Cardiopulmonary exercise testing (CPET) – Should I offer this in my preoperative clinic?

Problem-Based Learning Discussions

Prof. Bernhard Riedel **MBChB FCA FANZCA FASE MMed MBA PhD**
Dr. Hilmy Ismail **MD FRCA FFARCS (I) FANZCA**
Dr. Paris Dove **MBBS FANZCA**
Dr. Emily Traer **MBChB MRCS FRCA FANZCA**
Peter MacCallum Cancer Centre, Department of Anaesthesia, Perioperative and Pain Medicine

Perioperative cardiopulmonary exercise testing (CPET) is a dynamic and validated method of providing individualized and stratified preoperative risk assessments. It uses gas-exchange analysis during a symptom-limited exercise ramp protocol, typically conducted on a cycle ergometer. With increasing evidence that functional capacity cannot be accurately predicted at rest [1-4], CPET offers an objective method of assessing exercise tolerance, health status and identification of specific cardiopulmonary limitations. Each test is a point of care where surgical consent may be better understood by the patient and potential perioperative complications elucidated. Risk of complications may then be reduced through patient specific prehabilitation, optimization of modifiable risk factors, improved multi-disciplinary communication and planned postoperative care.

Learning objectives

1. Interpret CPET results using raw data tables and a 9 panel plot.
2. Apply CPET results to make preoperative recommendations to reduce perioperative risk.
3. Consider how patient involvement through CPET informs multidisciplinary management and

Case One

A 60-year-old patient with a past medical history of ischaemic heart disease (IHD), hypertension and dyslipidaemia, is referred to CPET for work-up prior to oesophagectomy. The patient underwent percutaneous coronary intervention 10 years earlier. Current medications include clopidogrel, telmisartan, ramipril, aspirin and a statin. The patient has not had a recent cardiology review and currently smokes 20 cigarettes per day

with a calculated 40 pack year history. Subjectively, the patient reports an excellent exercise tolerance with no episodes of angina.

CPET is conducted on an upright cycle ergometer on a 20 Watt/min ramp protocol. Anaerobic threshold (AT) is reached in 9.5 minutes and the test concluded at peak exercise after 13.5 minutes due to dyspnoea and fatigue. Of note, there is a plateau in oxygen pulse at peak exercise. The ECG trace shows sinus rhythm throughout but develops 3mm of ST depression in leads V3 to V6 at peak exercise in the absence of chest pain (Figure 1a). The ST segments normalize in recovery. The test results are provided below (Table 1 and Figure 1b). The patient has a BMI of 32kg/m² and BSA 2.0m².

Table 1: Case One CPET data

Data	Rest	AT	Peak	% Predicted Maximum at Peak Exercise
FEV_1 [L]	3.1			131%
MVV [L/min]	123			93%
Breathing Reserve [%]	23			
DLCO [mL/min/mmHg]	23.5			83%
$\dot{V}E/\dot{V}CO_2$	39.5	29.7	35.0	
$\dot{V}E$ [L/min]	11	30	95	
SpO_2 [%]	100	100	100	
HR [bpm]	83	117	156	98%
BP [mmHg]	119/65	145/70	160/80	Recovery 155/72
$\dot{V}O_2$ [mL/kg/min]	4.0	13.0	19.4	82%
O_2 pulse [mL/beat]	4.5	10.3	11.6	84%
RER	0.78	0.94	1.3	
Load [W]	0	69	122	100%
Blood results	Hb g/L	Albumin g/L	CRP mg/L	Transferrin Sats %
	142	38	4	28

FEV_1= forced expiratory volume in the first second of forced expiration, MVV = maximum voluntary ventilation, DLCO = lung diffusing capacity for carbon monoxide, $\dot{V}E$ = minute ventilation, $\dot{V}CO_2$= carbon dioxide output, SpO_2 = peripheral oxygen saturation, HR = heart rate, BP = blood pressure, $\dot{V}O_2$ = oxygen uptake, O_2 pulse = oxygen pulse, RER = respiratory exchange ratio, Hb = hemoglobin, CRP = C-reactive protein

Figure 1a: Case One ECG

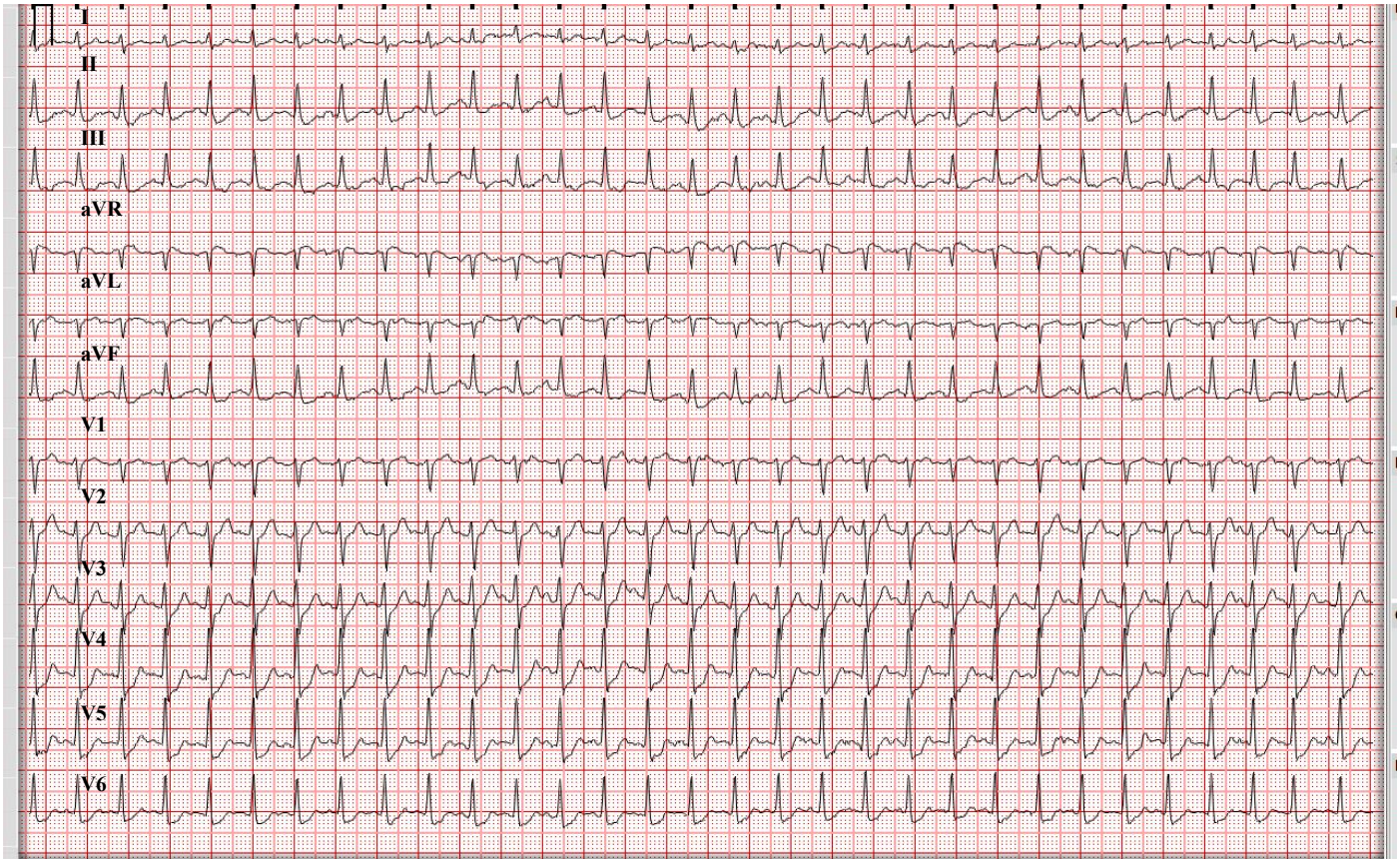
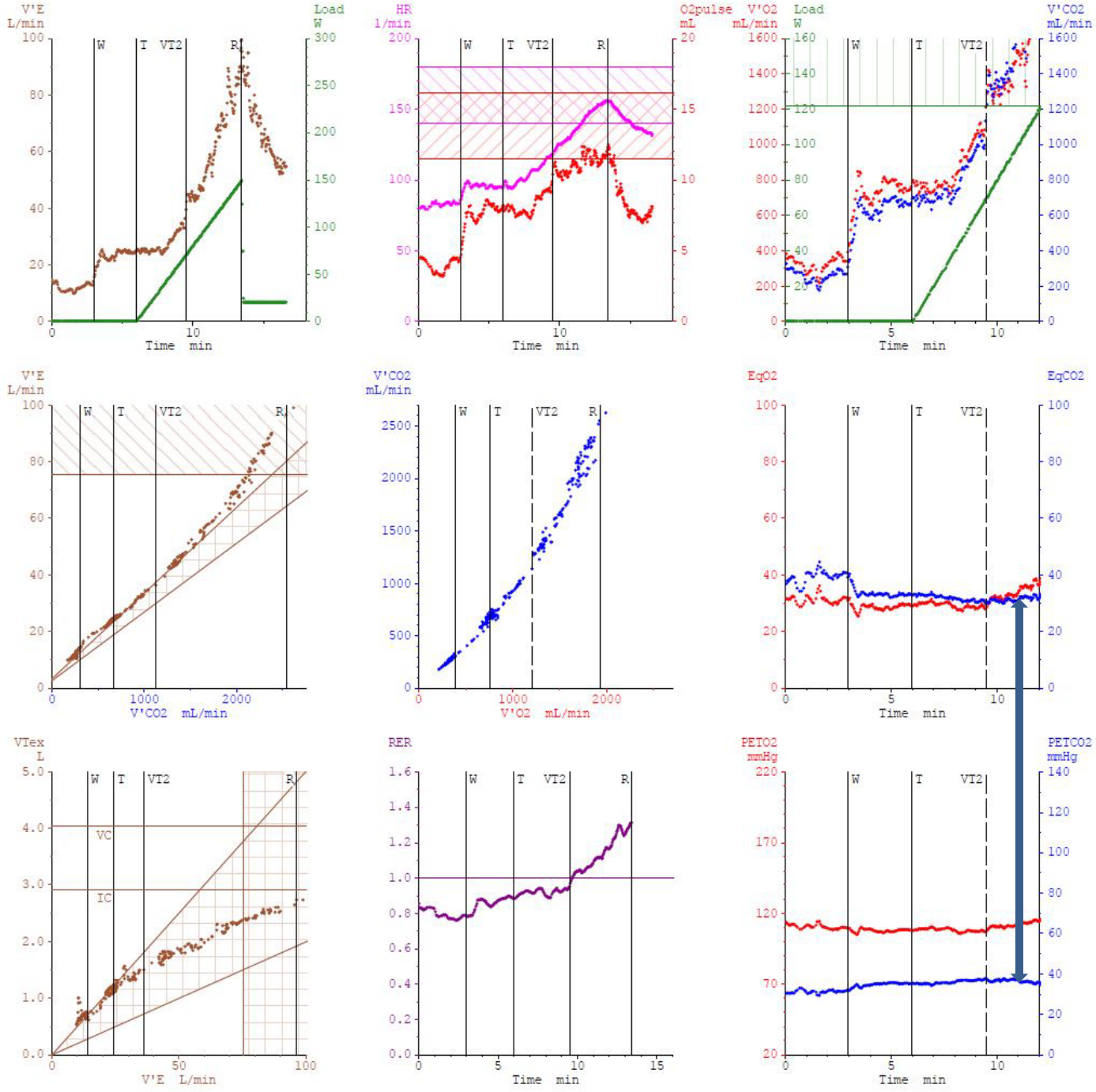


Figure 1b: 9 panel plot – based on the conventional UCLA method of displaying gas-exchange derived variables during CPET. The panels are numbered sequentially 1 – 9, from left to right, top row to bottom row.



W = unloaded cycling, T = loaded cycling, VT2 = anaerobic threshold, R = recovery, V'E = minute ventilation, HR = heart rate, V'O2 = oxygen uptake, V'CO2 = carbon dioxide output, EqO2 = ventilatory equivalents for oxygen, EqCO2 = ventilatory equivalents for carbon dioxide, VTex = tidal volume expired, RER = respiratory exchange ratio, PETO2 = end tidal pressure of oxygen, PETCO2 = end tidal pressure of carbon dioxide

Question 1

Is this a maximal exercise test that allows for objective interpretation? List the findings to back your conclusion.

Answer

This is a maximal exercise test supported by the following findings:

- Respiratory exchange rate (RER) of 1.3 at peak exercise; see panel 8.
    - A peak RER ≥1.10 is widely accepted as an indication of satisfactory patient effort during CPET [3 5].
- HR 156 bpm at peak (98% of predicted maximal heart rate); see panel 2.
- $\dot{V}O_{2peak}$ 19.4 mL/kg/min (82% of predicted); see panel 3 and 5 (x-axis).
- Peak work rate 122 W (100% predicted); see panel 1 and 3:
- Normal breathing reserve (MVV – $\dot{V}E_{peak}$/ MVV = 123 – 95/123 = 23%); see panels 4 and 7.
    - MVV (maximal voluntary ventilation) is the theoretical ventilatory limit of the respiratory system [1]. MVV can be estimated indirectly, by the calculation of FEV_1 x 35 – 40, or directly, measuring minute ventilation ($\dot{V}E$) over 10 – 15 seconds of breathing at maximal effort using a spirometer[1,6].
    - In healthy subjects, ventilatory demand does not normally encroach upon ventilatory capacity during exercise and as such, respiratory reserve is >15%[1]. It is important to note that breathing reserve demonstrates significant variability among the normal population and that $\dot{V}E_{peak}$ may approach MVV in fit individuals and in the elderly in the absence of disease[1].

