Received: 15 January 2022 | Revised: 1 May 2022 | Accepted: 22 May 2022

DOI: 10.1111/echo.15398

Echocardiography WILEY

CASE REPORT

Takotsubo syndrome in COVID-19: a case series study

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Background: Takotsubo syndrome is a clinical syndrome characterized by an acute and transient left ventricular systolic dysfunction related to an emotional or physical stressful event.

Case presentation: During the Covid-19 pandemic, five cases of Takotsubo syndrome in hospitalized, mechanically ventilated patients due critical SARS-CoV-2 infection have been identified at our institution. Here we present the electrocardiographic, echocardiographic and angiographic characteristics of this case series. All cases were initially suspected by echocardiography performed due an abnormal electrocardiogram, troponin elevation or clinical deterioration.

Conclusion: A high index of suspicion should be sought to identify Takotsubo syndrome and other cardiac complications associated with SARS-CoV-2 infection.

KEYWORDS
COVID-19, echocardiography, Takotsubo syndrome

1 | INTRODUCTION

Takotsubo syndrome (TTS) is a clinical syndrome characterized by an acute and transient left ventricular systolic dysfunction related to an emotional or physical stressful event.[1] Acute critical illness and sepsis are well known triggers for TTS.

During the Covid-19 pandemic, five cases of Takotsubo syndrome in hospitalized, intubated/mechanically ventilated patients due critical SARS-CoV-2 infection have been identified at our institution.

The aim of this paper is to present the electrocardiographic, echocardiographic and angiographic characteristics of this case series of Takotsubo syndrome. Along with this information, demographic, laboratory and outcomes are resumed in Table 1.

2 | CASE 1

Seventy-four year-old female with past medical history of systemic hypertension and overweight. Hospitalized in the intensive care unit due severe SARS-CoV-2 infection. She presented acute pulmonary oedema and hypotension while she was on extubation protocol. A 12-lead electrocardiogram showed shark-fin ST-segment elevation in leads V3-V6, DI and AVL (Figure 1). Transthoracic echocardiogram showed akinesia of the mid and apical segments of the left ventricle with hypercontractile basal segments and dynamic obstruction of the left ventricular outflow tract (Figure 2, Video 1). An emergent coronary angiography demonstrated absence of obstructive coronary artery disease (Figure 3A–C), and a left ventriculography showed the characteristic apical ballooning of TTS (Figure 3D, E and Video 2). The patient progressed to cardiogenic shock, multiorgan failure and expired 4 days later besides all medical efforts.

3 | CASE 2

Seventy-six year-old male with past medical history of type 2 diabetes mellitus and current smoker. On day 9 after hospitalization, while being mechanical ventilated due severe SARS-CoV-2, he presented

TABLE 1 Case series of Takotsubo syndrome in patients with COVID-19

Age/sex	Comorbidities	Days from Covid symptom onset to Takotsubo diagnosis (days since hospitalization to Takotsubo diagnosis)	EKG findings	Echo findings	Coronary angiography	Troponin I peak (ng/ml)	D dimer peak (ng/ml)	BNP peak (pg/ml)	Outcome
74/Female	HTN, obesity	24 (11)	ST-segment elevation	Apical ballooning, LV outflow obstruction. LVEF 38%	Absence of obstructive CAD	2.59	2845	6228	ARDS, cardiogenic shock, multiorgan failure, death
76/Male	T2DM, smoker	14 (9)	AV block, T-wave inversion	Apical ballooning. LVEF 35%	Bystander non-obstructive CAD	21.9	2950	2404	ARDS, multiorgan failure. Discharged home after 51 days
66/Male	HTN, Dyslipidemia	14 (4)	ST-segment elevation, ventricular bigeminy	Apical ballooning. LVEF 27%.	Absence of obstructive CAD.	0.76	>10,000	3172	ARDS, refractory cardiogenic shock, multiorgan failure, death
65/Male	HTN, T2DM, Dyslipidemia	26 (14)	Sinus tachycardia	Anterior and lateral wall akinesia. LVEF 40%	Absence of obstructive CAD	2.12	6743	113	ARDS, renal failure, refractory shock, death
75/Female	HTN, ischemic stroke	7 (6)	T-wave inversion	Apical ballooning. LVEF 34%	N/A	0.54	660	3510	ARDS, renal failure, mixed septic and cardiogenic shock, death

Abbreviations: HTN, hypertension; T2DM, type 2 diabetes mellitus; EKG, electrocardiogram; AV, atrio-ventricular; LV, left ventricular; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; ARDS, acute respiratory distress syndrome.

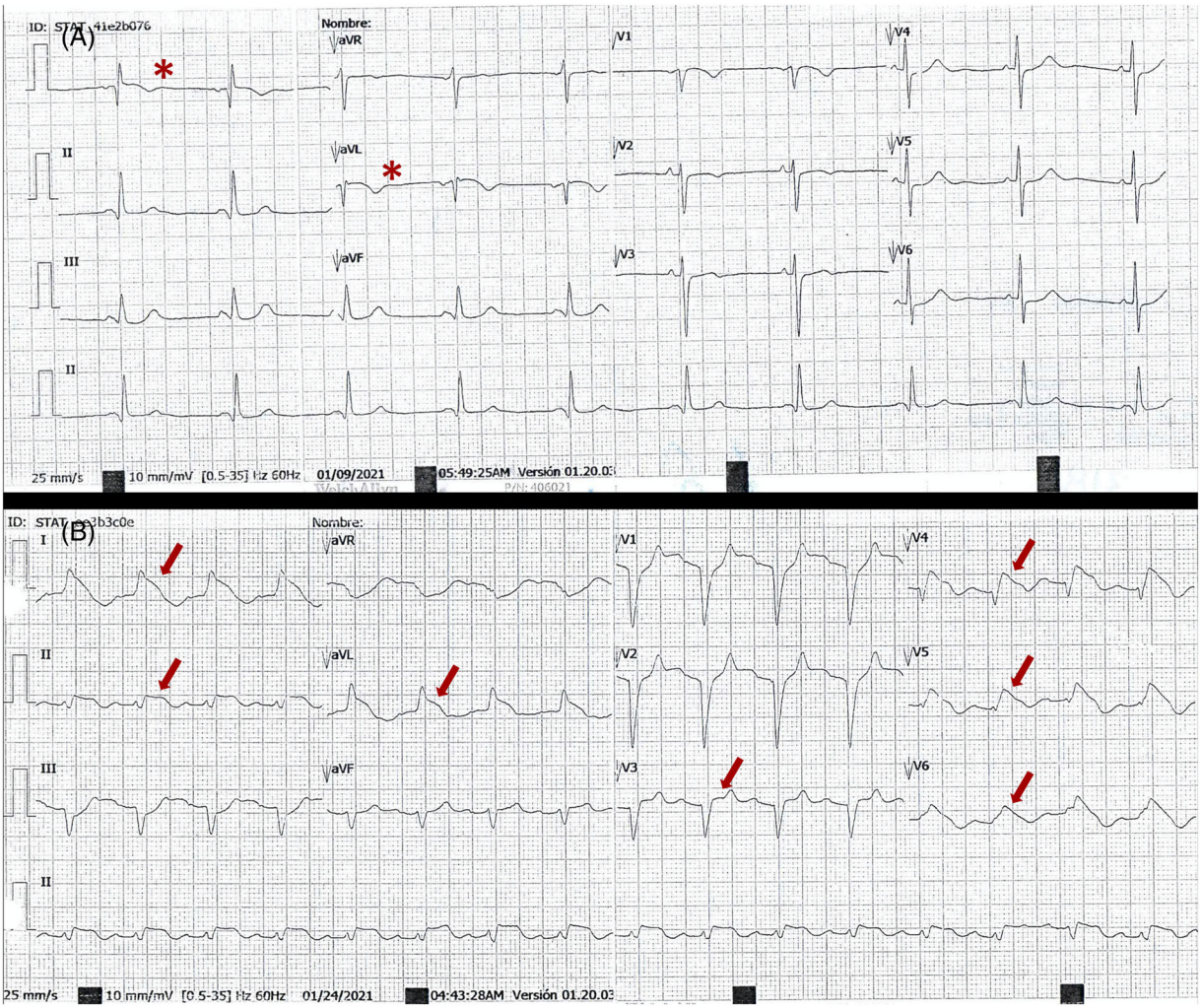


FIGURE 1 Admission 12-lead electrocardiogram and Shark-fin ST segment elevation caused by Takotsubo syndrome. (A) Admission 12-lead electrocardiogram showing normal sinus rhythm and asymmetric T-wave inversion in DI and aVL (*). (B) Twelve-lead electrocardiogram 15 days later demonstrating ST segment elevation in V3-V6, DI, DII and aVL (red arrows). Notice the Shark-fin pattern in V3-V6, DI and aVL. The patient was on extubation protocol when she presented these electrocardiographic anomalies

hypotension, and intermittent second and third-degree atrioventricular block (Figure 4A), transthoracic echocardiogram demonstrated apical ballooning of the mid and apical segments of the left ventricle (Video 3). An emergent coronary angiography demonstrated the absence of significant obstructive coronary artery disease, however a diffuse narrowing of the mid and distal segments of the left anterior descending coronary artery and non-significant coronary stenosis in the proximal and distal segments of the right coronary artery were found (bystander non-obstructive coronary artery disease) (Figure 5A–C and Video 4). A definitive dual-chamber pacemaker was implanted during the same procedure. In the following days he presented diffuse T-wave inversions (Figure 4B) and after 51 days of supportive care the patient was discharged home. A follow up transthoracic echocardiogram 1 month after discharge demonstrated recovery of the systolic function (Figure 6).

