The hepatopulmonary syndrome: new name, old complexities

In the most recent edition of her now classic textbook on hepatic and biliary disorders, Sheila Sherlock quotes a new term—the hepatopulmonary syndrome—to reflect the arterial hypoxaemia (<10.7 kPa) which occurs in about one third of patients with liver cirrhosis in the absence of detectable cardiorespiratory disease. This syndrome, originally defined by a group of Swedish investigators, may be seen in other chronic liver diseases, such as chronic active hepatitis, and it has also been reported in non-specific hepatic diseases. The purpose of this article is to review the most common structural and physiological findings of this syndrome, on the basis of results obtained with the inert gas technique. A better understanding of the pathophysiology of interactions between the liver and the lung should help to define the indications for liver transplantation and optimise its clinical management.

What is the structural basis?

Ryddell and Hoffbauer were the first to identify numerous postmortem intrapulmonary arteriovenous anastomoses in a young patient with juvenile cirrhosis, which were sufficient to justify his cyanosis. The anastomoses were seen between large arteries and veins near the hilum, as well as in the peripheral vascular bed. Hales in the same year and Kravath et al in 1971 reported similar findings in a few cases where liver disorders had occurred in early life. Berthelot and coworkers, however, were the first to document the postmortem structural changes with liver cirrhosis and different degrees of hypoxaemia, by using a true gold standard method (micro-opaque gelatin injections into the pulmonary vascular tree). In contrast to previous reports, the most conspicuous finding was a remarkable dilatation of the fine peripheral branches of the pulmonary artery at both the precapillary and the capillary levels of the lung (basically affecting arterial vessels up to 160 µm, in diameter). In addition, spider naevi were apparent on the pleura in half of the patients. Obvious peripheral arteriovenous communications were found in only one such patient. These vascular abnormalities contrasted with an otherwise intact pulmonary architecture. Thus there was no evidence of fibrosis or thickening of the alveolar wall or of the connective tissue septa. There seemed no correlation between the presence of finger clubbing, clinical cyanosis, or nodular shadows on the chest radiograph and the degree of the postmortem pulmonary arterial changes. In 1977 Stanley et al reported a case of hepatic cirrhosis and cyanosis. At necropsy there were precapillary arteriovenous anastomoses and pleural spider naevi. Morphometric analysis gave further evidence of unevenly distributed pulmonary vasodilatation in intracapillary arteries. No communications between precapillary vessels were seen, however, and electron microscopy showed the walls of small veins to be thickened by a layer of collagen. The walls of pulmonary capillaries and venules were also thickened, causing an approximately twofold increase in the minimum blood-gas interface distance, which might explain the reduced transfer factor shown in this patient. In 1978 Davis and coworkers described a patient with liver cirrhosis whose clinical and functional features were similar to those of the patient just described and in whom postmortem examination revealed changes limited exclusively to the pulmonary vasculature. The most outstanding finding was the presence of thin walled vessels measuring 60–80 µm in diameter (normal sized capillaries range from 8 to 15 µm) throughout the lower lobes. There were multiple pleural and subpleural arteriolar naevi. No anatomical arteriovenous malformations were seen histologically. Williams and associates found diffuse dilatation affecting all intra-acinar vessels and pleural spider naevi in hypoxaemic patients who had died from fulminating hepatic failure, though the vascular changes were generally not as severe as in cirrhosis. Precapillary anastomoses were seen in only one patient. Other postmortem studies have also failed to identify a precise anatomical pathway for intrapulmonary shunt and postulated an extrapulmonary site—for instance, between the portal and the pulmonary venous systems. More recently, MacNee et al described an unusual young patient who suffered from mildly impaired liver function caused by juvenile hepatic fibrosis. Lung biopsy showed leashes of vessels running into the alveolar walls. These vessels were excessive in size, diameter, and number, and consistent with the presence of minute arteriovenous communications.

All in all, these studies point to considerable structural derangement of the pulmonary microcirculation, sufficient to allow mixed venous blood to pass directly into the pulmonary veins. The common structural findings are the presence of widespread vasodilatation of the pulmonary vascular bed at the precapillary level (50–80 µm in diameter) near the gas exchange area; but larger arteriovenous anastomoses, which are not necessarily near gas exchange units, may be seen. The latter may develop through dilatation of normal capillaries to precapillary diameter or alternatively by the opening (by either recruitment or distensibility, or both) of anatomical precapillary pulmonary vascular communications. Such communications have been shown in the lungs of the normal dog and, possibly, in human lungs. In addition, a few pleural spider naevi have been reported. In view of this range of extensive pulmonary vascular abnormality in patients with liver diseases, Krowka and Cortese prefer the term intrapulmonary vascular dilatation.

