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Two consecutive major lower limb operations in a heart-lung transplant recipient during COVID pandemic: A case report and literature review

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Abstract
Introduction: Combined heart and lung transplant is a rare procedure performed for patients with congenital heart disease and end stage pulmonary disease. Due to improvement in survival, non-cardiac surgeries are frequently performed in these patients and anaesthetists are involved in their perioperative management. Apart from increasing the physical and mental health risks, COVID-19 pandemic has posed an additional challenge to health care providers in the management of these immunosuppressed patients.
Case presentation: We report a case of a 64-year-old female patient with a previous combined heart and lung transplant who underwent two consecutive lower limb surgeries during COVID pandemic.
Conclusion: Meticulous preoperative assessment involving multidisciplinary team, knowledge of the pathophysiology of heart–lung transplant patients, choosing appropriate anaesthetic technique is vital in successful management of these patients. Psychological implications of COVID-19 pandemic in immunosuppressed patients should be considered.

Keywords: Heart-lung transplant, COVID-19, immunosuppression, regional anaesthesia, general anaesthesia, mental health

Introduction
Combined heart and lung transplant (HLT) is a rare procedure in contrast to isolated heart or lung transplants. As per the interim report on cardiothoracic organ transplantation [1], 16 combined heart lung transplants were performed in UK from October 2017 to September 2020, whereas during the same period 460 heart-only and 441 lung-only transplants were performed. HLT is primarily performed for patients with congenital heart disease complicated by pulmonary hypertension, or end stage pulmonary diseases such as cystic fibrosis, emphysema and alpha-1 anti trypsin deficiency [2]. These patients are often young, and survival rates are 71% at 3 months, 63% at 1 year and 44% at 5 years [3]. As the survival rates improve, these patients are more likely to present for non-cardiac surgery, presenting their clinicians with a few specific perioperative challenges. The COVID-19 pandemic poses additional specific physical and mental health risks for these patients. There is very little evidence or guidance in the literature for managing such cases.
We report anaesthetic and perioperative management of a patient with heart-lung transplant who underwent two successive major lower limb procedures during COVID-19 pandemic.

Case report
A 64-year-old retired psychologist was scheduled to have left femur intramedullary nailing to prevent an imminent pathological fracture during the first wave of the COVID pandemic. She had a combined heart-lung transplantation 18 years previously for Eisenmenger's syndrome. She also suffered from hypertension, Parkinson's disease, protein C deficiency and chronic kidney disease. She had a single kidney following a nephrectomy in her childhood. Due to long term steroid therapy, she had osteoporosis and was under the care of a metabolic bone clinic. Her regular medications included tacrolimus 2 mg twice a day, prednisolone 3.5 mg once daily for immunosuppression, candesartan, alendronate, calcium tablets, aspirin, co-beneldopa and cotrimoxazole. She sustained an atypical subtrochanteric stress fracture of her left femur which was attributed to long term bisphosphonate therapy for osteoporosis.

She was at risk of the stress changes in the bone progressing to a complete unstable fracture, so her surgery was expedited and was performed as soon as elective limb reconstructive surgery was resumed at our institution at the end of the 1st wave, in June 2020.

She was seen jointly by the consultant orthopaedic surgeon and anaesthetist in a preoperative assessment clinic at the time when regular preoperative anaesthetic clinics had to be stopped due to COVID pressures on the staff. Surgical and anaesthetic options including the risks of delaying surgery until after the pandemic were discussed at length. After careful consideration of risks and benefits of general vs neuraxial anaesthesia during the COVID pandemic and thorough discussion with the patient, the patient consented for neuraxial anaesthesia with audio-visual distraction and sedation if required.

The patient's preoperative cardiovascular examination revealed the presence of both heart sounds with no murmur. She had good exercise tolerance, with no chest pain, orthopnoea, paroxysmal nocturnal dyspnoea or pedal oedema. On respiratory examination, she had a good bilateral air entry with no wheeze or added sounds. The airway examination revealed good mouth opening, Mallampati grade 1 and full range of neck movements. The investigations were as follows: Hb-134 g/L, platelets- 219 X 10^9/L, urea- 10.3 mmol/L, creatinine- 117mmol/L, eGFR- 42ml/min/1.73 m^2. The coagulation profile, liver function tests and serum electrolytes were within normal limits. The ECG showed sinus rhythm with a resting heart rate of 96bpm.

