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Improved Arterial Oxygenation by High Flow Nasal Cannula Oxygen Therapy in Older Patients with Severe Respiratory Failure in a Non-Intensive Hospital ward

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Abstract: Background. There are scant data about the effectiveness of high flow nasal cannula (HFNC) oxygen therapy in patients hospitalized with severe acute respiratory failure (ARF) in non-intensive medical wards, particularly regarding the effect on arterial oxygenation compared to conventional oxygen therapy (COT) and non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP). Methods. In a retrospective observational study, oxygenation parameters were measured before and immediately after HFNC initiation in 37 consecutive patients hospitalized in a geriatric ward in 2017. Results. HFNC was used as escalation therapy for untreatable hypoxia after failure of NIV/CPAP (n=18) or COT (n=19). Twenty-two patients died, 2 were transferred to the intensive care unit, while 13 were discharged alive. A "do not intubate" status was identified in 17 of the 22 deceased patients. Partial pressure of oxygen (pO2, p< 0.0001), oxygen saturation (SO2, p< 0.0001), pO2/fraction of inspired oxygen ratio (p=0.004) and peripheral SO2 measured by pulse oximetry (p< 0.0001) significantly increased soon after HFNC application. Oxygenation improvements were greater after escalation from NIV/CPAP and in patients discharged alive. Conclusion. HFNC significantly improved oxygenation in severe ARF after failure of COT or NIV/CPAP and may be particularly suitable for older patients hospitalized in non-intensive medical wards.

Keywords: high flow nasal cannula oxygen therapy; acute respiratory failure; geriatrics; acute non-intensive hospital setting

1. Introduction

Acute respiratory failure (ARF) is a frequent syndrome in older patients [1] and was the first hospital discharge diagnosis among persons aged ≥ 75 years in a nationwide Italian study [2]. In addition to the treatment of the underlying causes(s) [1], ARF management includes the application of non-invasive respiratory supports, i.e. conventional oxygen therapy (COT) and non-invasive mechanical ventilation (NIV), with the aim of avoiding intubation and invasive mechanical ventilation (IMV) [3].

High flow nasal cannula oxygen therapy (HFNC) is another type of non-invasive respiratory support [3–5]. A very high flow of heated and humidified gas mixture (oxygen plus room air) is administered through soft nasal prongs. The fraction of inspired oxygen (FiO2), i.e. the concentration of oxygen in the gas mixture, can be titrated from 21% (only room air) up to 100% [3–5]. The high flow generates a continuous positive pressure in the airways (about 5 cmH2O at a flow of 60 l/min with closed patient's mouth) which facilitates alveolar recruitment. In addition, a flow-dependent wash-out of expired gas in the dead space reduces carbon dioxide (CO2), while the muco-ciliary clearance is improved by the heated and humidified gas [3–5]. HFNC is mainly used to treat type 1 ARF (hypoxaemia without hypercapnia), while the co-existence of hypercapnia (type 2 ARF) often

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requests the application of NIV for providing higher mean airways pressures and unloading respiratory muscles [3–5]. In type 1 ARF, HFNC performs better that COT, mostly reducing intubation rate, and results at least as effective as NIV, with some evidence of lower mortality with HFNC compared to NIV [4]. Thus, the choice of the respiratory support for type 1 ARF should be individualized according to patients' clinical characteristics and local expertise [3].

HFNC is more tolerated and comfortable than NIV and provides undoubted benefits, such as ease of use and possibility for patients to speak, eat and drink without interrupting ventilation, qualifying as a potential excellent tool for frail older patients hospitalized in acute-care geriatric wards [3]. However, data on the use of HFNC in non-intensive settings are scant, particularly regarding the effect of HFNC on arterial oxygenation [3,6]. In this study, we investigated the effect of HFNC on some objective respiratory variables in all patients consecutively hospitalized for severe ARF in a geriatric hospital ward in 2017.

