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Effect of General Anaesthesia on Respiratory Function *

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Abstract. This review examines the possible mechanisms for the impairment in pulmonary gas exchange and ventilatory control associated with general anaesthesia. Venous admixture and physiological dead space are both increased during anaesthesia. These changes result from increased ventilation-perfusion inequality, an effect apparently mainly attributable to alteration in the intrapulmonary distribution of ventilation. Concomitantly, with these changes in pulmonary gas exchange anaesthesia is known to alter the mechanics of the respiratory system and, in particular, to decrease functional residual capacity in recumbent subjects. Recent research has renewed interest in the finding that anaesthesia also alters chest wall shape and motion. This review attempts to synthesize the available and increasing evidence which supports the hypothesis that anaesthesia-induced alterations in chest wall behavior are responsible for the associated changes in lung function and consequent impairment of pulmonary gas exchange. Finally, the important finding that anaesthetic agents depress the ventilatory response to hypercapnia and hypoxia is discussed.

Key words: $(A-a)PO_2$ – $(a-A)PCO_2$ – $\dot{V}/\dot{Q}$ – Intrapulmonary shunt – FRC – Lung compliance – Chest wall – Ventilatory control

Introduction

The alveolar to arterial oxygen tension gradient $(A-a)PO_2$ and the arterial to alveolar carbon dioxide tension gradient $(a-A)PCO_2$ are both increased by general anaesthesia [57]. It is the purpose of this paper to review current understanding of the changes in pulmonary function which accompany anaesthesia and to examine recent evidence implying that these changes are secondary to anaesthesia-induced

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alterations in chest wall behaviour. In addition, we shall briefly explore the alterations in ventilatory control which accompany general anaesthesia.

Pulmonary Gas Exchange During Anaesthesia

Impaired Oxygenation Due to Ventilation-Perfusion ($\dot{V}/\dot{Q}$) Mismatching

In their classic paper in 1958, Campbell and associates [10] examined the effects of anaesthesia-paralysis and mechanical ventilation in six supine patients. Three of these patients developed a higher $(A-a)PO_2$ than observed during spontaneous breathing. The authors suggested that "in the supine position with an intact chest the distribution of ventilation and blood flow are less 'ideal' during artificial ventilation than during natural breathing." Subsequent studies also demonstrated that the $(A-a)PO_2$ was increased during anaesthesia with spontaneous ventilation [46].

The concept of venous admixture has been of value in defining the causes of increased $(A-a)PO_2$. During general anaesthesia, increased venous admixture has been repeatedly demonstrated (Table 1) [10, 35, 47]. Venous admixture results from 1) anatomic shunts and 2) from "shunt-like" effects due to perfusion of underventilated or nonventilated alveoli or due to perfusion of alveoli in which the diffusion of gases across the alveolar capillary membrane is impaired. The multiple "inert" gas elimination technique [65] can discriminate between $\dot{V}/\dot{Q}$ mismatching and shunting without the necessity of the subject inspiring 100% oxygen. This technique has recently been applied to examine the effects of anaesthesia on venous admixture. Anatomic shunting is apparently not increased during anaesthesia-paralysis in healthy young subjects [56]. In these young subjects, increased $\dot{V}/\dot{Q}$ mismatching contributes more than shunting to the increased venous admixture found during anaesthesia-paralysis, but the amount of shunting does increase as the inspired oxygen concentration is raised [56]. Conversely, with anaesthesia in older patients with known preexisting pulmonary dysfunction, an increase in shunting played a much larger role than increased $\dot{V}/\dot{Q}$ mismatching in causing increased venous admixture [15].

Few studies have examined the effect of anaesthesia on diffusing capacity. The oxygen diffusing capacity in dogs [17] and the carbon monoxide diffusing capacity in humans [6] have been reported not to be affected by anaesthesia.

