Exercise-induced hypoxia among emergency department patients admitted for suspected COVID-19

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Received 22 January 2021
Accepted 31 July 2021
Published Online First 6 August 2021

To cite: Davies P, Jones T, Bartilotti-Matos F, *et al*. *Emerg Med J* 2021;**38**:794–797.

ABSTRACT

Background Exercise-induced hypoxia (EIH) has been assessed at ED triage as part of an assessment of COVID-19; however, evidence supporting this practice is incomplete. We assessed the use of a 1-minute sit-to-stand exercise test among ED patients admitted for suspected COVID-19.

Methods A case note review of all ED patients assessed for suspected COVID-19 between March and May 2020 at Monklands University Hospital was conducted. Demographic characteristics, clinical parameters, baseline blood tests and radiographic findings, hospital length of stay, intensive care and maximum oxygen requirement were obtained for those admitted. Using logistic regression, the association between EIH at admission triage and COVID-19 diagnosis was explored adjusting for confounding clinical parameters.

Results Of 127 ED patients admitted for possible COVID-19, 37 were ultimately diagnosed with COVID-19. 36.4% of patients with COVID-19 and EIH had a normal admission chest radiograph. In multivariate analysis, EIH was an independent predictor of COVID-19 (adjusted OR 3.73 (95% CI (1.25 to 11.15)), as were lymphocyte count, self-reported exertional dyspnoea, C-reactive peptide and radiographic changes.

Conclusions This observational study demonstrates an association between EIH and a COVID-19 diagnosis. Over one-third of patients with COVID-19 and EIH exhibited no radiographic changes. EIH may represent an additional tool to help predict a COVID-19 diagnosis at initial presentation and may assist in triaging need for admission.

Key messages

- What is already known on this subject?
- Exercise tests have been used as a triage tool in the ED for assessing the need for admission in possible COVID-19 cases. There is some evidence of exercise-induced hypoxia (EIH) associated with mechanical ventilation requirements. However, there is scant evidence of the frequency of EIH or a standardised approach to elicit it.
- What this study adds?
- We demonstrate an association between exertional desaturation, with a 1-minute sit-to-stand test, and being COVID-19 positive. EIH occurred in the absence of chest radiographic changes in one-third of cases. These findings provide a basis for consideration of the 1-minute sit-to-stand test as an adjunct to COVID-19 assessment.

BACKGROUND

COVID-19 has a highly variable presentation and course, ranging from asymptomatic to acute respiratory failure.[1] Exercise-induced hypoxia (EIH) occurs with disruption to alveolar gas exchange, as also in *Pneumocystis jirovecii* pneumonia (PJP) or interstitial lung disease (ILD), and may occur without radiographic changes.[2 3] EIH has been used anecdotally in EDs and is advocated in primary care guidelines and an international consensus document from the World Academic Council of Emergency Medicine, yet the evidence base for its association with COVID-19 is limited.[4–6] A recent systematic review identified only two studies which have investigated EIH in COVID-19.[7] One study focused on its use at discharge and identification of pulmonary embolism.[8] Another retrospective study of admissions to 70 UK hospitals assessed the association between EIH and subsequent need for mechanical ventilation. Despite a large cohort, only a small proportion of patients suspected of having COVID-19 (3%) were actually assessed for EIH, without procedural standardisation.[9] These studies are unable to estimate prevalence of EIH as a phenomenon in patients who tested positive for COVID-19 in the acute setting, nor contextualise any associations with routine clinical investigations. As highlighted by Kalin *et al*, such data are important in exploring the role of EIH testing in triaging the need for admission of suspected cases of COVID-19.[7]

A 1-minute sit-to-stand exercise test (1MSTST) was incorporated into the ED assessment of COVID-19 at our hospital in March of 2020. We examined the association of EIH and ultimate diagnosis of COVID-19 among patients admitted to hospital for suspected COVID-19.

METHODS

We conducted a retrospective medical record review of patients presenting to the Monklands University Hospital, Airdrie, UK ED inclusive of 31 March and 31 May 2020 and subsequently admitted to the hospital for suspected COVID-19. Inclusion

