Takotsubo cardiomyopathy in COVID-19: a case report. Haemodynamic and therapeutic considerations

Dirk van Osch 1*, Folkert W. Asselbergs 1,2, and Arco J. Teske 1

1 Department of Cardiology, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands; and 2 Institute of Cardiovascular Science and Institute of Health Informatics, Faculty of Population Health Sciences, University College London, Gower Street, London WC1E 6BT, UK

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Background
Cardiovascular complications are increasingly recognized during the current coronavirus disease 2019 (COVID-19) pandemic. Myocardial injury is most commonly described and its underlying mechanism is believed to be multifactorial. Next to Type 2 ischaemia, COVID-19 may lead to (peri)myocarditis or Takotsubo (or stress) cardiomyopathy.

Case summary
A 72-year-old woman was admitted to the intensive care unit for mechanical ventilation because of respiratory insufficiency secondary to COVID-19 viral pneumonia. Seven days after admission, she developed new negative T-waves and a prolonged QTc interval on electrocardiography (ECG). Troponin levels were mildly elevated. Echocardiography showed a poor left ventricular systolic function with apical ballooning consistent with the diagnosis Takotsubo cardiomyopathy. Seven days afterwards, the ECG and troponin levels normalized. Echocardiography showed improvement of left ventricular systolic function, however with persistent hypokinesia of the apical segments. Coronary artery disease was excluded using coronary computed tomography angiography. The patient was discharged home and follow-up echocardiography after 3 months showed normal contractility of the apical myocardial segments, with normalization of the left ventricular systolic function, as expected in Takotsubo cardiomyopathy.

Discussion
COVID-19 caregivers should be aware of Takotsubo cardiomyopathy as complication of COVID-19, since regular use of QT-prolonging drugs combined with prolongation of the QTc interval in Takotsubo cardiomyopathy may lead to life-threatening arrhythmias. Furthermore, Takotsubo cardiomyopathy may lead to acute heart failure and even cardiogenic shock. Frequent ECG monitoring of COVID-19 patients therefore is of paramount importance and timely echocardiography should be obtained when ECG abnormalities or haemodynamical problems occur.

Keywords
Takotsubo cardiomyopathy • Stress cardiomyopathy • COVID-19 • Coronavirus disease 2019 • Case report

Learning points
• Takotsubo cardiomyopathy is a potential cause of acute heart failure in coronavirus disease 2019 (COVID-19).
• Several pharmacological therapies are contraindicated or have to be used with caution in COVID-19 patients with Takotsubo cardiomyopathy.
• Several mechanisms may lead to myocardial injury in COVID-19 including (Type 2) ischaemia, myocarditis, and Takotsubo cardiomyopathy.
Introduction

Cardiovascular complications are increasingly recognized during the current coronavirus disease 2019 (COVID-19) pandemic. Myocardial injury is most commonly described with a reported incidence of 12% in hospitalized patients up to 23% in critically ill patients and is associated with an adverse prognosis.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing COVID-19 viral pneumonia may lead to both direct and indirect myocardial injury. Indirect myocardial injury is caused by hypotension, tachycardia, and hypoxia which can induce myocardial ischaemia due to a mismatch in myocardial oxygen demand and supply. This may also lead to acute decompensation of prior congestive heart failure. The finding that approximately 40% of hospitalized patients have underlying chronic cardiovascular or cerebrovascular disease suggest that this hypothesis might explain the relationship between troponin rise and adverse outcome. Furthermore, systemic and vascular inflammation along with hypercoagulability can trigger plaque rupture and lead to acute coronary syndrome in COVID-19.

Increasing evidence exists that COVID-19 can lead to acute (peri)-myocarditis. Two recent case reports describe findings on cardiac magnetic resonance (MR) imaging that are consistent with acute myocarditis. In one of these reports, endomyocardial biopsy showed evidence of myocardial inflammation with presence of T-lymphocytic infiltrates, without presence of the SARS-CoV-2 genome.

Recently, the first two reported cases of Takotsubo (or stress-) cardiomyopathy in COVID-19 have been published. Takotsubo cardiomyopathy is commonly triggered by physical triggers such as infection, respiratory failure, and systemic inflammatory response syndrome (SIRS). Therefore, it might complicate COVID-19. In this case report, we describe a case of Takotsubo cardiomyopathy in a COVID-19 patient at our institution and describe its significant effects on patient management and treatment which are relevant for this specific patient population.

