

# Cardiac Involvement in Patients Recovered From COVID-19 Identified Using Left Ventricular Longitudinal Strain

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## Research Article

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# Abstract

Coronavirus disease-19 (COVID-19) has been associated with subclinical myocardial dysfunction during its acute phase and a recurring pattern of reduced basal left ventricular longitudinal strain on speckle-tracking echocardiography (STE) in hospitalized patients. But a question still remains unanswered: speckle tracking echocardiography might also be suitable to detect residual myocardial involvement after acute stage of COVID-19?

**Methods and results:** We studied 100 patients recovered from COVID-19 with STE to evaluate global (GLS) and segmentar longitudinal strain (LS) and compared with a control group of 100 healthy individuals. STE was performed at a median of 130.35 +/- 76.06 days after COVID-19 diagnostic. Demographic and echocardiographic parameters are similar in both groups. Left ventricular ejection fraction (LVEF) and GLS were normal in COVID-19 patients (66.20 +/- 1.98% and -19.51 +/- 2.87%, respectively). A reduction in mean LS for the basal segments was found in COVID-19 (16.48 +/- 5.41%) when compared to control group (19.09 +/- 4.31%) ( $p < 0.001$ ).

**Conclusion:** The present study suggests that COVID-19 induced cardiac involvement could persist after recovery of the disease and may be detected by deformation abnormalities using STE. COVID-19 induced myocardial involvement often shows specific LV deformation patterns due to pronounced edema and/or myocardial damage in basal LV segments.

## Introduction

Coronavirus disease 2019 (COVID-19), resulting from infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is causing a worldwide pandemic with high morbidity and mortality. Until the present moment (mid March, 2021) a total of 127 million people were infected, with 2.78 million deaths and 71.8 million recovered. Although the respiratory system sees the major impact of the illness, increasing reports describe important cardiac manifestations [1–4].

Myocardial injury, characterized by cardiac biomarkers elevation and/or abnormalities on transthoracic echocardiography and cardiac magnetic resonance imaging have been yet reported in hospitalized COVID-19 patients [2, 5–9]. This myocardial damage can be caused directly by SARS-CoV-2 virus or by immunopathological sequelae of myocardial inflammation [10–12] and is associated with adverse outcomes and increased mortality [2, 7, 13, 14]. In addition, residual myocardial damage after recovery of the acute phase of the disease might have a significant impact on the patients' long-term prognosis and can culminate in SARS-CoV-2 induced myocardial fibrosis [9]. Furthermore, we suspected that systemic inflammation and hypoxemia may cause secondary myocardial injury in COVID-19.

A technique easily combined with standard echocardiographic measurements is 2-dimensional speckle tracking echocardiography (STE), which tracks unique speckle pathways during the cardiac cycle to determine myocardial deformation and strain. Strain evaluates myocardial dysfunction and the subclinical impairment of myocardial earlier and has been shown to be more sensitive and accurate in

detecting left ventricular (LV) dysfunction compared with the LV ejection fraction (LVEF), specially the Global Longitudinal Strain (GLS) [15–18]. STE quantifies myocardial deformation globally and regionally, regardless of the insonation angle or cardiac translational movements.

The analysis of segmental longitudinal strain (LS) patterns can be helpful in the identification of cardiac diseases when a characteristic abnormality is seen in conjunction with clinical data, such as the pathognomonic apical-sparing strain reduction seen in cardiac amyloidosis [19]. A recurring pattern of reduced basal left ventricular LS on STE was observed in hospitalized patients with COVID-19.

The question of whether chronic cardiac issues are present after COVID-19 recovery still remains and long-term follow-up is needed.

The aim of our study is to characterize the left ventricular LS patterns in COVID-19 recovered patients and compare with a control group of healthy patients, as whether COVID-19 could cause chronic cardiomyopathy was not known.

## Methods

This study was approved by and conducted according to the Institutional Review Board. This was a single-center prospective study of a hundred nonconsecutive patients admitted to our private institution from January 11, 2021, to February 24, 2021 with recovered COVID-19 diagnosed using nasopharyngeal polymerase chain reaction testing (Rt-PCR) in 89 patients (89%) and/or serological dosage of IgM (16 patients – 16%) and IgG (31 patients – 31%) to undergo clinically indicated transthoracic STE.

STE was performed by an experienced echocardiographer using S6 ultrasound systems (General Electric Vingmed Ultrasound, Milwaukee, WI) at a median of 130.35 +/- 76.06 days after Covid-19 diagnostic. Images were analyzed on a dedicated workstation using EchoPAC software (version 202, GE Ultrasound). Within this article, strain is referred to in absolute values. Global (GLS) and regional longitudinal deformation (LS) were assessed by determination of layer strain (basal, mid and apical levels) in all apical views based on the American Heart Association 17-segment model.

