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Research Article / Araştırma

Evaluation of Chest Pain and Dyspnea Symptoms Using Speckle-Tracking Echocardiography in Patients Recovering from COVID-19

Poliklinik Hastalarında Post-COVID-19 Göğüs Ağrısı ve Dispne'nin Speckle Tracking Ekokardiyografi ile Değerlendirilmesi

Timor Omar,[1] Doğan İliş,[1] Yusuf Oflu,[1] Muammer Karakayalı,[2] Halil Murat Bucak,[1] İnanç Artaç[2]

[1]**Department of Cardiology, Kars Harakani State Hospital, Kars, Turkey**
Kars Harakani Devlet Hastanesi, Kardiyoloji Bölümü, Kars, Türkiye
[2]**Department of Cardiology, Kafkas University Faculty of Medicine, Kars, Turkey**
Kafkas Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Kars, Türkiye

ABSTRACT

Objectives: At present, clinicians face plenty of patients complaining of post-COVID-19 chest pain and dyspnea. However, it remains to be seen if these symptoms indicate pathology of the cardiovascular system. We aimed to evaluate heart functions in outpatients with post-COVID-19 chest pain and dyspnea, using 2D speckle-tracking echocardiography (2D-STE).

Methods: This cross-sectional study recruited consecutive patients who presented to cardiology outpatient clinics between June 15, 2021, and July 15, 2021. A total of 78 patients had recovered from COVID-19 1-2 months before admission were included in the study. ECG and echocardiography, including 2D-STE images, were obtained for all patients. Findings were compared with sex- and an age-matched control group of 67 healthy adults.

Results: The median age was 38 (IQR, 34-45) years, and 64.1% were female. There were no significant differences between the patients and control group regarding laboratory, ECG, and echocardiography findings. Moreover, the left ventricle global longitudinal strain measurements in both the patient and control groups were within the normal ranges and did not show a significant difference (-20.5 [-21.8- -17.9] vs. -19.8 [-21.4- -18.9], p=0.894).

Conclusion: Post-COVID-19 chest pain and dyspnea are unlikely signs of cardiovascular involvement in outpatient young adults who have not been hospitalized with COVID-19.

Keywords: Chest pain, COVID-19, left ventricular global longitudinal strain, post-COVID-19 syndrome, transthoracic echocardiography

ÖZ

Amaç: Son zamanlarda hekimler, "Coronavirus Disease-2019 (COVID-19)" hastalığını geçirdikten sonra göğüs ağrısı ve nefes darlığı şikâyeti olan çok sayıda hastayla karşılaşmaktadır. Bununla birlikte, bu semptomların kardiyovasküler sistem patolojisiyle ilişiği de tam olarak açıklığa kavuşmadı. Bu sebeple, COVID-19 sonrası göğüs ağrısı ve dispnesi olan poliklinik hastalarında kalp fonksiyonlarının 2D speckle tracking ekokardiyografi (2D-STE) kullanılarak değerlendirilmesi amaçlandı.

Yöntem: Bu kesitsel çalışmaya, 15 Haziran 2021-15 Temmuz 2021 tarihleri arasında kardiyoloji polikliniğine başvuran ardışık hastalar alındı. Başvurudan 1-2 ay önce COVID-19'dan iyileşen toplam 78 hasta çalışmaya dahil edildi. Tüm hastaların elektrokardiyografisi ve 2D-STE görüntüleri incelendi. Bulgular, cinsiyet ve yaş bakımından benzer olan 67 sağlıklı yetişkinden oluşan kontrol grubuyla karşılaştırıldı.

Bulgular: Ortanca yaş 38 (IQR: 34-45) idi ve hastaların %64,1'i kadındı. Laboratuvar, elektrokardiyografi ve ekokardiyografi bulguları açısından hasta ve kontrol grubu arasında anlamlı fark bulunamadı. Ayrıca hem hasta hem de kontrol gruplarında sol ventrikül global longitudinal strain ölçümleri normal sınırlar içindeydi ve anlamlı bir fark göstermedi (-20,5 [-21,8- -17,9] vs. -19,8 [-21,4- -18,9], p=0,894).