Timeline

| Time         | Event                                                                 |
|--------------|----------------------------------------------------------------------|
| Day of admission | Admission to the intensive care unit for mechanical ventilation because of respiratory insufficiency secondary to coronavirus disease 2019 viral pneumonia. |
| +7 days      | Electrocardiography (ECG) showed new negative T-waves. High sensitive troponin-I levels were mildly elevated (454 ng/L, reference value 0–45 ng/L). Echocardiography showed a poor left ventricular systolic function [left ventricular ejection fraction (LVEF) of 30%] with apical ballooning consistent with the diagnosis Takotsubo cardiomyopathy. |
| +10 days     | Successful extubation and transfer to the ward.                        |
| +14 days     | Normalization of the ECG and troponin levels. Echocardiography showed important improvement of left ventricular systolic function to an LVEF of 45%, however with persistent hypokinesia of the apical segments. Additional coronary computed tomography angiography (CCTA) showed a low calcium score and a non-significant stenosis (<50%) in the proximal left anterior descending artery (CAD-RADS score of 1) excluding coronary artery disease as the cause of this clinical picture. |
| +22 days     | The patient was discharged.                                             |
| + 3 months   | Follow-up echocardiography showed normal contractility of the apical myocardial segments, with normalization of the left ventricular systolic function (LVEF 55%). |
with circumferential akinesia of the apex in the mid-ventricular and apical segments and circumferential hyperdynamic contractions of the basal segments consistent with the diagnosis Takotsubo cardiomyopathy (Figure 3, Videos 1–3). The InterTAK Diagnostic Score was 80 supporting the diagnosis Takotsubo cardiomyopathy (97.3% probability). Episodes of heavy anxiety and hypertension during nursing care were reported as possible trigger. Given the poor left ventricular systolic function and prior atrial fibrillation with a CHA2DS2-VASc score of 4, therapeutic low-molecular weight heparin was started (dalteparin, 7500 IU twice daily s.c.). Because the patient was still treated with low doses of norepinephrine, treatment with beta-adrenergic receptor blockers or angiotensin-converting enzyme inhibitors was not recommended.
ACE inhibitors to treat left ventricular dysfunction was postponed. Treatment with chloroquine was stopped because the prolonged QTc interval.

Initially, we chose not to perform a coronary angiography because of the typical echocardiographic pattern, the only slightly elevated cardiac biomarkers, the absence of ST-segment elevations and given the risk of transportation of an intubated patient with also a risk of further contamination of COVID-19 in the hospital. Cardiac MR was considered to exclude myocarditis as a cause of left ventricular dysfunction, however, this was considered to be unlikely given the only mildly elevated cardiac biomarkers, the high InterTAK Diagnostic Score and the typical echocardiographic pattern consistent with Takotsubo cardiomyopathy.

After 10 days of mechanical ventilation, the patient was successfully extubated and transferred to the ward where further recovery took place. Remarkably, there was a second rise in C-reactive protein to 150 mg/L (reference value 0–10 mg/L) the days after the diagnosis of Takotsubo cardiomyopathy was established. Treatment with ceftriaxone was started because of a possible pulmonary bacterial superinfection, however, blood- and sputum culture identified no micro-organisms. The troponin levels were normalized 7 days after the diagnosis of Takotsubo cardiomyopathy. At that time, the ECG showed sinus rhythm and normalization of the T-waves. Treatment with an ACE inhibitor (perindopril 2 mg once daily) was initiated; however, treatment was discontinued shortly afterwards because of symptomatic hypotension. Follow-up echocardiography showed important improvement of left ventricular systolic function to an LVEF of 45%, however, with persistent hypokinesia of the apical segments. For that reason, an additional coronary computed tomography angiography (CCTA) was obtained which showed a low calcium score and a non-significant stenosis (<50%) in the proximal left anterior descending artery (CAD-RADS score of 1) excluding coronary artery disease as the cause of this clinical picture (Figure 4).

