

Case Report

The effect of coincidental SARS-CoV-2 infection on pre-operative cardiopulmonary exercise testing

C. Whitfield,¹ M. Adamson² and R. Davies²

1 Specialty Trainee, 2 Consultant, Department of Anaesthesia, University Hospital of Wales, Cardiff, UK

Summary

This case report demonstrates the significant impact active infection with SARS-CoV-2 can have on functional capacity evaluated by cardiopulmonary exercise testing, even in minimally symptomatic individuals. A 75-year-old man underwent cardiopulmonary exercise testing before a right hemicolectomy; SARS-CoV-2 was incidentally diagnosed following his test. The patient underwent a period of isolation and recovery before a second pre-operative cardiopulmonary exercise test 6 weeks later. His resting pulmonary function tests did not vary between tests but his peak work, anaerobic threshold, oxygen pulse, pulse oximetry nadir, ventilation perfusion matching and heart rate response to exercise all improved significantly after this recovery period. These are unique results that add to the existing knowledge of the pathophysiology and management of SARS-CoV-2 in the peri-operative setting. While our patient demonstrated dramatic improvement in his functional capacity following 6 weeks of recovery, he remained in a high-risk group for surgery according to our local guidelines. Cardiopulmonary exercise testing has a valuable role in individualised risk assessment and shared decision-making in complex, urgent surgical cases where the benefits of delaying surgery to recover from SARS-CoV-2 infection should be balanced against the potential risks.

Correspondence to: M. Adamson
Email: Michael.Adamson@wales.nhs.uk

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Introduction

Cardiopulmonary exercise testing (CPET) provides an array of physiological data relating to a patient's response to graded exercise. This is widely used in pre-operative risk stratification to aid clinical decision-making regarding choice of surgical technique and suitability for major surgery. CPET also helps inform patients about their personal peri-operative risk.

COVID-19 is known to have a wide spectrum of clinical impacts, including silent presentation, on a variety of age groups. However, little information exists as to its influence on CPET findings [1]. In this report, we demonstrate the significant impacts on CPET results in a case where SARS-CoV-2 infection was identified following a grossly abnormal cardiopulmonary exercise test in the pre-operative assessment clinic. Furthermore, we wish to highlight that there was a marked improvement in his results on repeat testing, undertaken 44 days later, after a period of isolation and the resolution of his symptoms.

Report

A 75-y-old man (height 172 cm; weight 94 kg; BMI 31.8 kg.m⁻²) attended anaesthetic pre-operative assessment clinic before a planned right hemicolectomy for colonic cancer. His past medical history included hypertension, gout and iron deficiency

anaemia (haemoglobin 90 g.dl^{-1} , ferritin $8 \text{ } \mu\text{g.l}^{-1}$). He had never smoked, and his alcohol consumption was 60 units per week. His exercise tolerance was limited by dyspnoea on walking uphill. A resting ECG demonstrated first-degree heart block.

As part of his pre-operative assessment and risk stratification, he underwent CPET. Before the test, he did not trigger any of the COVID-19 symptom screening questions and his temperature was $36.5 \text{ }^\circ\text{C}$. Cardiopulmonary exercise testing was conducted on a cycle ergometer with a 15-Watt ramp protocol. His CPET was terminated after 6 min of exercise due to shortness of breath. He achieved a peak work of 52 Watts (46% predicted). Anaerobic threshold was not reached, but his peak oxygen consumption was $8.5 \text{ mlO}_2.\text{kg}^{-1}.\text{min}^{-1}$ (44% predicted). His ECG demonstrated no ischaemia or arrhythmia during exercise, but the heart rate response to exercise, oxygen pulse and change in oxygen consumption with increasing work rate ($\Delta \text{VO}_2/\text{WR}$) slopes were flattened (Fig. 1), consistent with oxygen delivery limitation. Resting pulmonary function tests were unremarkable (Table 1) but the ventilatory equivalents slope for carbon dioxide (VE/VCO_2) was 55, suggesting significant ventilation-perfusion mismatching. His peripheral oxygen saturations (S_pO_2) fell to 90% at peak exercise. Failure to reach an anaerobic threshold $\geq 11.0 \text{ mlO}_2.\text{kg}^{-1}.\text{min}^{-1}$, and a $\text{VE}/\text{VCO}_2 > 34$, placed this patient in a high peri-operative risk group according to our local risk stratification criteria.

