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BRIEF RESEARCH COMMUNICATIONS

Takotsubo Syndrome from Coronavirus Disease 2019



Takotsubo syndrome (TTS) or stress-induced cardiomyopathy is a rare form of acute, reversible left ventricular dysfunction. Catecholaminergic surge, myocardial inflammation, impaired microvascular perfusion, and electrophysiologic derangements may all contribute to its clinical manifestations of myocardial stunning and apical ballooning.¹

The novel coronavirus disease 2019 (COVID-19) has been associated with various cardiovascular manifestations, known as acute COVID-19 cardiovascular syndrome (ACovCS), which include but are not limited to acute coronary syndrome, myocarditis, microvascular disease, and TTS. The pathophysiology of myocardial injury seen in COVID-19 is thought to be secondary to a robust inflammatory response, including cytokine storm, which often is associated with elevated inflammatory markers (e.g., D-dimer, ferritin, lactate dehydrogenase, C-reactive protein, and erythrocyte sedimentation rate).^{2,3} The aim of this study was to explore the prevalence of TTS in patients with COVID-19.

We conducted a retrospective study of consecutive patients with polymerase chain reaction–confirmed COVID-19 who underwent

a transthoracic echocardiogram (TTE) at a single academic center between April 2020 and March 2021. The TTE reports of patients with confirmed COVID-19 were queried for the term “takotsubo,” “stress,” or “stress-induced cardiomyopathy” as well as for the presence of any regional wall motion abnormality (i.e., “hypokinesis,” “akinesis,” or “dyskinesis”). These TTEs were reviewed by three independent Core Cardiovascular Training Statement level III echocardiographers to confirm TTS on the basis of the characteristic presence of basal segment hyperkinesis with associated apical hypokinesis or “apical ballooning,” or atypical variants of TTS. Patients were excluded if they had preexisting epicardial coronary artery disease or acute myocardial infarction by chart review.

During our study period, a total of 1,308 patients were admitted with COVID-19, of whom 476 (36.4%) underwent a TTE during their index hospitalizations. Our query resulted in 47 TTEs, of which nine met echocardiographic criteria for typical TTS. Four were excluded because of the presence of coronary artery disease. The remaining five patients with COVID-19 and TTS had a mean age of 73 years, and three patients were women. The mean time from COVID-19 diagnosis to TTE was 1.6 days (1-3 days). Laboratory test results revealed elevated inflammatory markers and elevated cardiac biomarkers, in addition to the typical abnormalities seen on electrocardiogram and reduced left ventricular ejection fraction on TTE

Table 1 Patient characteristics, peak laboratory values, electrocardiographic findings, and transthoracic echocardiographic findings of patients meeting criteria for TTS

| Patient | Gender | Race | Age, y | Lactic acid, mmol/L | hs-TnT, ng/L | WBC count, 10 ³ /μL | D-dimer, μg/mL | LDH, U/L | Fibrinogen, mg/dL | ESR, mm/h | CRP, mg/L | ECG | Previous TTE LVEF, % | Takotsubo TTE LVEF, % |
|---------|--------|-------|--------|---------------------|--------------|--------------------------------|----------------|----------|-------------------|-----------|-----------|--|----------------------|-----------------------|
| 1 | M | Black | 63.0 | 2.8 | 429.0 | 39.2 | 3.6 | 510.0 | 483.0 | 120.0 | 314.0 | Sinus tachycardia, 2-mm STE in leads V ₃ –V ₆ | 70.0 | 35.0 |
| 2 | F | White | 68.0 | 1.9 | 92.0 | 17.9 | — | 341.0 | — | — | 61.0 | Sinus tachycardia, poor R-wave progression | 64.0 | 36.0 |
| 3 | F | Black | 91.0 | 3.7 | 140.0 | 14.0 | — | — | — | — | — | NSR, LBBB, lateral TWI | 70.0 | 42.0 |
| 4 | F | White | 79.0 | 8.7 | 2,325.0 | 10.4 | 1.2 | — | 434.0 | 68.0 | 20.0 | AF; 2- to 4-mm STE in leads V ₂ –V ₆ , <1-mm STD in leads II, III, and aVF | 65.0 | 29.0 |
| 5 | M | Black | 65.0 | 4.3 | 2,221.0 | 10.3 | 2.9 | 687.0 | 578.0 | 31.0 | 301.0 | Sinus tachycardia, lateral STE, inferior and anterolateral TWI | 60.0 | 33.0 |
| Mean | | | 73.2 | 4.3 | 1,041.4 | 18.4 | 2.6 | 512.7 | 498.3 | 73.0 | 174.0 | | 65.8 | 35.0 |

