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CASE REPORT
Coronary heart disease

Cardiac arrest and COVID-19: inflammation, angiotensin-converting enzyme 2, and the destabilization of non-significant coronary artery disease—a case report

Sébastien Colombier [1]*, Thabodhan Mahendiran[2], Lars Niclauss [1], and Matthias Kirsch [1]

[1]Department of Cardiovascular Surgery, Lausanne University Hospital CHUV, Rue du Bugnon 46, 1011 Lausanne, Switzerland; and [2]Department of Cardiology, Lausanne University Hospital CHUV, Rue du Bugnon 46, 1011 Lausanne, Switzerland

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Background The new β-coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to exhibit cardiovascular pathogenicity through use of angiotensin-converting enzyme 2 (ACE2) for cell entry and the development of a major systemic inflammation. Furthermore, cardiovascular comorbidities increase susceptibility to SARS-CoV-2 infection and the development of a severe form of COronaVIrus Disease 2019 (COVID-19).

Case summary We describe the case of a COVID-19 patient whose inaugural presentation was a refractory cardiac arrest secondary to the destabilization of known, non-significant coronary artery disease. Patient was supported by venoarterial extracorporeal life support. After 12 h of support, cardiac function remained stable on low vasopressor support but the patient remained in a coma and brainstem death was diagnosed.

Discussion Myocardial injury is frequently seen among critically unwell COVID-19 patients and increases the risk of mortality. This case illustrates several potential mechanisms that are thought to drive the cardiac complications seen in COVID-19. We present the potential role of inflammation and ACE2 in the pathophysiology of COVID-19.

Keywords COVID-19 • SARS-CoV-2 • Cardiac arrest • Extracorporeal life support • Case report

Learning points

- History of cardiac disease and cardiovascular risk factors increase susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the development of a severe form of COronaVIrus Disease 2019 (COVID-19).
- COVID-19 contributes to cardiac complication through several mechanisms.
- A major systemic inflammatory response promoting atherosclerotic plaque rupture and a pro-coagulant state.
- SARS-CoV-2 direct binding to myocardial and endothelial angiotensin-converting enzyme 2.
- Extracorporeal life support/extracorporeal membrane oxygenation and hemoadsorption appear as a therapeutic option in critical cases.

* Corresponding author. Tel: +41 213147367, Fax: +41 213142278, Email: sebastien.colombier@chuv.ch
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Introduction

Following the outbreak in 2003 of severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), the virus responsible for SARS, a link between cardiovascular disease and coronavirus infection was identified.[1] Belonging to the same Sarbecovirus subgenus, the new β-coronavirus, SARS-CoV-2, appears to exhibit similar pathogenicity through use of angiotensin-converting enzyme 2 (ACE2) for cell entry. We describe the case of a COronaVIrus Disease 2019 (COVID-19) patient whose inaugural presentation was a fatal cardiac complication of infection.

Timeline

Time	Events
Day 1	Gastrointestinal bleeding and anaemia.
Day 2	Myocardial infarction with high-sensitivity troponin T = 47 ng/L (normal <14 ng/L). Normal echocardiogram. Coronary angiography: single-vessel disease with a non-significant stenosis of the proximal left anterior descending (LAD) artery. Aspirin and Lisinopril initiation.
Day 63	Out-of-hospital refractory cardiac arrest, persistent ventricular arrhythmias, 60 min of low-flow. Surgical extracorporeal life support implantation via the right groin. Emergent coronary angiography: acute sub-occlusion at the site of the known LAD stenosis and a novel significant stenosis of the first marginal artery.
Day 64	High-sensitivity troponin T peak >22 000 ng/L. Lactatemia and pH normalization. Diffuse pulmonary interstitial infiltration despite adequate left ventricle unloading and partial myocardial recovery. Positive viral screening for severe acute respiratory syndrome coronavirus 2.
Day 65	Persistent coma and brainstem death diagnosis.

Case presentation

A 60-year-old man was admitted with gastrointestinal bleeding and anaemia [haemoglobin 90 g/L normal (130–180)]. Gastroscopy revealed a Forrest III gastric ulcer. During the admission, the patient experienced several episodes of acute chest pain. Investigations revealed untreated arterial hypertension, an electrocardiogram with antero-lateral ST-elevation in keeping with early repolarization (*Figure 1*), a small rise in high-sensitivity troponin T (hs-TnT) (47 ng/L, normal < 14), and a normal echocardiogram. Subsequent coronary angiography revealed single-vessel disease with a non-significant stenosis of the proximal left anterior descending (LAD) artery (*Figure 2*). Stress (adenosine) cardiac magnetic resonance imaging confirmed normal left ventricular function with no segmental wall-motion abnormalities, oedema, or inducible myocardial ischaemia. The patient remained stable and presented no further bleeding or cardiac symptoms. His coronary lesion was managed conservatively and he was discharged 5 days later on Aspirin (100 mg/day), Lisinopril (10 mg/day), Pantoprazole (40 mg/day). He refused statins due to a fear of side effects.

