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**ATRIAL STRUCTURE AND FUNCTION**

# Volumetric cine CMR to quantify atrial structure and function in patients with atrial dysrhythmias[#]

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*Purpose.* To implement a cardiac magnetic resonance (CMR)-based protocol to define atrial structure and function in individuals with paroxysmal atrial fibrillation (PAF), heritable cardiac conduction and myocardial disease with atrial dysrhtyhmias (HCCMD), and healthy controls. *Methods.* Fifteen controls, 20 PAF, and 12 HCCMD subjects underwent CMR examination including: multislice short-axis cine, multislice horizontal long-axis cine, and gadolinium-enhanced coronal plane magnetic resonance angiography (MRA) for pulmonary vein analysis. We also assessed for ventricular myopathy with delayed myocardial enhancement (DME) acquisitions. *Results.* Right and left ventricular measurements did not differ among the three groups. Seven heritable atrial dysrhythmia subjects and no control or PAF subjects demonstrated midmyocardial fibrosis of the basal interventricular septum by DME. Left atrial (LA) volume at the onset of atrial systole and minimal LA volume were significantly higher in PAF subjects compared to controls ($p < 0.05$ for both), LA percent emptying was significantly lower in PAF subjects ($p < 0.01$), and RA percent emptying was significantly lower in PAF subjects compared to controls ($p < 0.01$), though these differences were not significant when controlling for heart rate, age and gender. There was no significant difference in right atrial (RA) volumes among study groups. Atrial volumes and function did not differ significantly between heritable atrial dysrhtyhmia subjects and controls. PAF subjects had greater frequency of a right middle pulmonary vein (RMPV) than controls (6/20 vs. 3/15) that did not reach statistical significance. *Conclusions.* CMR can quantify atrial structure and function in patients with PAF compared to controls. This protocol could not detect abnormalities in atrial function in early affected patients with heritable cardiomyopathy and atrial premature beats.

*Key Words:* Atrial fibrillation; Atrial function; Atrial myopathy; Cardiovascular magnetic resonance

## 1. Introduction

Atrial fibrillation (AF) portends a 2-fold greater mortality rate compared to patients in sinus rhythm (1) even after controlling for coronary disease and stroke, perhaps explained by loss of the contribution of atrial function to cardiac performance. Two- and three-dimensional echocardiography techniques have sought to quantify atrial function, but tend to underestimate atrial volumes as obtained by magnetic resonance imaging (2). Additionally, inadequate acoustic windows with surface imaging limit assessment of the thin-walled and irregularly shaped atria with modalities such as echocardiography. Trans-esophageal imaging offers better resolution and flexibility (3), but requires patient sedation and carries some risk of esophageal trauma and depression of cardiopulmonary function. Cardiovascular magnetic resonance imaging (CMR) may be advantageous for atrial imaging by producing high-resolution cine loops in any plane and acquiring contiguous image planes covering a chamber of interest; thus, volumetric determinations are direct and do not require geometric assumptions.

We sought to implement a CMR-based protocol to identify differences in right and left atrial structure and function in patients with lone paroxysmal atrial fibrillation (PAF) compared to healthy controls. Additionally, our institution has identified a family with heritable cardiac conduction and myocardial disease (HCCMD) due to an autosomal dominant frameshift mutation in the lamin A/C gene (*LMNA*). Lamin A/C is a nuclear envelope protein whose mutations have been linked to dilated cardiomyopathy (DCM) with conduction defects, muscular dystrophies, and lipodystrophy (4, 5). The earliest manifestation of cardiomyopathy in this kindred is the development of atrial premature contractions, suggestive of an underlying atrial myopathy. We implemented our CMR protocol in these early affected individuals as well.

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## 2. Methods

### 2.1. *Study population*

Individuals with lone PAF, early affected HCCMD members and healthy controls were prospectively enrolled. Those with contraindication to magnetic resonance (e.g. pacemaker, defibrillator, ferromagnetic foreign body) were excluded. Lone PAF was defined as individuals with isolated episodes of atrial fibrillation and no structural heart disease by echocardiography. Early affected HCCMD subjects all had premature atrial complexes (PACs) on 24-hour ambulatory electrocardiographic monitoring, ranging from 2 to 550 PACs per hour, and overall normal ventricular function by echocardiography. All subjects gave written informed consent for participation in this Institutional Review Board-approved protocol.

