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Correlation between Left Atrial Strain and Subtle Cardiac Arrhythmias Detected by Holter Monitoring in Non-Cardiac Individual Recovering from COVID-19

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ABSTRACT
Background: Atrial fibrillation (AF) is the most often observed arrhythmia linked to COVID-19 pneumonia. Analysis of left atrial strain (LAS), a measure of LA contractility, has been applied in numerous therapeutic contexts, has been linked to the onset of AF.
Objective: The current study aimed to focus on correlation between left atrial strain and subtle cardiac arrhythmias detected by holter monitoring in noncardiac individual recovering from COVID-19.
Patients and methods: From March 2022 to August 2022, the Cardiology Department of the Faculty of Medicine at Zagazig University conducted a cross-sectional study on all COVID-19 survivors who had no cardiac issues. An automated piece of software was used to analyse the LA strain. Three phases of LA strain were reported: reservoir phase (LASr), conduit phase (LAScd), and contraction phase (LASct). The main result was the onset of AF.
Results: A total 76 patients were recruited for the current study. Patients were divided into two groups; ***Group I*** 15 patients with AF and ***Group II*** 61 Patients without AF. LAVI, LA strain reservoir, LA strain contraction and CRP were the most significant predictors of AF in post COVID patients. **Conclusion:** We found high incidence of LAS impairment using speckle tracking echocardiography that can predict AF in post COVID patients.
Keywords: Left atrial strain, Atrial fbrillation, COVID-19, Cross-sectional study, Zagazig University.

INTRODUCTION

In recent months, the global pandemic known as coronavirus disease 2019 (COVID-19), which is brought on by the SARS-CoV-2 coronavirus, has spread to more than 150 countries [1].

The respiratory system is the primary site of clinical symptoms in COVID-19 patients; however cardiovascular problems have also been noted in the first cases from Wuhan, the outbreak's epicentre [2]. COVID-19 can cause cardiac damage and have a severe impact on heart function. Furthermore, the latter is linked to a rise in illness severity and mortality outcomes [3, 4]. Even though 85% of individuals with COVID-19 only had minor symptoms, up to 15% of individuals experience serious consequences such sudden cardiac damage, acute respiratory distress syndrome, or arrhythmia [4].

The pathogenesis of the cardiac problems in COVID-19 is significantly influenced by a number of pro-inflammatory agents. According to earlier research, COVID-19 frequently combines ARDS (20%), arrhythmias (17%), shock (9%), and acute cardiac damage (7%) symptoms. Patients admitted to the intensive care unit (ICU) with COVID19 experienced a greater rate of arrhythmia (44%) [5].

According to **Guo *et al*.** [4], the total incidence rate of ventricular tachycardia (VT)/ventricular fibrillation (VF) during hospitalisation was 7%.

There is little evidence connecting myocardial injury in this cohort to arrhythmias such atrial fibrillation/flutter, Even if myocardial damage from Coronavirus disease 2019 (COVID-19) has been linked to unfavourable outcomes [6,7].

Left atrial strain (LAS), a measure of atrial deformation that has previously been shown to be predictive of AF and cardiovascular events in stable outpatients, can now be quantified thanks to recent developments in two-dimensional echocardiography (2DE), including speckle-based strain quantification [8].

With an incidence ranging from 1.9 to 43.9% in the critically ill, atrial fibrillation (AF) is common and significantly increases morbidity and mortality [9]. According to the most recent literature, AF is the most often recorded arrhythmia for patients with COVID-19, with a frequency between 19 and 36% [10].

A non-Doppler echocardiographic technique called left atrial (LA) strain (LAS) analysis evaluates LA function, stiffness, and fibrous remodelling based on LA myocardial deformation [11,12]. This method enables a precise analysis of the three main phases of LA function (reservoir, conduit, and contraction). Angle independence, reduced reverberation effects, practicability, and reproducibility are the key benefits of LAS over Doppler [11]. In numerous clinical scenarios, Bi-dimensional speckle tracking echocardiographic (2DSTE) features of LA dysfunction have been connected to the prevalence of AF, similar to ischemic stroke [13] or heart failure [14].

The current study aimed to focus on correlation between left atrial strain and subtle cardiac arrhythmias detected by holter monitoring in non-cardiac individual recovering from COVID-19.