Question 2

What is the anaerobic threshold and how do you determine this on the 9 panel plot?

Answer

In an incremental exercise test the anaerobic threshold (AT) is defined as the oxygen uptake value, at which aerobic metabolism is supplemented by anaerobic glycolysis[1,3,7]. The measurable metabolic changes occurring after AT are: a systematic increase in CO_2 production, an increase in the respiratory exchange ratio (RER; or ratio of $\dot{V}CO_2/\dot{V}O_2$), a rise in blood lactate levels with a fall in blood bicarbonate levels, and a decrease in blood pH[1,3,7]. For this reason, AT may also be described as the "lactate threshold"[7]. AT is determined by interpreting the 9 panel plot according to three set criteria outlined in the CPET consensus clinical guidelines[7]:

- Criterion 1: Identify excess $\dot{V}CO_2$ relative to $\dot{V}O_2$ (i.e. use the V-slope or modified V-slope method (see panel 5). The inflection observed in the $\dot{V}CO_2 - \dot{V}O_2$ relationship here is secondary to the buffering of anaerobic lactate *after AT* with consequent generation of more CO_2 (i.e. $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$).
- Criterion 2: Identify hyperventilation with respect to O_2 uptake, (i.e. locate the nadir of the ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}O_2$) slope (see panel 6) and a rise in the end tidal oxygen ($P_{ET}O_2$) slope (see panels 9). At this point, $\dot{V}E$ increases and is driven by the excess CO_2 of anaeroboic glycolysis without a corresponding increase in $\dot{V}O_2$.
- Criterion 3: Exclude hyperventilation with respect to CO_2 production (i.e. confirm a plateau or decrease in the ventilatory equivalents for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) occurring at the point determined by criterion 1 and 2 above; see panels 6 and 9).

It is worth noting the rise in $\dot{V}E/\dot{V}CO_2$ and decline in end tidal carbon dioxide ($P_{ET}CO_2$), as represented by divergent curves and depicted by the arrow in panel 6 and 9 (Figure 1b), is defined as the respiratory compensation point, and AT should occur before this point. This patient achieved AT at $\dot{V}O_2$ of 13mL/kg/min.

Question 3

What is the difference between $\dot{V}O_{2max}$ and $\dot{V}O_{2peak}$?

Answer

$\dot{V}O_{2max}$ is an end point where oxygen uptake cannot be increased further despite increasing workload[7] and may be derived by the Fick equation[3]: $\dot{V}O_{2max}$ = (HR x SV) x [C(a-v)O_2]. $\dot{V}O_{2max}$ is representative of the upper limit of an individual's functional capacity. This is the sum total of their cardiorespiratory, vascular, haematological, musculoskeletal and metabolic systems working at their physiological maximum[1,3,7]. In athletes $\dot{V}O_{2max}$ may be observed as a plateau in the $\dot{V}O_2$ at peak, though in practice, this is rarely seen in the typical patient who presents to cardiopulmonary exercise testing for perioperative evaluation[1,3,7].

The $\dot{V}O_{2peak}$ is the highest oxygen uptake value achieved during an incremental exercise test[1,3,5]. It is averaged over 20 – 30 seconds or 3 – 5 breaths during the final portion of incremental work[7]. $\dot{V}O_{2peak}$ is influenced by age and gender and is typically indexed to weight in kilograms (mL/kg/min). Occasionally, $\dot{V}O_{2peak}$ is indexed to body surface area (mL/m^2) and this may help overcome artificially high or low $\dot{V}O_{2peak}$ measures at extremes of body weight[8,9]. Non-athletes typically achieve $\dot{V}O_{2peak}$ and not $\dot{V}O_{2max}$. The advantages of the $\dot{V}O_{2peak}$ are that it is easy to identify on the 9-panel plot and it is reproducible on repeat testing[7]. The limitations of $\dot{V}O_{2peak}$ are that it is related to a patient's volitional effort and the provision of subject encouragement to reach a maximum effort[7]. Despite these limitations, there remains merit in evaluating $\dot{V}O_{2peak}$ given the increasing body of evidence correlating $\dot{V}O_{2peak}$ to perioperative outcomes[2,4,7,8,10]. Other useful metrics derived from peak exercise include HR_{peak} relative to age predicted maximum heart rate and RER_{peak} >1.1[5,7].

Question 4

Identify the CPET results that indicate the presence of myocardial ischemia during exercise.

Answer

This patient has 3 mm of ST depression in leads V3 to V6 at peak exercise that could suggest lateral territory myocardial ischemia, without chest pain. Heart rate and blood pressure remained stable throughout exercise and the patient was permitted to continue the test to their peak effort. According to guidelines[1,7]the ECG criteria for premature CPET termination are >2mm ST depression if the patient is symptomatic, or 4mm ST depression if the patient is asymptomatic, or >1mm ST elevation.

Another useful CPET derivative of the Fick equation is the oxygen pulse: $\dot{V}O_2$ / HR = SV x [C(a-v)O_2]. It is a surrogate marker for stroke volume that provides dynamic information about myocardial function[1,3]. The oxygen pulse describes the amount of oxygen extracted per heartbeat[1,3,11] assuming no impairments to oxygen extraction and normal chronotropic activity[3]. The normal shape of the $\dot{V}O_2$ / HR relationship is hyperbolic with a linear increase observed early in exercise as SV makes a significant contribution to increased cardiac output [1,3,11]. In late exercise, this reaches a plateau as further increases in cardiac output are supplemented by a rise in heart rate at high work rates[1]. A premature asymptote, described as a "flattened" oxygen pulse, is indicative of cardiogenic limitation to exercise[3,5,12] and, as seen in this case (panel 2), myocardial ischemia. A low peak oxygen pulse may also be observed in deconditioning if the patient has an arrhythmia such as atrial fibrillation, is on beta-blockers, or if exercise is terminated early for any cause[1].

Discussion

One of the first considerations when interpreting CPET results is to determine the adequacy of patient effort. A number of objective CPET variables are used for this purpose, including HR, RER and $\dot{V}O_2$ at peak exercise[7]. Subjective information from the patient can be obtained using the Borg Score and the reason they give for stopping the test. Comments and observations made by the CPET scientist and attending clinician may also provide assistance in interpreting CPET data.

In the absence of a plateau in $\dot{V}O_2$ other CPET criteria are used to assess whether the patient pushed themselves

to their physiological maximum[1,7]. The maximum heart rate response to exercise is estimated by the equation, 220 – age, though the standard deviation is large (± 15bpm)[1]. Achieving a maximum heart rate ≥85% predicted is regarded as excellent patient effort and may be taken as an indicator of a maximal test [1,3]. In practice case-by-case interpretation of maximum heart rate is necessary as resting tachycardia, atrial fibrillation, and prescribed beta-blockers are frequently seen among the clinical cohort of patients referred for perioperative assessment.

The respiratory exchange ratio (RER) is the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ measured from expired gas at the mouthpiece during exercise[1,3]. With increasing work rate and the evolution of anaerobic metabolism, the consequent bicarbonate buffering of hydrogen ions generated from lactic acidosis liberates more CO_2, leading to an increase in the RER[3]. A peak RER ≥1.1 is widely accepted as an indication of satisfactory patient effort during CPET[3,5]. The AT occurs at an RER somewhere in between 0.8 to 0.99, therefore, when RER = 1.0 AT has already passed[3]. Cessation of exercise at an RER <1.0, in the absence of patient symptoms and cardiac abnormalities generally signifies a lack of adequate patient effort, though this may also be seen in patients limited secondarily to respiratory disease or metabolic impairment [3.7].

External work is most accurately measured during CPET using an electronically braked cycle ergometer[1] as exercise is performed by large muscle groups with limited reliance on balance or cadence. In the setting of a steadily increasing work rate (WR), oxygen consumption should increase in a linear fashion[1]. The correlation of $\dot{V}O_2$ to work rate, or the $\Delta\dot{V}O_2$ /ΔWR slope, has been found to be remarkably constant, with a value of ~10 mL/W independent of age, gender, height or training[1]. As such, the $\Delta\dot{V}O_2$ /ΔWR relationship represents the gain of the system and any reduction in this metric indicates pathology affecting the heart, lungs, circulation, muscles or mitochondrial function[1].

Lactate production results through any, or a combination of the following[1]:

i) Exhaustion of oxygen delivery mechanisms; $DO_2 = CO \times [(Hb \times S_aO_2 \times 1.34) + (P_aO_2 \times 0.003)]$

ii) Relative use of glycolytic type II muscle fibres (high intensity work) over oxidative type I muscle fibres (low intensity work)

iii) Insufficiency of oxidative respiration at the cellular level (i.e. reduced number or enzymatic function of mitochondria).

While AT has become an important metric in CPET, it is only useful when interpreted together with the other variables including: baseline fitness, patient subjective effort, RER, $\dot{V}O_{2peak}$, oxygen pulse, chronotropic response to exercise, heart rate recovery, ECG changes, lung function, ventilatory efficiency and $\Delta\dot{V}O_2/\Delta WR$. The point at which AT arises varies across populations and occurs between 35 – 80% of peak $\dot{V}O_2$[1]. AT is influenced by the type of activity undertaken because of differences in muscle mass and fibre type used, with increasing values seen in arm crank, cycle ergometry and treadmill exercises respectively[1]. AT is higher in athletes, who have greater cardiorespiratory fitness compared to the deconditioned population[3]. AT is reached earlier in disease states[7]. In the elderly, AT occurs later in exercise as a proportion of a lower $\dot{V}O_{2peak}$ [1]. Unlike $\dot{V}O_{2peak}$, AT is non-volitional[7] and is easily reproduced with minimal effort for most patients[3] hence AT is widely referenced in perioperative literature.

Determination of AT assists the perioperative physician in a number of ways. Knowing AT enables us to establish a patient's baseline fitness and therefore, prescribe an individualised exercise-training program[1,5,11] based on Borg Scale, heart rate or Watts measured at AT. Inactive subjects have been shown to improve their AT and $\dot{V}O_{2peak}$ by 10 – 25% with exercise training[3]. AT can be utilised to predict perioperative risk for specific surgical cohorts [4,7,8,10] and to resourcefully triage postoperative disposition to the surgical ward or to a high dependency unit[4,8,10]. That is, CPET has a role in preoperative risk stratification, prehabilitation and postoperative care planning. After completion of CPET the patient in this case study was referred to a cardiologist for optimization of cardiac risk factors, with the recommendation of high dependency level care postoperatively.

Case Two

The colorectal surgical team have referred a 70-year-old patient to your CPET clinic for assessment prior to a major open abdominal cancer resection. They request your assessment in anticipation of a multidisciplinary team meeting. The patient is currently being worked up for exertional dyspnoea and is noted to have desaturated while undertaking a 6-minute walk test. Arterial blood gas demonstrates hypoxaemia on room air with a P_aO_2 of 55 mmHg and an alveolar – arterial gradient of 50 mmHg.

Clinical information includes a 90 pack per year ex-smoking history, IHD with distal left anterior descending coronary artery stenosis not amenable to coronary stenting, paroxysmal atrial fibrillation and non-insulin dependent diabetes mellitus with renal impairment. The patient has a BMI of 33 kg/m² and BSA 2.2 m².

You conduct a symptom-limited CPET with gas-exchange analysis on an upright cycle ergometer using a 15 Watt/min ramp exercise protocol. The test is stopped by the patient after 12.5 minutes of cycling due to dyspnoea and fatigue. The test results are provided below (Table 2 and Figure 2).

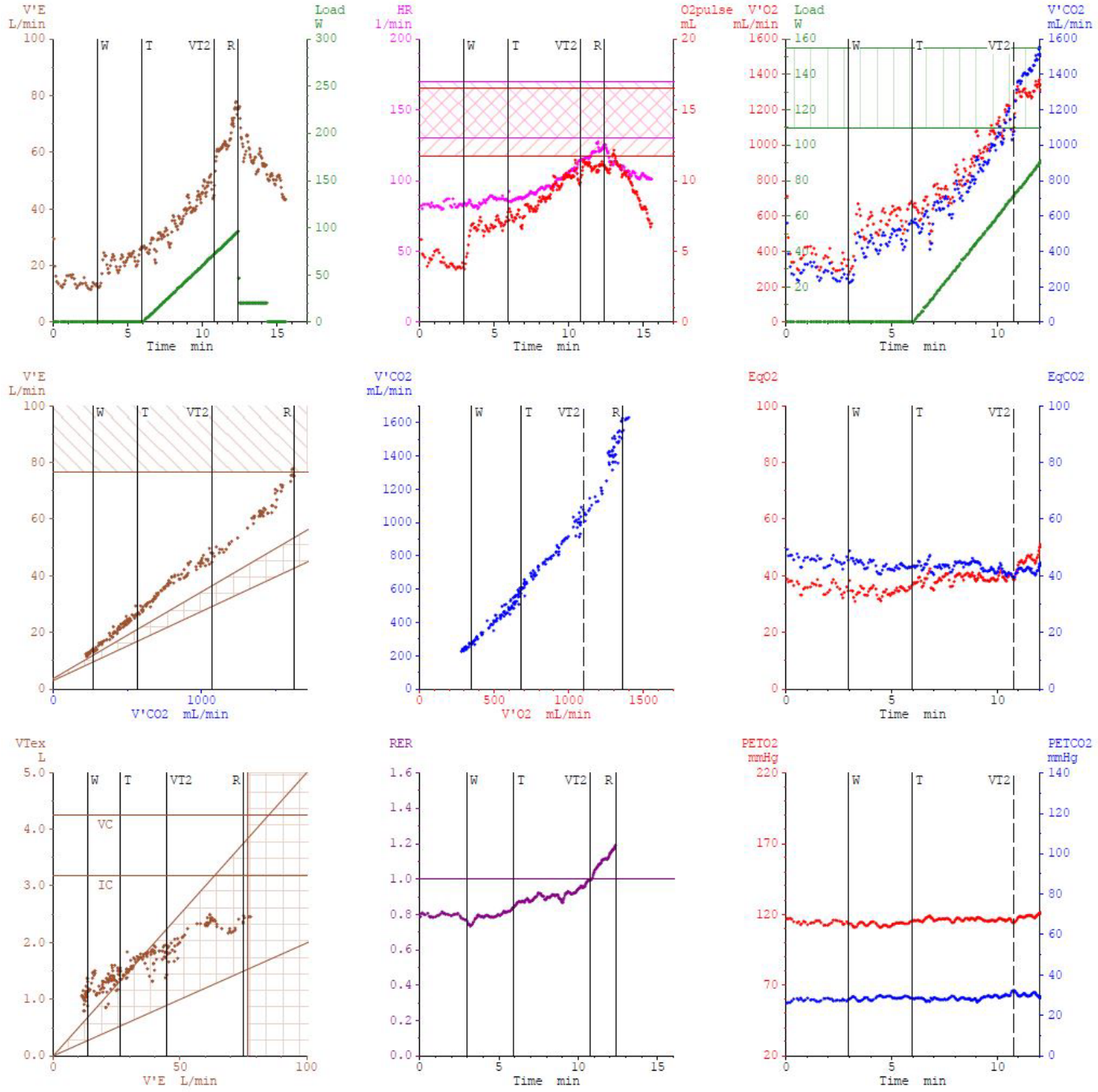
Table 2: Case Two CPET data

Data	Rest	AT	Peak	% Predicted Maximum at Peak Exercise
FEV_1 [L]	2.3			79% No reversibility with bronchodilator
FVC [L]	3.5			71%