### 2.2. *Image acquisition*

CMR exams were completed on a conventional 1.5 Tesla scanner (CV*i*, GE Healthcare) using a four-channel cardiac coil. The following acquisitions were included: multislice short-axis cine for ventricular volume determination, multislice horizontal long-axis cine for atrial volume determination, and contrast-enhanced coronal plane magnetic resonance angiography (MRA). Cine imaging was performed with either a steady-state free precession (SSFP) pulse sequence or a conventional fast cine gradient echo pulse sequence when excess flow artifact using SSFP precluded reliable atrial endocardial border identification.

**Table 1.** Characteristics of study population

| | PAF, N = 20 | HCCMD, N = 12 | Controls, N = 15 |
|---|---|---|---|
| Age, years | 50 ± 16 | 32 ± 8 | 37 ± 10 |
| Diabetes mellitus | 1 (5%) | 0 (0) | 0 (0) |
| Hypertension | 3 (15%) | 1 (9%) | 3 (20%) |
| Current smoker | 2 (10%) | 4 (33%) | 4 (27%) |
| Female | 3 (15%) | 9 (75%) | 8 (53%) |

Values are expressed as mean ± standard deviation or number (percentage) in subgroup.

### 2.3. *Image analysis*

All image data were analyzed offline using standardized software for CMR image analysis (MEDIS, Netherlands). Right and left atrial endocardial borders were traced manually in each phase of the cardiac cycle in each slice of the multislice acquisitions, and summing individual slice volumes according to Simpson's rule generated time-volume curves for both atria. Right and left ventricular volumes were obtained using standard techniques (6). In this study, papillary muscles were included in LV volumes, and atrial appendages were excluded from atrial volumes. All volumes were normalized to body surface area.

Maximal and minimal atrial volumes were read off from the volume-time curves (Fig. 1, labels B and A, respectively). Atrial percent emptying was calculated as 100% × (maximal volume − minimal volume)/maximal volume, or (B-A)/B × 100. From the volume-time curves, the onset of atrial systole was read off as point D (Fig. 1). In the majority of

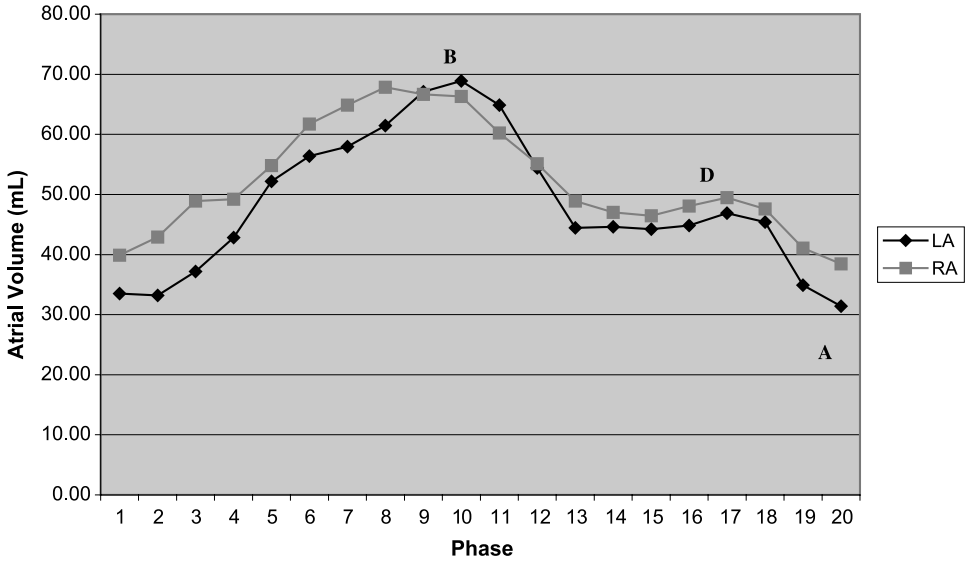


**Figure 1.** Left and right atrial volume-time curves derived from multislice, multiphase SSFP cine imaging in a normal volunteer. B = maximal atrial volume, D = onset of atrial systole, A = minimal atrial volume.

