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REGIONAL INVOLVEMENT IN LEFT VENTRICULAR STRAIN IN PATIENTS RECOVERED FROM COVID-19 PNEUMONIA

COVID-19 PNÖMONİSİ GEÇİRMİŞ HASTALARDA SOL VENTRİKÜL STRAİN DEĞERİNİN BÖLGESEL TUTULUMU

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ABSTRACT

Objective: COVID-19 patients with cardiovascular involvement have been shown to have a worse prognosis compared to those without cardiovascular compromise. This study aimed to investigate whether left ventricular (LV) global and regional strain is impaired in patients with COVID-19 with or without pneumonia after discharge.

Materials and Methods: Seventy-eight consecutive COVID-19 patients diagnosed by PCR test were enrolled in this cross-sectional study during their first follow-up visit to an outpatient clinic. All patients underwent two-dimensional echocardiography and speckle tracking echocardiography (STE) at the first follow-up visit. The patients were divided into two groups with or without pneumonia, and they were compared with the healthy control group.

Results: A total of 123 subjects were included in the study (78 with COVID-19 and 45 in the control group). Admission and follow-up hs-troponin-T concentrations were similar in both the control group and patients with varying severity of COVID-19. LV ejection fraction (EF) was similar in all groups. However, LV global longitudinal strain (GLS) was significantly lower in subjects with pneumonia compared to the control group and subjects without pneumonia. Regional strain analysis showed that subjects with pneumonia had significantly lower strain values at mid-anterior, mid-anteroseptal, apical-inferior, apical-lateral, and apex regions than subjects without pneumonia or the control group.

Conclusion: LV GLS and the regional strain were significantly impaired in COVID-19 patients with pneumonia compared to

ÖZET

Amaç: Kardiyovasküler tutulumu olan COVID-19 hastalarının, kardiyovasküler tutulumu olmayanlara göre daha kötü prognoza sahip olduğu gösterilmiştir. Bu çalışma, pnömonisi olan ve olmayan COVID-19 hastalarında taburculuk sonrası sol ventrikül (LV) global ve bölgesel strain değerinin bozulup bozulmadığını araştırmaktadır.

Gereç ve Yöntem: Bu kesitsel çalışmaya, PCR testi ile tanı konulan ve polikliniğimize başvuran 78 hasta dahil edildi. Tüm hastalara ilk muayenelerinde iki boyutlu ekokardiyografi ve speckle tracking ekokardiyografi (STE) yapıldı. Hastalar pnömonisi olan ve olmayan olarak iki gruba ayrıldı ve sağlıklı kontrol grubu ile karşılaştırıldı.

Bulgular: Çalışmaya toplam 123 kişi alındı (78 COVID-19 hastası, 45 sağlıklı kontrol). Hem kontrol grubunda hem de farklı ciddiyetteki COVID-19 hastalarında ilk ve takip hs-troponin-T değerleri benzerdi. Sol ventrikül ejeksiyon fraksiyonu (EF) tüm gruplarda benzerdi. Bununla birlikte, sağlıklı kontroller ve pnömonisi olmayan hastalara kıyasla pnömonisi olan hastalarda LV global longitudinal straini (GLS) anlamlı ölçüde daha düşüktü. Bölgesel strain analizi, pnömonisi olmayan hastalara ve kontrol grubuna kıyasla pnömonisi olan hastaların mid-anterior, mid-anteroseptal, apikal-inferior, apikal-lateral and apeks bölgelerinde önemli ölçüde daha düşük strain değerlerine sahip olduğunu göstermiştir.

Sonuç: Pnömonisi olmayan hastalara ve sağlıklı kontrollere kıyasla pnömonisi olan COVID-19 hastalarında sol ventrikül global ve bölgesel strain önemli ölçüde bozulmuştur. Bu bulgu, pnömonisi olan COVID-19 hastalarının, gizli sol ventrikül tutulumunun tes-

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those without pneumonia or in to control group. This finding indicates that COVID-19 subjects with pneumonia should undergo strain measurement to detect concealed LV involvement.

