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CASE REPORT
Heart failure

Coronavirus disease 2019-associated coronary endotheliitis and thrombotic microangiopathy causing cardiogenic shock: a case report

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Background Coronavirus disease 2019 (COVID-19) primarily affects the respiratory tract but serious cardiovascular complications have been reported. Up to one-third of patients admitted to the intensive care unit may develop an acute myocardial injury, characterized by cardiac troponin elevation. However, the pathology underlying COVID-19-associated myocardial injury has rarely been reported.

Case summary Three days after being diagnosed for a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a 52-year-old woman without a notable past medical history developed cardiogenic shock with severely reduced left ventricular ejection fraction (LVEF) at 25%. Coronary angiography was normal. Endomyocardial biopsy demonstrated coronary endotheliitis with multiple microvascular thromboses but no lymphocytic infiltrate and a negative polymerase chain reaction for SARS-CoV-2. The patient was implanted with a short-term LV assist device (Impella CP®, Abiomed, Aachen, Germany) and treated with therapeutic anticoagulation. She suffered from concomitant respiratory failure that required 14 days of orotracheal intubation, 10 days of dexamethasone, and broad-spectrum antibiotics. Clinical outcome was favourable with weaning of the Impella device after 6 days and full recovery of LVEF (65%) at 30 days. Cardiac magnetic resonance performed at Day 30 showed no evidence of myocarditis or scars and confirmed the normalization of LVEF.

Discussion This case highlights how COVID-19-associated coronary endotheliitis and thrombotic microangiopathy, in the absence of myocarditis, may induce transient severe LV dysfunction and cardiogenic shock.

Keywords COVID-19 • SARS-CoV-2 • Coronary endotheliitis • Cardiogenic shock • Impella • Myocarditis • Case report

ESC Curriculum 7.3 Critically ill cardiac patient • 6.2 Heart failure with reduced ejection fraction • 6.4 Acute heart failure • 7.1 Haemodynamic instability

Learning points

- Up to one-third of patients with coronavirus disease 2019 (COVID-19) present laboratory evidence of myocardial injury, of unknown origin in the vast majority of cases
- Coronary endotheliitis and thrombotic microangiopathy may induce left ventricular (LV) dysfunction and cardiogenic shock in COVID-19 patients.
- Early LV mechanical unloading and improved organ perfusion may be an effective treatment in this setting.

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Introduction

Since its outbreak in December 2019, coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains to this day a major public health issue worldwide. Among a broad spectrum of clinical cardiac manifestations of COVID-19 myocardial injury, heart failure, cardiogenic shock, and cardiac arrhythmias have been described.[1]

The exact incidence of new-onset heart failure in COVID-19 patients is not known but several cases of acute severe heart failure have been reported.[2,3] Although myocarditis has been proposed as a cause of myocardial injury and heart failure, the phenotype of myocardial inflammation in COVID-19 remains unclear and the exact pathophysiology of cardiac involvement is still a matter of debate. Various hypotheses have been suggested, such as migration of infected macrophages from the lungs, presence of a viraemic phase inside the myocardium, post-infectious auto-immunity, or occurrence of a cytokine storm triggered by the infection.[1,3] On endomyocardial biopsy, SARS-CoV-2 has been detected within the interstitial cells of the myocardium but rarely inside cardiomyocytes.[4]

We report to our knowledge the first case of COVID-19-associated cardiogenic shock due to coronary endotheliitis and thrombotic microangiopathy (TMA) in the absence of myocarditis.

Timeline

Day 0	Positive SARS-CoV2 polymerase chain reaction test on a nasopharyngeal swab sample taken in the context of fever
Day 3	Admission to hospital for fatigue, fever and shortness of breath. Severe left ventricular (LV) dysfunction demonstrated on echocardiography with moderate pericardial effusion subsequently treated by pericardiocentesis
Day 4	Development of cardiogenic shock, initiation of inotropes with no hemodynamic improvement. Coronary angiography, endomyocardial biopsy and LV assist device (Impella CP®) implantation. Orotracheal intubation because of respiratory failure
Day 5	Full-dose anticoagulation and aspirin were initiated following detection of coronary endotheliitis and thrombotic microangiopathy on endomyocardial biopsy
Day 10	Left ventricular assist device (Impella CP®) removal
Day 11	Initiation of broad-spectrum antibiotics and dexamethasone because of worsening respiratory failure
Day 21	Extubation
Day 23	Discharge from intensive care unit
Month 1	Normal biventricular function with no signs of myocarditis on transthoracic echocardiography and cardiac magnetic resonance
Month 1	Discharge home