Table 1. Effect of anaesthesia with spontaneous and mechanical ventilation on venous admixture, expressed as percentage of the cardiac output

Investigators (ref.)	Age of patient	FIO_2	Type of ventilation during anaesthesia	Venous admixture	
				Awake	Anaesthetized
Campbell et al. [10]	31	0.21	Mechanical	7.0	11.0
Marshall et al. [35]	41	1.00	Spontaneous	4.4	12.1
Price et al. [47]	21–27	0.25	Spontaneous	5.9	18.9
		1.00	Spontaneous	3.1	6.1
		0.25	Mechanical	...	15.1
		1.00	Mechanical	...	11.1

Other Mechanisms Affecting Oxygenation During Anaesthesia

1. Cardiac Output: It has been suggested that with a fixed intrapulmonary shunt the increased (A–a)PO_2 associated with anaesthesia might occur secondary to a fall in mixed venous oxygen content ($C_{\bar{v}}O_2$) produced by an anaesthetic-induced fall in cardiac output [30]. However, $C_{\bar{v}}O_2$ has been found to be increased by general anaesthesia [35]. Furthermore, it has been shown that intrapulmonary shunting varies directly with cardiac output in normal and diffusely diseased lungs and varies inversely with cardiac output in lungs with regional atelectasis [11]. Thus, PaO_2 may remain unchanged with alterations in cardiac output in normal or diffusely diseased lungs but not in lungs with regional atelectasis. A possible mechanism for the increase in shunting with increases in cardiac output, and vice versa, may be the interaction between cardiac output-induced alterations in pulmonary arterial pressure and hypoxic pulmonary vasoconstriction [5].

2. Changes in O_2-Carrying Characteristics of Haemoglobin: A shift to the left of the oxyhaemoglobin dissociation curve results in a lower PO_2 for a given O_2 content, i.e., an increase in (A–a)PO_2 if shunting remains constant. Anaesthetic agents have, however, not been found to produce a left shift of the oxyhaemoglobin dissociation curve [39, 60].

Impaired CO_2 Elimination

Severinghaus and associates, in 1957, documented that CO_2 elimination was impaired in anaesthetized-paralyzed man when the lungs were mechanically ventilated [59]. Campbell and colleagues [10] showed that this failure of CO_2 elimination was associated with an increase of physiological dead space (physiological dead space = alveolar + anatomical dead space) and subsequent investigators demonstrated that the latter was in part caused by the development of alveolar dead space [45]. Anatomic dead space may also be altered by anaesthesia. For instance, endotracheal intubation or tracheostomy will reduce anatomic dead space roughly by one-half, while extending the neck and protruding the jaw in a nonintubated subject may double the dead space [44]. Premedication with atropine [58] may also increase the anatomic dead space.

It has been stated that a major factor responsible for the increase in (a–A)PCO_2 during anaesthesia is underperfusion of nondependent lung regions secondary to moderate pulmonary hypotension [2]. Supporting this hypothesis is the finding of very high $\dot{V}/\dot{Q}$ ratios in anaesthetized-paralyzed volunteers which cannot be explained entirely by alterations in the distribution of ventilation [56].

Summary

Both $\dot{V}/\dot{Q}$ mismatching and increased right-to-left shunting contribute to increased venous admixture and increased (A–a)PO_2 during general anaesthesia. The relative contribution of the two seems to depend on the age of the patient and the presence or absence of preexisting lung disease. Increased $\dot{V}/\dot{Q}$ mismatching resulting in relative overventilation of nondependent lung regions appears to be the major mechanism for the increased (a–A)PCO_2 found during anaesthesia.

Causes of Ventilation-Perfusion Inequality During Anaesthesia

Distribution of Ventilation During Anaesthesia

When the subject is awake and inspiring from functional residual capacity, gas labelled with ^{133}xenon (^{133}Xe) is normally distributed nonuniformly with the dependent lung regions receiving more inspirate per unit lung volume than the nondependent lung regions [38]. During anaesthesia-paralysis with mechanical ventilation, this distribution of inspired gas per unit lung volume becomes more uniform when subjects lie in the lateral or supine postures [8, 53, 69]. In contrast, anaesthesia-paralysis with mechanical ventilation had little effect on the distribution of inspired gas in subjects lying prone and made this distribution less uniform than in the awake state when the subjects were in the sitting posture (Fig. 1) [53, 54]. In anaesthetized, spontaneously breathing subjects lying in the lateral decubitus position, intrapulmonary gas distribution between the two lungs has been examined utilizing endobronchial intubation [49]. In this study distribution was altered from that found in the awake condition [38] in that, with anaesthesia, there was preferential ventilation of the nondependent lung.

