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End-stage heart failure patients should be treated instantly despite a pandemic with all-time available technology to ensure best outcomes

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Since the earliest cases of coronavirus disease 2019 (COVID-19) infection were reported, our care delivery systems have been reorganized and challenged in unprecedented ways, specifically the cardiovascular community. COVID-19 poses a challenge for heart transplantation, affecting donor selection, immunosuppression, and post-transplant management. Left Ventricular Assist Device (LVAD) therapy is currently a viable option for patients with end-stage heart failure as a bridge to heart transplantation or destination therapy. Here, we present a therapeutic strategy for the management of acute HF with Intermacs profiles from 1 to 4, with or without Covid-19 infection, exemplified by serie of patients presenting with severe HF and successfully treated by LVAD therapy during the spread of the Covid-19 pandemic and the French national lockdown. This experience has shown that we still have the capacity to provide the right therapy for the right disease to the right patient. LVAD implantation seems to be the treatment of choice for advanced HF due to the lack of healthy donor hearts for cardiac transplantation. Covid or non-Covid context, we have to take care of our patients with end-stage HF the best we can.

Coronavirus disease 2019 (COVID-19) is a global pandemic that represents the biggest public health challenge in the 21st century. Since the earliest cases of COVID-19 infection were reported, our care delivery systems have been reorganized and challenged in unprecedented ways, specifically the cardiovascular community.^{1,2} COVID-19 poses a challenge for heart transplantation, affecting donor selection, immunosuppression, and post-transplant management.³

Most clinicians have noted a decline in the number of patients seeking medical care for non-COVID-19-related causes, which has raised concerns for significant collateral

damage in a lot of patients with cardiac disease and, in particular, patients with heart failure (HF), who are tenuous at baseline.⁴ End-stage HF patients were particularly affected not only by the increased risk of acquiring COVID-19 but also by transplant volume reduction to meet intensive care unit (ICU) bed, staffing, and medical equipment needs of the majority non-transplant population. The reduction of organ donors during lockdown period also contributed to their risk.⁵ However, advanced HF continues to be a life-threatening condition carrying a high mortality and morbidity, but which may become far worse during a pandemic.

Left ventricular assist device (LVAD) therapy is currently a viable option for patients with end-stage HF as a bridge to heart transplantation or destination therapy.⁶

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Table 1 Baseline characteristics and follow-up

Patient	1	2	3	4	5	6
Age/gender	51/M	33/F	39/M	57/M	59/M	67/M
Aetiology of HF	Ischaemic	Ischaemic	DCM	DCM	DCM	Ischaemic
Intermacs	4	4	2	3	3	1 (VA-ECMO)
Preoperative COVID-19 RT-PCR	Negative	Negative	Negative	Positive	Negative	Negative
Intended goal of pump support	BTC	BTT	BTT	BTT	BTT	BTD
Intensive care unit length-of-stay before LVAD implantation	2	10	9	12	20	29
Duration receiving LVAD support outside hospital (days)	29	18	22	30	21	72
Follow-up (3 months)	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing

Here, we present a therapeutic strategy for the management of acute HF with Intermacs profiles from 1 to 4, with or without COVID-19 infection, exemplified by series of patients presenting with severe HF and successfully treated by LVAD therapy (HeartMate 3, Abbott) during the spread of the COVID-19 pandemic and the French national lockdown.

Cases series

During the period from 2 March through 6 June, we identified six consecutive critically ill patients with end-stage left monoventricular HF in our institution from Intermacs 1 to 4. Their clinical characteristics are shown in *Table 1*.

Patient 1

A 51-year-old man with ischaemic cardiomyopathy had coronary artery bypass surgery in 2012. He was diagnosed with systolic severe HF with large anterior akinesia and left ventricular ejection fraction (LVEF) at 25%. He developed signs of congestive HF in 2019 with severe pulmonary hypertension (PH). He was Intermacs 4 and despite medical optimization and cardiac rehabilitation, his PH increased to 90 mmHg. He was admitted in February 2020 because of worsening dyspnoea with acute renal failure and hepatic cytolysis. The results of right heart catheterization showed extremely elevated pulmonary vascular resistance (PVR), with low cardiac output (CO) at 1.8 L/min/m². Vasoreactivity testing with inhaled nitric oxide showed partially reversible PH based on decreased PVR from 8.5 to 5.1 Wood Units. After failure of all attempts to stabilize his condition with optimal medical therapy, and because of his PH, we decided to implant an LVAD promptly as a bridge to candidacy. LVAD implantation was performed on 2 March 2020. After the surgery, he needed concomitant transitory percutaneous right ventricular (RV) assistance for 5 days. He had a septic shock on 11 March 2020 cured by antibiotics. He was discharged one month later on 2 April 2020. Today, he is home, well, without signs of COVID-19 infection and with normal pulmonary arterial pressure, awaiting a heart transplant.