Case presentation

A 52-year-old woman visited the emergency department because of worsening shortness of breath (SOB) accompanied by new-onset pleuritic substernal chest pain and dizziness. Three days earlier, she was tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction testing of a nasopharyngeal swab specimen. Initially, her symptoms were mild with asthenia, myalgia, and SOB. The patient had no cardiovascular risk factors, no regular medication, and her medical history was unremarkable except for a non-disabling Raynaud Syndrome.

The patient appeared in respiratory distress (respiratory rate 28/min), tachycardic (111 b.p.m.), and with cutaneous signs of hypoperfusion despite preserved arterial blood pressure (120/80 mmHg). Oxygen saturation was 98% on 28% of the inspired oxygen fraction. Cardiomegaly and signs of pulmonary interstitial oedema were observed on the chest X-ray.

The 12-lead electrocardiogram showed sinus rhythm with small QRS complexes in the peripheral leads without significant repolarization abnormalities (*Figure 1*). Metabolic acidosis with partial respiratory compensation, hyperlactataemia at 6 mmol/L [upper reference limit (URL) 1.6 mmol/L], and PaO_2 of 42 kPa were observed on arterial blood gas (*Table 1*). Blood tests showed normal electrolytes, increased inflammatory markers, elevated high sensitive cardiac troponin-T (321 ng/L; URL 14 ng/L), and N-terminal pro-B-type natriuretic peptide (8789 ng/L, URL 300 ng/L) (*Table 1*). Kidney function was normal (creatinine 53 µmol/L; URL 80 µmol/L) and liver enzymes were slightly elevated (AST 154 U/L, URL 42 U/L; ALT 139 U/L, and URL 42 U/L) (*Table 1*).

Transthoracic echocardiography (TTE) revealed a normal-sized left ventricle with severely reduced left ventricular ejection fraction (LVEF) at 25%, diffuse hypokinesia, and preserved right ventricular systolic function (*Figure 2*, *Video 1* and Supplementary material online, *Videos S1–S3*). There was a moderate pericardial effusion (16 mm) with slight compression of the right ventricle but no significant mitral or tricuspid inflow respiratory variations. Despite the absence of clinical signs of tamponade, it was decided after a multidisciplinary meeting to perform pericardiocentesis with the aim to improve the symptoms and low-output state. A total of 150 mL of serous fluid was drained revealing acute and chronic inflammatory cells (214 M/L leucocytes) with a macrophage predominance (72%) on histological analysis. Pericardial fluid analysis showed elevated lactate dehydrogenase (1665 U/L) and albumin (19 g/L). No malignant cells were found, and the culture was sterile.

Despite pericardiocentesis the patient developed progressive circulatory failure at which point Norepinephrine (0.2 µg/kg/min) and Dobutamine (5 µg/kg/min) were initiated. As haemodynamic failed to improve under pharmacologic support, a short-term LV assisted device (Impella CP®) was implanted via a left arterial femoral approach (*Figure 3A*). Coronary angiography revealed normal epicardial coronary arteries (*Figure 3B* and *C*). Endomyocardial biopsy of the right ventricle demonstrated no inflammatory infiltration, but rather thrombotic microangiopathy (TMA) of the coronary capillaries with endothelial cell activation (endotheliitis) characterized by enlarged nuclei and capillary thrombosis (*Figure 4A* and *B*). Polymerase chain reaction analysis of the samples was negative for SARS-CoV-2 mRNA.