Two-D grayscale harmonic images and three consecutive cardiac cycles of each view were obtained, captured at a frame rate between 40 and 60 fps. The endocardial contour was manually adjusted, whereas only segments with accurate tracking by carefully visual evaluation were accepted to exclude imaging artifacts. Segments with poor strain curves were excluded.

LV deformation was analyzed in a control group consisted of 100 healthy patients who had no cardiopulmonary diseases according to their medical history, physical examination and electrocardiogram, who underwent echocardiography study as part of routine pre-surgical risk stratification.

Comparisons between groups were performed using Welch's *t* test for normally distributed continuous variables, and *p* level of < 0,001 was considered statistically significant.

## Results

A hundred patients with recovered COVID-19 underwent STE, with 1.633 (96.06%) myocardial segments of a total of 1.700 segments included in the analysis; 67 (3.94%) were excluded for poor quality of imaging.

Comorbidities such as hypertension and diabetes are rare and diagnosed in 26 (26%) and 11 (11%) patients of the COVID-19 group, respectively.

The majority of the patients had no symptoms/mild symptoms (83%), 5 patients had moderate symptoms needing hospitalization but no intubation and 2 (2%) had severe evolution with the need of intubation and mechanical ventilation, but all the patients in the COVID-19 group recovered well although almost half of them (46%) still have mild symptoms at the moment of echocardiogram (short of breath, thoracic pain, palpitations, loss of smell and/or taste).

The mean patient age was 46.93 +/- 15.24 years, and 59% were women; the mean control group age of 39.17 +/- 9.25 years ( $p < 0.001$ ) with 50% of women. Although this significant age difference the body surface area (BSA), the heart rate (HR) and left ventricle diastolic diameter (LVDD) were similar in both groups (respectively BSA = 1.85 +/- 0.22 m<sup>2</sup> vs 1.82 +/- 0.23 m<sup>2</sup>;  $p = 0.196$ , HR = 74.44 +/- 13.10 bpm vs 69.55 +/- 10.19 bpm;  $p = 0.003$ , and LVDD = 47.75 +/- 3.70 mm vs 47.47 +/- 3.78 mm;  $p = 0.088$ ) (Table 1).

Table 1  
Demographic and echocardiographic features

Variable	Covid-19 (n = 100)	Control (n = 100)	p-value
Age (years)	46.93 +/- 15.24	39.17 +/- 9.25	< 0.001
Sex (female)	59	50	0.071
BSA (m <sup>2</sup> )	1.85 +/- 0.22	1.82 +/- 0.23	0.196
LVEF (%)	66.02 +/- 1.98	68.60 +/- 5.33	< 0.001
LVDD (mm)	47.55 +/- 3.70	47.47 +/- 3.78	0.884
HR (bpm)	74.44 +/- 3.10	69.55 +/- 10.19	0.003

Data are mean +/- standard deviation; BSA body surface area; LVEF left ventricle ejection fraction; LVDD left ventricular diastolic diameter; HR heart rate.

Although the left ventricular ejection fraction (LVEF) was between the range of normality in both groups, a small but significant difference was found between the 2 groups (66.20 +/- 1.98% in the COVID-19 group vs 68.60 +/- 5.33% in the control group:  $p < 0.001$ ).

Left ventricular GLS for the COVID-19 group was 19.51 +/- 2.87% and was in between the 95%CI for normal, healthy patients with preserved LV function (19.7% - 95% CI: 20.4 to 18.9%) [20].

Regional LS values per myocardial segment for Covid-19 and control group are on Table 2, with no statistical difference between them all, in each group.

Table 2  
Regional LS values per myocardial segment

Wall	Segment	COVID-19 (%)	control (%)	p-value
Septal	Basal	14.34 +/- 5.13	18.10 +/- 3.02	<b>&lt; 0.001</b>
	Medium	19.70 +/- 4.01	20.52 +/- 2.68	0.079
	Apical	22.56 +/- 4.98	24.34 +/- 3.92	0.023
Lateral	Basal	16.98 +/- 5.76	18.29 +/- 5.21	0.001
	Medium	20.08 +/- 5.62	19.39 +/- 4.51	0.326
	Apical	23.09 +/- 5.28	23.02 +/- 4.91	0.924
Anterior	Basal	17.44 +/- 5.68	20.41 +/- 4.69	<b>&lt; 0.001</b>
	Medium	20.40 +/- 5.73	21.41 +/- 3.15	0.072
	Apical	21.32 +/- 6.05	23.63 +/- 4.79	0.003
Inferior	Basal	17.23 +/- 4.48	19.56 +/- 3.60	<b>&lt; 0.001</b>
	Medium	21.38 +/- 4.11	21.05 +/- 3.25	0.551
	Apical	23.76 +/- 4.26	24.32 +/- 4.48	0.409
Absolute values are mean +/- standard deviation. LS longitudinal strain.				