Clinically, most patients with pulmonary vascular derangement are cyanosed and have finger clubbing and a hyperkinetic circulation. They may complain of shortness
of breath and platypnoea (shortness of breath induced by the upright position and relieved by recumbency). Although most of them show the typical stigmata of severe liver dysfunction (spider naevi and cutaneous telangiectasiae, among other signs) and have abnormal results in liver function tests, in a few cases gas exchange abnormalities may antedate manifestations of severe hepatic failure. 18 Whereas conventional pulmonary function tests give normal results, these patients show a wide range of arterial oxygen tension (Pao2). This Pao2 may be normal, yet as a result of hypoxaemia there is an increased alveolar to arterial Po2 difference (A-aDo2). Alternatively, some patients have mild to moderate arterial hypoxaemia and some may even need long term oxygen therapy. Transfer factor (carbon monoxide diffusing capacity, TLco) may be normal or moderately to severely reduced. Chest radiographs may be normal or show bilateral increased basilar interstitial markings consistent with widespread intrapulmonary fine vascular malformations. Cardiac catheterisation may show normal or low pulmonary pressures and intracardiac shunts are absent. In a few cases, however, pulmonary hypertension has been documented. 4 The vascular abnormalities can be identified, invasively, by pulmonary angiography or, non-invasively, by techniques such as technetium-99m labelled macroaggregated albumin (99Tc-MAA) whole body scanning or two dimensional contrast enhanced echocardiography. 4 Pulmonary angiography may show a "spongy" distal arterial tree with multiple vessels; arteriovenous communications are discrete and uncommon. The presence of extrapulmonary radionuclide 99TcMAA activity over the kidneys and brain suggests a right to left intrapulmonary shunt. Normally the albumin particles (20-60 μm in diameter) should be trapped in the pulmonary capillary bed (less than 15 μm in diameter). Two dimensional contrast enhanced echocardiography seems to be a most useful non-invasive approach, which identifies echoes (microbubbles of air or indocyanine green) in the left atrium within three to six beats of their visualisation in the right heart cavities. 4 In normal conditions echogenicity in the left heart chambers is not detected because microbubbles (as large as 60–90 μm) are trapped in the pulmonary capillary. Krowka et al 19 have shown that a positive contrast enhanced echocardiogram is commonly seen in candidates for liver transplantation even in the absence of arterial hypoxaemia, thereby suggesting the coexistence of such intrapulmonary vascular dilatations with advanced liver failure. Contrast enhanced echocardiography, however, cannot differentiate between the different types of vascular malformations (that is, precapillary, capillary and pleural dilatations versus direct arteriovenous communications).

What is the physiological basis?

Until the early 1970s low arterial oxygen saturation in patients with cirrhosis had been variously attributed to one or more of the following mechanisms: 20 changes in the affinity of oxyhaemoglobin, intrapulmonary and portopulmonary shunts, alveolar-capillary diffusion limitation for oxygen, and ventilation-perfusion (VA/Q) inequalities, the latter being caused by an increased closing volume 21 or failure of hypoxic pulmonary vasoconstriction to develop, or both. 21, 22 A rightward shift in the oxygen dissociation curve occurs in many patients. This decreased affinity of haemoglobin for oxygen appears to be related to an increased concentration of 2,3-diphosphoglycerate within the red blood cell. This right shift of the oxyhaemoglobin dissociation curve cannot, however, explain the degree of arterial hypoxaemia. The importance of the other three mechanisms has remained speculative. Cigarette smoking, a common habit in patients with alcoholic cirrhosis, can increase closing volume, producing peripheral Airways dysfunction and airway obstruction, a contributory factor to both reduced TLco and VA/Q mismatching. Until recently no method has been capable of distinguishing intrapulmonary shunt, VA/Q mismatch, and limitation of diffusion. The only available approaches were based on the use of the respiratory gases, TLco, or radioactive tracers, none of which are capable of separating these three intrapulmonary determinants of hypoxaemia. In addition, the use of high inspired oxygen fractions to assess intrapulmonary shunting may itself alter both the bronchial and the pulmonary vascular tone and this affects pulmonary gas exchange, giving a different result from that obtained with the patient breathing air.