**Table 2.** Results of ventricular and atrial quantification in PAF and Earl affected HCCMD subjects versus controls

| Variable | PAF (N = 20) | HCCMD (N = 12) | Controls (N = 15) |
|---|---|---|---|
| LV EDV, mL/m$^2$ | 61 ± 12 | 63 ± 10 | 62 ± 18 |
| LV ESV, mL/m$^2$ | 25 ± 8 | 26 ± 6 | 26 ± 8 |
| LV EF, % | 60 ± 8 | 58 ± 7 | 59 ± 4 |
| RV EDV, mL/m$^2$ | 47 ± 9 | 41 ± 9 | 46 ± 11 |
| RV ESV, mL/m$^2$ | 22 ± 7 | 19 ± 7 | 22 ± 7 |
| RV EF, % | 53 ± 10 | 53 ± 10 | 52 ± 12 |
| LA max, mL/m$^2$ | 31 ± 8 | 28 ± 8 | 27 ± 9 |
| LA onset systole, mL/m$^2$ | 24 ± 7* | 19 ± 6 | 19 ± 6 |
| LA min, mL/m$^2$ | 18 ± 6* | 13 ± 5 | 13 ± 4 |
| LA stroke volume, mL/m$^2$ | 6 ± 2 | 5 ± 2 | 6 ± 2 |
| LA EF, % | 27 ± 8* | 30 ± 12 | 32 ± 5 |
| LA percent emptying | 44 ± 8* | 52 ± 11 | 52 ± 7 |
| RA max, mL/m$^2$ | 29 ± 10 | 28 ± 9 | 25 ± 9 |
| RA onset systole, mL/m$^2$ | 23 ± 8 | 20 ± 6 | 20 ± 7 |
| RA min, mL/m$^2$ | 18 ± 7 | 15 ± 5 | 14 ± 6 |
| RA stroke volume, mL/m$^2$ | 5 ± 2 | 5 ± 2 | 6 ± 2 |
| RA EF, % | 24 ± 9* | 30 ± 13 | 31 ± 9 |
| RA percent emptying | 39 ± 8 | 47 ± 9 | 47 ± 7 |

Asterisk indicates statistically significant difference ($p < 0.05$) compared to controls in univariate analyses; analysis of covariance controlling for age, gender, and heart rate rendered these differences non-significant.

cases, this point was the second of two peaks corresponding to active atrial contraction after passive atrial emptying. Atrial stroke volume, ASV, was calculated as volume at onset of atrial systole − minimal volume (ASV = D − A). Atrial ejection fraction was calculated as 100% × atrial stroke volume/atrial volume at onset of atrial systole (ASV/D × 100) (7, 8). Two controls and one PAF subject had atrial volume-time curves that yielded only one peak precluding estimations of the volume at onset of atrial systole and subsequent functional calculations for these patients.

Atrial wall thickness was measured from double inversion recovery images acquired in the transverse or vertical long axis planes in a slice just above the coronary sinus. Thickness of both the right atrial free wall as well as the interatrial septum was measured when visible.

MRA images were analyzed in a volumetric viewer that allowed for visualization of data in any plane as well as volume renderings (9). Pulmonary vein ostial diameters were obtained by generating an oblique plane demonstrating the maximal diameter for each pulmonary vein. Variants of pulmonary vein (PV) anatomy were also recorded based on methodology published by Kato et al. Typical PV anatomy was defined as the anastomoses of all four pulmonary veins to the respective atria in a normal fashion. A short common left trunk was defined as the junction of the left superior and left inferior pulmonary veins (LSPV, LIPV) immediately distal to the left atria (LA) such that instead of distinct anastomoses for each LPV, the junction of the two at the atrial border forms a single ostium. A long common left trunk was defined as the junction of the LSPV and LIPV occurring more distally prior to common anastomosis with the LA (9).

**Table 3.** Pulmonary vein diameters, expressed in millimeters, in PAF and HCCMD subjects vs. controls

| | PAF (N = 20) | HCCMD (N = 12) | Controls (N = 15) |
|---|---|---|---|
| RIPV | 16 ± 2 | 16 ± 1 | 15 ± 3 |
| RSPV | 16 ± 3 | 16 ± 3 | 16 ± 2 |
| LIPV | 16 ± 3 | 14 ± 2 | 16 ± 2 |
| LSPV | 18 ± 3 | 17 ± 3 | 17 ± 2 |

**Table 4.** Pulmonary vein anatomy in PAF and HCCMD subjects vs. controls

| | PAF | HCCMD | Controls |
|---|---|---|---|
| Typical PV anatomy | 13 | 9 | 12 |
| Short common left trunk | 0 | 1 | 0 |
| Long common left trunk | 1 | 1 | 0 |
| RMPV | 6 | 1 | 3 |