FEV_1 / FVC ratio [%]	65			
MVV [L/min]	92.4			78%
Breathing Reserve [%]	13			
DLCO [mL/min/mmHg]	15.1			47%
$\dot{V}E/\dot{V}CO_2$	45.2	39.3	41.9	
$\dot{V}E$ [L/min]	11	40	80	
SpO_2 [%]	96	93	94	
HR [bpm]	82	114	122	81 %
BP [mmHg]	144/49	159/85	182/72	Recovery 176/70
$\dot{V}O_2$ [mL/kg/min]	3.3	10.5	12.9	63%
O_2 pulse [mL/beat]	4.1	9.6	11.0	78%
RER	0.79	0.98	1.15	
Load [W]	0	71	94	71%
Blood results	Hb g/L	Albumin g/L	CRP mg/L	Transferrin Sats %
	156	37	10	31

FEV_1= forced expiratory volume in the first second of forced expiration, FVC = forced vital capacity, MVV = maximum voluntary ventilation, DLCO = lung diffusing capacity for carbon monoxide, $\dot{V}E$ = minute ventilation, $\dot{V}CO_2$= carbon dioxide output, SpO_2 = peripheral oxygen saturation, HR = heart rate, BP = blood pressure, $\dot{V}O_2$ = oxygen uptake, O_2 pulse = oxygen pulse, RER = respiratory exchange ratio, Hb = hemoglobin, CRP = C-reactive protein

Figure 2: 9 panel plot – based on the conventional UCLA method of displaying gas-exchange derived variables during CPET. The panels are numbered sequentially 1 – 9, from left to right, top row to bottom row.



W = unloaded cycling, T = loaded cycling, VT2 = anaerobic threshold, R = recovery, V'E = minute ventilation, HR = heart rate, V'O2 = oxygen uptake, V'CO2 = carbon dioxide output, EqO2 = ventilatory equivalents for oxygen, EqCO2 = ventilatory equivalents for carbon dioxide, VTex = tidal volume expired, RER = respiratory exchange ratio, PETO2 = end tidal pressure of oxygen, PETCO2 = end tidal pressure of carbon dioxide

Question 1

Identify the CPET-derived data in support of a respiratory aetiology to explain this patient's exercise limitation. Ensure that you distinguish between indices of ventilatory inefficiency, and mechanical ventilatory limitation.

Answer

- The absence of cardiac limitation as seen by a normal $\Delta\dot{V}O_2$ /ΔWR slope and oxygen pulse (see panel 2) and no ischemic symptoms or ECG changes during exercise.
- Desaturation during exercise.
- Reduced FEV_1 and DLCO.
- Low $\dot{V}O_{2peak}$ 12.9mL/kg/min (63% of predicted); see panel 3
- Elevated $\dot{V}E/\dot{V}CO_2$ of 39.3 at AT (normal <35 at AT); see panel 6
- Low breathing reserve (MVV – $\dot{V}E_{peak}$/ MVV = 92.4 – 80/92.4 = 13%; normal >15%); see panels 4 and 7.

A low breathing reserve (< 15%) indicates mechanical ventilatory limitation [1] and $\dot{V}E/\dot{V}CO_2$ slope of >30 [3 5] or $\dot{V}E/\dot{V}CO_2$ at AT >35 (see panels 4 and 6, respectively) indicates ventilatory inefficiency[1,7].

Question 2

What additional tests might you consider after analysing the CPET results and why?

Answer

- D-dimer levels for screening or preferably a definitive CT pulmonary angiogram to investigate for pulmonary embolism
- High resolution CT scan to assess for pulmonary fibrosis
- Transthoracic echocardiogram to assess for pulmonary hypertension

- An arterial blood gas on room air and 100% oxygen to assess for right to left anatomical shunt

Question 3

Explain the mechanism of increased $\dot{V}E/\dot{V}CO_2$ in patients with chronic lung disease.

Answer

Increased $\dot{V}E/\dot{V}CO_2$ represents V/Q mismatching, and increased physiologic dead space in patients with chronic lung disease[1,3,4,10]. Differential diagnoses include chronic obstructive pulmonary disease (COPD), congestive cardiac failure (CCF), pulmonary embolism and pulmonary hypertension. As $\dot{V}E/\dot{V}CO_2$ deviates further from normal, the likelihood of secondary pulmonary hypertension increases[5]. $\dot{V}E/\dot{V}CO_2$ may also be increased in voluntary hyperventilation or states of increased ventilatory drive[1,4,10].

Question 4

Explain the importance of the observed desaturation during exercise.

Answer

Desaturation by ≥5% is considered abnormal during CPET[1,3,5] and warrants further investigation into the underlying etiology[1,3,5]. Laboratories do vary in practice and many will use thresholds of <80 – 85% desaturation for exercise termination[1,3]. Exercise-induced desaturation is observed in COPD, interstitial lung disease (ILD) and pulmonary hypertension[5] and its presence is indicative of advanced pathology[5].

Discussion

CPET is frequently utilised to determine the cause of exertional dyspnoea[1,3,5]. In this case, it is apparent that respiratory pathology is the major underlying disease process responsible for the patient's exercise limitation. As the patient's heart rate did not reach their age-predicted maximum, and work rate at peak was low, maximal myocardial work was not reached. Therefore, cardiac limitation cannot be assumed despite the patient's history of coronary artery disease. Resting pulmonary function tests do not give information about a patient's functional status, nor do they provide guidance about the patient's physiological reserve. Research supports the objectivity of CPET in this field [1,13]. In one study, marked variability was observed between the measured peak $\dot{V}O_2$ during exercise testing and the degree of airflow obstruction on pulmonary function testing[13]. This illustrates how CPET may out-perform spirometry for the assessment of functional capacity in respiratory disease. CPET has also been shown to be more sensitive than a 6-minute walk test in measuring exercise capacity in COPD after bronchodilator therapy[1].

The $\dot{V}E/\dot{V}CO_2$ relationship provides information about the effectiveness of V/Q matching in the lungs[5,7,8]. A normal $\dot{V}E/\dot{V}CO_2$ is described as being <32–34 at AT [1] and in healthy young individuals it is usually <30[1,5]. The $\dot{V}E/\dot{V}CO_2$ slope value is independent of the test protocol used and the type of exercise conducted, with reported demonstrable re-test accuracy[3]. Reduced ventilatory efficiency, as shown here by the high $\dot{V}E/\dot{V}CO_2$ ratio, suggests either a low arterial P_aCO_2 (seen in acute hyperventilation, or in states of increased ventilatory drive) or increased physiologic dead space[1,4,7,10]. An elevated $\dot{V}E/\dot{V}CO_2$ is commonly seen in patients with COPD, ILD, heart failure and pulmonary hypertension[3-5,7,10]. Disease severity and prognosis correlate with the degree of deviation from normal[3,5,7]. As such, $\dot{V}E/\dot{V}CO_2$ is a powerful tool in perioperative risk stratification[5,7] and acts as a risk predictor for postoperative morbidity and mortality for a number of surgical procedures[8,14-17].

Best practice management of chronic respiratory disease includes pulmonary prehabilitation and exercise training, which has been associated with improved lung function [18,19]. CPET can be utilised to evaluate the

impact of such therapeutic interventions[1]. The foundations of pulmonary prehabilitation have since been adopted in perioperative medicine, with the aim of reducing the incidence of postoperative pulmonary complications such as pneumonia [20-23]. Pulmonary prehabilitation before surgery for lung cancer has been associated with reduced postoperative pulmonary complications in observational studies[24]. Prospective studies have also shown improved post-operative recovery through a decrease in time of chest tube placement and length of hospital stay[25]. Pulmonary bundles of care including iCOUGH [21], demonstrate a reduction in postoperative pneumonia and other respiratory complications in surgical ward patients[20,21]. In patients scheduled for elective upper abdominal surgery, prehabilitation with a 30-minute physiotherapy session, halved the incidence of postoperative pulmonary complications (number needed to treat = 7 and 95% confidence interval 5 -14) [26].

The principles of pulmonary prehabilitation can be introduced on the day of CPET by teaching patients deep breathing and coughing exercises. Written educational material may be provided allowing patients to practice cycles of deep breathing exercises at home. Such education was given to the patient above, as well as referral to a respiratory physician for optimization. After 3 weeks of inhaled corticosteroid therapy and deep breathing exercises, the patient re-presented to CPET. Between tests, the patient did not engage in a prescribed exercise program due to knee pain, but did perform the breathing exercises. Subsequent oxygen saturations at rest, and on room air improved to 98% with a nadir of 94% when exercising. In spite of this improvement, as well as an increase in ventilatory efficiency of 5% from baseline, it was concluded at shared decision making that non-operative management was more suited to the patient's personal goals and preferences. Despite not choosing to have surgery, the patient's quality of life was improved through this respiratory optimization and improved symptom control.

Case Three

A 75-year-old patient diagnosed with distal oesophageal adenocarcinoma is referred for CPET to assess baseline functional capacity prior to commencement of neoadjuvant chemoradiotherapy, and to undertake risk stratification in anticipation of surgical resection. The patient lives independently at home and currently takes medication for hypercholesterolemia and gastroesophageal reflux disease.

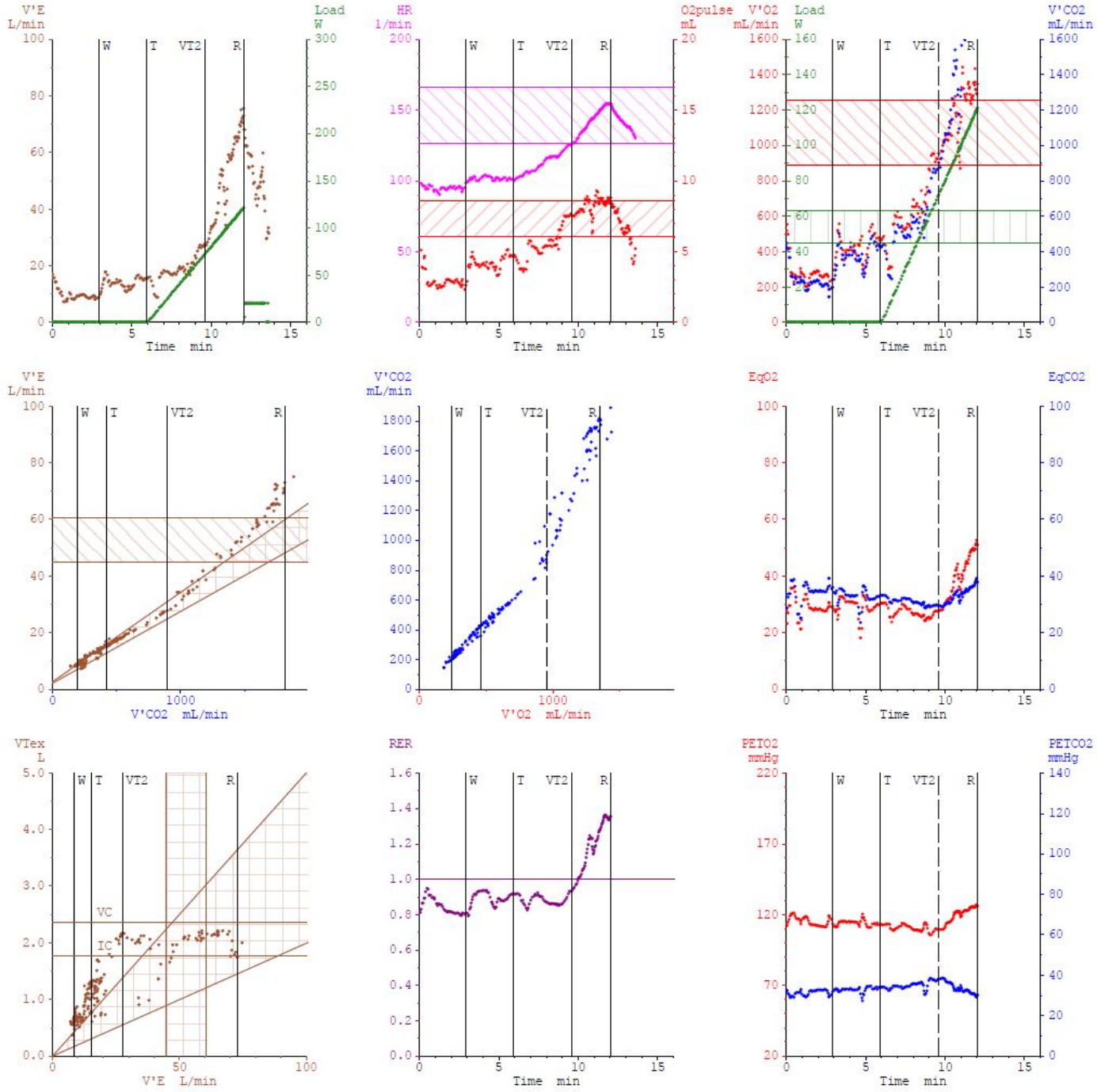
CPET with gas-exchange analysis is conducted on an upright cycle ergometer with a 20 Watt/min ramp protocol. The test is terminated by the patient after 12 minutes of cycling because of exhaustion. The patient has a BMI of 25kg/m² and BSA 1.65m².

