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ELECTROPHYSIOLOGY

Left atrial functions in the early period after cryoballoon ablation for paroxysmal atrial fibrillation

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Abstract

Purpose: In patients with paroxysmal atrial fibrillation (PAF), functional changes are observed in the left atrium (LA) after pulmonary vein isolation (PVI) procedure. Although previous studies have investigated the altered mechanical functions of the LA with radiofrequency (RF) ablation, changes in the LA functions in the early period after cryoablation (CB-2) have not been clearly demonstrated. This study aims to explore the early periodical changes in mechanical functions of the LA in patients with PAF who underwent CB-2 based ablation through the help of echocardiographic methods which contain Doppler and strain parameters.

Methods: Consecutive 77 patients (mean age: 57.5 ± 11.2; 57% men) with PAF underwent CB-2 were prospectively analyzed. All patients were in sinus rhythm before and after the procedure. The LA dimensions, the LA reservoir strain, the LA atrial contractile strain and the LA conduit strain and left ventricular diastolic function parameters were evaluated by Doppler echocardiography before and 3 months after the procedure.

Results: Acute procedural success was achieved in all cases. No major complications were observed. LA reservoir strain and LA contractile strain showed significant recovery after the procedure. (28.3 ± 12.8 vs. 34.6 ± 13.8, $p < .001$ and −10.8 ± 7.9 vs. −13.9 ± 9.3, $p = .014$ respectively). No significant change was demonstrated in other echocardiographic parameters.

Conclusion: Significant improvement in mechanical functions may occur even in the early period after cryoballoon ablation in patients with PAF.

KEYWORDS
ablation, Atrial fibrillation, cryoballoon, left atrial function, strain

Abbreviations: 2D-STE, two-dimensional speckle-tracking echocardiography; ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CB, cryoballoon; CV, cardioversion; EHRA, European Heart Rhythm Association; EP, electrophysiology; LA, left atrium; LAscd, left atrial conduit strain; LAsct, left atrial contractile strain; LAsr, left atrial reservoir strain; LAVI, left atrial volume index; LV, left ventricle; MRI, magnetic resonance imaging; NOAC, novel oral anticoagulation; PV, pulmonary vein; PVI, pulmonary vein isolation; RF, radiofrequency; TDI, tissue doppler imaging; TR, tricuspid regurgitation; TSP, transseptal puncture.

1 | INTRODUCTION

While atrial fibrillation (AF) is related to increased mortality and morbidity in patients, it also places a heavy burden on global health systems. AF through various pathophysiologic mechanisms leads to atrial dilatation, dysfunction, and fibrosis.[1] Being one of the most common reasons for increased volume and mechanical dysfunction of the left atrium (LA), AF also distorts the mechanical function of the heart globally. Mechanical remodeling takes place when the increased compliance of the atria leads to decreased contractility and increased tension on the atrial myocardium.[2] Restoration of the normal sinus rhythm has become a significant target in the treatment of patients with AF since the studies showed that controlling the AF leads to improvement in the mechanical functioning of the LA.[3] Pulmonary vein isolation (PVI) is the established therapy of invasive management of AF, considered as the cornerstone step of AF. The "Fire and Ice" trial proved the non-inferiority of cryoballoon ablation (CB-2) to RF-PVI in patients with paroxysmal AF (PAF).[4] CB-2 has been found to have high procedural success and shorter procedural duration, high durability of PVI and convincing clinical results in various clinical conditions.[5–8] Preferred ablation pathway and the degree of ablation to control the AF are vital and can contribute to the disruption of the mechanical functioning of the LA.[9] There are many studies in which the effects of PVI modality with radiofrequency catheter ablation (RF) on the LA function of patients with AF are evaluated.[10,11] Especially in the early periods following RF ablation, disrupted mechanical functions of the LA in patients with PAF have been shown through cardiac magnetic resonance imaging (MRI) and echocardiographic methods which also contains Doppler parameters.[12–14] Although former studies have explored the impacts of RF ablation on the function of the LA, they lack a clear illustration of the altered LA functions in early periods after a CB-2 procedure is done. This prospective study aims to explore the early periodical changes in mechanical functions of the LA in patients with PAF who underwent CB-2 based PVI through the help of echocardiographic methods which contain Doppler and strain parameters.

