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Biatrial arrhythmogenic substrate in patients with hypertrophic obstructive cardiomyopathy

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) in patients with hypertrophic obstructive cardiomyopathy (HOCM) may be caused by a primary atrial myopathy. Whether HOCM-related atrial myopathy affects mainly electrophysiological properties of the left atrium (LA) or also the right atrium (RA) has never been investigated.

OBJECTIVE The purpose of this study was to characterize atrial conduction and explore differences in the prevalence of conduction disorders, potential fractionation, and low-voltage areas (LVAs) between the RA and LA during sinus rhythm (SR) as indicators of potential arrhythmogenic areas.

METHODS Intraoperative epicardial mapping of both atria during SR was performed in 15 HOCM patients (age 50 ± 12 years). Conduction delay (CD) and conductin block (CB), unipolar potential characteristics (voltages, fractionation), and LVA were quantified.

RESULTS Conduction disorders and LVA were found scattered throughout both atria in all patients and did not differ between the RA and LA (CD: 2.9% [1.9%–3.6%] vs 2.6% [2.1%–6.4%], $P = .541$; CB: 1.7% [0.9%–3.1%] vs 1.5% [0.5%–2.8%], $P = .600$; LVA: 4.7% [1.6%–7.7%] vs 2.9% [2.1%–7.1%], $P = .793$). Compared to the RA, unipolar voltages of single potentials (SPs) and fractionated potentials (FPs) were higher in the LA (SP: P75 7.3 mV vs 10.9 mV; FP: P75 2.0 mV vs 3.7 mV). FP contained low-voltage components in only 18% of all LA sites compared to 36% of all RA sites.

CONCLUSION In patients with HOCM, conduction disorders, LVA, and FP are equally present in both atria, supporting the hypothesis of a primary atrial myopathy. Conceptually, the presence of a biatrial substrate and high-voltage FP may contribute to failure of ablative therapy of atrial tachyarrhythmias in this population.

KEYWORDS Atrial fibrillation; Atrial myopathy; Hypertrophic obstructive cardiomyopathy; Mapping; Myectomy

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Introduction

With an incidence surpassing 20%, atrial fibrillation (AF) is the most common atrial tachyarrhythmia in patients with hypertrophic obstructive cardiomyopathy (HOCM) and has a substantial impact on quality of life.[1] Patients with HOCM often tolerate episodes of AF poorly. Unfortunately, the treatment of AF in HOCM patients is a challenging task. Maintenance of sinus rhythm (SR) by catheter ablation therapy seems to be less effective in these patients compared to other populations.[2] A recent meta-analysis showed that after multiple catheter ablation procedures, freedom from atrial arrhythmia is only 56.1% at 3-year follow-up in this population.[2]

From a pathophysiological perspective, the high incidence of AF and low success rates of catheter ablation can be attributed to a complex and extensive arrhythmogenic substrate. It is generally assumed that HOCM patients have an underlying

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primary atrial cardiomyopathy—beyond secondary changes due to left atrial (LA) pressure and volume overload—which affects both atria.[3–5] Atrial myocyte hypertrophy and interstitial fibrosis already are present at an early age[3] and can be found in both the right atrium (RA) and LA, supporting the concept of a primary atrial myopathy.[4] The impact of structural alterations on atrial electrophysiological properties in HOCM patients is unknown. For example, atrial hypertrophy may increase potential voltages and intra-atrial conduction velocities (CVs) due to a decrease in intercellular resistances but also could decrease potential voltages and CV due to the nonuniform distribution of gap junctions.[5,6]

There is a paucity of mapping studies performed in HOCM patients, and electrophysiological properties including potential arrhythmogenic substrates in the atria in this population have not been investigated.[7] Previous mapping studies performed in patients with and without coronary artery and/or valvular heart disease demonstrated that intraoperative high-resolution mapping of the atria during SR can identify electropathology related to AF development and maintenance.[8–10]

The aim of this study was to characterize atrial conduction in HOCM patients by performing atrial high-resolution epicardial mapping before septal myectomy. In addition, differences in the prevalence of conduction disorders and potential morphology between the RA and LA during SR were explored as indicators of potential arrhythmogenic areas.

Methods

Study population

The study population consisted of 15 successive adult patients with HOCM undergoing elective surgical septal myectomy at Erasmus Medical Center Rotterdam between November 2020 and January 2022. Exclusion criteria included previous ablative therapy or cardiac surgery, history of AF, or atrial pacemaker leads. All patients provided written informed consent. The study was approved by the institutional medical ethical committee (MEC-2014-393). Patient characteristics (eg, age, medical history, and cardiovascular risk factors) were obtained from the patient's medical record.

Abbreviations

AF: atrial fibrillation

CB: conduction block

CD: conduction delay

cCDCB: continuous conduction delay conduction block

CV: conduction velocity

FP: fractionated potential

HCM: hypertrophic cardiomyopathy

HOCM: hypertrophic obstructive cardiomyopathy

LA: left atrium

LDP: long double potential

LVA: low-voltage area

RA: right atrium

SDP: short double potential

SP: single potential

SR: sinus rhythm

Baseline and clinical parameters

Data were retrieved from medical records and included demographic characteristics, implantable cardioverter-defibrillator therapy, comorbidities, pharmacologic therapy before myectomy, genetic testing, and echocardiographic parameters. Echocardiographic parameters included atrial dimensions, systolic and diastolic ventricular function, and valvular dysfunction. Cardiac rhythms of all patients were continuously recorded from the moment of arrival on the surgical ward to the end of the fifth postoperative day using bedside monitors (Draeger Infinity™, Draeger, Lübeck, Germany). Automatic algorithms were used to detect early postoperative AF episodes lasting >30 seconds, and all episodes were manually cross-checked. Patients who underwent myectomy were routinely seen at the outpatient clinic at 3 months and 1 year postoperatively and underwent telemonitoring at 6 months. During this visit, an electrocardiogram was obtained, and based on patients' complaints, an additional Holter monitoring was performed.