Table 3a: Case Three CPET data prior to neoadjuvant therapy

Data	Rest	AT	Peak	% Predicted Maximum at Peak Exercise
FEV_1 [L]	2.5			125%
MVV [L/min]	100			128%
Breathing Reserve [%]	21			
DLCO [mL/min/mmHg]	22.3			101%
$\dot{V}E/\dot{V}CO_2$	33.7	29.2	36.7	
$\dot{V}E$ [L/min]	7	27	79	
SpO_2 [%]	100	99	100	
HR [bpm] HRR_1 [bpm]	90	125	154	106% Recovery 135
BP [mmHg]	130/85	155/83	172/80	Recovery 150/90
$\dot{V}O_2$ [mL/kg/min]	4.2	15.1	20.6	122%
O_2 pulse [mL/beat]	2.8	7.6	8.5	109%
RER	0.84	0.94	1.35	
Load [W]	0	72	120	222%
Blood results	Hb g/L 139	Albumin g/L 36	CRP mg/L 2.0	Transferrin Sats % 18

FEV_1= forced expiratory volume in the first second of forced expiration, MVV = maximum voluntary ventilation, DLCO = lung diffusing capacity for carbon monoxide, $\dot{V}E$ = minute ventilation, $\dot{V}CO_2$= carbon dioxide output, SpO_2 = peripheral oxygen saturation, HR = heart rate, HRR_1 = heart rate at 1 minute recovery, BP = blood pressure, $\dot{V}O_2$ = oxygen uptake, O_2 pulse = oxygen pulse, RER = respiratory exchange ratio, Hb = hemoglobin, CRP = C-reactive protein

Figure 3a: 9 panel plot – based on the conventional UCLA method of displaying gas-exchange derived variables during CPET. The panels are numbered sequentially 1 – 9, from left to right, top row to bottom row.



W = unloaded cycling, T = loaded cycling, VT2 = anaerobic threshold, R = recovery, V'E = minute ventilation, HR = heart rate, V'O2 = oxygen uptake, V'CO2 = carbon dioxide output, EqO2 = ventilatory equivalents for oxygen, EqCO2 = ventilatory equivalents for carbon dioxide, VTex = tidal volume expired, RER = respiratory exchange ratio, PETO2 = end tidal pressure of oxygen, PETCO2 = end tidal pressure of carbon dioxide

Question 1

Summarise and interpret the results of this CPET.

Answer

This is a maximal exercise test as evidenced by a $\dot{V}O_{2peak}$ of 20.6 mL/kg/min, RER_{peak} 1.35, HR_{peak} 154bpm and peak work rate of 120W, all of which exceed the age-predicted maximum values. CPET provides objective evidence of favourable physiological reserve in this patient. The AT value of 15.1 mL/kg/min, $\dot{V}O_{2peak}$ of 20.6 mL/kg/min, and $\dot{V}E/\dot{V}CO_2$ of 29.2 at AT place this patient in the low-risk category for postoperative complications [11]. Therefore, it is reasonable to consider surgery as a viable treatment option. The patient is advised to sustain an exercise regime during neoadjuvant chemoradiotherapy as deconditioning with a 15 – 20% decline in AT and $\dot{V}O_{2peak}$ from baseline values during neoadjuvant therapy can be observed [27-30].

Question 2

You see this patient again in CPET clinic after neoadjuvant therapy is completed. Side effects of treatment include reduced energy levels and poor appetite. Their BMI and BSA, however, have remained unchanged. List the CPET variables that indicate that the patient is now at a higher risk of postoperative complications (Table 3b and Figure 3b below) compared to the baseline CPET.

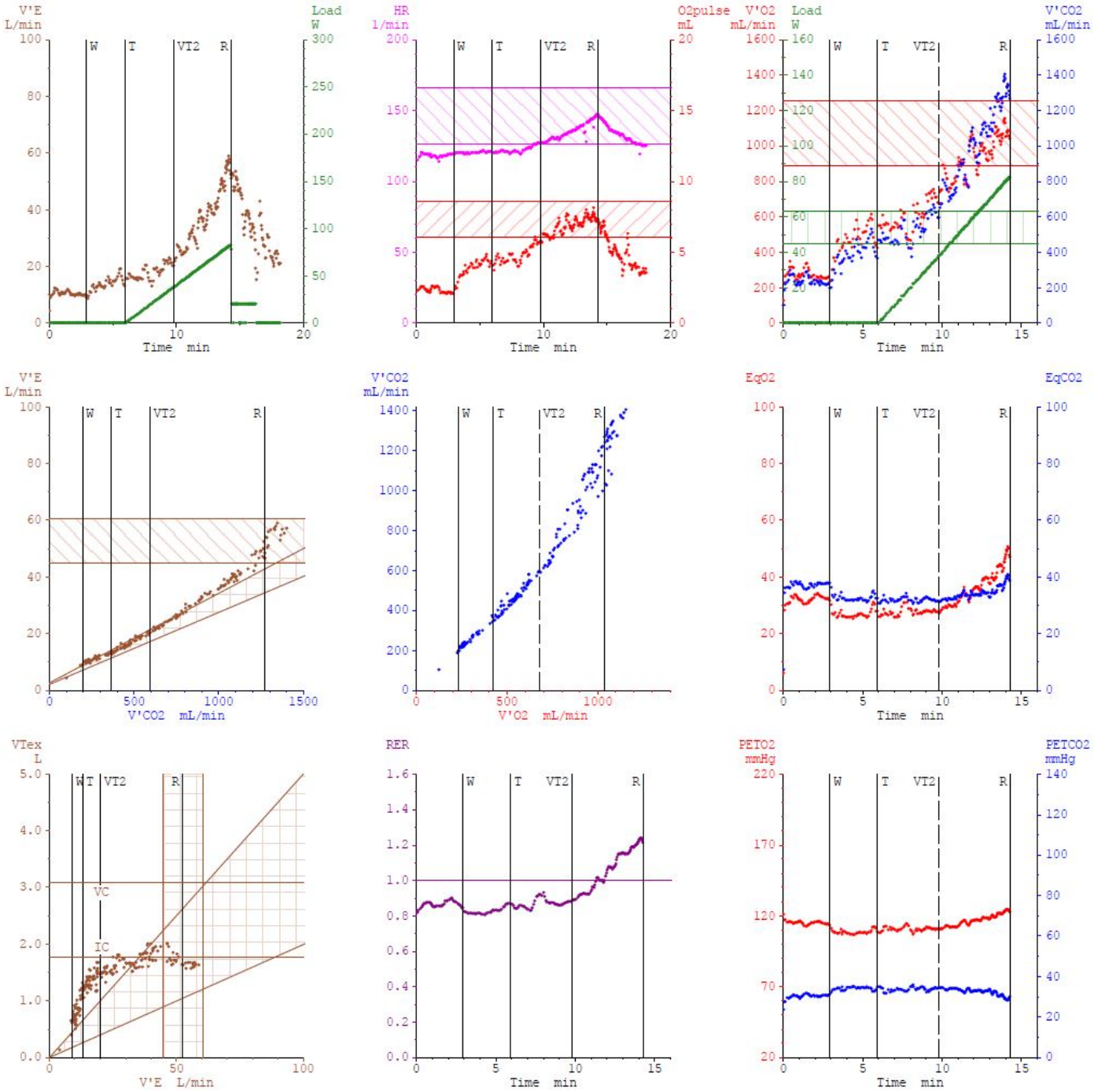
Table 3b: Case Three CPET data after neoadjuvant therapy

Data	Rest	AT	Peak	% Predicted Maximum at Peak Exercise
$\dot{V}E/\dot{V}CO_2$	36.9	31.3	37.9	
$\dot{V}E$ [L/min]	10	22	60	
SpO_2 [%]	99	98	99	
HR [bpm] HRR_1 [bpm]	120	127	147	101% Recovery 140
BP [mmHg]	135/90	156/85	166/80	Recovery 145/95

$\dot{V}O_2$ [mL/kg/min]	4.4	10.1	16.5	95%
O_2 pulse [mL/beat]	2.3	5.3	7.3	99%
RER	0.87	0.88	1.20	
Load [W]	0	38	82	152%
Blood results	Hb g/L	Albumin g/L	CRP mg/L	Transferrin Sats %
	112	23	18	12

$\dot{V}E$ = minute ventilation, $\dot{V}CO_2$= carbon dioxide output, SpO_2 = peripheral oxygen saturation, HR = heart rate, HRR_1 = heart rate at 1 minute recovery, BP = blood pressure, $\dot{V}O_2$ = oxygen uptake, O_2 pulse = oxygen pulse, RER = respiratory exchange ratio, Hb = hemoglobin, CRP = C-reactive protein

Figure 3b: 9 panel plot – based on the conventional UCLA method of displaying gas-exchange derived variables during CPET. The panels are numbered sequentially 1 – 9, from left to right, top row to bottom row.



W = unloaded cycling, T = loaded cycling, VT2 = anaerobic threshold, R = recovery, V'E = minute ventilation, HR = heart rate, V'O2 = oxygen uptake, V'CO2 = carbon dioxide output, EqO2 = ventilatory equivalents for oxygen, EqCO2 = ventilatory equivalents for carbon dioxide, VTex = tidal volume expired, RER = respiratory exchange ratio, PETO2 = end tidal pressure of oxygen, PETCO2 = end tidal pressure of carbon dioxide

Answer

- Reduced AT = 10.1 mL/kg/min; see panels 5, 6 and 9 using the three criteria for AT determination.
- Reduced $\dot{V}O_{2peak}$ = 16.5 mL/kg/min (95% predicted); see panel 3
- Increase in $\dot{V}E/\dot{V}CO_2$ to 31.3 at AT; see panel 6.
- Resting tachycardia with HR 120bpm; see panel 2.
    - The normal chronotropic response to exercise should be >25 bpm from baseline to AT and >40 bpm rise in HR from baseline to peak exercise respectively.
- Poor heart rate decline in the recovery phase (low risk is depicted by >12bpm reduction in HR after 1 minute recovery); see panel 2 (147 – 140 = 7bpm).
- Flatter profile of the oxygen pulse (slope and at peak exercise); see panel 2.
- Hypoalbuminemia and anaemia, likely due to raised inflammatory markers on blood test results.

Question 3

What strategies can you implement to optimize this patient's fitness for surgery?

Answer

- The following multidisciplinary approach may be considered:
    - To improve functional status, refer to a physiotherapist for guidance on a structured exercise prescription and pulmonary prehabilitation in the period prior to surgery. Schedule a repeat CPET test in 4 weeks.
    - Do a complete haematinic evaluation for possible iron deficiency and consider a haematology consult for further anaemia management.
    - Refer to a dietician for nutritional education and supplementation to manage the self-reported reduced appetite and low albumin level.
    - Consider a psychology referral if the patient exhibits signs of anxiety and/or depression.

- Consider a group education session (e.g. Surgery School) to prepare the patient for an Enhanced Recovery After Surgery (ERAS) program.