2 | METHODS

2.1 | Patient population

Between January 2019 and January 2021, consecutive 77 PAF patients with preserved left ventricular ejection fraction underwent second-generation cryoballoon ablation at the Istanbul University-Cerrahpasa, Electrophysiology (EP) Division for symptomatic PAF. PAF was defined as AF that terminates spontaneously or with intervention within 7 days of onset. Patients with left atrial thrombus, who were in other than sinus rhythm during the procedure, uncontrolled thyroid dysfunction, contraindication to anticoagulation, pregnancy, previous AF ablation, severe valvular disease and a LA size >60 mm were excluded. Severity of symptoms was recorded according to European Heart Rhythm Association (EHRA) score. Informed consent was taken from each patient before the procedure. The study was in compliance with the principals outlined in the Declaration of Helsinki and approved by the local Ethics Committee.

2.2 | Preprocedural management

Transesophageal echocardiography and baseline echocardiography were performed in all patients on the morning of the day of the procedure. Apart from echocardiography, no additional preprocedural imaging was performed. In patients on vitamin K antagonists, anticoagulation was continued throughout the procedure aiming at an INR of 2–3. In patients treated with novel oral anticoagulants (NOACs), the drug was discontinued ≥24 h prior to the procedure and re-initiated 6 h post-ablation at half the regular dose, and at full dose the following day.

2.3 | Procedural management

All procedures were performed under deep sedation using midazolam, fentanyl, and propofol. Prior to transseptal puncture (TSP), diagnostic catheter was introduced via the right femoral vein and positioned within the coronary sinus. Single TSP was performed via the right femoral vein under fluoroscopic guidance using a modified Brockenbrough technique and an 8.5F transseptal sheath (SL1, St. Jude Medical, Inc., St. Paul, MN, USA). The transseptal sheath was exchanged over a guidewire for a 12F steerable sheath (Flexcath Advance, Medtronic, Inc., Minneapolis, MN, USA). A heparin bolus was administered targeting an activated clotting time of >300 s. A 28 mm cryoballoon (Arctic Front Advance, Medtronic, Inc. Mineapolis, MN, USA) was then advanced through the FlexCath sheath and positioned at the antrum of each pulmonary vein (PV) guided by the circular mapping catheter (Achieve, Medtronic, Inc. Mineapolis, MN, USA). The ablation strategy was wide antral isolation and additional LA lesions were not allowed. The protocol recommended the use of 240 s cryo-applications for all four PVs using a freeze-thaw-freeze technique was performed. To minimize the risk of phrenic nerve injury, right phrenic nerve pacing was performed by an electrode catheter in the superior vena cava, and capture was confirmed by palpation and intermittent fluoroscopy. Application of cryo-energy was terminated immediately upon attenuation or loss of phrenic nerve capture. The procedural endpoint was defined as persistent PVI verified by spiral mapping catheter recordings 30 min after the last energy application. All the PVs were isolated during the procedure. In cases where AF occurred during the procedure, when not terminated by ablation, sinus rhythm was restored by cardioversion (CV). The duration of the procedures was nearly 60 min.

2.4 | Postprocedural management

Following ablation, all patients underwent transthoracic echocardiography to rule out a pericardial effusion. All patients were treated with

proton-pump inhibitors twice daily for 6 weeks. Anticoagulation was continued for at least 3 months and thereafter based on the individual CHA DS-VASC score. To prevent early recurrence, an antiarrhythmic drug was administered throughout the 3 months blanking period.

2.5 | Echocardiographic acquisition

All patients were in sinus rhythm during echocardiographic examination. The transthoracic echocardiogram examinations were performed using a Philips EPIQ7 ultrasound system (Philips Medical Systems, Andover, Massachusetts, USA), equipped with a 1–5 MHz X5-1 sector array transducer by an experienced echocardiographer who was blinded to clinical data. LA diameter was evaluated from apical long axis views. Biplane LA volume was evaluated from apical four- and two-chamber views and indexed to body surface area to derive the indexed LA volume (LAVI). Diastolic function was evaluated from transmitral E and A velocities, average of the septal and lateral annular e' velocity and E/e' ratio, LAVI measurements, and tricuspid regurgitation (TR) velocities. Electromechanical conduction time was defined as the onset of the P-wave to the onset of the tissue Doppler imaging (TDI)-derived late diastolic (A') velocity at the lateral and medial mitral annulus. Intra- and interobserver agreement were assessed using Bland-Altman analysis.