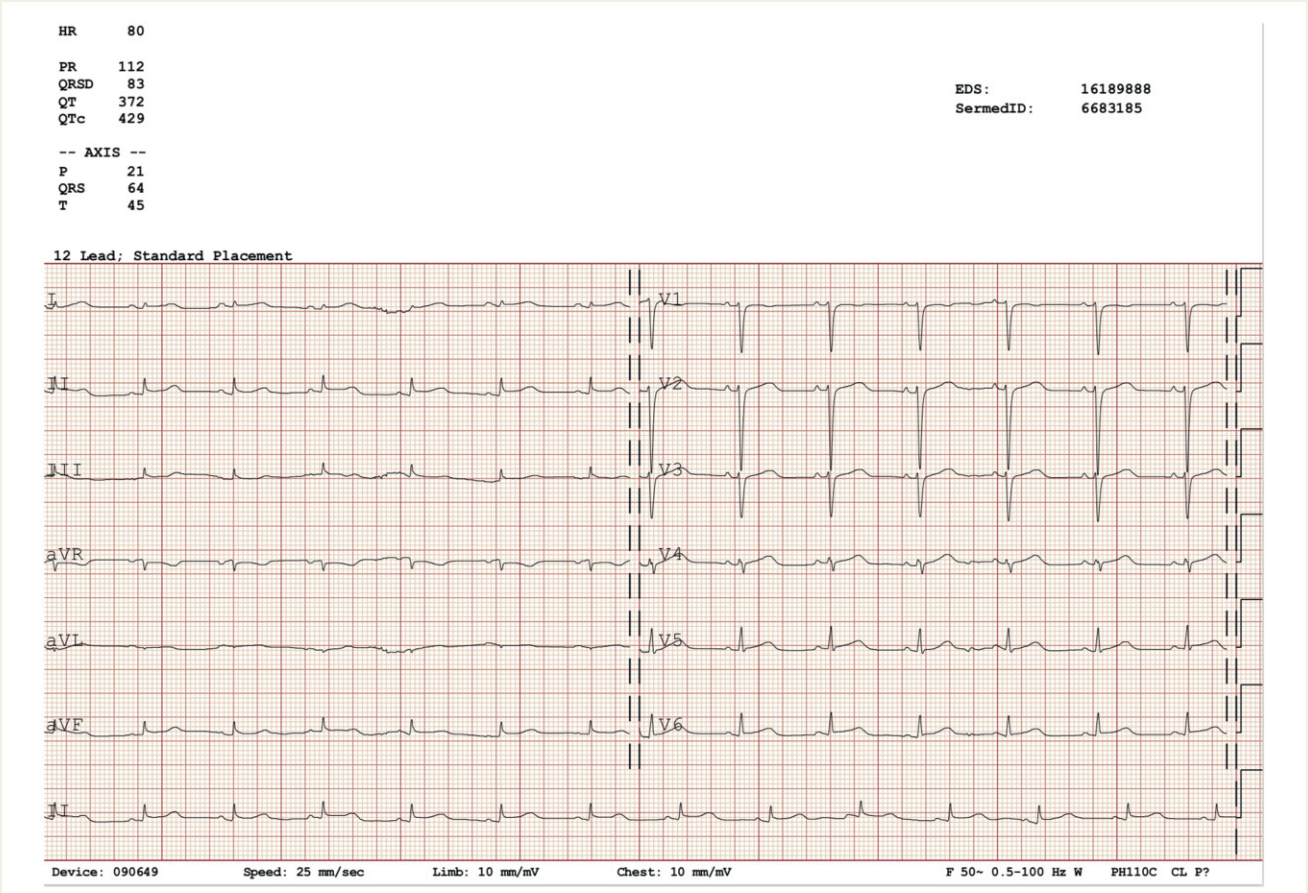


Figure 1 Twelve-lead electrocardiogram upon admission: sinus rhythm at 83/min, normal cardiac axis with narrow QRS, low QRS voltage in the limb leads, absence of significant repolarization abnormalities.