Question 4

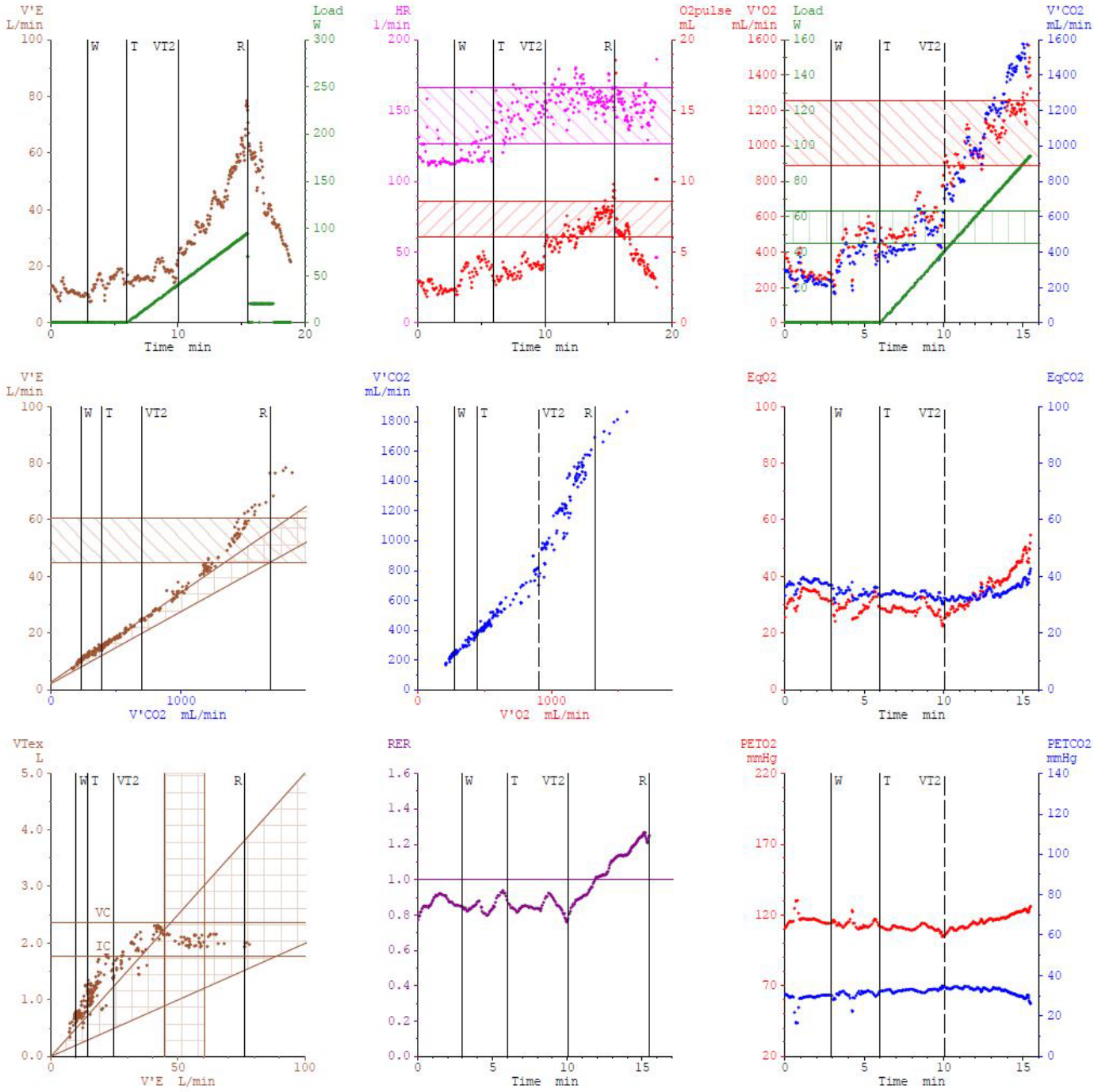
After 4 weeks of prehabilitation and a dedicated exercise program the patient undergoes repeat cardiopulmonary exercise testing. Summarise and interpret your findings from the CPET results below (Table 3c and Figure 3c).

Table 3c: Case Three CPET data after prehabilitation

Data	Rest	AT	Peak	% Predicted Maximum at Peak Exercise
$\dot{V}E/\dot{V}CO_2$	37.8	30.0	38.1	
$\dot{V}E$ [L/min]	8	30	75	
SpO_2 [%]	99	98	100	
HR [bpm] HRR_1 [bpm]	108	155	170	117% Recovery 160
BP [mmHg]	128/82	150/83	175/80	Recovery 158/95
$\dot{V}O_2$ [mL/kg/min]	4.2	14.9	19.7	117%
O_2 pulse [mL/beat]	2.3	5.9	7.3	100%
RER	0.88	0.99	1.24	
Load [W]	0	62	95	169%
Blood results	Hb g/L 124	Albumin g/L 33	CRP mg/L 3.0	Transferrin Sats % 15

$\dot{V}E$ = minute ventilation, $\dot{V}CO_2$= carbon dioxide output, SpO_2 = peripheral oxygen saturation, HR = heart rate, HRR_1 = heart rate at 1 minute recovery, BP = blood pressure, $\dot{V}O_2$ = oxygen uptake, O_2 pulse = oxygen pulse, RER = respiratory exchange ratio, Hb = hemoglobin, CRP = C-reactive protein

Figure 3c: 9 panel plot – based on the conventional UCLA method of displaying gas-exchange derived variables during CPET. The panels are numbered sequentially 1 – 9, from left to right, top row to bottom row.



W = unloaded cycling, T = loaded cycling, VT2 = anaerobic threshold, R = recovery, V'E = minute ventilation, HR = heart rate, V'O2 = oxygen uptake, V'CO2 = carbon dioxide output, EqO2 = ventilatory equivalents for oxygen, EqCO2 = ventilatory equivalents for carbon dioxide, VTex = tidal volume expired, RER = respiratory exchange ratio, PETO2 = end tidal pressure of oxygen, PETCO2 = end tidal pressure of carbon dioxide

Answer

This is a maximal exercise test as evidenced by a $\dot{V}O_{2peak}$ of 19.7mL/kg/min, RER_{peak} 1.24, HR_{peak} 170 bpm (117% predicted maximal heart rate) and peak work rate of 95W, all of which show an improvement after prehabilitation. An AT of 14.9 mL/kg/min and $\dot{V}E/\dot{V}CO_2$ of 30.0 at AT, places this patient back in a low-risk perioperative category. The tachycardia seen at rest is still present, but is improved compared to the previous test.

Optimization of modifiable risk factors after neoadjuvant therapy has increased the physiological capacity of this patient. While CPET provides objective evidence of accrued homeostatic reserve, high dependency care should be planned postoperatively because of the procedural risk involved. Surgical options should only proceed once the patient is fully informed of the risks of having major surgery with curative intent, whilst also being given the opportunity to express their life values and goals in the context of their disease and treatment options. This process of shared decision making (SDM); discussing whether to proceed with major curative surgery, palliative surgery, or non-surgical management is complex. In this case, the CPET results before, and after prehabilitation, were instrumental in guiding the multidisciplinary discussion of risk vs. benefit. The patient opted for operative intervention which was successful and made a full recovery.

Discussion

Clinician-based subjective assessment of patient functional status and surgical risk is notoriously poor at forecasting postoperative morbidity and mortality[2]. Objective, evidence-based, and resourceful means of risk stratifying preoperative patients prior to major surgery are necessary to mitigate modifiable risks, plan prehabiliation, guide intra- and post-operative management and inform SDM discussions for complex patients [31]. A recent multicentre, prospective, cohort study found CPET improved predictions of moderate or severe postoperative complications[2]. Cardiopulmonary exercise testing however, is resource intensive, and as such, we need to identify the cohort of patients for whom CPET will provide the greatest benefit. It is recommended that tools such as the such as the Duke Activity Score Index (DASI), the American College of Surgeons

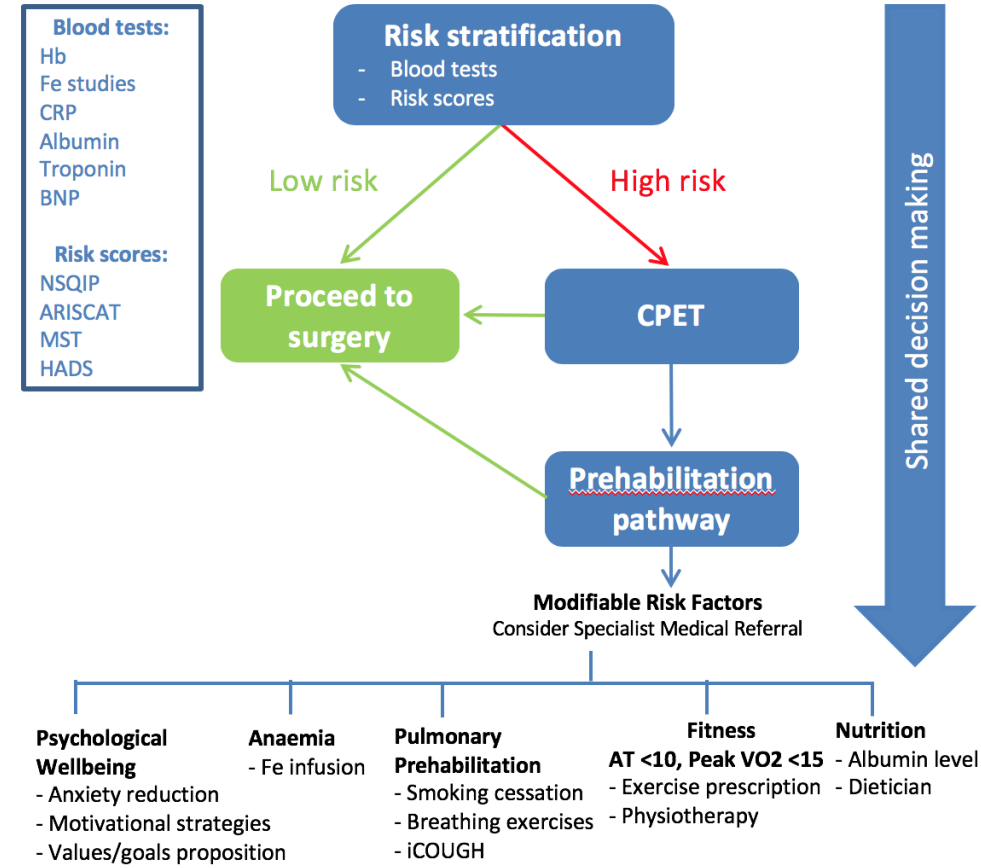
National Quality Improvement Program (NSQIP) risk calculator and biomarkers such as B-type natriuretic peptide (BNP) and troponin, are utilized for this purpose[2,8,31]. Research suggests that patients embarking upon neoadjuvant therapy and high-risk surgery, such as in this case, should undergo CPET triaging irrespective of their underlying burden of comorbid disease because of the deconditioning of chemoradiotherapy treatment[7,8]. The association between CPET-derived indices of physical fitness and postoperative outcomes have been summarised in multiple systematic reviews[4,8,10,32].

AT, peak $\dot{V}O_2$, and $\dot{V}E/\dot{V}CO_2$ have consistently shown prognostic value[4,7,8,10,17,33,34]. These CPET-derived variables have been studied over a wide range of major surgical procedures including abdominal aortic aneurysm surgery, hepatobiliary surgery, liver and cardiac transplant surgery, upper gastrointestinal surgery, colorectal surgery, urological surgery, and thoracic surgery[3,8,9,11,14-17,33,35,36]. Different surgical approaches, institutional variations and patient cohorts may impact the external validity of CPET data[8]. As perioperative care pathways evolve, current research aims to identify individualized CPET thresholds for different types of procedures[8]. However, broadly speaking, patients at increased risk of postoperative morbidity and mortality seem to have an AT <10 – 11 mL/kg/min and peak $\dot{V}O_2$ <15 – 16 mL/kg/min[8,14-17,33-35].

The stress of major surgery and recovery can compromise the homeostatic reserve of our high-risk patients, leading to postoperative morbidity and mortality[37]. CPET data empowers the perioperative physician at preoperative counselling to inform on strategies for prehabilitation, medical optimization and shared decision-making. The data also aids forward planning of intraoperative management and postoperative disposition or consideration of palliative care [4,7,8,10,17]. This consequently allows for better utilization of our health care resources, but more importantly, better patient outcomes [4,7,8,10,17]. As value = outcome / cost in healthcare, any reduction in complications is a reduction in cost. Conversely, low risk patients identified via CPET can be safely cared for on the general surgical ward postoperatively at lower costs than HDU/ICU[4]. Both categories of patients should receive treatment within the framework of institutional ERAS pathways to reduce variability in perioperative management.

In order that each patient can better withstand the homeostatic disturbance of surgery, evidence directs us toward a holistic approach to encourage physical and mental resilience in our patients[38.39]. Prehabilitation encompasses this multimodal ideology with the focus on preoperative exercise training, nutritional supplementation, anaemia optimization, smoking cessation, psychosocial wellbeing and patient participation in their perioperative care through education (see Figure 5) [38-40].

Figure 5: Prehabilitation



Hb = hemoglobin, CRP = C-reactive protein, BNP = B-type natriuretic peptide, NSQIP = National Surgical Quality Improvement Program risk calculator, ARISCAT = Assess Respiratory Risk in Surgical Patients in Catalonia study – score for postoperative pulmonary complications, MST = malnutrition screening tool, HADS = Hospital Anxiety and Depression Scale, Fe = iron, iCOUGH = incentive spirometry, coughing and deep breathing, oral care, understanding, getting out of bed, head of bed elevation

As an example, "Surgery School" utilises the multidisciplinary team to deliver patient education about each of these elements of prehabilitation in an interactive, classroom-based environment[31,41]. Comradery is built through empathy as the patients learn together about the expectations for their surgical journey[31,41]. In addition, patient-centred education improves compliance, as they feel a sense of ownership over their care and responsibility towards outcomes[41]. Encouraging a patient to attend Surgery School with a relative or friend

also brings motivation into prehabilitation, within the framework of an external person providing support, encouragement and accountability for prehabilitation. The process of prehabilitation can be either initiated, or otherwise facilitated at a patient's CPET appointment, as this is an opportunity to target all of these modifiable risk factors.

CPET guides exercise prescription to improve fitness before surgery and reduce perioperative risk, by increasing physiological reserve. Exercise training has been proven to be beneficial among many patient populations including those with COPD, stroke, heart failure and claudication[4,10,36]. Exercise training is safe, feasible and improves health-related quality of life [27,36]. However, more robust research is required to demonstrate a clear link between exercise training and clinically relevant postoperative outcomes[38]. CPET provides an objective method to interrogate the efficacy of exercise training and the whole package of prehabilitation[10]. CPET allows for a structured, responsive exercise prescription to be individualised to the patients baseline functional capacity, and can be based on their heart rate, Borg Scale or Watts achieved at AT.