Two months later, the patient presented with an out-of-hospital cardiac arrest. Cardiopulmonary resuscitation was started immediately by nearby witnesses. He was transferred to our hospital with an automatic mechanical chest compression device in place. On arrival, rhythm analysis revealed persistent ventricular arrhythmias refractory to treatment. Arterial blood gas analysis demonstrated a severe mixed acidosis [pH 6.8, normal (7.35–7.45); PCO_2 = 65 mmHg, normal (35–45); HCO_3 = 10 mmol/L, normal (22–26); PO_2 = 168 mmHg, normal (73–103)], hyperlactatemia (12.5 mmol/L, normal <2), and moderate anaemia (haemoglobin = 110g/L). Extracorporeal life support (ECLS) was successfully implanted surgically via the right groin after a total low-flow time of 60 min. With the ECLS at full flow, successful defibrillation was achieved with a return to sinus rhythm. Antero-lateral ischaemia was suspected on the electrocardiogram (*Figure 3*). Emergent coronary angiography revealed an acute sub-occlusion at the site of the known LAD stenosis and a significant stenosis (70%) of the first marginal artery (*Figure 4*). Due to a gastric bleeding, the return of TIMI 3 flow in the LAD following insertion of the guidewire and normalization of electrocardiogram on ECLS support, an angioplasty-stenting was planned one day later once concerns of active bleeding had been allayed.

After 12 h of ECLS, cardiac function remained stable on low vasopressor support with hs-TnT reaching a peak of >22 000 ng/L (*Supplementary material, Tables 1* and *2*). Transoesophageal echocardiography performed with full flow ECLS and IV dobutamine (600 µg/min) demonstrated preserved left ventricular function. A chest computed tomography revealed diffuse pulmonary interstitial infiltration despite adequate left ventricle unloading (*Figure 5*). Following the weaning of sedation, the patient remained in a coma and brainstem death was diagnosed. However, a nasopharyngeal viral screen returned positive for SARS-CoV-2, thus contraindicating organ donation.

Discussion

This case illustrates several potential mechanisms that are thought to drive the cardiac complications seen in COVID-19. Of note, COVID-19 was not initially suspected due to the nature of the presentation and the absence of signs of infection such as fever. However, our patient had several of risk factors that are reported to increase susceptibility to SARS-CoV-2 infection, and the development of a severe form of COVID-19. Half of patients hospitalized with COVID-19 have cardiovascular comorbidities.[2,3] The prevalence of hypertension and cardiovascular disease in COVID-19 patients are reported to be 30% and 14.5%, respectively.[2,3] Rates are even higher in patients requiring mechanical ventilation/intensive care and are two-fold higher in non-survivors.[2,4,5] Our