2. Materials and Methods

Patients and setting

In this retrospective observational study, we reviewed the medical records of all consecutive patients admitted to the Unit of Geriatrics, Azienda Ospedaliera di Cosenza (Cosenza, Italy), from January 1th to December 31th, 2017, and who were treated with HFNC during stay in the ward. In 2017 the Unit discharged 739 patients with a mean length of stay of 9.5 days. NIV has been used in the Unit since 2010, and 105 patients were treated with NIV only in 2017.

At admission, patients (or their close relatives) provided written consent for use of medical records for observational research. The study adhered to the Declaration of Helsinky and the protocol was approved by the Institutional Review Board of the Azienda Ospedaliera di Cosenza (January 9, 2023, according to deliberation n. 406 of September 19, 2021).

The original study sample consisted of 39 patients, but 2 women were excluded since they started HFNC in the Intensive Care Unit (ICU) as weaning from IMV and were later transferred to the study unit where they continued HFNC. The remaining sample thus included 37 patients who started HFNC in the study unit. This cohort was divided into a group of patients who were discharged alive (positive outcome, 13 patients) and a group of 22 patients who died in the unit plus 2 patients who were transferred to the ICU (negative outcome, 24 patients). Vital signs and physiological parameters were collected in the clinical records as part of routine clinical care. The pre-morbid functional status referring to 15 days before admission was retrospectively measured at admission by the Activities of Daily Living (ADL) score [7].

Respiratory supports and HFNC

The respiratory supports applied to patients before starting HFNC included one of the followings: (i) NIV, delivered through a face mask as bi-level pressure support with inspiratory pressure ranging from 14 to 20 cmH2O and expiratory pressure between 4 and 6 cmH2O; (ii) continuous positive airway pressure (CPAP) through a Boussignac mask with oxygen flow of at least 15 L/min; (iii) COT, delivered through nasal prongs or Venturi mask. FiO2 during NIV/CPAP or COT was calculated as follows: 21 (FiO2 of room air) + (3 × l/min of O2 flow) [8]. The clinical decision of resorting to HFNC, at the sole discretion of treating physicians, was mainly dictated by the incapacity to obtain a value of peripheral oxygen saturation (SpO2) ≥ 92% after at least one hour of treatment with COT, NIV or CPAP.

The HFNC device (Airvo 2 with Optiflow interfaces by Fisher & Paykel Healthcare) included the air-oxygen blender which adjusted the measured FiO2 at values between 21 and 100%, flow up to 60 L/min and temperature at 31-37 °C. The adjusted gas mixture was delivered via a circuit and large bore bi-nasal soft prongs. HFNC oxygen therapy was usually started with a FiO2 of ≥ 50% and flow of at least 40 l/min. Both parameters were titrated to obtain a SpO2 > 92%. HFNC therapy was then continued for 24 hours a day (with the exception of 2 patients for whom HFNC was alternated with NIV during the day).

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Pre-post study

The values of selected respiratory variables measured before the application of HFNC - while patients were still treated with the other type of respiratory support - were compared with the values obtained in each patient soon after HFNC was initiated, with patients serving as their own controls. Such variables included: pH, partial pressure of oxygen (pO2), partial pressure of CO2 (pCO2), oxygen-hemoglobin saturation (SO2) and the pO2 /FiO2 ratio, all obtained by arterial blood gases (ABG) analysis; SpO2 and the SpO2 /FiO2 ratio, measured non-invasively by pulse oximetry. For ABG measurements, values of each variable from the last ABG analysis prior to HFNC application were compared with those measured in the first ABG after HFNC initiation. Basal SpO2 and the correspondent SpO2 /FiO2 were measured few minutes before switching to HFNC and compared with values detected not later than 30 minutes after HFNC application.

Statistical analyses

Continuous data were expressed as mean ± standard deviation (SD) for normally distributed data, or as median and interquartile range for not normally distributed data. Normally distributed data were analyzed by t-test for paired and unpaired data, while not normally distributed data were analyzed by Wilcoxon test for paired and unpaired data. Categorical data were expressed as number and percentages and Chi-squared test was performed. For all statistical analyses, a p value lower than 0.05 was considered statistically significant. Statistical analysis was carried out using SPSS V20.0 program for Windows (SPSS Inc., Chicago, Illinois, USA).