Keywords: COVID-19, pneumonia, left ventricle, regional strain

piti için strain ekokardiyografi ile değerlendirilmesi gerektiğini göstermektedir.

Anahtar Kelimeler: COVID-19, pnömoni, sol ventrikül, bölgesel strain

INTRODUCTION

COVID-19 is a multisystem disease that predominantly affects respiratory system (1). During the course of the disease, several systems including cardiovascular system are involved in many aspects (2, 3). First patients in Wuhan diagnosed with COVID-19 had myocardial involvement with an increase in high-sensitivity troponin I (hs-cTnI) levels (4, 5). Most of those patients with myocardial involvement were further admitted to the intensive-care unit (ICU), which indicates a more serious course of COVID-19 occurs when myocardial involvement is added to the pulmonary involvement (4).

Patients with cardiovascular risk factors are shown to be susceptible to more serious disease with wide-range of cardiac and cardiovascular involvements such as myocarditis, myocardial infarctions, and pulmonary embolism (6-9). Moreover, COVID-19 patients with elevated cardiac markers tend to have unfavorable prognosis (10). Although cardiac involvement by elevated cardiac biomarkers is observed in a substantial subset of patients with poor prognosis, transthoracic echocardiography (TTE) is normal or near-normal in many of these patients.

Strain imaging, which measures regional myocardial deformation of the ventricular myocardium, has been shown to detect myocardial involvement in hypertension, diabetes mellitus, and various systemic diseases prior to apparent changes in TTE (11-13). Limited data encourages the utilization of strain imaging for detection of myocardial involvement in COVID-19 patients. Recently, it was demonstrated that left ventricular global longitudinal strain (LV-GLS) was decreased in patients hospitalized for severe COVID-19 in comparison to non-severe COVID-19 patients despite similar LV ejection fraction (EF) (14). However, extensive evidence is still lacking concerning the role of strain imaging to detect myocardial involvement in patients with COVID-19 especially after recovery.

This study purposed to investigate the subclinical cardiovascular involvement by regional speckle tracking after recovery in COVID-19 patients without apparent myocardial involvement on TTE.

MATERIALS AND METHODS

Study design and participants

Seventy-eight consecutive COVID-19 patients who were diagnosed by PCR test admitted to our institute and discharged between March 2020 and June 2020 were enrolled in this cross-sectional study during their first follow-up visit to the outpatient clinic. Forty-five healthy individuals were enlisted as the control group. Patients with a history of prior cardiovascular disease (ischemic heart disease, heart failure, dilated or hypertrophic cardiomyopathy, and severe valvular disease) and those with pre-existing systemic disease that has cardiovascular involvement were taken out of the study.

Demographic features of the study group and the agents administered for the treatment of COVID-19 were recorded for each patient. Venous blood samples were drawn upon admission and at first follow-up visit in the outpatient clinic for complete blood count and measurement of high-sensitive troponin-T (hs-TnT), NT-proBNP, C-reactive protein (CRP), and serum ferritin concentration. All patients underwent TTE at the first follow-up visit. Patients with apparent cardiac involvement and regional wall abnormality on TTE were excluded. Written informed consent was taken from all participants. The study was conducted in accordance with the Helsinki declaration and approved by the local ethics committee (Date: 25/09/2020, No: 2020/1185).

Participants were categorized into three groups as follows: the control group, patients without pneumonia, and patients with pneumonia.

Echocardiography and strain imaging

2D TTE was performed on all patients with a iE33xMATRIX ultrasound system (Philips Medical Systems, Andover, Massachusetts) with a X5-1 (1-5 MHz) transducer according to the guidelines recommendations. All views were recorded as digital images and then reanalyzed. Global longitudinal strain (GLS) of the LV were measured by 2D STE in all patients. The CMQ option of the Philips IE33, QLAB 10.8.5 software was used for deformation analysis. Three consecutive cardiac cycles from the apical 4-, 3-(long axis), and 2-chamber views were obtained at 42–56 frames per second and then stored. First, for each view, the operator placed three points (two points at the base of the LV and one point at the apex) at the end of diastole. The endocardial and epicardial borders were then automatically traced by the software. Adjustments were made by the operator if required. Each wall of the LV was segmented into three (base, mid, and apical) equal parts automatically, and 17 segmental strain curves were obtained to give the so-called bull's-eye plots (figure 1).