Epicardial mapping

Epicardial high-resolution mapping during SR was performed before commencement of extracorporal circulation.[11] A temporal unipolar epicardial pacemaker wire attached to the RA appendage served as a reference electrode, and the indifferent electrode was connected to subcutaneous tissue of the thoracic cavity.

Epicardial mapping was performed with a 192-electrode array (electrode diameter 0.45 mm, interelectrode distances 2.0 mm). Mapping was conducted by shifting the electrode array in a systematic order along predefined areas of the RA and LA, as previously described in detail.[11]

From every mapping site, signals were recorded for 5 seconds during SR, including a surface electrocardiographic lead, a calibration signal of 2 mV and 1000 ms, a bipolar reference electrogram, and all unipolar epicardial electrograms. Data were stored on a hard disk after amplification (gain 1000), filtering (bandwidth 0.5–400 Hz), sampling (1 kHz), and analog-to-digital conversion (16 bits).

Data analysis

Unipolar electrograms were semiautomatically analyzed using custom-made software, as previously described in detail.[11] Electrograms with injury potentials, recording sites with ≥25% excluded or missing electrograms, and atrial extrasystoles were excluded from analysis.

The steepest negative slope of an atrial potential was marked as the local activation time. All annotations were manually checked by 2 investigators. Potentials were classified as single potentials (SPs; 1 deflection) and fractionated potentials (FPs), including short double potentials (SDPs; interval between deflections <15 ms), long double potentials (LDPs; deflection interval ≥15 ms), or FPs (≥3 deflections). The voltage of each unipolar potential type was defined as the peak-to-peak amplitude of the steepest deflection.[12]

In line with previous mapping studies, the proportion of potentials with an amplitude <1.0 mV was defined as low-voltage area (LVA) during SR.[13] Local effective CV was computed from local activation times using discrete velocity

vectors.[14] The variance in CV is defined as the difference between the 5th and 95th percentiles (*Δ P95 – P5*).[15] Conduction delay (CD) and conduction block (CB) were defined as the difference in local activation times between 2 adjacent electrodes of 7–11 ms and ≥12 ms, respectively.[9,10] Uninterrupted CD and CB lines were defined as continuous conduction delay and block (cCDCB) lines. Both the amount (%) and lengths (mm) of CD, CB, and cCDCB lines were calculated.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 24 software (IBM Corp., Armonk, NY). All data were tested for normality. Normally distributed continuous variables are given as mean ± SD, and skewed variables as median [interquartile range]. Differences between RA and LA were compared using the Mann-Whitney *U* test or Student *t* test. $P < .05$ was considered significant.

Results

Patient characteristics

Clinical characteristics of the study population (N = 15) are summarized in Table 1. All patients (mean age 50 ± 13 years; 5 male [33%]) underwent surgical myectomy and mitral valve repair. All patients presented with normal right and left ventricular systolic function and impaired left ventricular diastolic function. Most of the patients (87%) had LA dilation. Significant tricuspid valve regurgitation was absent in all patients. One patient (7%) experienced a single event (<24 hours) of paroxysmal AF 3 years before surgical myectomy in the setting of a severe coronavirus disease (COVID) infection. The other patient did not have any documented AF episodes before surgical myectomy. Five patients (33%) developed *de novo* postoperative AF. None of the patients had documented AF episodes during 1-year follow-up after myectomy. Genetic testing revealed pathogenic or likely pathogenic variants in 10 patients (83%), and 2 patients (17%) had negative genetic test results for HOCM (Table 1). Three patients objected to genetic testing.

Table 1 Characteristics of HOCM patients (N = 15)

Age (y)	50 ± 13
Male	5 (33)
Left ventricular systolic function	
Normal	15 (100)
Left ventricular diastolic dysfunction	
Grade 1	3 (20)
Grade 2	11 (73)
Grade 3	1 (7)
Right ventricular systolic function	
Normal	15 (100)
MV regurgitation	
Mild	9 (60)
Moderate–severe	6 (40)
TV regurgitation	0 (0)
Left atrial dilation	13 (87)
Right atrial dilation	0 (0)
History of AF	
Paroxysmal	1 (7)
ICD	3 (20)
Pathogenic or likely pathogenic variants	
Negative	2 (17)
MYH7	5 (42)
MYBPC3	4 (33)
RAF1	1 (8)
ACE inhibitor/ARB	3 (20)
Antiarrhythmic drug	
Class I	0 (0)
Class II	11 (73)
Class III	0 (0)
Class IV	3 (20)
Digoxin	0 (0)

Values are given as n (%) or mean (± standard deviation).
ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; HOCM = hypertrophic obstructive cardiomyopathy; ICD = implantable cardioverter-defibrillator; MV = mitral valve; TV = tricuspid valve.

