Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Case Report

COVID Convalescence—A Boon or Bane in Cardiac Surgery?: A “Second Hit” Hypothesis

Srinath Damodaran, MD, DM*, Shreedhar S. Joshi, MD, FCA, DM†, Sunil Kumar V, MD, FNB‡, Pooja Natarajan, MD, FNB, Thruthani Kumaran, DNB, DNB, MNAMS, FICS||

*Department of Anaesthesia, Narayana Institute of Cardiac Sciences, Narayana Health City, Bangalore, Karnataka, India
†Department of Anaesthesia and Intensive Care, Narayana Institute of Cardiac Sciences, Narayana Health City, Bangalore, Karnataka, India
‡Department of Cardiac Critical Care, Narayana Institute of Cardiac Sciences, Narayana Health City, Bangalore, Karnataka, India
||Department of Cardio-thoracic Surgery, Narayana Institute of Cardiac Sciences, Narayana Health City, Bangalore, Karnataka, India

The coronavirus disease 2019 (COVID-19) pandemic continues to affect healthcare services. As elective cardiac surgical services resume, clinicians will encounter COVID-19-recovered patients for cardiac surgery. The hyperimmune pathophysiology of COVID-19 and exposure to the inflammation of cardiac surgery, cardiopulmonary bypass, mechanical ventilation, blood transfusion, and perioperative infections could lead to exacerbated responses, exemplified by systemic inflammatory response syndrome and cascade to multiorgan dysfunction syndromes. The authors present a patient with coronary artery disease undergoing off-pump coronary artery bypass surgery after the institutional protocol of two COVID-19 reverse-transcriptase polymerase chain reaction tests reported negative. Intraoperatively, unexplained hypoxemia was observed, which warranted cardiopulmonary bypass support to complete the grafting. After multiple attempts of failed weaning, intra-aortic balloon pump and high inotropes helped to wean. The patient had a stormy postoperative course, with low oxygenation, bleeding, low-cardiac-output syndrome, rhabdomyolysis of lower limb muscles, requiring multiple blood and blood product transfusion, and renal replacement therapy. Despite the corrective measures, severe hyperkalemia and cardiac arrest ensued. IgG antibodies to the severe acute respiratory distress syndrome coronavirus-2 virus were tested considering the unexplained hypoxemia. A “convalescent COVID-19” patient with “first hit” at primary infection, encountering a “second hit” of surgery and perioperative insults, might have a hyperimmune response. This “second hit” hypothesis should be considered when COVID-19 convalescent (COVID-19 symptomatic or asymptomatic) patients undergo cardiac surgery and present with unusual complications.

Case Report

A 62-YEAR-OLD male, with coronary artery disease, was scheduled for elective coronary artery bypass grafting (CABG). He was a long-term diabetic and hypertensive on regular medications. The preoperative evaluation of other organ systems was unremarkable. Investigations of renal function, liver function, chest X-ray, and coagulation parameters were within normal limits. However, the blood count revealed lymphopenia that had no clinical correlation. Echocardiography demonstrated normal functionality but coronary angiography showed significant triple-vessel disease. As per institutional protocol, screening was done twice before surgery for severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) by reverse-transcriptase
polymerase chain reaction (RT-PCR) test. These tests were done seven days apart, with a negative report for coronavirus disease 2019 (COVID-19) in both instances. A high-resolution computer tomography scan of the chest was performed that revealed nothing overt. He was retained in hospital-based quarantine isolation for the waiting period of the RT-PCR testing and subsequently transferred to the cardiac unit on the eve of scheduled off-pump CABG surgery.

