



# Can cardiopulmonary exercise testing predict the peri-operative inflammatory response in patients undergoing surgery for colorectal cancer?

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Cardiopulmonary exercise testing (CPET/CPX) has gained favour since the 1990s as a means of assessing cardiovascular and pulmonary function. CPET provides two key outcomes which are the oxygen consumption at the anaerobic threshold ( $\text{VO}_2$  at AT) and oxygen consumption at peak exercise ( $\text{VO}_2$  at peak). A number of studies have demonstrated that patients with a  $\text{VO}_2$  at AT  $<11$  mL/min/kg or  $\text{VO}_2$  at peak  $<19$  mL/min/kg have increased peri-operative mortality and complications (1-3). This test is used to counsel patients about operative risk and inform clinicians of patients who would benefit from planned high dependency or intensive care in the immediate post-operative period. An association between poor CPET performance and increased post-operative morbidity in patients with rectal cancer has been demonstrated (4,5). A systematic review examining the predictive role of CPET in patients undergoing surgery for colorectal cancer has also been performed previously, which reviewed seven studies (1,418 patients) and established that an AT below threshold was associated with increased complications, but not an increased risk of anastomotic leak (6).

In this issue of the journal McSorley (7) and colleagues examined the relationship between CPET variables and systemic inflammatory response (SIR) in the pre- and post-operative period and additionally the relationship to post-operative complications was examined.

The markers of pre- and post-operative SIR are the modified Glasgow Prognostic Score (mGPS) and C-reactive protein (CRP) respectively. Their study

used a prospectively maintained database to perform a retrospective observational study of 38 patients who underwent CPET over a 9-year period from 2008–2017. Extensive demographic data, information regarding surgical procedure and the CRP and albumin measurements were recorded. The mGPS was calculated from the pre-operative CRP and albumin (8).

The patients were predominantly male (79%) and over 65 years (79%). Almost two thirds of patients had a laparoscopic procedure. Thirty-nine percent of patients experienced a complication but only 8% had a complication that was registered as a Clavien-Dindo 3 or above (9), which required major intervention by definition. The study identified an association between increasing American Society of Anaesthesiology (ASA) score and reduced  $\text{VO}_2$  at peak, confirming that those patients who are clinically deemed less fit do have less cardiovascular reserve when objectively measured.

The study found no association between pre-operative inflammatory response as measured by mGPS and  $\text{VO}_2$  at AT. There was a trend for patients with a higher pre-operative ASA to have a raised pre-operative systemic response but this did not reach statistical significance ( $P=0.058$ ). The authors did identify an association between  $\text{VO}_2$  at AT and increased ASA grade, but this association was not found with any of the other measured patient demographics, tumour characteristics or pre-operative inflammatory response.

The primary outcome measure of the study did not

identify a relationship between  $VO_2$  at AT and post-operative inflammatory response as measured by CRP on day 3 or 4 post-operatively and there was no relationship between  $VO_2$  at AT and post-operative complications. With attention focussed on the  $VO_2$  at peak an association between decreased  $VO_2$  at peak and increased ASA was found, mirroring the other major CPET outcome. There was an association found between decreased  $VO_2$  at peak and pre-operative inflammation with raised mGPS.

There is an increased focus on measuring the systemic inflammation in the peri-operative period with a number of studies examining the relationships that influence the systemic inflammatory response, particularly in relation to surgical approach. It is reported that the post-operative CRP is lower in patients undergoing laparoscopic surgery within an enhanced recovery program although it rises in those patients who experience a complication (10). Similarly, there are reported differences in pre-operative SIR between right sided tumours, which have a higher pre-operative SIR than rectal tumours as evidenced by mGPS and neutrophil-lymphocyte ratio (NLR) and that a high pre-treatment SIR measured by mGPS and NLR is associated with decreased survival in patients with metastatic colorectal cancer (11,12).

Whilst the authors quote papers that describe a relationship between post-operative inflammatory response and patients' experiencing complications following surgery, it is important to recognise that the relationship described is an association and causation is not established (13,14). It is not unreasonable to propose that the rise in the post-operative inflammatory response is because of the complication rather than the complication following a post-operative inflammatory response. The fact that this pilot study did not establish the associations defined as primary outcomes is unlikely to diminish research in this area. The limited size of the cohort limits the sensitivity of the study. What will need to be addressed in future studies is whether the systemic inflammatory response contributes to the development of complications or is simply a consequence of them?

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