4 | CASE 3

Sixty-six year-old male with past medical history of systemic hypertension and dyslipidemia. Hospitalized in the intensive care unit due severe SARS-CoV-2 infection. Four days after admission, while mechanically ventilated, presented hypotension and ST-segment elevation in leads V4-V6 and DI (Figure 7A). Bedside transthoracic echocardiography showed akinesia of the mid and apical segments of the left ventricle with hypercontractile basal segments (Figure 8 and Video 5). An emergent coronary angiography demonstrated absence of obstructive coronary artery disease (Figure 9A–C), and a left ventriculography showed apical ballooning (Figure 9D, E and Video 6). In the following days he presented ventricular bigeminy (Figure 7B). The patient progressed to cardiogenic shock, multiorgan failure and expired 3 days later besides all medical efforts.

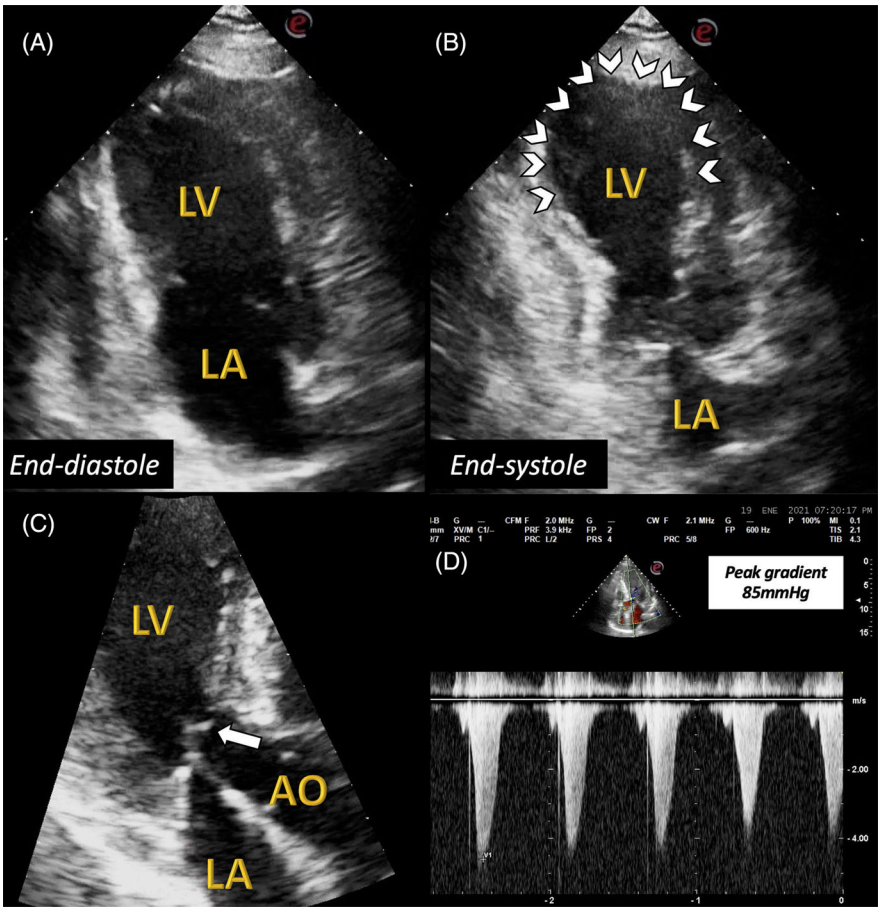
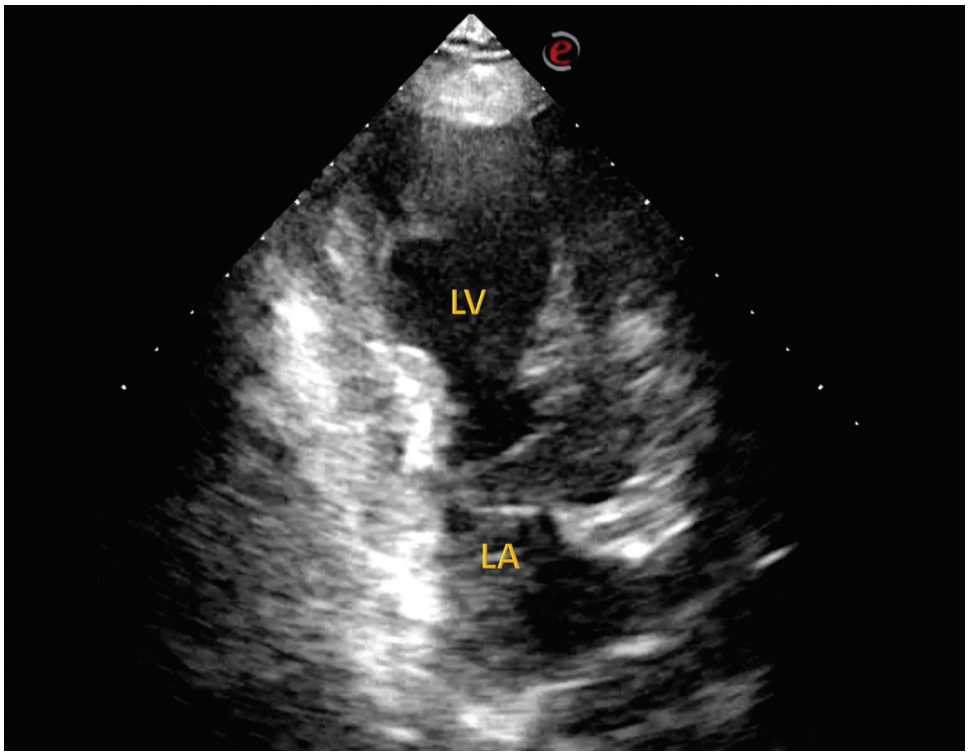


FIGURE 2 Apical ballooning and dynamic left ventricular outflow obstruction. (A) End-diastolic frame 2-chamber view transthoracic echocardiogram. (B) End-systolic frame 2 chamber view transthoracic echocardiogram demonstrating apical ballooning (arrowheads). (C) Zoomed apical 3-chamber view signaling the systolic anterior motion of the mitral valve causing left ventricular outflow obstruction (arrow). (D) Continuous Doppler showing the characteristic Dagger-shaped Doppler signal caused by a dynamic obstruction of the left ventricular outflow tract. LA = left atrium; LV = left ventricle; AO = aorta



VIDEO 1 Transthoracic echocardiogram apical 2-chamber view showing apical ballooning. LA = left atrium; LV = left ventricle