Patient 2

A 33-year-old woman had suffered from a transmural anterior wall myocardial infarction in 2019. We performed a coronary angiography, which showed a local dissection in the left anterior descending artery without thrombus nor stenosis. The coronary arteries were otherwise normal. During the following months, she developed severe symptoms of HF. The echocardiography revealed severe dilated cardiomyopathy (DCM) with LVEF at 25%, a low CO, and mild PH, but her RV function was normal. She was Intermacs 4 with three acute decompensations during 1 year. She came to the ICU at the beginning of March 2020 because of severe shortness of breath and postprandial abdominal pain. We decided to do an urgent LVAD implantation as a bridge to transplantation. Our decision was based on our fear not to have a graft on the right time if we decided to transplant first. On the other hand, we wanted to get her home as soon as possible to minimize her potential exposure to COVID-19, while staying in hospital where COVID-19 patients are being admitted every day. Abbott's HeartMate 3TM LVAD implantation was performed on 13 March 2020, with simple post-operative course. At 6 months, she is still perfectly well at home.

Patient 3

A 39-year-old man was diagnosed with idiopathic DCM in 2013 following resuscitation from an out-of-hospital cardiac arrest caused by ventricular fibrillation. Troponin level was persistently low at 0.41 ng/L after this cardiac event and cardiac magnetic resonance showed dilated cardiomyopathy with late patchy contrast enhancement on inferolateral and septal wall without confirm or rule out the diagnosis of acute myocarditis. At that time, we did not have any histologic proof of the aetiology of his cardiomyopathy. The patient was treated with a dual chamber implantable cardioverter-defibrillator (ICD) and usual medications with a good response for three years. He developed ventricular tachycardia (VT) in 2016, and conduction disturbances with complete atrioventricular block. Genetic testing for DCM was negative, as was the standard exhaustive aetiological assessment including infectious diseases. Despite optimal medical treatment and upgrade of

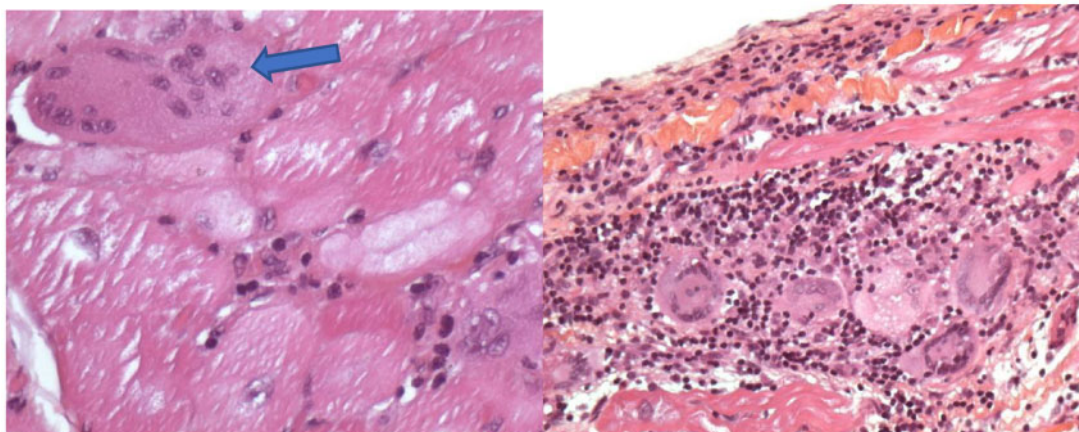


Figure 1 Anatomopathological findings of Patient 3: giant cell myocarditis. Active giant-cell myocarditis with lymphocytes, eosinophils, plasma cells, and prominent multinucleated giant cells are invading the normal myocardium. Inflammatory infiltrate through damaged myocardium showing numerous multinucleated giant cells (arrow) without any evidence of granulomata organization (haematoxylin-eosin, $\times 200$ and $\times 40$).

his ICD with resynchronization, he had two acute HF decompensations in late 2019 and in February 2020.

