THE ASSESSMENT OF CARDIAC FUNCTION IMPAIRMENT IN CORONAVIRUS DISEASE 2019 PATIENTS USING TWO-DIMENSIONAL SPECKLE TRACKING IMAGING COMBINED WITH TEI INDEX AND SERUM NT-PROBNP

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ABSTRACT

Introduction: *After the outbreak of the Corona Virus Disease 2019 (COVID-19), there have been reports of impaired cardiac function in patients infected with this coronavirus. The tests are mostly based on myocardial injury markers and routine cardiac ultrasound examinations, which are mostly seen in critically ill patients. In this study, two-dimensional speckle tracking imaging (2DSTI) combined with Tei index and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) were used to more sensitively diagnose cardiac function impairment in COVID-19 patients.*

Materials and methods: *For some COVID-19 patients in our hospital, there were 68 cases of mild disease (including mild and common types) and 11 cases of severe disease (4 cases of severe death), and 10 healthy volunteers were included as the control group. On the basis of conventional echocardiography in all subjects, the left ventricular end-diastolic volume (LV-EDV), left ventricular end-systolic volume (LV-ESV), and left ventricular ejection fraction (LV-EF) were obtained by Simpson method, the left ventricular Tei index by tissue Doppler, and the left ventricular global peak longitudinal strain (GLPS), left ventricular global peak radial strain (GRPS), and left ventricular global peak circumferential strain (GCPS) by 2DSTI offline analysis. The COVID-19 patients were subjected to quantitative detection of serum NT-proBNP for statistical analysis.*

Results: *Left ventricular GLPS, left ventricular GRPS, and left ventricular GCPS in COVID-19 patients were significantly lower than those in the control group ($P<0.05$): The left ventricular GLPS was more significant ($P<0.01$), and the severe group (including the death group) < the mild group < the control group. The left ventricular Tei index: The severe group (including the death group) of COVID-19 was significantly higher than the mild group and the control group ($P<0.05$), and there was no statistical significance between the mild group and the control group. NT-proBNP: The severe group of COVID-19 was significantly higher than the mild group ($P<0.05$). Although the LV-EF in the COVID-19 patients was significantly lower than that in the control group ($P<0.05$), except for 2 sever cases less than 50%, the rest were all ≥50%; although there was a significant difference in LV-ESV among multiple groups ($P<0.05$), but there was no significant difference for the pairwise comparison, and there was no significant difference in LV-EDV.*

Conclusion: *2DSTI can more sensitively detect latent cardiac function impairment in COVID-19 patients, and the left ventricular GLPS is the most sensitive. Tei index is an effective indicator to reflect the degree of cardiac function impairment. NT-proBNP has significant significance in predicting the severity of cardiac dysfunction. The combined application of the three can significantly increase the predictive performance of cardiac function impairment, provide a diagnostic basis for cardiac function impairment with preserved ejection fraction, and predict the degree of impairment. Our study demonstrated that the cardiac function of COVID-19 patients is impaired to varying degrees.*

Keywords: *2DSTI, Tei index, NT-proBNP, COVID-19 patients, left ventricular function.*

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Introduction

Several reports have revealed that after the Corona Virus Disease 2019 (COVID-19) infection, in addition to typical respiratory symptoms, patients may also have cardiovascular system symptoms, and due to systemic inflammatory response and immune system disorders, the incidence of myocardial injury significantly is elevated[1, 2]. The Corona Virus Disease 2019 Diagnosis and Treatment Program (Trial 7th version) issued by the National Health Commission of the People's Republic of China mentioned that myocardial cell degeneration and necrosis can be observed, and the infiltration of a few monocytes, lymphocytes and/or neutrophils in the interstitium can be observed. Partial vascular endothelium slough off, and intimal inflammation and thrombosis are formed[3]. Routine echocardiography of COVID-19 patients (without severe underlying cardiac diseases) in our hospital showed that the left ventricular ejection fraction (LV-EF) was generally ≥50%. Two-dimensional speckle tracking imaging (2DSTI) is a new technology in the field of cardiac color Doppler ultrasound, which reflects the real-time motion and deformation of the myocardium by tracking the spatial motion of intramyocardial ultrasound echo speckles.