PATIENTS AND METHODS

From March 2022 to August 2022, a cross-sectional study was conducted at the Cardiology Department, Faculty of Medicine, Zagazig University. All patients

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recuperating from COVID-19 who had no cardiac issues were included in the study. Patients with known organic cardiac diseases like rheumatic heart disease, ischemic heart disease, heart and muscle disease, and pericarditis. Patients having a history of CHF, permanent AF, permanent atrial and/or ventricular flutter, heart failure, systemic hypertension, diabetes, dyslipidemia, obstructive sleep apnea, or any of these disorders are also included in this study.

A total 76 patients were recruited for the current study. Patients were divided into two groups; ***Group I*** 15 patients with AF and ***Group II*** 61 Patients without AF.

All participants were subjected to the following:

Full history taking were obtained including symptoms (onset and duration of palpitation), duration of COVID19 infection and any history of procedures done. Medication history of drugs taken was reported. Complete physical examination and the vital signs and local examination including additional heart sounds namely S3 and S4 and to discover and exclude any murmur were done. Laboratory investigations included white blood cell count and its differential count.

All patients underwent tests for troponin, D-dimer, and high-sensitivity C-reactive protein (CRP). Using the holter device, patients' heart rates and rhythms were observed for 24 hours. An echocardiogram was performed on the heart to rule out organic heart disease.

LAS analysis:

An automated speckle tracking programme with a mode specifically for LAS analysis was used to achieve the results. The three stages of the LAS (LAScd) are the reservoir strain in systole, the conduit strain in early diastole, and the contraction strain in late diastole. LASr has a positive value while LASct and LACcd have negative values. An ideal apical four-chamber image was used to automatically calculate the LAS values for each phase. The LA endocardial border was manually modified as necessary after the regions of interests (ROI) were mechanically produced. The QRS complex served as the initial zero-baseline strain ECG reference point. All LAS procedures were carried out by an experienced cardiologist who was deaf to clinical information [15].

LA cycle: Using the LA longitudinal strain curve, the computer automatically calculated the LAS values. The LA reservoir function represents the initial peak positive deflection when using the QRS complex as a zero-reference point. At the start of the P wave contraction, the value of the LA contraction function was established. The difference between the values of LASr and LASct was used to determine the value of the LAS conduit function. The definition and measurement of the LA phases were carried out in accordance with the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [11].

Ethical Approval:

The study was approved by the Ethics Board of the Zagazig University and an informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All data was collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Qualitative data was expressed as absolute frequencies (number) and relative frequencies (percentage), and quantitative data was expressed as the mean and SD, and median (range).

Descriptive statistics were used to describe demographic and key clinical characteristics of the study population. Chi-square test ($\chi 2$) was used to calculate difference between two or more groups of qualitative variables. Student's t-test/Mann Whitney test was used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values. P value was set at ≤ 0.05 for significant results and ≤ 0.001 for high significant result.

RESULTS

Table 1 shows that there was statistically significant difference in age (P= 0.002) in relation to AF where patients in *Group I* were statistically older than patient in *Group II*. About 66.7% of patients in *Group I* were female while 59.1% of patients in *Group II* were female with no statistically significant difference in sex (P= 0.770). Table 1 summarizes and compares the demographic data of the studied groups.

Table (1): Comparison between the two groups concerning demographic data among post COVID patients

Variable		Post COVID-19				p-value [b]
		Group I (N=15)		Group II (N=61)		
		No	%	No	%	
Age (years)	Mean ± SD	41.67 ± 1.29		32.41 ± 10.4		0.002* (S)
	(Range)	40-43		22-58		
Sex	Male (n= 30)	5	33.3	25	40.9	0.770 [a] (NS)
	Female (n=46)	10	66.7	36	59.1	
Comorbidities	HPN	0	0.0	5	8.2	0.576 [a]
	DM	0	0.0	5	8.2	0.576 [a]
	Dyslipidemia	0	0.0	5	8.2	0.576 [a]
	Smoking	5	33.3	5	8.2	0.022* [a]
BMI	Mean ± SD	29.35 ± 4.9		27.7 ± 4.11		0.769 (NS)
	(Range)	25.4-36.1		20.26-35.4		
HR	Mean ± SD	87.6 ± 12.08		82.5 ± 7.15		0.092 (NS)
	(Range)	721-100		67- 96		
SBP	Mean ± SD	130 ± 0.0		122.6 ± 10.5		0.016* (S)
	(Range)	130-130		110-140		
DBP	Mean ± SD	75 ± 5.27		77.14 ± 6.2		0.339 (NS)
	(Range)	70-80		70-90		
WBCs	Mean ± SD	0.66 ± 0.09		2.18 ± 0.84		0.001* (HS)
CRP	Mean ± SD	38.67 ± 10.56		27.27 ± 20.19		0.006* (S)
	(Range)	26-51		5-77		

*[a]: Chi-square test, [b]: Mann Whitney test, *P-value is statistically significant.*

Table 2 shows that there were statistically significant differences in APCs, tachycardia, LAVI, LA strain reservoir, and LA strain contraction. There was no statistically significant difference regarding VPC, bradycardia, LVEDV, LVESV, and EF.