Over the past few years pulmonary gas exchange in cirrhosis has been revisited by using the multiple inert gas elimination technique. 24 This approach estimates the functional distribution of VA/Q ratios in the lung on the basis of the pattern of elimination of dissolved infused inert gases of different solubility. This technique also allows computation of the Pao2 that would be expected from the amount of VA/Q mismatching and intrapulmonary shunting if no limitation of diffusion, postpulmonary shunts (bronchial and thebesian circulations and portopulmonary communications) or substantial pulmonary parenchymal oxygen uptake were present. Thus alveolar to capillary dlsuequilibrium for oxygen would cause the predicted Pao2 to be considerably higher than the measured Pao2.

With this technique the effect of VA/Q relationships on pulmonary gas exchange has been investigated in five separate studies, which included a constellation of patients with liver cirrhosis and different degrees of abnormal gas exchange, the Pao2 ranging from normal to extremely low. 25-29 (table). The fist study explored the role of VA/Q mismatch in 15 patients with cirrhosis (mostly alcoholic) and mild to moderate hepatocellular dysfunction, all of them smokers. 25 They were otherwise all clinically stable. The hypoxic response was also assessed by getting the patient to breathe air and low and high oxygen fractions. Under baseline conditions the patients showed mild systemic and pulmonary vasodilatation, a normal Pao2, mild hypoxaemia, a small shift to the right of the oxy-
The distributions of VA/Q ratios displayed mild abnormalities of VA/Q relationships: a small proportion of the cardiac output perfused regions with a low VA/Q ratio. Shunt was conspicuously absent. When patients breathed 11% oxygen both pulmonary artery pressure and vascular resistance increased, whereas VA/Q distributions remained unchanged. Limitation of oxygen diffusion was not observed as measured PaO₂ did not differ from the predicted PaO₂. By contrast, when patients breathed 100% oxygen a small shunt (less than 2% of cardiac output) became apparent and there was some worsening of VA/Q mismatch in the absence of pronounced haemodynamic changes. One of the most interesting findings of this study was that the eight patients who had low arterial oxygen saturations, regardless of the presence of other associated stigmata, showed greater liver dysfunction and lower systemic and pulmonary vascular resistance, and also less hypoxic vascular response, lower PaO₂, and more VA/Q mismatching than the seven individuals without spider naevi. This suggested that the presence of spider naevi may be one of the most useful clinical markers of altered blood vessels in patients with cirrhosis. Thus, although this study confirmed a depressed pulmonary vascular tone, as shown by others, some vasoconstriction was still present. These data are consistent with enhancement of the development of alveolar units with low VA/Q ratios by inadequate pulmonary vascular tone. Interestingly, when the hypoxic vascular response is enhanced VA/Q mismatching is improved, a phenomenon also shown in patients with primary pulmonary hypertension or idiopathic pulmonary fibrosis. If the site of hypoxic pulmonary vasoconstriction is in small arteries (less than 500 μm in diameter), as it predominantly is, then clearly all the structural vascular changes will necessarily interfere with the ability of the pulmonary vessels to correct in response to alveolar hypoxia.

In the next study, summarised in the table, Mélot and coworkers looked further at the contribution of intrapulmonary and extrapulmonary determinants of PaO₂ from data obtained in 10 subjects with cirrhosis, seven of whom had mild hypoxaemia. The major conclusion was that the principal cause of the reduced PaO₂ was VA/Q mismatching. In a third study, in 14 patients with non-alcoholic liver cirrhosis, most of them non-smokers, with mild degrees of hypoxaemia, Hedenstierna and coworkers concluded that hypoxaemia can be explained by a combination of intrapulmonary shunting and VA/Q mismatch. Predicted PaO₂ was 0.3 kPa higher than measured PaO₂ in the six more hypoxaemic patients (PaO₂ < 11.5 kPa), suggesting the coexistence of limitation of oxygen diffusion in these patients.