3. Results

Table 1 shows general descriptive and clinical variables in the overall population of 37 patients and in the 2 groups with positive or negative outcome. Amongst the 22 patients deceased in the ward, 1 patient died immediately after endotracheal intubation before being transferred to the ICU, 1 patient refused intubation and 17 patients were deemed by ward physicians (7 patients) or consulting intensivists (10 patients) as not eligible for endotracheal intubation and ICU admission ("do not intubate patients"), based on comorbidity, age, actual clinical conditions and previous functional and cognitive status.

Table 1. Descriptive and clinical variables.

	Overall population (n=37)	**Negative outcome group (n=24)**	**Positive outcome group (n=13)**	**p**
Age, years	82.0±7.6	81.1±8.3	83.9±6.1	0.300
Sex (males/females)	22/15	15/9	7/6	0.608
Current smoking	8 (21.6)	6 (25.0)	2 (15.4)	0.497
Dementia	22 (59.5)	14 (58.3)	8 (61.5)	0.849
Bedsores	9 (24.3)	7 (29.2)	2 (15.4)	0.350
Hypertension	22 (59.5)	15 (62.5)	7 (53.8)	0.608
Type 2 diabetes mellitus	12 (32.4)	9 (37.5)	3 (23.0)	0.370
Chronic heart failure	14 (37.8)	7 (29.2)	7 (53.8)	0.139
Chronic kidney disease	11 (29.7)	5 (20.8)	6 (46.2)	0.107
Chronic coronary disease	5 (13.5)	3 (12.5)	2 (15.4)	0.806
Atrial fibrillation	9 (24.3)	6 (25.0)	3 (23.0)	0.896
COPD	16 (43.2)	9 (37.5)	7 (53.8)	0.337
Current malignancies	13 (35.1)	10 (41.7)	3 (23.0)	0.258
ADL ≤ 3 before admission	22 (59.5)	15 (62.5)	7 (53.8)	0.608
Home oxygen therapy	3 (8.1)	1 (4.1)	2 (15.3)	0.232
Causes of acute respiratory failure				

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Acute Heart Failure	16 (43.2)	8 (33.3)	8 (61.5)	0.098
Aspiration	8 (21.6)	7 (29.2)	1 (7.6)	0.129
Pneumonia	11 (29.7)	7 (29.2)	4 (30.8)	0.918
Aspiration pneumonia	3 (8.1)	2 (8.3)	1 (7.6)	0.945
Interstitial lung disease	1 (2.7)	1 (4.1)	0 (0)	0.999
Sepsis	12 (32.4)	10 (41.7)	2 (15.3)	0.103
COPD exacerbation	8 (21.6)	4 (16.7)	4 (30.8)	0.319
ARDS	3 (8.1)	3 (12.5)	0 (0)	0.538
Bronchiectasis exacerbation	1 (2.7)	0 (0)	1 (7.6)	0.351
Acute stroke	7 (18.9)	6 (25.0)	1 (7.6)	0.199

Values are expressed as number (percentage) or mean ± standard deviation. Abbreviations: n, number; COPD, chronic obstructive pulmonary disease; ADL, activities of daily living; ARDS, adult respiratory distress syndrome.

The level of pre-hospital baseline disability was substantial, as ADL score measured about two weeks before admission was 3 or less in about 60% of patients (up to 62.5% in the negative outcome group). The sum of the percentages of ARF causes exceeded 100%, since more than one cause of ARF could be ascertained in the majority of patients. Acute heart failure (43.2%), pneumonia (29.7%) and sepsis (32.4%) were the most prevalent causes of ARF in this unselected population.

Eighteen patients were supported with NIV or CPAP before starting HFNC, while the remaining 19 patients were pre-treated with COT (Table 2). Pre-HFNC ABG analysis was performed in all 37 patients and showed that 12 out the 37 patients had significant hypercapnia, i.e. $pCO2 \geq 60$ mmH. ABG analysis control during HFNC was available in 31 out the 37 patients and was performed within 24 hours from HFNC application (Table 2).

Table 2. Clinical severity and hospital management.