On transfer to the operating room, his baseline vitals recordings were unremarkable, with an oxygen saturation of 97% on room air. Under local anesthesia, an invasive radial arterial blood pressure monitoring line was inserted and arterial blood gas (ABG) analysis at this stage was normal. Induction of anesthesia was accomplished with a standardized narcotic, benzodiazepine, and muscle relaxant-based technique. Subsequently, he was intubated with an appropriately sized endotracheal tube (ETT). After confirmation of the ETT position, the patient was connected to the anesthesia circuit. Controlled ventilation with volume-controlled mode was chosen, with a tidal volume of 8 mL/kg. This was increased to 8 cmH2O. A repeat ABG showed marginal oxygenation. Common causes of desaturations were evaluated that included checking of the ventilator and circuits, ETT, pulse oximetry probe position, and end-tidal carbon dioxide monitoring. Both pleural cavities were opened by the surgeon, revealing adequate lung expansion. The fraction of inspired oxygen (FIO2) was increased to 1, ETT suctioning was done to clear out secretions, and positive end-expiratory pressure was increased to 8 cmH2O. A repeat ABG showed marginal improvement of the arterial partial pressure of oxygen (PaO2) (Table 1). Transesophageal echocardiography was performed to rule out intracardiac shunts, patent foramen ovale causing right-to-left shunt, severe tricuspid regurgitation, new-onset mitral regurgitation, right ventricular (RV) and left ventricular (LV) dysfunction, and acute pulmonary embolism. Grafting to the obtuse marginal artery was performed on a beating heart. Considering the low PaO2:FIO2 ratio, a decision was made to establish CPB to graft the posterior descending artery. An attempt to separate from CPB resulted in hypoxia, worsening hemodynamics, and ventricular fibrillation. CPB was re-established and the heart was defibrillated. The grafts when examined appeared to be functioning well, and in the absence of any mechanical or metabolic cause of instability, a decision was made to put in additional vein grafts to the distal left anterior descending artery and OM vessels. A second attempt to wean off CPB was unsuccessful due to low cardiac output and low PaO2. An intra-aortic balloon pump (IABP) was inserted in the right femoral artery to augment cardiac function. After a further 45-minute rest on CPB, the patient was successfully weaned. The stentum was left open with a retractor in situ, due to borderline hemodynamics and high vasoactive support (epinephrine 0.1 μg/kg/min, norepinephrine 0.1 μg/kg/min, levosimendan 0.1 μg/kg/min). A pulmonary artery catheter was floated that revealed normal pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac index (CI). The patient was transferred to the intensive care unit (ICU), with a PaO2:FIO2 ratio of 170 mmHg and a CI of 2.3 L/min/m2. Hematuria was noticed.

In the ICU, the patient was placed on controlled ventilation, with an FIO2 of 100% and a positive end-expiratory pressure of 15 cmH2O. His vital parameters stabilized over a few hours, with a modest dose of vasoactive support (epinephrine 0.05 μg/kg/min and levosimendan 0.05 μg/kg/min) and an IABP. Inhaled nitric oxide was commenced in a dose of 40 PPM to counter borderline PaO2, but did not significantly improve oxygenation. The serial ABG during the perioperative period is depicted in Table 1. The patient was atrioventricular sequentially paced at 90 beats/min, with an underlying sinus rhythm of 45 beats/min. Multiple transfusions of packed red cells and blood products were needed in view of generalized bleeding. A cell saver was attached to the mediastinal drains to salvage lost blood. All transfusions were directed with thromboelastographic (TEG) and coagulation screen monitoring. Interestingly, the patient persistently had a prolonged reaction time and a low maximum amplitude on the TEG despite targeted transfusions. The activated clotting time readings were persistently high, between 600 and 700 seconds. He subsequently developed a low-cardiac-output state secondary to high drain output a few hours later, necessitating re-exploration that revealed generalized bleeding. His vasoactive support levels

| Timeline                  | PaO2:FIO2 (mmHg) | PaCO2 (mmHg) | PEEP (cmH2O) |
|---------------------------|-----------------|-------------|--------------|
| Baseline on spontaneous ventilation (T0) | 220 | 35 | - |
| Post induction mechanical ventilation (T1) | 220 | 35 | 5 |
| During OM grafting off pump (T2) | 83 | 60 | 5 |
| After maneuvers to improve oxygenation (T3) | 90 | 42 | 8 |
| At chest closure attempt (T4) | 70 | 52 | 8 |
| Final successful weaning from CPB (T5) | 208 | 58 | 12 |
| POD 1 in ICU (T6) | 128 | 41 | 10 |
| POD 2 in ICU just before RRT initiation (T7) | 127 | 39 | 10 |