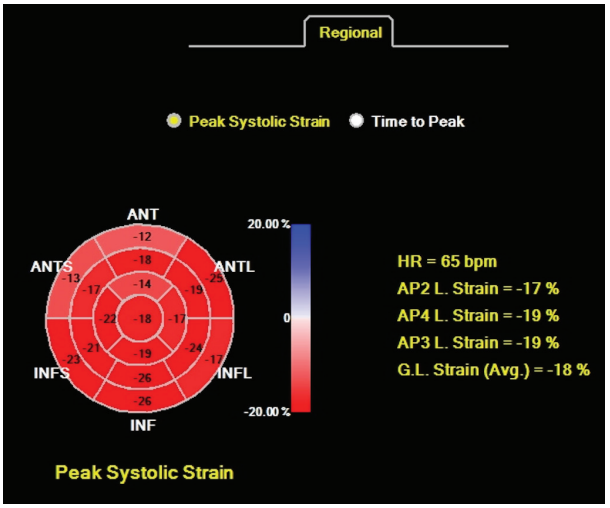

Figure 1: Bull's eye image of LV regional longitudinal strain with speckle-tracking imaging

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-wilk test was used for testing data distribution. Data are presented as mean ± standard deviation or median (min-max) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. Mann Whitney U and Kruskall Wallis tests were used for group comparisons. Categorical variables were compared using the Pearson chi-square test. Pearson and Spearman's correlation analysis were performed to identify the relation between the myocardial strain and markers of myocardial involvement and severity of COVID-19. P value of <0.05 was accepted to be statistically significant.

RESULTS

One hundred twenty-three subjects were enrolled in the study (78 in COVID-19, 45 in the control group). Table 1 shows demographic characteristics and laboratory measurements of COVID-19 patients and the control groups. COVID-19 patients and control group were similar with respect to age, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, smoking and heart rate. Admission and follow-up hs-TnT concentrations were similar in both the control group and in patients with varying severity of COVID-19.

Table 2 shows standard TTE measurements. Subjects with COVID-19 had higher left atrium (LA) diameter compared to control group. Like LA diameter, E/A ratio was lower in subjects with COVID-19 compared to control group. Nevertheless, LV EF was similar in all groups. LV-GLS was lower in subjects with pneumonia compared to control group and subjects without pneumonia. Regional strain analysis, as shown in table 3, showed that subjects with pneumonia had significantly lower strain values at mid-anterior, mid anteroseptal, apicoinferior, apicolateral and apical regions compared to control group and to subjects without pneumonia.

ROC curve analysis demonstrated that hs-TnT value above 7.065 pg/ml on admission was predictive for a decrease in LV-GLS with 54.1% sensitivity, 76.3% specificity (p=0.008, AUC 0.679, 95% CI 0.557-0.801) (figure 2).

DISCUSSION

This observational cross-sectional study sought to evaluate changes in LV global and regional strain in COVID-19 patients with apparently normal or near normal LV EF. Our findings reveal that, although not statistically significant, COVID subjects with pneumonia have higher hs-TnT concentration both on admission and follow-up compared to control group and to subjects without pneumonia. The patients and control group had similar LV EF. However, LV-GLS and regional strain was significantly impaired in COVID-19 patients with pneumonia compared to the other groups. Given the worse prognosis in COVID-19 patients with cardiovascular involvement, this finding indicates that COVID-19 subjects with pneumonia should undergo strain measurement for detection of concealed LV involvement.