In a fourth study, from the Mayo Clinic team, eight patients with cirrhosis, severe hypoxaemia and orthodeoxia (arterial hypoxaemia accentuated by the upright position and improved during recumbency) were studied. There was a large shunt in all but one patient, and this and the increased VA/Q mismatch (basically due to low VA/Q areas) each contributed about half to the hypoxaemia. In two patients PaO₂ increased substantially (> 60 kPa) when they breathed 100% oxygen. There was evidence of mild limitation of oxygen diffusion also, as mean predicted PaO₂ was significantly larger than the measured PaO₂ (by 0.7 kPa). These investigators considered that the gas exchange abnormalities in cirrhosis were essentially due to both intrapulmonary shunt and VA/Q mismatch, but that a component of impaired diffusion could not be ruled out. Using the multiple inert gas elimination technique, Castaing and Manier found even larger shunts and mild VA/Q mismatch in six patients with cirrhosis and severe hypoxaemia, as well as evidence for impairment of oxygen diffusion (mean predicted PaO₂ was 1.3 kPa greater than the measured PaO₂), suggesting the coexistence of a diffusion defect or postpulmonary or extrapulmonary shunting (that is, portopulmonary anastomoses), or both. In view, however, of the relatively high PaO₂ in the mesenteric (portal) circulation and the relatively small percentage of cardiac output contributing to splanchnic blood flow, the latter mechanism seems most unlikely to contribute to hypoxaemia.

An additional study using the multiple inert gas elimination technique has contributed to our knowledge of the basis of arterial hypoxaemia in patients with liver cirrhosis. Agusti and associates investigated six normoxaemic patients with cirrhosis before and during exercise. They showed that exercise did not modify the efficiency of the lung as a gas exchanger per se, because VA/Q mismatching remained unchanged and no limitation of oxygen diffusion ensued. As in their previous study, this group was unable to show a correlation between the pulmonary gas exchange indices and results of lung function tests for peripheral airways dysfunction. In addition, their work emphasises the interplay between intrapulmonary (VA/Q mismatch) and extrapulmonary factors (minute ventilation and cardiac output) modulating PaO₂. They showed that the abnormal VA/Q inequality at rest did not result in arterial hypoxaemia because both the high minute ventilation and the high cardiac output maintained PaO₂ within the normal range by their well-documented effect on alveolar Po₂ and mixed venous Po₂, respectively. The high cardiac output in these patients, a common haemodynamic feature of patients with liver cirrhosis, is one of the principal mechanisms of adjustment of gas exchange in pulmonary disease. There are three potential ways in which cardiac output may have a key role in pulmonary gas exchange. The most influential is via the effect on the oxygen content of the mixed venous blood; the other two are alteration of the transit time of the red blood cell through the pulmonary capillary network and redistribution of blood flow within the lung.

Another complex problem is why TLCO is so commonly reduced in the hepatopulmonary syndrome in view of the presence of, firstly, little or no small airways dysfunction; secondly, intrapulmonary vascular abnormalities with low or even absent pulmonary vascular tone; and, thirdly, high cardiac output. One possible explanation for reduced TLCO in the standing position could be that the combination of gravity plus a reduced pulmonary arterial pressure would induce a larger than normal regional of little or no perfusion at the lung apex and hence low regional diffusion-perfusion ratios in relation to total diffusing capacity. If TLCO measurements were lower in the standing than in the supine position in these patients, this hypothesis could be confirmed. Healthy individuals are known, however, to have a larger diffusing capacity in the supine position. A “diffusion-perfusion defect,” as suggested for cirrhosis by Genovesi and associates, has also been implicated in the oxygen diffusion gradient in dilated pulmonary vessels. These investigators postulated that the pronounced pulmonary vasodilatation at the capillary or precapillary level in cirrhosis would cause substantial VA/Q inequality, mainly characterised by areas of low or extremely low VA/Q ratios. In addition, it was suggested that there may be inadequate diffusion of oxygen to the centre of the enlarged capillaries in the lung, resulting in partially deoxygenated blood. The achievement of alveolar-capillary equilibrium for oxygen also depends on the transit time of the red blood cell. The inordinately high cardiac output usually present in patients with liver cirrhosis, resulting in a shorter transit time, would further exaggerate the limitation of diffusion by
this mechanism. Although gravitational blood flow differences may conceivably be enhanced by the low pulmonary vascular tone, causing diffusion-perfusion imbalance and possibly increasing hypoxaemia in the upright position, this hypothesis has been neither confirmed nor refuted.