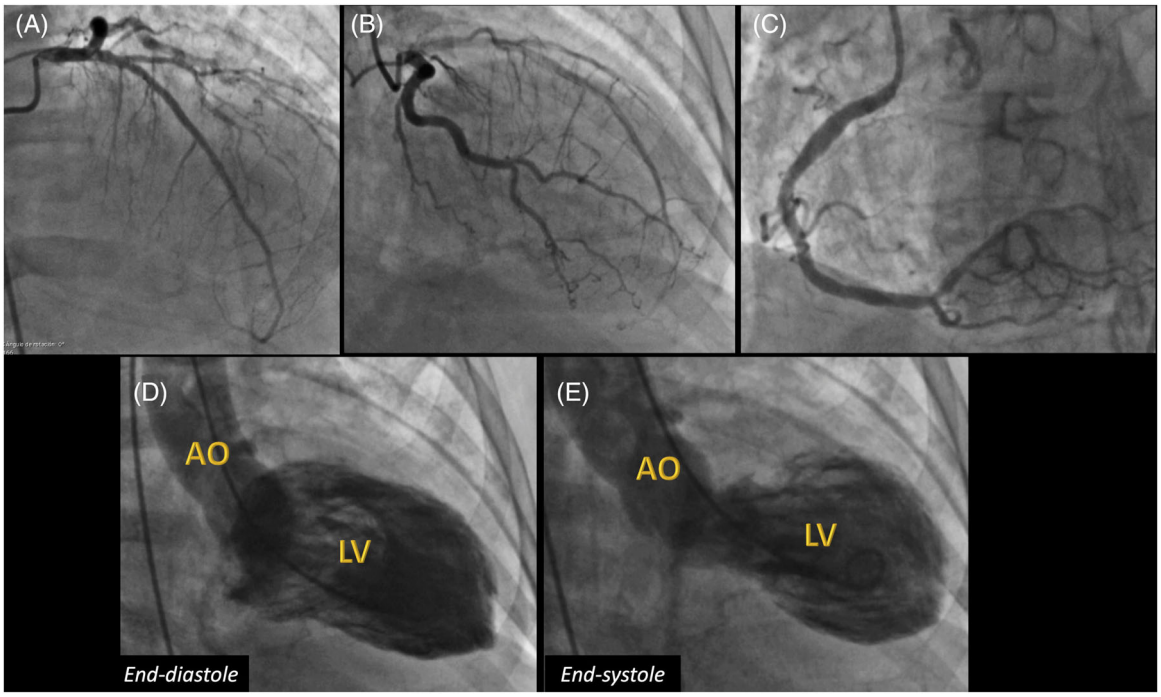
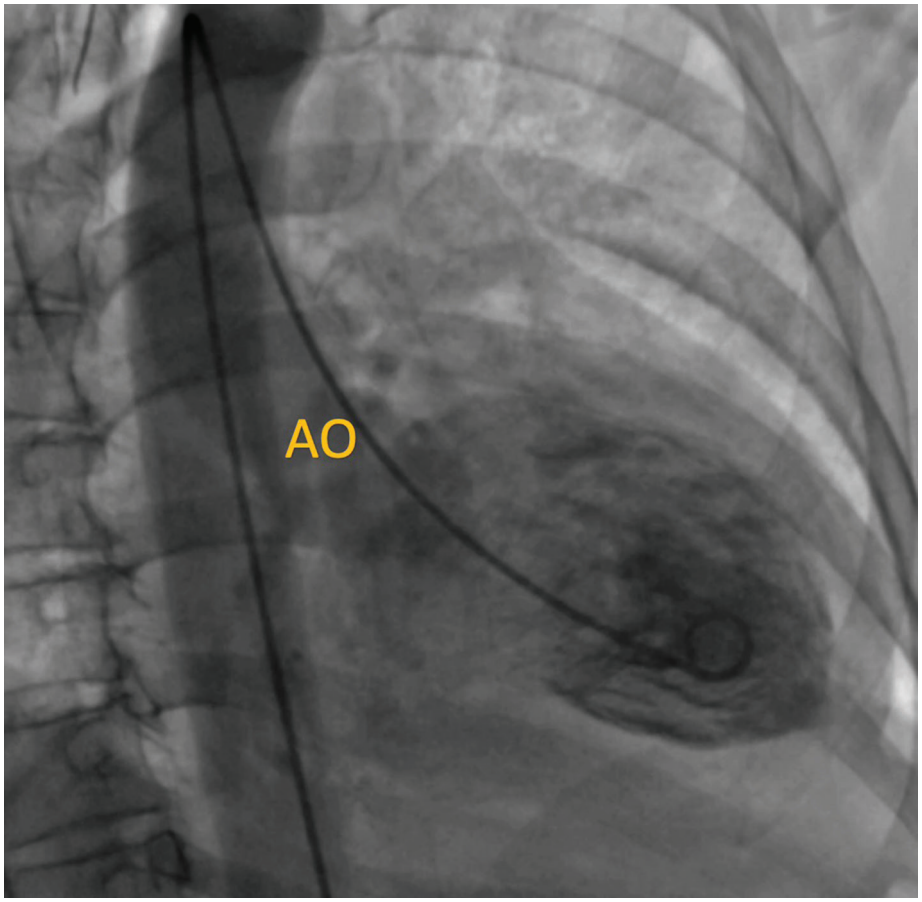


FIGURE 3 Coronary angiography and left ventriculogram showing apical ballooning. Coronary angiography demonstrating the absence of obstructive coronary artery disease in the left anterior descending coronary artery (A), circumflex coronary artery (B) and right coronary artery (C). Left ventriculography showing the end-diastolic frame (D) and end-systolic frame (E). Notice the characteristic apical ballooning. LV = left ventricle; AO = aorta



VIDEO 2 Left ventriculography demonstrating the characteristic apical ballooning of Takotsubo syndrome. AO = aorta

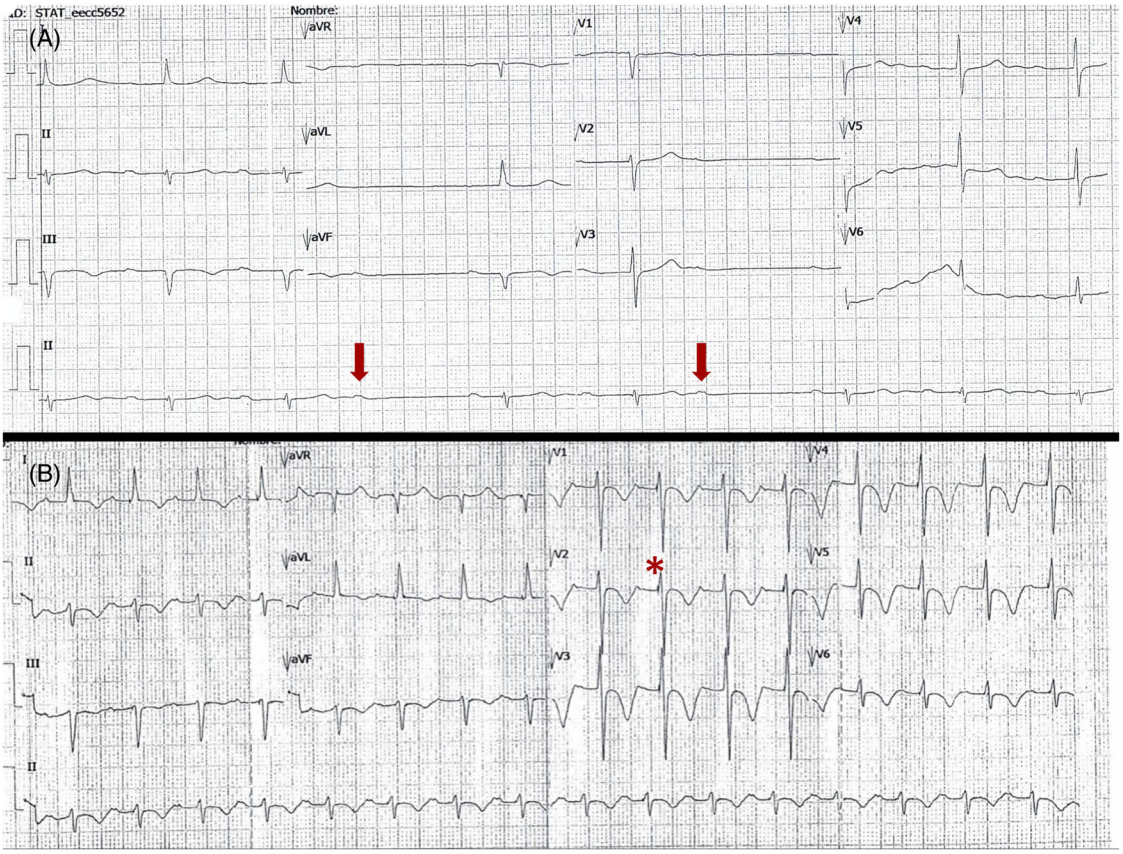
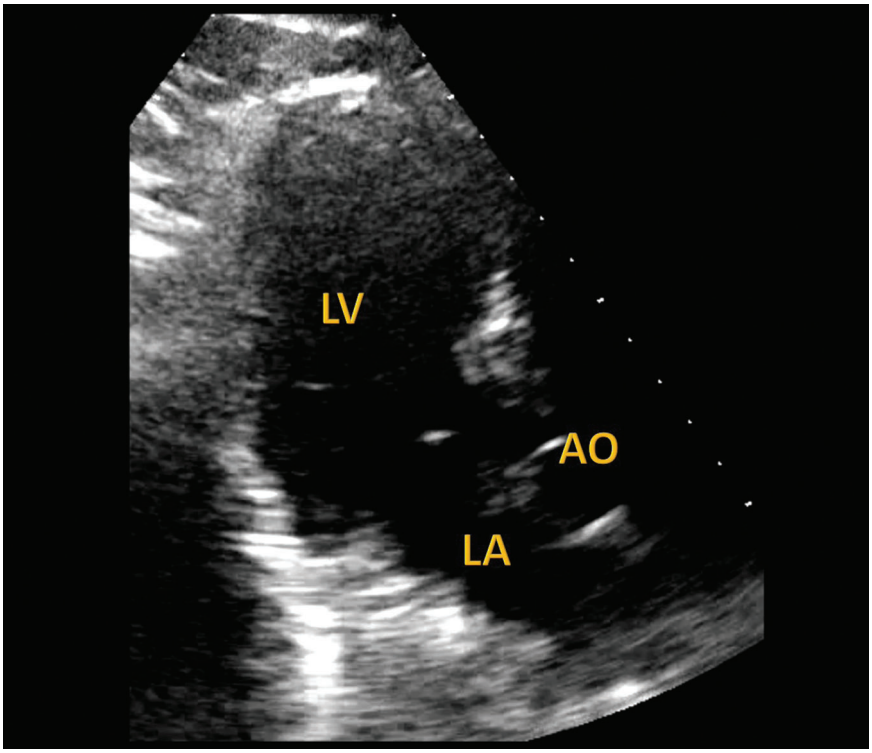


FIGURE 4 Electrocardiogram showing Atrioventricular block and diffuse T-wave inversions. (A) 12-lead electrocardiogram demonstrating a second-degree type 1 atrioventricular block. Non-conducted P waves (arrows). The patient presented intermittent complete atrioventricular block (not shown). (B) 12-lead electrocardiogram in the following days demonstrating diffuse T-wave inversions. Notice the pacing ventricular stimulus artifact (*)

