Analysis of Oxygen Transport to the Brain When Two or More Parameters are Affected Simultaneously

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We composed a model, combining oxygen transport system from blood to tissue with the oxygen consumption system at the tissue. The aim of this study is to apply it to the brain tissue under conditions when two or more oxygen transport parameters are affected simultaneously. The following values were assumed. Critical tissue Po_2 ($Pcrit_{O_2}$) 2 mmHg; oxygen consumption above this level 3 $ml \cdot min^{-1} \cdot 100g^{-1}$; diffusion coefficient from blood vessel to tissue (Dvt) 0.2 $ml \cdot min^{-1} \cdot mmHg^{-1} \cdot 100g^{-1}$; cerebral bloow flow (CBF) 50 $ml \cdot min^{-1} \cdot 100g^{-1}$; hemoglobin 15 $g \cdot 100\ ml^{-1}$. The Hill equation was used for oxygen dissociation curve with n of 2.7 and P_{50} of 27.0 mmHg.

The changes of oxygen consumption of the brain ($\dot{V}o_2$) were analyzed when 2 or more of 5 parameters, Pa_{O_2}, CBF, Dvt, P_{50} and hemoglobin decreased simultaneously from their respective normal values.

As the number of parameters affected increased, the level at which oxygen consumption begins to be affected became higher. With all five parameters combined, a reduction down to 78 per cent of normal resulted in tissue hypoxia. We conclude that the oxygen consumption of the brain is fairly resistant when only one parameter is affected, but it becomes increasingly vulnerable when several parameters are affected simultaneously. A clinically important finding is that the brain is particularly vulnerable to a combination of hypocapnia and a decreased level of 2,3DPG. (Key words: oxygen consumption, brain, combined model, tissue Po_2, critical Po_2)

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We recently proposed a model which combines the oxygen transport system with the tissue oxygen consumption system[1]. This paper aims to analyze the oxygen transport and oxygen consumption of the brain tissue when two or more parameters of the oxygen transport to the brain are affected.

When we apply model analysis to oxygen transport system, we tend to analyze an individual component in detail. Few models have been proposed which combine the oxygen transport system with the oxygen consumption system at the tissue level, and even then they are relatively complex and difficult to grasp intuitively[2,3]. Yet it

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Table 1. Symbols, meanings and assumed normal values

$\dot{V}mr_{O_2}$	metabolically required O_2	3 $ml \cdot min^{-1} \cdot 100g^{-1}$
$Pcrit_{O_2}$	Critical tissue Po_2	2 mmHg
Dvt	Diffusion coefficient	0.2 $ml \cdot mmHg^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$
CBF	Cerebral blood flow	50 $ml \cdot min^{-1} \cdot 100\ g^{-1}$
$\dot{V}o_2$	consumed $\dot{V}o_2$ ($CMRo_2$)	3 $ml \cdot min^{-1} \cdot 100\ g^{-1}$
Hb	Hemoglobin	15 $g \cdot 100\ ml^{-1}$
P_{50}	Po_2 at which So_2 equals 50%	27.0 mmHg
ODC	Oxygen Dissociation Curve	Hill equation exponent-n of 2.7 P_{50} of 27.0 mmHg.

is vital to combine the two systems in a relatively simple manner. The aim of such a combined model is twofold. First, we need a self-consistent, yet intuitively understandable model. Second, we need a model in which we can analyze the oxygenation status when two or more parameters of oxygen transport/consumption are affected simultaneously; for example, both blood flow and P_{50} decrease at the same time.

We succeeded in composing such a model and present here the result under conditions when two or more parameters of oxygen transport are affected simultaneously.

Methods and Procedures

The basis for the model has already been described elsewhere[1]. In essense, it consists of 3 components, oxygen consumption at the tissue level ($\dot{V}o_2$), diffusion from the vessel to the tissue, and transport by the blood. The result of the model is essentially a solution of 3 simultaneous equations describing these three components. The important point is the assumption that the oxygen transport and consumption of the three systems are identical.

The first describes the relationship between tissue Po_2 (Pts_{O_2}) and the oxygen consumption[4].

$$\dot{V}o_2 = F(Pts_{O_2}) \qquad 1)$$

Hypoxia we define as the $\dot{V}o_2$ being less than the metabolic requirement($\dot{V}mr_{O_2}$).