After 22 days, the patient was discharged home on direct anticoagulation and statin therapy. Three months after the diagnosis Takotsubo cardiomyopathy, the patient visited our outpatient clinic. Echocardiography at that time showed normal contractility of the apical myocardial segments, with normalization of the left ventricular function.
systolic function (LVEF 55%), as expected in Takotsubo cardiomyopathy.

**Discussion**

Takotsubo cardiomyopathy as a complication of COVID-19, may result in significant clinical deterioration and have profound implications on pharmacological treatment options. Remarkably, there are no reports of Takotsubo cardiomyopathy during prior corona-related epidemics (severe acute respiratory syndrome or Middle East respiratory syndrome).

It is important that caregivers of COVID-19 patients are aware of the possible cardiovascular complications that coexist with this disease. Frequent ECG monitoring of COVID-19 patients is of paramount importance herein, because early detection of cardiac comorbidity may reduce adverse outcome. As in this case, Takotsubo cardiomyopathy commonly leads to severe prolongation of QTc, with the risk of life-threatening arrhythmias.\(^8\) This risk might be further increased given the fact that many COVID-19 patients are treated with QT-prolonging drugs such as chloroquine or for instance haloperidol.\(^9\)\(^,\)\(^10\) Furthermore, Takotsubo cardiomyopathy causes left ventricular dysfunction and may even lead to cardiogenic shock. If haemodynamical problems occur in COVID-19 patients, echocardiography is warranted to exclude heart failure secondary to Takotsubo cardiomyopathy, myocarditis or ischaemia.

Takotsubo cardiomyopathy is a self-limiting disease typically resulting in normalization of the ECG and of left ventricular systolic function within 1–2 weeks. Treatment is therefore supportive and aims at minimizing complications. Temporary treatment of left ventricular dysfunction with beta-adrenergic receptor blockers and ACE inhibitors might be considered if haemodynamically tolerated, however no randomized controlled trials concerning optimal medical therapy exist.\(^11\) In cardiogenic shock, positive inotropic agents should be used with caution since these drugs may further activate catecholamine receptors and may worsen the patients clinical status. In refractory cardiogenic shock, mechanical circulatory support should be considered.\(^11\)

A recent report speculated on the main mechanisms to explain the increase in troponin which is regularly observed in COVID-19 patients admitted at the ICU.\(^12\) These include (i) ACE2-receptor-mediated direct cardiac damage, (ii) hypoxia induced myocardial injury, (iii) cardiac microvascular damage, and (iv) SIRS which could result in a cytokine storm. None of the aforementioned has been proven, although mechanism 2 and 3 seem very likely. Our case provides the observation on the occurrence of the fourth postulated mechanism and warrants further investigation. COVID-19 infection could be subdivided into distinct phases: the early infection stage followed by the pulmonary phase which sometimes progresses into the (extrapulmonary systemic) hyperinflammatory phase which is characterized by a clinical picture of acute respiratory distress syndrome, SIRS/shock and signs of cardiac failure.\(^13\) It is in this last clinical phase that inflammatory markers are markedly increased as well as elevations of troponin are observed. It seems reasonable to hypothesize that during this...
hyperinflammatory phase optimal circumstances develop for a Takotsubo cardiomyopathy: acute anxiety with increased beta-adrenergic tone in the period preceding respiratory failure, the episode(s) of severe hypoxia, and SIRS.

In conclusion, COVID-19 can be complicated by Takotsubo cardiomyopathy. COVID-19 caregivers should be aware of this complication, since regular use of QT-prolonging drugs combined with prolongation of the QTc interval in Takotsubo cardiomyopathy may lead to life-threatening arrhythmias. Furthermore, Takotsubo cardiomyopathy may lead to heart failure and even cardiogenic shock. Frequent ECG monitoring of COVID-19 patients therefore is of paramount importance and echocardiography should be obtained when haemodynamical problems occur. Our observation warrants further investigation regarding the incidence of Takotsubo cardiomyopathy complicating COVID-19 and its potential impact on treatment and outcome.

Lead author biography

Dirk van Osch obtained his Medical Doctor degree in 2013 and is currently working as a resident at the Cardiology Department of the University Medical Center Utrecht, The Netherlands. In 2017, he obtained his PhD degree in the field of inflammation-related complications after cardiac surgery.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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