Reference values: lactic acid, 0.5 to 2.0 mmol/L; hs-TnT, <22 ng/L; WBC count, 3.5 to 11.0 × 10³/μL; D-dimer, <0.40 μg/mL; LDH, 116 to 245 U/L; fibrinogen, 180 to 409 mg/dL; ESR, 0 to 33 mm/h; CRP, <5 mg/L.

AF, atrial fibrillation; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; F, female; hs-TnT, high-sensitivity troponin T; LBBB, left bundle branch block; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; M, male; NSR, normal sinus rhythm; STD, ST-segment depression; STE, ST-segment elevation; TWI, T-wave inversion; WBC, white blood cell.

Drs. Kanelidis and Miller contributed equally to this report.

Conflicts of interest: None.

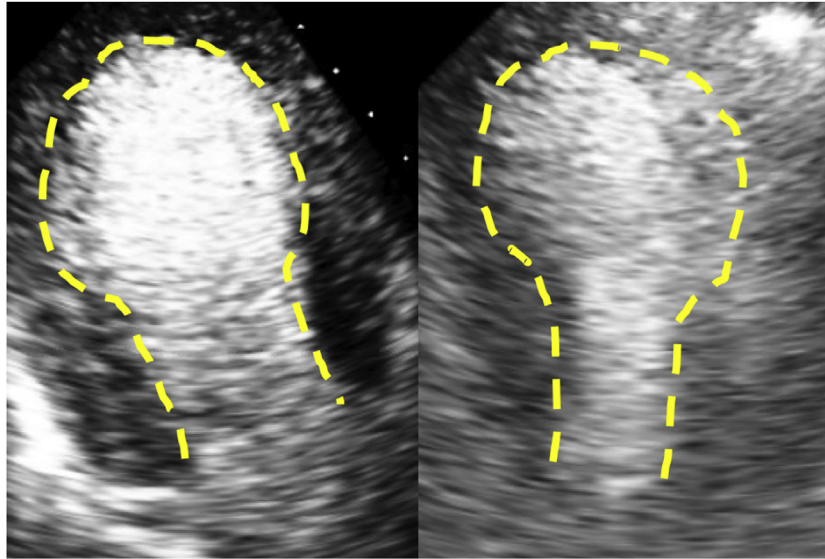


Figure 1 Transthoracic echocardiograms of two patients with confirmed COVID-19 with TTS. Basal segment hyperkinesis and apical hypokinesis or “apical ballooning” can be seen on contrast-enhanced apical two-chamber views.

(Table 1). TTE demonstrated the typical “apical ballooning” pattern often seen in TTS (Figure 1). We did not find any atypical variants of TTS. The ischemic electrocardiographic findings improved over time in all patients, and in the three patients with ST-segment elevation, ST segments returned to baseline an average of 13 days after the initial electrocardiographic examination. In our cohort, the prevalence of typical TTS in patients with COVID-19 was 1%.

Our single-center retrospective review adds to the growing literature on ACovCS. A systematic review of all published cases describing TTS in patients with COVID-19 found only 12 cases at the time of publication.⁴ Our study highlights the association between COVID-19 and TTS and how TTS may be appreciated more readily by reviewing TTEs with attention to typical wall motion abnormalities seen in TTS. At our center alone, we found five patients with presumed TTS compared with only 12 cases previously published in the literature. We also had a high percentage of hospitalized patients with COVID-19 who underwent a TTE (36.4%), often because of elevated high-sensitivity troponin T levels. To increase specificity, we excluded coexisting coronary artery disease, which may confound the true prevalence of TTS.