He was admitted to the ICU in April 2020 for cardiogenic shock. His COVID-19 polymerase chain reaction (PCR) was negative. Cardiac evaluation revealed severe left ventricular hypokinesis, low CO, and good RV function. Despite inotropic support, the patient's liver enzymes and creatinin increased greatly, requiring higher dose of inotropes. In order to achieve haemodynamic stability, a decision was made to give LVAD support as a bridge to transplantation. On Day 9, he was taken to the operating room (OR) for implantation of a HeartMate 3TM LVAD. Anatomopathological findings found giant cell myocarditis (*Figure 1*), which we decided not to treat with immunosuppressive drugs, given the risk for infection (including a potential severe form of COVID-19 infection). Over the next 2 days, dobutamin was weaned and the patient was discharged to the cardiac rehabilitation centre on post-operative day 22. The patient is currently well at home and is awaiting a transplant.

Patient 4

A 57-year-old man presented with out-of-hospital cardiac arrest in 2015. Echocardiography showed DCM with LVEF of 45% and good RV function. Genetic testing showed a mutation in the MYH7 gene, which is a pathogenic variant for hypertrophic cardiomyopathy or dilated cardiomyopathy. He had two atrial fibrillation ablations and VT ablation in 2016. His LVEF decreased to 35% in 2019. He presented with fever and cough at the emergency department on 21 March 2020. COVID-19 was diagnosed in the patient based on rapid test-polymerase chain reaction (RT-PCR) testing. Chest computed tomography (CT) revealed multiple patchy ground-glass opacities in both lower lobes. The initial treatment was supportive, and he was discharged from hospital 2 days later. Almost 1 month later, on 12 April 2020, he called emergency medical services for shortness of breath. He was admitted to the ICU immediately with acute respiratory distress and arterial hypotension. The RT-PCR test for COVID-19 was still positive. Point-of-care cardiac ultrasonography revealed severely depressed left ventricular function (10%), while he was receiving

dobutamine. We did not find a pulmonary embolism or novel infection. Ultra-sensitive cardiac troponin was persistently low. Acute decompensation of cardiomyopathy was irreversible, with a lot of non-sustained VT, and persistent kidney failure. We decided, together with infectiologists, to implant a HeartMate 3TM at least 40 days after the first symptoms of COVID-19 to avoid the spread of infection in the OR to our medical staff despite personal safety protection measures. The first negative result for RT-PCR was on 21 April 2020, 1 month after his first symptoms. The surgery was scheduled on 27 April 2020. He was discharged 30 days later, after surgical pericardial and pleural drainage at post-operative day 9. The anatomopathological findings showed hypertrophic cardiomyopathy with no signs of acute myocarditis. Furthermore, he's on continued LVAD support with persistent low LVEF, confirming irreversible HF.

Patient 5

A 59-year-old man was diagnosed with idiopathic DCM in 2012. He became a frequent flyer in 2019 despite optimal medical management and cardiac resynchronization therapy, and in December, he had his first cardiogenic shock event requiring dobutamin. He went to the cardiac rehabilitation centre in January and then came to our centre for pre-operative evaluation for heart transplantation without contraindication. Unfortunately, he was admitted for cardiogenic shock on 15 April 2020 and had atrial fibrillation. Despite atrioventricular node ablation, he remained in refractory shock. He was listed for heart transplantation, but after waiting for 10 days without call for a graft, we decided to perform a HeartMate 3TM implantation on 4 May 2020 as a bridge to transplantation. After a few days on IV dobutamin, he had a simple postoperative course and left our institution for cardiac rehabilitation 21 days later. He had a pleural effusion many weeks later which was drained, and today he's perfectly well, with ongoing LVAD support, and without COVID-19 infection.

