

Lung function corner

Transfer coefficient of the lung for carbon monoxide and the accessible alveolar volume: clinically useful if used wisely

Case history

A 67-year-old morbidly obese female (body mass index: $46.3 \text{ kg}\cdot\text{m}^{-2}$) with a history of long-term cigarette smoking (>30 pack-years) was referred from Cardiology to Respiriology due to progressive dyspnoea and recent findings of extensive mosaic attenuation of the lungs on a high-resolution computed tomography (HRCT) scan (figure 1). She had been followed by Cardiology on the grounds of multivalvular disease (severe aortic stenosis and moderate mitral regurgitation), ischaemic heart disease, hypertension and hypercholesterolaemia.

The patient reported exertional dyspnoea in the past 5 years, which had worsened markedly in the past year. In fact, her dyspnoea has progressed from a previous grade of 2 according to the 1–5 Medical Research Council scale to a current grade of 4. Apart from occasional, non-productive cough she denied any other respiratory symptom. As part of her pre-operative assessment for potential transcatheter aortic valve implantation, a chest radiograph showed ill-defined, bilateral haziness which was deemed inconsistent with her current haemodynamic status. As mentioned, a subsequent chest HRCT scan (figure 1) prompted referral to the respiratory service.

Question

How can the pulmonary function testing (PFT) laboratory be helpful in guiding further

investigations to uncover the cause(s) of the abnormalities observed on chest HRCT?

Answer

The mosaic pattern of lung attenuation seen in figure 1 is characterised by a patchwork of regions of differing attenuation with well-defined borders

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Figure 1 A non-contrasted chest HRCT scan on inspiration showing diffuse areas of mosaic attenuation of the lungs with enlarged central pulmonary vessels and pulmonary artery trunk (3.6 cm).

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Transfer coefficient of the lung for carbon monoxide (KCO) and alveolar volume (VA) increase the yield of clinical information obtained from transfer factor of the lung for carbon monoxide (TLCO) measurements in clinical practice <http://ow.ly/AVgu30na1vu>



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corresponding to the secondary pulmonary lobules [1]. As expected by the secondary lobules' anatomy, the mosaic pattern may be due to pulmonary vascular, small airway or infiltrative lung disease [2]. Infiltrative lung disease and airway disease can be reliably differentiated by an experienced radiologist. However, pulmonary vascular disease is often misinterpreted as an airway disease [1]. Comparing inspiratory and expiratory CT scans can be helpful in indicating the presence of gas trapping secondary to small airway disease although the support for this approach comes mainly from studies involving patients with high likelihood of gas trapping, *e.g.* asthma, bronchiolitis obliterans and cystic fibrosis [3–5]. Thus, clinical interpretation of PFTs in the current scenario should be focused on answering the following question: is the patient's mosaic pattern on chest HRCT more likely related to an airway- or a pulmonary vascular-centred disease?

Table 1 Standard pulmonary function tests pre- and post-inhaled bronchodilator

	Pre-bronchodilator	Post-bronchodilator
Spirometry		
FEV1 % pred	71	74
FVC % pred	75	74
FEV1/FVC	0.68	0.72
FEV1/SVC	0.64	0.65
FEF25–75% % pred	63	62
Body plethysmography		
TLC % pred	78	81
VC % pred	72	74
IC % pred	128 [#]	121 [#]
FRC % pred	69 [#]	67 [#]
ERV % pred	32 [#]	29 [#]
RV % pred	62 [#]	68 [#]
RV/TLC	0.47	0.46
Airway resistance		
R_{aw} % pred	122	138
sR_{aw} % pred	147	142
Gas exchange		
VA % pred	72	76
VA/TLC	0.89	0.90
T_{lCO} % pred	40 [#]	38 [#]
K_{CO} % pred	62 [#]	58 [#]

FEV1: forced expiratory volume in 1 s; FVC: forced expiratory volume; SVC: slow vital capacity; FEF25–75%: forced expiratory flow between 25 and 75% of FVC; TLC: total lung capacity; VC: vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; ERV: expiratory reserve volume; RV: residual volume; R_{aw} : airway resistance; sR_{aw} : specific airway resistance; VA: accessible alveolar volume; T_{lCO} : transfer factor of the lung for carbon monoxide; K_{CO} : transfer coefficient of the lung for carbon monoxide. #: abnormal test results (outside the 95% confidence interval).