Sonuç: COVID-19 geçiren hastaların göğüs ağrısı ve dispne şikayetleri, COVID-19 hastalığını ayakta atlatan genç erişkinlerde olası kardiyovasküler tutulum ile ilişkili değildir.

Anahtar sözcükler: COVID-19, göğüs ağrısı, post-COVID-19 sendromu, sol ventrikül global longitudinal strain, transtorasik ekokardiyografi

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Address for correspondence: Timor Omar, MD. Kars Harakani Devlet Hastanesi, Kardiyoloji Bölümü, Kars, Türkiye
Phone: +90 531 910 95 30 **E-mail:** tbigmurad@gmail.com

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Introduction

Post-acute COVID-19 syndrome (PACS) is defined as persistent symptoms 3-4 weeks longer than the initial onset of COVID-19 symptoms.[1,2] Two of the most common symptoms, suggestive of cardiovascular involvement, present in PACS are chest pain and dyspnea, affecting ~20% of patients recovering from COVID-19.[2] However, whether these symptoms are a component of the non-specific PACS milieu or indicate pathology in the cardiovascular system which has remained elusive. This uncertainty adds to patients', as well as clinicians' concerns: Clinicians, particularly family physicians, are increasingly confronting a significant number of patients with post-COVID-19 chest pain and dyspnea.[3]

2D speckle-tracking echocardiography (2D-STE) is a valuable technique for evaluating myocardial function (ventricular global longitudinal strain) in many conditions, including subclinical myocardial dysfunction in post-COVID-19 patients.[4] It has been shown that approximately one-third of COVID-19 patients show deterioration in the left ventricular global longitudinal strain (LVGLS) during hospitalization and one-quarter during follow-up.[5] Perhaps, patients recovering from COVID-19 and with symptoms of chest pain and dyspnea have a myocardial injury, which can easily be revealed with LVGLS using echocardiography. If so, a degradation in LVGLS is expected in this group of patients.

The literature lacks detailed data investigating post-COVID-19 chest pain and dyspnea in outpatients from a cardiological perspective exclusively. To better understand this issue from a cardiological view of point, we evaluated the heart functions using electrocardiogram (ECG) and echocardiography, including 2D-STE, in outpatients presenting with chest pain and dyspnea and in those recovered from COVID-19. Thus, our aim was to reveal any myocardial injury due to COVID-19 in these cases. In this way, we can provide informative data to clinicians facing more and more such cases.

Methods

Consecutive patients who presented to the cardiology outpatient clinic with persistent chest pain and dyspnea were included in this cross-sectional study. The subjects had recovered from COVID-19 1-2 months before admission. Emergency conditions, and comorbidities that may cause deterioration in LVGLS analysis, were determined as exclusion criteria. Acute coronary syndrome, heart failure (left ventricle ejection fraction <50%), atrial fibrillation, severe cardiac valve disorders, renal failure (eGFR <30 ml/min/1.73 m^2), severe chronic obstructive pulmonary disease, anemia (hemoglobin level under 11.9 for females and 13.6 for males), and being under 18-years-old were the exclusion criteria. A sex- and age-matched control group consisting of 67 healthy adults was formed. Findings of the patients were compared with the control group. Demographics and laboratory results on admission were recorded for all the subjects.

ECG analysis was performed by a blinded cardiologist (M.K), using a standardized comprehensive ECG reading protocol.[6] It included intervals, rate, QRS morphology, premature atrial and ventricular contract, and T-wave abnormalities. Corrected QT interval was calculated using the Fridericia formula.[7]

Echocardiographic images were obtained using Philips Epiq7 (Philips Healthcare, Inc., Andover, MA, USA) and recorded by standard techniques. According to the American Echocardiography Association guidelines,[8] the left ventricular end-systole and end-diastolic diameters, left atrium diameter, interventricular septum thickness, left ventricular posterior wall thickness, and right atrium and ventricle diam-