The CPET findings suggested that this patient had significantly reduced exercise capacity with features consistent with heart failure. He was considered very high risk for major surgery and transthoracic echocardiogram and iron transfusion were arranged for the same day. Routine measurement of observations before the iron infusion revealed a temperature of $37.8 \text{ }^\circ\text{C}$, and he reported feeling generally fatigued. The patient was sent to a community testing centre for a SARS-CoV-2 polymerase chain reaction test and his iron infusion and echocardiogram were postponed. The SARS-CoV-2 test was positive and he underwent 14 days of isolation.

The patient did not require hospitalisation but felt fatigued for several weeks. He returned to pre-operative assessment clinic 6 weeks following his initial clinic appointment, allowing time for recovery from SARS-CoV-2 infection. Transthoracic echocardiogram showed normal left ventricular function (ejection fraction $>55\%$) and no significant structural abnormalities. His second CPET was conducted 30 min after an intravenous infusion of 1.8 g ferric derisomaltose. His test was terminated due to leg fatigue after 11 min of exercise, having reached a peak work of 118 watts (108% predicted). His anaerobic threshold was $9.0 \text{ mlO}_2.\text{kg}^{-1}.\text{min}^{-1}$ and peak oxygen consumption $16.1 \text{ mlO}_2.\text{kg}^{-1}.\text{min}^{-1}$ (80% predicted). Oxygen pulse, heart rate

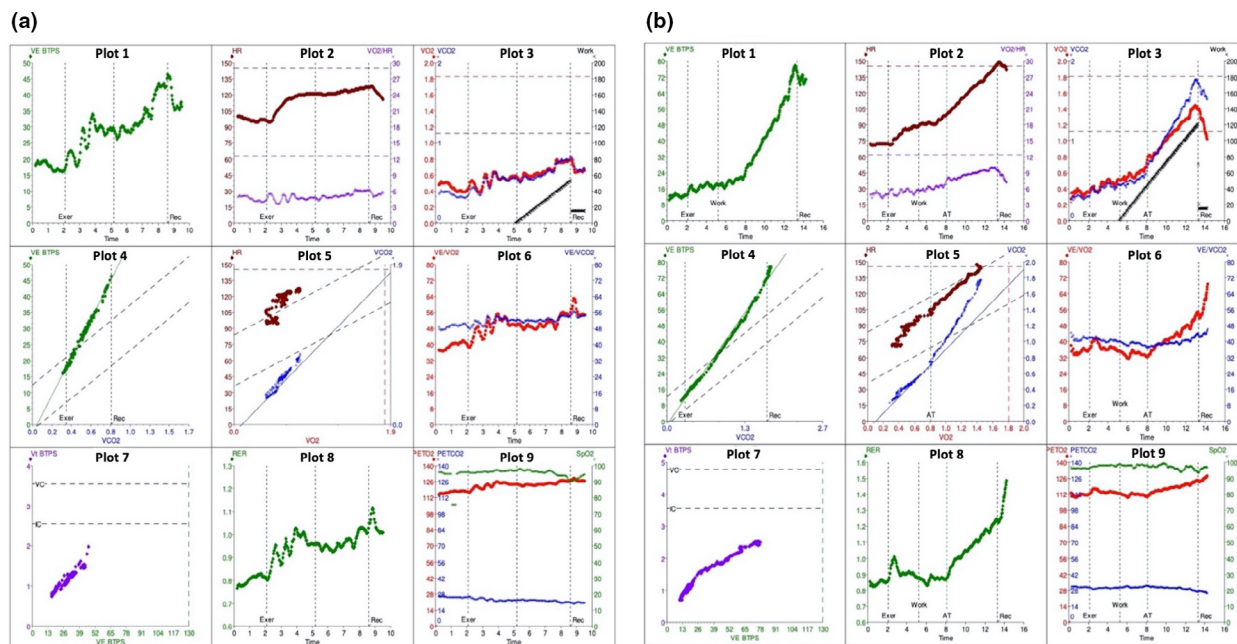


Figure 1 Nine-panel plots displaying results obtained from (a) the initial cardiopulmonary exercise test ; and (b) the repeat cardiopulmonary exercise test 6 weeks later. Comparison of plot 2 between tests demonstrates the change in heart rate response (maroon) and oxygen pulse (purple). Comparison of plot 3 between tests demonstrates the change in the $\Delta \text{VO}_2/\text{WR}$ gradient (red). Comparison of plot 4 between tests demonstrates the improved VE/VCO_2 gradient (green).