VIDEO 3 Apical 3-chamber view transthoracic echocardiogram demonstrating apical ballooning. LA = left atrium; LV = left ventricle; AO = aorta



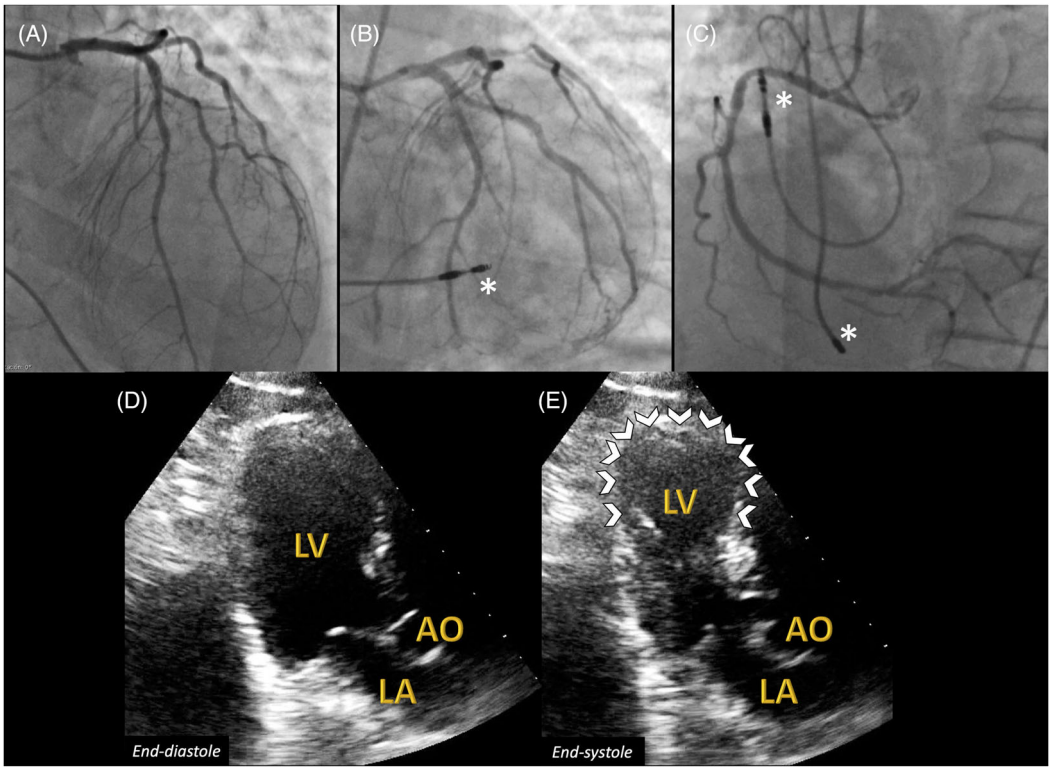
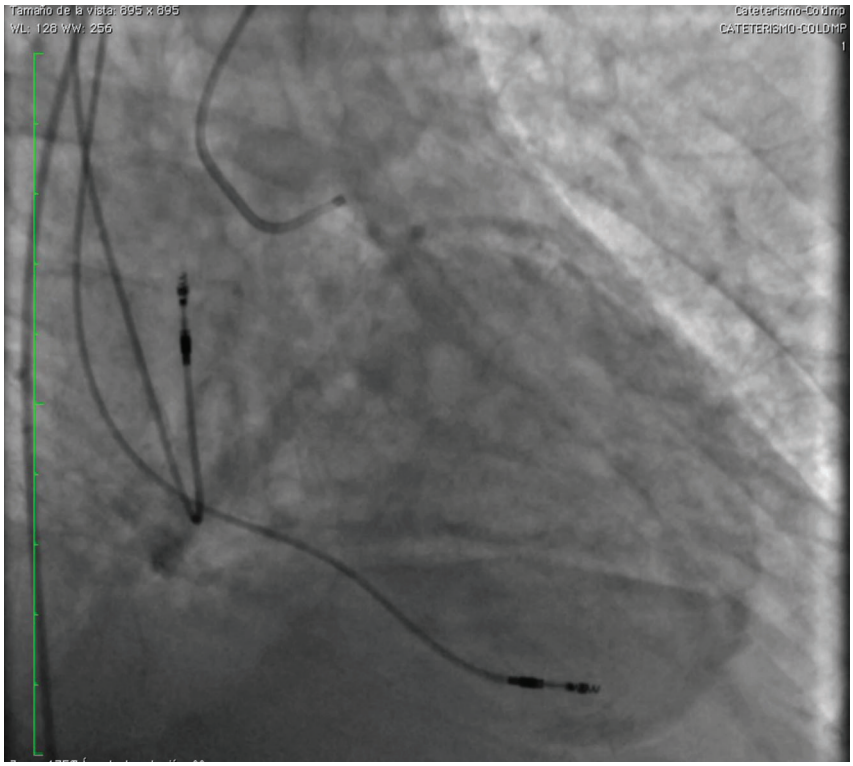


FIGURE 5 Coronary angiography demonstrating bystander non-obstructive coronary artery disease and echocardiography showing apical ballooning. Coronary angiography demonstrating the absence of significant obstruction or acute plaque rupture in the left anterior descending coronary artery (A), circumflex coronary artery (B) and right coronary artery (C). Notice a diffuse narrowing of the mid and distal segments of the left anterior descending coronary artery and the presence of non-significant coronary stenosis in the proximal and distal segments of the right coronary artery (bystander non-obstructive coronary artery disease). (*) Pacemaker leads implanted in the same procedure due intermittent complete atrioventricular block. (D) End-diastolic frame 3-chamber view transthoracic echocardiogram. (E) End-systolic frame 3-chamber view transthoracic echocardiogram demonstrating apical ballooning (arrowheads). LA = left atrium; LV = left ventricle; AO = aorta



VIDEO 4 Coronary angiography demonstrating the absence of significant obstruction or acute plaque rupture in the left anterior descending coronary artery, Notice a diffuse narrowing of the mid and distal segments of the left anterior descending coronary artery

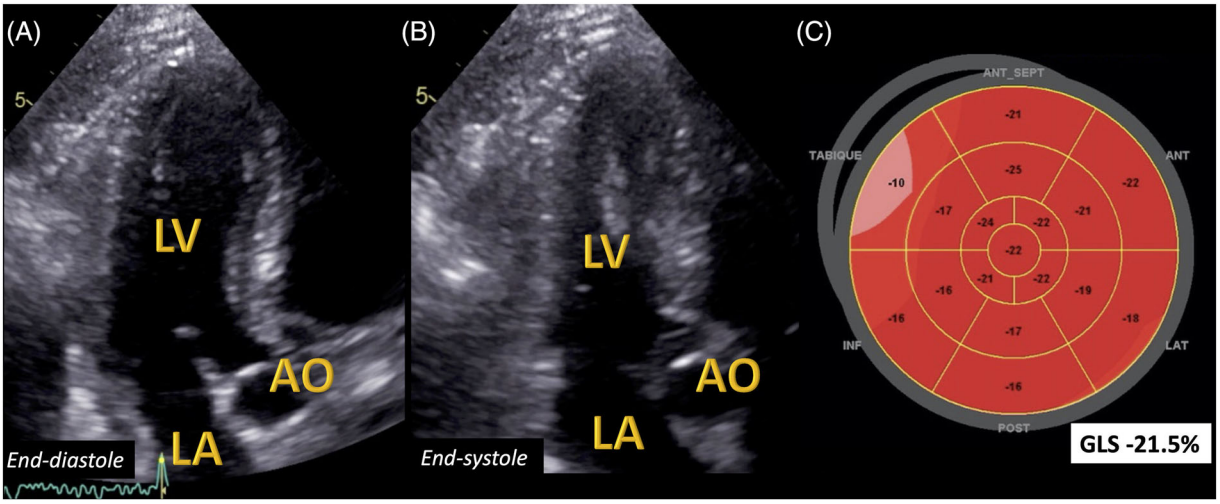


FIGURE 6 Follow up echocardiogram demonstrating recovery of systolic function. Follow up transthoracic echocardiogram 1 month after discharge (A) End-diastolic frame 3-chamber view. (B) End-systolic 3-chamber view and (C) Global Longitudinal Strain (GLS) bull's-eye plot. Notice the contractility recovery of the mid and apical segments. LA = left atrium; LV = left ventricle; AO = aorta; GLS = global longitudinal strain