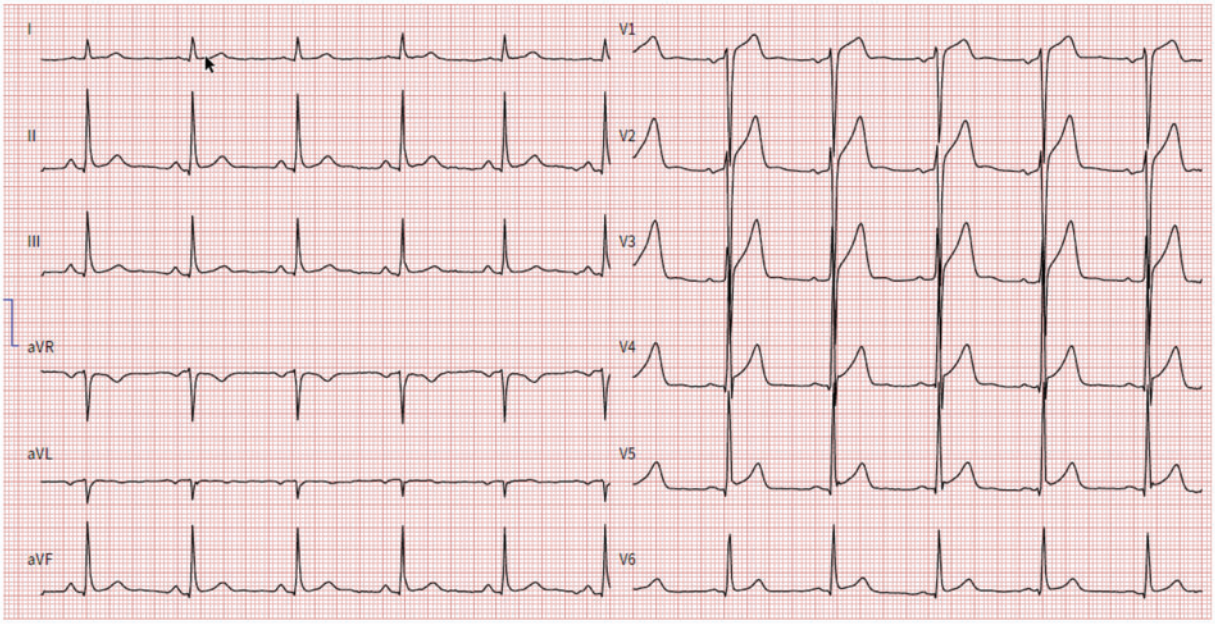

Figure 1 Electrocardiogram on admission showed antero-lateral ST-elevation in keeping with early repolarization during an asymptomatic period.

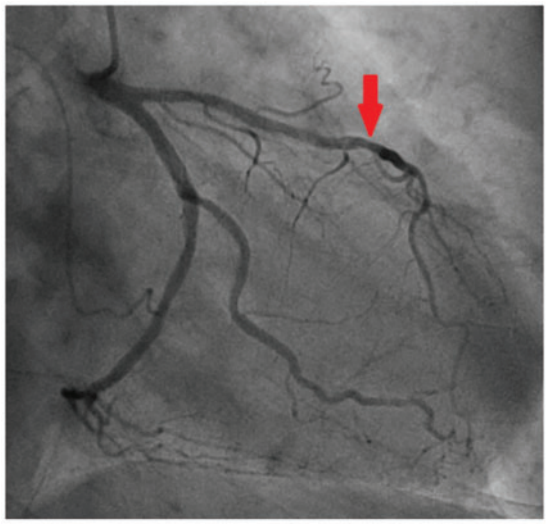

Figure 2 First coronary angiogram (right anterior oblique caudal view) with a non-significant stenosis of the proximal left anterior descending artery (red arrow).

patient had a history of hypertension (2.5-fold higher risk) and coronary artery disease (16-fold higher risk).[5] In addition, the recent initiation of an ACE inhibitor may have theoretically increased cardiac ACE2 expression, thus providing more cellular entry points for SARS-CoV-2. However, it must be emphasized that, whilst awaiting a definitive clinical trial, observational data has not found that ACE inhibitor use affects the risk of COVID-19.[6,7]

Cardiac complications have been reported in 8% of all COVID-19 patients and between 25% and 44% of those admitted to intensive care.[5,8] Increased troponin levels appear to be an important predictor of adverse outcomes. One study found raised troponin among only 1% of survivors compared with >50% of non-survivors.[2] In-hospital mortality is also significantly higher among patients with myocardial injury (60.9%) compared to those without myocardial injury (25.8%).[8] Several mechanisms have been proposed to explain the myocardial injury in COVID-19 patients including coronary plaque rupture, cytokine storm, hypoxic injury, coronary spasm, microthrombi, and endothelial injury.[9]

Considering the abruptness of the presentation and the coronary angiography results, the most plausible pathophysiological explanation for our case is cardiac arrest secondary to acute myocardial infarction. However, COVID-19 may have contributed to this coronary complication through several mechanisms.