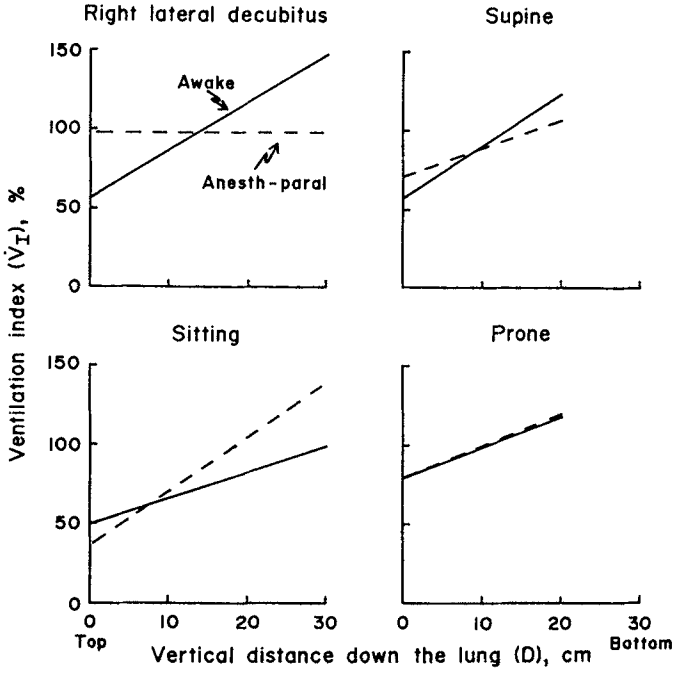

Fig. 1. Intrapulmonary distribution of tidal volume in four body positions. The ventilation index ($\dot{V}_I$) % on the ordinate expresses the degree of uniformity of gas distribution. When $\dot{V}_I$ = 100%, the inspired gas is uniformly distributed. $\dot{V}_I > 100\%$ indicates relative hyperventilation per unit lung volume and $\dot{V}_I < 100\%$ relative hypoventilation per unit lung volume. With anaesthesia-paralysis, ventilation per unit lung (gas) volume became more uniform in the right lateral and supine positions and less uniform in the sitting position. In the prone position, anaesthesia-paralysis had no effect on the ventilation per unit lung (gas) volume. (From Rehder et al [54]. By permission of the American Physiological Society)

Distribution of Perfusion During Anaesthesia

Studies using ^{133}Xe [34, 69] have been unable to detect any significant change in the vertical distribution of regional perfusion during anaesthesia-paralysis. This, however, may reflect insensitivity of the xenon technique. The extremely high $\dot{V}/\dot{Q}$ ratios found in anaesthetized-paralyzed subjects during an inert gas clearance study [56] are difficult to explain on the basis of altered ventilation alone and imply that some alteration in blood flow distribution probably occurred.

The effect of anaesthesia on hypoxic pulmonary vasoconstriction is the focus of recent investigation [7, 37]. Several volatile anaesthetic agents appear to vary between species. Intravenous anaesthetic agents have not been found to attenuate the vasoconstriction. This variability between different anaesthetic agents in reducing hypoxic pulmonary vasoconstriction would imply that this effect is probably not a significant universal cause of the widened $(A-a)PO_2$ found during anaesthesia since the latter occurs irrespective of the type of anaesthetic.

Summary

The preferential ventilation of the dependent lung regions found in awake spontaneously breathing subjects lying supine or in the lateral decubitus posture is reduced by anaesthesia-paralysis.

Preferential ventilation of the nondependent lung occurs in anaesthetized, spontaneously breathing subjects lying in the lateral decubitus position. Although anaesthetics may produce some alteration in pulmonary blood flow distribution, this distribution persists during anaesthesia in being mainly gravity-dependent. Individual anaesthetics may impair hypoxic pulmonary vasoconstriction.

Effect of Anaesthesia on the Mechanical Properties of the Respiratory System

The distribution of inspired gas within the lungs depends on both the mechanical properties of the lungs and airways and also the relative allocation of expanding forces acting on the lung.