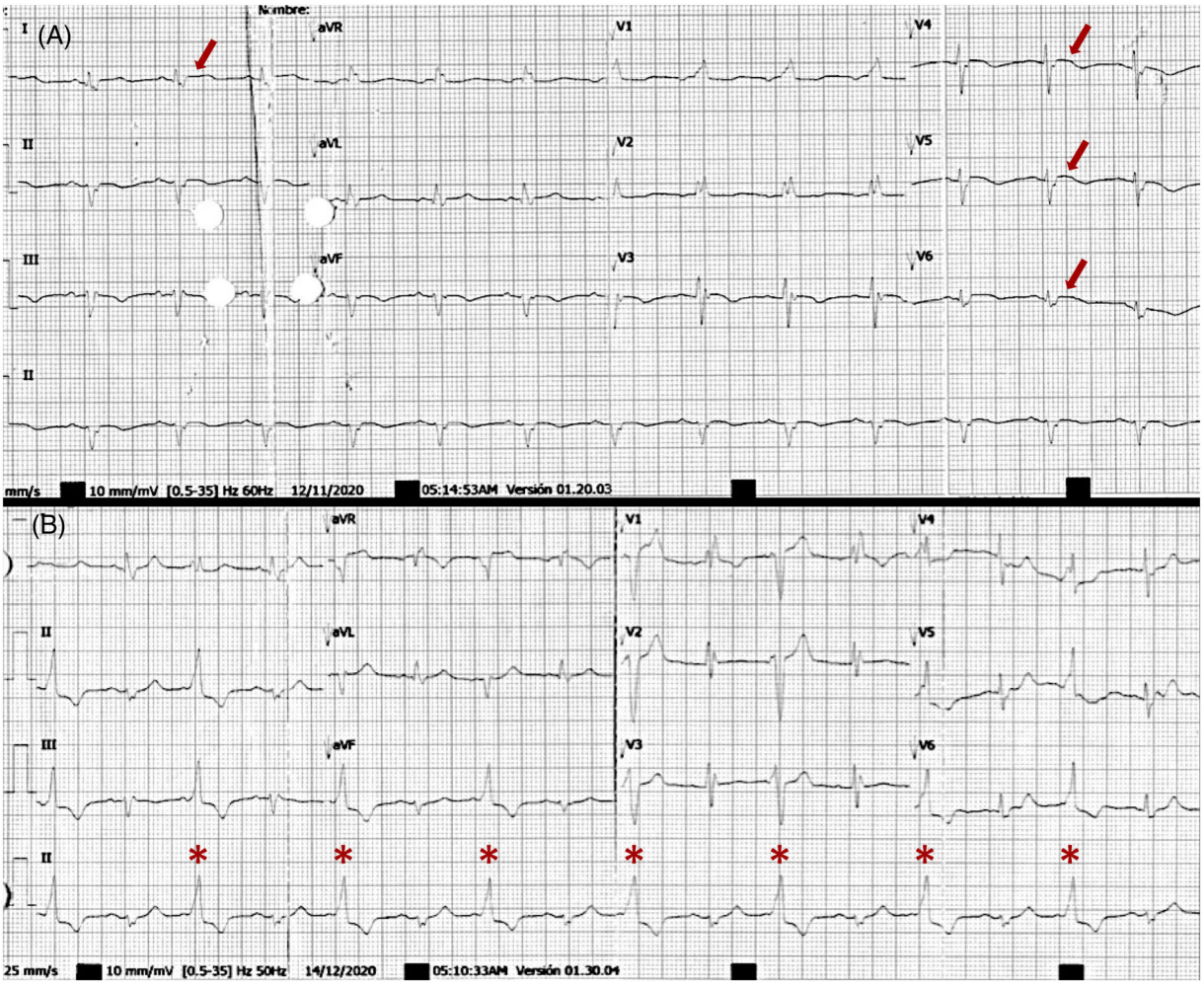


FIGURE 7 Electrocardiogram showing ST-segment elevation and ventricular bigeminy. (A) Twelve-lead electrocardiogram signaling the ST-segment elevation in leads V4-V6 and DI (arrows). (B) Twelve-lead electrocardiogram in the following days demonstrating ventricular bigeminy (*)

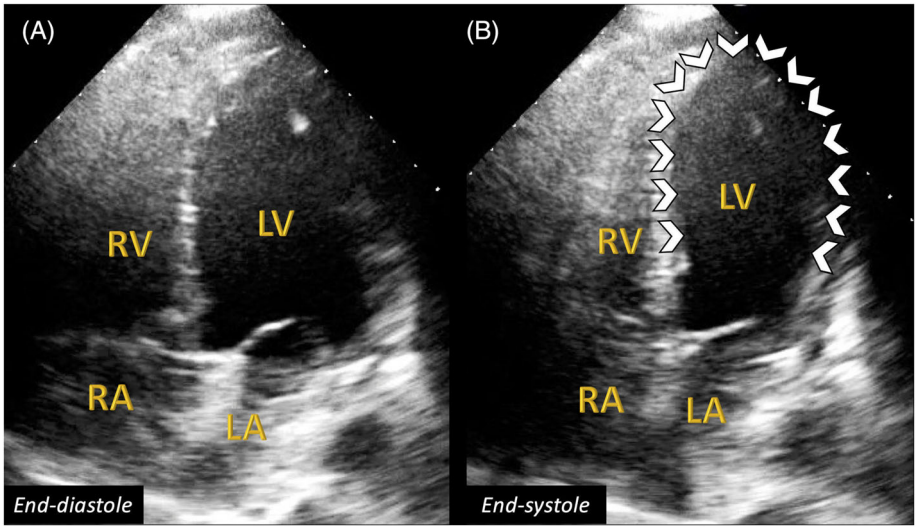
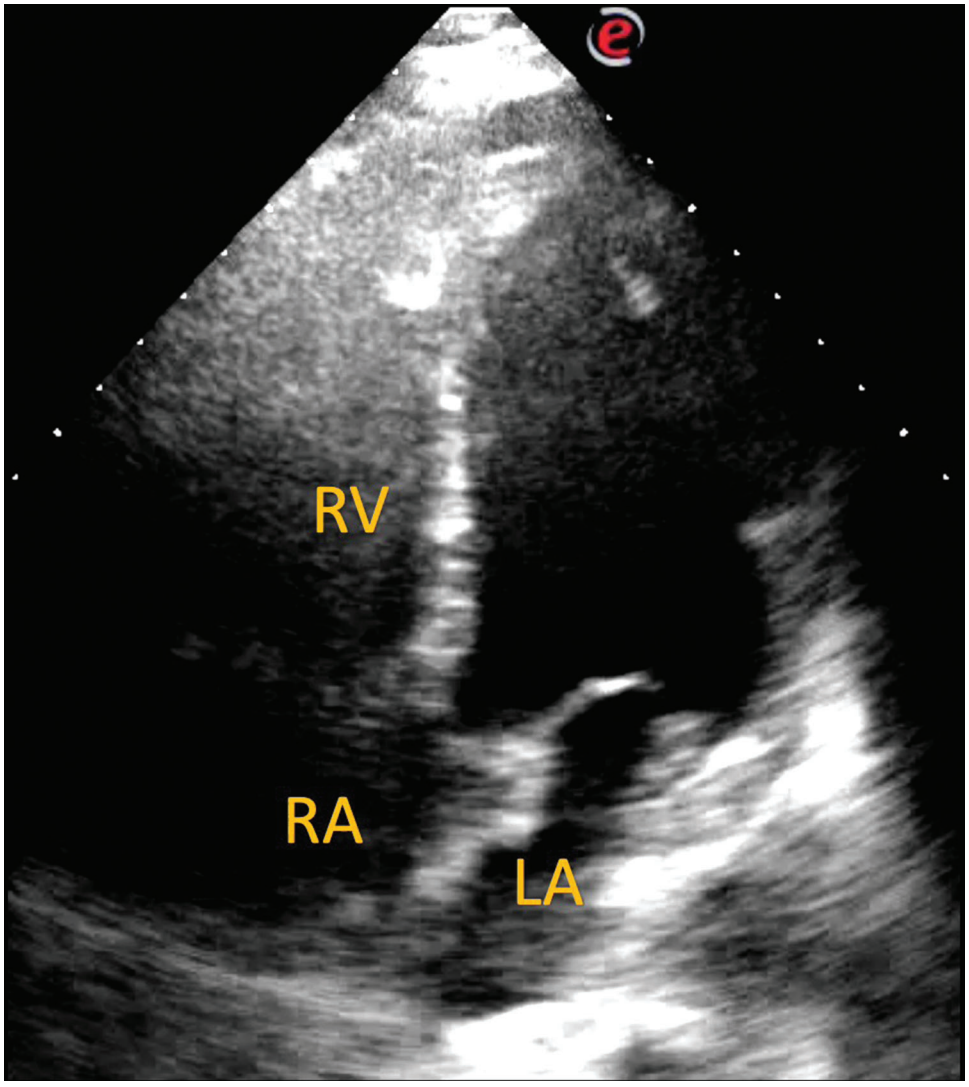


FIGURE 8 Apical 4-chamber view demonstrating apical ballooning. (A) End-diastolic frame 4-chamber view transthoracic echocardiogram. (B) End-systolic frame 4-chamber view transthoracic echocardiogram demonstrating apical ballooning (arrowheads), (video 8). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle



VIDEO 5 Apical 4-chamber view demonstrating akinesia of de mid and apical segments. LA = left atrium; RA = right atrium; RV = right ventricle