### 2.4. *Statistical analysis*

All continuous variables are presented as mean ± standard deviation. To compare the three groups with respect to each outcome, an analysis of covariance model was fit to the data, controlling for age, gender, and heart rate. These three covariates potentially confound the relation between groups and the outcomes. All significant group effects were followed up with multiple comparisons to examine differences between controls and PAF subjects and HCCMD participants, separately. Fisher's exact test was used to compare PAF subjects and controls with respect to the presence of a right

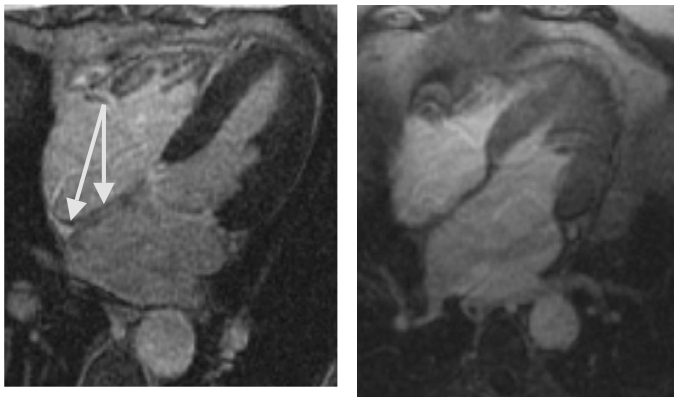

**Figure 2.** Possible hyperenhancement of the interatrial septum (arrow) in a subject with paroxysmal atrial fibrillation (left) compared to absence of atrial septal hyperenhancement in a normal control (right).

middle pulmonary vein (RMPV). P-values of $< 0.05$ were considered statistically significant.

## 3. Results

CMR exams from four control subjects were excluded due to: poor image quality precluding analysis, gating difficulties due to profound bradycardia, premature termination of exam due to patient claustrophobia, and inadequate image acquisition due to equipment malfunction. The remaining study population consisted of 20 PAF subjects, 12 subjects with HCCMD, and 15 healthy controls; characteristics of each group are presented in Table 1. All subjects were in sinus rhythm at the time of CMR examination.

Measures of ventricular and atrial size and function are summarized in Table 2. Right and left ventricular size and function were normal in all PAF, HCCMD and control subjects. There was no statistically significant difference in right or left ventricular volumes and ejection fractions among groups.

While overall maximum left atrial volume did not differ significantly between PAF subjects and controls, LA volume at the onset of atrial systole and minimal LA volume were significantly higher in PAF subjects compared to controls ($p < 0.05$ for both). Left atrial percent emptying, a measure of active LA function, was significantly lower in PAF subjects ($p < 0.01$). There was no significant difference in right atrial volumes among study groups, though right atrial percent emptying was significantly lower in PAF subjects compared to controls ($p < 0.01$). Analysis of covariance controlling for age, heart rate, and gender rendered these differences nonsignificant. There were no statistically significant differences in atrial measurements for HCCMD subjects compared to controls.

Pulmonary vein diameter measurements and anatomic variants are summarized in Tables 3 and 4. All pulmonary vein diameters of HCCMD and PAF subjects were comparable to controls. The PAF group had no significant difference in frequency of RMPV compared to controls (6/20 vs. 3/15, $p = 0.7$ from Fisher's Exact test).

Measurement of atrial wall thickness in the three study groups did not reveal a significant difference. While the DME sequence has not been validated for visualization of atrial fibrosis, we did observe possible hyperenhancement of the atrial septum in two PAF subjects (Fig. 2) that was not present in any of the controls.

## 4. Discussion

Using a comprehensive CMR-based protocol, we identified significant differences in atrial structure and function in patients with so-called "lone" atrial fibrillation compared to healthy controls. Abnormalities of both right and left atrial performance indices suggested the presence of an atrial myopathy in the absence of other structural heart disease in patients with PAF. In subjects with heritable cardiac conduction system and myocardial disease, we did not detect any difference in atrial structure or function. Pulmonary vein ostial diameters were comparable in all three groups. We were able to quantify both right and left atrial volumes using a more comprehensive protocol than what has been used in the past (8); most echocardiographic studies have been limited in their ability to quantify right atrial volumes.