	Overall population (n=37)	**Negative outcome group (n=24)**	**Positive outcome group (n=13)**	**p**
Altered mental status	23 (62.2)	17 (70.8)	6 (46.2)	0.139
Admission SBP, mmHg	121.4±25.4	124.4±30.1	116.0±13.9	0.351
Admission DBP, mmHg	73.2±11.4	74.2±13.1	71.6±8.0	0.517
Admission body temperature, °C	36.4±0.8	36.5±0.8	36.3±0.8	0.529
Inotropic therapy	10 (27.0)	7 (29.2)	3 (23.0)	0.690
NIV or CPAP before HFNC	18 (48.6)	13 (54.2)	5 (38.5)	0.361
COT before HFNC	19 (51.4)	11 (45.8)	8 (61.5)	0.361
ABG analysis pre-HFNC, days from admission	5 (2-8)	3 (1-8)	6 (5-7)	0.418
ABG analysis during HFNC, days from HFNC initiation	0 (0-1)	0 (0-1)	1 (0-1)	0.177
HFNC initiation, days from admission	6 (2-9)	3.5 (1-9)	7 (6-9)	0.179
HFNC initial flow, l/min	55.1±7.6	58.3±3.8	49.2±9.3	**<0.0001**
HFNC alternated with NIV	2 (5.4)	2 (8.3)	0 (0)	0.531
Length of HFNC therapy, days	4 (2-7)	2 (1-5.25)	6 (5-10)	**0.011**
Length of hospital stay, days	13 (7-18)	9.5 (4-15)	21 (13-25)	**0.002**

Values are expressed as number (percentage), mean ± standard deviation, or median (interquartile range). Abbreviations: n, number; mmHg, millimeters of mercury; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIV, non-invasive ventilation; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; COT, conventional oxygen therapy; ABG, arterial blood gases.

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Table 3 depicts the pre-post comparisons of respiratory values in the total group, showing significantly improved blood oxygenation after switching from initial respiratory supports to HFNC. The effect of HFNC in improving oxygenation was more evident in patients with positive outcome (Table 4), although these patients had lower initial level of oxygenation. In addition, HFNC significantly improved oxygenation particularly in patients pre-treated with NIV/CPAP, in whom HFNC significantly improved oxygenation without the need of increasing FiO2 (Table 5). Of note, switching from COT to HFNC also determined a significant pH increase, due to reduced pCO2 (Table 5).

Table 3. Pre-post comparisons of respiratory values in the total study sample.

	Before HFNC	During HFNC	p
Arterial blood gases (n=31)			
pH	7.41±0.08	7.42±0.1	0.496
pCO_2	47.3±13.2	47.1±12.7	0.888
pO_2	53.7±14.3	76.0±17.4	**<0.0001**
SO_2	86.0±5.9	94.0±6.4	**<0.0001**
pO_2/FiO_2	98.3±30.2	122.9±43.2	**0.004**
Pulse oximetry (n=37)			
SpO_2	87.9±5.4	95.5±2.9	**<0.0001**
FiO_2	60.1±16.0	65.8±14.9	0.078
SpO_2/FiO_2	1.6±0.5	1.5±0.4	0.657

Values are expressed as mean ± standard deviation. Abbreviations: n, number; HFNC, high flow nasal cannula; pCO_2, arterial partial pressure of carbon dioxide; pO_2, arterial partial pressure of oxygen; SO_2, oxygen-hemoglobin saturation; FiO_2 , fraction of inspired oxygen; SpO_2, peripheral oxygen saturation measured by pulse oximetry.

Table 4. Pre-post comparisons of respiratory values stratified according to the clinical outcome.