The myocardial work index is the Tei index, which can comprehensively evaluate the systolic and diastolic function of the heart. As the cardiac function decreases, the Tei index increases. N-terminal pro brain natriuretic peptide (NT-proBNP) is a marker of heart failure, has good stability in blood, and has good anti-interference properties to some drugs[4]. In this study, the strain parameters of 2DSTI were combined with the tissue Doppler Tei index and the quantitative observation of NT-ProBNP, in order to more sensitively monitor the myocardial damage caused by COVID-19 from multiple perspectives.

Materials and methods

General data

Some COVID-19 patients who received treatment in the Shanghai Public Health Clinical Center Affiliated to Fudan University from March 2020 to May 2020 were selected. The classification adopted the Corona Virus Disease 2019 Diagnosis and Treatment Program (Trial 7th version) issued by the National Health Commission of the People's Republic of China[3].

A total of 79 cases were enrolled, 11 severe cases (4 cases with poor outcome) included 10 males and 1 female, and 68 mild cases (including mild and common types) included 41 males and 27 females, aged 18-83 years (median: 47.5, quartile: 25-64). The 10 healthy controls were selected, excluding those with severe underlying cardiac diseases. This research was approved by the Ethics Committee of the Shanghai Public Health Clinical Center Affiliated to Fudan University.

Instruments and methods

Mindray Resona8 multifunctional ultrasonic diagnostic instrument, the probe SP5-1u (frequency 1-5MHz), and Mindray TTQA random analysis software were used. The subjects were placed in the left lateral position or supine position (the severe group), in a calm state, and connected to the synchronous ECG leads. The frame rate of the instrument was adjusted to meet 50-65 frames/s, the structure of the cardiac chamber and ventricular wall was displayed completely. On-machine acquisition met 3-5 consecutive cardiac cycles of views of left ventricular apical four-chamber (A4C), apical three-chamber (A3C), apical two-chamber (A2C) long axis and left ventricular basal segment, papillary muscle, apical segment horizontal short axis.

The dynamic map acquisition was completed for storage, and Mindray speckle-tracking software was used for offline analysis to obtain the left ventricular global peak longitudinal strain (GLPS), left ventricular global peak radial strain (GRPS), and left ventricular global peak circumferential strain (GCPS). Left ventricular end-diastolic volume (LV-EDV), left ventricular end-systolic volume (LV-ESV), and left ventricular ejection fraction (LV-EF) were measured by Simpson method.

Tissue Doppler was used to acquire left ventricular velocity map of mitral annulus, and calculation was performed according to Tei index = (time from mitral valve closure to re-opening - ejection time) / ejection time × 100% (average of three measurements). The 3 mL of venous blood from COVID-19 patients was collected and placed in the EDTA anticoagulation tube, centrifuged at 3000 r/min for 10 min. The plasma was collected, and NT-proBNP was detected by the MQ60Puls automatic immunochemiluminescence analyzer using immunofluorescence method, as shown in Figure 1.

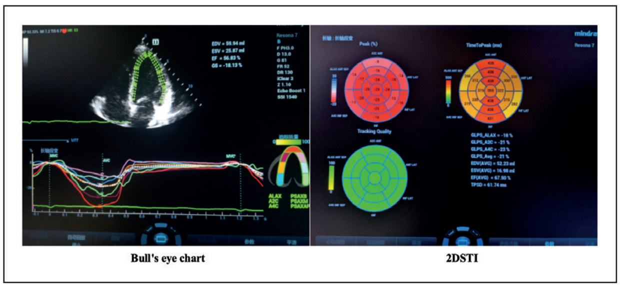

Figure 1: Echocardiography.

Statistical analysis

The medical software was used for statistical analysis. All measurement data were expressed as medians and quartiles (25, 75%). The comparison of measurement data among multiple groups was performed using a non-parametric test (Kruskal-Wallis test) and followed by pairwise comparison using the Jonckheere-Terpstra test. $P<0.05$ was considered statistically significant.