Abbreviations: CPB, cardiopulmonary bypass; FIO2, fraction of inspired oxygen concentration; OM, obtuse marginal artery; PaO2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; POD, postoperative day; RRT, renal replacement therapy; T0-T7, timeline.
had significantly increased (epinephrine 0.12 μg/kg/min, nor-
epinephrine 0.12 μg/kg/min, vasopressin 0.1 μg/kg/min, and
dobutamine 3 μg/kg/min). The CI varied between 1.5 and 1.8
L/min/m², and the systemic vascular resistance ranged between
650 and 750 dynes/s/cm⁻⁵, indicating myocardial pump failure
and a vasodilatatory state. The following morning the chest
was washed to relieve a tamponade. Serum IgG and D-dimer levels
were investigated suspecting COVID-19 convalescence state, as
the perioperative hypoxia was unexplained. The IgG was posi-
tive, indicating prior infection with COVID-19. His D-dimer
level and CRP level were reported high at 1,028 ng/mL and
141 mg/L, respectively. Heparin-induced thrombocytopenia
screen was negative. Due to the coagulopathic state of the
patient, no anticoagulant or antiplatelet therapy was instituted.
The patient developed oliguria, with gradually worsening lactic
acidosis, along with hyperkalemia. Hence, renal replacement
therapy (RRT) was commenced. On the third postoperative day,
the patient manifested bilateral lower limb ischemic changes
and muscle rigidity. High creatine kinase (34,460 U/L) and lac-
tate dehydrogenase levels (1998 U/L) confirmed the diagnosis
of rhabdomyolysis. An arterial Doppler study revealed poor
flow in both the lower limbs. The hyperkalemic state and meta-
bulic acidosis continued to worsen on RRT and culminated in a
 cardiac arrest. Extracorporeal membrane oxygenation was con-
sidered but not offered, given the patient’s advanced critical
state with no reversibility quotient.

Discussion

The authors report this case to highlight the perioperative
complications encountered in managing a convalescent
COVID-19 patient during elective cardiac surgery. Asympto-
tomatic COVID-19 disease continues to be a predominant pre-
sentation in patients infected with SARS-CoV-2. Elective
cardiac surgical services have resumed, with perioperative pro-
tocols aimed at minimizing risk to the healthcare professional
and providing safety to patients from acquiring COVID-19
during their hospital stay. Varied protocols exist depending on
endemic factors and the prevalence of the disease. Screening
with RT-PCR for SARS-CoV-2 is an integral part of the preop-
erative workup. Testing for antibodies as a screening modal-
ity has been reviewed without any conclusion. The patient in
operative RT-PCR tests as per institutional protocol. But the unex-
plained perioperative hypoxemia, excessive bleeding, and
raised D-dimer values triggered IgG antibody testing for
SARS-CoV-2. The presence of these antibodies confirmed the
diagnosis of convalescence of COVID-19.

In the current global COVID-19 pandemic, patients present-
ing for elective cardiac surgery can lie in the symptomatic/
asymptomatic spectrum. Recently recovered COVID-19
patients have cardiac myocardial inflammation, myocardial
edema, fibrosis, and RV dysfunction. A German study,
comprising 100 recently recovered COVID-19 patients
with the confirmed disease (tested by RT-PCR), was followed
up with cardiac magnetic resonance imaging (CMRI). The
majority of these patients received home-based therapy based
on disease severity. Seventy-eight percent of this cohort had
reductions of LV ejection fraction, LV volumes, late gadolin-
ium, and pericardial enhancement. At the time of the CMRI,
70% of these patients had tested positive for high-sensitive tro-
ponin T, whereas only 15% had high-sensitive troponin T dur-
ing their disease period. Endomyocardial biopsy of severely
affected patients has revealed active lymphocytic inflamma-
tion. This observation suggested a similar severity of cardiac
dysfunction in hospitalized and home-based therapy. RV dilata-
tion and dysfunction were predominant echocardiographic
findings in comparison to LV pathology, indicative of RV
involvement secondary to pulmonary lesions. Biventricular
cardiac involvement and secondary changes to pulmonary
pathophysiology result in heart failure, which is a complex
endpoint in COVID-19 patients. Whether these findings are
of significance in convalescent patients and lead to increased
perioperative adverse events is speculative.