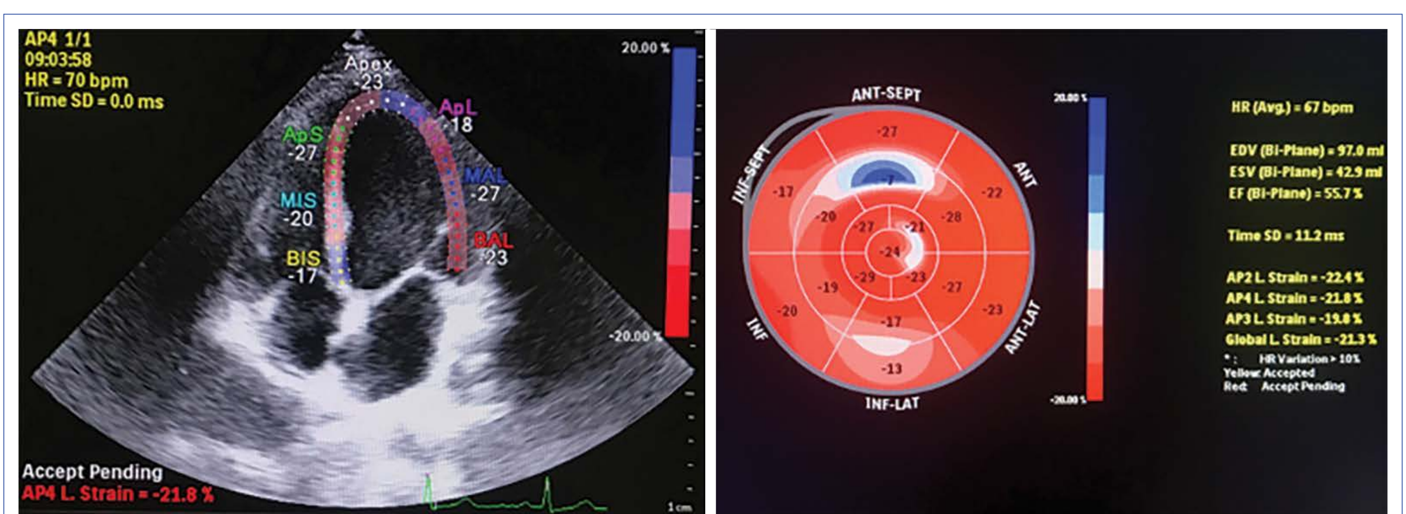

Figure 1. An example of the left ventricle global longitudinal strain speckle-tracking of a patient from apical four chamber views.

Table 1. Demographic , clinical, and laboratory characteristics

	Overall (patient+control groups) (n=145)	Patient (n=78)	Control (n=67)	p
Female, n (%)	93 (64.1)	54 (69.2)	39 (58.2)	0.168
Age (years), median (IQR)	38 (34-45)	38.5 (34-46)	37 (34-44.5)	0.426
BMI (kg/m^2) median (IQR)	26 (24-28.4)	25.19 (23-28.3)	26.26 (24.4-28.7)	0.062
Laboratory findings at admission				
Hgb (g/dL), mean±SD	14.43±1.58	14.24±1.53	14.65±1.63	0.123
WBC (×10^3/µL), median (IQR)	7.1 (6.1-8.2)	7 (6-8.2)	7.2 (6.4-8.1)	0.527
PLT (×10^3/µL), median (IQR)	270 (247-303)	281 (258-325)	265 (244-288)	0.004
Glucose (mg/dL), median (IQR)	91 (86-98)	92 (87-102)	90 (85-96)	0.192
Hs-TnT (ng/L), median (IQR)	6.42 (5.20-7.97)	6.55 (5.5-8)	6.2 (5-7.75)	0.495
ProBNP (pg/mL), median (IQR)	21 (12-50)	22 (15-44)	20 (10-53)	0.556
CRP (mg/L), median (IQR)	2.78 (1-4)	3 (1.57-4.12)	2.2 (0.76-3.89)	0.003
Creatinine (mg/dL), mean±SD	0.71±0.15	0.70±0.15	0.73±0.15	0.215
D-dimer (µg/mL), median (IQR)	204 (155-307)	205 (165-305)	201 (150-307)	0.405
Lymphocyte (×10^3/µL), median (IQR)	2.2 (1.8-2.69)	2.1 (1.7-2.5)	2.27 (3.4-4.96)	0.071
Neutrophil (×10^3/µL), median (IQR)	4.2 (3.4-4.96)	4.34 (3.35-4.9)	4.18 (3.47-4.96)	0.774
Comorbidities				
Hypertension, n (%)	16 (11)	10 (12.8)	6 (9)	0.459
Diabetes, n (%)	13 (9)	7 (9)	6 (9)	0.997
Cigarette smoking, n (%)	27 (18.6)	13 (16.7)	14 (20.9)	0.514
Hyperlipidemia, n (%)	8 (5.5)	5 (6.4)	3 (4.5)	0.611
Asthma, n (%)	7 (4.8)	5 (6.4)	2 (3)	0.337