The second describes diffusion of oxygen from the vessel to the tissue ($\dot{V}pt_{O_2}$) being the product of diffusion coefficient (Dvt or conductance) and the pressure difference. We assumed the head pressure, the capillary Po_2 (Pcp_{O_2}) is equal to Pv_{O_2}.

$$\dot{V}pt_{O_2} = Dvt \cdot (Pv_{O_2} - Pts_{O_2}) \qquad 2)$$

The third is the Fick equation. $\dot{V}av_{O_2}$ indicates oxygen carried and released to the tissue. Q stands for the blood flow.

$$\dot{V}av_{O_2} = Q \cdot (Ca_{O_2} - Cv_{O_2}) \qquad 3)$$

It should be noted that three values of oxygen consumption/transport are in balance in a steady state. This should apply even when $\dot{V}o_2$ is less than $\dot{V}mr_{O_2}$ and the tissue is hypoxic. Although such condition may not last very long, the oxygen store in the tissue is so small that this steady state is still applicable. It is precisely this kind of condition that this model attempts to analyze. This equation-system can be solved by an appropriate method.

In applying this model to the brain tissue, we adopted the custom and used an expression per 100g of tissue. They are listed in table 1. It is the same table as is listed in ref 1. The same function was used for equation 1

Table 2. Levels at which $\dot{V}O_2$ first begins to decrease, and is down to 50% of normal. Values expressed in per cent of normals

	$\dot{V}O_2$ begins to decrease	$\dot{V}O_2$ down to 50% of normal
Single parameter		
Pa_{O_2}	26	15
CBF	36	15
Diff	42	17
P_{50}	44	16
Hb	36	14
2 parameters		
Pa_{O_2} + CBF	44	29
Pa_{O_2} + Diff	52	33
Pa_{O_2} + P_{50}	46	18
Pa_{O_2} + Hb	47	29
CBF + Diff	59	30
CBF + P_{50}	60	30
CBF + Hb	61	39
Diff + P_{50}	65	38
Diff + Hb	59	28
P_{50} + Hb	59	30
3 parameters		
Pa_{O_2} + CBF + Diff	63	38
Pa_{O_2} + CBF + P_{50}	61	31
Pa_{O_2} + CBF + Hb	64	44
Pa_{O_2} + Diff + P_{50}	66	40
Pa_{O_2} + Diff + Hb	63	38
Pa_{O_2} + P_{50} + Hb	61	31
CBF + Diff + P_{50}	72	46
CBF + Diff + Hb	70	44
CBF + P_{50} + Hb	70	44
Diff + P_{50} + Hb	72	46
4 parameters		
less Pa_{O_2}	77	54
less CBF	73	47
less Diff	71	45
less P_{50}	71	48
less Hb	73	48
all 5 parameters	77	55

as was used in the previous study.

Five parameters affecting the oxygen supply/transport were used as input variables; Pa_{O_2}, CBF, Dvt, P_{50} and hemoglobin. The $\dot{V}O_2$, Pts_{O_2} and Pv_{O_2} were obtained when 2 or more of these 5 variables were affected simultaneously ranging from zero to their respective normal values.

In order to separate the effect of Pa_{CO_2} on P_{50} from the independent change in 2,3DPG, we also studied with the 2,3DPG level at half and one-tenths of normal. CBF was assumed to change with Pa_{CO_2} in two ways. One is that it decreases linearly with Pa_{CO_2} down throughout the entire range. The other is that it decreases linearly with Pa_{CO_2} down to 20 mmHg, then to level off. For the relationship between