Microvascular COVID-19 lung vessels obstructive thrombo-
inflammatory syndrome (Micro CLOTS) is a hypothesis pro-
posed to explain the complement cascade mediated by massive
alveolar epithelial and vascular endothelial damage microvascu-
lar thrombosis. Alveolar capillary microthrombi were nine times
more prevalent in comparison to influenza H1N1 infections. Alveolar
microthrombi were observed in lung biopsies of asympto-
tomatic carriers of COVID-19 as an incidental finding. COVID-
19 is a prothrombotic state, with reports of venous, arterial, and
catheter-related thrombosis. Acute pulmonary embolism contin-
ues to be the most common thrombotic manifestation of COVID-
19. Lower limb ischemia and rhabdomyolysis are potential
complications of IABP-initiated ischemia complicated by a pro-
thrombotic state. Cross-links between inflammation and
prothrombotic state are evident by laboratory markers of raised
D-dimers, fibrinogen, factor VIII, von Willebrand factor, and
decreased antithrombin levels.

The exacerbation of inflammatory cascade in recovered
COVID-19 patients undergoing surgery in convalescence can be
explained by a “first and second hit” theory. The contained
inflammation in the primary disease (first hit) can be exacer-
bated by stimuli of mechanical ventilation, infection, stasis,
thrombosis, bleeding, ischemia, hypoxia, blood transfusions,
and transfusion-related acute lung injury (second hit), and
cause a second uncontrolled inflammatory cascade, culminat-
ing in multiple organ dysfunction syndromes. In such scenar-ios, avoiding the second hit by reducing inflammation with
lung-protective strategies, thromboprophylaxis, early prone
ventilation in the postoperative period, antifibrinolytic therapy
and peripheral vascular screening are evolving concepts.

In the current clinical setting, with the presence of IgG anti-
bodies for SARS-CoV-2 and 2 preoperative negative RT-PCR,
the authors postulated a convalescent phase of recent past
COVID-19 asymptomatic disease in their patient. RT-PCR
continues to be the gold standard for diagnosing COVID-19 to
date. False-negative results vary from 2% to 29% across the
globe due to factors related to viral load, sampling techniques,
and timing of testing in the disease course. Pretest probability
is the clinical likelihood of a person having COVID-19
depending on local COVID-19 prevalence, SARS-CoV-2
exposure history, and symptoms. Pretest probability helps validate the result of RT-PCR or guide further testing. Repeat testing is known to overcome the limitations in RT-PCR sensitivity, but it should be at the discretion of the treating team. Institutional protocol, with testing RT-PCR twice 7 days apart to rule out false-negative results, was followed. With seroprevalence of 0.22% to 47% across the population, the use of antibodies for testing as a routine preoperative screening protocol is far from being cost-effective. But, using antibodies to test inconclusive RT-PCR and RT-PCR not correlating with the clinical scenario is recommended, as was performed in the presented patient in the postoperative period. ELISA for antibodies specific to SARS-CoV-2 were performed and resulted positive for IgG in the presented patient. There are seven types of human coronavirus infections including SARS-CoV-2, SARS-CoV, and MERS-CoV. Cross-reactivity of antibodies across the SARS virus family does exist, but the small number of patients infected per year and the younger age population affected more with the low pathogenicity SARS virus make it clinically less likely for this cross-reactivity to affect the decision-making in the COVID-19 pandemic.11

The first episode of desaturation and hypoxemia possibly was an exacerbated inflammation due to mechanical ventilation (second hit) potentiated by altered hemodynamics during the verticalization of the heart, mitral regurgitation, worsening diastolic function, increased pulmonary capillary wedge pressure, and subsequent pulmonary venous congestion.1 The pulmonary Micro CLOTS pathophysiology evolved extensively during the case, with the lowest recorded PaO2:FIO2 ratio of 70 mmHg. Cardiac dysfunction secondary to residual COVID-19 is speculative unless preoperative CMRI defines myocardial inflammation. Limb ischemia and rhabdomyolysis are extensions of the prothrombotic state complicated by IABP insertion and high-dose vasopressor. Thrombotic microangiopathy was observed to be disproportionately high in COVID-19 patients, even in those not hospitalized. Thoracic microangiopathy is characterized by low platelet count, elevated D-dimer, and LDH levels. These laboratory values are difficult to interpret in the settings of cardiac surgery and CPB, but a preoperative assay might alert the clinician. The role of perioperative dexamethasone in cardiac surgery is not outlined in this setting. The benefits of plasma exchange on CPB and plasma adsorber filtration on RRT are yet to be ascertained in the perioperative cardiac surgical patient.