Following Impella CP® implantation and further supported by the hypothesis of a cardiogenic shock due to coronary microcirculatory thrombotic damage, aspirin, and full-dose intravenous anticoagulation were initiated. Six days later, the patient's haemodynamic profile improved and the Impella CP® assist device could be successfully weaned. There was no significant arrhythmia during the intensive care unit stay. Concomitant respiratory failure, mainly related to SARS-CoV-2 induced acute respiratory distress syndrome (ARDS), required 17 days of orotracheal intubation, antibiotics (iv amoxicillin-clavulanic acid then iv piperacillin/tazobactam), and dexamethasone 6 mg daily for a total of 10 days as proposed in the RECOVERY trial.[5] Apart from the heart and lungs, no other organ was affected by the systemic endothelial cell activation.

The patient was eventually discharged from the intensive care unit after 20 days. Before hospital discharge, TTE revealed a normalized biventricular systolic and diastolic function (Supplementary material online, *Figure S1*, *Video 2*, Supplementary material online, *Video S4*). Cardiac magnetic resonance (CMR) confirmed good biventricular function (*Video 3*) (LVEF and RVEF of 59% and 59%, respectively) and gadolinium enhancement sequences ruled out signs of myocarditis or infarction scars (Supplementary material online, *Figure S2*).

The final diagnosis was cardiogenic shock due to transient severe LV dysfunction induced by COVID-19-associated coronary endotheliitis and TMA.

Discussion

It is widely accepted that the pathophysiology of SARS-CoV-2 invasion is mainly related to viral entry into respiratory epithelial cells via membrane-bound angiotensin-converting enzyme 2 (ACE-2).[6] Microangiopathy and alveolar-capillary microthrombi are now well described as additional manifestations of lung damage in patients with COVID-19.[7] Indeed, SARS-CoV-2 ARDS can originate both from epithelial and endothelial damage of the alveolar-capillary barrier.[8] Interestingly, ACE-2 can also be found on vascular endothelial cells and therefore SARS-CoV-2 may potentially cause systemic endotheliitis, with endothelial cells apoptosis and inflammation in virtually all organs.[9] Coronavirus disease 2019 (COVID-19)-related atypical TMA has been described in various organs including the kidney even if the established definition of TMA is not always met.[10]

Table 1 Laboratory data

Variable	Admission	Day 5	Reference range
PO_2	9.78 (FiO_2 21%)	9.7 (FiO_2 45%)	11.07–14.4 kPa
PCO_2	4.00	4.6	4.26–6 kPa
pH	7.25	7.48	7.35–7.45
$HCO3^-$	12.8	29	22–26 mmol/L
Lactates	6	1.3	0.5–1.6 mmol/L
High sensitive cardiac troponin T	321	1226	<14 ng/L
Creatine kinase	1121	7000	33–187 U/L
NT-proBNP	8789	12 000	<300 ng/L
C-reactive protein	2.4	65	0–10 mg/L
AST	154	266	11–42 U/L
ALT	139	108	9–42 U/L
Gamma-glutamyltranspeptidase	108	46	9–35 U/L
Total bilirubin	6	5	7–25 µmol/L
White cell count	15.8	15	4–11 G/L
Haemoglobin	187	95	120–160 g/L
Haematocrit	52.9	28.4	37–47%
Platelet count	145	104	150–350 G/L
Creatinine	53	51	44–80 µmol/L
Blood urea nitrogen	7.8	8.0	3.2–7.5 µmol/L

ALT, alanine aminotransferase; AST, Aspartate transaminase; FiO_2, fraction of inspired oxygen; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure in oxygen.