Firstly, SARS-CoV-2 infection is characterized by the development of systemic inflammatory response syndrome (SIRS) with up-regulation of pro-inflammatory cytokines.[1,8] Furthermore, markers of systemic inflammation are significantly higher in COVID-19 patients who develop cardiac complications, with C-reactive protein levels 3-times higher than those without cardiac complications.[8] Systemic inflammation is known to destabilize atherosclerotic plaques and promote plaque rupture.[10] Likewise, systemic inflammation is known to promote a pro-coagulant state increasing the risk of coronary thrombosis. A combination of these factors may have been responsible for the rupture of a plaque at a stenosis that was deemed non-significant 2 months earlier. A further plausible mechanism is coronary spasm which can occur at the site of known coronary stenosis[11] and has been associated with inflammation of the coronary adventitia.[12]

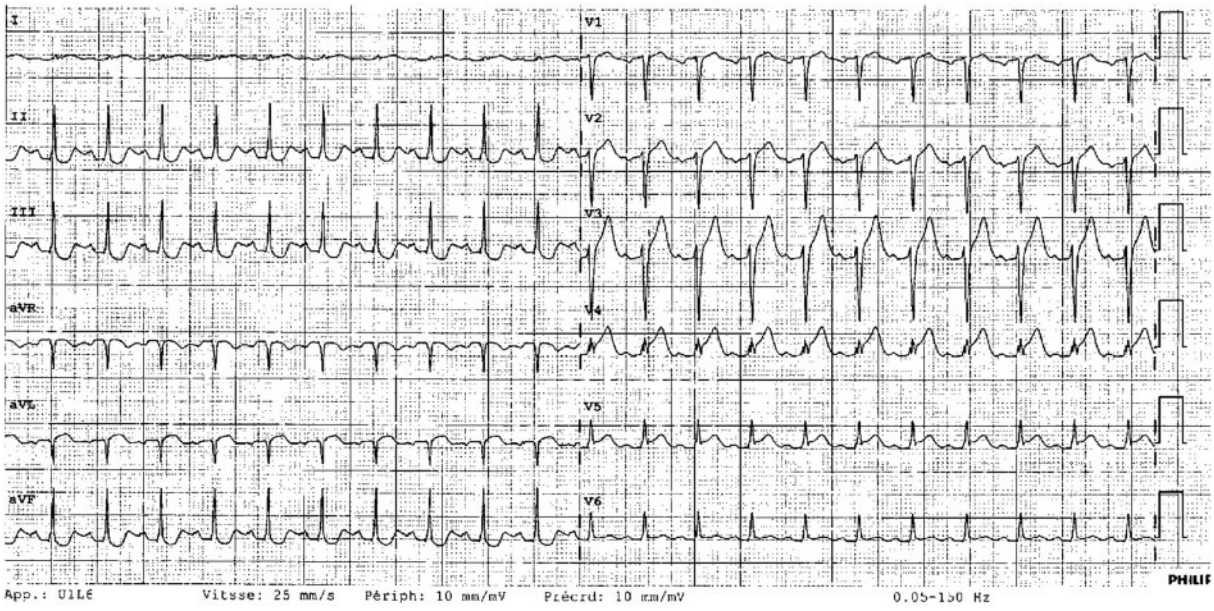

Figure 3 Post-extracorporeal life support implantation electrocardiogram showed antero-lateral ischaemia. ST-segment elevation was observed in leads V3–V5. Reciprocal ST changes were noted in the inferior leads (II, III, aVF).

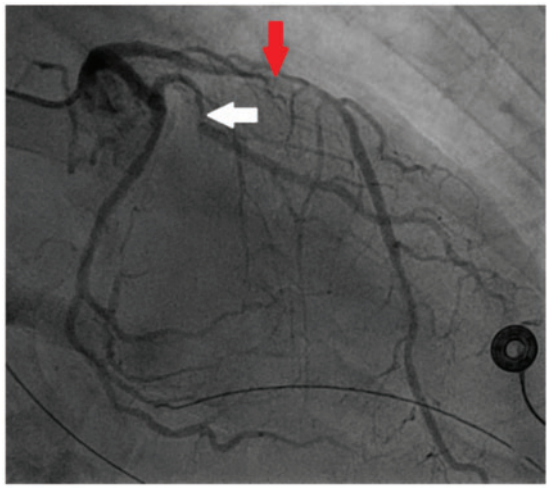

Figure 4 Post-cardiac arrest coronary angiogram (right anterior oblique cranial view) with an acute left anterior descending sub-occlusion (red arrow) and a significant stenosis (70%) of the first marginal artery (white arrow).

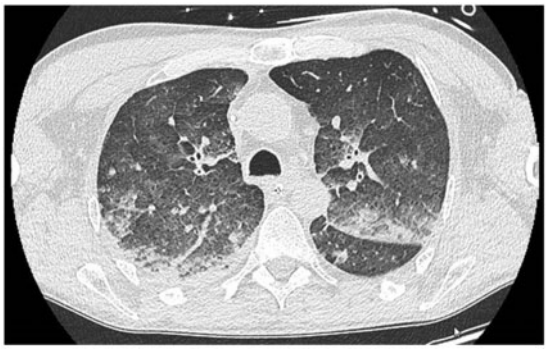

Figure 5 Chest computed tomography revealed a diffuse pulmonary interstitial infiltration.