2.6 | Speckle tracking echocardiography

The left ventricle (LV) and LA speckle tracking analyses were performed offline by experienced operators using customized speckle tracking computer software (Qlab, Philips). Briefly, the LV endocardium was traced semi-automatically in all three apical views, to define the wall region of interest. An 18 segment-model was implemented for the evaluation of wall motion. The global longitudinal strain was automatically calculated as the average of 18 segments. For left atrial strain, the LA contour was delineated in end-systole excluding PVs and the LA appendage. LA myocardium was automatically generated using the R-R gating for further analysis. LA strain was obtained automatically in the apical four- and two-chamber views. LA myocardial deformation analysis was studied in all three phases of the atrial cycle (reservoir, conduit, and contraction). More specifically, the LA reservoir strain (LASr) was measured as the peak positive value, at the end of the LA filling before mitral valve opening. LA atrial contractile strain (LASct) was defined as the peak strain during atrial contraction. LA conduit strain (LAScd) was measured as the difference between peak reservoir and peak contractile strain, representing the atrial mechanics during the passive LA filling phase, after the opening of the mitral valve, and before LA contraction.

2.7 | Statistical analysis

SPSS Statistics V25 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Variables were expressed as mean ± standard deviation if normally distributed, median (minimum, maximum) if not. Categorical data were expressed as ratios. The distribution of the numerical data was evaluated through Kolmogorov Smirnov and/or Shapiro Wilk tests. Paired *t*-test was used to compare the measurements before and after the ablation procedure. A two-tailed *p*-value equal to or less than .05 was accepted to be significant.

TABLE 1 Clinical characteristics of study patients.

Parameter	Study population ($n = 77$)
Age, years	57.5 ± 11.2
HT *n* (%)	39 (51%)
DM *n* (%)	19 (25%)
CAD *n* (%)	9 (12%)
HPL *n* (%)	11 (14%)
PM/ICD *n* (%)	3 (4%)
AAD *n* (%)	62 (81%)
EHRA class	2.7 ± 0.68
HAS-BLED	1 ± 1.1
CHA2DS2-VASC	1.68 ± 1.4

Abbreviations: AAD, antiarrhythmic drug; CAD, coronary artery disease; CHA2DS2-VASC, congestive heart failure-hypertension-age (≥75)-diabetes mellitus-stroke/TIA/thromboembolism-vascular disease-age(65-74)-sex category; DM, diabetes mellitus; HAS-BLED, hypertension-abnormal liver or renal function-stroke-bleeding-labile INR-elderly-drugs or alcohol; HPL, hyperlipidemia; HT, hypertension; ICD, implantable cardioverter defibrillator; PM, pacemaker.

3 | RESULTS

A total of 77 patients with PAF underwent PVI by CB-2. All patients were included and completed initial echocardiography and followed up 3 months after the procedure with a control echocardiogram. All patients were in sinus rhythm at the time of ablation and after the procedure. No major complications were observed.

3.1 | Baseline characteristics

Patient demographics and clinical characteristics were presented in Table 1. The mean age was 57.5 ± 11.2 years and 44 patients were men (57%). None of the patients had undergone a prior ablation procedure. The mean CHA2DS2-VASC score was 1.68 ± 1.4.

4 | 2D-ECHOCARDIOGRAPHIC PARAMETERS

The LA dimension, measured from the long apical axis, was 41.3 ± 6 mm before the procedure and 41.4 ± 6 mm ($p = .25$) 3 months after the procedure. LAVI, measured using the biplane method and corrected for body surface area, was non-significant. E and A wave velocities were measured by using Doppler method and although velocities before

TABLE 2 Comparison echocardiographic parameters of the patients before and 3 months after the procedure.