Mapping data

SR cycle length ranged from 830 to 1252 ms and was on average 1015 ± 148 ms. A total of 58,897 atrial potentials (RA 38,001; LA 20,896) were recorded from a median of 756 [interquartile range: 710–943] recordings sites across both atria.

Regional differences in conduction heterogeneity

Figure 1 (top) shows interindividual variations in the location and severity of conduction disorders within the atria of 3 HOCM patients. These maps demonstrate that (1) conduction disorders are also extensively present outside the pulmonary vein area; (2) the LA appendage may be more affected than the LA posterior wall; and 3) the RA can be severely affected as well. In 1 example patient (Figure 1, top left), the RA is more affected than the LA.

Lines of CD, CB, and cCDCB were found in in both atria of all 15 patients (Figure 1, bottom). In the entire study population, the amount of conduction disorders did not differ between the LA and RA (LA vs RA CD: 2.9% [1.9%–3.6%] vs 2.6% [2.1%–6.4%], $P = .54$; CB: 1.7% [0.9%–3.1%] vs 1.5% [0.5%–2.8%], $P = .60$; cCDCB: 4.6% [3.6%–6.2%] vs 4.8% [3.4%–7.5%], $P = .63$) (Table 2).

Lengths of the longest line of CD, CB, and cCDCB in the RA were 15 [11–21] mm, 23 [19–42] mm, and 45 [25–57] mm, respectively, which did not differ from the lengths of the longest lines of CD, CB, and cCDCB in the LA (CD: 16 [12–25] mm; CB 13 [6–26] mm; cCDCB 31 [21–37] mm; $P > .05$).

Figure 2 shows the relative frequency distribution histograms of CV for the RA and LA separately. Although there were no differences in localized areas of conduction disorders (CB, CD, and cCDCB) between LA and RA, median CV was significantly higher in the LA (96.6 [87.8–100.0] cm/s vs 88.2 [84.6–91.7] cm/s; $P = .011$). Also, there was a larger proportion of areas with either low CV or high CVs, resulting in a larger variance of CV in the LA (134.2 cm/s) compared to the RA (109.5 cm/s).

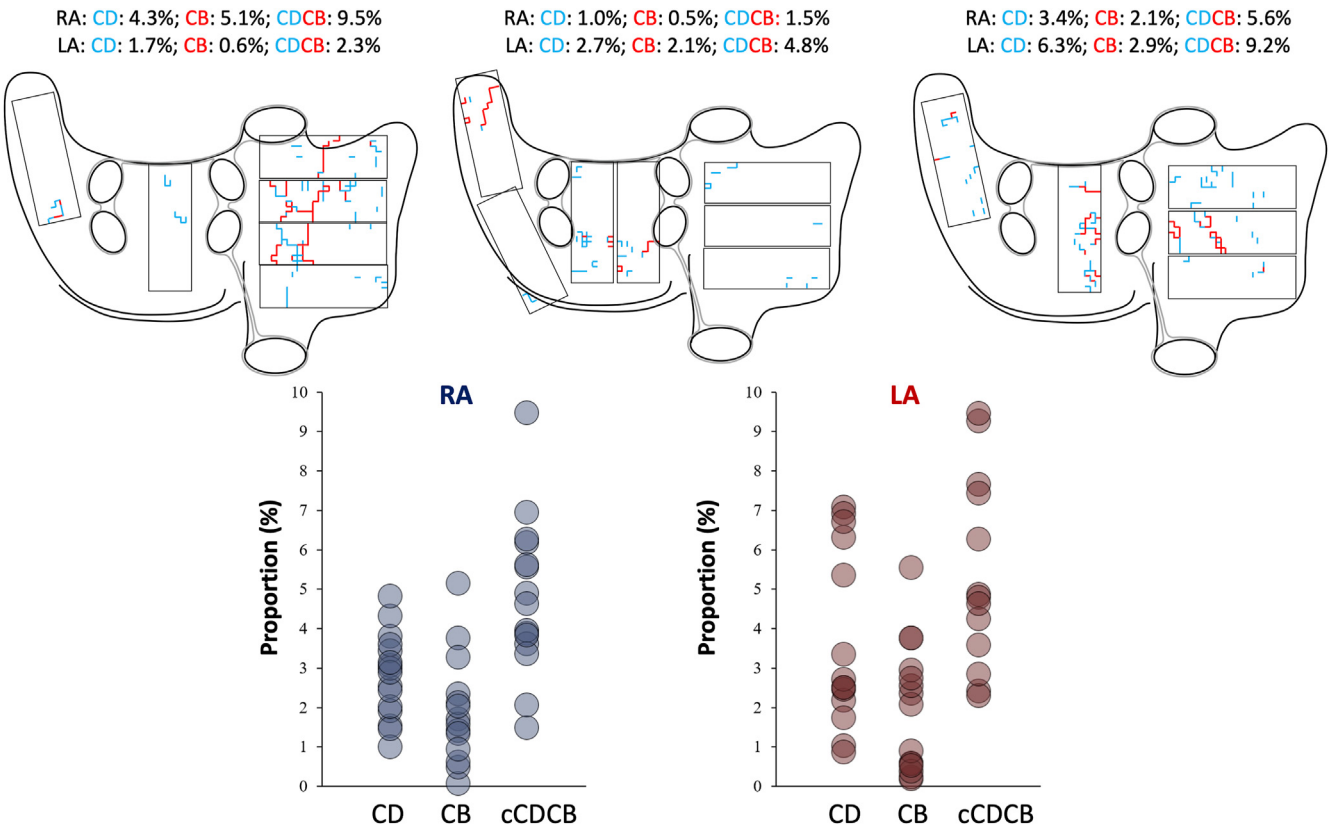

Figure 1
Prevalence of conduction disorders. **Top:** Spatial distribution of conduction disorders in 3 patients with hypertrophic obstructive cardiomyopathy. *Red lines* and *blue lines* indicate lines of conduction block (CB) and conduction delay (CD). **Bottom:** Prevalence of conduction disorders in the right atrium (RA) and left atrium (LA) of all patients. cCDCB= continuous conduction delay conduction block.