In this case study, the patient received neoadjuvant chemoradiotherapy and CPET highlights the decrement impact of such treatment upon functional status. A blinded interventional pilot study demonstrated a significant reduction in AT and $\dot{V}O_{2peak}$ in consecutive rectal cancer patients after neoadjuvant chemoradiotherapy[27]. Those patients that underwent a 6-week structured exercise training program showed a return of AT and $\dot{V}O_{2peak}$ back to baseline, while the control group continued to demonstrate a decline in functional capacity from baseline [27]. Similar treatment-related deconditioning has been observed in patients with gastroesophageal cancer receiving neoadjuvant chemotherapy [28-30]. A number of clinical trials are in progress to further examine the effect of exercise programs implemented during neoadjuvant therapy and their impact on fitness, symptoms, surgical and cancer outcomes [42,43]. As perioperative clinicians, we should strive to better quantify and qualify our prehabilitation programs[4] to best serve high risk patients, particularly at the 6–12 week window of opportunity between neoadjuvant treatment and surgery[4,10].

Multimodal prehabilitation centred around CPET, allows practitioners to deliver on the value-based proposition of healthcare (value = outcomes / cost) through optimization of modifiable risk factors (e.g. anaemia, nutrition, physical activity, smoking, alcohol, mental well-being) and by targeting health promotion and patient education[44]. A recent US review suggested that 2 out of 3 patients are malnourished prior to gastrointestinal surgery with an associated 3-fold increased morbidity and 5-fold increased mortality[45]. Despite this, only 1 in 5 hospitals surveyed in the US provided nutritional screening and only 1 in 5 patients received nutritional optimization preoperatively[45]. Health economic data indicates that for every $1 invested in nutritional optimization, there are estimated $52 in hospital savings[45]. Early identification and treatment of preoperative anaemia with the adoption of a system-wide patient blood management program, resulted in reduced blood transfusions, reduced hospital length of stay, reduced patient mortality and considerable health-care savings[46]. Physiotherapist-led preoperative breathing-exercise training for patients receiving upper abdominal surgery has shown to decrease postoperative pulmonary complications rates by half[26]. Similarly, small randomized-controlled trials utilizing multimodal prehabilitation, have demonstrated a reduction in postoperative complications by 50%[47]. Prehabilitation is an evolving a risk-adapted approach to perioperative medicine[48] balanced against our finite health resources, perioperative physicians are at the cornerstone of opportunity for ensuring improved patient outcomes after surgery and reduced healthcare costs through CPET.

Case Four

A 31-year-old patient is booked for laparotomy and resection of a retroperitoneal sarcoma. An acute onset cardiomyopathy secondary to neoadjuvant anthracycline chemotherapy was diagnosed prior to presenting for

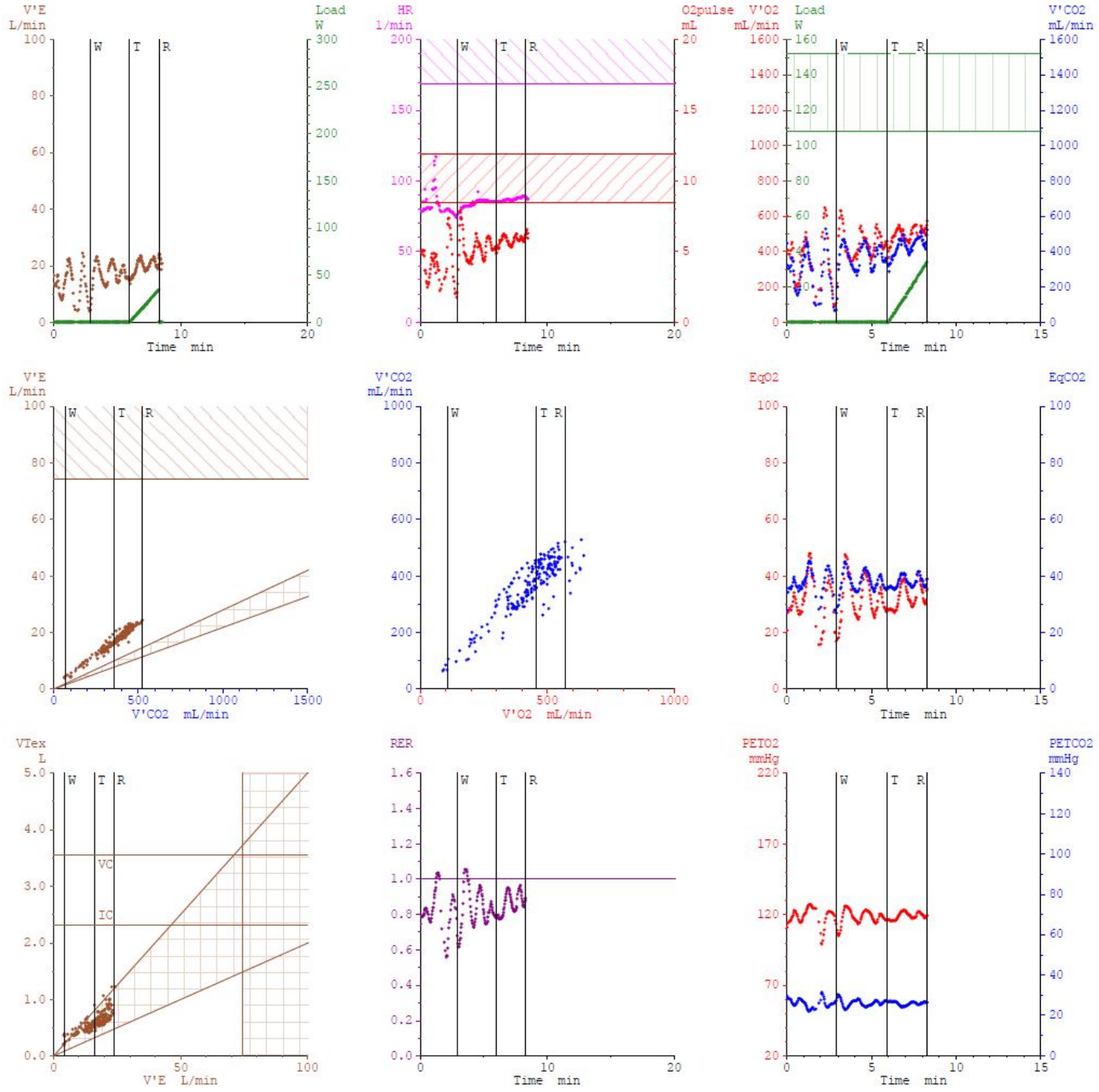
CPET. The patient is managed medically with an ACE inhibitor, diuretics including spironolactone, ivabradine, digoxin and amiodarone. The most recent transthoracic echocardiogram reports an ejection fraction of 20% and grade 4 global systolic dysfunction. The CPET referral form asks you to risk stratify this patient and to triage their postoperative disposition. You begin exercise on a 10 Watt/min ramp protocol. The test is stopped after 8.1 minutes of cycling on an upright cycle ergometer when the patient complains of feeling light headed. The test results are provided below. The patient has a BMI of 28 kg/m² and BSA 1.8 m².

Table 4: Case Four CPET data

Data	Rest	AT	Peak	% Predicted Exercise	Maximum at Peak
FEV_1 [L]	3.0				58.5%
MVV [L/min]	110				90 %
Breathing Reserve [%]	82				
DLCO [mL/min/mmHg]	15				62%
$\dot{V}E/\dot{V}CO_2$	39.8	35.7	37.5		
$\dot{V}E$ [L/min]	8	13	20		
SpO_2 [%]	100	96	98		
HR [bpm] HRR_1 [bpm]	76	85	89		47 % Recovery 85
BP	95/50	70/45	70/48		Recovery 90/60
$\dot{V}O_2$ [mL/kg/min]	2.8	6.1	7.0		27%
O_2 pulse [mL/beat]	2.7	5.3	5.9		58%
RER	0.89	0.78	0.88		
Load [W]	0	3	34		26%
Blood Results	Hb g/L 95	Albumin g/L 35	CRP mg/L 45	Transferrin Sats % 21	

FEV_1= forced expiratory volume in the first second of forced expiration, MVV = maximum voluntary ventilation, DLCO = lung diffusing capacity for carbon monoxide, $\dot{V}E$ = minute ventilation, $\dot{V}CO_2$= carbon dioxide output, SpO_2 = peripheral oxygen saturation, HR = heart rate, HRR_1 = heart rate at 1 minute recovery, BP = blood pressure, $\dot{V}O_2$ = oxygen uptake, O_2 pulse = oxygen pulse, RER = respiratory exchange ratio, Hb = hemoglobin, CRP = C-reactive protein

Figure 4: 9 panel plot – based on the conventional UCLA method of displaying gas-exchange derived variables during CPET. The panels are numbered sequentially 1 – 9, from left to right, top row to bottom row.



W = unloaded cycling, T = loaded cycling, VT2 = anaerobic threshold, R = recovery, V'E = minute ventilation, HR = heart rate, V'O2 = oxygen uptake, V'CO2 = carbon dioxide output, EqO2 = ventilatory equivalents for oxygen, EqCO2 = ventilatory equivalents for carbon dioxide, VTex = tidal volume expired, RER = respiratory exchange ratio, PETO2 = end tidal pressure of oxygen, PETCO2 = end tidal pressure of carbon dioxide

Question 1

Is this a maximal exercise test? List the findings to back your conclusion.

Answer

This is a submaximal test.

- AT is not achieved; see panels 5, 6 and 9 using the three criteria for AT determination
- RER is <1.0 at peak; see panel 8
- Low peak $\dot{V}O_2$ of 7.0 mL/kg/min (30% of predicted); see panel 3

A low maximal HR of 90 (45% of predicted) is observed (see panel 2). Ivabradine selectively inhibits the sinoatrial node and may be responsible for the patient's poor chronotropic response to exercise.

Question 2

Identify the CPET data that support a cardiac etiology to explain this patient's exercise limitation.

Answer

- Symptom limited test secondary to light-headedness
- Exercise-induced decrease in systolic blood pressure
- AT not achieved; see panels 5, 6 and 9 using the three criteria for AT determination
- Low oxygen pulse at peak exercise; see panel 2
- $\dot{V}O_2$/WR <10 mL/W; see panel 3
- Oscillatory breathing during exercise suggestive of heart failure; see panel 1, 3, 6 and 9
- Poor heart rate recovery at 1 minute after cessation of exercise (< 12bpm difference in HR from peak exercise to 1 minute recovery; 89 – 85 = 4 bpm); see panel 2
- Normal breathing reserve (MVV – $\dot{V}E_{peak}$/ MVV >15%; 110 – 20/110 = 82%); see panels 4 and 7

Question 3

What is your interpretation of the patient's blood pressure response to exercise and during recovery?

Answer

In health, systolic blood pressure increases with workload and diastolic blood pressure remains unchanged or may slightly decrease [1]. A reduction in systolic blood pressure should raise concern of significant cardiac pathology including myocardial ischemia, ventricular dysfunction or ventricular outflow tract obstruction [1 3]. Hypotension during exercise may also be caused by medications (e.g. diuretics, ACE inhibitors), autonomic dysregulation (e.g. diabetes) or hypovolaemia [1]. This patient has a low blood pressure prior to cardiopulmonary exercise testing in the context of heart failure. The symptomatic reduction in blood pressure with exercise is demonstrative of heart failure severity and is compounded by medical therapy. This is an absolute indication to stop the test and to continue monitoring during the recovery phase until baseline status has returned [1]. The blood pressure returned back to the pre-test level with recovery in this patient.

Question 4

What is your interpretation of the patient's heart rate response during the exercise and recovery phase of CPET?

Answer

Heart rate normally increases in proportion to work rate during incremental exercise. This is a result of increased sympathetic and decreased parasympathetic nervous system activity[49]. The rate of change in heart rate, or chronotropic response, can be affected by a number of factors such as age, fitness, type of exercise, body posture, medications (e.g. beta blockers) and heart transplantation[50]. In this case, selective inhibition of the sinoatrial node with ivabradine may have contributed to the chronotropic incompetence that was observed (<80 – 85% predicted maximum heart rate for age at peak exercise)[51]. The heart rate at 1 minute into the recovery phase (85 bpm) is within 12 bpm of the heart rate value at peak (89 bpm) and this suggests a lack of parasympathetic reactivation normally observed in healthy individuals[3,49].

Discussion

Heart failure is the predominant pathology responsible for this patient's exercise limitation, though an element of global deconditioning is also likely to be contributing to the overall functional impairment. Cardiac output cannot be increased sufficiently to meet the metabolic demands of exercising skeletal muscle and end-organ perfusion is compromised, leading to presyncope and test termination. This occurs before sufficient anaerobic metabolism takes place such that AT is not achieved.

CPET provides important prognostic information for patients with heart failure[3,5]. It is used to prescribe exercise for cardiac rehabilitation [3], to assess the efficacy of heart failure treatment[3,5], and to guide patient selection for advanced heart failure therapies such as placement of ventricular assist devices and heart transplantation[3,5,12,52]. Peak oxygen consumption is predictive of death in patients with heart failure, regardless of beta-blocker status, or whether patients have reduced or preserved ejection fraction[53]. Weber Classes A, B, C, and D corresponding to peak $\dot{V}O_2$ >20, 16 – 20, 10 – 15.9, and <10 mL/kg/min respectively are used for risk stratification in patients with cardiac failure, and also for pre-surgical assessment[5,11]. This patient's exercise test was used to assess heart failure severity and to monitor for reversibility of cardiac toxicity caused by anthracycline chemotherapy before surgery.

Valuable information about functional status, disease severity and prognosis can be gained, even from this submaximal CPET [12]. As discussed earlier, the oxygen pulse ($\dot{V}O_2$/HR ratio) provides dynamic information about cardiac function[12], and corresponds to stroke volume changes during exercise[3,5,54]. In this example, a low oxygen pulse suggests an inability of the heart to augment stroke volume in response to increasing workload [3,5]. Thus, a flat oxygen pulse may be an early warning of evolving myocardial ischemia[3,5,12] and in some patients, will be corroborated by ECG changes during exercise.

The ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ relationship) can also provide useful data in the submaximal exercise test. In fact, $\dot{V}E/\dot{V}CO_2$ is superior to peak $\dot{V}O_2$ at predicting outcomes and prognosis in heart failure[3,5] with a value of >34 pertaining to high risk[3]. As the $\dot{V}E/\dot{V}CO_2$ slope deviates further from normal, the risk of cardiac-related adverse events proportionately increases, as demonstrated in the Ventilatory Classification System (Class I < 30, Class II 30 – 35.9, Class III 36 – 44.9, Class IV ≥45)[3,5,55].

The exercise associated pattern of oscillatory breathing (EOB) seen in this case is pathognomonic of heart failure and independently conveys a poor prognosis, irrespective of reduced or preserved ejection fraction[5,56]. This breathing pattern is characterised by a cyclical pattern of hyperpnoea and hypopnoea, with an amplitude of ≥15% of the average resting value, for ≥ 60% of exercise[3,5]. Oscillatory breathing has been shown to strengthen the predictive value of $\dot{V}E/\dot{V}CO_2$ and peak $\dot{V}O_2$ for morbidity and mortality[57].

Chronotropic incompetence is quoted in the literature as an attenuated heart rate response to exercise and is referenced as <80–85% of the age-predicted maximum[3,49-51]. It has been associated with increased mortality in patients presenting for surgery with coronary artery disease[3,49,51]. However, medications (e.g. beta blockers) may confound its interpretation[3,49-51]. Heart rate recovery, a manifestation of returning parasympathetic nervous system tone[49], is defined as the difference between the heart rate at peak exercise and the heart rate at 1 minute of recovery (HRR_1), and it is normally >12 bpm [5]. It is a powerful, independent predictor of all-cause mortality when adjusted for age, gender, exercise capacity, the presence or absence of co-morbidities

such as hypertension, IHD, chronic lung disease and the use of beta blockers[3,49]. Subject effort does not impact HRR_1 and as such, it remains valuable even in submaximal tests such as illustrated in this case discussion[49]. HRR_1 adds value to $\dot{V}E/\dot{V}CO_2$ in predicting risk of death or hospitalization in patients with heart failure[58]. The analysis of heart rate during CPET may have even broader applications. In one study, cardiopulmonary exercise testing was found to be superior to stress ECG for identifying inadequately treated coronary heart disease, by investigation of the change in heart rate to work rate relationship (e.g. ΔHR-WR slope)[59].

In this case study, the process of SDM resulted in a patient led decision for a non-surgical approach, and further cardiac prehabilitation was pursued. Myocardial function somewhat recovered to an EF of 35% and grade 3 global systolic dysfunction. Over time, the patient reported feeling better, with improved exercise tolerance. Although routine transthoracic echocardiogram is not recommended for preoperative risk assessment in the absence of specific cardiac lesions (e.g. obstructive heart abnormality, severe pulmonary hypertension, undiagnosed cardiomyopathy) [60], echocardiographic findings may influence anaesthetic technique and intraoperative management. For this patient, demonstrating reversibility of the cardiomyopathy broadened the spectrum of chemotherapeutic agents available for cancer treatment. It was the full integration of cardiovascular, respiratory, haematological and metabolic assessment offered by CPET, however, that helped this patient and their treating team make an informed decision about the risk-benefit profile related to surgical intervention.

Conclusion

CPET is traditionally performed as a diagnostic test, however, its utility is far more extensive. It offers a means to identify and optimize modifiable risk factors, to educate and motivate our patients and to guide exercise prescriptions and assess the results of prehabilitation. Used within a multidisciplinary context, and

in shared decision making, CPET can help the patient to understand their choices framed in the context of their health, disease status and quality of life. In this role CPET aligns with the evidence base for major surgery and is essential in the armamentarium of the perioperative medicine clinician[4,10,16].

- CPET is an objective clinical test which interrogates functional capacity to assess perioperative risk.
- The results of CPET can help elucidate the underlying etiology of functional decline, including deconditioning, cardiac and respiratory pathology; representing an opportunity to optimize modifiable risk factors.
- A growing body of evidence supports the role of CPET in preoperative risk stratification to guide prehabilitation strategies, multidisciplinary management, postoperative care planning, patient-centred education and shared decision making.

MCQs

1. Which feature of the 9-panel plot is used to determine AT?
    a. The $\dot{V}O_2$ value when RER > 1.1
    b. The $\dot{V}O_2$ value when HR is > 85% of age-predicted maximum.

c. The modified V-slope method, which detects the inflection point of CO_2 from a tangent of $\Delta \dot{V}CO_2/\Delta\ O_2 = 1.0$

d. Identification of hyperventilation relative to CO_2 production.

Answer c

AT is defined as the oxygen uptake value, at which aerobic metabolism is supplemented by anaerobic glycolysis [1 3 7]. The measurable metabolic changes occurring after AT are: a systematic increase in CO_2 production, an increase in the respiratory exchange ratio (RER; or ratio of $\dot{V}CO_2/\dot{V}O_2$), a rise in blood lactate levels with a fall in blood bicarbonate levels, and a decrease in blood pH [1 3 7]. RER does not define the detection of AT, however AT > 1.0 indicates AT has already been reached[3]. The criterion used to identify AT are:

- Criterion 1: Identify excess $\dot{V}CO_2$ relative to $\dot{V}O_2$ (i.e. use the V-slope or modified V-slope method). The inflection observed in the $\dot{V}CO_2 - \dot{V}O_2$ relationship here is secondary to the buffering of anaerobic lactate *after AT* with consequent generation of more CO_2 (i.e. $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$).
- Criterion 2: Identify hyperventilation with respect to O_2 uptake, (i.e. locate the nadir of the ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}O_2$) slope and a rise in the end tidal oxygen ($P_{ET}O_2$) slope. At this point, $\dot{V}E$ increases and is driven by the excess CO_2 of anaeroboic glycolysis without a corresponding increase in $\dot{V}O_2$.
- Criterion 3: Exclude hyperventilation with respect to CO_2 production (i.e. confirm a plateau or decrease in the ventilatory equivalents for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) occurring at the point determined by criterion 1 and 2 above.

2. AT is seen as an inflection on the V-slope where the production of CO_2 increases in relation to O_2 uptake. What other CPET variables assist in the determination of AT?

   a. $\dot{V}E/\dot{V}CO_2$ remains constant or continues to decrease while $\dot{V}E/\dot{V}O_2$ rises.

   b. There is a fall in $P_{ET}O_2$

c. There is enhanced isocapnic buffering.

d. There is a fall in $P_{ET}CO_2$

Answer a

AT is the point when anaerobic respiration is required to sustain ATP production [1 3 7]. The consequent metabolic acidosis leads to an increase in P_aCO_2 matched with a proportional increase in $\dot{V}E$ [1 3 7]. Therefore at AT, the $\dot{V}E/\dot{V}CO_2$ relationship remains constant or decreases as $\dot{V}E/\dot{V}O_2$ starts to rise [7]. The phase during CPET when $P_{ET}O_2$ begins to rise and $P_{ET}CO_2$ remains stable is termed isocapnic buffering [1]. A fall in $P_{ET}CO_2$ at AT would indicate there was non-specific hyperventilation. The absence of a fall in $P_{ET}CO_2$ at AT excludes hyperventilation as the increase in $\dot{V}E$ is proportional to $\dot{V}CO_2$ [7].

3. Select the statement(s) which are true:

   a. Cardiac output normally increases linearly with respect to $\dot{V}O_2$

   b. $\dot{V}O_2$ and WR should increase linearly

   c. $\dot{V}O_{2peak}$ is volition independent

   d. $\dot{V}O_{2peak}$ is reproducible and is largely independent of ramp gradient

Answers a, b, d

In the setting of a steadily increasing work rate, oxygen consumption increases at a constant rate of ~10 mL/W and is independent of age, gender, BSA or training [1]. $\dot{V}O_{2peak}$ is reported as an absolute value in mL/min or L/min indexed to bodyweight (mL/kg/min or L/kg/min) or body surface area ($mL/m^2/min$) and is volitional dependent.

4. True or false. $\dot{V}O_{2max}$…..

   a. …is the highest oxygen uptake value measured during an incremental exercise test and can be determined in most patients.

b. …is a physiological end point where oxygen uptake cannot be increased further despite an increase in work and is often seen in highly trained athletes.

c. …is represented by $\dot{V}O_{2max}$ = (HR x SV) x [C(a-v)O_2]

d. …is rarely seen in the typical patient presenting to CPET

Answers a = false, b = true, c = true, d = true

$\dot{V}O_{2max}$ is an end point where oxygen uptake cannot be increased further despite increasing workload [7] and may be derived by the Fick equation [3]: $\dot{V}O_{2max}$ = (HR x SV) x [C(a-v)O_2]. $\dot{V}O_{2max}$ is representative of the upper limit of an individual's functional capacity. This is the sum total of their cardiorespiratory, vascular, haematological, musculoskeletal and metabolic systems working at their physiological maximum [1 3 7]. In athletes $\dot{V}O_{2max}$ may be observed as a plateau in the $\dot{V}O_2$ at peak, though in practice, this is rarely seen in the typical patient who presents to cardiopulmonary exercise testing for perioperative evaluation [1 3 7].
$\dot{V}O_{2peak}$ is the highest oxygen uptake measured during an incremental exercise test and as such represents the upper limit of an individual's functional capacity [1 3 5].

5. True or false. $\dot{V}O_{2peak}$ …

a. …is averaged over 20 seconds (or 3 – 5 breaths) during the final period of incremental work.

b. …provides an accurate representation of a patient's exercise limitation as shown by a plateauing of the O_2-WR relationship.

c. …is not related to a patient's volition or response to encouragement.

d. …is a useful variable in the assessment of a patient's overall exercise capacity and prediction of postoperative outcomes.

Answers a = true, b = true, c = false, d = true

$\dot{V}O_{2peak}$ can be altered by a patient's volition or with encouragement [7]. However, this does not mean it is not a useful CPET measurement. Indeed, $\dot{V}O_{2peak}$ referenced to patient's age predicted maximum or

BSA is increasingly being used to describe exercise limitation [8]. $\dot{V}O_{2peak}$ may help identify patients that can be encouraged to undertake a prehabilitation program.

6. Premature termination of CPET testing is advised:
    a. …in the setting of dyspnoea and chronic atrial fibrillation.
    b. …in the setting of multiple premature ventricular complexes.
    c. …in the setting of ST depression of >3 mm and the patient is asymptomatic.
    d. None of the above.

Answer d

According to guidelines the ECG criteria for premature CPET termination are >2mm ST depression if the patient is symptomatic, or 4mm ST depression if the patient is asymptomatic, or >1mm ST elevation [1 7]. Dyspnoea alone is not a reason to limit a test unless saturations fall markedly [1]. AF is not a reason to limit a test unless a lack of rate control leads to a fall in blood pressure [7]. Atrial and ventricular ectopic beats are not uncommon.

7. Select which of the following statements are true:
    a. RER is a ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ measured from gas exchange at the mouthpiece.
    b. RER is affected by diet.
    c. A peak RER of >1.1 is reassurance the patient worked hard during CPET.
    d. RER of <0.6 is physiologically implausible.

Answers a, b, c, d

The respiratory exchange ratio (RER) is the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ measured from expired gases at the mouthpiece during exercise[1 3]. This differs to the respiratory quotient (RQ), which is the ratio of CO_2 produced to O_2 consumed at the cellular level [1]. During steady state conditions, RER approximates to RQ and therefore RER may be used to determine whether carbohydrate or fat is the predominant fuel

source for the production of CO_2 [1]. At rest with a balanced diet, this ratio is normally about 0.8 [1]. This increases with exercise as $P_{ET}CO_2$ increases in response to aerobic and anaerobic respiration and $P_{ET}O_2$ decreases with greater O_2 uptake by working muscles [1]. To standardize CPET results patients are asked to starve for 2 hours before CPET [1]. A peak RER of > 1.1 is widely accepted as an indication of satisfactory patient effort [3 5].

8. Select which of the following statements are true:
    a. The $\dot{\boldsymbol{V}}E/\dot{\boldsymbol{V}}CO_2$ relationship provides information on dead space and V/Q matching.
    b. Normal $\dot{\boldsymbol{V}}E/\dot{\boldsymbol{V}}CO_2$ is described as >35 as AT.
    c. Elevated $\dot{\boldsymbol{V}}E/\dot{\boldsymbol{V}}CO_2$ is commonly seen in patients with COPD, interstitial lung disease, heart failure and pulmonary hypertension.
    d. Patients with cardiac failure do not generally exhibit oxygen desaturation.

Answers a, c, d

Normal $\dot{\boldsymbol{V}}E/\dot{\boldsymbol{V}}CO_2$ is <32–34 at AT and often <30 in healthy young individuals [1 5]. Unlike patients with lung disease, desaturation is less common in isolated cardiac disease [5]. Oxygen pulse ($\dot{\boldsymbol{V}}O_2$/HR) is a surrogate marker for stroke volume [1 3] sensitive to cardiac disease and may show a poor response to increased work rate in the setting of heart failure [3 5 12].

9. Which of the following statements are correct with respect to the maximal voluntary ventilation (MVV)?

a. MVV may be estimated as: FEV_1 x 40
b. It is the volume of gas inhaled and exhaled per minute
c. It is the maximal minute ventilation possible in one minute
d. It guides measurement of peak performance of lung and respiratory muscles

Answers a, c, d

MVV is maximal voluntary ventilation and it is the theoretical ventilatory limit of the respiratory system [1]. It is estimated indirectly by multiplying FEV_1 x 35 or 40, or can be measured directly with spirometry [1].

