STRETCH-INDUCED INCREASE IN RESTING METABOLISM OF ISOLATED PAPILLARY MUSCLE

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ABSTRACT A mathematical model of oxygen diffusion into quiescent papillary muscles in vitro is developed. The model incorporates a continuous sigmoidal function relating the rate of oxygen consumption and the partial pressure of oxygen within the tissue. The behavior of the model is explored over a wide range of external oxygen partial pressures, oxygen consumption/partial pressure relations, oxygen diffusivities, muscle dimensions, and resting metabolic rates, while the muscle is subjected to simulated stretches of various extents in order to test the assertion that the stretch-induced increase in basal metabolic rate observed experimentally implies the existence of an anoxic core region of papillary muscles in vitro. The model predicts the existence of an oxygen diffusion-mediated stretch response of resting papillary muscle metabolism, but one which is quantitatively insignificant compared with experimentally observed values. The classic Hill diffusion model, which explicitly predicts an anoxic core, likewise predicts stretch effects of magnitudes smaller than those frequently observed. It is concluded that the increment in basal metabolism of papillary muscles subjected to stretch in vitro cannot be taken as evidence of oxygen diffusion limitation in unstretched preparations.

INTRODUCTION

When a resting isolated muscle is stretched its metabolic rate increases. This effect (the stretch or Feng effect) occurs in many (Feng, 1932; Euler, 1935; Clinch, 1968), but not all (Feng, 1932; Whalen et al., 1958; Baskin and Gaffin, 1965) skeletal muscles, smooth muscle (rabbit rectococcygeus muscle: C. L. Gibbs private communication), and cardiac muscle (Lee, 1960; Whalen, 1960; Cranefield and Greenspan, 1960; Gibbs et al., 1967; Poole and Sonnenblick, 1967; Loiselle 1979*a*; see also Fig. 1 and Table I). The effect can be abolished or reduced by various metabolic inhibitors (Feng, 1932; Euler, 1935; Clinch, 1968) and enhanced by alkaline solutions (Euler, 1935), hypertonic solutions (Yamada, 1970) or agents which potentiate active force development (Clinch, 1968). The effect is independent of temperature and the presence of amino acids (Loiselle 1979*a*), and is remarkably insensitive to the partial pressure of oxygen (Feng, 1932; Loiselle, 1979*a*). Several authors (Cranefield and Greenspan, 1960; McDonald, 1966; Coleman, 1967) have attributed the stretch effect in papillary muscles to the existence of a hypothetical anoxic core region, the extent of which is diminished by stretching the muscle.

The hypothesis of an anoxic core in isolated papillary muscle preparations rests on the concept of a "critical diameter," as developed by A. V. Hill (1928). By assuming that the rate of muscle oxygen consumption is independent of the oxygen partial pressure, Hill showed that the oxygen consumption would fall to zero in the central core of muscles the diameter of which exceeds some critical value that depends only on the resting metabolic rate and the diffusivity of oxygen. This concept of a critical diameter, with its associated anoxic core or oxygen diffusion-limited region, is well entrenched in the literature dealing with isolated cardiac muscle preparations (Whalen, 1961; Rakusan, 1971; Gibbs, 1978). Indeed it is commonly invoked as an explanation of the inverse relationship between active stress development and muscle cross-sectional area (Kelly and Hoffman, 1960; Bing et al., 1971), although other explanations have been advanced (Frezza and Bing, 1976; Snow and Bressler, 1977; Loiselle, 1979*b*; Loiselle and Gibbs, 1979; Delbridge and Loiselle, 1981).

The crux of the anoxic core hypothesis is the assumption that the rate of oxygen consumption is completely independent of the oxygen concentration or partial pressure. (In the absence of the respiratory pigments hemoglobin and myoglobin, oxygen concentration = $\beta \times P_{O_2}$, where β is the (Bunsen) solubility coefficient and P_{O_2} is the oxygen partial pressure.) This assumption is a reasonable first approximation and leads to a straightforward analytical solution of the diffusion equation (Hill, 1928). It has been known for some time, however, that the rate of oxygen consumption is independent of the concentration only down to some (albeit low) critical P_{O_2} in whole muscle (Hill, 1948; Stainsby and Otis, 1964; Gore and Whalen, 1968), cell suspensions (Kempner, 1937), and mitochon-