	Negative outcome			Positive outcome		
	Before HFNC	During HFNC		Before HFNC	During HFNC	
Arterial blood gases						
	(n=19)		**p**	**(n=12)**		**p**
pH	7.39±0.08	7.41±0.12	0.544	7.44±0.07	7.44±0.07	0.749
pCO_2	47.9±15.7	47.5±15.4	0.888	46.4.±8.6	46.3±7.0	0.979
pO_2	56.7±16.9	74.2±18.0	**<0.0001**	48.9±6.7	78.9±16.8	**<0.0001**
SO_2	86.0±6.2	92.7±7.9	**0.005**	85.9±5.5	96.3±1.6	**<0.0001**
pO_2/FiO_2	99.6±30.3	111.2±45.9	0.225	96.3±31.3	141.6±31.9	**0.003**
Pulse oximetry						
	(n=24)		**p**	**(n=13)**		**p**
SpO_2	87.4±6.4	94.9±3.4	**<0.0001**	88.9±2.9	96.6±1.5	**<0.0001**
FiO_2	62.8±16.9	70.2±15.2	0.081	55.1±13.6	57.5±10.5	0.628
SpO_2/FiO_2	1.49±0.4	1.42±0.3	0.506	1.7±0.5	1.7±0.3	0.924

Values are expressed as mean ± standard deviation. Abbreviations: HFNC, high flow nasal cannula; n, number; pCO_2, arterial partial pressure of carbon dioxide; pO_2, arterial partial pressure of oxygen; SO_2, oxygen-hemoglobin saturation; FiO_2 , fraction of inspired oxygen; SpO_2, peripheral oxygen saturation measured by pulse oximetry.

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Table 5. Pre-post comparisons of respiratory values stratified according to respiratory support before HFNC.

	NIV or CPAP before HFNC			COT before HFNC		
	Before HFNC	During HFNC		Before HFNC	During HFNC	
Arterial blood gases						
	(n=17)		**p**		**(n=14)**	**p**
pH	7.38±0.09	7.38±0.12	0.872	7.44±0.06	7.46±0.05	**0.042**
pCO_2	49.3±16.3	50.5±14.3	0.654	44.8±8.1	42.9±9.2	0.346
pO_2	56.1±18.3	79.6±18.4	**<0.0001**	50.8±6.5	71.7±15.7	**<0.0001**
SO_2	85.3±7.2	93.2±8.4	**0.007**	86.9±3.8	95.1±2.5	**<0.0001**
pO_2/FiO_2	92.0±32.0	133.2±44.3	**0.001**	105.9±26.9	110.6±39.9	0.665
Pulse oximetry						
	(n=18)		**p**		**(n=19)**	**p**
SpO_2	88.6±5.1	95.4±3.9	**<0.0001**	87.3±5.7	95.6±1.8	**<0.0001**
FiO_2	71.6±12.6	66.1±16.1	0.158	49.3±10.5	65.4±14.2	**<0.0001**
SpO_2/FiO_2	1.3±0.2	1.5±0.4	**0.008**	1.9±0.5	1.5±0.3	**0.011**

Values are expressed as mean ± standard deviation. Abbreviations: NIV, non-invasive ventilation; CPAP, continuous positive airway pressure; COT, conventional oxygen therapy; HFNC, high flow nasal cannula; n, number; pCO_2, arterial partial pressure of carbon dioxide; pO_2, arterial partial pressure of oxygen; SO_2, oxygen-hemoglobin saturation; FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation measured by pulse oximetry.

4. Discussion

While HFNC is widely used in the ICU settings, there is poor evidence regarding its safety and effectiveness in patients hospitalized in non-intensive wards [6]. Our study included 37 consecutive elderly patients affected by very severe ARF, as demonstrated by a mean baseline pO2/FiO2 ratio of about 100 obtained during baseline treatment with COT (19 patients) or NIV/CPAP (18 patients). A poor arterial oxygenation was the reason for escalating from COT or NIV/CPAP to HFNC in these severely ill patients. We found a significant increase in arterial oxygenation after application of HFNC, not only in the subgroup of patients pre-treated with COT, but particularly after escalation from NIV/CPAP. Furthermore, patients discharged alive displayed a better HFNC-related oxygenation response compared to patients with negative outcome, indicating a higher clinical resilience. This is a crucial issue, because failure to correct hypoxia is an important predictor of intubation during NIV [9]. While in previous reports HFNC increased oxygenation more than COT [4], some studies reported slightly higher oxygenation with NIV than with HFNC [10–14]. In a recent randomized trial, however, the opposite result was obtained, with the HFNC group that reached higher oxygenation level than patients randomized to NIV [15]. Substantial differences, however, between these randomized studies that have compared gas exchange with HFNC and NIV and our report should be highlighted. First, our consecutive patients started HFNC after recognized failure of NIV/CPAP to correct hypoxia, thereby reflecting a different clinical scenario from that of patients with only moderate ARF randomized to HFNC or NIV; second, our patients had much more severe ARF than those observed in previous randomized trials; third, previous trials were conducted in the ICUs and enrolled younger patients [10–14]. Thus, HFNC may indeed be more effective than NIV/CPAP in improving oxygenation in severely ill elderly patients with particularly low pO2/FiO2, as also suggested by the evidence that HFNC prevented intubation better than NIV in patients with pO2 /FiO2 lower than 150 [16], a benefit possibly resulting from improved oxygenation with HFNC. However, although our Unit has developed an acceptable expertise in NIV use (105 patients treated with NIV only in 2017), it cannot be ruled out that local factors, including undetected patient-ventilator asynchronies, low levels of expiratory pressure (about 5 cm H2O), discomfort, air leaks and the lower technological performance of ventilators commonly used in non-ICU settings respect