Unipolar voltages

There were no differences in median unipolar potential voltages per patient between RA and LA (RA: 4.6 [3.8–6.3] mV; LA: 5.6 [4.6–6.9] mV; $P = .138$) (Table 2). Likewise, the amount of LVA, which was found in both atria in all patients, did not differ between the RA and LA (4.7% [1.6%–7.7%] vs 2.9% [2.1%–7.1%]; $P = .79$).

However, the shape of the relative frequency distribution histograms of all unipolar potential voltages differs between the RA and LA because of a larger proportion of high (between 15 and 38 mV) voltages in the LA (Figure 3). In contrast, unipolar voltages >15 mV in the RA were scarce, and the maximal voltage was only 19.5 mV.

Figure 4 shows typical examples of color-coded voltage maps of the RA and LA separately, obtained from the same patient. These voltage maps clearly show that the magnitude of unipolar voltages is considerably higher in the LA compared to the RA.

Most unipolar potentials consisted of SP (85.7%), followed by SDP (9.1%), LDP (3.9%), and FP (1.3%). There was no difference in the prevalence of various potential types between the LA and RA ($P > .05$) (Table 2). Figure 4 (middle panels) show the relative frequency distribution of unipolar voltages for each different potential type (Supplemental Table 1). The tail of the histograms, starting from P75, illustrates that both SP and SDP have a larger proportion of higher potential voltages in the LA than in the RA (LA vs RA for SP: P75 10.9 mV vs 7.3 mV, P95 19.1 mV vs 11.0 mV; LA vs RA for SDP: P75 6.3 mV vs 3.9 mV, P95 10.5 mV vs 6.6 mV). Likewise, unipolar potential voltages of FP recorded from the LA are considerably higher (LA P75: 3.7 mV vs RA P75: merely 2.0 mV). P95 at the RA (3.4 mV) was even lower than P75 in the LA. Unipolar voltages of LDP were comparable between both atria (LA vs RA P75: 3.4 mV vs 2.6 mV, P95: 6.9 mV vs 7.7 mV)

Relationship between potential fractionation and LVAs

Figure 5 shows examples of the spatial distribution of LVA and different potential types within the mapping region of the left atrioventricular groove of 2 patients. In both patients, there were multiple large areas from which FPs (SDP, LDP, and FP) were recorded, but only a small amount of these FPs contained low-voltage components (using the frequently used cutoff value of 1.0 mV in clinical studies for low-voltage potentials). As summarized in Supplemental Table 2, large proportions of recording sites containing FPs (SDP, LDP, and FP) are not labeled as LVA. Remarkably, FP contained low-voltage components in only 18% of all LA sites compared to 36% of all RA sites.

Postoperative AF

When comparing patients with and those without early postoperative AF, unipolar potential characteristics and

Table 2 Conduction heterogeneity and electrogram characteristics

	RA	LA	*P* value
Voltage (mV)	4.6 [3.8–6.3]	5.6 [4.6–6.9]	.138
LVA (%)	4.7 [1.6–7.7]	2.9 [2.1–7.1]	.793
CV (cm/s)	88.2 [84.6–91.7]	96.6 [87.8–100.0]	.011
SP (%)	87.5 [82.7–91.5]	84.6 [78.4–89.6]	.275
SDP (%)	7.8 [5.0–10.2]	11.0 [8.1–15.3]	.097
LDP (%)	4.2 [1.6–6.7]	2.3 [0.4–5.6]	.295
FP (%)	0.7 [0.3–2.2]	1.2 [0.8–2.0]	.870
CD (%)	2.9 [1.9–3.6]	2.6 [2.1–6.4]	.541
CB (%)	1.7 [0.9–3.1]	1.49 [0.5–2.8]	.600
cCDCB (%)	4.6 [3.6–6.2]	4.8 [3.4–7.5]	.631
Max length CD (mm)	15 [11–21]	16 [12–25]	.455
Max length CB (mm)	23 [19–42]	13 [6–26]	.063
Max length cCDCB (mm)	45 [25–57]	31 [21–37]	.112

Values are given as median [interquartile range] unless otherwise indicated. CB = conduction block; CD = conduction delay; cCDCB = continuous conduction delay conduction block; CV = conduction velocity; FP = fractionated potential; LDP = long double potential; LVA = low-voltage area; SDP = short double potential; SP = single potential.