Table (2): Comparison between the two groups concerning Holter monitor and echocardiographic findings among post COVID patients

Variable		Post COVID-19				P-value
		Group I (N=15)		Group II (N=61)		
		No	%	No	%	
Arrhythmias						**P-value [a]**
▪ APCs		5	33.3	41	67.2	0.021*
▪ VPCS		0	0.0	5	8.2	0.576
▪ Bradycardia		0	0.0	5	8.2	0.576
▪ Tachycardia		15	100.0	25	40.9	0.000**
						P-value [b]
LVEDV (mm)	Mean ± SD	51 ± 1.69		49.9± 3.13		0.148
	(Range)	49-53		45-56		
LVESV (mm)	Mean ± SD	29.33 ± 3.2		31.25 ± 2.14		0.135
	(Range)	25-32		27-35		
EF (%)	Mean ± SD	69 ± 4.47		69.21 ± 4.13		0.489
	(Range)	69- 75		60-75		
LAVI (mL/m^2)	Mean ± SD	23.04 ± 4.7		15.66 ± 1.29		0.000*
	(Range)	15.8-32.62		14-17		
LA strain reservoir	Mean ± SD	46.27 ± 9.86		24.98 ± 10.56		0.000*
	(Range)	33-60		15-45		
LA strain contraction	Mean ± SD	-10.33 ± 2.1		-6.44 ± 2.6		0.000*
	(Range)	-12 - -6		-10 - -2.5		

*[a]: Chi-square test, [b]: Mann Whitney test. *p-value is statistically significan.t*

Table 3 showed that using logistic regression analysis, LAVI, LA strain reservoir, LA strain contraction and CRP were the most significant predictor of AF in post COVID patients while LVEDV, LVESV, EF, SBP, WBCs, APC and tachycardia were not significant.

Table (3): Logistic regression analysis to predict the associated factors with AF

Variable	B	S.E.	Sig.	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
LVEDV (mm)	0.12	0.228	0.57	1.13	0.72	1.77
LVESV (mm)	-0.29	0.26	0.27	0.74	0.44	1.25
EF (%)						
LAVI	3.7	0.16	0.04*	1.24	1.1	2.45
LA strain reservoir	5.1	0.2	0.03*	1.67	1.07	3.1
LA strain contraction	-2.68	0.09	0.04*	0.61	0.18	0.86
CRP	4.5	0.29	**0.03***	2.5	2.1	4.68
SBP	0.29	0.06	0.57	0.368	0.21	1.67
WBCS	0.23	0.18	0.72	0.68	0.41	1.91
APC	-0.58	0.075	0.81	0.13	0.05	3.1
Tachycardia	0.67	0.003	0.68	0.35	0.221	1.9

Table 4 shows significant sensitivity and specificity of LAVI, LA strain reservoir and LA strain contraction and CRP in identifying AF, where AUC of LAVI = 0.87, LAVI greater than or equal 21.5 had sensitivity 100% and specificity 77% in diagnosing patient with or without AF, also, AUC of LA strain reservoir =0.0.879, LA strain reservoir greater than or equal 31.5 had sensitivity of 100% in diagnosing patient with or without AF, also AUC of LA strain contraction =0.874, LA strain contraction greater than or equal -9.5 had sensitivity of 85.5% and specificity of 66.7% % in excluding patient with RF, in addition AUC of CRP = 0.97, CRP greater than or equal 33 had sensitivity 85.5% and specificity 66.7% in diagnosing patient with or without AF. ROC curve showing that LA strain reservoir had good diagnostic potientials than LA strain contraction where sensitivity was 100 % vs 85.5% respectively for AF diagnosis.

