Left Ventricular Performance in Patients With Severe Acute Respiratory Syndrome
A 30-Day Echocardiographic Follow-Up Study

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Background—Severe acute respiratory syndrome (SARS) is characterized by an overaggressive immune response. Myocardial performance may be impaired in cytokine-mediated immune reactions.

Methods and Results—Forty-six patients with established clinical diagnosis of SARS were studied prospectively. Transthoracic echocardiographic examinations were done at the acute stage of infection and 30 days later. Among them, 14 patients required mechanical ventilation. The clinical course, laboratory data, SARS-CoV antibody titers, and results of reverse transcriptase–polymerase chain reaction were studied. Significantly higher left ventricular index of myocardial performance (IMP) (0.42±0.13 versus 0.33±0.09, P<0.001), longer isovolumic relaxation time (102.9±15.7 versus 81.6±14.7 ms, P<0.001), lower flow propagation velocity (69.6±15.7 versus 83.8±19.7 cm/s, P=0.011), and Doppler-derived cardiac output (4.69±1.01 versus 5.49±1.04 L/min, P<0.001) were observed during acute infection when compared with those at 30 days. No significant valvular disease or pulmonary hypertension was found. At baseline, a lower mean left ventricular ejection fraction (LVEF) (65.3±12.8% versus 71.4±5.7%, P=0.03) and a higher mean IMP (0.51±0.11 versus 0.40±0.12, P=0.017) were found in patients who required mechanical ventilation. A decrease in LVEF correlated moderately with an elevated lactate dehydrogenase level (r=−0.605, P<0.001), whereas a higher IMP correlated weakly with an increase in creatine kinase level (r=0.38, P=0.016). Histological examination of the heart in the patient with the lowest EF (30.2%) revealed no interstitial lymphocytic infiltrate or myocyte necrosis.

Conclusions—Subclinical diastolic impairment without systolic involvement was observed in patients with SARS. This impairment may be reversible on clinical recovery. (Circulation. 2003;108:1798-1803.)

Key Words: diastole • echocardiography • myocardial contraction
Global left ventricular systolic function was represented by the modified biplane Simpson left ventricular ejection fraction (LVEF) as recommended by the American Society of Echocardiography.5

Doppler Measurements

The index of myocardial performance (IMP) of the left ventricle was measured as described,6,7 with the pulsed wave Doppler sample volume placed at the tips of the mitral valve leaflets in the apical 4-chamber view. The time interval between the mitral valve closure and opening “a” was measured. With the pulsed wave Doppler sample volume located just below the aortic annulus from the apical long-axis view, the time interval from the onset to the end of the aortic ejection flow “b” was measured. The IMP was calculated as (a−b)/b. Since interval “a” comprised isovolumic contraction time (ICT), aortic ejection time (ET), and isovolumic relaxation time (IVRT), the index represented the sum of [(ICT+IVRT)/ET].

Stroke volume was derived from multiplying the time-velocity integral of the pulsed wave Doppler tracing just below the aortic annulus by the cross-sectional area of left ventricular outflow tract as determined from the parasternal long-axis view. Cardiac output (CO) was then calculated as the product of the heart rate and the stroke volume.

Mitrail inflow parameters measured were peak early (E) and late diastolic (A) velocities and deceleration time (DT). Flow propagation velocity (FPV) was measured from the color M-mode Doppler images of the mitral atrioventricular flow with the aliasing limit lowered to ~40 cm/s. The slope of the first aliasing velocity along the far left red-to-blue color map transition was then measured.

Pulmonary venous flow parameters measured were the systolic (S), diastolic (D), and atrial flow reversal velocities (PVA). The IVRT, the interval from aortic valve closure to mitral valve opening, was measured by placing the sample Doppler in the area between the mitral valve tips and the left ventricular outflow tract.

Pulsed tissue Doppler imaging was obtained with the sample gate placed at the lateral base of the left ventricular wall in the apical 4-chamber view. The 3 main components, systolic (Sm), early diastolic (Em), and late diastolic myocardial (Am) velocities, were recorded. Interrogation at multiple sites was not performed, in order to minimize the examination time.

Intraobserver and interobserver variability for IMP ranged from 4.8±3.8% and 5.6±5.0%, respectively, and was determined to be ≤5±5% and ≥9±6% for FPV. For the measurement of the biplane Simpson EF, intraobserver and interobserver variability was 1.4±1.7% and 1.6±2.1%, respectively.

SARS-CoV Antibody Titers and RT-PCR Tests

Blood samples were taken on admission on day 0 and on days 7, 14, 21, and 28 for SARS-CoV antibody titers, which were determined through the use of immunofluorescence assay. A positive test was defined as either seroconversion from negative to positive or a 4-fold rise in titers. Respiratory secretions and stool specimens were sent for RT-PCR tests.

