Introduction

Sepsis and septic shock are major health problems with high morbidity and mortality that affect millions of people across the globe each year.[1,2] Septic cardiomyopathy is a common finding in septic shock patients; an understanding of whether it can worsen a patient’s prognosis remains elusive.[3] However, septic cardiomyopathy clearly will make hemodynamic and tissue perfusion more vulnerable in septic shock patients.[4]

Currently, the most accepted definition of myocardial dysfunction in septic shock is based on a left ventricular ejection fraction (LVEF) of <45–50%.[5,6] A meta-analysis showed that the presence of a low LVEF was neither a sensitive nor specific predictor of mortality in septic shock patients.[7] A longitudinal strain is a sensitive echocardiographic tool to evaluate LV systolic function.
and is associated with hospital mortality in septic shock patients. Carasso et al. noted that longitudinal strain was more sensitive than LVEF in detecting abnormalities in LV systolic function. Despite the fact that strain measurement is a novel technique, there is a possibility that it is the longitudinal function rather than the strain measurement that makes this method more sensitive than the LVEF in the detection of septic cardiac depression.

The conventional longitudinal function measurement includes mitral annular plane systolic excursion (MAPSE) and tissue Doppler velocity measurement of mitral annulus (Sa). Several studies have used MAPSE as a good parameter of systolic function. Others have used Sa to represent longitudinal systolic function. However, whether longitudinal function parameters such as MAPSE and Sa will be more sensitive than LVEF when detecting cardiac depression in septic shock patients has not yet been fully analyzed. We hereby performed an observational study to investigate the LV longitudinal systolic function in septic shock patients with normal LVEF.

**Methods**

**Ethical approval**

The study was conducted according to the *Declaration of Helsinki* and was approved by the ethics committee of Peking Union Medical College Hospital (Approval Number: S617). The written informed consent was obtained from the next of kin of all of the patients.

**Study population**

This was a case-control study conducted at a 40-bed Intensive Care Unit (ICU) in Peking Union Medical College Hospital. Septic shock patients admitted to the ICU from March 1, 2016 to September 1, 2016 were studied. Diagnosis of septic shock was made based on the new definition that was developed by the sepsis definitions task force; the definition of septic shock included: sepsis patients with persisting hypotension requiring vasoressors to maintain mean arterial pressure ≥65 mmHg (1 mmHg = 0.133 kPa) and a serum lactate level >2 mmol/L, despite adequate volume resuscitation. Sepsis was defined as life-threatening organ dysfunction consequent to the infection.

**Statistical analysis**

Statistical analysis was performed using the SPSS version 13.0 statistical software package (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as the mean ± standard deviation (SD) or median (inter-quartile range). Categorical variables were presented as the number and the percentages. Continuous variables were compared with the use of Student’s *t*-test or Mann-Whitney *U*-test. Categorical variables were compared with Chi-square test or Fisher’s exact test. Statistical significance was defined as a value of *P* < 0.05.

**Echocardiography**

Heart rate and blood pressure were obtained from the monitor at the onset of examination. Images were recorded for offline analysis. Two intensivists who were experienced with echocardiography performed the echo examination. To reduce the interobserver variability, both of the performers were present during each echo examination to double check the results, and a third echocardiographer was consulted if there was disagreement.

Echocardiograms were performed using an echocardiograph (Sonosite, M-Turbo, California, USA) with a 2.5-MHz phased-array probe. Electrocardiograph was recorded continuously during the echo examination. Three cardiac cycles were analyzed and averaged. Patients were in the semi-left lateral position during the examination. Echocardiographic M-mode and Doppler measurements were taken in a standard manner.

LVEF was obtained using the modified biplane Simpson’s method from apical two- and four-chamber views. Indexes of longitudinal systolic function measurements were taken from the apical four-chamber view. MAPSE was obtained by putting the cursor along the mitral ring and measuring the difference between the highest and lowest point of the M-mode sinusoid wave. A value of lower than 10 mm represented systolic dysfunction. Tricuspid annular plane systolic excursion (TAPSE) was obtained by putting the M-mode cursor along the lateral part of the tricuspid valve ring. Sa was performed in the apical four-chamber views by placing a 5-mm sample volume at the lateral site of the mitral annulus in accordance with the American Society of Echocardiography recommendations. The e’ was the annular motion of the mitral valve in early diastole using tissue Doppler imaging. Filters and gains were adjusted to achieve the optimal signal-to-noise ratio.