Functional Residual Capacity (FRC)

Numerous studies have found that anaesthesia decreases the FRC of subjects lying in recumbent postures [51]. This decrease in FRC is variable but, in the supine position, averages 16% of the awake value. It occurs on induction of anaesthesia and is not changed by the type, depth, or duration of anaesthesia, the percentage of oxygen inspired, or the concomitant use of muscle relaxants [14, 23, 24, 50, 67]. The magnitude of this FRC reduction is inversely correlated to the associated increase in $(A-a)PO_2$ found during anaesthesia [24, 25].

Several mechanisms have been suggested as potential causes for this FRC decrease [23, 55]. Increase in central blood volume would reduce thoracic gas volume and has been inferred as a cause of the decrease in FRC with anaesthesia [28]. There is, however, no current experimental evidence that this occurs [27]. Gas trapping behind closed airways would also result in an apparent reduction in FRC as measured by gas dilution or nitrogen clearance. However, simultaneous

measurement of FRC by the N_2 washout technique and body plethysmography revealed similar reductions in FRC [67]. Miliary atelectasis causing increased elastic lung recoil would also be a cause of FRC decreasing with anaesthesia [4]. Convincing radiological evidence for this is lacking. If atelectasis did occur, it would potentially be increased by the use of 100% inspired oxygen [13], yet the reduction in FRC with anaesthesia is independent of the inspired oxygen concentrations [14, 23]. This hypothesis also does not explain the finding that sitting subjects, unlike recumbent subjects, do not decrease their FRC with anaesthesia [48]. A reduction in thoracic cavity volume due to inward displacement of the rib cage and/or elevation of the diaphragm would also reduce FRC. This occurs with chest strapping [62]. At FRC the inward lung recoil is equal and opposite to the outward recoil exerted by the chest wall. Thus, either an increase in lung recoil with no change in chest wall recoil or a decrease in chest wall recoil at low lung volumes, not balanced by a corresponding decrease in lung recoil, would decrease FRC. The possibility that anaesthesia decreased chest wall recoil was first raised in the study of anaesthetized subjects lying supine by Westbrook et al. [67]. The measured lung elastic recoil at FRC was found to be less than that required to balance the normal known value of chest wall recoil at that lung volume in awake subjects lying supine. A reduction in chest wall recoil would be associated with a shift of the chest wall pressure-volume curve to the right. Such a shift has been observed with isoflurane anaesthesia of supine subjects [50].

Lung Compliance and Lung Elastic Recoil

Anaesthesia with or without muscle paralysis decreases lung compliance and increases lung recoil [51, 67]. The mechanisms underlying these changes remain obscure. Atelectasis during anaesthesia was originally proposed as a mechanism [4]. However, radiological evidence for atelectasis is lacking, the decrease in lung compliance with anaesthesia is not reversed by hyperinflation [67], and, furthermore, the percentage reduction in lung compliance with anaesthesia is usually greater than the concomitant decrease in FRC [51]. This evidence would also imply that airway closure reducing the number of distensible alveoli is not a major cause for the decrease in compliance with anaesthesia. There is no evidence to suggest that anaesthesia increases interstitial lung water [36]. The failure to demonstrate significant differences in compliance with various agents and depth of anaesthesia argues against direct pharmacological action decreasing lung compliance, as does the finding that anaesthesia does not decrease lung compliance in the sitting position [48].

Other conditions associated with breathing at low lung volumes such as chest strapping are also associated with a decrease in lung compliance and increase in lung elastic recoil [62]. These changes have been attributed to a decrease in the compliance of the surface film lining the alveoli [62] such as seen in in vitro lungs held at low transpulmonary pressures [71]. Anaesthesia may decrease lung compliance by a similar effect. In addition, most anaesthetic agents are lipid soluble and might be expected to have a direct effect on surfactant function. In an in vitro study, however, anaesthetics were found to have little direct effect on surfactant function [68].

Airway Resistance

Most inhalational anaesthetics in current clinical use reverse pharmacologically-induced bronchospasm and bronchodilate in vitro tracheobronchial muscle preparations [3, 26]. However, in man airway resistance approximately doubles on induction of anaesthesia [21, 50]. This discrepancy may relate in part to the fall in FRC associated with anaesthesia producing a reduction of airway calibre due to the interdependence of lung parenchyma and airways [9].