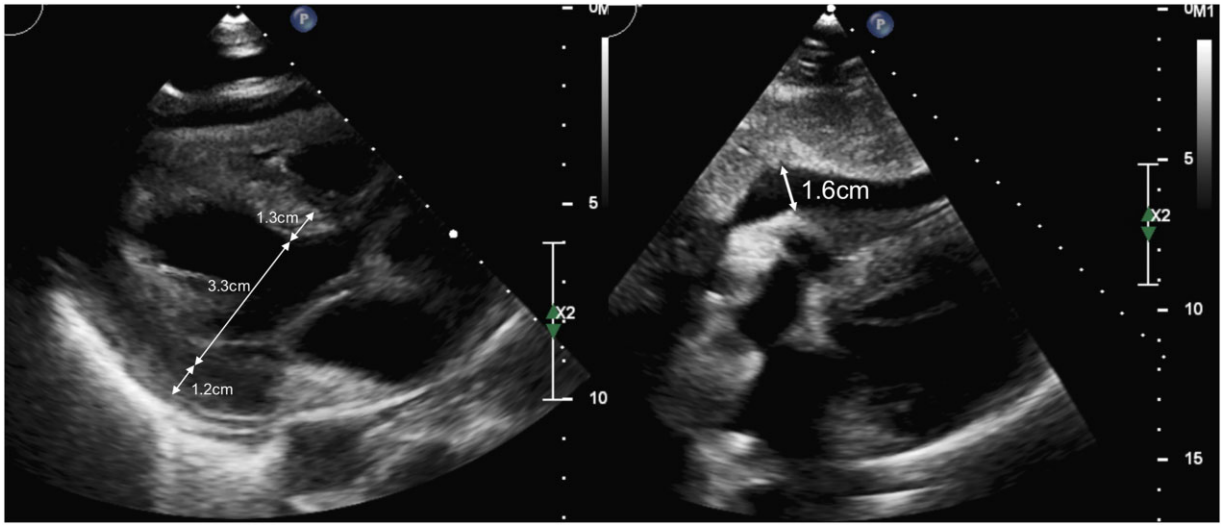


Figure 2 Telediastolic parasternal long-axis view (left image) showing a severely reduced ejection fraction and telediastolic subcostal view (right image) with moderate pericardial effusion.

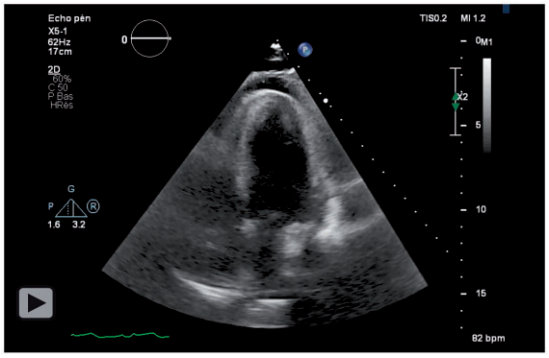
The present case suggests that endotheliitis and TMA in the coronary microcirculation, even in the absence of associated myocarditis, could lead to acute heart failure and cardiogenic shock. Endothelial activation may lead to capillary thrombosis and cellular apoptosis, as found in our endomyocardial biopsy. In our patient, we postulate that endothelial activation was triggered by the cytokine storm rather than by direct viral toxicity since SARS-CoV 2 mRNA was not detected in the endomyocardial biopsy. However, the absence of the virus should be taken with caution since electron microscopy was not performed on our biopsy samples.

To our knowledge, coronary endotheliitis due to COVID-19 has been rarely described and this case highlights one possible pathophysiological mechanism by which SARS-CoV-2 infection could induce myocardial injury. Myocardial injury characterized by troponin

release occurs in 8–28% of patients with COVID-19 depending on disease's severity and is associated with a worse prognosis.[1] Most cases of elevated cardiac troponin are not related to direct infection of the heart but rather due to indirect myocardial injury, secondary to respiratory failure and systemic inflammation.[11] Another well-described cause of myocardial injury and heart failure in COVID-19 patients is Takotsubo syndrome related to catecholamine-induced microvascular dysfunction triggered by physical or emotional stress.[12] However, this syndrome is typically associated with regional wall motion abnormalities, which were not present in our patient.

In addition, it has been suggested that SARS-CoV-2 can induce acute myocarditis.[2] However, typical histological findings or classic CMR criteria for myocarditis have rarely been reported in this setting. Escher *et al.*[13] showed that SARS-CoV2 RNA was present in the biopsies of 5 out of 105 COVID-19 patients with suspected myocarditis or unexplained heart failure but only 1 patient had active myocarditis according to the Dallas criteria. Tavazzi *et al.*[4] reported the presence of viral particles in the interstitial tissue in one patient with a cardiogenic shock and COVID-19. In another report, SARS-CoV2 mRNA was identified on endomyocardial biopsies in two COVID-19 patients with clinically suspected myocarditis but without positive Dallas criteria on biopsy samples.[14] Myocardial injury may thus originate either from myocardial inflammation seen in typical myocarditis or from endotheliitis of the coronary microcirculation. In the present case, the biopsy did not display any evidence of inflammatory infiltrates within the myocardium (leucocytes, myocyte degeneration, and necrosis), the hallmark of myocarditis.