The mean LS for the basal segments was reduced in COVID-19 (16.48 +/- 5.41% ) when compared to control group (19.09 +/- 4.31%), with statistically significant difference between the groups ( $p < 0.001$ ) (Figs. 1 and 2). This reduction in LS in COVID-19 group was most prominent on anterior, inferior and septal basal segments (Table 2). LS values were similar for medium and apical segments in both groups.

## Discussion

To our knowledge, this is the first study in the literature evaluating LV mechanics by STE in long-term follow-up of recovered COVID-19 patients.

Indices of longitudinal strain are known to strongly correlate with the levels of lymphocytic infiltrates in endomyocardial biopsy (EMB) samples [21] and with the amount of edema detected by cardiac magnetic resonance (CMR) [22]. Moreover, the diagnostic performance of LS in acute myocarditis has been validated by showing preferential alteration of subepicardial deformation that was consistent with tissue characteristics established by CMR [23]. So, although CMR and EMB are the gold standards for the

diagnosis of myocarditis, the evidence shows a good correlation between echocardiographic strain and CMR [24].

Speckle-tracking echocardiography works as a “digital biopsy” and it could become an essential diagnostic tool for myocarditis and other cardiomyopathies [25].

Previous report using CMR in 100 individuals recovered from COVID-19 detected cardiovascular involvement in 78 of them, irrespective of preexisting conditions, the severity and overall course of the COVID-19 presentation, the time from the original diagnosis, or the presence of cardiac symptoms [26]. This study was corroborated by another autopsy study [27].

There are a few studies showing reduction in GLS during acute hospitalized patients, regardless of the severity of the COVID-19, even in the presence of normal LVEF [5,9,18,28-31] compatible with subclinical LV dysfunction.

In corroboration to our findings, other studies using STE for diagnosis of cardiac involvement during acute COVID-19 showed reduction of LS in more than one of the basal LV segments [9,32], despite normal LVEF and even in the presence of normal GLS. And in one study abnormal LV deformation patterns were still observed in 3 patients after recovery from acute stage, indicating residual myocardial involvement [9]. Furthermore, CMR showed late enhancement predominantly in the basal inferolateral/anterolateral LV segments indicating myocardial fibrosis or scars, respectively [8,9,33]. This basal injury pattern reflects the susceptibility of certain myocardial regions to inflammatory or systemic stressors rather than a geographic predilection specific to COVID-19.

Another plausible hypothesis, more specific to COVID-19, involves the viral receptor, angiotensin-converting enzyme 2 (ACE2). This membrane-bound enzyme is responsible for production of angiotensin [1-7], leading to well-described anti-inflammatory and anti-thrombotic effects [34]. ACE2 is highly expressed in fat, and epicardial adipose tissue (EAT) is more prominent in the atrioventricular groove and lateral LV wall, closer to the basal segments [35]. Loss of ACE2 has been shown to result in heart failure with preserved LVEF, mediated in part by EAT inflammation. Thus, COVID-19 binding of ACE2 may occur more prominently in areas of high EAT, such as the basal LV, and cause subclinical dysfunction via inflammatory downstream effects [32].

Case reports and series of patients with various forms of myocarditis, including influenza myocarditis, have described a similar pattern of reduced basal strain on STE [36,37]. Abnormal basal LS has also been seen in infiltrative cardiomyopathies including, Anderson-Fabry disease [38].

## Conclusions

The present study suggests that COVID-19 induced cardiac involvement could persist after recovery of COVID-19 and may be detected by deformation abnormalities using STE. COVID-19 induced myocardial

involvement often shows specific LV deformation patterns due to pronounced edema and/or myocardial damage in basal LV segments.

Whether myocardial viral activity in the absence of clinical evidence of myocarditis might result in long-term consequences is unknown, but the findings of our study indicate the need for ongoing investigation of the long-term cardiovascular consequences of COVID-19.

Further studies with large patient sample size will be needed to confirm and expand on our findings.

## Declarations

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**Conflicts of interest:** All Authors declare that they have no conflict of interest.

**Availability of data and material:** not applicable

**Code availability:** not applicable

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