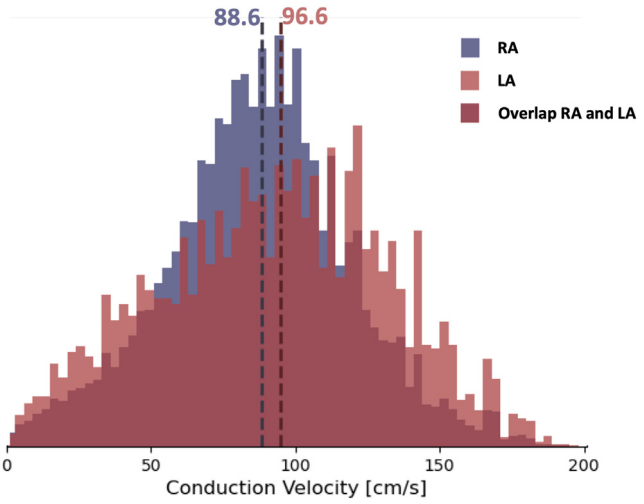

Figure 2
Conduction velocity histograms. *Red histograms* and *blue histograms* show the relative frequency distribution of all conduction velocities in the right atrium (RA) and left atrium (LA), respectively. *Longitudinal lines* represent the median conduction velocity.

conduction abnormalities in the RA differed (Supplemental Table 3). Patients who developed early postoperative AF had lower unipolar potential voltages, lower CVs, and longer and more lines of CB and cCDCB in the RA compared to patients who remained in SR (all $P < .05$). In contrast, LA conduction and potential characteristics were similar between patients with and those without early postoperative AF.

Influence of pathogenic variants

Five patients (42%) had MYH7 mutations, and 4 patients (33%) had MYBPC3 mutations. Conduction and potential characteristics of these specific pathogenic variants are given in Supplemental Table 4.

Discussion

Key findings

In HOCM patients, conduction disorders during SR not only are confined to the pulmonary vein area and can be extensively present in other LA sites or the RA. There is a larger proportion of high unipolar potential voltages in the LA compared to the RA. Importantly, FPs in both atria mainly contained high-voltage deflections. On average, both atria are equally affected with respect to local conduction disorders and LVA, although CV was higher and had a larger variance in the LA compared to the RA. Patients with early postoperative AF had more extensive, pre-existing conduction abnormalities and lower voltages in the RA than patients who remained in SR.

HOCM-related structural remodeling

Several studies have raised the question whether the arrhythmogenic substrate in patients with HOCM is only located in the LA due diastolic left ventricular dysfunction and mitral regurgitation, or also because of other factors such as a primary atrial myopathy, which affects both atria.[3,4,16–18] Although evidence is scarce, the presence of an intrinsic atrial myopathy consisting of myocyte hypertrophy and disarray as part of the molecular disease also has been suggested. In a recent case report describing an AF patient with hypertrophic cardiomyopathy (HCM) who underwent an orthotropic heart transplantation, atrial histology demonstrated cardiomyocyte hypertrophy and disarray in both atria.[4] Likewise, in a histologic and electrophysiological study in a mouse model of HCM, young mice already had increased atrial cardiomyocyte size, conduction heterogeneity index, and shortened atrial action potential in both atria compared to controls.[3]

Myocardial disarray and fibrosis, which generally characterize the left ventricle in HCM, are also seen in the right ventricle of patients with HCM.[19] This suggests that structural damage can be found in the RA as a consequence of right ventricular dysfunction or as part of the same molecular disease. More specifically, specific mutations in sarcomeric and nonsarcomeric genes have recently been associated with increased incidence and onset of AF in patients with HCM.[20–22]

Atrial electropathology

Without the confounding effects of progressive adverse remodeling by AF in our study population, our findings provide additional support for the hypothesis of a primary atrial myopathy in HOCM patients that affects both atria. In all patients, conduction disorders, LVA, and FP were not restricted to the LA. More importantly, these potentially arrhythmogenic areas were equally present in the RA and LA despite having only LA volume overload.

Similar mapping studies have been performed by our group in patients with unrepaired atrial septal defects or ischemic heart disease. In patients with atrial septal defects