In our patient with preserved right ventricular function, Impella CP® was a valuable alternative to veno-arterial extra-corporal membrane oxygenation as it allowed both stable systemic circulatory support and LV unloading. To our knowledge, this is the first Impella CP® implantation for a cardiogenic shock due to coronary endotheliitis caused by COVID-19, while in the setting of fulminant myocarditis with cardiogenic shock early LV mechanical assistance has been advocated.[15]



Video 1 Apical four-chamber view on admission showing a severely reduced ejection fraction and moderate pericardial effusion.

Conclusion

Management of cardiac complications in COVID-19 patients is part of our daily routine and we are now understanding better the cardiovascular pathophysiology of SARS-CoV2 aggression. It appears that SARS-CoV2 infection-associated myocardial damage is related to various mechanisms; lymphocytic myocarditis (rare), myocardial

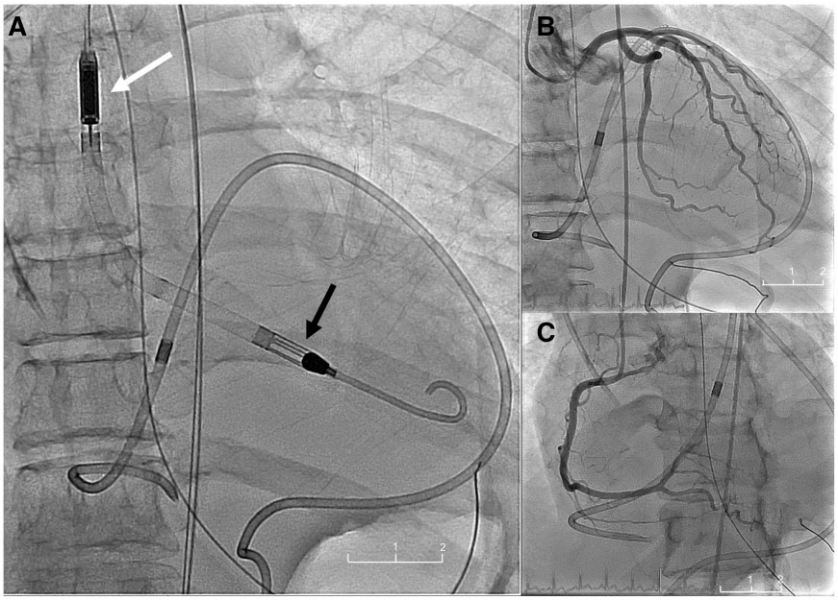


Figure 3 Angiographic image of the Impella CP® heart pump implanted in the left ventricle (*A*): Blood inlet area (black arrow) that pulls blood from the left ventricle to the ascending aorta (white arrow). Coronary angiography: Left coronary artery in right anterior oblique caudal view (*B*) and right coronary artery in left anterior oblique view without epicardial stenosis.