Parameter	Before cryoablation ($n = 77$)	3th month after cryoablation ($n = 77$)	p-value
LA diameter (mm)	41.3 ± 6	41.4 ± 6	.25
LAVI (ml/m^2)	31 ± 11.5	30 ± 10.9	.288
LA strain-LAsr	28.2 ± 12.8	34.6 ± 13.8	<.001
LA strain-LAscd	−18.1 ± 9	−19.4 ± 10.4	.271
LA strain- LAsct	−10.9 ± 7.9	−14 ± 9.3	.014
LV endo-average strain	−20.4 ± 3.8	−21.4 ± 8	.287
LA-EMT lateral (ms)	94.5 ± 19.3	98.4 ± 19.1	.052
LA-EMT medial (ms)	74 ± 19.2	77.2 ± 19.9	.176
E/e'	9.5 ± 2.8	9.6 ± 3.1	.684
E wave velocity (m/s)	83 ± 19.7	82.1 ± 19.7	.69
A wave velocity (m/s)	65.6 ± 20.6	68.2 ± 18.7	.35
TRV (m/s)	2.44 ± 0.3	2.43 ± 0.3	.81
Medial E/e'	10.3 ± 3.2	10.3 ± 3.7	.99
Lateral E/e'	8.8 ± 3.1	8.8 ± 2.9	.87

Abbreviations: LA, left atrium; ms, milliseconds; m/s, meters/second; EMT, electromechanical time delay; TRV, tricuspid regurgitation velocity; LAsr, Left atrium reservoir strain; LAscd, Left atrium conduit strain; LAsct, Left atrium contractile strain; LAVI, Left atrium volume index.

the procedure were shown to be increased in the 3rd-month control echocardiography, the difference was not statistically significant. Likewise, there were no significant differences in lateral and septal E/é values, indicators of diastolic dysfunction. Prolongation, observed in the electromechanical delay time of lateral and medial mitral annular tissues was found to be statistically non-significant. Details of echocardiographic data was presented in Table 2.

4.1 | Speckle tracking echocardiography analysis

The LA and the LV strain parameters at baseline and at 3 months after the procedure are listed in Table 2. Significant increase was observed in the value of LAsr in the 3rd-month control of the patient population ($p < .001$) (Figure 1). LASct value was significantly lower than the basal value ($p = .014$) (Figure 2), on the other hand, the reduction in the value of LAScd was found statistically insignificant. Repeat echocardiographic LA strain measurements of 10 randomly selected participants were taken by the same observers and by another experienced reader 2 weeks later, which allowed for the determination of intra-class correlation coefficients (ICC) as a measure of intra-observer and interobserver agreement. The ICC values ranged from 0.873 to 0.966, indicating good interobserver and intraobserver repeatability. There were no significant differences observed between the values of the LV endocardial average strain before and after the procedure.

5 | DISCUSSION

The main finding of this study was the observation showing significant recovery after CB-2 ablation of LASr and LA contractile strain. AF is associated with progressive mechanical and electrical remodeling of the atria. Invasive treatment of AF has first consisted of PVI by the RF ablation method which is followed by CB ablation therapy, a method being used more and more frequently nowadays. Although there are multiple studies evaluating the electrical remodeling subsequent to CB-2, there is a shortage of studies on the subject of alterations in the mechanical function of LA. And if any change is present there is currently no standard method available for the measurement. It is well-known that the RF ablation method requires RF energy to be applied in order to create thermal injury in the LA tissue. Most of the time, a large-sized RF ablation area is needed to end AF successfully. Generally, in contrast to primary PV isolation and subsequent CB ablation method, additional ablation lines may be required for roof, anterior wall, septum, mitral isthmus and/or posterior annulus and if necessary for fractionated atrial electrograms to restore the sinus rhythm effectively. RF ablation leads to coagulation necrosis and strong inflammatory responses through the migration of mononuclear cells and neutrophils, as well as the rapid increase of inflammatory markers.[15] Furthermore, RF ablation by increasing the fibrotic tissue in the wall of the LA leads to structural changes which causes progressive remodeling. While the LA reservoir function stays relatively the same, conduit function of the LA decreases.[16] On the other hand, CB leaves the endocardium intact and creates a more homogeneous lesion. Studies on RF ablation illustrated by various imaging modalities including cardiac MRI and echocardiography depicted that the degree of ablation is correlated with the degree of disruption in left atrial mechanical functions, especially in the early period following RF ablation.[17,18] Among the patients with PAF who were followed after RF ablation therapy, left atrial functions failed to improve in some of them while in the others reverse remodeling took place only after 6 months.[19] Our study is unique in the sense that it has serially assessed the left atrial