COVID-19 is a multi-systemic disease predominantly affecting respiratory system. Among the systems affected by COVID-19, cardiovascular involvement has been shown to predict mortality. Conventionally, cardiac biomarkers including Troponin-I and –T and cardiovascular imaging have been used to evaluate cardiovascular involvement in COVID-19. Elevation in cardiac biomarkers have been reported to increase mortality in these patients (10). However, in a substantial proportion of patients, 2D-TTE is normal despite a clear elevation in cardiac biomarkers. The study of Clark et al. which enrolled 22 collegiate athletes with prior mildly symptomatic or asymptomatic COVID-19 infection has reported late gadolinium enhancement by CMR in 9% of the subjects (18). Given the predictive role of cardiovascular involvement on mortality in COVID-19, advanced imaging techniques including STE may be helpful to identify patients with cardiovascular involvement, but apparently normal on TTE.

STE is one of the advanced echocardiographic techniques which may provide further data concerning the LV function in patients with COVID-19. Accumulated evidence indicates that LV GLS can be used to estimate global LV myocardial tissue damage (17, 19). Regional and global LV function can be determined using strain analysis. Several studies have shown that strain analysis could be utilized to detect LV ischemia even in asymptomatic patients (20). However, its utility in COVID-19 patients with normal LVEF has not been investigated extensively.

Table 1: Demographic features and laboratory measurements of the study groups

	Control group (n=45)	Without pulmonary involvement (n=35)	With pulmonary involvement (n=43)	p-value
Age (year)	46.5±13.3	48.3±13.7	50.7±13.7	0.340
Gender, n (%) Male Female	14 (31.1%) 31 (68.9%)	17 (48.6%) 18 (51.4%)	26 (60.5%) 17 (39.5%)	0.021
HT, n (%)	11 (24.4%)	13 (37.1%)	11 (25.6%)	0.401
DM, n (%)	6 (13.3%)	5 (14.3%)	8 (19%)	0.740
COPD, n (%)	3 (6.7%)	4 (11.4%)	3 (7%)	0.699
Smoker, n (%)	16 (35.6%)	9 (25.7%)	9 (20.9%)	0.295
HR (bpm)	76.2±13.5	78.9±12.8	82.1±13.7	0.136
Laboratory findings at hospital admission				
Hgb (gr/dl)	13.3 (11-16)	13.1 (8-17)	12.8 (8-17)	0.043
Leukocyte (10^3/µl)	7 (4.4-13.5)	5.9 (0.8-9.8)	4.6 (3.6-16)	0.060
Lymphocytes (10^3/µl)	2.2 (1.1-6.9)	1.5 (0.2-2.7)	1 (0.1-5)	
Hs-troponin-T (pg/ml)	3.5 (3-30)	4 (2-59)	6.1 (2-37)	0.713
Pro-BNP (pg/ml)	34.5 (4-209)	80.8 (7-711)	78 (12-793)	0.245
CRP (mg/L)	2 (0-24)	23.5 (1.6-235)	29.3 (0-127)	
D-dimer (µg/L)	475 (210-1330)	450 (270-7340)	900 (320-18550)	0.182
Ferritin (ng/ml)	32 (3-212)	942 (167-1718)	1396 (338-1654)	0.411
Laboratory findings after discharge				
Hgb (gr/dl)	13 (11-17)	12.8 (8.5 -15.9)	13.2 (8.8-16.4)	0.135
Leukocyte (10^3/µl)	6.9 (4.4-13.5)	5.9 (2.4-10.8)	6.8 (4.1-19.6)	0.052
Lymphocytes (10^3/µl)	2.3 (1.1-6.9)	1.8 (0.5-3.8)	2.3 (1.1-4.5)	0.007
Hs-troponin-T (pg/ml)	3.5 (3-30)	3.8 (1-59)	5.9 (2-37)	0.198
Pro-BNP (pg/ml)	34 (4-803)	56.2 (5-1674)	64.2 (5-621)	0.413
CRP (mg/L)	2 (0-24)	1.4 (0-17)	3.3 (0-39)	0.065
D-dimer (µg/L)	435 (210-1330)	315 (180-920)	365 (170-2600)	0.175
Ferritin (ng/ml)	32 (3-212)	34.2 (7-359.5)	160 (51-1010)	0.018
Treatment				
Hydroxychloroquine, n (%)	-	35 (100%)	43 (100%)	
Azithromycin, n (%)	-	12 (34.3%)	21 (48.8%)	
Favipiravir, n (%)	-	5 (14.3%)	10 (23.3%)	
Steroid, n (%)	-	0	5 (11.6%)	
Immune modulator, n (%)	-	7 (20%)	10 (23.3%)	
Antibiotics, n (%)	-	17 (48.6)	17 (39.5%)	
Hospital stay (days)	-	3.2 (0-18)	6.1 (0-33)	