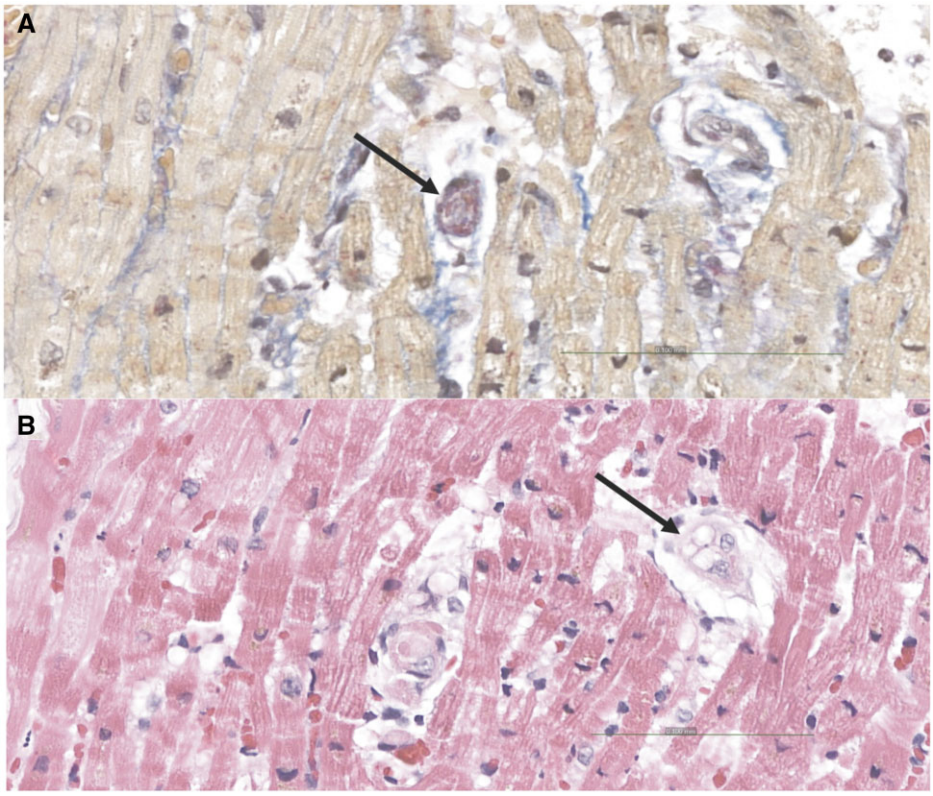
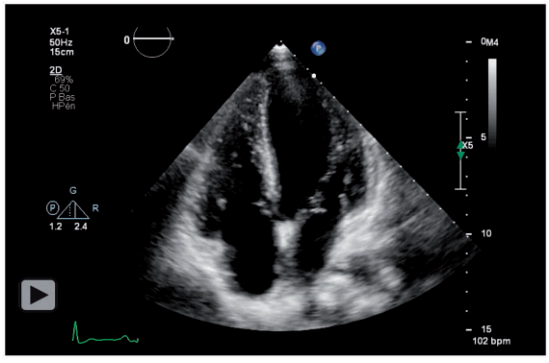
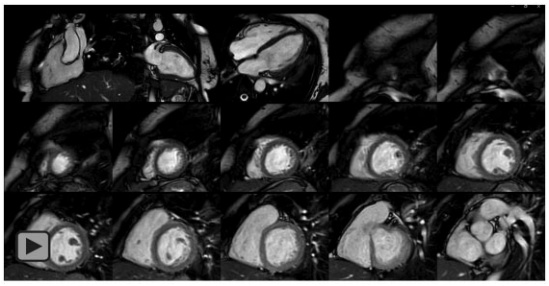


Figure 4 Right ventricle biopsy sampling. (*A*) Right ventricle myocardial biopsy with microvascular thrombosis and fibrin deposit (black arrow) on acid fuchsin–Orange G staining. (*B*) Endothelial cells activation with changes in cells architecture and morphology (black arrow) on haematoxylin and eosin staining.



Video 2 Apical four-chamber view before discharge showing normalized left ventricular ejection fraction.



Video 3 At 1-month follow-up, cardiac magnetic resonance cine sequences revealing a normalized left ventricular ejection fraction without regional wall motion abnormalities.

injury secondary to a cytokine storm, or coronary endotheliitis. Interestingly, despite the presence of ACE-2 on cardiomyocytes, SARS-CoV2 does not seem to show cardiotropism since the virus was rarely found inside cardiomyocytes on endomyocardial biopsy.

This report highlights the observation that cardiogenic shock in COVID-19 may be secondary to coronary endotheliitis, thrombotic microangiopathy, and microthrombosis and can be successfully treated by mechanical cardiac unloading and therapeutic anticoagulation.

Lead author biography

Dr méd. Valérian Valiton, born in 1988, graduated from medical school of University of Geneva in 2014. He completed his cardiology residency at Geneva University Hospitals in 2021. His main interests include acute heart failure, myocarditis, cardiovascular impacts of COVID-19, and advanced heart failure therapies.

Supplementary material

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

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 images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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