BMI: Body mass index; Hgb: Hemoglobin; WBC: White blood count; PLT: Platelet; hs-TnT: High-sensitivity troponin T; BNP: B-type natriuretic peptide; CRP: C-reactive protein.

eters were measured. Measurements of mitral inflow included the peak early (E-wave) and late (A-wave) diastolic filling velocities and calculation of E/A ratio. Early diastolic mitral, septal, and lateral annular velocities (e′) were measured in the apical four-chamber view.[9] The left ventricular ejection fraction was measured using the modified Simpson's rule.[10]

LVGLS was analyzed by another cardiologist (D.I), blinded to study data, using the Qlab13 (Philips Healthcare, Andover, Massachusetts) program (Fig. 1). While the end-diastole is regarded as the peak R wave of the electrocardiogram, end-systole was estimated aortic valve closure. Mean global longitudinal strain (GLS) was calculated by averaging the peak GLS values of apical two-chamber, apical three-chamber, and apical four-chamber images. Automatic endocardial margins were perceived at the end-systole. Manual corrections were made to secure accurate tracking where required and to include the left ventricle (LV) wall thickness. Speckle-tracking analysis was performed per the Consensus Document of the EACVI/ASE/Industry Task Force to standardize right ventricle (RV) and LV myocardial deformation imaging.[11,12]

The country's Ministry of Health and Kafkas University Faculty of Medicine Ethics Committee approved the study protocol (Date: May 26, 2021; Number 80576354-050-99/180).

Statistical Analysis

SPSS software (Version 20.0, SPSS, Inc., Chicago, IL, institutionally registered software) was used for statistical analyses. The Kolmogorov-Smirnov test was used for normality test. Continuous variables were represented as mean±standard deviation for normally distributed and median (IQR) for not normally distributed variables. Categorical variables were defined as a percentage. While an independent t-test was used to analyze continuous data showing normal distribution, Mann-Whitney U-test was used to analyze variables not showing normal distribution. P<0.05 was considered statistically significant.

Results

Demographic, medical, and echocardiographic data of 95 consecutive patients presenting to cardiology outpatient clinics from June 15, 2021, to July 15, 2021, were recorded. Seventeen cases (two heart failure, one hypertrophic cardiomyopathy, two anemia, one renal failure, two chronic obstructive pulmonary disease, and nine because of inadequate echocardiographic for STE analysis) were excluded due to exclusion criteria. After that, the final study group included 78 patients (median age