to ICU ventilators, may have contributed to the observed lower oxygenation with NIV/CPAP than with HFNC [14]. Even so, our results mirror the practice of non-intensive hospital medical wards, the setting where most of the ARF older patients are currently managed. Of note, 12 of our 37 patients had hypercapnic respiratory failure, but HFNC did not affect pCO2 levels and even significantly increased pH values in the switching from COT. With this regard, trials are currently studying the role of HFNC as an alternative to NIV in the treatment of mild-to-moderate hypercapnic respiratory failure due to exacerbations of chronic obstructive pulmonary disease (COPD) [17].

Since a "do not intubate" status was clinically pre-determined in 17 of the 22 deceased patients, such high mortality (59%) is not surprising and was comparable to the 50% mortality rate observed in a study of younger patients (mean age 75 years) hospitalized in non-ICU wards [6]. In addition to being a consequence of patients' severe clinical conditions, high in-hospital mortality may also reflect poor monitoring and delayed or missed intubation [6]. The decision to admit frail geriatric patients to ICU for intubation is often controversial, but untreatable hypoxia is a crucial factor for deciding to start IMV [3,9]. The HFNC-related oxygenation improvement is hence an important goal in the management of terminally ill geriatric patients and may reduce the recourse to unjustified intubation [9].

This study also provides an interesting insight into the issue of ARF in older patients. We observed that heart failure, sepsis and pneumonia were more frequent etiologies of ARF than acute exacerbation of COPD [1,18]. ARF may be an epiphenomenon of terminal illnesses - including degenerative cerebral diseases - and many patients had more than one underlying causes [1,18].

Our observational analysis needs to be replicated in larger, multicenter and more homogenous ARF populations. Potential strengths, however, include: the measurement of respiratory parameters soon after HFNC application, making it likely that oxygenation improvements may be fully attributed to HFNC; the "real-world" observation of non-invasive management of patients usually excluded from randomized trials; the fact that HFNC was used as "escalation therapy" after failure of NIV/CPAP or COT in correcting hypoxia.

In conclusion, we observed that HFNC - used as escalation therapy for untreatable hypoxia during COT or NIV/CPAP - significantly increased arterial oxygenation without causing hypercapnia in ARF patients admitted to a geriatric non-intensive ward. HFNC is better tolerated than NIV, assures continuous ventilation without interruptions, does not compromise normal nutrition and oral hydration and allows patients to continue communicating with others, thereby reducing the risk of dehydration, malnutrition and delirium [3–5,18]. It should also be mentioned that, compared to NIV, HFNC decreased inspiratory effort in type 1 ARF, thus mitigating the risk of self-inflicted lung injury [5], and this may have contributed to the lower mortality observed during HFNC [4]. Further studies are needed for better investigating the promising role of this technique in non-intensive hospital practice.

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Informed Consent Statement: At admission, patients (or their close relatives) provided written consent for use of medical records for observational research.

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Conflicts of Interest: The authors declare they have no conflict of interest regarding the study.

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