Patient 6

A 66-year-old man presented with ischaemic cardiomyopathy. He had an anterior myocardial infarction in 2018 with many clinical sequelae. His LVEF was 20% with persistent severe symptoms of HF despite medical treatment and resynchronization therapy. His past medical history included a stroke in the middle cerebral artery territory, and another one in the cerebellar territory whose origin was cardioembolic, but with few clinical sequelae. He had severe PH (pulmonary arterial pressure at 81 mmHg and SVR 5 Wood Units). An LVAD was planned as bridge to decision. Unfortunately, on 4 June 2020, he developed acute pulmonary oedema and cardiogenic shock. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) was inevitable to stabilize his condition. He received a HeartMate 3™ on 9 June 2020. The post-operative course was complicated: RV failure, tracheotomy, pleural drainage, multiple sepsis, and paresis acquired in the ICU. He left the ICU after being weaned of his tracheotomy 2 months later, and is currently in ambulatory state on LVAD support in our cardiac rehabilitation centre.

Discussion

This single-centre case series describes six successful HeartMate 3™ implantations during the French national lockdown due to the COVID-19 pandemic. All patients survived, and five were discharged within 30 days following implantation. One patient contracted COVID-19 infection before LVAD implantation and developed cardiogenic shock within 21 days. Though some cardiac injuries are reversible in the context of COVID-19 infection, preexisting cardiac conditions may be exacerbated by COVID-19 and result in severe chronic HF.⁷ All patients tested negative by COVID-19 RT-PCR on nasopharyngeal swab test preoperatively to authorize the surgery. The five other patients did not contract the virus after implantation with standard precautions of care. Social distancing and strict precautions applied by caregivers has been applied for those patients considered vulnerable.

For some doctors, the need to protect caregivers and preserve critical care capacity may affect their decisions. For everyone, radical transformation of the healthcare system will affect the ability to maintain high-quality care.⁸ Our major focus has been to prevent high-risk patients with chronic disease from infection. But our experiences show that patients with serious chronic disease, such as HF, may have changed their behaviour if symptoms occurred to avoid hospitalizations. Amplifying the messages that those with chronic conditions should practice social distancing and stay home may have confused and frightened patients with HF, leading them to delay evaluation for advanced congestive or low output symptoms, and result in worse outcomes.⁹ In a recent Danish report, the admission rates for worsening HF and the incidence rates of new-onset HF declined by 30% in Denmark after the country's lockdown. However, the 15-day mortality rate for admitted HF patients with COVID-19 diagnosis was 37%.¹⁰

Additionally, many centres have inactivated the heart transplant waiting lists to meet ICU bed, staffing, and

medical equipment needs of the majority non-transplant population.¹¹ Furthermore, a lack of donors was observed and seems to be multifactorial: safety measures applied to organ procurement organizations, mandatory PCR test, CT scans to exclude possible asymptomatic COVID carriers, less car accidents, and less non-COVID patients admitted to ICUs due to confinement leads to less potential organ donors.

Answers to many questions remain unclear, including still limited available knowledge of the virus and its impact on heart transplant recipients compared to patients on LVAD support. A theory about the potential protective effect of immunosuppression has been reported, mitigating the 'cytokine storm' related to COVID-19 poor outcomes.¹² Dexamethasone may reduce mortality for patients receiving either invasive mechanical ventilation or oxygen alone in a recent study.¹³ In the other hand, in a recent report of 28 heart transplant recipients with COVID-19, 79% were hospitalized, 25% required mechanical ventilation, and 25% died, suggesting poor outcomes.¹⁴

Conclusion

In this unprecedented context, our main goal was to evaluate ways to treat people with non-COVID-19-related disease, especially in patients with end-stage HF. Left ventricular assist device implantation has been considered in our centre as a first choice to treat patients to get at-risk patients home and out of the hospital, minimizing their exposure to COVID-19. Left ventricular assist device therapy presents several advantages, especially in the context of a pandemic; it is always available, which allowed us to anticipate and plan implants in the OR, and secure ICU beds. As well, by implanting earlier (Intermacs 4), we improved patient status by stabilizing their condition and keeping them safe at home. We also may have been able to reduce hospital length-of-stay as patients' physical condition at baseline was associated with less complications.

This experience has shown that we still have the capacity to provide the right therapy for the right disease to the right patient. Left ventricular assist device implantation seems to be the treatment of choice for advanced HF due to the lack of healthy donor hearts for cardiac transplantation. COVID or non-COVID context, we have to take care of our patients with end-stage HF the best we can.

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