Table 2. Electrocardiographic and echocardiographic characteristics

	Overall (n=145)	Patient (n=78)	Control (n=67)	p
Electrocardiogram features				
Heart rate (b.p.m), median (IQR)	75 (70-88)	80 (74-90)*	75(67-80)*	0.004**
PR interval (msec), median (IQR)	144 (132-159)	144 (130-160)	144 (132-155)	0.855
QRS interval (msec), median (IQR)	94 (88-100)	91 (88-98)	94 (88-100)	0.147
QTc (msec), median (IQR)	424 (412-440)	426 (415-446)	424 (412-434)	0.181
T-wave change, n (%)	11 (7.6)	6 (7.7)	5 (7.5)	0.958
Fragmented QRS, n (%)	12 (8.3)	6 (7.7)	6 (9)	0.783
Bundle branch block, n (%)	7 (4.8)	6 (7.7)	1 (1.5)	0.082
Premature atrial/ventricular contraction, n (%)	5 (3.4)	2 (2.6)	3 (4.5)	0.529
Echocardiography features				
LVDD (mm), median (IQR)	46 (42-48)	46 (44-48)	44 (41-48)	0.075
LVSD (mm), median (IQR)	30 (28-34)	30 (28-33)	30 (28-34)	0.839
IVS (mm), median (IQR)	8.5 (8-9)	8.25 (8-9)	8.5 (8-9)	0.872
PW (mm), median (IQR)	7 (7-8)	7 (7-8)	7 (7-8)	0.135
LA (mm), median (IQR)	32 (30-34)	32 (30-34)	32 (30-34)	0.656
RV (mm), median (IQR)	32 (30-34)	32 (30-34)	32 (29-34)	0.544
RA (mm), median (IQR)	32 (31-35)	32 (31-35)	33 (31-36)	0.239
Ejection fraction (%), median (IQR)	65 (61-67)	65 (60-66)	65 (61-67)	0.211
E/A ratio, median (IQR)	1.2 (1.03-1.5)	1.16 (0.9-1.51)	1.3 (1.1-1.47)	0.123
E/e' ratio, median (IQR)	6.4 (5.3-7.67)	6.35 (5.4-7.08)	6.4 (5.55-8)	0.474
TAPSE (mm), median (IQR)	21 (20-23)	21 (20-23)	21 (20-22)	0.527
TDI S', cm/s, median (IQR)	12 (12.8-13.8)	12.8 (12.2-13.5)	13 (12-14.45)	0.304
PASP (mmHg), median (IQR)	9 (8-12)	9 (8-12)	8 (8-12)	0.286
LVGLS (%), median (IQR)	-20 (-21.7-18.15)	-20.5 (-21.8-17.9)	-19.8 (-21.4-18.9)	0.894

**The comparison was made between the patient and healthy control groups. QTc: Corrected QT; LVDD: Left ventricle end-diastolic diameter; LVSD: Left ventricle end-systolic diameter; IVS: Interventricular septum thickness; PW: Left ventricular posterior wall thickness; LA: Left atrium diameter; RV: Right ventricle diameter; RA: Right atrium diameter; TAPSE: Tricuspid annular plane systolic excursion; TDI S': Tissue Doppler imaging systolic wave S' velocity; PASP: Pulmonary arterial systolic pressure; LVGLS: Left ventricle global longitudinal strain.

38 [IQR, 34-45] years, 64.1% of female). Demographic, clinical, and laboratory characteristics are summarized in Table 1. Of 78 patients, only three had been hospitalized for COVID-19, and the high sensitive troponin T (hs-TnT) level of two patients had been elevated (33 pg/ml and 42 pg/ml, respectively, reference limit<14 pg/ml) during hospitalization.

The distribution of the symptoms on examination was as follows; atypical chest pain in 59, atypical chest pain and dyspnea in five, typical chest pain in three, typical chest pain and dyspnea in four, and dyspnea in seven patients. Treadmill exercise test of those with typical chest pain was negative. Besides, no pathological finding was found on the chest X-ray of patients with dyspnea.

There were no significant differences between the patient and control groups regarding demographic characteristics and comorbidities, including hypertension, diabetes, smoking, hyperlipidemia, and asthma. Laboratory findings were within the normal range and were similar between the patient and control groups, except for platelet and C-reactive protein levels, which were within normal ranges also (Table 1) (median [IQR], 281 [258-325] vs. 265 (244-288), p=004 and 3 (1.57-4.12) vs. 2.2 [0.76-3.89], p=0.003, respectively).