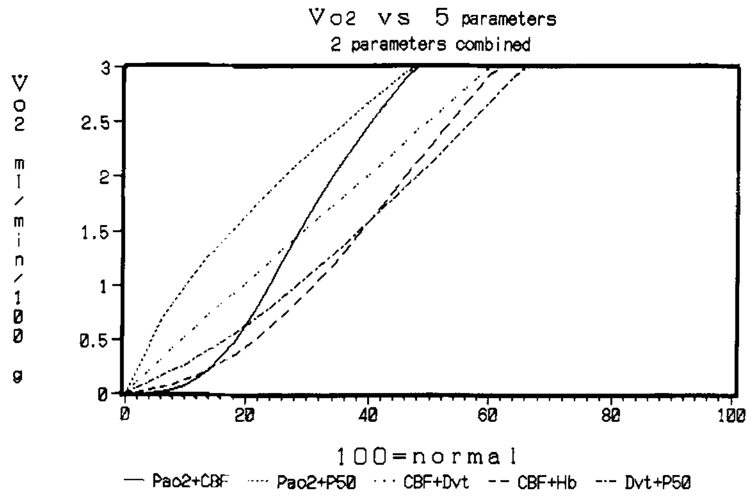

Fig. 1. Effects of reduction of 2 parameters out of five on the $\dot{V}O_2$ are shown. The abscissa is expressed as percentage of normal for individual parameters. A reduction down to 65% of normal is required for resulting tissue hypoxia when Dvt and P_{50} levels are simultaneously affected.

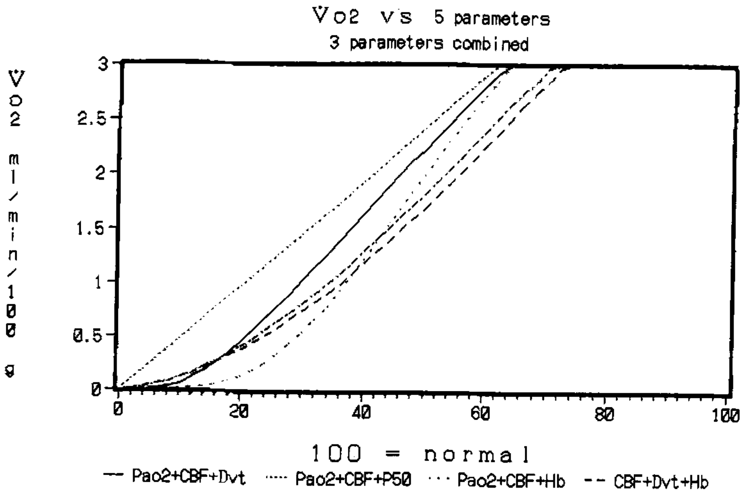

Fig. 2. Effects of reduction of 3 parameters out of five on the $\dot{V}O_2$ are shown. A reduction down to 72% of normal are required for resulting tissue hypoxia when CBF + Dvt + P_{50} or Dvt + P_{50} + Hb levels (latter not shown) are simultaneously affected.

2,3DPG, pH and P_{50}, the following formula was adopted.

$$[P_{50} = 27 * 10\hat{}\{-.48 * [pH - 7.4 - (2,3DPG - 4) * .13]\}$$

where "10^X" indicates the exponent X to the base of 10. With 2,3DPG levels at half normal and 10% normal, this formula achieves P_{50}'s of 20 and 16 mmHg, respectively.

As a separate example of using this analysis, we applied this to the reported values at the summit of Mount Everest[6,7]. We calculated in two ways. First, the internal accomodations have not taken place yet. Reported values of Pa_{O_2} and arterial pH only are used. CBF is assumed half normal due to hypocapnia (assumed). Second, the accomodations have taken place: hemoglobin has increased (reported), 2,3DPG has increased minimally (reported) and CBF has recovered to 70% normal (assumed).

Results

Under normal conditions, the Pts_{O_2} was found to be 21.8 mmHg as compared to the $Pcrit_{O_2}$ of 2 mmHg, indicating a good reserve of oxygen