Statistical Analysis

Continuous numeric variables are expressed as mean value±SD and as frequency number (%) for dichotomous variables. Variables derived from echocardiography and laboratory investigations were compared between the distinct groups by using an unpaired Student’s t test and compared within the same group by using a paired Student’s t test. Univariate regression analysis was performed to assess the relation between LV dysfunctional parameters and laboratory investigational findings. Statistical significance was defined at a level of P<0.05. All statistical tests were analyzed with SPSS software (version 11.0).

Results

The mean age of the patients was 41.4±13.9 years, with a range from 19 to 72 years. There were 17 men and 29 women. Fourteen (30.4%) required positive-pressure ventilation at the time of first echocardiogram. The usual starting tidal volume and positive end-expiratory pressure administered were 8 mL/kg body wt and 10 cm H2O, respectively, and they were adjusted as required. The mean interval time between the onset of symptoms and first echocardiogram was 18.7±7.5 days. At presentation, the patients had the following symptoms: fever >38°C (97.8%), chills (50%), cough (47.8%), malaise (37%), myalgia (34.8%), rigors (26.1%), sputum (19.6%), dyspnea (15.2%), diarrhea (15.2%), sore throat (6.5%), headache (6.5%), and rhinorrhea (2.2%). None had
chest pain or overt heart failure. Forty-one patients (89.1%) were found to have positive anti–SAR-CoV antibodies during their course of illness, and a positive PCR test result was observed in 24 patients (52.2%). All patients were in sinus rhythm, and electrocardiograms showed right bundle-branch block in 7 patients (15.2%).

None of the patients had significant valvular lesions. Trace to mild mitral regurgitation was found in 17 patients (36.9%), whereas trace to mild aortic regurgitation was detected in 2 patients (4.3%). No significant pulmonary hypertension was found, and the mean systolic pulmonary artery pressure was 33±7 mm Hg. Follow-up echocardiograms were available in only 40 patients, as 6 patients died before the follow-up examination. Table 1 shows the echocardiographic data and essential laboratory findings at baseline and follow-up. Significantly higher left ventricular IMP (0.42±0.13 versus 0.33±0.09, P=0.001), longer IVRT (102.9±15.7 versus 81.6±14.7 ms, P=0.001), lower FPV (69.6±15.7 versus 83.8±19.7 cm/s, P=0.011), lower Doppler-derived CO (4.69±1.01 versus 5.49±1.04 L/min, P=0.001), and lower Em (17.3±4.2 versus 19.3±4.8 cm/s, P=0.009) were observed at the time of acute infection when compared with those at 30 days.

At baseline, the LVEF was significantly lower (65.3±12.8% versus 71.4±5.7%, P=0.03) and the IMP was significantly higher (0.51±0.11 versus 0.40±0.12, P=0.017) in the group of patients who required mechanical ventilation (n=14) when compared with those who did not (n=32) (Figures 5 and 6). However, other parameters including
Postmortem examination was performed on the 39-year-old woman who died with an LVEF of 30.2%. On gross examination, the left ventricle was slightly enlarged and the heart was not flabby. There was no evidence of myocardial infarct or vegetation. The coronary arteries were patent. There was no evidence of atherosclerosis, thrombosis, or embolism. The cardiac valves were structurally normal. Circumferential sections of both the right and left ventricles were sent for histological examination. There was no evidence of interstitial lymphocytic infiltrate or necrosis of myocardial fibers.

Discussion

Our findings suggest that left ventricular performance was subclinically impaired during the acute phase of SARS infection and that it may be reversible on clinical recovery. This reversibility was observed in all patients irrespective of the severity of their disease. In addition, the impairment appeared to be worse in those more critically ill patients, as defined arbitrarily by the need of mechanical ventilation at baseline.

In our study, several echocardiographic parameters were used to assess the left ventricular systolic and diastolic function. The value of IMP in left ventricular dysfunction has been validated in patients with idiopathic dilated cardiomyopathy\(^6\) and severe symptomatic heart failure with ischemic or nonischemic etiology.\(^9\) Its independence on loading con-
Impaired ventricular relaxation and increase in chamber stiffness will produce directionally opposite changes in the transmitral flow velocities and deceleration time profile. Results from animal studies also demonstrated the limitation of pulmonary venous Doppler pattern in assessing diastolic dysfunction. In addition, the wide range of age in the study group may lead to a heterogeneous spectrum of transmitral flow velocity patterns that render subtle changes in diastolic filling difficult to be detected. The small number of patients (n=9) may also limit the power to detect minor changes in the group that needed mechanical ventilation.