Table (4): Diagnostic potential of LA strain in predication of AF in post COVID patients with ROC curve

Test Result Variable(s)	Cut off level	AUC	95% CI	Sensitivity	Specificity	P-value
LAVI	≥21.5	0.87	0.08-0.92	100%	77%	0.04
LA strain reservoir	≥ 31.5	0.879	0.82- 0.79	100%	67.2%	0.000*
LA strain contraction	≥ -9.5	0.874	0.77- 0.97	85.5%	66.7%	0.000*
CRP	≥33	0.97	0.2-0.88	100%	90.2%	0.01*

DISCUSSION

The coronavirus sickness 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently attracted attention worldwide, spreading to more than 150 nations in a pandemic [1].

There have been new reports of other organ involvements in the course of the disease, such as the neurological system [16] and the heart involvement, in addition to the typical respiratory symptoms and pulmonary [17] (which may be severe) [4].

The circulatory manifestations of COVID-19 and the detrimental effects of cardiovascular involvement on prognosis are becoming more widely known. In the case of COVID-19, cardiac involvement mostly relates to myocardial injury and manifests as increased troponin levels among other myocardial injury biomarkers [17].

With an incidence ranging from 1.9 to 43.9% in the critically ill, the frequency of atrial fibrillation (AF) dramatically raises morbidity and death [9]. Atrial fibrillation (AF) is the arrhythmia that has been identified most frequently in COVID-19 patients [10]. It seems to occur more frequently in COVID-19 patients who perish away [18]. LAS analysis of the left atrium is a non-Doppler echocardiographic approach, employs the deformation of the LA myocardium to represent LA contractility and assess the function, stiffness, and fibrous remodelling of the LA [12]. We aimed in the present study, to evaluate the link between left atrial strain and subtle cardiac arrhythmias detected by Holter monitoring in non-cardiac individual recovering from COVID-19.

According to relation between AF and demographic data among post COVID patients, we showed that there was statistically significant difference in age but there was no statistically significant difference in sex in relation to AF where patients with AF were statistically older than patient without AF where age of the studied patients in AF ranging from 40-43 years old with mean 41.67 (SD 1.29) years old while age of the studied patients without AF ranging from 22-58 years old with mean 32.41 (SD 10.4) years old, also 33% of AF patients where smokers vs 8.2% of non-AF patients where smokers with statistically significant difference. There was statistically significant difference in SBP, WBCs, CRP in relation to AF post COVID-19 where SBP was statistically higher in AF patients than no AF cases, and CRP was statistically higher in higher in AF patients than no AF cases, there was no statistically significant difference regrading other laboratory investigation.

Also, **Beyls *et al***. [15] found that 16/79 patients (20%) had AF documented, and that patients in the AF group were older than those in the no AF group (73 [65-76] vs. 65 [59-70] years; P= 0.026).

Tleyjh *et al.* [19] followed up 222 patients after being discharged from King Fahad Medical City. Older age was identified as risk factors for developing post-COVID syndrome. Shockingly, patients with DM had lower tendency to be symptomatic after the acute COVID-19 illness.

Similarly, **Pavli *et al.*** [20] reported that more than one third of the symptomatic patients had CVS risk factors or other co-morbidities in general.

Our result demonstrated that there was statistically significant difference in APCs and tachycardia, LAVI and LA strain reservoir and contraction in relation to AF occurrence, there was no statistically difference regarding other echocardiographic data.

In agreement with our study, **Beyls *et al*.** [15] demonstrated that LAS parameters of the 2 groups differed significantly in terms of echocardiographic parameters. The LASr and LAScd of the AF group were considerably worse than those of the control group (P values 0.002 and 0.0001, respectively): 20.2 [12.3; 27.3] vs. -30.5 [23.8; 36.2] % and 8.1 [6.3; 10.9] vs. 17.2 [5.0; 10.2] %. LASct did not differ significantly between groups (P= 0.31).

The LAVI was found to be lower in COVID-19 patients with AF as compared to COVID-19 patients without AF, according to **Goerlich *et al*.** [21]; this information shows that LA dysfunction arose suddenly rather than as a result of continuing remodelling. Lower LAS may be a more accurate predictor of atrial damage in this group than LAVI, according to the correlation between LAS and AF in COVID-19. Lower LAS may also be a higher-risk COVID-19 phenotype that needs to be closely watched for cardiac disorders like AF.