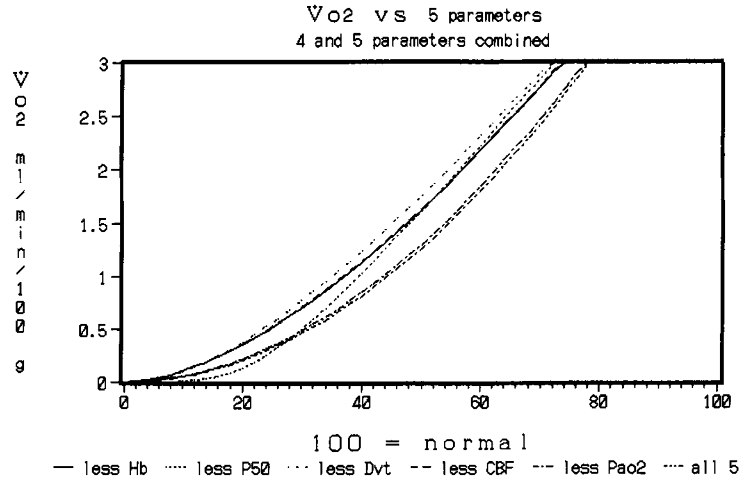

Fig. 3. Effects of reduction of 4 parameters out of five and of all 5 parameters on the $\dot{V}o_2$ are shown. A reduction down to 77% of normal are required for resulting tissue hypoxia when CBF + Dvt + P_{50} + Hb levels are simultaneously affected. Addition of Pa_{O_2} (all 5 parameters) moves the curve to the right slightly.

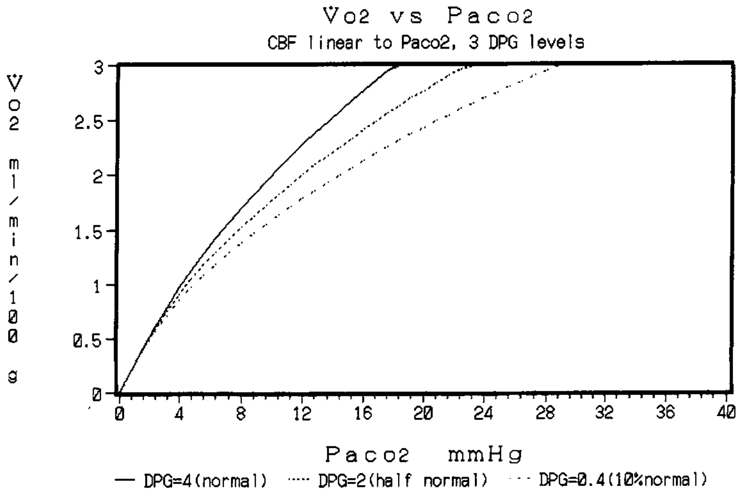

Fig. 4. The effects of Pa_{CO_2} decrease, causing reductions both in CBF and in P_{50}, are shown at 3 different levels of 2,3DPG with the assumed linear relationship between Pa_{CO_2} and CBF. With 2,3DPG half normal, a decrease in Pa_{CO_2} to 23 mmHg begins to affect the oxygen consumption. With 2,3DPG 10% normal, even a modest decrease in Pa_{CO_2} down to 29 mmHg begins to affect the oxygen consumption.

transport in relation to oxygen consumption. For any single parameter, a decrease at least down to 50% of normal is required before oxygenation for the brain tissue is affected.

In table 2, we summarized the levels at which $\dot{V}o_2$ values begin to decrease and those at which they reach 50% of normals. They are expressed in per cent of normals. It could be seen easily that as the number of parameters affected increases, so do levels of parameters at which the $\dot{V}o_2$'s begin to decrease and are down to 50% of normals.

Figure 1 indicates the effects of reduction of 2 parameters out of five on the $\dot{V}o_2$. A reduction only down to 65% of normal are required for resulting in tissue hypoxia when Dvt and P_{50} are affected simultaneously. A larger reduction is required for causing tissue hypoxia when Pa_{O_2} is one of the two parameters affected.

Figure 2 indicates the effects of reduction of 3 parameters out of five on the $\dot{V}o_2$. A reduction only down to 72% of normal are required for resulting in tissue hypoxia when a combination of D, P_{50} and hemoglobin levels