The patient's transplant centre was contacted. She was on 6-monthly follow up and her last visit to the transplant centre was 4 months prior. Her latest echocardiography revealed good left ventricular systolic function with an ejection fraction of 68%. Right ventricular function was within normal limits and she had no significant valvular abnormalities. Her lung function tests were stable with FeV1- 2.4 L and FVC- 3.4 L. Her chest X-ray revealed hyper-expanded lung fields but no other abnormalities. Pre-operative tacrolimus levels were 4.6 ng, within the normal target range of 4-6 ng. As per the advice from the transplant team, her prednisolone dose was increased to 7 mg once daily prior to surgery. She showed no symptoms of acute rejection. Due to the COVID pandemic, cardiac biopsy was not performed.

The patient was admitted to the hospital after strict isolation for 14 days prior to surgery and a negative COVID PCR test done 3 days before the surgery.

The hospital policy at the time was to wear level 2 personal protective equipment (PPE) for procedures involving aerosol generating bone surgery. As per the policy, all the procedures were performed with level 2 PPE. On arrival in the anaesthetic room, pulse oximetry, automated non-invasive blood pressure measurement and electrocardiography were applied. 20G and 18G intravenous cannula were inserted. An invasive arterial line was inserted in the right radial artery. Under full aseptic precautions, combined spinal and epidural anaesthesia (CSE) was performed with the patient in sitting position, at the L 4-5 interspace. An epidural catheter was inserted using the loss of resistance technique at 4.5cms and fixed at 10 cm to the skin. 3 ml of 0.5% heavy bupivacaine with 200 mcg of preservative-free morphine was administered intrathecally, and a sensory level at T10 was achieved. The patient remained stable throughout the surgery. Blood loss was minimal and she had 1.5 L of compound sodium lactate solution. After the surgery, she was transferred to the post-operative recovery unit.

During her stay in the recovery unit, there was one episode of the patient feeling dizzy and complaining of chest pain. Examination revealed hypotension which responded to 0.5 mg of metaraminol. A 12-lead ECG was done and showed no new changes. The epidural catheter was removed in recovery as the epidural follow-up services were disrupted during the COVID pandemic. The patient was prescribed oxycodone patient-controlled analgesia (PCA), regular paracetamol and PRN oral morphine for post-operative pain relief. She was transferred to a side room in the ward. As per the advice of infection control department, a physiotherapist and a nurse were exclusively designated to look after the patient and entry to the patient's room was minimised to prevent COVID transmission during hospital stay.

Postoperatively she continued to experience severe pain. Acute pain service (APS) team were involved early but despite multiple changes and titrations in the analgesic regimen, the patient was in distress and suffered from nausea and vomiting secondary to opioids. She was unable to perform physiotherapy due to pain. On post-operative day 5, X- ray and CT scan of the operated femur were performed and, unfortunately, revealed an undisplaced extraarticular periprosthetic fracture extending up to the neck of the femur. During the initial surgery a reconstruction nail was used. Consequently, further surgery was considered appropriate to exchange the proximal locking bolt for cephallomedullary fixation.

In addition, the patient's tacrolimus levels reduced to 3ng and after advice from the transplant team, the tacrolimus dose was increased to 3 mg twice a day and prednisolone to 15mg once a day.

During the pre-assessment prior to the second –urgent-operation, the patient was found to be in a very low mood, tearful, extremely anxious about undergoing a second major surgery within a week from the initial surgery, fearful about contracting COVID and dying in the hospital. The situation was made worse by the fact that at the time no relatives were allowed to visit patients and that on site clinical psychology services were unavailable due to pandemic restrictions. Therefore, psychological counselling was done mostly by the anaesthetic team on the day of surgery and postoperatively, with all the limitations.