DM: Diabetes Mellitus, COPD: Chronic obstructive pulmonary disease, HR: Heart Rate, CRP: C-reactive protein

Baycan et al. have studied STE in 100 patents admitted with COVID-19 (14). The authors divided COVID-19 patients into subgroups according to the severity of pulmonary involvement They reported that LV GLS and right ventricular (RV) longitudinal strain were significantly impaired in COVID-19 patients with severe pulmonary involvement compared to patients with non-severe pulmonary involvement. The authors also reported that LV GLS and RV longitudinal strain was independently predictive for mortality (14).

Our findings show that LV GLS and regional strain is significantly impaired in patients with pneumonia compared to control group and those without pneumonia. Although there were no statistically significant differences in hs-TnT concentration among the groups; patients with

Table 2: 2D Transthoracic echocardiography and global longitudinal strain analysis of the groups

	Control group (n=45)	Without pulmonary involvement (n=35)	With pneumonia (n=43)	p-value
LVEDV (ml)	127.1±25.5	139.1±23.6	139.9±24.9	0.030[b]
LVESV (ml)	49.0±14	53.9±13.9	55.7±10.2	0.145
EF (%)	65.1±4.3	65.3±5.1	64.5±4.6	0.721
LV mass index (ml/m^2)	99.2±24.4	102.4±27.6	100.3±24	0.872
LVEDD (mm)	44±4.1	45.6±3.8	45.7±4	0.103
LA (mm)	32.9±4.3	35.9±4.3	36.6±4.4	0.001[a,b]
RV (mm)	25.9±2.6	26.8±2.1	27.3±2.2	0.028[b]
RA (mm)	31.1±2.9	31.2±3.4	31.9±3	0.428
E/A ratio	1.2±0.4	1±0.3	0.9±0.3	0.000
E/e' ratio	8.5±2.6	9±3.8	8.9±2.6	0.618
LVGLS (%)	-18.1±2.8	-18.1±3.8	-15.5±3.2	0.000[b,c]
LVS-2C (%)	-18±3.8	-18.5±5.6	-14.5±6.8	0.002[b,c]
LVS-3C (%)	-17.4±3.7	-17.7±4.4	-14.6±4.1	0.001[b,c]
LVS-4C (%)	-19.1±3.6	-18.9±4.7	-16.2±3.8	0.001[b,c]
LAVI	18.8±6.3	20±7.6	18±5.5	0.473
TAPSE (mm)	22.6±3.4	21.8±3.5	20.9±3.8	0.81
sPAP (mmHg)	18±4.7	26±5.5	26.6±4.7	0.000[a,b]

[a]: p<0.05 between the control group and the subjects without pneumonia; [b]: p<0.05 between the control group and the subjects with pneumonia; [c]: p<0.05 between the subjects without pneumonia and the subjects with pneumonia

