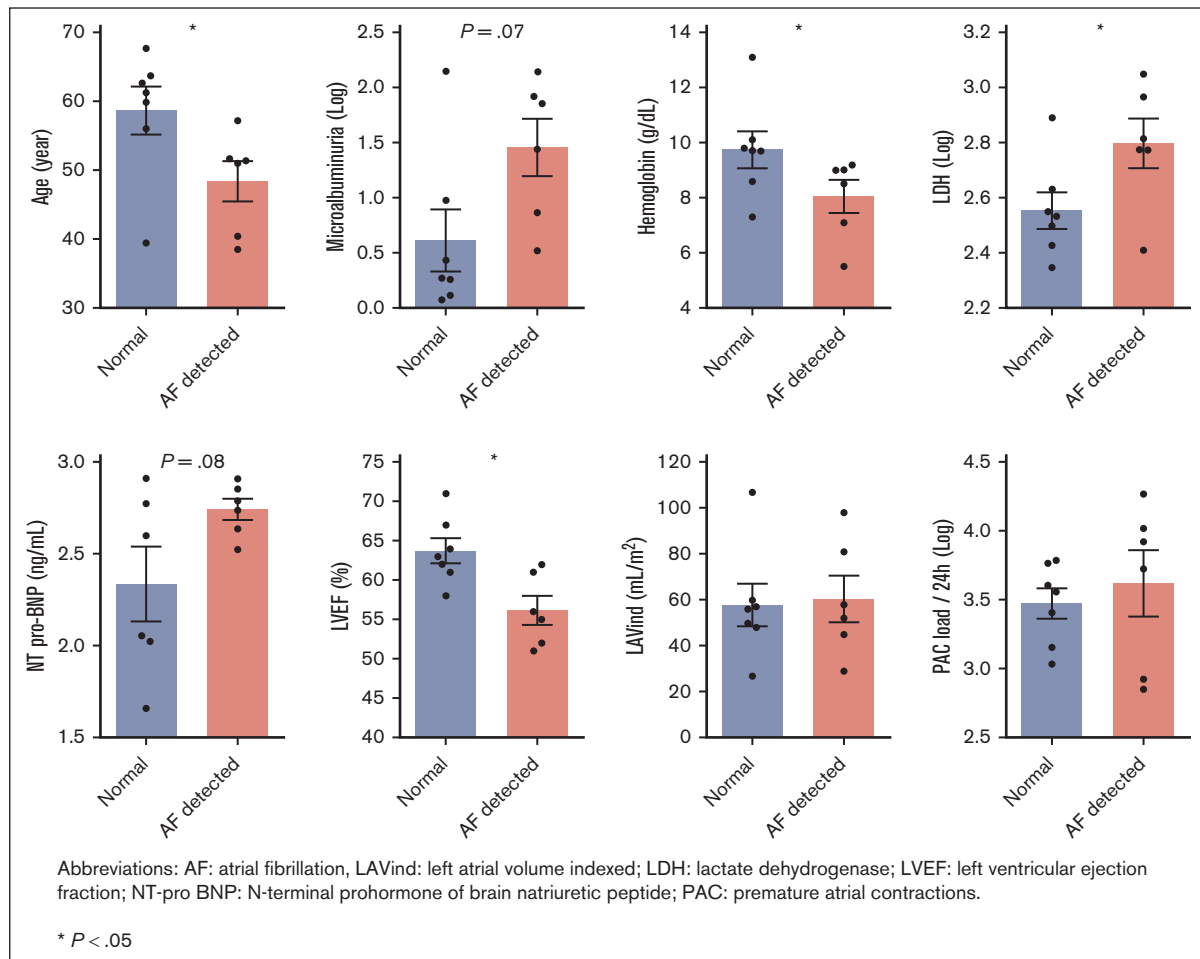


Figure 1. Predictive factors of AF using LDMR among patients presenting ESVEA, excessive supraventricular ectopic activity on 24-hour Holter.

All analyses were performed using SPSS 26 (IBM, Armonk, NY). Data are presented as percentages for categorical variables and mean $\pm$ standard deviation or median (interquartile range) for continuous variables. Comparisons between groups for continuous variables were performed using 1-way analysis of variance. The χ^2 test was used to compare dichotomous variables. A P value $< .05$ indicated statistical significance.