The second procedure involved removal of the locking screws from the femoral nail and insertion of new screws into the femoral head. CSE with invasive arterial monitoring was again the technique of choice, albeit with moderate/deep sedation with Propofol TCI on the patient's request. The surgery was uneventful and patient was stable throughout the surgery. Postoperatively, the patient was transferred to a high dependency unit (HDU) for overnight stay; the epidural infusion continued for pain relief. On postoperative day 2, before discharging from the HDU, the epidural catheter was removed and morphine PCA and regular analgesics were prescribed. Following discharge to the ward, patient's pain persisted though to a lesser degree and required regular follow-ups from the APS. Postoperatively she continued to suffer from anxiety and fears. This was recognised and consequently we ensured very close follow-up reviews on a daily basis, as well as

offering psychological support. Subsequently, the patient made successful recovery and was discharged home without any concerns.

Discussion

Heart-lung transplant patients may need operations for various transplant and non-transplant related conditions [4]. Advances in transplantation techniques, immunosuppression and improved anaesthetic management and post-operative care have contributed to an improving survival rate [5]. General surgical procedures are more commonly performed in these patients [6]. According to Bhatia *et al*. [7], orthopaedic procedures are required in 8% of the orthotopic heart transplant patients. The indications include fractures and dislocations, osteoarthritis, and femoral head avascular necrosis. Complications include intraoperative fractures, wound infection, bleeding, prosthetic dislocations, pulmonary embolism, pneumonia and acute kidney injury [8]. Although our centre is a quaternary referral centre, to our knowledge, this is the only such case, with the added challenges of performing the case during the COVID-19 pandemic.

Physiology of transplanted heart and specific anaesthetic considerations

Cardiac transplantation involves removal of the diseased heart, transection of the aorta, main pulmonary artery and denervation of the heart [5]. The atrial cuff of the recipient is left behind. Even though it remains innervated, conduction does not occur through the atrial suture line. As a result, the ECG may contain 2 P waves, the 2nd P wave originating from the donor atrium. However, intrinsic cardiac mechanisms such as the Frank-Starling effect, and formation of impulses are well preserved. Alpha and beta adrenoreceptors are intact and the heart responds normally to circulating catecholamines [9, 10]. The denervated heart lacks the ability to maintain the cardiac output with reflex tachycardia in the presence of hypovolemia or vasodilatation [11]. Therefore, cardiac output is primarily dependent on preload and is initially augmented via increased stroke volume and subsequently maintained by increased heart rate, secondary to circulating catecholamines.

In the absence of parasympathetic innervation, the transplanted heart has a resting heart rate of 90-100 beats per minute. Valsalva manoeuvre and carotid massage have no effect on heart rate. The transplanted heart may be more susceptible to arrythmias [12]. First degree heart block is common. 20% of the patients may require a pacemaker for bradyarrhythmia [13]. Although, significant ventricular arrythmias are uncommon, their presence indicates possible graft rejection or coronary artery disease [4]. Heart rate does not respond to muscle relaxants such as pancuronium, anticholinergics such as atropine and glycopyrrolate, anticholinesterases and digoxin, nifedipine, phenylephrine or nitroprusside [5]. However, direct acting drugs such as adrenaline, isoprenaline and ephedrine increase the heart rate. Ephedrine has both direct and indirect actions and its overall effect is said to be reduced [11]. Exercise capacity is suboptimal after cardiac transplantation. Oxygen delivery, peak cardiac output and heart rate are reduced in these patients [17].

The transplanted heart is susceptible to coronary atherosclerosis. Coronary artery disease is seen in 10-20% of the patients after one year and in up to 50% by 5 years [14]. Immunological injury, ischemic injury or presence of risk factors such as smoking, hypertension, diabetes and hyperlipidaemia or their combination are implicated in atherosclerosis [5]. Myocardial ischemia is usually silent in these patients. There is some evidence that cardiac reinnervation is possible and this may explain angina, vasovagal episodes and cardiac arrest after administration of neostigmine [15, 16].