Regarding significant sensitivity and specificity of LAVI, LA strain reservoir and LA strain contraction and CRP in identifying AF in our study, AUC of LAVI 0.87, LAVI greater than or equal 21.5 had sensitivity 100% and specificity 77% in diagnosing patient with or without AF, also, AUC of LA strain reservoir 0.0.879, LA strain reservoir greater than or equal 31.5 had sensitivity of 100% in diagnosing patient with or without AF, also AUC of LA strain contraction 0.874, LA strain contraction greater than or equal -9.5 had sensitivity of 85.5% and specificity of 66.7% % in excluding patient with RF, in addition AUC of CRP 0.97, CRP greater than or equal 33 had sensitivity 85.5% and specificity 66.7% in diagnosing patient with or without AF.

This was in line with the findings of **Jasic-Szpak *et al*.** [22] who discovered that LA strain contraction offers a small amount of prognostic data about the occurrence of AF. These LA strain components could aid direct screening and ongoing AF risk management if they are included in the diagnostic methodology. One of the LA functional indices, the LA strain, has been successfully used as a prognosticator, enhancing the evaluation of AF risk in a variety of clinical situations [23,24,25].

Its ability to represent various LA functional features, such as reservoir, conduit, and booster pump components, in the context of left ventricular (LV) filling is what gives this special imaging biomarker its wide range of applications. LA strain analysis appears to be trustworthy and repeatable, which may both support its usage for predictive purposes. According to multiple studies, LA remodelling brought on by a number of cardiovascular diseases, including hypertension, diabetes, and ischemic heart disease, may manifest as reduced LA reservoir function [26,27].

The LAS reservoir parameter measures LA compliance and also is a marker for the likelihood that AF will develop after cardiac surgery, heart failure, or an ischemic stroke [12].

Many studies looked into the connection between LA strain and poor results in COVID-19 patients.

According to the **Beyls *et al*.** [15] study, The cutoff value of 11% discovered was comparable to previously established cutoff values in a number of cardiovascular diseases, and the LAScd was a potent predictor of AF. For instance, it has been observed that the LA conduit function (12.65.7%) in Chagas disease is a good predictor of AF because the LA conduit function is depressed [28].

In the ***Beyls et al.*** [15] trial, COVID-19 AF group's LASr values were considerably worse (30.5 [23.8-36.2] % vs. 20.2 [12.3-27.3] %; P= 0.002). In our work, we assessed the LA strain's ability to predict the development of dyspnea and exercise intolerance following the recovery from COVID-19. While the LA strain reservoir was 46.27 9.86 in symptomatic AF patients and contraction was -10.33 2.1, the LA strain reservoir was 24.98 10.56 in asymptomatic AF patients and contraction was -6.44 2.6. **Goerlich *et al*.** [21] observed identical LASr values to those in the current study (30.4 [26.1- 35.8] % vs. 22.3 [20.6-27.8] % in symptomatic versus normal cases), and they demonstrated that the LASr parameter was a standalone predictor of AF in post-COVID-19 patients. According to **Di Vilio *et al*.** [29], patients with cardiac damage had significantly higher LA volume index and CRP levels. It was found that individuals who had cardiac damage were more likely to get AF (28 of 70 [40.0%] versus 23 of 210 [10.4%]; P= 0.0001) and that they were also more likely to die. In post COVID patients, CRP was substantially linked to new arrhythmias, according to research by **RavAcha *et al*.** [30].

Additionally, according to **Kelesoglu *et al*. (31)** patients with new onset AF exhibited greater CRP levels than those who did not. More conclusive epidemiologic information is required. Given the high frequency of electrolyte problems in ill individuals [3] and the documented effects of various medicines empirically used to treat SARS-CoV-2 infections, including chloroquine, on myocyte repolarization, raising the likelihood of QT prolongation and consequent arrhythmias, high vigilance by the treatment teams is required to prevent iatrogenic harm. While these patients were recovering, evaluation of LV and LA shape and function may serve as important cues for prognostic classification [32].

CONCLUSION

In our study, we targeted the patients recovered from COVID-19, left atrial strain was assessed trying to explain the cardiac involvement and if it is the cause of the so called" long COVID". We found high incidence of LAS impairment using speckle tracking echocardiography that can predict atrial fibrillation in post COVID patients.

DECLARATIONS

- **Consent for Publication:** I confirm that all authors accept the manuscript for submission
- **Availability of data and material:** Available
- **Competing interests:** None
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- **Conflicts of Interest:** The authors declare no conflicts of interest regarding the publication of this paper.

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