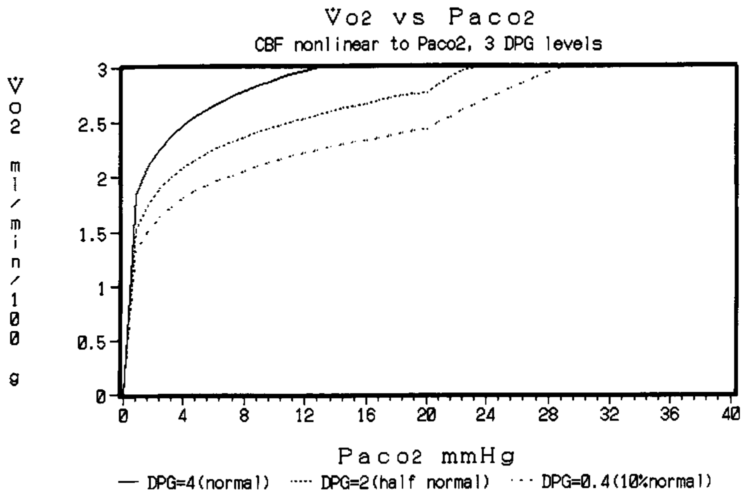

Fig. 5. The effects of Pa_{CO_2} decrease, causing reductions both in CBF and in P_{50}, are shown at 3 different levels of 2,3DPG with the assumed non-linear relationship between Pa_{CO_2} and CBF. The main parts of the curves are grossly different from those in figure 4, indicating the importance of CBF for oxygen supply.

Table 3. Calculated results at the summit of Mount Everest Units are similar to those in table 1

	accomodation (−)		accomodation (+)	
Pa_{O_2}	28	(R)	28	(R)
Pa_{CO_2}	7.5	(R)	7.5	(R)
pH	7.76	(R)	7.76	(R)
Dvt	0.2	(a)	0.2	(a)
CBF	25	(a)	35	(a)
P_{50}	18.1	(a1)	18.4	(Ra1)
Hb	15	(a)	18.7	(R)
$\dot{V}o_2$	2.38		2.94	
Pbr_{O_2}	1.58		1.96	

*(R) indicates that the value is reported in ref 7.

(a) indicates that the values is assumed by the author.

(a1) indicates that the P_{50} is calculated from P_{50} at pH of 7.40, assuming the Bohr factor of −0.48.

(Ra1) indicates that the P_{50} at 7.40 is reported (27.4: ref 7), and the P_{50} at pH 7.76 is calculated similarly.

or a combination of CBF, Dvt and P_{50} are affected simultaneously. Again a larger reduction is required when Pa_{O_2} is one of the three parameters affected.

Figure 3 indicates the effects of reduction of 4 parameters out of five and also those of all 5 parameters on the $\dot{V}o_2$. A reduction only down to 77% of normal are required for resulting tissue hypoxia when CBF, D, P_{50} and hemoglobin levels with or without Pa_{O_2} are affected simultaneously.

Figure 4 indicates the effects of simultaneous reduction of cerebral blood flow and P_{50}, both caused by a reduction in Pa_{CO_2}, at 3 different 2,3DPG levels when CBF is assumed to change linearly with Pa_{CO_2}. With 2,3DPG 10% normal, a Pa_{CO_2} of 28 mmHg decreases the $\dot{V}o_2$ below normal and that of 9 mmHg decreases the $\dot{V}o_2$ down to a half of the normal.

Figure 5 indicates the effects of simultaneous reduction of cerebral blood flow and P_{50} caused by a reduction in Pa_{CO_2}, but when CBF is assumed to change linearly with Pa_{CO_2} only down to 20 mmHg.

Table 3 indicates the reported and assumed values for parameters, and results obtained from these at the summit of Mount Everest. It clearly indicates the merit of accomodation for the brain oxygenation.

Discussion

This model is particularly advantageous if we intend to analyze oxygen transport under conditions where two or more parameters are affected simultaneously. This study is indeed a good example showing just that.

The original analysis indicated that, to cause brain hypoxia, any single parameter of these five has to decrease at least down to 44% by itself (P_{50})[1]. For Pa_{O_2}, a value as low as 26 mmHg is required for causing hypoxia. If two or more parameters are affected at the same time, however, it becomes increasingly easier to reach such a level to affect the oxygen supply to the tissue. It is especially important when we consider the effect of hyperventilation and of the resulting low Pa_{CO_2}.