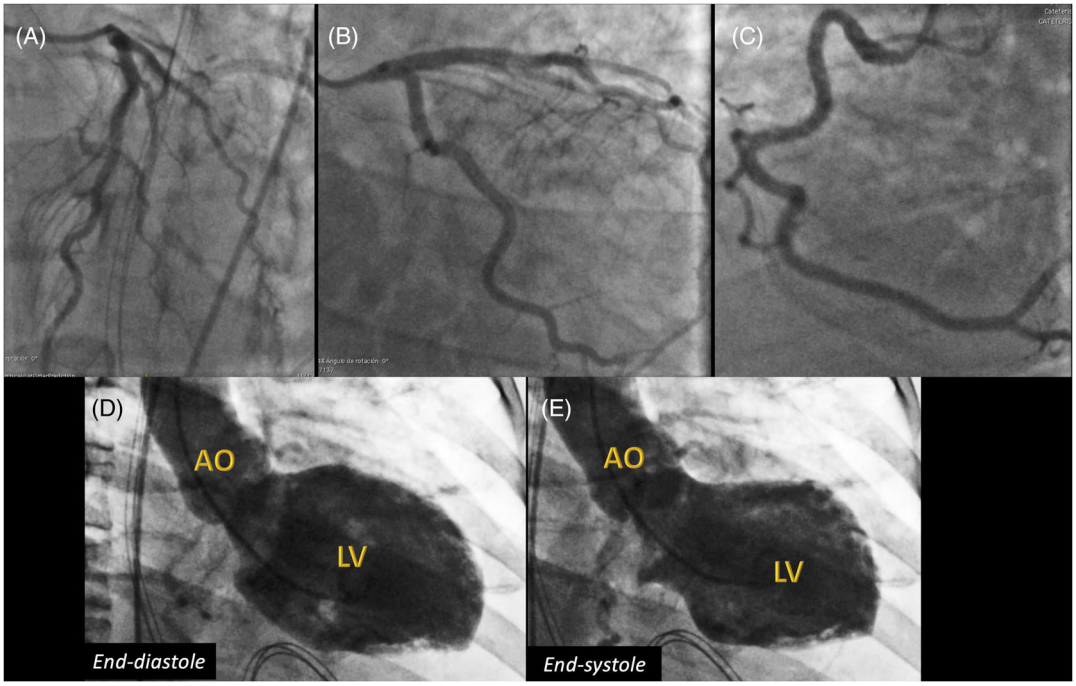
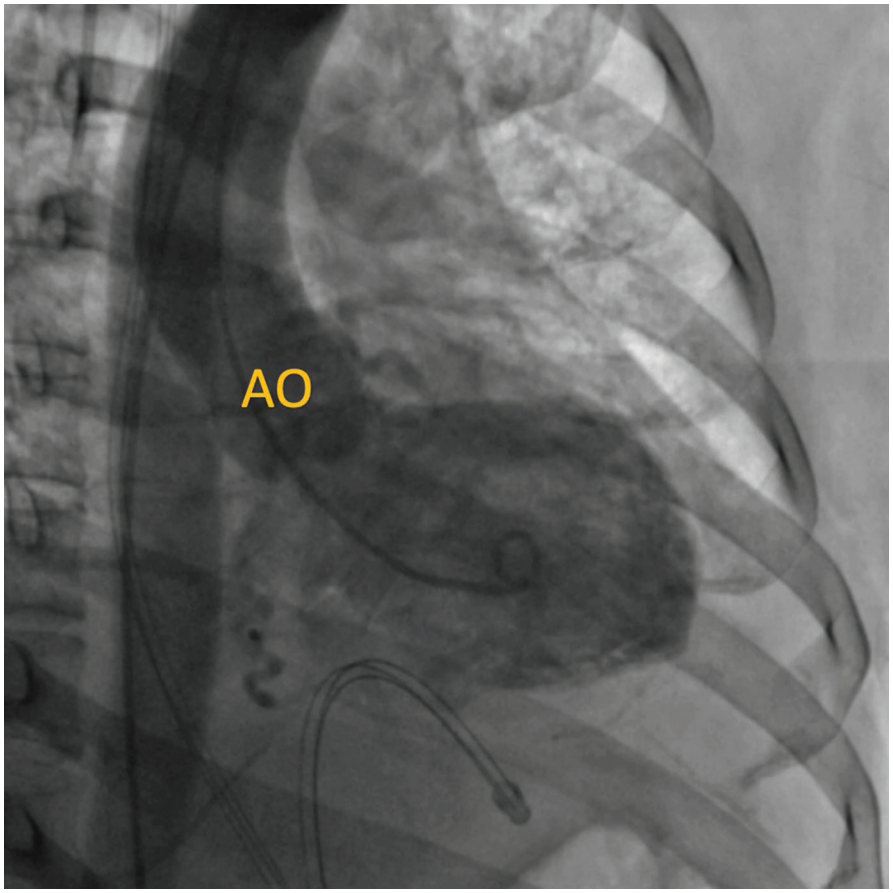


FIGURE 9 Coronary angiography and left ventriculogram showing apical ballooning. Coronary angiography demonstrating the absence of obstructive coronary artery disease in the left anterior descending coronary artery (A), circumflex coronary artery (B) and right coronary artery (C). Left ventriculography showing the end-diastolic frame (D) and end-systolic frame (E). Notice the characteristic apical ballooning. LV = left ventricle; AO = aorta



VIDEO 6 Left ventriculography showing hyper-contractility of the basal segments and akinesia/dyskinesia of the mid and apical segments. AO = aorta

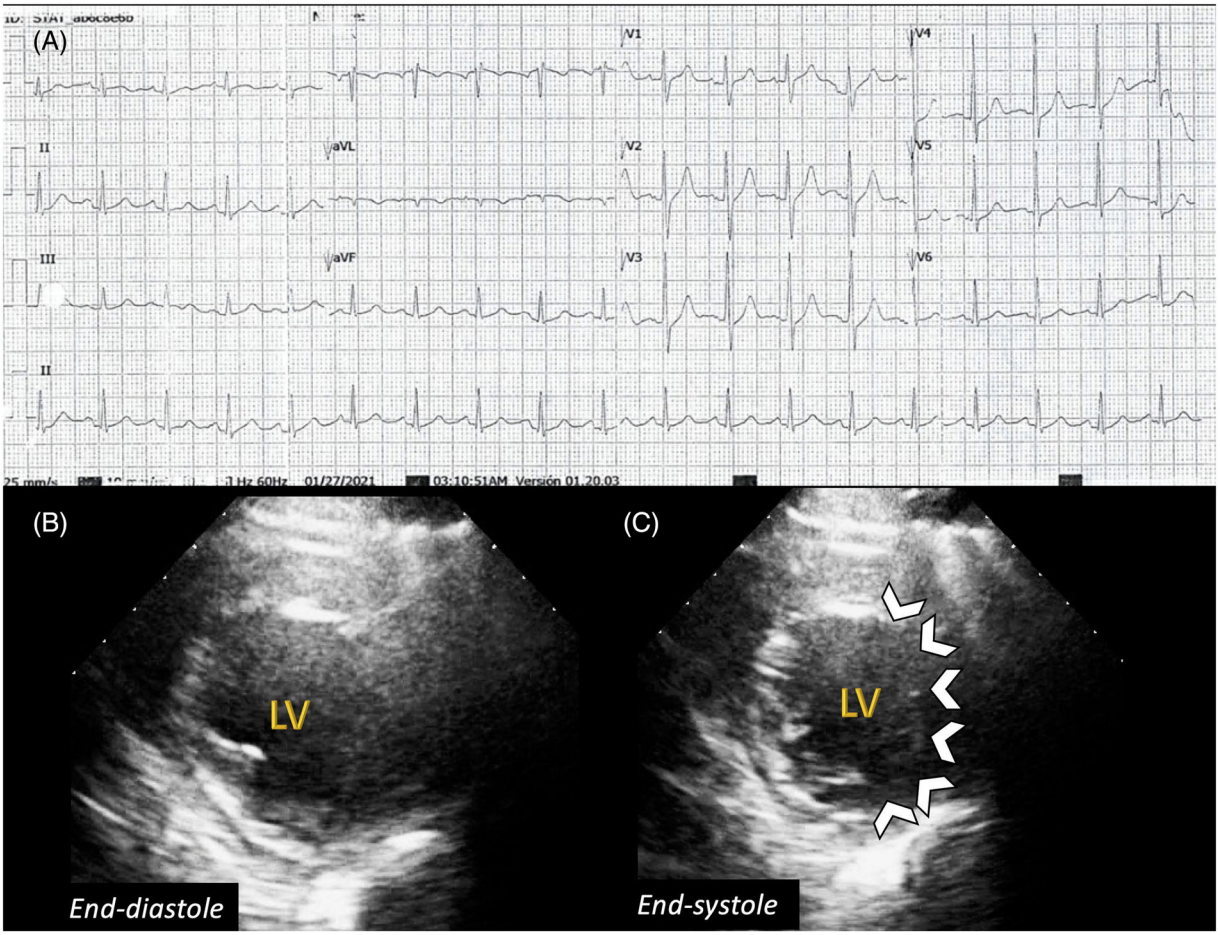


FIGURE 10 Electrocardiogram and echocardiogram in focal Takotsubo syndrome. (A) Twelve-lead electrocardiogram showing sinus tachycardia and absence of repolarization abnormalities. (B) End-diastolic frame short axis view transthoracic echocardiogram. (C) End-systolic frame short axis view demonstrating anterior and lateral wall akinesia (arrowheads). LV = left ventricle

5 | CASE 4

Sixty-five year-old male with past medical history of systemic hypertension, type 2 diabetes mellitus and dyslipidemia. Hospitalized in the intensive care unit due severe SARS-CoV-2 infection. After 14 days of hospitalization, while mechanically ventilated he presented hypotension, renal failure and worsening pulmonary function. A 12-lead electrocardiogram showed sinus tachycardia without repolarization abnormalities (Figure 10A), and a bedside transthoracic echocardiogram demonstrated anterior and lateral wall akinesia (Figure 10B and C). A coronary angiography showed no evidence of obstructive coronary artery disease (Figure 11A–C), and a left ventriculogram demonstrated anterolateral akinesia (Figure 11D–E and Video 7). The patient progressed to multiorgan failure, refractory shock and died 2 days later.