Physiology of transplanted lungs and specific anaesthetic considerations

Physiological consequences of lung transplantation are due to disruption of innervation, lymphatics and bronchial circulation. The transplanted lung is denervated distal to the bronchial anastomosis. Due to alterations in the mechanics of the rib cage and vertebral column secondary to thoracotomy, there is a large decrease in total lung capacity (TLC), forced expiratory volume (FEV1) and forced vital capacity (FVC) in the early post-operative period [18]. However, the lung functions return to preoperative values by 6 months [19].

As a result of denervation, the cough reflex is not elicited distal to the anastomosis. Therefore, the patients will be able to protect their airways only when fully awake and extubation should be delayed until the patient is fully conscious and responding to verbal commands [20]. Denervation does not appear to affect the transplanted lung's response to exercise and carbon dioxide [21]. The lymphatic drainage is disrupted during transplantation. As a result, the transplanted lung is particularly vulnerable to pulmonary oedema. Cautious fluid administration is recommended [2].

Lung function tests may be normal, but lung compliance is reduced and ventilation-perfusion mismatch may occur [11].

Rejection and specific anaesthetic considerations

Rejection can be acute or chronic. 60% of the acute rejections occur within 3 months of transplantation [22] but it can happen at any time. Chronic rejection of the heart can be manifested as accelerated coronary atheroma and myocardial ischemia. Since patients with a denervated heart do not experience chest pain, they may complain of excessive tiredness and dyspnoea which may progress to heart failure [23]. Bradyarrhythmias are often seen during episodes of rejection. Yearly coronary angiography is performed in many centres. Lung rejection is often characterised by symptoms similar to chest infection, such as dyspnoea, fatigue, desaturation with or without pyrexia and radiological changes. Bronchoalveolar lavage and transbronchial lung biopsy can distinguish between the two conditions.

In combined HLT patients, chronic rejection mainly affects the lungs in the form of obliterating bronchiolitis with deteriorating lung functions. Patients with suspected rejection should be managed in transplant centres as surgery and anaesthesia in the presence of rejection poses a significant clinical challenge and is accompanied by increased morbidity and mortality.

Immunosuppression and other drugs

Cyclosporin, tacrolimus, azathioprine, mycophenolate mofetil and corticosteroids are common immunosuppressive drugs used in heart-lung transplant patients. In addition to

these drugs, patients are often on anti-hypertensive agents, diuretics, antifungal and antiviral agents. Vitamin D, calcium and bisphosphonates are often prescribed to treat osteoporosis and improve bone density. The detailed discussion of these drugs are beyond the scope of this article. However, major side effects including hepatotoxicity, nephrotoxicity and drug interactions with neuromuscular blocking agents should be borne in mind.

COVID pandemic and psychological stress

Transplant patients have been burdened by additional stress in the wake of COVID-19 pandemic. Immunosuppression, accompanying comorbidities increase the risk of poor COVID-related outcomes [24]. High rates of anxiety, depression and post-traumatic stress disorder have been reported during the COVID pandemic [25]. Transplanted patients also have increased risk of developing mental health issues [26]. Fear of contracting COVID-19 during hospital stay, isolation from families, stress of the major surgery can contribute to anxiety and fear of death as seen in our patient. Further, the detrimental effect of psychological factors on post-operative surgical complications, pain, length of stay, higher health care cost and quality of life has been well established [27].

Preoperative evaluation

The following preoperative investigations should be performed: full blood count, serum electrolytes, urea and creatinine ECG, chest x-ray, pulmonary function tests, liver function tests, echocardiography.

The patient's transplant centre should be contacted as early as possible and all the relevant details regarding immunosuppressive drug therapy, recent angiography and biopsy results should be obtained. Ensuring that there are no signs and symptoms of acute rejection is vital. Blood levels of immunosuppressive agents should be measured and any adjustments to the dose made under transplant team's guidance. Medications should be continued up to the day of operation.