To conclude, convalescent COVID-19 patients increasingly will present for elective cardiac surgical procedures in the near future. They pose a higher risk in the perioperative phase. Negating the “second hit” by avoiding CPB, ventilation-associated lung injury, postoperative infection states, and transfusion-related acute lung injury is not always feasible. These cases could very easily “snowball” into high resource utilization with a low success rate. Routine testing of IgG antibodies preoperatively, prophylactic steroid therapy, and restratifying surgical techniques are debatable options. Extended evaluation of the heart (CMRI), pulmonary function testing, and coagulation testing (D-dimer and TEG) can be of help in COVID-19-recovered patients for perioperative risk stratification. By default, in the current COVID-19 pandemic, the patient manifesting a severe perioperative inflammatory response should trigger a suspicion of COVID-19 even though they were deemed negative preoperatively by RT-PCR. It is prudent to outline these risks while seeking consent from patients for surgery, as the pathophysiologic manifestations of the COVID-19 disease process during the convalescence phase continue to evolve, with no cardiac risk stratification scoring system in place to encompass this scenario.

References

1 Lisboa Bastos M, Tavaziva G, Abidi SK, et al. Diagnostic accuracy of serological tests for COVID-19: Systematic review and meta-analysis. BMJ 2020;370:m2516.
2 Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-19 identified using magnetic resonance imaging. JACC Cardiovasc Imaging 2020. https://doi.org/10.1016/j.jcmg.2020.05.004; Accessed 10 July 2020. [e-pub ahead of print].
3 Puntmann VO, Carej ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.3557; Accessed 10 July 2020. [e-pub ahead of print].
4 Szekely Y, Lichter Y, Taieb P, et al. Spectrum of cardiac manifestations in COVID-19: A systematic echocardiographic study. Circulation 2020;142:342–53.
5 Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): An atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc 2020;22:95–7.
6 Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endotheliitis, thrombosis, and angiogenesis in covid-19. N Engl J Med 2020;383:120–8.
7 Tian S, Hu W, Niu L, et al. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020;15:700–4.
8 Panigada M, Bottino N, Tagliabue F, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18:1738–42.
9 Teuben MPIJ, Pleifer R, Teuber H, et al. Lessons learned from the mechanisms of posttraumatic inflammation extrapolated to the inflammatory response in COVID-19: A review. Patient Saf Surg 2020;14:28.
10 Woloshin S, Patel N, Kesselheim AS. False negative tests for SARS-CoV-2 infection - challenges and implications. N Engl J Med 2020;383:e38.
11 Ma Z, Li P, Ji Y, et al. Cross-reactivity towards SARS-CoV-2: The potential role of low-pathogenic human coronaviruses. Lancet Microbe 2020;1:e151.
12 Ioannidis J. The infection fatality rate of COVID-19 inferred from seroprevalence data. medRxiv 2020. https://doi.org/10.1101/2020.05.13.20101253; Accessed 10 July 2020. [e-pub ahead of print].
13 Murhekar MV, Bhatnagar T, Selvaraju S, et al. Prevalence of SARS-CoV-2 infection in India: Findings from the national serosurvey, May–June 2020. Indian J Med Res 2020;152:48–60.
14 Kovoor JG, Tivey DR, Williamson P, et al. Screening and testing for COVID-19 before surgery. ANZ J Surg 2020. https://doi.org/10.1111/ans.16260; Accessed 10 July 2020. [e-pub ahead of print].
15 Kellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020. https://doi.org/10.1016/j.jvs.2020.04.483; Accessed 10 July 2020. [e-pub ahead of print].
16 Merrill JT, Erkan D, Winakur J, et al. Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications. Nat Rev Rheumatol 2020;16:581–9.