Results of routine PFTs are shown in table 1. Spirometry was essentially within normal limits with a trend towards mild and proportional decrease in FEV1 and FVC either pre- or post-bronchodilator [6]. Body plethysmography also suggested a trend towards restriction with a borderline decrease in TLC, a high IC and a low ERV. There was no evidence of gas trapping either absolute (high RV) or relative (high RV/TLC); in fact, FRC and RV were low. The VA, as determined by methane dilution in the single-breath T_{lCO} measurement [7], was normal-to-low in tandem with TLC, *i.e.* the VA/TLC ratio was within normal limits (>0.8) [8–10]. Thus, there was no significant maldistribution of ventilation [9, 10]. Of note, the haemoglobin-corrected T_{lCO} was severely reduced as well as the K_{CO} (T_{lCO}/VA ratio) [11]. Inhaled bronchodilator had no significant effect on the recorded variables (table 1).

Collectively, these results indicate: an incipient restrictive ventilatory defect coupled with other findings (increased IC, decreased FRC, decreased ERV and decreased RV) which could be largely ascribed to patient's body habitus (morbid obesity) [12]; associated with an out-of-proportion decrease in T_{lCO} and a severe impairment in gas exchange efficiency (low K_{CO}).

Thus, a pulmonary vascular aetiology was considered the most likely reason behind the observed mosaic pattern on the patient's HRCT.

Clinical follow-up

Based on the PFTs data suggesting pulmonary vascular disease and the mosaic pattern on HRCT with an enlarged pulmonary artery trunk, an urgent transthoracic echocardiogram confirmed pulmonary hypertension (PH). A ventilation/perfusion (V'/Q') scan was requested with a specific concern of thromboembolic disease [13]; in fact, it did show multiple segmental mismatched V'/Q' deficits. A CT pulmonary angiogram confirmed chronic thromboembolic material within dilated central pulmonary arteries. Right heart catheterisation results were consistent with pre-capillary PH (mean pulmonary arterial pressure: 39 mmHg, pulmonary arterial wedge pressure: 10 mmHg). In this context, the patient was diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) [13] and referred to the institutional PH clinic.

Discussion

The transfer of any inspired gas with the ability of binding to haemoglobin (*e.g.* O_2) in the red blood cells (RBCs) crossing the pulmonary capillaries depends on [14]:

- the pre-haemoglobin resistance to gas flow (literally from the mouth to the interior of the

RBCs), collectively called the “membrane” component; and

- the concentration and binding properties of haemoglobin.

When carbon monoxide (CO) is used instead of O_2 to assess the integrity of this complex process (haemoglobin’s affinity for CO is 230 times that of O_2), it has been shown that ~80% of the T_{LCO} signal comes from the blood phase, *i.e.* the number of RBCs and/or the number of open capillary vessels (capillary volume, VC) [15]. It is therefore understandable that T_{LCO} is considered a “window to the pulmonary microcirculation” [16]. It may also partially explain why a low T_{LCO} is associated with increased areas of high ventilation–perfusion relationship [17]. It follows that patients with chronic obstructive pulmonary disease presenting with a low T_{LCO} need to ventilate in excess to a given metabolic load (*i.e.* poor exertional ventilatory efficiency) to overcome an enlarged physiological dead space [18]. Patients with low T_{LCO} (<50% predicted) are also at higher risk of presenting with another source of increased ventilatory stimuli: hypoxaemia [19]. Thus, a low T_{LCO} may be associated with a high respiratory neural drive on exertion, a key correlate of exertional dyspnoea [20]. It is not surprising, therefore, that a low T_{LCO} is an independent predictor of decreased physical activity in this patient population [21].

The clinical interpretation of T_{LCO} , however, might be confounded by the fact that it is critically dependent on:

- 1) the lung volume at which it is measured and, importantly,
- 2) “how many” gas exchanging unities at a given lung volume have received the inhaled gas mixture [22, 23].