Airway Closure

The role of airway closure in impairing pulmonary gas exchange during anaesthesia is unresolved and needs further clarification [52]. The relationship between closing capacity (CC) (defined as the absolute lung volume at the onset of phase IV single breath oxygen test) and FRC during anaesthesia is believed to determine whether airway closure occurs during anaesthesia. As measured by the single breath oxygen test, CC did not change between the awake and anaesthetized states in supine healthy subjects [18, 22]. Because FRC decreased with anaesthesia in these studies, (FRC-CC) decreased. In contrast, anaesthesia-paralysis of patients lying supine was found not to change their mean (FRC-CC) when CC was measured with the foreign gas bolus technique [29], a technique generally held to be more reliable than the single breath oxygen test. Patients in this last study were divided into two groups on the basis of whether their FRC exceeded CC or was less than CC when awake and lying supine. In both groups FRC and CC decreased with anaesthesia-paralysis. In those patients whose preoperative FRC exceeded CC (mean age 37 years), (FRC-CC) fell with anaesthesia-paralysis because the latter decreased FRC more than CC. With patients whose preoperative CC exceeded FRC (mean age 57 years), anaesthesia-paralysis decreased CC more than FRC so that the value for (FRC-CC) became less negative. Increase in lung recoil with anaesthesia [67] may explain the decrease in CC in both the young and old groups. If atelectasis occurred during anaesthesia-paralysis in the second (older) group, this would further increase lung recoil and explain why these patients developed a more marked decrease of CC with anaesthesia-paralysis.

Effect of Anaesthesia on the Expanding Forces Acting on the Chest Wall

The nonuniform distribution of inspired gas in the awake state has been ascribed to the vertical pleural pressure gradient [38]. Recent research [1] suggests that this vertical pleural pressure gradient may be the result of, rather than the cause of, the nonuniform distribution of inspired gas. This is because the isolated lung and thoracic cavity have different shapes at a given volume with a uniform distending pressure, a difference which is further exaggerated by the influence of gravity. *In vivo* the two structures must conform to one another and their resulting deformation produces the vertical distribution of regional lung volumes and, hence, the pleural pressure gradient.

Although changes in shape of the respiratory system that accompany breathing under normal conditions in awake man appear insufficient to alter the general vertical distribution of inspired gas or regional lung volumes, changes in the latter

are produced by gross changes in thoracic configurations [19]. ^{133}Xe studies of volunteers in the lateral decubitus position demonstrate that anaesthesia-paralysis increases the vertical gradient of regional lung volumes such that the nondependent alveoli were larger and the dependent alveoli were smaller than when awake [53]. This suggests that anaesthesia-paralysis alters thoracoabdominal mechanics and, hence, the pattern of expansion of the respiratory system. Evidence supporting this was found by Froese and Bryan [16] in their radiological examination of diaphragmatic end-expiratory position and motion during both anaesthesia and muscle paralysis. In recumbent subjects they observed that both conditions caused a cephalad shift of the diaphragm which was most pronounced in its dependent region. Diaphragmatic motion during spontaneous breathing, both when the subject was awake and anaesthetized, occurred predominantly in the dependent region, whereas with muscle paralysis and mechanical ventilation the majority of diaphragmatic movement occurred in its nondependent region.

John Snow is credited as the first to document that anaesthesia alters the pattern of chest wall motion. In 1858 he wrote [61] that the inhalation of chloroform leads to breathing "sometimes only performed by the diaphragm whilst the intercostals are paralysed." Observation of these alterations in chest wall motion have long been used clinically to help gauge the depth of anaesthesia [40]. Recent studies have attempted to quantify the relative contributions of the rib cage and abdomen-diaphragm to tidal volume breathing during anaesthesia. When awake and lying supine, the rib cage contribution to quiet spontaneous breathing is less than that contributed by the diaphragm [28, 63]. This percentage rib cage contribution to spontaneous breathing is markedly reduced following induction of anaesthesia. Conversely, with anaesthesia and mechanical ventilation, with [28, 64] or without [20, 28, 63] muscle paralysis, the displacement of the rib cage increases dramatically.