10. The following statements about breathing reserve are true:

a. Breathing reserve is the difference between MVV and peak minute ventilation ($\dot{V}E_{peak}$) during exercise.

b. Normal breathing reserve is normally >15% of the MVV.

c. Breathing reserve correlates poorly with pulmonary disease.

d. Breathing reserve shows an age-related decline related to an increase in dead space.

Answers a, b

Breathing reserve will be affected by pulmonary pathology hence shows a strong correlation [1].

Breathing reserve is related to the volume of expired air rather than dead space [1].

References

1. ATS/ACCP Statement on cardiopulmonary exercise testing. American journal of respiratory and critical care medicine 2003;**167**(2):211-77 doi: 10.1164/rccm.167.2.211[published Online First: Epub Date]|.
2. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet (London, England) 2018;**391**(10140):2631-40 doi: 10.1016/s0140-6736(18)31131-0[published Online First: Epub Date]|.
3. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010;**122**(2):191-225 doi: 10.1161/CIR.0b013e3181e52e69[published Online First: Epub Date]|.
4. Levett DZ, Grocott MP. Cardiopulmonary exercise testing for risk prediction in major abdominal surgery. Anesthesiology clinics 2015;**33**(1):1-16 doi: 10.1016/j.anclin.2014.11.001[published Online First: Epub Date]|.
5. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 2012;**126**(18):2261-74 doi: 10.1161/CIR.0b013e31826fb946[published Online First: Epub Date]|.
6. Lumb A. *Nunn's Applied Respiratory Physiology*. 8th Edition ed: Elsevier, 2016.
7. Levett DZH, Jack S, Swart M, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. British journal of anaesthesia 2018;**120**(3):484-500 doi: 10.1016/j.bja.2017.10.020[published Online First: Epub Date]|.
8. Older PO, Levett DZH. Cardiopulmonary Exercise Testing and Surgery. Annals of the American Thoracic Society 2017;**14**(Supplement_1):S74-s83 doi: 10.1513/AnnalsATS.201610-780FR[published Online First: Epub Date]|.
9. Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. The Journal of thoracic and cardiovascular surgery 2001;**121**(6):1064-8 doi: 10.1067/mtc.2001.113596[published Online First: Epub Date]|.
10. Levett DZ, Grocott MP. Cardiopulmonary exercise testing, prehabilitation, and Enhanced Recovery After Surgery (ERAS). Canadian journal of anaesthesia = Journal canadien d'anesthesie 2015;**62**(2):131-42 doi: 10.1007/s12630-014-0307-6[published Online First: Epub Date]|.
11. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. Circulation 2016;**133**(24):e694-711 doi: 10.1161/cir.0000000000000406[published Online First: Epub Date]|.
12. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. JACC. Heart failure 2016;**4**(8):607-16 doi: 10.1016/j.jchf.2016.03.022[published Online First: Epub Date]|.
13. Ganju AA, Fuladi AB, Tayade BO, Ganju NA. Cardiopulmonary exercise testing in evaluation of patients of chronic obstructive pulmonary disease. The Indian journal of chest diseases & allied sciences 2011;**53**(2):87-91
14. Kasivisvanathan R, Abbassi-Ghadi N, McLeod AD, et al. Cardiopulmonary exercise testing for predicting postoperative morbidity in patients undergoing hepatic resection surgery. HPB : the official journal of the International Hepato Pancreato Biliary Association 2015;**17**(7):637-43 doi: 10.1111/hpb.12420[published Online First: Epub Date]|.
15. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. British journal of anaesthesia 2016;**116**(2):177-91 doi: 10.1093/bja/aev454[published Online First: Epub Date]|.
16. Tolchard S, Angell J, Pyke M, et al. Cardiopulmonary reserve as determined by cardiopulmonary exercise testing correlates with length of stay and predicts complications after radical cystectomy. BJU international 2015;**115**(4):554-61 doi: 10.1111/bju.12895[published Online First: Epub Date]|.
17. Wilson RJ, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. British journal of anaesthesia 2010;**105**(3):297-303 doi: 10.1093/bja/aeq128[published Online First: Epub Date]|.
18. Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. American journal of respiratory and critical care medicine 2006;**173**(12):1390-413 doi: 10.1164/rccm.200508-1211ST[published Online First: Epub Date]|.

19. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest 2007;**131**(5 Suppl):4s-42s doi: 10.1378/chest.06-2418[published Online First: Epub Date]|.
20. Wren SM, Martin M, Yoon JK, Bech F. Postoperative pneumonia-prevention program for the inpatient surgical ward. Journal of the American College of Surgeons 2010;**210**(4):491-5 doi: 10.1016/j.jamcollsurg.2010.01.009[published Online First: Epub Date]|.
21. Cassidy MR, Rosenkranz P, McCabe K, Rosen JE, McAneny D. I COUGH: reducing postoperative pulmonary complications with a multidisciplinary patient care program. JAMA surgery 2013;**148**(8):740-5 doi: 10.1001/jamasurg.2013.358[published Online First: Epub Date]|.
22. Boston University School of Medicine - Surgery. I COUGH. Secondary I COUGH n.d. https://www.bumc.bu.edu/surgery/quality-safety/i-cough/.
23. Central Manchester University Hospitals - NHS Foundation Trust. I COUGH UK. Secondary I COUGH UK 2018. http://www.cmft.nhs.uk/information-for-patients-visitors-and-carers/enhanced-recovery-programme/icoughuk.
24. Saito H, Hatakeyama K, Konno H, Matsunaga T, Shimada Y, Minamiya Y. Impact of pulmonary rehabilitation on postoperative complications in patients with lung cancer and chronic obstructive pulmonary disease. Thoracic cancer 2017;**8**(5):451-60 doi: 10.1111/1759-7714.12466[published Online First: Epub Date]|.
25. Benzo R, Wigle D, Novotny P, et al. Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. Lung cancer (Amsterdam, Netherlands) 2011;**74**(3):441-5 doi: 10.1016/j.lungcan.2011.05.011[published Online First: Epub Date]|.
26. Boden I SE, Browning L, et al. . Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double blinded, multicentre randomised controlled trial. BMJ. 2018;360:j5916. AORN journal 2018;**108**(4):461-67 doi: 10.1002/aorn.12369[published Online First: Epub Date]|.
27. West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. British journal of anaesthesia 2015;**114**(2):244-51 doi: 10.1093/bja/aeu318[published Online First: Epub Date]|.
28. Jack S, West MA, Raw D, et al. The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2014;**40**(10):1313-20 doi: 10.1016/j.ejso.2014.03.010[published Online First: Epub Date]|.
29. Navidi M, Phillips AW, Griffin SM, et al. Cardiopulmonary fitness before and after neoadjuvant chemotherapy in patients with oesophagogastric cancer. The British journal of surgery 2018;**105**(7):900-06 doi: 10.1002/bjs.10802[published Online First: Epub Date]|.
30. Sinclair R, Navidi M, Griffin SM, Sumpter K. The impact of neoadjuvant chemotherapy on cardiopulmonary physical fitness in gastro-oesophageal adenocarcinoma. Annals of the Royal College of Surgeons of England 2016;**98**(6):396-400 doi: 10.1308/rcsann.2016.0135[published Online First: Epub Date]|.
31. Grocott MPW, Plumb JOM, Edwards M, Fecher-Jones I, Levett DZH. Re-designing the pathway to surgery: better care and added value. Perioperative medicine (London, England) 2017;**6**:9 doi: 10.1186/s13741-017-0065-4[published Online First: Epub Date]|.
32. Lee CHA, Kong JC, Ismail H, Riedel B, Heriot A. Systematic Review and Meta-analysis of Objective Assessment of Physical Fitness in Patients Undergoing Colorectal Cancer Surgery. Diseases of the colon and rectum 2018;**61**(3):400-09 doi: 10.1097/dcr.0000000000001017[published Online First: Epub Date]|.
33. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Journal of the American College of Cardiology 2014;**64**(22):e77-137 doi: 10.1016/j.jacc.2014.07.944[published Online First: Epub Date]|.
34. Hennis PJ, Meale PM, Grocott MP. Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. Postgraduate medical journal 2011;**87**(1030):550-7 doi: 10.1136/pgmj.2010.107185[published Online First: Epub Date]|.
35. Goodyear SJ, Yow H, Saedon M, et al. Risk stratification by pre-operative cardiopulmonary exercise testing improves outcomes following elective abdominal aortic aneurysm surgery: a cohort study. Perioperative medicine (London, England) 2013;**2**(1):10 doi: 10.1186/2047-0525-2-10[published Online First: Epub Date]|.

36. O'Doherty AF, West M, Jack S, Grocott MP. Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. British journal of anaesthesia 2013;**110**(5):679-89 doi: 10.1093/bja/aes514[published Online First: Epub Date]|.
37. Sankar A, Beattie WS, Wijeysundera DN. How can we identify the high-risk patient? Current opinion in critical care 2015;**21**(4):328-35 doi: 10.1097/mcc.0000000000000216[published Online First: Epub Date]|.
38. Levett DZ, Edwards M, Grocott M, Mythen M. Preparing the patient for surgery to improve outcomes. Best practice & research. Clinical anaesthesiology 2016;**30**(2):145-57 doi: 10.1016/j.bpa.2016.04.002[published Online First: Epub Date]|.
39. Wynter-Blyth V, Moorthy K. Prehabilitation: preparing patients for surgery. BMJ (Clinical research ed.) 2017;**358**:j3702 doi: 10.1136/bmj.j3702[published Online First: Epub Date]|.
40. Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology 2014;**121**(5):937-47 doi: 10.1097/aln.0000000000000393[published Online First: Epub Date]|.
41. University Hospital Southampton - NHS Foundation Trust. Press release: Hospital's innovative 'surgery school' transforming fitness of patients. Secondary Press release: Hospital's innovative 'surgery school' transforming fitness of patients 2018. http://www.uhs.nhs.uk/AboutTheTrust/Newsandpublications/Latestnews/2018/October-2018/Press-release-Hospital's-innovative-'surgery-school'-transforming-fitness-of-patients.aspx.
42. NIH U.S. National Library of Medicine - ClinicalTrials.gov. Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT). Secondary Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) 2018. https://clinicaltrials.gov/ct2/show/NCT03082495.
43. NIH U.S. National Library of Medicine - ClinicalTrials.gov. The Effects of a 9 Week Exercise Programme on Fitness and Quality of Life in Rectal Cancer Patients After Chemoradiotherapy and Before Surgery (SRETP). Secondary The Effects of a 9 Week Exercise Programme on Fitness and Quality of Life in Rectal Cancer Patients After Chemoradiotherapy and Before Surgery (SRETP) 2016. https://clinicaltrials.gov/ct2/show/NCT01914068.
44. Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? Anaesthesia 2019;**74 Suppl 1**:20-26 doi: 10.1111/anae.14505[published Online First: Epub Date]|.
45. Williams JD, Wischmeyer PE. Assessment of perioperative nutrition practices and attitudes-A national survey of colorectal and GI surgical oncology programs. American journal of surgery 2017;**213**(6):1010-18 doi: 10.1016/j.amjsurg.2016.10.008[published Online First: Epub Date]|.
46. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion 2017;**57**(6):1347-58 doi: 10.1111/trf.14006[published Online First: Epub Date]|.
47. Barberan-Garcia A, Ubre M, Roca J, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. Annals of surgery 2018;**267**(1):50-56 doi: 10.1097/sla.0000000000002293[published Online First: Epub Date]|.
48. Grocott MPW, Edwards M, Mythen MG, Aronson S. Peri-operative care pathways: re-engineering care to achieve the 'triple aim'. Anaesthesia 2019;**74 Suppl 1**:90-99 doi: 10.1111/anae.14513[published Online First: Epub Date]|.
49. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. The New England journal of medicine 1999;**341**(18):1351-7 doi: 10.1056/nejm199910283411804[published Online First: Epub Date]|.
50. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;**93**(8):1520-6
51. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Journal of the American College of Cardiology 2002;**40**(8):1531-40
52. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;**83**(3):778-86

53. Peterson LR, Schechtman KB, Ewald GA, et al. The effect of beta-adrenergic blockers on the prognostic value of peak exercise oxygen uptake in patients with heart failure. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2003;**22**(1):70-7
54. Abbott TEF, Minto G, Lee AM, Pearse RM, Ackland GL. Elevated preoperative heart rate is associated with cardiopulmonary and autonomic impairment in high-risk surgical patients. British journal of anaesthesia 2017;**119**(1):87-94 doi: 10.1093/bja/aex164[published Online First: Epub Date]|.
55. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. Circulation 2007;**115**(18):2410-7 doi: 10.1161/circulationaha.107.686576[published Online First: Epub Date]|.
56. Dhakal BP, Lewis GD. Exercise oscillatory ventilation: Mechanisms and prognostic significance. World journal of cardiology 2016;**8**(3):258-66 doi: 10.4330/wjc.v8.i3.258[published Online First: Epub Date]|.
57. Sun XG, Hansen JE, Beshai JF, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. Journal of the American College of Cardiology 2010;**55**(17):1814-23 doi: 10.1016/j.jacc.2009.10.075[published Online First: Epub Date]|.
58. Arena R, Guazzi M, Myers J, Peberdy MA. Prognostic value of heart rate recovery in patients with heart failure. American heart journal 2006;**151**(4):851.e7-13 doi: 10.1016/j.ahj.2005.09.012[published Online First: Epub Date]|.
59. Chaudhry S, Kumar N, Behbahani H, et al. Abnormal heart-rate response during cardiopulmonary exercise testing identifies cardiac dysfunction in symptomatic patients with non-obstructive coronary artery disease. International journal of cardiology 2017;**228**:114-21 doi: 10.1016/j.ijcard.2016.11.235[published Online First: Epub Date]|.
60. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. The Canadian journal of cardiology 2017;**33**(1):17-32 doi: 10.1016/j.cjca.2016.09.008[published Online First: Epub Date]|.