Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

merely reflects the proportion of patients with a baseline pain score of 40–59 mm. This demonstrates that positive effects on cut-off thresholds can originate mainly from the distribution of data. That aside, we agree that reducing pain levels among patients with severe or moderate pain is the main target and that the use of cut-off-derived outcomes may be favourable in some situations.[7] However, trialists should still determine clinically important risk reductions when calculating the sample size.[5] Absolute, relative, and cut-off threshold outcomes all have shortcomings. As suggested by Araujo and colleagues,[1] the optimal scale may depend on the baseline pain level. Still, the power calculation is based on a one-scale effect size, which the trial is powered to detect. Using different scales in the same trial defies the basics of the power calculation and could make it difficult to analyse whether trials are adequately powered and increase the risk of a type 1 error by multiple testing. Therefore, we currently recommend against adaptive MCID strategies.

Because there are currently no tests that can reliably detect individuals at high risk of severe postoperative pain, we find it important to distinguish between types of pain trials. For trials aiming to improve standard regimens administered perioperatively to all individuals, the effect of the total population should be considered. For trials aiming to optimise treatment for those individuals who experience moderate to severe pain, this population should be used. Still, the interventions able to reduce severe pain also work on mild pain and *vice versa*. Because of floor effect, patients with mild pain cannot benefit as much on an absolute scale as patients with severe pain. However, this can be partially accommodated by using a relative MCID value, particularly in heterogeneous patient cohorts. Further, publication of individual patient data enables investigation of the effect in relevant subgroups (e.g. high pain responders).

Finally, the MCID can be influenced by other factors such as the adverse event profile, baseline risk, patient and system inconvenience, costs, and compounded outcome effects (e.g. a split effect between pain relief and opioid requirements).[4,6] Therefore, MCID may change between a harmless systemic basic analgesic (e.g. paracetamol) and an invasive, costly intervention with risk of adverse events (e.g. epidural).

In conclusion, using patient-relevant MCID as effect size is key in correctly powering a trial and subsequently interpreting whether the observed effect of the intervention is clinically relevant.

Declarations of interest

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Impaired systemic oxygen extraction long after mild COVID-19: potential perioperative implications

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Editor—The extraordinary number of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections worldwide has made it inevitable that patients who have recovered from COVID-19 will present for anaesthesia and surgery. Recent data indicate that in the USA alone, approximately one-third of the population had been infected by the end of 2020.[1] With this in mind, we read with interest the recent correspondence by Silvapulle and colleagues[2] underscoring the wide range of symptoms that often follow recovery from COVID-19 and the complexity of considering residual physiologic abnormalities when assessing perioperative risk. They note that patients suffering from 'long COVID' have been reported to exhibit demonstrable abnormalities in several biomarkers as well as cardiac, neurological, haematologic, renal, hepatic, and endocrine impairment. Based on current evidence, the authors suggest that patients previously experiencing mild COVID-19 but without clear evidence of these sequelae can be regarded as having minimal additional perioperative risk. In this context, the relatively young person who suffered mild COVID-19 a year earlier and complains of exertional fatigue but admits to being sedentary and unfit, and has no objective evidence of cardiopulmonary disease or other organ dysfunction will likely raise little concern.

Although the morbidity and mortality associated with severe COVID-19 have appropriately received considerable attention, most SARS-CoV-2 infections result in relatively mild, self-limited symptoms not requiring hospitalisation. Nonetheless, some of these patients subsequently experience persistent fatigue and reduced exercise capacity that is not attributable to cardiopulmonary impairment diagnosed by conventional means.[3] Several mechanisms have been proposed including anaemia, deconditioning, and red blood cell abnormalities.[4] However, many of the studies describing these mechanisms were conducted in patients after hospitalisation, within a few months of recovery.

A central focus of perioperative management has always been maintenance of systemic oxygen delivery (DO_2) and tissue perfusion. Toward this end, research has defined how the fundamental relationships between DO_2, tissue oxygen consumption (VO_2), and oxygen extraction (EO_2) shift from the intraoperative setting where VO_2 tends to be reduced, to the postoperative period when VO_2 increases.[5] Although a range of postoperative complications have been linked to suboptimal tissue DO_2,[6,7] the incidence of these complications appears relatively low in relation to the documented incidence of perioperative hypoxaemia,[8,9] particularly when considered in light of potential coincidence with other common factors such as anaemia, hypovolaemia, and transient hypotension. A contributing factor may be that, as with most physiological systems, evolutionary pressure has yielded compensatory mechanisms for reduced DO_2 to many organs. Under most circumstances, when DO_2 is low, VO_2 is maintained by augmented EO_2 to prevent tissue hypoxia.[10] This compensatory EO_2 reserve persists until limits that vary among tissue beds are reached and VO_2 becomes DO_2-dependent. Ultimately, in the perioperative setting where alterations in regional VO_2/DO_2 balance occur with regularity, it is probable that this EO_2 reserve is working continuously 'behind the scenes' for organ protection.

But what if this seemingly occult protective mechanism is impaired? Clinical experience imparts heightened suspicion of tissue vulnerability in patients with defined end-organ dysfunction or risk factors for reduced functional reserve such as aging, smoking, diabetes mellitus, or hypertension. But how does this affect that relatively young person who admits to being sedentary and unfit but has no objective evidence of cardiopulmonary disease, and whose only other notable medical history is mild COVID-19 a year earlier? A recent report proposed the existence of a specific 'long COVID phenotype' with exertional intolerance and dyspnoea despite normal pulmonary function,[11] raising the question of whether there is more to this patient than meets the eye.