6 | CASE 5

Seventy-five year-old female with past medical history of hypertension, previous ischemic stroke and stage II chronic kidney disease. While mechanically ventilated due severe SARS-CoV-2 infection in the intensive care unit she presented cardiogenic shock. A 12-lead electrocardiogram showed diffuse T-wave inversions (Figure 12A) and a bedside echocardiogram demonstrated akinesia of the mid and apical segments of the left ventricle (Figure 12B–E and Video 8). The patient was complicated with a urinary tract infection, renal failure, refractory shock and expired 6 days later.

7 | DISCUSSION

We describe five cases of Takotsubo syndrome associated with Covid-19, four out of five with the typical apical ballooning and one with an atypical presentation (anterolateral akinesia). Coronary angiography was performed in 80% of the cases to rule out acute coronary syndrome. Unlike with other reports where survival was 91.6%,[2] TTS was associated with an 80% mortality in this case series. Differences that may explain this disparity are (1) all patients were intubated/mechanically ventilated due severe acute respiratory distress syndrome. Mechanical ventilation in COVID-19 is associated with an 8–67% mortality worldwide. (2) Predictors of death such as older

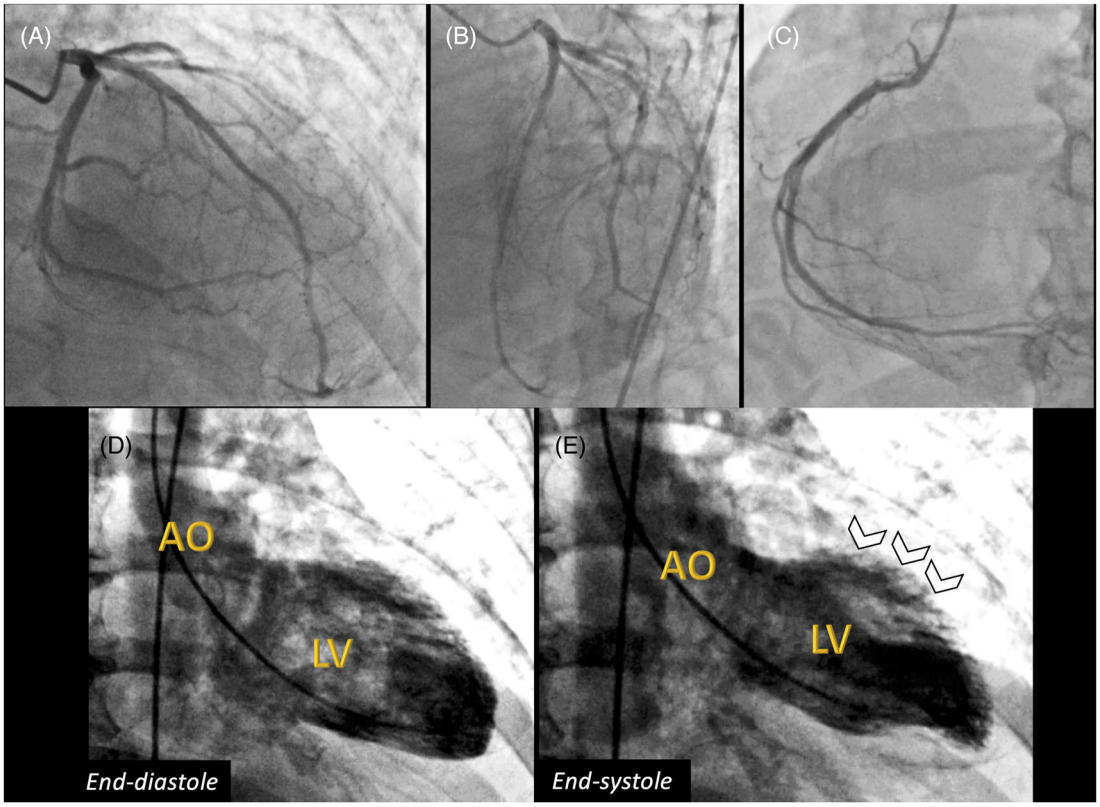
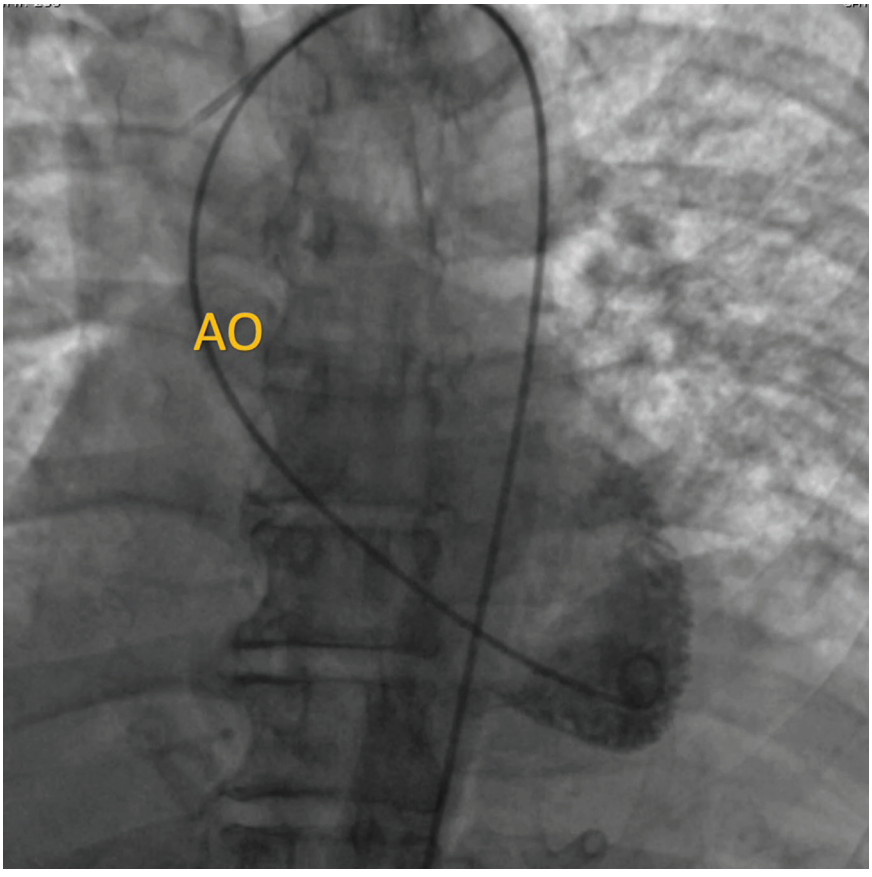


FIGURE 11 Coronary angiography and left ventriculogram demonstrating anterolateral akinesia. Coronary angiography demonstrating the absence of obstructive coronary artery disease in the left anterior descending coronary artery (A), circumflex coronary artery (B) and right coronary artery (C). Left ventriculography showing the end-diastolic frame (D) and end-systolic frame (E). Notice the anterolateral akinesia (arrowheads). LV = left ventricle; AO = aorta

