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MASS LAW PREDICTS HYPERBOLIC HYPOXIC VENTILATORY RESPONSE

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1. INTRODUCTION

Opening the Oxford Arterial Chemoreceptor symposium in 1966, R. W. Torrance, paraphrased Churchill's radar praise, if memory serves, "Never have so many labored so long over so little to so great an end".

In this hypothetical and speculative analysis of hypoxia's effects on the carotid body and ventilation, I have relied primarily on the extensive research of S. Lahiri, D. F. Wilson and their associates at the University of Pennsylvania.[1-6] In working with polarographic oxygen electrodes in which the electron-oxygen reaction is so clearly regulated by the law of mass action, I came to recognize the similarity to carotid body function. Several years ago I asked Britton Chance whether the mass action law applies to the electron-oxygen reaction at cytochrome oxidase. He immediately replied, "It has to". These hypotheses derive from his caveat.

2. CAROTID BODY PHYSIOLOGY AND BIOCHEMISTRY

HVRp is the relationship of $\dot{V}_E$(expired ventilatory rate, liters per min) to acute stable isocapnic hypoxia plotted as PaO_2 (arterial oxygen tension, torr). HVRp is generally reported as fitting a hyperbola with an estimated ventilatory asymptote at about 32 torr PaO_2 at which $\dot{V}_E \Rightarrow \infty$ (Fig. 1). The commonly used equation describing it is:

$$\dot{V}_E = A/(PaO_2 - 32) + B \qquad \text{(Eq. 1)}$$

where A is the CB sensitivity (about 200 liters/min at PaO_2=33 torr) and B is the non-CB component of ventilatory drive at rest, typically 4 L/min.[7]

Carotid body metabolic rate is very high ($\dot{V}_{O_2} \approx 9$ ml/dl/min), about 2.5 times $\dot{V}_{O_2}$ of cerebral cortex). Its blood flow through enlarged capillaries or sinusoids is about 20 ml/g/min, much higher than expected for that metabolic rate, such that its capillary and venous blood PO_2 had been expected to closely track arterial PO_2. However Lahiri et al in 1993 reported direct optical measurement of CB microvascular (CBM) PO_2 (by fluorescence quenching). Their arterial to CBM SO_2 (oxygen saturation) difference,

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computed (by me) from PO_2, was 8% in normoxia, 27% at PaO_2=40 torr and 31% at PaO_2=30 torr. This implies either a 70% fall of blood flow or greatly increased O_2 consumption in hypoxia, which I have not attempted to include in these attempts to predict the effect of the mass law. For simplicity, I here assume negligible A-V SO_2 differences, assigning all the diffusion gradient to tissue. The conclusions are about the same if some gradient is in blood.

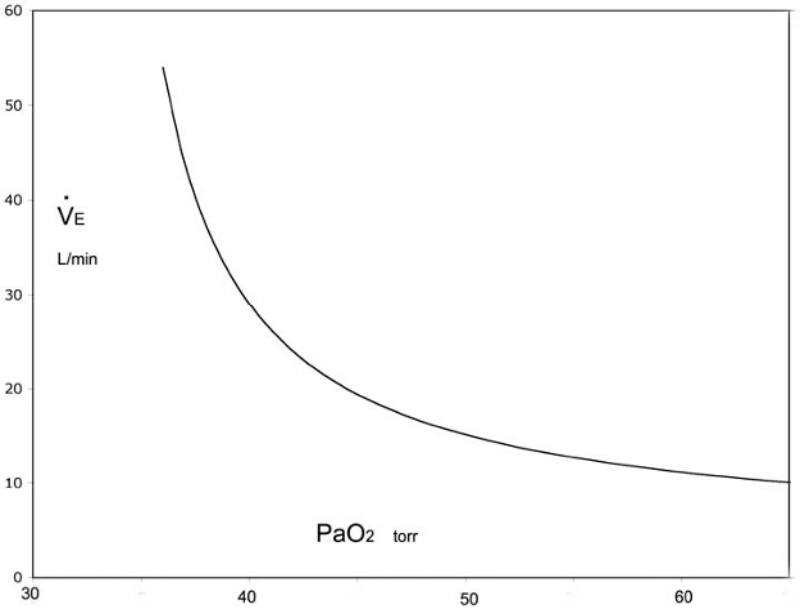

Figure 1. The human ventilatory response to isocapnic acute hypoxia (HVRp) is described as a hyperbola with an estimated asymptote of infinite ventilation at PaO_2 = 32 torr.

The high metabolic rate creates a diffusion gradient for oxygen between arterial blood and the glomus cell mitochondria. A variety of values have been reported for tissue or cytochrome (PcO_2) from a calculated value of less than 10 torr[8] and oxygen micro-electrode values of 0-15 torr[9] up to 70 torr.[10] I chose a gradient of 32 torr (arterial to oxidase) both as a mean of the widely discrepant values. I thus assume that that PcO_2 = 0 at the observed 32 torr isocapnic HVRp asymptote.

An important but questionable assumption is that tissue metabolic rate is independent of its PO_2 above the critical threshold of oxygen delivery. This critical threshold in dilute vigorously stirred isolated mitochondria was shown to be <1 torr PO_2.[11] O_2 consumption ***begins*** to fall at the critical threshold. The critical threshold PaO_2 for the carotid body is assumed here to be 32 torr (Fig. 2), below the range of PO_2 used in measurement of HVRp. That is to say that CB hypoxic stimulation does not imply decreased CB oxygen consumption.

3. MASS LAW APPLIED TO CYTOCHROME OXYGEN REDUCTION

I assume that the CB tissue oxygen diffusion gradient is independent of PaO_2 over the range at which we test ventilatory response. I assume that mitochondrial redox