**What is the mechanism?**

Whether the mechanism underlying the vascular abnormalities in the lung is related to failure of metabolism or failure of production of one or several circulating vasoactive substances by the damaged liver cells or to altered metabolism of some of the recently discovered paracrine factors synsed by endothelial cells is unknown. Many potential pulmonary vasodilating agents, including prostacyclin, atrial natriuretic factor, and platelet activating factor, have been detected, thereby potentially contributing to depression of hypoxic pulmonary vasoconstriction. Additional evidence has arisen from a recent experimental study in a rat model of biliary cirrhosis; this concluded that abnormalities of gas exchange induced by liver cirrhosis are related to a reversible attenuation of hypoxic pulmonary vasoconstriction. Similarly, the finding that the attenuated pulmonary vascular reactivity was restored after an infusion of angiotsins II suggests that the depressed hypoxic vascular response was partially reversible. The authors postulated that long term effects of vasodilating agents in cirrhosis may lead to accumulation of intracellular cyclic guanosine monophosphate (cGMP) or adenosine monophosphate (cAMP), or both, leading to vasodilation and depressed hypoxic pulmonary vasoconstriction. The latter could be restored in part by angiotsins II via stimulation of hydrolysis of cGMP and perhaps cAMP.

We may postulate therefore that a wide range of gas exchange abnormalities may occur in patients with chronic liver disorders. At one end of the range a few patients with advanced liver dysfunction and numerous hepatic stigmata may have pronoucated systemic and pulmonary vasodilatation with varying degrees of depressed hypoxic vasoconstriction and of arterial hypoxaemia, caused mainly by intrapulmonary shunt, perfusion to units with a low VA/Q ratio, and, possibly, some limitation of oxygen diffusion. The response of PaO2 to 100% oxygen breathing may help to determine the principal mechanism of hypoxaemia in these patients. For instance, if PaO2 remains essentially unchanged while the patient is breathing 100% oxygen, then the predominant underlying mechanism of hypoxaemia should be intrapulmonary shunting due to the presence of truly (anatomical) arteriovenous communications. If, however, PaO2 increases moderately (less than 80 kPa), depending on the range of cardiac output and arteriovenous oxygen difference, the presence of a true arteriovenous communication still cannot be ruled out. Alternatively, a substantial rise of PaO2 (above 80 kPa) excludes the existence of anatomical intrapulmonary shunt, and then VA/Q inequality emerges as the principal cause of abnormalities of arterial blood gases. In contrast, at the other end of the range, patients may have a normal circulatory state and normal gas exchange. In between, however, most of the patients would have, according to the severity of liver failure, impaired systemic and pulmonary haemodynamics and an abnormal hypoxic pulmonary vascular response, leading to the deterioration in pulmonary gas exchange. These individuals would have varying degrees of arterial hypoxaemia induced by mild to moderate VA/Q mismatching due to areas of low VA/Q ratios but no shunt or limitation of oxygen diffusion. Thus the intriguing question of whether blood flow through the pulmonary capillary vessels equal to or greater than 50 μm in diameter, instead of in the normal range of 8–15 μm, constitutes intrapulmonary shunting, VA/Q mismatch, or disequilibrium of oxygen diffusion may ultimately be answered by saying that it is a bit of all three, at least in those patients with more severe hypoxaemia.