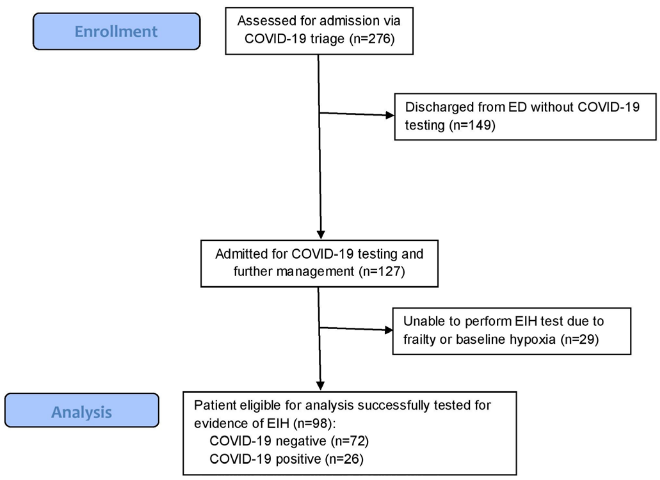

Figure 1 A STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flowchart demonstrating the pathway for patient selection. EIH, exercise-induced hypoxia.

criteria for the COVID-19 assessment pathway were a clinical suspicion of COVID-19 plus at least one of the following: fever, new continuous shortness of breath, new continuous cough, influenza-like symptoms or immunocompromised status. All patients ascribed to this pathway were recorded. Patients underwent a 1MSTST for EIH by ED nursing staff at triage, as part of an initial set of routine physical observations. Subsequent assessment of clinical condition, and history performed by middle grade physicians determined the need for admission. For this test, patients stood from sitting, unassisted by their upper extremities, as frequently as possible for 1 min and the oxygen saturation was measured immediately after exercise. Those hypoxic at rest (SpO_2<=92%) or physically unable to perform the test were excluded (see figure 1). Results were recorded in the ED medical record, which was used to identify the patient cohort. EIH was defined as a SpO_2 drop of ≥3% as per previous studies.[4 10] Decision on admission was made as usual practice by a consultant physician.

Patient demographic characteristics and results of a COVID-19 assessment tool that encompassed clinical observations, history and routine physical examination were recorded. Also collected were admission clinical findings (oxygen saturations, self-reported dyspnoea, reported length of symptoms) and baseline investigations (lymphocyte count, C-reactive peptide (CRP) and chest radiograph findings). The primary outcome was a diagnosis of COVID-19 during hospitalisation, and was based on PCR positivity for SARS-CoV2 or, if PCR negative, a consultant clinical diagnosis based on history and investigations.

We used univariate logistic regression to assess for an association between EIH and a COVID-19 diagnosis. Potential confounders of this association were considered in this analysis: age, sex and pre-existing medical conditions including chronic obstructive pulmonary disorder, pulmonary embolism and ILD. Factors associated in the univariate analysis with a $p<0.1$ with COVID-19 diagnosis were entered into a multivariate model examining the relationship of EIH and COVID-19 diagnosis (STATA V.16.1, StataCorp LP, Texas, USA). Missing data (<5% for all variables) were excluded from the individual analyses. In addition to those included in this primary analysis, subsequent ED presentations and admissions of patients evaluated in the ED for COVID-19 yet discharged were recorded.

This audit of an established clinical practice did not require formal ethical approval.

RESULTS

Two hundred seventy-six patients were evaluated in the ED for possible COVID-19; and 127 were admitted for possible COVID-19 (n=127) (figure 1). Of these, 29 did not undergo a 1MSTST due to frailty or baseline hypoxia (figure 1). Of the 98 patients admitted who were tested for COVID-19 and completed the EIH assessment, 27.5% (n=27) desaturated ≥3% after exercise.

Thirty-seven patients were ultimately diagnosed with COVID-19, 29 of whom were PCR positive, the remainder were diagnosed by a consultant physician either on clinical grounds (n=4) or in addition to suggestive radiological findings (n=4). Demographic and clinical characteristics of those admitted and as stratified by COVID-19 diagnosis are provided in table 1. Of the non-COVID-19 diagnoses (n=72), 54.2% were non-respiratory in origin. Patients diagnosed with COVID-19 demonstrated higher rates of self-reported dyspnoea at admission (89.2% vs 62.2%), higher median CRP (65 mg/L (34–139) vs 6 mg/L (6–46)), and a lower median lymphocyte count (1.1×10^9/L (0.8–1.7) vs 1.7×10^9/L (1.1–2.4)) (table 1). Of those diagnosed with COVID-19, 46.3% (n=11) demonstrated EIH in contrast with 22.2% (n=16) with an alternative diagnosis.

In patients who tested positive for COVID-19 and with EIH, 36.4% (n=4) did not have suggestive radiographic changes; and of note, none of these patients had a raised CRP (>100 mg/L) and two had a normal lymphocyte count. In this cohort, a high CRP (>100 mg/L) was only seen in 36.4% (n=4), while a normal lymphocyte count was observed in 63.6% (n=7).