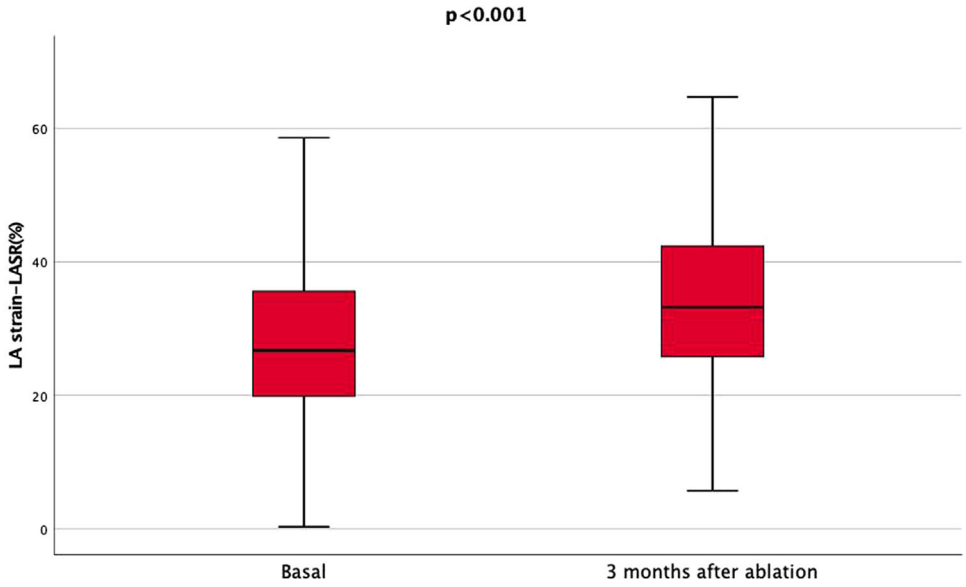

FIGURE 1 A significant increase in the LA diameter is seen in the 3rd month. LA, left atrium. [Color figure can be viewed at wileyonlinelibrary.com]

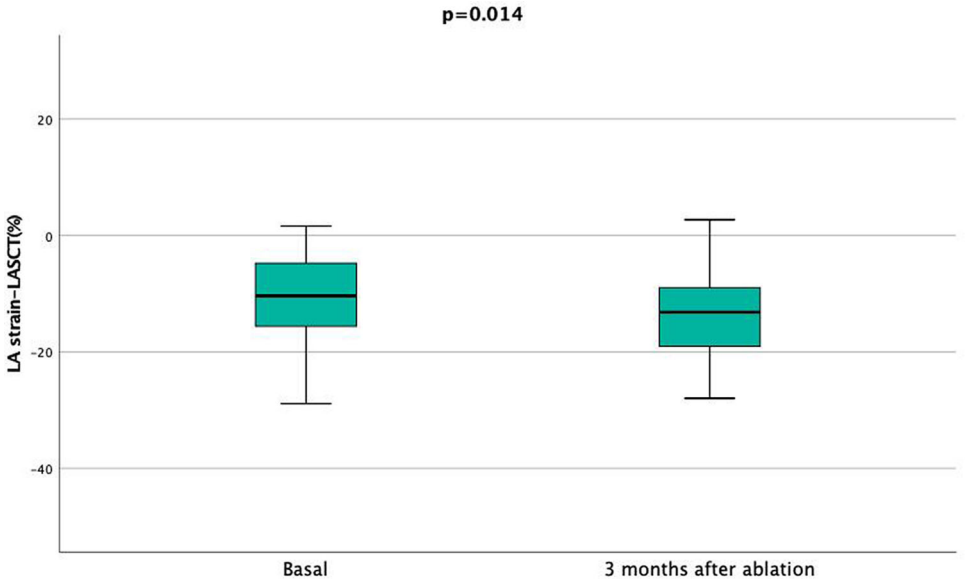

FIGURE 2 Changes in speckle tracking echocardiography parameters of the LA after pulmonary vein isolation by cryoballoon. LA, left atrium; PV, pulmonary vein. [Color figure can be viewed at wileyonlinelibrary.com]