Overall, 254 patients with SCA were included in Drepacoeur registry.^{1,6} During the study period, 64 (25%) presented AH on 24-hour Holter, among whom 23 patients (9%) without stroke or AF history underwent LDMR and were further included in this analysis. The most common LDMR modality was 14-day Holter (91%), whereas an ILC was implanted in 2 patients. Among patients with LDMR, 13 (57%) were prescribed for AH on 24-hour Holter (AH group), whereas 10 (43%) constituted the control group. Detailed characteristics of the study population is provided in Table 1. Briefly, the median age was 53 years [49; 61], with 48% being male. Most of them were under hydroxyurea therapy (74%). Left ventricular ejection fraction was preserved for all patients, and they showed a major increase in left atrial (LA) volume (57 mL/m² [48; 69]; normal value < 34 mL/m² in the non-SCD population).¹⁰

Compared with the control group, patients showing AH on 24-hour Holter were no different in terms of demographic, biological, or echocardiography data (Table 1). They were more likely to be under antithrombotic regimen (54% vs 10%; $P = .03$), and expectedly, their PAC load per 24 hours was higher, whereas their premature ventricular complex load was lower. Strikingly, LDMR identified sustained paroxysmal AF in 6 patients with AH (46%), whereas none was detected in the control group ($P = .01$). The diagnosis further led to anticoagulation therapy initiation for thromboembolic primary prevention in 3 patients (50%). The 3 other patients were already under anticoagulation therapy for a history of venous thromboembolism. Notably, among the 2 patients with ILC, 1 was diagnosed 1 month after implantation (2 hours of AF), whereas the other experienced weekly AH episodes that were difficult to classify, without a formal AF diagnosis.

Among the AH group, those diagnosed with AF were younger (60 ± 9 vs 48 ± 7 years; $P = .03$) and had a deeper hemolytic anemia (lower hemoglobin and higher lactate dehydrogenase plasma level), along with more important cardiorenal impairment (lower left ventricular ejection fraction along with a trend to higher N-terminal prohormone of brain natriuretic peptide and microalbuminuria; Figure 1).

In this study, LDRM diagnosed sustained AF in >45% of patients with SCA presenting AH on 24-hour Holter, whereas none was observed in the control group. These results are in line with previous work showing that early LA dilation along with the development of myocardial fibrosis, low-grade systemic inflammation, and frequent hydroelectrolytic disorders could act as arrhythmogenic triggers in patients with SCA.¹

These data strongly support the screening management strategy recently suggested by our team (supplemental Figure 1).^{1,3} We underline in the latter work the crucial diagnosis value of 24-hour Holter to diagnose AH in patients with SCA who are older than >47 years or those showing major LA remodeling (>55 mL/m²), with a Positive Predictive Value 33% and a Negative Predictive Value of 92%. However, the association between AH and the occurrence of sustained AF episodes in daily life remains a central question to further refine the management of these patients. To our knowledge, this is the first report exploring the value of LDRM in selected patients with SCD to enhance the detection of sustained AA. The alarming paroxysmal AF prevalence observed (46%) in patients identified at risk vs its absence among the control group underlines the urgent need for systematic and standardized rhythm monitoring. Early diagnosis of paroxysmal AF could lead to a timely introduction of anticoagulation and antiarrhythmic therapies, potentially reducing cardioembolic stroke and heart failure burden among these young patients.^{3,5,9,11,12}

In patients showing AH on 24-hour Holter, sustained AF diagnosis using LDRM was associated with younger age, deeper anemia with higher lactate dehydrogenase level, and cardiorenal impairment, a known complication of chronic intravascular hemolysis.¹³⁻¹⁵ We previously showed that LA dilation was associated with AH on 24-hour Holter, but interestingly, among AH group, LA volume was not predictive of AF occurrence. These data need to be tempered, given the low number of patients, but suggest the existence of a multihit mechanism, in which LA remodeling plays an important part in AH development, alongside precipitating factors inherent to patients with hemolytic anemia (ie, chronic inflammation, atrial fibrosis, or hypoxemia), ultimately leading to AF.^{6,16-20}

This study further calls into question the value of starting early anticoagulation for primary prevention in these patients, who may have a relatively low AF burden, a strategy with well-described limitations in the general population.^{9,21} However, patients with SCD have a particularly high thrombotic risk profile, with an excess risk of stroke history not related to cerebral vasculopathy in patients with AH.^{1,3,7,22,23} The low power of this study does not allow for us to provide a clear therapeutic course of action but offers sufficient data to support the initiation of a multicenter therapeutic trial regarding the modality and timing of anticoagulation therapy in this unique population.

Long-duration rhythm monitoring appears to be a core screening exploration tool for diagnosing paroxysmal AF in patients with SCA with AH on 24-hour Holter. Deployment of this screening management at a larger scale requires further evaluation but offers the potential for promising strategies to reduce the burden of cerebrovascular complications in patients with SCA.

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