Table 1 Comparison of cardiopulmonary exercise testing (CPET) findings between baseline and 6 weeks after SARS-CoV-2 infection.

Variables	Baseline CPET while positive for SARS-CoV-2	CPET six weeks after SARS-CoV-2 infection, following recovery)	% Change
Reason for terminating CPET	Shortness of breath and dizziness	Leg fatigue	N/A
Peak work	52 Watts (46% predicted)	118 Watts (108% predicted)	+126%
Peak VO ₂	8.5 mlO ₂ .kg ⁻¹ .min ⁻¹ (44% predicted)	16.1 mlO ₂ .kg ⁻¹ .min ⁻¹ (80% predicted)	+89%
Anaerobic threshold	Not reached	9.0 ml.kg ⁻¹ .min ⁻¹	N/A
VE/VCO ₂ slope	55	37	-24%
O ₂ pulse trajectory	Flattened	Normal	N/A
Delta VO ₂ /WR slope	Flattened	Normal	N/A
Heart rate response	Flattened	Normal	N/A
Oxygen uptake efficiency slope	996	1460	+47%
FEV1	114% predicted	114% predicted	No change
FVC	121% predicted	124% predicted	+3%
FEV1/FVC ratio	0.71	0.69	N/A

FEV1, forced expiratory volume; FVC, forced vital capacity.

response and Δ VO₂/WR slope were normal consistent with normal oxygen delivery (Fig. 1). Resting pulmonary function tests were unchanged (Table 1) but his VE/VCO₂ at anaerobic threshold was 37 and there was no oxygen desaturation during exercise. The repeat CPET demonstrated remarkable improvement in his cardiorespiratory fitness following recovery from SARS-CoV-2 infection; however, he was still considered high-risk for major surgery as per local CPET risk stratification.

Nineteen days following his second CPET and intravenous iron infusion, the patient underwent laparoscopic right hemicolectomy according to our local colorectal enhanced recovery protocol. His pre-operative haemoglobin was 131 g.dl⁻¹ and he avoided peri-operative blood transfusion. Postoperatively, he was electively admitted to the post-anaesthesia care unit (PACU) and was discharged home 2 days postoperatively.

Discussion

Infection with SARS-CoV-2 is associated with a spectrum of manifestations ranging from asymptomatic infection to devastating multi organ-system disease. This report illustrates that a patient with minimal symptoms suffering from only minor fatigue and a mild pyrexia, may have significant cardiorespiratory abnormalities uncovered by CPET. Our patient had very high ventilatory equivalents for carbon dioxide, indicating a significantly increased dead space and ventilation-perfusion mismatch. The patient underwent oxyhaemoglobin desaturation to 90% at peak exercise and this was associated with a reduced peak workload and peak oxygen consumption, flattening of oxygen pulse, heart rate response and Δ VO₂/WR slope. These findings are consistent with inadequate cardiovascular compensation to hypoxia. Ageing is known to decrease sympathetic nervous system responses to hypoxic stress, thus contributing to decreased tolerance of hypoxia in older individuals [1]. However, this case demonstrates the potential sequelae of SARS-CoV-2 to compound this phenomenon, a finding of particular relevance in elderly surgical patients. Notably, resting pulmonary function tests performed before CPET showed no abnormalities, a finding which is consistent with other reports of lung function testing in SARS-CoV-2 [2].