**General characteristics of all patients**

Sixty-two consecutive septic shock patients who were admitted to the ICU were screened for enrollment. Seven were
excluded because of poor image quality, six were excluded because of an LVEF below 50%, three were excluded because of valvular disease, and one was excluded because of acute coronary syndrome. Ultimately, 45 septic shock patients were selected as the study group. Another 45 nonsepsis patients were selected as the control group. The mean ages of the two groups were 62.5 ± 13.8 years old and 59.7 ± 15.6 years old, respectively, and 48.9% vs. 46.7% were men. No difference was found in cardiovascular risk factors between the two groups. The study group had higher Acute Physiology and Chronic Health Evaluation (APACHE II; 22.3 ± 10.7 vs. 12.4 ± 3.9, t = 2.765, P = 0.003) and SOFA scores (11.2 ± 3.2 vs. 2.5 ± 0.9, t = 14.560, P < 0.001). Ten patients in the study group died in the hospital, while no deaths were found in the control group [Table 1].

**Respiratory support and hemodynamic data**

The proportion of patients on ventilation in the two groups was similar (86.7% vs. 75.6%, χ² = 1.813, P = 0.178). The positive end-expiratory pressure (PEEP) level (6 ± 2 cmH₂O vs. 5 ± 1 cmH₂O, t = 1.538, P = 0.125) and plateau pressure (18 ± 5 cmH₂O vs. 17 ± 3 cmH₂O, t = 1.505, P = 0.140) in the two groups were not significantly different. The study group had a higher heart rate than the control group (99 ± 20 beats/min vs. 81 ± 17 beats/min, t = 4.376, P < 0.001). No patients in the control group were prescribed norepinephrine, while all patients in the study group were infused with norepinephrine with a median dose of 0.26 μg·kg⁻¹·min⁻¹. The mean arterial blood pressure between the two groups was not significantly different (86 ± 14 mmHg vs. 91 ± 14 mmHg, t = −1.736, P = 0.086) [Table 1].

**Echocardiographic measurements**

There were no differences found between the two groups in terms of LV diastolic internal diameter and systolic internal diameter (47.6 ± 6.2 mm vs. 47.9 ± 2.7 mm, t = −0.220, P = 0.826; 29.8 ± 6.5 mm vs. 28.4 ± 3.8 mm, t = 1.105, P = 0.274, respectively). There was also no difference in the LVEF in the two groups (64.6% ± 9.3% vs. 67.2% ± 8.8%, t = −1.426, P = 0.161). No significant difference was found on the E-wave peak velocity, A-wave peak velocity, or e’ peak velocity between the two groups (73.4 ± 20.9 cm/s vs. 73.7 ± 20.1 cm/s, t = −0.016, P = 0.961; 84.8 ± 24.2 cm/s vs. 80.2 ± 12.1 cm/s, t = 0.842, P = 0.518; and 9.8 ± 3.0 cm/s vs. 10.8 ± 2.3 cm/s, t = −1.812, P = 0.073, respectively).

MAPSE in the study group was much lower than in the control group (1.2 ± 0.4 cm vs. 1.5 ± 0.2 cm, t = −4.945, P < 0.001). In the study group, Sa was lower than in the control group (10.2 ± 2.7 cm/s vs. 11.8 ± 2.9 cm/s, t = −2.796, P = 0.014). In the study group, TASPE was also significantly lower than in the control group (1.9 ± 0.4 cm vs. 2.3 ± 0.4 cm, t = −4.216, P < 0.001) [Table 2 and Figures 1a-1d].

**Discussion**

The present study found that the values of MAPSE and Sa were lower in septic shock patients with normal LVEF than in nonsepsis patients. The result indicates that for septic shock patients, longitudinal systolic function, such as MAPSE and Sa, might already have been compromised before an obvious low ejection fraction emerges.

Although no evidence confirmed the association between septic cardiomyopathy and mortality, it would precipitate the hemodynamic instability of septic shock patients.[7,18] Thus, the detection of cardiac depression should be an integral part of hemodynamic management in septic shock patients. The finding in this study was worth considering in the management of hemodynamics in septic shock. First, we could have a better chance to discover the LV dysfunction.