performance shortly after cryoablation using a uniform method. In our study in addition to the transmitral flow velocities, a diastolic dysfunction parameter that is, highly dependent on the strain patterns, 2D-STE, a non- Doppler-based method assessing the mechanical functions of the LA was also used. LA strain and strain rate imaging using tracking of acoustic kernels by 2D-STE, a novel angle-independent tool for measuring myocardial stretch with the ability to quantitatively analyze global and regional LA contractility and relaxation, could therefore serve as a noninvasive tool to identify contractile dysfunction while overcoming the existing limitations of Doppler-based technologies.[20]

In a previous study which is performed using 2D-STE method and includes the patients with persistent and paroxysmal AF, peak atrial longitudinal strain parameter which is measured before the procedure has been shown to be effective in predicting the AF recurrences occurring 3 months after the procedure in both patients with LA size in normal ranges and patients with an enlarged LA.[21] The results of our study detected no significant change in the parameters of diastolic functions. Despite the non-significant increase in the left atrial dimension, a significant improvement was detected in the parameters, LAsr and LAsct which shows the ability of compliance and

contractility of the LA through the 2D-STE method. The average value of LA reservoir and contractile strain parameters were found to be lower than the normal reference range, but it subsequently recovered to the slightly lower limit of normal average value. This can be considered clinically significant.[22] The use of angiotensin-converting enzyme inhibitor (ACEi), ARBs, and ARNIs may have an effect on atrial remodeling. When compared between patients included in the study before and after cryoballoon treatment, there was no difference found between the use of these drugs, which suggests that the improvement in parameters related to left atrial function may be due to the effect of the treatment rather than the drugs used. This result is in compliance with the former studies which have also pointed out that left atrial mechanical function is an independent variable, regardless of the left atrial dimension. Although significant improvement in left atrial mechanical functions was observed, no improvement was detected in the LV endocardial average strain values.

5.1 | Limitations

The major limitation of the present study is relatively small sample size. Additionally this study lack of conclusion on persistent or long standing persistent AF patients, due to enrollment of PAF. In four of the patients who were included in the study, the 2D-STE measures were taken after the CV. For this reason observation of the improved left atrial functions of these patients in the 3rd month control measures may be associated with post-CV stunning interfering with the basal rates. Even though the progression of left atrial functions in patients with PAF is detected in our study, it is still unknown whether the early periodical effects of cryoablation therapy on patients with persistent AF are.

6 | CONCLUSION

LASr is an indicator of left atrial compliance and LA contractile strain is an indicator of left atrial contractility. Significant improvement in mechanical functions may occur even in the early period after cryoballoon ablation in patients with PAF.

AUTHOR CONTRIBUTIONS

Ali Ugur Soysal: Conception of design or analysis and interpretation of data or both drafting the article or revising it, providing interlectual content of importance to the work described, final approval of the version to be published. Sila Ozturk: Conception of design or analysis and interpretation of data or both final approval of the version to be published. Sukriye Ebru Onder: drafting the article or revising it, final approval of the version to be published. Adem Atici: Conception of design or analysis and interpretation of data or both final approval of the version to be published. Hasan Tokdil: Conception of design or analysis and interpretation of data or both drafting the article or revising it, final approval of the version to be published. Utku Raimoglu: Conception of design or analysis and interpretation of data or both providing interlectual content of importance to the work described, final approval of the version to be published. Asli Gulfidan: Conception of design or analysis and interpretation of data or both providing interlectual content of importance to the work described, final approval of the version to be published. Hakan Yalman: Conception of design or analysis and interpretation of data or both providing interlectual content of importance to the work described final approval of the version to be published. Eser Durmaz: Drafting the article or revising it, final approval of the version to be published. Baris Ikitimur: Final approval of the version to be published. Kivanc Yalin: Conception of design or analysis and interpretation of data or both drafting the article or revising it, providing interlectual content of importance to the work described, final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data is available and permission might be sought per reasonable request.

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