SARS-CoV-2 is thought to bind to the angiotensin converting enzyme (ACE)-2 receptor, which normally catalyses the hydrolysis of angiotensin 2. The ACE-2 receptors are expressed in many tissues, but most abundantly in the upper and lower respiratory tract [3]. In some patients, when the virus reaches the lower respiratory tract it triggers a pathological immune response resulting in changes to the lung alveoli and pulmonary vasculature. This mechanism may explain why SARS-CoV-2 infection can lead to diffuse alveolar damage, which is associated with widespread type 2 pneumocyte hyperplasia, epithelial necrosis, fibrin deposition, hyaline membrane formation and inflammation [4]. Infection with SARS-CoV-2 may also cause alveolar endothelial dysfunction through aberrant vasodilation, arteritis and microvascular thrombosis [4]. The alveolar and epithelial damage combine to produce the ventilation-perfusion mismatch typical of COVID-19 pneumonitis. Generalised

inflammation can cause dysfunction in other body systems and, although this patient had no clinical evidence of it, myocarditis could also play a role in early fatigue on physical exertion [5].

The combination of these pathophysiological mechanisms could explain the reversible ventilation-perfusion mismatching evident in this patient's CPET results. The extent to which fibrotic lung damage is long lasting appears to vary and this could relate to the degree of inflammation generated in the cytokine mediated host response to infection [6]. There are suggestions that a genetic predisposition may exist in some populations making them higher risk of more significant cytokine release in response to SARS-CoV-2 infection [4].

While the natural history of the resolution of COVID-19 is diverse, it is prudent to consider how this timeline may impact on peri-operative risk. In this case, the patient demonstrated a significant improvement in functional capacity following several weeks of recovery. Surgical decision-making may be influenced by CPET outcomes, and the very poor CPET performance following his first test may have precluded surgery. Although our patient remained in a higher risk group following his second CPET, the lower risk enabled surgical options which would otherwise may not have been offered. This is important in planning operative management, postoperative care setting and in giving a patient a realistic representation of risk during their peri-operative period.

This case also highlights the significant recovery of functional capacity, which can happen several weeks following an infection from COVID-19 even in minimally symptomatic individuals. This may not only impact on CPET assessment outcome but might also impact on clinical outcomes of morbidity, mortality and hospital stay [7]. It is possible this patient would have improved further if given even longer to recuperate. Recent clinical guidance states that where possible surgery should be delayed at least seven weeks following SARS-CoV-2 infection [7]. CPET could play a valuable role in individualised risk assessment and shared decision-making in complex urgent surgical cases where the benefits of delaying surgery need to be weighed against the potential risks.

Our patient's comorbidities included iron deficiency anaemia. Anaemia is associated with poor cardiorespiratory fitness, but recent international studies have concluded that the contribution of anaemia to reduced exercise capacity is small [8]. Iron deficiency itself is also associated with reduced exercise capacity owing to its role in oxygen delivery and cellular respiration, however, studies in athletes have demonstrated that intravenous iron transfusion does not lead to increased aerobic capacity [9]. As such we do not think the iron transfusion administered 30 min before our patient's second CPET would explain his improved exercise capacity. Furthermore, treatment of iron-deficiency anaemia would have no effect on the ventilation perfusion mismatch and would not explain his improved VE/VCO₂.

Finally, Perioperative Exercise Testing and Training Society (POETTS) guidelines advise screening for symptoms of SARS-CoV-2 before CPET, and suggest that CPET should not be conducted in any symptomatic patients [10]. Before entering our clinic waiting room, patients have their temperature taken and are asked standard COVID-19 screening questions, based on national guidance. This case demonstrates that standard screening questions can miss cases of SARS-CoV-2 infection. As per POETTS guidance, we treat CPET as an aerosol generating procedure and conduct tests in a ventilated room in 'airborne' personal protective equipment [10]. Following this case, we have introduced mandatory SARS-CoV-2 polymerase chain reaction screening tests for every patient before their CPET.

This case has highlighted the significant physiological impact that even minimally symptomatic SARS-CoV-2 infection may have on cardiorespiratory performance. The predominant features were reduced exercise capacity, ventilation-perfusion mismatching and evidence of oxygen delivery limitation whereas resting pulmonary function tests remained largely unaffected. There was a significant improvement in cardiorespiratory fitness following 44 days of recovery and this aligns well with the latest guidance on the timeframe to wait before undertaking surgery in patients with COVID-19 [7]. It is important to perform CPET after an appropriate period of recovery to ensure accurate pre-operative risk stratification can be undertaken and allow patients to make an informed decision on surgical options in conjunction with members of the peri-operative team.

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