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**Table 1**: General characteristics of the sepsis shock group and nonsepsis group (n = 45)

| Items                      | Study group          | Control group         | t or χ² | P     |
|----------------------------|----------------------|-----------------------|---------|-------|
| Age (year)                 | 59.7 ± 15.6          | 62.5 ± 13.8           | −0.901* | 0.370 |
| Sex (male), n (%)          | 22 (48.9)            | 21 (46.7)             | 0.044   | 0.833 |
| APACHE II                  | 22.3 ± 10.7          | 12.4 ± 3.9            | 2.765*  | 0.003 |
| SOFA                       | 11.2 ± 3.2           | 2.5 ± 0.9             | 14.560* | <0.001|
| Cardiovascular risk factors, n (%) |                     |                      |         |       |
| Hypertension               | 12 (26.7)            | 16 (35.6)             | 0.829   | 0.362 |
| Diabetes mellitus          | 6 (13.3)             | 10 (22.2)             | 1.216   | 0.114 |
| Coronary heart disease     | 3 (6.7)              | 1 (2.2)               | 1.047   | 0.306 |
| Chronic renal failure      | 5 (11.1)             | 4 (8.9)               | 0.123   | 0.725 |
| Patients on ventilation, n (%) | 39 (86.7)           | 34 (75.6)             | 1.813   | 0.178 |
| PEEP (mmHg)                | 6 ± 2                | 6 ± 1                 | 1.538*  | 0.125 |
| Pplat (mmHg)               | 18 ± 5               | 17 ± 3                | 1.505*  | 0.140 |
| Oxygen saturation (%)      | 98 ± 2               | 99 ± 1                | −1.065* | 0.293 |
| NE (µg·kg⁻¹·min⁻¹)         | 0.26 (0.06–2.60)     | −                     |         | <0.001|
| HR (beats/min)             | 99 ± 20              | 81 ± 17               | 4.376*  | <0.001|
| MAP (mmHg)                 | 86 ± 14              | 91 ± 14               | −1.736* | 0.086 |
| Prognosis, n (%)           | 10 (22.2)            | 0                     | 11.250  | <0.001|

The data were presented by mean ± standard deviation, median (inter-quartile range) or n (%). *t value. NE: Norepinephrine; PEEP: Positive end expiratory pressure; Pplat: Plateau pressure; APACHE: Acute Physiology and Chronic Health Evaluation; HR: Heart rate; MAP: Mean arterial pressure; SOFA: Sepsis-related Organ Failure Assessment.
role in maintaining normal function. During ventricular contraction, the base of the heart moves toward the apex; the magnitude of the movement is believed to be proportional to systolic function. Therefore, the assessment of long-axis function provides a simple and fast evaluation of the LV systolic function that is especially useful for ICU patients without an optimal image.

The value of MAPSE in the study group, although still within the normal range, was much lower than that in the control group. Because the echo examination can be performed at least once per day, continuous monitoring of MAPSE to detect a decrease in the value is completely feasible in the critical care setting. If we can discover a decreasing trend in MAPSE, irrespective of whether it is within the normal range, care should be taken that myocardial depression might have already occurred.

Subendocardial muscle fibers that are longitudinal and responsible for long-axis function are more susceptible earlier. Second, this method was much easier than LVEF measurement in the critical care setting.

It is well known that the LVEF cannot only be influenced by intrinsic contractility but can also be affected by the preload and afterload of the heart during the examination. However, we performed the echo after initial resuscitation; thus, the possibility of hypovolemia could be ruled out. Vieillard Baron et al.\textsuperscript{[19]} found in their study that after early resuscitation, the LV volume remained in a normal range, and the stroke index was uniquely determined by the systolic function. No difference in MAP was found between the two groups, indicating that there was little chance for afterload to influence the LVEF. Thus, the LVEF of the two groups were mainly the reflection of LV contractility.

Although the majority of myocardial fibers are arranged circumferentially, longitudinal fibers also play an important role in maintaining normal function. During ventricular contraction, the base of the heart moves toward the apex; the magnitude of the movement is believed to be proportional to systolic function. Therefore, the assessment of long-axis function provides a simple and fast evaluation of the LV systolic function that is especially useful for ICU patients without an optimal image.\textsuperscript{[120]} The value of MAPSE in the study group, although still within the normal range, was much lower than that in the control group.\textsuperscript{[21]} Because the echo examination can be performed at least once per day, continuous monitoring of MAPSE to detect a decrease in the value is completely feasible in the critical care setting. If we can discover a decreasing trend in MAPSE, irrespective of whether it is within the normal range, care should be taken that myocardial depression might have already occurred.