In univariate analyses, COVID-19 was associated with a lymphocyte count $<1.0\times10^9$/L, a CRP >100 mg/L, self-reported dyspnoea and chest radiographic changes suggestive of COVID-19 and EIH. In multivariate analysis, adjusting for age, sex and underlying respiratory comorbidity, EIH was an independent predictor of COVID-19 diagnosis (adjusted OR 3.73, 95% CI (1.25 to 11.15)), as were the other investigations (table 2).

Of 149 patients discharged from the ED, 19 (13.1%) demonstrated EIH, these patients included 6 with chronic obstructive pulmonary disease/ILD, 2 post-COVID-19 (>14 days) and 7 with an 'unspecified viral illness'. Of all ED discharges, 24 (16.1%) reattended ≤14 days of presentation. Three reattending patients were diagnosed with COVID-19, of which two had EIH at initial attendance.

DISCUSSION

This observational study of normoxic patients admitted with suspected COVID-19 demonstrates an association between EIH and subsequent COVID-19 diagnosis. A large proportion of patients with EIH had normal radiographic and biochemical (CRP) investigations, suggesting EIH may complement existing triaging or severity scoring systems. The 1MSTST is validated as a surrogate for the 6-minute walk test in ILD and has significant infection control benefits in a healthcare setting.[9]

Several pathophysiological processes have been posited for COVID-19-induced respiratory failure, including pulmonary shunting, classical low-compliance acute respiratory distress syndrome and thromboembolism.[11 12] PJP has similar symptomatology and radiographic appearance, and perfusion defects are well recognised. EIH identifies PJP from infections such as bacterial pneumonia, where oxygen saturations rise on exertion.[2 4]

Table 1 Demographic characteristics, admission investigations and outcomes of patients for those admitted for possible COVID-19

	All admitted patients		Patients completing EIH assessment			
			COVID-19 infection		No COVID-19 infection	
	n=127		n=26		n=72	
Patient demographics	n (%)	95% CI (SD) (IQR)	n (%)	95% CI (SD) (IQR)	n (%)	95% CI (SD) (IQR)
Age (years)	57.8	(±16.3)	51.6	(±13.0)	55.1	(±15.6)
Male	52 (40.9%)	32.3% to 50.0%	12 (46.2%)	26.6% to 66.6%	27 (37.5%)	26.4% to 49.7%
Female	75 (59.1%)	50.0% to 67.7%	14 (53.8%)	33.4% to 73.4%	45 (62.5%)	50.3% to 73.6%
Respiratory medical history						
None	107 (84.3 %)	76.7% to 90.1%	25 (96.2%)	80.3% to 99.9%	61 (84.7 %)	74.3% to 92.1%
Chronic Obstructive Pulmonary Disease	14 (11.0 %)	6.2% to 17.8%	0 (0%)	–	7 (9.7 %)	4.0% to 19.0%
Pulmonary fibrosis	4 (3.2 %)	0.9% to 7.9%	1 (3.8%)	0.1% to 19.6%	2 (2.8 %)	0.3% to 9.7%
Chronic Pulmonary Thromboembolism	2 (1.6 %)	0.2% to 5.6%	0 (0%)		2 (2.8 %)	0.3% to 9.7%
Admission investigations						
EIH ≥3%	27 (27.6 %)	18.3% to 37.1%	11 (42.3 %)	23.4% to 63.1%	16 (22.2 %)	13.2% to 33.6%
Median CRP (mg/L)	16	(6–65)	65	(34–139)	6	(6–22)
CRP >100 mg/L	22 (18.2 %)	11.8% to 26.2%	9 (39.1%)	19.7% to 61.4%	5 (7.1%)	2.4% to 15.9%
Median lymphocyte count ($\times10^9$/L)	1.5	(0.9–2.2)	1.3	(0.9–1.9)	1.9	(1.2–2.5)
Lymphocyte <1.0×10^9/L	35 (28.0%)	20.3% to 36.7%	8 (32.0%)	14.5% to 53.5%	12 (16.9%)	9.0% to 27.7%
CXR findings						
Suggestive of COVID-19	20 (16.3%)	3.3% to 24.0%	14 (56.0%)	34.9% to 75.6%	1 (1.4%)	0.4% to 7.8%
Indeterminate	14 (11.4%)	6.4% to 18.4%	4 (16.0%)	4.5% to 36.1%	5 (7.2%)	2.4% to 16.1%
Not suggestive of COVID-19	89 (72.4%)	63.6% to 80.0%	7 (28.0%)	12.1% to 49.4%	63 (91.3%)	82.0% to 96.7%
Length of symptoms (days)	6	(2–14)	8.5	(4–14)	6	(3–14)
Self-reported dyspnoea	89 (70.1%)	61.3% to 77.9%	23 (88.5%)	69.8% to 97.6%	45 (62.5%)	50.3% to 73.6%
Patient outcomes						
Supplemental oxygen	29 (22.8%)	15.9% to 31.1%	11 (42.3%)	23.4% to 63.1%	6 (8.3%)	3.1% to 17.3%
Median length of stay (days)	4	(2–6)	4	(3–6)	3	(2–6)

CRP, C-reactive protein; EIH, exercise-induced hypoxia.