**What are the therapeutic implications?**

Another way of confirming the hypothesis that abnormal pulmonary gas exchange in patients with cirrhosis is, in part, related to an inadequate pulmonary vasculature would be to investigate gas exchange before and after liver transplantation. If both pulmonary vasodilatation and depressed hypoxic pulmonary vasoconstriction are related to the severe liver failure, hepatic transplantation would be expected to improve overall gas exchange, provided that the latter were not due to fixed pulmonary vascular derangement. Indeed, there have been several reports showing, in general, an improvement in pulmonary gas exchange after liver transplantation. As early as 1968 it was reported that hypoxaemia was attenuated after orthotopic liver transplantation in three children. More recently, an improvement in both arterial blood gases and control of breathing after liver transplantation was documented. Further evidence came from Eriksson and associates, who reported the effects of liver transplantation in six hypoxaemic patients with advanced liver disease and moderate to severe VA/Q mismatch, as determined with the multiple inert gas elimination method. Transplantation was present in two patients only (3% and 20% of cardiac output), but there were no data suggesting limitation of oxygen diffusion. After transplantation there was a pronounced improvement in gas exchange, as shown by complete resolution of the VA/Q abnormalities and shunt, and a rise in PaO2 to 12 months after the surgical procedure; moreover, finger clubbing and cyanosis also disappeared. Similarly, Stoller et al described a patient with primary biliary cirrhosis and severe hypoxaemia in whom both reduction of intrapulmonary shunt (measured in terms of respiratory gases) and complete resolution of finger clubbing had occurred by one year after liver transplantation. Reversibility of the hepatopulmonary syndrome has also been shown in three patients whose pulmonary problems were reversed three to four months after liver transplantation. Current experience from Sweden suggests that restoration of pulmonary oxygenation takes longer (several months) after liver transplantation if the prime cause of hypoxaemia is intrapulmonary shunt, whereas gas exchange is improved in a few weeks when the principal determinants is VA/Q mismatch. This would suggest that, whereas VA/Q mismatch is an early cause of abnormal gas exchange, the development of shunt indicates more severe and advanced pulmonary vascular disease. There have also been two reports showing spontaneous resolution of the hepatopulmonary syndrome after recovery from severe liver dysfunction (advanced severe hepatitis and parasitic liver infection).

If all these investigations after transplantation are confirmed in a larger series of patients, with both haemodynamic and respiratory measurements, then arterial hypoxaemia as an exclusion criterion for liver transplantation will need to be reconsidered. In the meantime an open mind should be kept on whether vasoactive drugs have a therapeutic role in modulating normal gas exchange. Preliminary trials of drugs such as almitrine bismesilate (which is a proved pulmonary vasoconstrictor in both acute and chronic pulmonary disorders) and propranolol (advocated for the treatment of portal hypertension) have not so far been successful. Other possibilities, such as the use of somatostatin, are under study. The alternative of invasive therapeutic procedures, such as embolisation of peripheral small vessel arteriovenous fistulas and plasma exchange, has also been disappointing. Very recently, the
first case of dramatic improvement of shunt has been documented. Medical treatment, with cyclophosphamide and corticosteroids, was given for severe hypoxaemia related to the hepatopulmonary syndrome, which was caused by non-cirrhotic liver damage (nodular regenerative hyperplasia with grade 1 portal hypertension and mild liver dysfunction).

**Summary**

On the basis of previous work, and our own experience and findings, and the considerations discussed above, we propose a set of four diagnostic criteria for the hepatopulmonary syndrome:

1. Presence of chronic hepatic disease (alcoholic, post-necrotic, or primary biliary cirrhosis or active chronic hepatitis)—severe liver dysfunction may not be mandatory;
2. Absence of intrinsic cardiopulmonary disease, with normal chest radiograph or with nodular basal shadowing;
3. Pulmonary gas exchange abnormalities—an increased alveolar-arterial oxygen gradient (≥ 2.0 KPa) with or without hypoxaemia;
4. The extrapulmonary appearance of intravenous radiolabelled microspheres or a positive contrast enhanced echocardiogram, suggesting intrapulmonary vascular abnormalities.

Although these four criteria appear straightforward, there may be other features that are not always present—namely:

1. Low transfer factor (diffusing capacity);
2. Shortness of breath, with or without platypnoea and orthodeoxia;
3. Increased cardiac output and reduced pulmonary vascular pressures;
4. Small (or no) increase in pulmonary vascular resistance when the patient is breathing low oxygen mixtures.

From the physiological viewpoint, the hepatopulmonary syndrome provides an excellent model for clinical research in the pathophysiology of pulmonary gas exchange. So far it has been possible to show that arterial hypoxaemia in this condition is (1) partitioned into components resulting from $VA/Q$ mismatching, intrapulmonary shunt, and limitations of oxygen diffusion; (2) modulated by the interplay between the intrapulmonary and the extrapulmonary disease determinants of $P_{aO_2}$, such as cardiac output and minute ventilation; (3) vulnerable to the influence of inadequate pulmonary vascular tone; and (4) resolved when the injured liver is replaced and hepatic function is restored to within normal limits.

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