Numerous studies have established the positive relationship between LA dilation and AF (10). The Framingham study estimated a hazard ratio for developing AF of 1.39 for every 5-mm increase in LA size (11). It is also known that AF itself reduces atrial function, perhaps explaining the adage, "AF begets AF."

Although CMR has the capability to measure atrial appendage volume, we did not include it in atrial total volume measurements. This likely accounts for our smaller uncorrected atrial volumes compared to studies including the appendage; Järvinen et al. included the atrial appendage in LA quantification and found normal maximal LA volumes to average between 79–115 ml while our results showed an average between 65–139 ml (7). Our smaller volumes are closer to those of previous studies that used angiography and echocardiography which excluded the atrial appendages (12, 13).

Previous studies have varied in their methods of determining the onset of atrial systole. Tseng et al. inspected atrial volume-time curves and chose the second of two peaks as the onset of atrial systole (14). Echocardiography-based studies with simultaneous recording of the electrocardiogram allow identification of the P-wave to indicate the onset of atrial systole (15). In the absence of techniques for accurate noninvasive ECG recording during MR imaging, we employed the former method. Alternatively, we could have obtained phase contrast acquisitions to record A-V valve inflow velocities and obtain the delay to onset of active atrial emptying, but this would not have been simultaneous with atrial volume acquisitions.

In two controls and one PAF subject, lack of a clear second peak on the atrial time-volume curve precluded CMR cine-based atrial function analysis. This may be due to an increased heart rate leading to a shortened atrial pre-ejection period; heart rates ranged from 75 to 100 bpm in these 3 subjects with atrial time-volume curves unsatisfactory for atrial systole identification.

Lack of significance of results may be obscured by use of two different cine acquisition pulse sequences, a steady-state free precession sequence in most and a conventional fast cine gradient echo in those with excessive artifact on SSFP imaging. These techniques have been shown to produce differences in ventricular volume calculations within the same individual (16), and it is not unreasonable to expect similar differences when using these different techniques to quantify atrial volumes.

After adjusting for heart rate, age and gender, we found no difference among study groups in atrial volumes or function.

Previous investigators have found a negative correlation between HR and LA maximum and minimum volumes (7, 14). Additionally, age of PAF subjects tended to be greater than age of control subjects ($p < 0.05$). Sandstede et al. found certain ventricular parameters to be age-dependent (17). Tseng et al. report that after normalizing to body surface area, LA percent emptying is higher in females than in males (14).

Despite its dependence on manual tracing, atrial border detection and volume determination from Simpson's rule with cine MRI may be less operator-dependent than other imaging modalities such as two-dimensional echocardiography due to the volumetric nature of the acquisition. Three-dimensional echocardiographic techniques may be an alternative, but do not provide simultaneous assessment of myocardial scar, which may be an important contributor to substrate for arrhythmia. Studies that directly compare 3-D surface echocardiography-based (18) and CMR-based measurement of atrial volumes and pulmonary vein anatomy are warranted.

Comparison of our findings of mechanical atrial function with electrical changes as seen with signal-averaged electrocardiography of P-waves may allow for further understanding of atrial electromechanical interactions. Koide et al. found that filtered P-wave duration with signal-averaged electrocardiography was significantly more sensitive and specific than echocardiographically-determined left atrial dimension as a predictor of progress of PAF to chronic AF (19). We are also performing ongoing studies assessing for ventricular myopathy with delayed myocardial enhancement (DME) acquisitions, which may reveal midmyocardial fibrosis that has previously been described only at autopsy in HCCMD members; normal ventricular function in the early affected cohort evaluated in this study makes significant myocardial fibrosis at this stage less likely. DME imaging in PAF subjects and controls revealed no evidence of ventricular myocardial scar. Given the intriguing findings of possible atrial septal fibrosis by DME in PAF subjects, further optimization and validation of the DME sequence to visualize atrial fibrosis is warranted. Also, lack of significant difference in atrial wall thickness may not represent lack of a difference in atrial mass; further studies are ongoing using optimized acquisition techniques designed for volumetric measurement of atrial mass.

Using CMR data, we have established right and left atrial volumetric and functional measurements in two groups of patients with atrial dysrhythmias and normal controls. The image acquisition and analysis protocol may be useful as part of a comprehensive diagnostic strategy in patients with atrial fibrillation and other forms of cardiomyopathy that manifest with atrial arrhythmias.

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