A decrease in Pa_{CO_2} reduces the CBF and the P_{50} simultaneously, though not exactly the same magnitude. A Pa_{CO_2} of 20 mmHg reduces the CBF down to near 50% normal[5], yet it reduces the P_{50} only down to 21 mmHg, or 77% of normal. If, however, it is combined with a decrease in 2,3DPG, then a decrease in Pa_{CO_2} severely affects the oxygen supply. As shown in figure 5, at 2,3DPG of 50% of normal, $\dot{V}O_2$ starts decreasing at Pa_{CO_2} of 22 mmHg with otherwise normal blood. At 2,3DPG of 10% of normal, a modest decrease in Pa_{CO_2} to 28 mmHg affects the oxygen supply to the brain. We may interpret this finding to suggest a use of old stored blood plus hypocapnia is a vary dangerous combination in view of the oxygen supply to the brain. Decreases of 2,3DPG down to half normal and 10% normal probably fit to the blood stored for several days and for few weeks.

A combination of decreased P_{50} and hemoglobin with CBF unaffected is also common in the clinical condition. A large amount of blood loss and transfusion combined with a decreased hemoglobin level is an example. Under clinical conditions, however, this combination may be accompanied with some degree of compensatory increase in CBF, which is not incorporated in this model.

Even a combination of 3 parameters, CBF, P_{50} and hemoglobin, is not uncommon. This could be a very dangerous situation where even a very modest reduction of the three parameters may result in hypoxia. It may have an important clinical relevance. If it is accompanied by another parameter, it may be even more serious.

In studying the effects of Pa_{CO_2} both on CBF and P_{50}, we made two different assumptions. The first is that the CBF is proportional to Pa_{CO_2} down all the way to zero. The other is that the CBF does not decrease further once Pa_{CO_2} reached the level of 20 mmHg. The real values of CBF are likely to exist between these two assumed extremes[5]. The real result may therefore be estimated to exist between the two. It should be noted that, in the range of 2,3DPG of half normal and below, the level of Pa_{CO_2} at which the $\dot{V}O_2$ starts decreasing is above 20 mmHg. It is, therefore, independent of the assumption of CBF and Pa_{CO_2} below 20 mmHg. The different shapes of the curves between figure 4 and 5 again stress the importance of CBF and of avoiding severe hypocarbia.

Of the five parameters incorporated in the model, the diffusion parameter (Dvt) is least known and difficult to evaluate under clinical conditions. Furthermore, although it is assigned independently from the CBF, there is no question that CBF and Dvt are, in fact, interdependent upon each other.

A relatively small contribution of Pa_{O_2} to reduction of other parameters is interesting. The Pa_{O_2} reduction combined with that of other parameters added little. In retrospect, it is easy to interpret. Starting from the normal value of 100 mmHg, a reduction of Pa_{O_2} reduces the oxygen transport little until it reaches the steep portion of the oxygen dissociation curve. At Pa_{O_2} of 70% of normal

(70 mmHg), the oxygen saturation is still 94%, which is 96% of normal value. For the Pa_{O_2} reduction to cause hypoxia, a relatively large reduction is required together with that of other parameters.

This analysis provides an insight into the oxygen consumption of, and its transport to, the tissue as a whole in a self-consistent manner. We can analyze the effects of more than one parameter of reducing oxygen transport on the oxygen consumption; usual logic of "keeping other parameters constant" is not required. When the tissue cannot utilize oxygen due to hypoxia, then the transport of oxygen decreases concomitantly. If the tissue uses less oxygen, then the load for the transport decreases as much. Such self-consistency is what we really aimed at in developing and using this model. Figures presented here are examples showing the power of such a model.

Ten combinations are possible respectively for 2 or 3 parameters affected simultaneously. Figures 2 and 3 do not show them all. We omitted those combinations, the results of which do not differ substantially from those shown. Some combinations gave almost identical results. With the reduction of CBF or that of Hb, the amount of oxygen delivered decreases by the same magnitude in this model. A near identical result is expected. This may not be so under clinical condition, however.

The calculation in table 3 is a good examples which show the power of this type of analysis. Without accomodation, three factors affects the brain oxygenation; Pa_{O_2}, CBF and P_{50}. The oxygen supply and consumption decreased by more than 20%. With accomodation, however, hemoglobin increased considerably. A reduction in CBF is assumed somewhat less. Though the increase in P_{50} is minimal, the oxygen supply and consumption is almost normal. All subjects in this expedition were accomodated for not less than 5 weeks at 6,300 m[7]. Though not adequately studied, it is reasonable to assume that CBF tends to increase back towards normal despite the marked degree of hyperventilation. The apparently normal cerebral function of this subject (CP) is explicable from this analysis.

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