Although the pathophysiology of TTS is not fully understood, most TTS occurs in the setting of severe emotional, medical, or physical stress and is driven by excessive sympathetic nervous system activation and a heightened catecholamine state.⁵ Studies have shown that serum levels of epinephrine and norepinephrine are higher in patients with TTS compared to those experiencing myocardial infarction, but this has not yet been studied in patients with COVID-19.⁶ Furthermore, patients with COVID-19 could also have some degree of microvascular dysfunction that predisposes them to TTS.⁷ COVID-19 is known to be associated with a severe inflammatory response, including cytokine storm, which is manifested by high fevers and significantly elevated inflammatory markers; this may be another possible mechanism for the development of TTS.²

Our data suggest that patients with COVID-19 and elevated cardiac biomarkers as well as elevated inflammatory laboratory

testing consistent with ACovCS should undergo TTE and ischemic evaluation to rule out stress-induced cardiomyopathy or acute coronary syndrome.

Given the clinical context and limited resources during the height of the COVID-19 pandemic, acute myocardial infarction was not excluded in all patients by coronary angiography. Also, repeat TTE for left ventricular recovery was not performed in all of the patients, as two of the patients died and two have pending outpatient TTEs. One of the patients with a follow-up TTE did have an improved left ventricular ejection fraction of 60%, back to baseline. Another limitation is that atypical variants of TTS may have been missed despite our efforts to keep the search query broad for any wall motion abnormalities.

The true prevalence of TTS in patients with COVID-19 may be confounded by missing data, atypical variants of TTS, or the presence of coexisting coronary artery disease. In our cohort, the prevalence of TTS in patients with COVID-19 was approximately 1%.

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REFERENCES

1. Lyon AR, Citro R, Schneider B, Morel O, Ghadri JR, Templin C, et al. Pathophysiology of takotsubo syndrome: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;77:902-21.
2. Chilazi M, Duffy EY, Thakkar A, Michos ED. COVID and cardiovascular disease: what we know in 2021. *Curr Atheroscler Rep* 2021;23:37.

3. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med* 2020;383:2255-73.
4. Singh S, Desai R, Gandhi Z, Fong HK, Doreswamy S, Desai V, et al. Takotsubo syndrome in patients with COVID-19: a systematic review of published cases. *SN Compr Clin Med* 2020;2:2102-8.
5. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;39:2032-46.
6. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of takotsubo syndrome. *Circulation* 2017;135:2426-41.
7. Galiuto L, De Caterina AR, Porfidia A, Paraggio L, Barchetta S, Locorotondo G, et al. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in apical ballooning or tako-tsubo syndrome. *Eur Heart J* 2010;31:1319-27.

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Averaged Transaortic Mean Gradient during Atrial Fibrillation Does Not Accurately Reflect Aortic Stenosis Severity



The diagnosis of severe aortic stenosis (AS) is challenging when a small aortic valve area (AVA) is associated with low gradients not consistent with severe AS. Low-gradient AS (LGAS) is present in a significant proportion of patients with AS and is commonly due to low forward flow states. Atrial fibrillation (AF) is associated with lower forward flow compared with sinus rhythm (SR)¹ and may result in underestimation of AS severity by the flow-dependent mean gradient (MG).²⁻⁴ We aimed to compare forward flow parameters and transaortic valve MG in the same patient(s) during AF versus SR.

The institutional review board approved this study. Adult patients with transthoracic echocardiographic studies performed during both AF and SR (study period 2000-2020) with AVAs ≤ 1.0 cm² or indexed AVAs ≤ 0.6 cm²/m² during index transthoracic echocardiography were included. Patients were identified retrospectively. The average of three beats during SR and a minimum of five beats during AF was used for all measurements, according to guidelines using cycles with the least variation of RR intervals and as close as possible to the normal heart rate. The biplane method of disks (modified Simpson's rule) was used to assess left ventricular ejection fraction (LVEF). Left ventricular outflow tract diameter was measured on each transthoracic echocardiogram separately. Transaortic valve flow rate was estimated from the formula described by Namasivayam *et al.*⁵ Continuous variables are summarized as median (interquartile range). Normality of distribution was tested using the Shapiro-Wilk test. The matched-pairs *t* test was used to compare echocardiographic parameters in the same patient(s) between AF and SR in normally distributed variables, and the paired Wilcoxon test was used for non-normally distributed variables; patients acted as their own controls. Repeated-measures analysis of variance was used to adjust for possible confounding factors.