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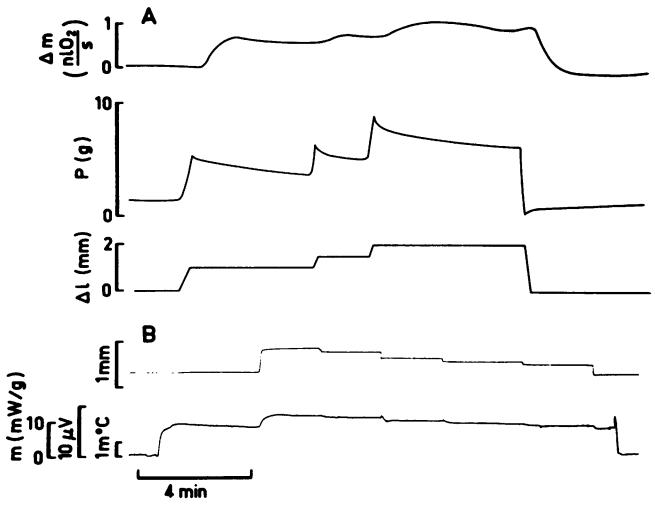

FIGURE 1 *A*, original records of increment in resting oxygen consumption, Δm, (nl O_2/s, upper trace) of a rat papillary muscle (r_o = 0.5 mm, l_o = 7.0 mm) in response to elongations (lower trace) of 1.0, 1.5, and 2.0 mm. Middle trace shows resting or passive force developed in response to elongation; initial resting load was 1.0 g wt; maximal active force development was 3 g wt. At maximal Δl, Δm was ~25% with respect to a value of 4 nl O_2/s under the 1-g wt load. Muscle bathed in Krebs solution and aerated with 95% O_2 at 27°C. (Description of oxygen electrode system given in Chapman et al., 1981.) *B*, Original records of resting heat production, *m*, (mW/g, also shown as thermopile output (μV) in response to increase in muscle temperature (m°C) when Krebs solution drained from muscle/thermopile) of a rat papillary muscle (r_o = 0.325 mm, l_o = 6.0 mm; P_{O_2} = 0.95 atm at 27°C) subject to passive isotonic loads of (from left to right) 1, 12, 8, 4, 2, and 1 g wt, resulting in elongations shown in upper trace. Rightmost step on length trace caused by returning muscle to its prestretch length under the 1-g wt load. Leftmost and rightmost part of heat trace: muscle under Krebs solution so thermopile output is zero; artifact at right caused by resubmerging the muscle/thermopile in Krebs solution. Under the 12-load, Δm was ~30% with respect to a value of 8.8 mW/g under the 1-g wt load. Note that this muscle would not be expected to show a stretch response under the classical oxygen diffusion-limitation hypothesis (see Fig. 10). (Description of thermopile system given in Loiselle and Gibbs, 1979.)

dria in vitro (for a review, see Wittenberg, 1970). Below the critical P_{O_2}, given as 0.5–5.0 mmHg (Hill, 1948; Stainsby, 1965; Wittenberg, 1970; Rakusan, 1971), the rate of oxygen consumption depends on the oxygen partial pressure, probably in a sigmoidal manner (Kempner, 1937; Stainsby and Otis, 1964; Gore and Whalen, 1968; Wilson et al., 1977). Recent evidence from in vivo studies is even harsher on the oxygen consumption/concentration independence proposition. Jöbsis and colleagues (Jöbsis, 1974; Rosenthal et al., 1976; Jöbsis et al., 1977) have shown that in cerebral cortex tissue at rest, the terminal cytochrome of the respiratory chain is not at the extremely low reduction levels seen in mitochondria in vitro. Indeed, they suggest that a critical P_{O_2} may not exist at all under normobaric conditions, i.e., the plateau of the oxygen consumption/concentration relation may be shifted into the hyperbaric range of oxygen partial pressures. Either of these departures from the assumed oxygen consumption/concentration independence (i.e., whether the critical P_{O_2} is to be found in the region of low [in vitro] or high [in vivo] values) has a profound effect on the hypothetical anoxic core as elaborated below.

GLOSSARY

d_0, Muscle diameter (mm).
K, (Krogh's) oxygen diffusion constant ($cm^2 \cdot min^{-1} \cdot atm^{-1}$).
l_0, Muscle length (mm).
Δl, Extent of stretch (mm).
m, Variable metabolic rate ($mW \cdot g^{-1}$).
m_0, m_1, m_2, Parameters describing relationship between metabolic rate and oxygen partial pressure: $m = m_0 (1 - e^{-m_1 p})^{m_2}$.
$\overline{m}$, Prestretch resting metabolic rate ($mW \cdot g^{-1}$).
$\overline{m}'$, Poststretch resting metabolic rate ($mW \cdot g^{-1}$).
Δm, Stretch-induced increase in resting metabolic rate (%).
P_{O_2}, Partial pressure of oxygen.
p, Variable partial pressure of oxygen (atm).
p_a, Partial pressure of oxygen on the central axis of the muscle prior to stretch.
p'_a, Partial pressure of oxygen on the central axis of the muscle following stretch.
p_0, Partial pressure of oxygen at the surface of muscle (atm).
Δp_a, Increment in oxygen partial pressure on the central axis of the muscle: required for numerical integration procedure to determine $p = p(r)$.
r, Variable radius (mm).
Δr, Increment in variable radius (required for numerical integration procedure).
r_0, Prestretch muscle radius (mm).
r'_0, Poststretch muscle radius (mm).
r_c, The critical radius at which the oxygen concentration p drops to zero (mm).