In this study, patients predominately had mild to moderate COVID-19 as patients hypoxic at rest were excluded; however, 42.3% developed an oxygen requirement and one patient required intubation during their hospital admission. Of note, we found a sizeable proportion (36.4%) of patients with COVID-19 and EIH who exhibited no radiographic changes or significantly elevated CRP at admission (63.6%). Chest radiograph is poorly sensitive early in the clinical course,[13] and EIH may therefore represent an additional risk stratification tool for patients with COVID-19 pneumonitis prior to radiological evidence.

As highlighted in a recent systematic review, there remains little published data on EIH and COVID-19, and none of its role within the ED.[7] One recent paper has highlighted a modest association of EIH with critical care needs.[9] Due to public health interventions and falling case numbers at the time of this study, this was not powered to explore concomitant associations. Yet a real-world, single-centre, account of a standardised method for assessment of EIH in the first wave of the pandemic is presented, thus providing an indication of its frequency and demonstrating its association with COVID-19. However, further work is required to better discern the

Table 2 Association of exercise-induced hypoxia and other clinical findings with COVID-19 diagnosis among patients admitted for suspected COVID-19

	Unadjusted OR			Adjusted OR*		
	OR	95% CI	P value	aOR	95% CI	p(LR)
EIH >3%	2.57	0.99 to 6.68	**0.053**	3.73	1.25 to 11.15	**0.018**
CRP >100 mg/L	5.43	2.05 to 14.43	**0.001**	6.00	2.16 to 16.62	**0.001**
Lymphopenia <1.0×10^9/L	3.58	1.55 to 8.24	**0.003**	5.05	1.99 to 12.86	**0.001**
COVID-19 suggestive CXR changes	15.60	6.00 to 40.57	**<0.001**	20.87	7.06 to 61.72	**<0.001**
Self-reported dyspnoea	5.01	1.63 to 15.37	**0.001**	5.21	1.66 to 16.34	**0.001**
Pre-EIH test oxygen saturations	0.89	0.75 to 1.06	**0.183**	–	–	–
Duration of symptoms	0.99	0.96 to 1.04	**0.977**	–	–	–

*Adjusted for age, sex and underlying respiratory comorbidity (Chronic obstructive pulmonary disease, pulmonary fibrosis, chronic pulmonary embolic disease).
CRP, C-reactive peptide; EIH, exercise-induced hypoxia; p(LR), p value calculated by likelihood ratio.

significance of EIH with regard to triaging safe discharge in the ED.

This study has limitations. It focused on a small subgroup of patients requiring admission with COVID-19 but were not hypoxic at triage on ED presentation. Discharged patients were not tested for SARS-CoV-2 as per UK governmental guidance in March 2020 which recommended that only inpatients undergo a PCR test for COVID-19. This restriction was due to severely limited testing capacity and in this period there was no community testing available. In addition, some patients referred as direct medical admissions might have been missed. This cohort therefore does not represent the full spectrum of COVID-19. Notably, some patients were recorded as unable to physically complete the test; since these decisions were made by different ED staff, this presents a risk of bias and may have affected the strength of associations. Finally, a minority of patients with a discharge diagnosis of COVID-19 were PCR negative. Although PCR testing is dependent on the time course and the quality of swab, this practice presents a risk of misdiagnosis. However, this practice was a pragmatic and conventional approach taken within the first wave of the pandemic that mirrored other large studies conducted on COVID-19.[14]

We used a standardised approach to demonstrate an association between EIH and COVID-19. This 1MSTST is reproducible and is easily used in a supervised prehospital setting. As EIH can be seen without radiological and biochemical changes, further prospective studies are required to better define the significance of EIH in COVID-19.

Contributors PD and TJ worked equally as lead authors in the conception and formation of this manuscript at all stages. In addition, FB-M, AR and TC provided substantial contributions to the conception, design and drafting of the work. Finally, CS provided editorial oversight and supervision of the project.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Approval for this retrospective observational audit of clinical practice was obtained from the Caldicott Guardian in NHS Lanarkshire.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data generated or analysed during this study are included in this published article.

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