These studies suggest that anaesthesia impairs the phasic activity of intercostal muscles and, together with the finding that halothane anaesthesia nearly completely abolished intercostal electromyographic activity [63], imply that the intercostal motor neuron pool is more depressed by anaesthesia than the phrenic nerve motor neuron pool. In addition, in two of the above studies [28, 63], halothane anaesthesia produced paradoxical rib cage motion which was exacerbated by airway obstruction, indicating that the tonic stabilizing activity of the intercostal muscles was reduced or abolished by anaesthesia. Tonic electromyographic activity in the diaphragm is also reduced or abolished by halothane anaesthesia [41]. This finding may in part explain the cephalad displacement of the diaphragm during anaesthesia of subjects lying supine [16].

Summary

Anaesthesia of recumbent subjects with and without muscle paralysis decreases FRC and lung compliance and increases lung recoil. The latter may partly account for the recent finding that CC decreases with anaesthesia. Recent studies have quantified the alterations in rib cage and diaphragm shape and motion induced by anaesthesia. These changes are associated with changes in both the tonic and phasic electromyographic activity in both the intercostal and diaphragmatic muscles.

Control of Ventilation Under Anaesthesia

Ventilatory Response to Hypercarbia and Hypoxia

Most inhalational and intravenous anaesthetic agents depress central ventilatory drive as defined by the carbon dioxide tension/ventilation response curve [33, 42]. The magnitude of the resulting decrease in minute ventilation for a given $PaCO_2$ depends both on the particular agent and its dose [42]. Sedative doses of anaesthetics do not significantly affect minute ventilation [32, 33]. It has not been established whether these effects represent depression of the brain stem chemoreceptor or "controller" [43], or an interaction between altered neural control and altered pulmonary mechanics [12, 63].

It used to be commonly believed that the peripheral chemoreceptor response to hypoxia and acidosis was maintained during anaesthesia. Recent studies with nitrous oxide, halothane, and enflurane in man have shown, however, that these agents significantly depress the ventilatory response to hypoxia even when used in subanaesthetic, sedative concentrations [32, 33, 70] (Fig. 2). With these anaesthetic agents, the chemical drive to ventilation is thus totally dependent on the response to carbon dioxide. In contrast, barbiturates and narcotics depress the ventilatory response to hypoxia in proportion to the depression these agents produce in the ventilatory response to hypercapnia [31, 66].

Summary

Anaesthetic agents in doses required to produce anaesthesia but not sedation depress the ventilatory response to hypercapnia. Even subanaesthetic doses of inhalational anaesthetics significantly depress the ventilatory response to hypoxia.

Conclusion

General anaesthesia disturbs intrapulmonary gas exchange both in terms of oxygenation and carbon dioxide elimination. Although many factors appear to be involved, the following may be the sequence of events. The initial effect of anaesthesia is on the shape and motion of the chest wall which in turn alters the mechanical properties of both the chest wall and the lung. Intrapulmonary gas distribution is altered secondarily. Regional pulmonary blood flow does not adjust to this although intraregional changes may take place. An increased mismatching of ventilation to perfusion occurs and some of the low ventilation-to-perfusion areas may progress into frank shunts. The development of lung regions with high

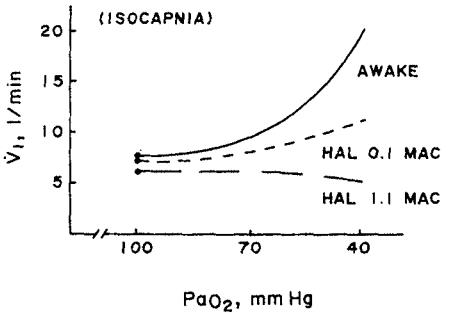

Fig. 2. Ventilatory response in l/min to isocapnic hypoxia in awake, sedated (0.1 MAC halothane), and anaesthetized (1.1 MAC halothane) man. One MAC (minimal alveolar concentration) is the end-tidal concentration required to prevent 50% of subjects moving in response to skin incision. One MAC halothane in man equals an end-tidal concentration of 0.76%. Note the reduction in minute ventilation induced by hypoxia at 0.1 MAC halothane and the absence of a response in minute ventilation at 1.1 MAC halothane. (Redrawn from the original diagram provided by Dr. R. L. Knill)

ventilation-to-perfusion ratios contributes to the inefficient elimination of carbon dioxide.

Anaesthetic agents diminish the homeostatic ventilatory responses to hypercarbia and hypoxia.

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