A multidisciplinary team involving surgeons, anaesthetists, transplant specialists, psychologists should perform pre-operative evaluation and planning in order to improve patient outcome and satisfaction.

Anaesthetic technique

General and regional anaesthesia are thought to be safe in HLT patients who have no signs of rejection [28, 29]. No technique has been found to be superior to the other.

During general anaesthesia, airway management may pose difficulties due to Cushingoid features secondary to chronic steroid therapy. Both intubation and extubation should be smooth in order to avoid damage to the tracheal suture line. The induction agents used during general anaesthesia reduce preload and depress the myocardial activity and may lead to severe hypotension [5], so doses should be careful titrated. Volatile agents are well tolerated. Muscle relaxants like suxamethonium, atracurium and vecuronium have been used without any problems in heart and lung transplantation [5, 30]. However, data in combined heart-lung transplantation is scarce. General anaesthesia carries an increased risk of post-operative chest infection due to the loss of cough reflex and impaired mucociliary clearance. As discussed above, patients need to be completely reversed and conscious before extubation [11].

Both spinal and general anaesthesia has been administered successfully in heart-lung transplant patients. Although there is a concern about exaggerated hypotensive response, neuraxial anaesthesia has been successfully administered in well hydrated patients with minimal haemodynamic changes [20].

Careful fluid administration is recommended in order to avoid pulmonary oedema. On the other hand, dehydration can lead to severe hypotension and increases the risk of nephrotoxicity of immunosuppressive agents. Standard peri-operative monitoring such as ECG, oxygen saturation, non-invasive blood pressure, end tidal carbon dioxide is mandatory. The need for invasive arterial line and central line has to be determined on an individual basis considering the risks and benefits. Our patient had invasive arterial line sited during both the procedures. We felt that risks of siting the central venous catheter would outweigh the benefits in our patient. Appropriate antibiotic prophylaxis should be administered and transplant patients may need prolonged antibiotic therapy post-operatively.

The potential benefits of regional anaesthesia over general anaesthesia during COVID pandemic have been widely discussed [31]. They include avoidance of aerosol generating procedures (intubation and extubation), reduction in resource and financial costs of personal protective equipment, preservation of immune function, improved post-operative analgesia and earlier discharge. However, the authors do stress that anaesthetic choices should be tailored to the needs and wishes of the patient.

Post-operative care

Post-operative care setting depends on pre-operative condition, proposed surgery and perioperative events. Multidisciplinary team including acute pain physicians, physiotherapists, clinical psychologists, surgeons and transplant team should be actively involved in post-operative management. Particular attention should be paid to reported pain scores as pain disproportionate to the surgery may indicate complications, as in our case. Fluid balance, and signs of infection have to be carefully monitored.

Immunosuppressive drugs should be continued post-operatively. Blood concentrations should be maintained within the therapeutic range. Advice of the transplant team should be sought in case the dose or regimen needs to be modified [20].

Redeployments, shortage of staffing due to isolations, working from home, etc. during the COVID pandemic lead to disruption of many patient services as seen in our case. All possible support should be given to the patients using available resources. Additional care must be taken to make sure that the immunocompromised patients are cared for in a COVID-safe environment. Hospital staff including doctors, nurses, physiotherapists, pharmacists, porters etc who are involved in the care of immunosuppressed patients should avoid coming in contact with suspected or true COVID positive patients as much as possible. Local hospital policy should be strictly adhered to.

Conclusion

In the future, HLT patients will increasingly present for non-transplant-related surgery. Thorough pre-operative assessment by a multi-disciplinary team involving anaesthetist and surgeon, preoperative anaesthetic

assessment and APS teams with input from the transplant centre team and, if required, an on-site clinical psychologist is essential. Appropriate anaesthetic technique should be selected on an individual basis, with certain advantages of neuraxial anaesthesia as demonstrated in our patient. The particular pathophysiology of HLT should be considered. With the COVID pandemic continuing to impact healthcare across the world, it is imperative to consider its implications on peri-operative management, selecting appropriate anaesthetic technique and psychological support for these challenging patients.

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