The modified biplane Simpson method has been used as a standard parameter for assessing global LV systolic function. However, it suffers from the drawback of inadequate endocardial definition in nonechogenic subjects, requiring assumptions on ventricular geometry and dependence on loading conditions of the heart. Tissue Doppler echocardiography may provide new information on regional systolic and diastolic LV function. In our study, to minimize the risk of inadvertent infection to the echocardiographer, only the basal lateral myocardial velocities were measured. This site has the potential advantage of a greater longitudinal contractile activity when compared with the ventricular septum because of its abundance of longitudinal fibers. At baseline, the LVEF was significantly lower in the group requiring mechanical ventilation than those who did not (65.3±12.8 versus 71.4±5.7%, P=0.03), whereas the Sm appeared higher in the former group but was not statistically significant. This may be related to the suboptimal number of sites of tissue Doppler interrogation and a wide range of Sm values in a small number of patients in the mechanically ventilated group. Significantly lower Doppler-derived cardiac output was observed at baseline (4.69±1.01 versus 5.49±1.04 L/min, P<0.001) when compared with that at follow-up, despite the fact that there was no significant change in LVEF, Sm, and left ventricular volumes. This was primarily due to a significant difference between the heart rate at baseline and follow-up (78±19 versus 89±13 bpm, P=0.003). Similarly, the relative shortening of ejection time at follow-up (Table 1) was probably due to such difference rather than systolic dysfunction, as the IMP was lower and other systolic parameters were unchanged at follow-up. The exact cause of the difference in heart rate was uncertain, and it remains to be studied whether the slower heart rate at baseline was related to the drug therapy such as intravenous ribavirin or other causes. The shortening of IVRT at follow-up may also be related to this significantly higher heart rate, although we postulated that there should be some improvement in the echocardiographic parameters on disease recovery. Overall, it appears that SARS only impairs diastolic function and spares systolic function.

The laboratory findings in our patients were similar to those from other series. Elevated LDH was found to be associated with decreased LVEF. The elevated LDH might reflect the severity of tissue damage and inflammation. We hypothesized that the temporary impairment in the echocardiographic parameters in the acute phase might be due to the cytokine storm resulting from an overaggressive host immune response to SARS infection. Tumor necrosis factor (TNF),

Figure 5. IMP at time of first echocardiogram between non–mechanically ventilated and mechanically ventilated patients.

Figure 6. Left ventricular EF at time of first echocardiogram between non–mechanically ventilated and mechanically ventilated patients.
and the interleukin (IL)-1 family and the IL-6 family of cytokines have been implicated as proinflammatory mediators in heart failure, and they have significant negative inotropic effects. In accordance with this postulation, the parameters in our study were worse in patients with more critical disease and more exuberant immune reaction and then improved in the convalescent phase when the acute inflammatory response subsided.

Direct SARS-CoV infection of the myocytes causing active myocarditis might also contribute to the impairment in myocardial function. Coronavirus-induced myocarditis and its subsequent progression into dilated cardiomyopathy have been described in a rabbit model. However, myocarditis in humans by coronavirus is rarely reported. To avoid inadvertent infection of health care workers, postmortem examination in our study was kept to a minimum; histological evidence of myocarditis. Nevertheless, it has been shown that <10% of patients in whom myocarditis was suspected on clinical grounds had positive biopsy specimens, as assessed by the Dallas criteria.

Since the changes in the echocardiographic parameters were generally mild and reversible, a more severe impairment of left ventricular function in patients with SARS, like the one with a LVEF of 30.2%, may suggest an aggravation of an occult underlying heart disease or the presence of other additional secondary causes of left ventricular impairment. Secondary infections may impair cardiac function and were present in 3 of our mechanically ventilated patients, but the infections were all controlled with appropriate antibiotic treatment during the initial studies. No secondary bacterial infection was detected in those who did not require mechanical ventilation. Secondary infections could not fully account for the entire observed phenomenon because the reversible impairment of left ventricular performance was observed in both groups of patients. The worse echocardiographic parameters in those patients requiring mechanical ventilation might also be related to the positive-pressure ventilation, as by impeding ventricular filling, positive-pressure ventilation can reduce cardiac output. The use of intravenous ribavirin and methylprednisolone alone in other clinical situations has not been reported to be associated with significant depression of left ventricular function. It remains to be studied whether the observed impairment in echocardiographic parameters would be contributed by the combination use of these two drugs.

The available evidence in this study does not suggest a major cardiac involvement in patients with SARS. There was subclinical diastolic dysfunction during acute infection, although the power of the study is limited, particularly in subgroup analysis, due to the small studied population. The observed decrease in left ventricular performance during acute infection phase probably is related to a systemic inflammatory condition under the influence of proinflammatory cytokines, which is not unique to SARS. The current hypothesis of cytokine-mediated temporary impairment of left ventricular performance warrants further studies with measurements of circulatory levels of cytokines such as TNF-α and IL-1β in addition to echocardiographic studies. Histological correlations, particularly in patients with significant impairment in systolic or diastolic function, will be invaluable. Since SARS-CoV is a highly contagious virus and the present findings of left ventricular impairment were largely subclinical, routine echocardiography in clinical service for patients without cardiovascular symptoms is not warranted.

Conclusions

Subclinical diastolic dysfunction without systolic impairment was observed in SARS. The echocardiographic parameters were worse in the more critically ill patients. The impairment may be reversible on recovery. Further studies are required to establish the underlying mechanism and its clinical significance.

References

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