Table 3: Regional strain analysis of the study groups

	Control group (n=45)	Without pulmonary involvement (n=35)	With pneumonia (n=43)	p-value
Basal anterior (%)	-19.6±9.4	-20.9±7.5	-18.6±9,5	0.543
Basal anteroseptal (%)	-18.1±6.7	-16.5±8.5	-14.1±8.8	0.066
Basal inferoseptal (%)	-16.7±6.5	-14.6±7.2	-14.8±6.9	0.294
Basal inferior (%)	-20.2±9.3	-15.4±9.1	-17±6.4	0.035[a]
Basal inferolateral (%)	-19.8±8.3	-20±9.2	-18±7.8	0.494
Basal anterolateral (%)	-20.9±7.5	-20.3±9.4	-19.5±6.3	0.688
Mid anterior (%)	-18.1±9.6	-17.7±9.9	-12.6±9	0.015[b]
Mid anteroseptal (%)	-21.4±7.8	-17.9±12.5	-15.2±10.2	0.020[b]
Mid inferoseptal (%)	-23.5±6.5	-23.3±8.9	-20±8.4	0.079
Mid inferior (%)	-20.3±8.8	-21.5±9.3	-19.6±9.8	0.679
Mid inferolateral (%)	-19.3±8.2	-19.3±11.3	-16.1±10.9	0.263
Mid anterolateral (%)	-21.8±9	-20±8.6	-18±9.3	0.150
Apical anterior (%)	-16.2±7.5	-16.6±7.4	-14±5.6	0.179
Apical septal (%)	-22.3±5.9	-22.2±8.8	-19.5±8.7	0.168
Apical inferior (%)	-22.1±8.8	-25±6.2	-19.4±7.1	0.007[c]
Apical lateral (%)	-17.5±8	-19.6±6.4	-14±5.4	0.001[b,c]
Apex (%)	-18.7±5	-20.1±4.8	-16.1±3.3	0.000[b,c]

[a]: p<0.05 between the control group and the subjects without pneumonia; [b]: p<0.05 between the control group and the subjects with pneumonia; [c]: p<0.05 between the subjects without pneumonia and the subjects with pneumonia

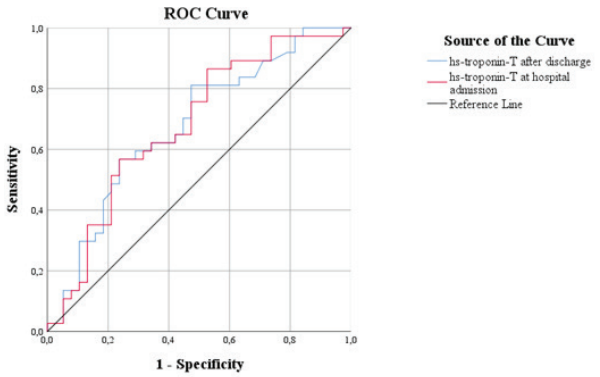

Figure 2: ROC curve demonstrating the sensitivity and specificity of high-sensitive TroponinT for predicting a decrease in LV global longitudinal strain

pulmonary involvement tended to have slightly increased hs-TnT concentrations compared to those without pulmonary involvement. With this in mind, we suggest that COVID-19 patients with pulmonary involvement should not only receive 2D-TTE, but also undergo strain echocardiography to detect myocardial damage which is indicated by LV GLS and regional strain.

In our study, COVID-19 patients and the control group had similar LVEF. LV GLS and regional strain is significantly impaired in COVID-19 patients with pneumonia compared to those without pneumonia or to healthy control group. Strain analysis may be helpful in detection of cardiovascular involvement of COVID-19 patients with normal LVEF.

CONCLUSION

Cardiovascular involvement has been shown to predict mortality in COVID-19. LV-GLS and regional strain was significantly impaired in COVID-19 patients with pneumonia compared to those without pneumonia or to healthy control group. COVID-19 subjects with pneumonia should undergo strain measurement for detection of concealed LV involvement.

Ethics Committee Approval: This study was approved by Istanbul University Clincial Research Ethics Committee (Date: 25.09.2020, No: 2020/1185).

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Author Contributions: Conception/Design of Study- E.B.K., B.E., D.B.; Data Acquisition- B.E., P.K.Ö., E.A.G., A.M.; Data Analysis/Interpretation- B.E., Z.G.D., T.D.; Drafting Manuscript- E.B.K., P.K.Ö., E.A.G.; Critical Revision of Manuscript- B.E., Z.G.D., T.D., D.B., A.M.; Final Approval and Accountability- E. B.K., B.E., P.K.Ö., Z.G.D., E.A.G., T.D., D.B., A.M.; Material or Technical Support- P.K.Ö.; Supervision- E.B.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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