VIDEO 7 Left ventriculography showing anterolateral akinesia. AO = aorta



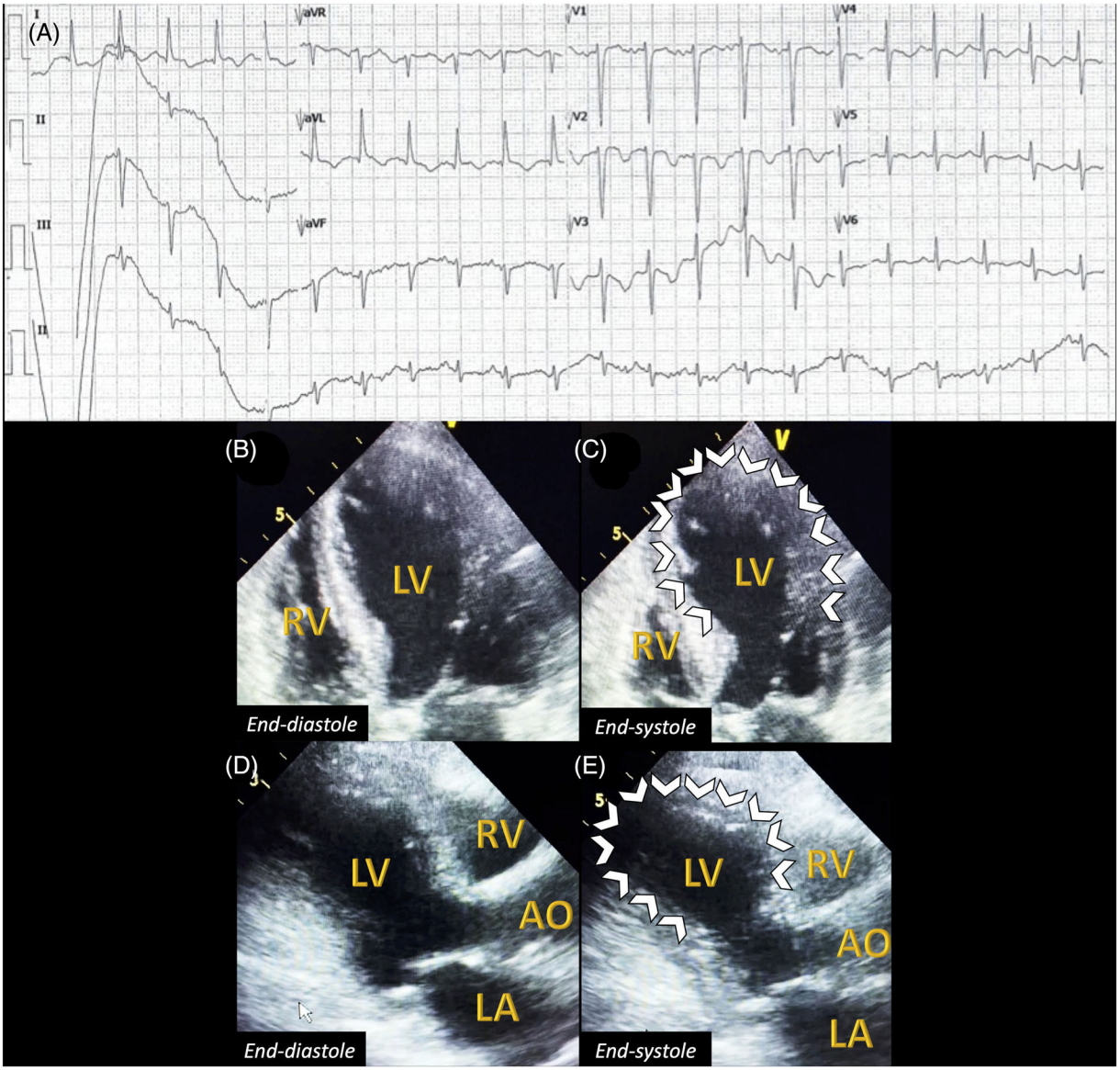


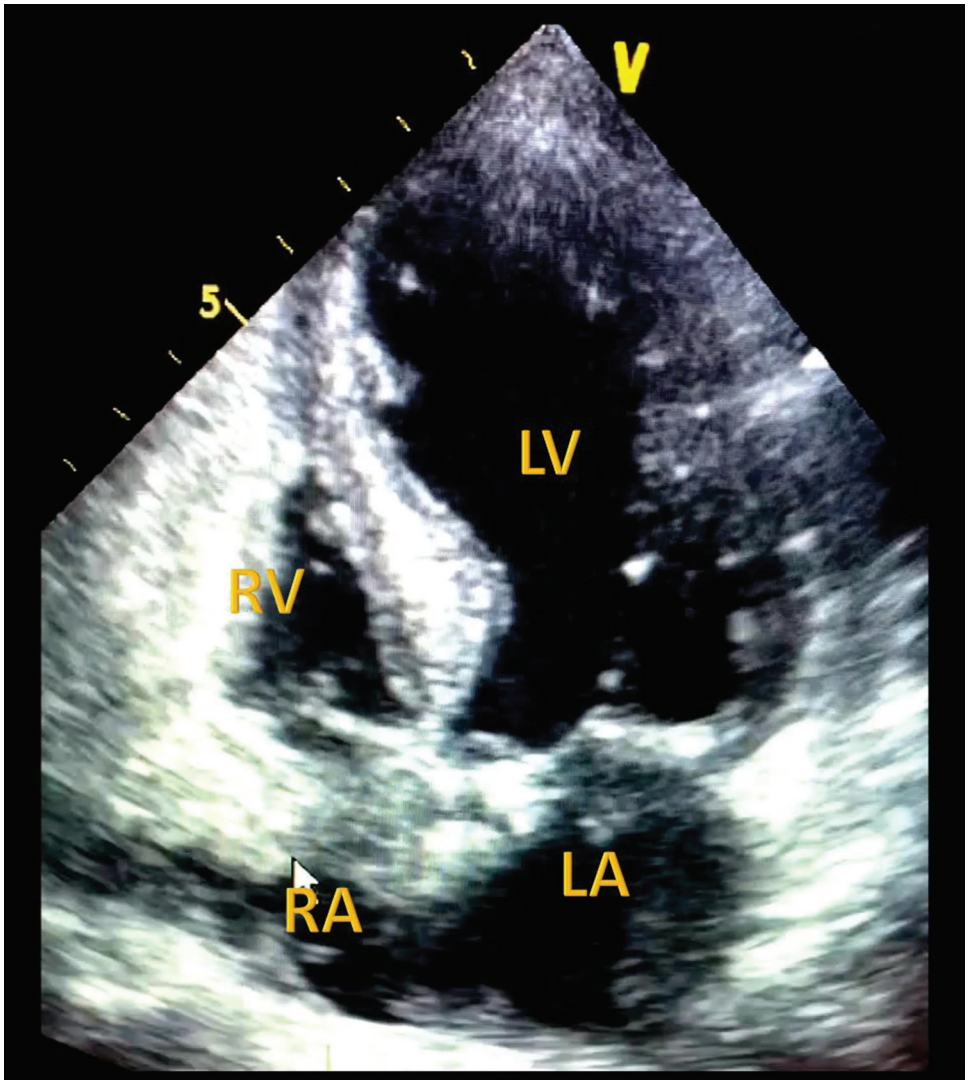
FIGURE 12 Electrocardiogram showing sinus tachycardia and diffuse T-wave inversions and transthoracic echocardiogram showing apical ballooning. (A) Twelve-lead electrocardiogram showing sinus tachycardia and diffuse T-wave inversions. (B) End-diastolic frame 4-chamber v iew transthoracic echocardiogram. (C) End-systolic frame 4-chamber view transthoracic echocardiogram demonstrating apical ballooning (arrowheads), (D) End-diastolic frame parasternal long axis view and (E) End-systolic parasternal long axis view signaling the apical ballooning of the mid and medial segments (arrowheads). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle

age (mean age 71.2 years old), need of vasopressors, high oxygen index and renal failure were present in all patients.[3] (3) Mean ejection fraction was 35% which itself is related with a worse prognosis[4] and (4) As opposed with a meta-analysis of 12 cases of Takotsubo syndrome in patients with COVID-19 where mean symptom onset to TTS was 8.3 ± 3.6 days, a late presentation of TTS was found in our case series (mean time of symptom onset to TTS 14 ± 7.9 days), which may represent a different spectrum of patients (late presentation represents a severe hyperinflammation phase associated with a worse prognosis).[5]

Giustino et al. Reported five cases of TTS at The Mount Sinai Hospital. None of the patients underwent coronary angiography to rule out coronary artery disease and two of them eventually required mechanical ventilation and died (with one of them while in extracorporeal membrane oxygenation).[6]

Pathophysiological connections between COVID-19 and Takotsubo syndrome are attributable to three factors: overactive immune response from cytokine storm, sympathetic nervous system surge, and the development of micro-vascular dysfunction.[7] In COVID-19 patients, microvascular dysfunction can stem from a systemic inflammatory response, as well as from the formation of microthrombi during a state of hypercoagulability.[8]

We recognize as a limitation of the study that cardiac magnetic resonance nor endomyocardial biopsy was performed to differentiate with acute myocarditis. This is especially significant in case 4 where an atyp-



VIDEO 8 Transthoracic apical 4-chamber view echocardiogram demonstrating apical ballooning. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle

ical TTS was found (anterolateral akinesia). Since death occurred early in four out of five cases, recovery of systolic function was documented only in case 2. However, acute myocarditis commonly presents with global systolic dysfunction and when a regional/segmental form is seen, the inferolateral wall is usually affected. The pattern of dysfunction in acute myocarditis is unlikely to be one of apical ballooning.[1] Other findings that support the diagnosis of myocarditis by echocardiography such as pericardial effusion and increased wall thickness (reflecting myocardial oedema) where absent in this case series.[9] Furthermore, data from endomyocardial biopsies and autopsies in clinically suspected SARS-CoV-2 myocarditis are scarce, with no definitive proof that SARS-CoV-2 causes direct cardiomyocyte damage.[10–13] Finally, there is an interrelation between the underlying pathophysiological mechanisms of TTS and myocardial injury in patients with COVID-19, being the hypercoagulability and immune-mediated cellular injuries the most widely accepted.[13]

8 | CONCLUSION

SARS-Cov-2 infection is a trigger for Takotsubo syndrome, hospitalized patients presenting clinical deterioration, elevated cardiac biomarkers, arrhythmias or repolarization abnormalities on electrocardiography should be further evaluated with bedside echocardiography for diagnosing Takotsubo syndrome and other cardiac complications associated with SARS-CoV-2 infection.

ACKNOWLEDGEMENTS

The authors received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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How to cite this article: Arroyo-Rodríguez C, Victoria-Nandayapa JR, López-Aceves M, et al. Takotsubo syndrome in COVID-19: a case series study. *Echocardiography*. 2022;39:920–934. https://doi.org/10.1111/echo.15398