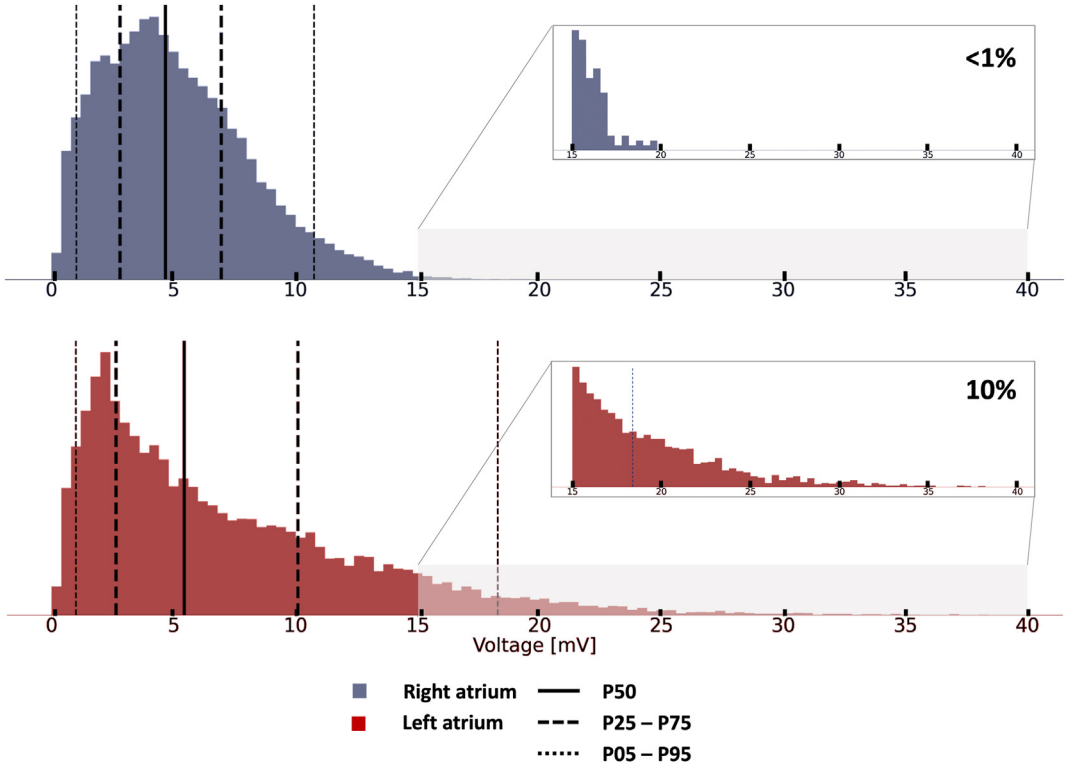

Figure 3
Unipolar voltage histograms. Relative frequency distribution of all unipolar voltages in the right atrium **(top)** and left atrium **(bottom)**. *Longitudinal lines* represent (from **right** to **left**) P5, P25, P50, P75, and P95 of unipolar voltages (P = percentile).

(N = 26; age 47 ± 14 years) experiencing severe right-sided volume overload, the amount of RA conduction disorders (median CB: 2.1%, CD: 3.2%) was comparable to patients with HOCM (median CB: 1.7%, CD: 2.9%) despite the absence of RA dilation in the current study.[23] These RA conduction abnormalities are assumed to be involved in the initiation and perpetuation of AF in patients with atrial septal defects.[23,24]

The patients with atrial septal defects and HOCM are relatively young, and conduction disorders might not yet be as pronounced as in older patients, who frequently develop AF. In comparison, we previously investigated the extent of conduction disorders in patients with ischemic heart disease (N = 209; age 66 ± 10 years) who were significantly older than HOCM patients (age 50 ± 13 years) and therefore likely to have more extensive electrical remodeling.[25–27] However, patients with ischemic heart disease exhibited even less conduction disorders (median CB: 0%–1.4%, CD: 0%–1.4%) in the RA compared to patients with HOCM (median CB: 1.7%, CD: 2.9%) in the current study.[27] Hence, conduction disorders are severe in both atria in patients with HOCM, and the presence of this extensive biatrial arrhythmogenic substrate provides additional support for the hypothesis of a primary atrial myopathy in the lack of a direct head-to-head comparison.

Regional differences in electrophysiological properties

Although the electrophysiological properties of the RA and LA were mainly comparable, there also were differences between both atria. We observed a larger proportion of high voltages and a larger variance in CV in the LA. These changes could be the consequence of atrial hypertrophy, which may occur mainly in the LA due to volume and/or pressure overload. The effects of atrial hypertrophy are incompletely understood.[5,6] In the cable theory of signal propagation, atrial hypertrophy may cause a decrease in intercellular resistances, thereby increasing CV. In contrast, atrial hypertrophy may be associated with nonuniform distribution of gap junctions and atrial fibrosis, thereby decreasing CV. These opposite consequences of atrial hypertrophy may vary from region to region and could explain the observed larger variance in CV.

Early postoperative AF

Patients who developed early postoperative AF had more extensive, pre-existing conduction abnormalities and lower potential voltages in the RA, and not the LA, compared to patients who did not develop postoperative AF. Early postoperative AF is a common complication in HOCM patients after cardiac surgery (36% incidence) and is also a strong risk factor for late postoperative AF.[28] Although various clinical factors are considered as metrics for this development, the association with right-sided electrophysiological abnormalities is novel in this disease. However, the results should be treated with caution because of the limited number of patients and require further investigation.[28,29]