Subendocardial muscle fibers that are longitudinal and responsible for long-axis function are more susceptible
Table 2: Echocardiographic parameters of the sepsis shock group and nonsepsis group (n = 45)

| Categories          | Study group | Control group | t    | P    |
|---------------------|-------------|---------------|------|------|
| LVDD (mm)           | 47.6 ± 6.2  | 47.9 ± 2.7    | −0.220 | 0.826 |
| LVSD (mm)           | 29.8 ± 6.5  | 28.4 ± 3.8    | 1.105 | 0.274 |
| LVEF (%)            | 64.6 ± 9.3  | 67.2 ± 8.8    | −1.426 | 0.161 |
| E-wave (cm/s)       | 73.4 ± 20.9 | 73.7 ± 20.1   | −0.016 | 0.961 |
| A-wave (cm/s)       | 84.8 ± 24.2 | 80.2 ± 12.1   | 0.842 | 0.518 |
| e’ (cm/s)           | 9.8 ± 3.0   | 10.8 ± 2.3    | −1.812 | 0.073 |
| E/e’                | 7.7 ± 2.1   | 8.1 ± 2.1     | −0.506 | 0.614 |
| TAPSE (cm)          | 1.9 ± 0.4   | 2.3 ± 0.4     | −4.216 | <0.001 |
| Sa (cm/s)           | 10.2 ± 2.7  | 11.8 ± 2.9    | −2.796 | 0.014 |
| MAPSE (cm)          | 1.2 ± 0.4   | 1.5 ± 0.2     | −4.945 | <0.001 |

All data were presented by mean ± SD. LVDD: Left ventricular diastolic internal diameter; LVSD: Left ventricular systolic internal diameter; LVEF: Left ventricular ejection fraction; E-wave: Early wave of mitral inflow detected by pulse Doppler; A-wave: Mitral inflow occurs with atrial systole detected by pulse Doppler; e’: The annular motion of the mitral valve in early diastole using tissue Doppler imaging; TAPSE: Tricuspid annular plane systolic excursion; Sa: Tissue Doppler velocity measurement of mitral annulus; MAPSE: Mitral annular plane systolic excursion; SD: Standard deviation.

to ischemia and injury.[22] Although no evidence support reduced overall coronary perfusion during septic shock, microvascular alteration may be associated with focal ischemia. Certainly, the most vulnerable part would be the subendocardial fiber.[23] This can explain why the longitudinal function would be more easily affected in septic shock patients.

Several studies found that global longitudinal strain measured through the speckle tracking method can detect LV impairment.[8,9] Nevertheless, in a critical care setting where patients are predominantly ventilated, obtaining optimal image quality for strain measurements can be challenging. Consequently, the longitudinal strain value obtained based on poor image quality may not accurately reflect actual LV deformation. In addition, reproducibility and standardization of reference values are not uniform across echocardiography systems because manufacturers use different algorithms.[24] However, MAPSE, also representing longitudinal function, will be easier to obtain and will be less influenced by the image and technology.

TAPSE is a good marker of the right ventricular systolic function.[25,26] Singh et al.[27] stated in their study that TAPSE was reflective of biventricular function in critically ill patients. A prior study demonstrated that the proportion of the right heart dysfunction in septic shock patients was approximately 31%.[28] In this study, TAPSE in the study group, also within the normal range, decreased significantly, indicating that the right heart was also affected when LV longitudinal function was impaired. Positive ventilation might influence the TAPSE by way of increasing right ventricular afterload.[29] However, in this study, the PEEP and plateau pressures were not different between the two groups. Thus, the possibility of ventilator-related TAPSE decreasing in septic shock patients could be ruled out. The ventricular interdependence might also play a role in the decrease of TAPSE. A previous study demonstrated that 30% of the contraction force of the RV comes from the left ventricle.[30] When the left ventricle is affected in septic shock, the right ventricle is as well.

This study had several limitations. First, this was a single-center case-control study, selection bias was not impossible. Second, instead of being a serial observation, echocardiographic measurements were performed only once for each patient. Therefore, we were not able to acquire the time point when longitudinal function recovers. If more time points were evaluated, the result would be more robust and clinically meaningful. Third, we did not investigate the longitudinal function of septic shock patients whose LVEF was below 50%; therefore, we failed to explain if the MAPSE and Sa would continue to decrease to an even lower level as the LVEF drops to a value of <50%. Age might also be a confounding factor in this study. Patients in both groups almost reached 60 years old, thus, the results of this research might not be applicable to younger patients.

In conclusion, compared to LVEF, the longitudinal systolic function might be more sensitive in the detection of cardiac depression in septic shock patients. In the heart function appraisal of septic shock patients with normal LVEF, more attention should be given to longitudinal function parameters such as MAPSE and Sa.

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Conflicts of interest
There are no conflicts of interest.

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