Regarding the first point, T_{LCO} increases as the alveoli are distended because the surface area for gas exchange increases and because the alveolar–capillary membrane may become thinner. Conversely, as the lung deflates T_{LCO} decreases because the surface area decreases while it may become progressively thicker [24]. However, alveolar distension also compresses the lung capillaries, whereas alveolar emptying gives more space to capillary filling [25] (although this is partially compensated by a squeezing effect on the total intra-thoracic blood volume at very low lung volumes) [26]. It follows that [24–26]: from mid-lung volumes upwards, T_{LCO} increases less than it would be expected from the increase in VA because the latter effect is partially counterbalanced by a (small) decrease in VC; and from mid-lung volumes downwards, T_{LCO} decreases less than it would be expected from the decrease in VA because VC decreases less than the VA [23]. The final result is a curvilinear, exponential-like increase in the VC/VA ratio as the VA diminishes. Translating those concepts to T_{LCO} measurements,

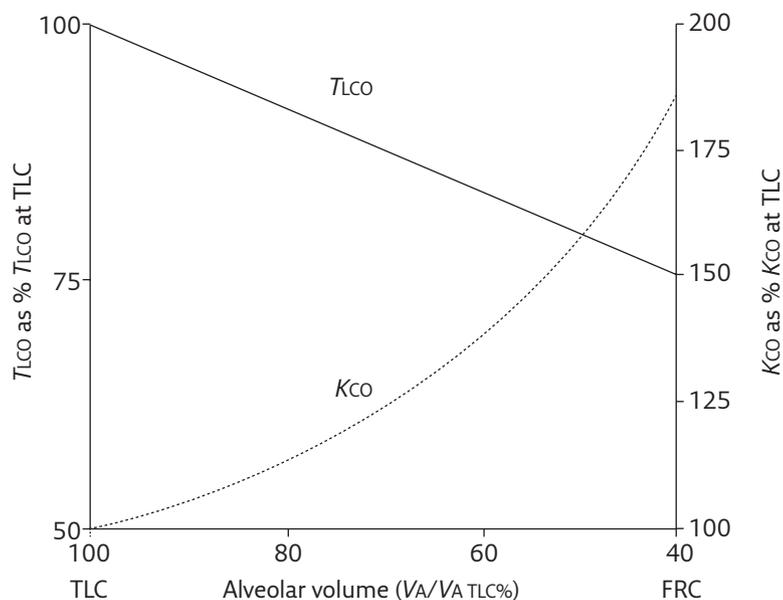


Figure 2 The linear decrease in T_{LCO} as the accessible VA decreases is associated with an exponential increase in K_{CO} . For instance, T_{LCO} decreases ~25% while K_{CO} increases by ~90% from TLC to FRC. It follows that at a given VA below TLC, K_{CO} (% predicted) will always be a higher value than T_{LCO} (% predicted). See the text for further elaboration on the clinical interpretation of those measurements. VA/VA TLC%: accessible VA as a percentage of the VA found at TLC. Modified from [23] with permission from the publisher.

they imply an essentially linear decrease in T_{LCO} but an exponential increase in K_{CO} (T_{LCO}/VA) as VA decreases (figure 2) [23]. These considerations carry important messages:

- they might lead to a “pseudo-normal” K_{CO} in a restrictive defect that decreases both T_{LCO} and VA [27]; and
- 1 “unit” change in VA does not lead to 1 “unit” change in T_{LCO} across all possible VA values, *i.e.* it is highly misleading to state that “the T_{LCO}/VA ratio represents T_{LCO} corrected by lung volume”.

Concerning the second point, it should be remembered that during the T_{LCO} manoeuvre we measure only the fraction of TLC which can be accessed by the inhaled mixture (which is provided by VA), a volume that depends on how well the peripheral units connect with the large airways [10, 28]. In most healthy subjects, the VA/TLC ratio is ≥ 0.85 [8, 29] or ≥ 0.80 [9] provided that the subject performed a maximal inspiratory manoeuvre. However, in the presence of airway disease and extensive maldistribution of ventilation, VA will be a poor representation of the lungs as a whole (TLC) and VA/TLC ratio is < 0.80 – 0.85 [28]. This might lead to a “pseudo-normal” K_{CO} in an obstructive defect that decreases VA [27].