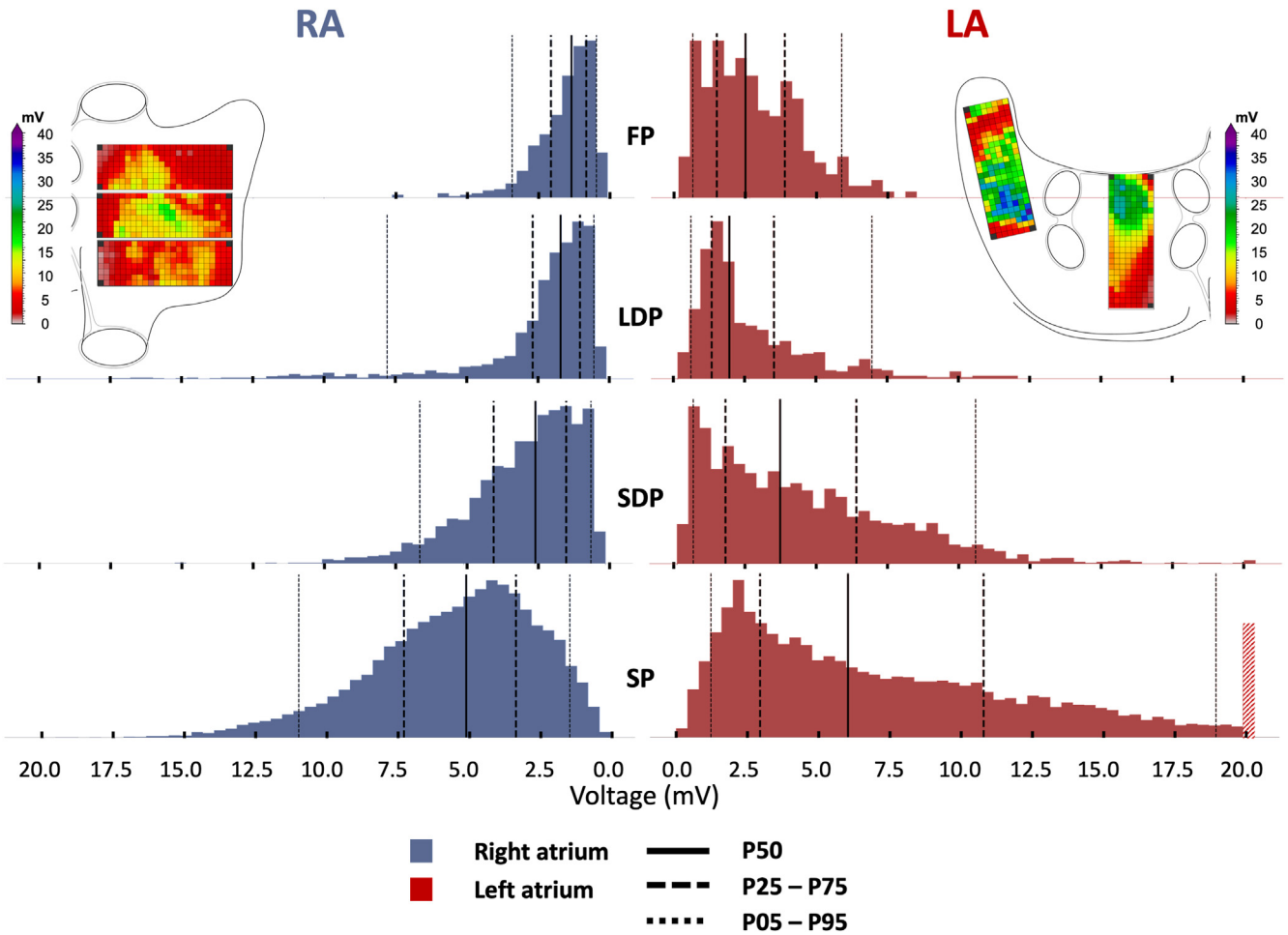

Figure 4

Unipolar voltages of different potential morphologies. Color-coded voltage maps of right atrium (RA) and left atrium (LA) obtained from the same patient. Relative frequency distribution of all unipolar voltages for each potential morphology recorded from either the RA (**left**) and LA (**right**) are shown. *Longitudinal lines* represent P5, P25, P50, P75, and P95 of unipolar voltages (P = percentile). *Striped bars* represent an overflow bin for values >20.0 mV. FP = complex fractionated potential; LDP = long double potential; SDP = short double potential; SP = single potential.

Clinical outlook

In the general population, catheter ablation plays an important role in the management of atrial tachyarrhythmias, including AF. However, in patients with HCM, treatment of AF with catheter ablation currently is suboptimal. It has relatively low efficacy in preventing AF recurrences, with an increased need for repeat procedures and long-term antiarrhythmic drug therapy.[2] In a meta-analysis comparing patients with HCM with control patients, freedom from AF recurrence after a single procedure was only 38.7% in the HCM group and 49.8% in the control group (odds ratio 2.25; 95% confidence interval 1.09–4.64; $P = .03$).[30] The low success rate in this population is attributed to an extensive arrhythmogenic substrate beyond the pulmonary veins.[31,32] In addition, patients with HCM may have atrial hypertrophy and/or increased atrial wall thickness resulting in frequent nontransmural lesions.[33,34]

Conceptually, our observational findings may provide additional rationale as to why catheter ablation in patients with HOCM may have worse outcomes than in the general population. First, we observed biatrial electropathology, which may be even more pronounced in both atria of HOCM patients who have AF. Second, the high unipolar LA potential voltages may hamper formation of transmural lesions, giving rise to AF recurrences after pulmonary vein isolation. Third, the large amount of high unipolar voltages in the LA is also associated with a large mismatch between LVA and FP. Voltage mapping–guided catheter ablation is a frequently used approach to increase the success rates in patient with persistent types of AF. Although FP also can be physiological in nature (eg, heterogeneous fiber orientation), they often are assumed to represent slowing of conduction and therefore to also contain low-voltage components.[12] Hence, if this approach were to be applied in an HOCM patient with the conventional cutoff values for LVA during SR, a potentially extensive arrhythmogenic substrate may be missed.