Secondly, the direct binding of the SARS-CoV-2 virus to ACE2 constitutes a second mechanism of myocardial and endothelial injury.[1] ACE2 permits direct entry of the virus into myocytes with subsequent down-regulation of its associated cardio-protective effects. This hypothesis is supported by the detection of virus particles in myocardial samples from COVID-19 patients presenting with cardiogenic shock.[1,13] Myocardial biopsy was not performed in our case to validate this hypothesis. Initial theories on the role of ACE2 in COVID-19 predicted that ACE inhibitors/angiotensin receptor blockers may have increased susceptibility to SARS-CoV-2 and increased its pathogenicity due to increased ACE2 expression. The SARS-CoV-2 binds to ACE2 inducing its endocytosis and disappearance from the endothelial cell surface. The subsequent inactivation of ACE2 pathways theoretically results in numerous deleterious cardiac effects.[1,10,14] However, emerging evidence, albeit from observation data, now suggests a possible protective role of these medications in the context of COVID-19.[7] A proposed mechanism is that these medications up-regulate ACE2 expression, and thus subsequent soluble ACE2 which may

Table 1 Patient arterial blood gazes evolution, with pH and lactataemia curves

Arterial blood gaz Hours after admission	pH	PO_2 (mmHg)	PCO_2 (mmHg)	HCO_3 (mmol/L)	Lactatemia (mmol/L)	Glucose (mmol/L)	K+ (mmol/L)
0	6.8	167	64	10	12.5	14.7	4.8
0.5	7.19		34	13	12	12	4.2
1	7.16	134	51	18	12.5	10	4.5
2	7.24	46	41	17	7	8	3.9
4	7.25	117	41	14	6.24	9	3.5
5	7.2	101	52	18	6.6	11	3.9
6	7.24	245	35.5	15	6.8	9.4	3.3
7	7.25	108	38	17	6.9	9.6	3.8
9	7.22	112	47	19	5.35	11.4	3.6
11	7.33	86	34	17	5.5	12	3.6
13.5	7.24	106	45	19	5.2	10.5	3.7
15	7.25	100	43	18	5.12	9	3.5
17	7.26	104	42	19	4.9	8	4.2
28	7.34	107	38	20	3	6.5	4
24	7.4	134	35	21	1.7	9	5.9
29	7.43	100	34	23.5	1.3	7	4.9

Table 2 Main laboratory parameters

Parameters	Patient	Normal ranges
Leucocytes (G/L)	11.7	(4–10)
C-reactive protein	38	<5
Lactate dehydrogenase	355	(135–225)
Fibrinogène	1.2	(2–4)
TP (50%)	50	(80–100)
NT-proBNP (ng/L)	<50	<263

act as a 'dummy' receptor, thus lowering circulating levels of SARS-CoV-2.[14]

On a final note, it is possible that despite the successful treatment of refractory cardiac arrest in this case, ECLS may have exacerbated the viral-induced inflammatory state. However, numerous factors promote the development of SIRS, which could theoretically contribute to the cytokine storm seen with COVID-19.[15] The use of cytokine hemoadsorption therapy (Cytosorb®) with ECLS/extracorporeal membrane oxygenation could represent an interesting therapeutic adjunct in critically unwell COVID-19 patients. Hemoadsorption therapy has been shown to be beneficial in cases of acute respiratory distress syndrome through a reduction in inflammation and its associated mortality.[15] This system could break the inflammatory storm and reduce associated cardiac complications.

Conclusion

Myocardial injury is frequently seen among critically unwell COVID-19 patients and increases the risk of mortality. Our case unites several of the proposed mechanisms thought to be responsible for the high rate of cardiac complications seen with COVID-19. Furthermore, the role of ACE2 and inflammation in its pathophysiology should not be underestimated.

Lead author biography

Sébastien Colombier is a 35-year-old cardiac surgeon, European Board of CardioThoracic Surgery certified, working in Lausanne University Hospital (CHUV), Switzerland. He performed a fellowship in the cardiovascular surgery unit, La Pitié Salpêtrière University Hospital, Paris, France. His research interest includes ECLS and ECMO, assist devices, heart failure, and hemoadsorption.

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 author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient's next of kin in line with COPE guidance.

Conflict of interest: none declared.

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