Recently published data indicate that this may well be the case. Singh and colleagues[4] performed invasive cardiopulmonary exercise testing (iCPET) on 10 patients (mean age=48 yr; range, 28–79 yr; nine out of 10 female) with persistent exertional limitation 11 (1) months after mild COVID-19. None of the patients had abnormalities evident on chest CT imaging, pulmonary function testing, or resting echocardiogram, and all had normal haemoglobin levels. Study results were compared with those of a matched control group of 10 patients with normal exercise capacity and no history of COVID-19. As shown in Table 1, relative to control patients at rest, DO_2 was the same for post-COVID-19 patients but VO_2 and systemic EO_2 were modestly reduced. At peak exercise, when functional reserve mechanisms normally increase both DO_2 and EO_2, the difference in VO_2 and EO_2 between control and post-COVID-19 patients was more profound. Importantly, this disparity occurred despite a peak exercise response for heart rate and DO_2 that was similar for both groups. These results indicate that exercise capacity was primarily limited by impaired systemic EO_2 of such severity that what should have been an adequate increase in DO_2 was insufficient to allow for an increase in VO_2. Although patients who are deconditioned can exhibit impaired EO_2 with exercise,[12] preservation of the capacity to increase heart rate and cardiac output adequately at peak exercise in post-COVID-19 patients makes deconditioning a less likely singular explanation for their exercise limitation. In fact, several patients included in the study had already completed supervised exercise rehabilitation programs by the time of their iCPET. The lack of objective evidence for the presence of other factors such as anaemia, impaired cardiac or pulmonary function, or superimposed non-COVID infection suggests a possible microvascular/molecular abnormality. It is worth noting the overlap between the clinical presentations of patients with post-COVID-19 exercise limitation and patients with myalgic encephalitis/chronic fatigue syndrome.[13] The causal hypothesis of myalgic encephalitis/chronic fatigue syndrome has also been linked to preceding infection including human herpes virus, enterovirus, influenzae, Epstein–Barr virus (EBV), and *Borrelia burgdorferi*.[14,15]

Table 1 Baseline characteristics and relevant cardiopulmonary exercise data. Data are presented as %, mean (standard deviation), or median (inter-quartile range [IQR]). Data adapted from Singh and colleagues.[4] FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SaO_2, oxygen saturation in arterial blood; DO_2, oxygen delivery; VO_2, oxygen consumption; EO_2, oxygen extraction ratio, CPET, cardiopulmonary exercise testing.

	Post-COVID-19 (n=10)	Controls (n=10)	P-value
Characteristics			
Age, yr (range)	48 (28–79)	48 (40–68)	0.87
Female/male	9/1	8/2	0.53
BMI (kg m^{-2})	28 (6)	24 (6)	0.11
Haemoglobin (g dl^{-1})	13.4 (1.1)	14.2 (1.4)	0.16
Interval time from acute infection (months)	11 (1)	Not applicable	
Pulmonary function tests			
FEV_1 (% predicted)	97 (1)	100 (1)	0.34
FVC (% predicted)	96 (1)	104 (1)	0.19
FEV_1/FVC (% predicted)	101 (3)	98 (5)	0.18
CPET – resting			
SaO_2 (%)	98 (IQR 97–98)	98 (IQR 97–98)	0.64
Mixed venous O_2 saturation (%)	73 (3)	66 (6)	0.01
Stroke volume index (ml m^{-2})	36.3 (10.3)	40.3 (12.8)	0.44
Cardiac index (L min^{-1} m^{-2})	3.2 (0.6)	2.8 (0.5)	0.13
DO_2 (ml kg^{-1} min^{-1})	1.41 (0.24)	1.24 (0.35)	0.23
VO_2 (ml min^{-1} kg^{-1})	3.69 (0.5)	4.38 (0.8)	0.04
Systemic EO_2 (ratio)	0.26 (0.03)	0.36 (0.01)	0.01
CPET – peak exercise			
VO_2 (ml min^{-1} kg^{-1})	16.7 (4.2)	33.5 (12.9)	0.001
Heart rate (% predicted)	84 (8)	84 (2)	0.85
SaO_2 (%)	98 (IQR 98–98)	97 (IQR 97–98)	0.01
Mixed venous O_2 saturation %)	50 (10)	22 (5)	<0.0001
DO_2 (ml kg^{-1} min^{-1})	3.6 (1.4)	4.2 (1.5)	0.33
Systemic EO_2 (ratio)	0.49 (0.1)	0.78 (0.1)	<0.0001
Cardiac index (L min^{-1} m^{-2})	7.8 (3.1)	8.4 (2.3)	0.59
Stroke volume index (ml m^{-2})	54.1 (20.8)	63.5 (22.2)	0.34

Given the broad heterogeneity of symptoms associated with COVID-19, the complexity of accurately measuring EO_2, and the fact that a substantial number of people have undoubtedly experienced mild but undiagnosed SARS-CoV-2 infection,[1] it is difficult (if not impossible) to define the incidence, much less the consequences, of impaired EO_2 reserve after mild COVID-19 in the surgical population. Ultimately, we agree with Silvapulle and colleagues[2] that at present the best approach to perioperative risk assessment in post-COVID-19 patients is tangible, objective evaluation of multiorgan sequelae. Nonetheless, clinicians should be aware that a deficit may exist that can mimic impaired tissue DO_2 despite normal cardiopulmonary function and haemoglobin level, and potentially enhance the adverse consequences of perioperative hypoxaemia, anaemia, or impaired tissue perfusion. We are just beginning to learn about the long-term sequelae of even mild COVID-19, underscoring the need to be vigilant to the potential for a broader perioperative impact of prior SARS-CoV-2 infection.

Declarations of interest

The authors declare no conflicts of interest.

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