Based on our observational data, we hypothesize that it may be beneficial to consider adapting AF substrate modification strategies for HOCM patients. High-power and/or longer radiofrequency applications may be required in order to achieve transmural lesions in the high-voltage areas.[31,32] Because FPs mainly contain high-voltage components in this population, potential arrhythmogenic areas are missed

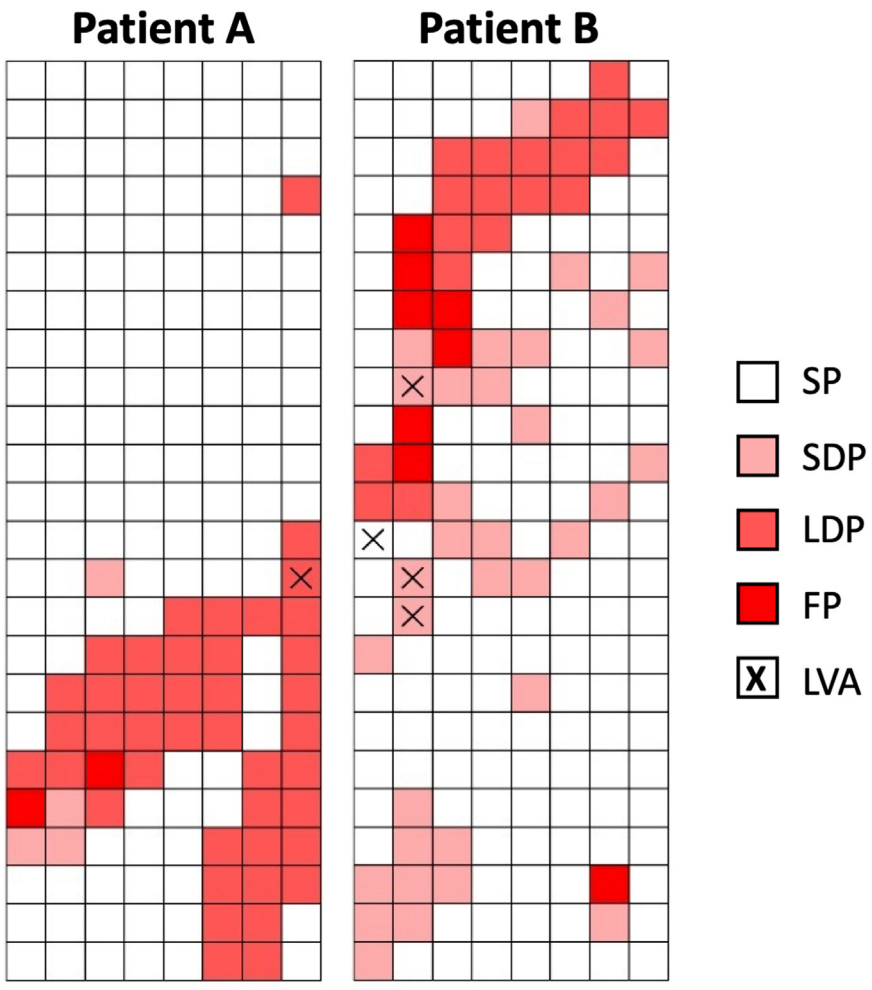

Figure 5
Mismatch between low-voltage areas (LVAs) and fractionated potentials (FPs). Examples of maps showing the spatial distribution of LVA *(crosses)* and different potential types (short double potential [SDP], long double potential [LDP], FP) within the mapping region of the left atrioventricular groove of 2 patients. Most fractionated potentials did not contain low-voltage components. SP = single potential.

when ablation is guided by voltage mapping for identification of LVAs only. Furthermore, the presence of a biatrial arrhythmogenic substrate indicates that patients with HOCM could especially benefit from an extensive lesion set to treat AF beyond the pulmonary veins, including the RA. Several groups have investigated the use of concomitant surgical ablation (Cox maze IV) during surgical myectomy in HOCM patients, involving both the RA and LA.[35] Pooled freedom from AF at 5 years was 70.6% (95% confidence interval 65.8–75.7).[35] These favorable long-term outcomes are comparable to outcomes of concomitant surgical ablation in patients with mitral valve disease. Correlation between lesion sets, wall thickness, and electrophysiological (ablation) parameters might be an important step in further improving our understanding of the AF-related substrate and ablation outcomes in HOCM patients.

Study limitations

Reported outcomes are observational in nature, and causal relationships cannot be claimed due to lack of head-to-head comparison, small sample size, and absence of histopathology. Because of to the relatively young age of HOCM patients, LA size, and specific cardiovascular risk factors, a head-to-head comparison with a matched control group that also underwent epicardial mapping was not feasible. In addition, histopathology could not be obtained in the current study as a consequence of *in vivo* mapping, and LA appendage amputation is not routinely performed in HOCM patients at risk for AF in our center. However, detailed analyses of myocyte hypertrophy and disarray in the atria would provide further insight into the relationship between atrial structure and the presence of fractionated, low-voltage potentials.

In daily clinical practice, ablation is guided by endocardial and not epicardial mapping procedures. Previous simultaneous endocardial and epicardial mapping studies have demonstrated that patterns of activation and potential features on both sites during SR are mainly comparable.[36] In addition, the epicardial mapping approach assures better close-contact recordings than conventional endocardial mapping, thereby decreasing the chance that low-voltage potentials and FPs are the result of poor contact. Additional pacing

maneuvers were not performed in this study, which could unmask rate and direction electropathology. Future studies with long-term follow-up and larger sample size, including patients with history of AF, are required to directly correlate preoperative clinical characteristics, such as specific genetic mutations,[22] electrophysiological parameters, and potentially AF development (and recurrence after AF ablation).

Conclusion

In patients with HOCM, conduction disorders, LVA, and FP were equally present in both atria, supporting the concept of a primary atrial myopathy. In addition, not LA but RA conduction abnormalities were more pronounced in patients who developed postoperative AF. Conceptually, the presence of a biatrial substrate and high-voltage FP may contribute to failure of ablative therapy of atrial tachyarrhythmias in this population.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.01.022.

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