Twelve patients constituted the study population (median age, 84 years; 51-93 years; eight of 12 men [67%]). The median duration

between the two echocardiographic examinations was 5 months (0.2-12 months). SR preceded AF in six patients (50%), with a median duration of 8 months (0.4-12 months). AF preceded SR in the remaining six patients (50%), with a median duration of 4 months (0.2-6 months).

Echocardiographic data in patients while in AF versus SR are shown in [Table 1](#). AVA was not different between AF and SR (0.90 cm² [0.66-0.98 cm²] vs 0.86 cm² [0.57-1.08 cm²], *P* = 1.00). LVEF was lower during AF (53% [22%-71%] vs 61% [21%-70%], *P* = .04). Stroke volume index (38 mL/m² [23-46 mL/m²] vs 42 mL/m² [31-51 mL/m²], *P* = .03), forward flow rate (223 mL/sec [169-284 mL/sec] vs 234 mL/sec [188-319 mL/sec], *P* = .02), transaortic averaged peak velocity (3.5 m/sec [2.6-4.5 m/sec] vs 3.9 m/sec [3.2-4.7 m/sec], *P* = .041) and MG (31 mm Hg [17-50 mm Hg] vs 37 mm Hg [24-51 mm Hg], *P* = .048) were significantly lower during AF compared with SR when adjusted for difference in LVEF ([Figure 1](#)).

The highest recorded peak velocity during AF was 4.0 m/sec (2.9-4.9 m/sec) and was not different from the averaged 3.9 m/sec (3.2-4.7 m/sec) (*P* = .70) or highest 4.0 m/sec (3.3-4.7 m/sec) (*P* = .25) peak velocity during SR. The highest recorded MG during AF was 39 mm Hg (22-61 mm Hg) and was also not different from the averaged 37 mm Hg (24-51 mm Hg) (*P* = .83) or highest 37 mm Hg (31-51 mm Hg) (*P* = .50) MG during SR.

The first major finding of this study was that AF was associated with lower forward flow and lower averaged transaortic peak velocity and MG compared with SR in the same patient despite no difference in calculated AVA. Our study showed that AF was associated with lower forward flow compared with SR in the same patient, consistent with what was demonstrated in a smaller case series among three patients.² Other studies have shown similar findings by both invasive⁶ and noninvasive measurements⁷ when comparing different populations of patients in AF versus SR. Guidelines recommend normalization of forward flow and reassessment of AS severity in low-flow LGAS, for example, with hemodynamic dobutamine stress echocardiography in patients with reduced LVEFs. However, there are no explicit recommendations to restore SR where feasible and reassess AS severity in patients with AF and LGAS, likely related to the lack of data demonstrating utility of such a strategy.

Our second major finding was that in this cohort, the highest transaortic peak velocity and MG during AF were comparable with the values obtained during SR. The averaged peak velocity and MG were lower during AF, as AF is associated with lower forward flow and averaging incorporates lower signals. Underestimation of AS severity when the MG is obtained during AF² was corroborated by recent studies showing that the averaged MG during AF versus SR underestimated AS severity as determined by computed tomographic aortic valve calcium score.^{3,4} In one study,³ single high signals meeting criteria for severe AS (i.e., peak velocity 4 m/sec or MG 40 mm Hg) were present in 33% of patients with AF and LGAS. Although overall aortic valve calcium scores in patients with AF and LGAS were as high as in patients with SR and high-gradient AS, the presence versus absence of these high signals in patients with AF and LGAS was associated with higher aortic valve calcium score.³

These findings collectively should alert sonographers and clinicians to the high probability of inappropriately low averaged peak velocity and MG relative to the severity of AS when faced with LGAS during AF and to the significance of the highest peak velocity and MG during AF. Additional studies in other