Results

The 2DSTI demonstrated that left ventricular GLPS, left ventricular GRPS, and left ventricular GCPS in COVID-19 patients were significantly lower than those in the control group (P<0.05): The left ventricular GLPS was more significant (P<0.01), and the severe group (including death group) < mild group < control group. The left ventricular Tei index: The severe group (including the death group) of COVID-19 was significantly higher than the mild group and the control group (P<0.05), and there was no statistical significance between the mild group and the control group. NT-proBNP: The severe group of COVID-19 was significantly higher than the mild group (P <0.05). Although the LV-EF in the COVID-19 patients were significantly lower than those in the control group (P<0.05), except for 2 severe cases less than 50%, the rest were all ≥50%; although there was a significant difference in LV-ESV among multiple groups (P<0.05), but there was no significant difference for pairwise comparison, and there was no significant difference in LV-EDV, as shown in Table 1 and Figure 2.

Discussion

Clinical studies and data have revealed that COVID-19 patients have different degrees of myocardial injury[5-7], and some patients have atypical clinical manifestations, which may be with first symptoms of cardiovascular system such as chest tightness, palpitations, chest pain, etc. Typical symptoms and signs of cardiovascular emergencies and severe cases may be masked, leading to missed diagnosis. This further suggests that we should pay attention to the differential diagnosis of dyspnea, blood oxygen saturation, and shock caused by acute cardiovascular emergencies and severe cases and critical COVID-19 infection[8]. Echocardiography is an important method to detect cardiac function. The routine echocardiography of COVID-19 patients in our hospital demonstrated that in patients without severe underlying cardiac diseases, LV-EF was measured more than 50%. Because traditional cardiac function measurement (M-mode, two-dimensional, Simpson method) is subject to a certain degree of subjectivity and is dependent on operator experience, and the detection sensitivity of subclinical myocardial function abnormalities is low, whether COVID-19 patients have occult cardiac injury or not needs further exploration. 2DSTI is often used to evaluate the global and local systolic and diastolic function of the ventricular wall in various myocardial involvement diseases such as coronary heart disease and cardiomyopathy[9, 10].

	Control group (n = 10)	Mild group (n = 68)	Severe group (n = 7)	Death group (n = 4)	P*
Left ventricular GLPS	-17.50 (-21.0~-17.0)	-13.0 (-15.50~-12.0)	-11.0 (-11.75~-10.25)	-8.0 (-12.50~-6.0)	0.000001
Left ventricular GRPS	27.50 (22.0~36.0)	17.0 (11.0~24.50)	14.0 (7.25~19.50)	15.50 (-2.0~20.50)	0.013709
Left ventricular GCPS	-19.0 (-20.0~-15.0)	-13.0 (-15.50~-11.0)	-13.0 (-16.0~-12.0)	-17.0 (-17.50~-14.50)	0.005633
Left ventricular Tei index	0.475 (0.450~0.50)	0.510 (0.450~0.590)	0.685 (0.550~0.870)	0.660 (0.555~0.775)	0.001838
Serum NT_proBNP	____	8.52 (4.0~57.38)	531.0 (310.0~1307.0)	5935.85 (778.15~14099.0)	0.000002
LV-EDV	98.50 (92.0~115.0)	100.0 (81.50~117.50)	102.0 (90.75~124.50)	83.50 (59.50~107.50)	0.634042
LV-ESV	27.0 (23.0~37.0)	40.0 (32.0~51.0)	43.0 (32.50~49.50)	38.50 (28.50~61.0)	0.004844
LV-EF	69.50 (68.0~71.0)	58.50 (55.0~63.0)	61.0 (51.75~62.50)	53.50 (50.0~59.50)	0.000545

Table 1: The 2DSTI demonstrated left ventricular GLPS, left ventricular GRPS, and left ventricular GCPS in different groups.

Kruskal-Wallis test. Data were presented as medians (quartiles).

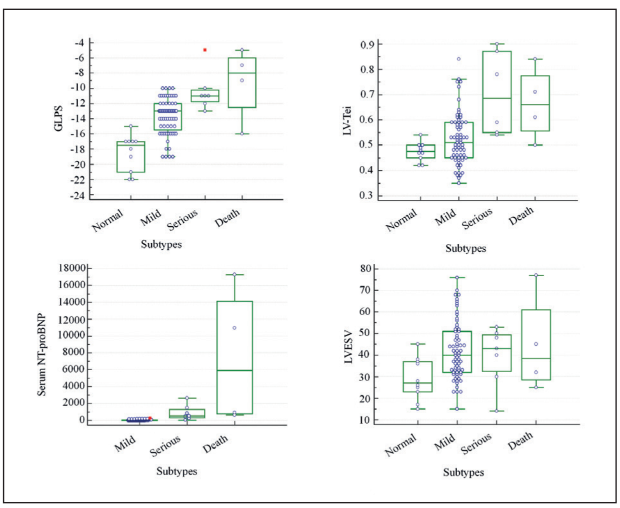

Figure 2: The subtypes in different groups.