How to deal with these potential pitfalls in VA and K_{CO} interpretation? We suggest the following simplified interpretation algorithm when T_{LCO} is reduced (figure 3) [23].

When VA is normal there is a high negative predictive value for restriction (because VA is always a fraction of TLC; thus, if VA is normal so is TLC in

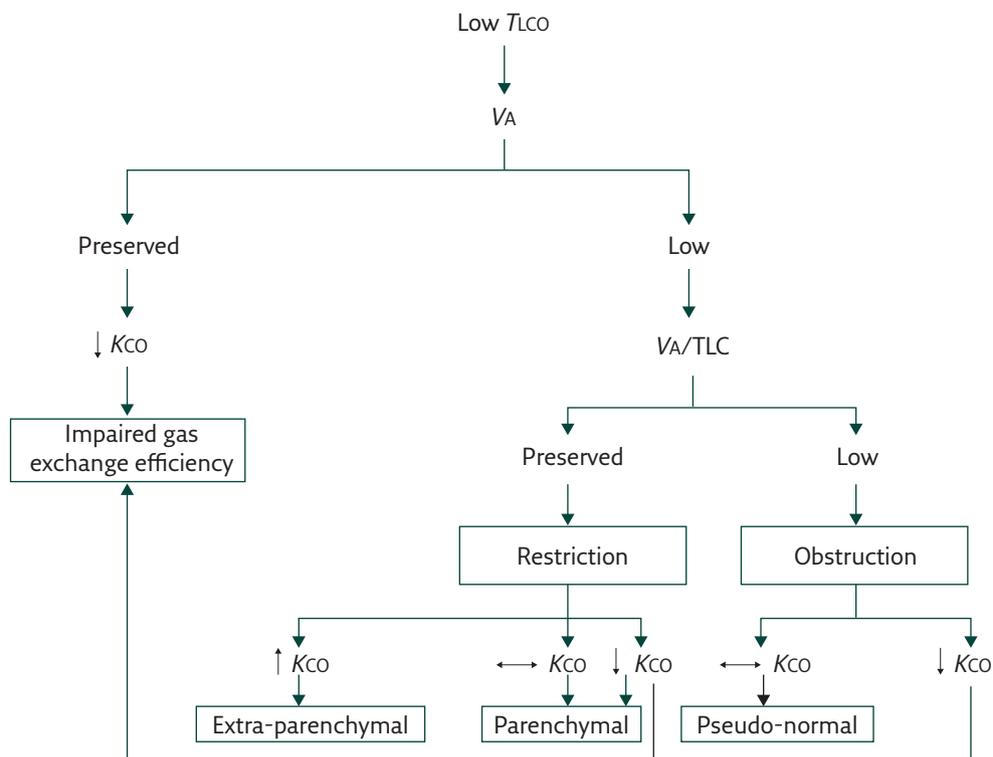


Figure 3 A simplified algorithm for the differential diagnosis of a low $TLCO$ taking into consideration the potential pitfalls involved in interpretation of the accessible VA and KCO . Symbols \uparrow , \downarrow and \leftrightarrow represent values above, below and within the normal range, respectively. See the text for further elaboration.

the great majority of subjects) [30]. If obstruction with maldistribution of ventilation were present, it would decrease VA secondary to a low VA/TLC [31]. It follows that a normal VA , when associated with a low KCO (provided there is no anaemia or recent smoking), suggests pulmonary vascular disease (e.g. PH or vasculitis), intrapulmonary right-to-left shunting or early emphysema, i.e. mild enough to not (yet) be associated with a low VA/TLC .

When VA is low the next step is to check the VA/TLC ratio.