Considering electrocardiogram, all features showed similarity between the patient and control groups except for heart rate, which was clinically within normal ranges also (80 [74-90] vs. 75 [67-8], p=0.004). Frequencies of T-wave change, fQRS, bundle branch block, and premature contraction were similar between the patient and control groups (7.7% vs. 7.5%, p=0.958, 7.7% vs. 9%, p=0.783, 7.7% vs. 1.5%, p=0.082, and 2.6% vs. 4.5%, p=0529, respectively) (Table 2).

Regarding echocardiographic characteristics, all parameters, including left and right side functions, were found within normal ranges in both groups and did not show a significant difference (Table). Moreover, LVGLS measurements in both the patient and control groups were within the normal ranges and did not show a significant difference (-20.5 (-21.8- -17.9] vs. -19.8 [-21.4- -18.9], p=0.894) (Table 2).

Discussion

Our study provides data that laboratory and cardiological features, including LVGLS of young adults suffering from post-COVID-19 chest pain and dyspnea, were ordinary and similar to healthy populations.' Of note, our study comprised only outpatient subjects and young adults beyond crucial cardiovascular risk factors and comorbidities. Moreover, only three had been hospitalized with COVID-19, and only two had been suggestive of cardiac involvement (elevated hs-TnT level) during hospitalization.

To the best of our knowledge, the literature lacks data investigating post-COVID-19 chest pain and dyspnea from a cardiological perspective; in this context, our study is preliminary. On the other hand, many papers are available investigating post-COVID-19 cardiac involvement irrespective of symptoms and reporting discordant results. According to Baruch et al.[5] in 80 COVID-19 survivors, most heart functions, which had been impaired during hospitalization, improved 3 months after discharge. However, a quarter of patients still had abnormal LVGLS compared with the initial analysis. Similarly, Özer et al.[13] demonstrated impaired LVGLS values in over half of those who had a myocardial injury during hospitalization and in one-third of all at 1-month follow-up. The median age of our study population was 38 years. Unlike to our study, both studies involved an older population than our population (57.7 and 59.9 years, respectively). Besides, they included hospitalized patients, indicating more severe COVID-19 infection, and those with higher cardiac risk factors and comorbidities. Another point worth mentioning is that the follow-up analysis was performed irrespective of the presence of symptoms. These patients were not within our inclusion criteria.

On the contrary, there are also studies showing the opposite. A study demonstrated no proof of persistent cardiac dysfunction on echocardiography performed 40 days after hospital discharge following recovery from COVID-19.[14] Of note, this study did not involve an STE study to identify more subtle myocardial changes. Another research, which is very similar to ours regarding population demographics, is a prospective study of 149 health care workers. There were no differences in cardiac magnetic resonance characteristics, including cardiac functions, hs-TnT level, and N-terminal pro-BNP at 6 months post-infection versus age, sex, and ethnicity matched seronegative controls.[15] Similar to our study, the population had relatively fewer comorbidities, and only one patient had severe COVID-19. This report did not include ECG and LVGLS analysis, however.

One of the primary aims of this study was to raise awareness among primary care professionals who are increasingly confronting with many patients with post-COVID-19 chest pain and dyspnea. In reference to the current study, post-COVID-19 chest pain and dyspnea in young adults who have not required hospitalization and those without comorbidity and laboratory abnormalities are unlikely due to cardiovascular pathology. Nevertheless, it should be kept in mind that PACS may have significant cardiovascular manifestations, particularly in patients who have been hospitalized with COVID-19, the elderly, and those with significant cardiovascular risk factors and comorbidities. Further studies compromising elderly and heterogeneous populations with cardiovascular risk factors and comorbidities are needed in this field.

Conclusion

This study could give helpful insights into the currently mostly enigmatic issue that post-COVID-19 chest pain and dyspnea are unlikely signs of cardiovascular involvement in outpatient young adults who have not been hospitalized with COVID-19.

Disclosures

Ethics Committee Approval: The study was approved by The Kafkas University Faculty of Medicine Ethics Committee (Date: 26/05/2021, No: 80576354-050-99/180).

Informed Consent: Written informed consent was obtained from all patients.

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