Myocardial strain and strain rate are the most important parameters of STI technology, which can reflect the relative deformation degree of myocardial tissue in the cardiac cycle and quantitatively evaluate the changes of myocardial systolic and diastolic function, and myocardial longitudinal, radial, and rotational motion strain can comprehensively reflect ventricular function. Since it is not disturbed by the angle of the sound beam, it is an effective means for detecting potential abnormal myocardial function early in the follow-up process by quantitatively analyzing the myocardial deformation and obtaining multiple sets of motion parameters[11]. This study demonstrated that the left ventricular GLPS, left ventricular GRPS, and left ventricular GCPS were reduced to varying degrees in COVID-19 patients, especially the left ventricular GLPS was more sensitive. The mechanism of myocardial injury caused by COVID-19 may be related to the direct myocardial cell injury caused by virus infection through angiotensin-converting enzyme 2 (ACE2) receptors. ACE2 receptors widely present in the body, and the receptor-related signaling pathways can play a role in myocardial injury[12]. The combined use of left ventricular GLPS, left ventricular GRPS and left ventricular GCPS can provide an effective basis for left ventricular function impairment.

The Tei index was first proposed by medical scientist Chuwa Tei[13], which refers to the ratio of the sum of ventricular isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) to ejection time (ET), namely Tei index = (ICT + IRT) / ET or Tei index = (time from mitral valve closure to re-opening - ejection time) / ejection time × 100%. Tei C et al. reported that the normal value of Tei index in the left ventricle was 0.39 ± 0.05 in adults[14]. It has been reported that there is no statistical difference in the left ventricular Tei index between the severe group and the mild group of COVID-19[15], but this study demonstrated that the left ventricular Tei index in the severe group was significantly higher than that in the control and the mild group ($P<0.05$) (there was no significant difference between the mild group and the control group). The reason may be that the sample size of the severe group in the previous study was significantly smaller than that in this study.

NT-proBNP is a neuroendocrine hormone synthesized and secreted by the ventricle, and the biologically inactive N-terminal brain natriuretic peptide precursor produced by the cleavage of the precursor of BNP. When the ventricular load and ventricular wall tension change, the secretion increases. Its half-life is longer, the plasma concentration is higher, the individual differences are relatively low, the protein properties are not affected by external conditions, and the stability is relatively good. Compared with BNP, it can more accurately reflect the functional state of the myocardium[16, 17]. There have been many reports that whether it is mild or severe, the levels of serum myocardial necrosis markers in COVID-19 patients are elevated to varying degrees, but the risk of cardiac damage in severe patients is higher, approximately 22.2-31%, while that of mild cases are approximately 2%-4%, and the risk of cardiac injury in deceased patients is higher than that in survivors, approximately 28%-88.9%[6, 7]. This study demonstrated that serum NT-proBNP was significantly higher in the severe group of COVID-19 than in the mild group ($P<0.01$), and was found to be more significant in the death group, suggesting that persistently abnormal elevation of NT-proBNP may be associated with poor prognosis.

Conclusion

In conclusion, after COVID-19 infection, it will cause different degrees of damage to the heart, and it is difficult to obtain evidence of occult cardiac function damage by conventional echocardiography. 2DSTI-related parameters have high sensitivity in predicting occult myocardial damage, Tei index can reflect myocardial damage and its predictive performance increases with the elevation in the degree of damage, and NT-proBNP is meaningful for estimating the severity of myocardial damage. The combined application of the three can improve the diagnostic efficiency of myocardial damage and provide a diagnostic basis for cardiac dysfunction with preserved ejection fraction.

At the same time, the further follow-up study is needed on the changes and outcomes of cardiac function in COVID-19 patients during hospitalization, shortly after discharge, and long-term follow-up. In addition, due to the small sample size of this study, whether the abnormally increased NT-proBNP is related to adverse outcomes and its value need further research.

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