- If the VA/TLC ratio is low (<0.8) indicating obstruction with ventilation distribution abnormalities [10, 28], the KCO might turn “normal”. In this scenario, no further valid inferences can be made regarding KCO ; however, if KCO is low despite those caveats (which, as mentioned, would otherwise tend to increase the $TLCO/VA$ ratio), there is extensive impairment in pulmonary gas exchange efficiency, e.g. severe emphysema [32].
- If the VA/TLC ratio is normal (≥ 0.8), the only explanation for a low VA is a low TLC , i.e. restriction [30]. Thus:
 - 1) A high KCO indicates a predominance of VC over VA due to: a) incomplete alveolar expansion but preserved gas exchange units frequently leading to $KCO >120$ – 140% or even higher, i.e. extra-parenchymal restriction (e.g. pleural, chest wall or neuromuscular disease) [11]; b) an increase in pulmonary blood flow from areas of diffuse (pneumonectomy) or localised (local destructive lesions/atelectasis) loss of gas exchange units to areas with preserved parenchyma frequently leading to more modest increases in KCO (although a high KCO can also be seen with normal or near-normal VA when there is increased pulmonary blood flow or redistribution such as left-to-right shunt and asthma); and c) extra-vascular haemoglobin, i.e. alveolar haemorrhage.
 - 2) A low KCO points towards intra-parenchymal restriction with impaired gas exchange efficiency as in some interstitial lung diseases (ILD) [33].
 - 3) A normal KCO is consistent with intra-parenchymal restriction with preserved KCO . This is the most common finding in patients with HRCT abnormalities showing a pattern consistent with idiopathic interstitial pneumonia [33]. Thus, a normal KCO should not be misinterpreted as indicative of “no ILD” [34, 35]. In this context, a normal KCO may either indicate that the main mechanism underlying the low $TLCO$ is loss of lung volume (e.g. fibrotic ILD) or the low VA led to a normalisation of KCO due to the curvilinear increase in KCO as VA decreases (figure 2).

Table 2 Key recommendations to avoid frequent pitfalls in the interpretation of T_{LCO} , K_{CO} and VA in clinical practice

Recommendation	Justification
Always rule out anaemia and recent smoking (<i>i.e.</i> CO inhalation) as a cause for a low T_{LCO} .	Decreases the number of haemoglobin sites available for CO binding and higher CO back-pressure, respectively.
The T_{LCO}/VA ratio does not represent “ T_{LCO} corrected by lung volume”. To avoid confusion and misinterpretation, K_{CO} should always be used instead of T_{LCO}/VA .	A one unit change in VA does not necessarily lead to one unit change in T_{LCO} .
A “preserved” K_{CO} should never be interpreted as indication of no major pulmonary pathology.	In both obstructive and restrictive diseases VA may decrease out-of-proportion to T_{LCO} leading to a “pseudo-normal” K_{CO} .
The first step in the interpretation of K_{CO} in the presence of a low VA is to check the VA/TLC ratio.	If low (<0.8) there is maldistribution of ventilation, frequently leading to a “pseudo-normal” K_{CO} .
Rule out submaximal inspiration (inspired volume should be at least 85% of the largest VC) as the cause of a low VA before interpreting a high K_{CO} .	Due to the marked increase in K_{CO} as VA decreases, relatively small decrements in the latter has a major impact on K_{CO} .
Always grade the functional impairment based on decrease in T_{LCO} not in K_{CO} .	

Owing to the trend for K_{CO} to be higher than T_{LCO} regardless the underlying reason(s), the severity of functional impairment should always be graded based on T_{LCO} based on the European Respiratory Society recommendations: mild (less than lower limit of normal, but above 60% predicted according to the recently published Global Lung Initiative equations [36]), moderate (40–60% predicted) and severe (>40% predicted) [6].

In the present case, a low VA but normal VA/TLC (coupled with the absence of obstruction on spirometry, gas trapping or high specific airway resistance) is not consistent with maldistribution of ventilation due to small airway disease. Thus,

VA decreased in proportion to a low TLC , *i.e.* secondary to the patient’s morbid obesity and/or to the known trend for CTEPH patients to present with mild restriction due to microatelectasis and fibrotic changes [37]. As shown in figure 2, K_{CO} should increase as VA decreases if there was no impairment in gas exchange efficiency; in fact, this is one of the justifications as to why obesity is associated with a high K_{CO} [38]. It follows that the only plausible explanation for a low K_{CO} in the present case is a low VC, *i.e.* a pulmonary vascular disease. Some key interpretative issues regarding T_{LCO} and its derived measurements are provided in table 2.

Key points

- Clinical interpretation of the T_{LCO} frequently benefits from associated analysis of the accessible VA , VA/TLC ratio and the diffusion coefficient (K_{CO}).
- The T_{LCO}/VA ratio (K_{CO}) should not be erroneously interpreted as “ T_{LCO} corrected by lung volume” because a one unit change in VA does not lead to one unit change in T_{LCO} across all possible VA values.
- Preserved VA and a low K_{CO} (provided the absence of anaemia or recent smoking) suggests pulmonary vascular disease, intrapulmonary right-to-left shunting or early emphysema.
- A low VA in the presence of a normal VA/TLC ratio suggests restriction: a low K_{CO} points towards intra-parenchymal restriction with impaired gas exchange efficiency whereas a high K_{CO} is consistent with extra-parenchymal restriction.
- A low VA in the presence of a low VA/TLC ratio indicates obstruction with ventilation distribution abnormalities: whereas a preserved K_{CO} is not amenable to interpretation, a low K_{CO} indicates extensive impairment in pulmonary gas exchange efficiency, *e.g.* severe emphysema.
- A normal K_{CO} should not be used to rule out major pulmonary pathology, particularly when VA is reduced.

Self-evaluation questions

In each of the following patients, please indicate which is the most likely underlying diagnosis which could explain the observed abnormalities (indicated by a # symbol).

1.

TLC % pred	Tlco % pred	VA % pred	VA/TLC	Kco % pred
132#	52#	64#	0.56#	87

- a) Idiopathic PH
- b) Neuromuscular disease
- c) Emphysema
- d) Asthma
- e) ILD

2.

TLC % pred	Tlco % pred	VA % pred	VA/TLC	Kco % pred
50#	68#	44#	0.97	145#

- a) Idiopathic PH
- b) Neuromuscular disease
- c) Emphysema
- d) Asthma
- e) ILD

3.

TLC % pred	Tlco % pred	VA % pred	VA/TLC	Kco % pred
91	54#	82	0.86	64#

- a) Idiopathic PH
- b) Neuromuscular disease
- c) Emphysema
- d) Asthma
- e) ILD

4.

TLC % pred	Tlco % pred	VA % pred	VA/TLC	Kco % pred
69#	44#	67#	0.93	58#

- a) Idiopathic PH
- b) Neuromuscular disease
- c) Emphysema
- d) Asthma
- e) ILD

5.

TLC % pred	Tlco % pred	VA % pred	VA/TLC	Kco % pred
107	112	99	0.82	129#

- a) Idiopathic PH
- b) Neuromuscular disease
- c) Emphysema
- d) Asthma
- e) ILD

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Conflict of interest

None declared.

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Suggested answers

1. c. Moderately reduced $\bar{T}LCO$. Low V_A is associated with a low V_A/TLC and a high TLC indicating extensive ventilation distribution abnormalities in the context of an obstructive airway disease. Of note, despite low V_A/TLC , K_{CO} is reduced indicating extensive impairment in gas exchange efficiency. Collectively, emphysema is the most likely explanation for these findings.
2. b. Mildly reduced $\bar{T}LCO$. Markedly low V_A is associated with an equally low TLC and preserved V_A/TLC . Thus, K_{CO} is supra-normal. Collectively, these results are in line with extra-parenchymal restriction. Given the options available, neuromuscular disease is the most likely explanation for these findings (differentials being pleural and chest wall disease).
3. a. Moderately reduced $\bar{T}LCO$. V_A , TLC and V_A/TLC are within normal limits. Thus, K_{CO} is reduced. Collectively, the results are in line with impaired intrapulmonary gas exchange efficiency in the absence of restriction or significant airway disease. Given the options available, idiopathic PH is the most likely explanation for these findings (differentials being other pulmonary vascular diseases and right-to-left shunt).
4. e. Moderate-to-severe impairment in $\bar{T}LCO$. Low V_A is associated with an equally low TLC and preserved V_A/TLC . K_{CO} is also reduced. Collectively, the results are in line with intra-parenchymal restriction. Given the options available, ILD (with impaired gas exchange efficiency) is the most likely explanation for these findings.
5. d. Preserved $\bar{T}LCO$ but supra-normal K_{CO} in the context of normal TLC . Given the options available, asthma is the most likely explanation for these findings (differential being left-to-right shunt).

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