METHODS

Overview

A mathematical model of the diffusion of oxygen into a papillary muscle is developed following Hill (1928). The dependence of oxygen consumption on oxygen concentration or partial pressure is assumed to be sigmoidal. The parameters governing the shape of this sigmoidal relation (the location of the shoulder or critical P_{O_2} and the steepness of the concentration-dependent region of the curve to its left, see Fig. 2) may be varied independently. The amplitude of the plateau to the right of the shoulder is given by the basal (resting) metabolic rate of the muscle. Thus, for a simulated muscle of given length and radius, which is consuming oxygen at some constant (i.e., time-invariant) rate in a given external oxygen concentration, the diffusion equation can be solved for the chosen form of the consumption/concentration relation. This solution yields the oxygen concentration (always nonzero) on the central axis. The muscle is then subjected to a simulated stretch of chosen extent and the diffusion equation is solved again for the new geometric conditions. This leads to an increased oxygen concentration on the axis (and at all other locations as well) and hence to a new (increased) basal oxygen consumption when averaged over the simulated muscle volume. The magnitude of

TABLE I

COMPARISON OF OBSERVED WITH THEORETICALLY EXPECTED EFFECTS OF STRETCH

Reference	Preparation	Species	Experimental temperature	Measured variable	Passive load	$\Delta l/l_o$	r_o	n	Δm
			°C			(%)	(mm)		(%)
Cranefield and Greenspan (1960)	Papillary muscle	Cat	35	$\Delta\dot{V}_{O_2}$		50*	0.2–0.6	8	0
							0.65–1.1	33	9–86
Lee (1960)	Papillary muscle	Cat	37	$\Delta\dot{V}_{O_2}$	2 g/mm²			7	32
					6 g/mm²		0.3–0.6	9	66
					12 g/mm²			7	89
Whalen (1960)	Trabeculae	Rat	28	$\Delta\dot{V}_{O_2}$		30*		16	22
						100*	0.35		55
	Carneae	Rat	37	$\Delta\dot{V}_{O_2}$		30*		21	20
	Papillary muscle	Cat	37	$\Delta\dot{V}_{O_2}$		30*	0.35	8	30
Gibbs et al. (1967)	Papillary muscle	Rabbit	20	ΔH	12 g	30*	0.5	2	200
Pool and Sonnenblick (1967)	Papillary muscle	Cat	26	ΔCP	2 g			20	57
Loiselle (1979)	Papillary muscle	Rat	27	ΔH	1–12 g	30‡	0.3–0.5	8	5–70
Hill's Mathematical Model (1928) (Fig. 10)						30	0–0.65		0
							1.0		12
Current mathematical model (Fig. 5)					$m_1 = 1$; $m_2 = 1$	30	1.0		5.5
					$m_1 = 20$; $m_2 = 5$	30	1.0		0.13
					$m_1 = 1$; $m_2 = 4$	30	1.0		6.5
					$m_1 = 25$; $m_2 = 15$	30	1.0		0.11

$\Delta\dot{V}_{O_2}$ = change in oxygen consumption; ΔH = change in rate of heat production; ΔCP = change in rate of creatine phosphate utilization; Extensions ($\Delta l/l_0$) measured with respect to resting length under zero load (*) or a load of 1 g (‡). n, number of observations. r_o and Δm values are means unless a range is given.

this simulated stretch effect can then be compared to stretch effects experimentally determined in isolated papillary muscles (Fig. 1; Table I).

Assumptions of the Model

(*a*) The muscle is a right circular cylinder.
(*b*) Longitudinal diffusion is negligible (i.e., end-effects may be ignored).
(*c*) Diffusion is spatially homogeneous (i.e., the system is radially symmetric).
(*d*) Elongation (stretch) is homogeneously distributed throughout the length of the muscle.
(*e*) Muscle volume remains constant throughout a stretch.

Mathematical Development

The rectilinear form of the diffusion equation in three dimensions is (after Hill)

$$\frac{\partial p}{\partial t} + m(x, y, z, t) = K\left(\frac{\partial^2 x}{\partial p^2} + \frac{\partial^2 y}{\partial p^2} + \frac{\partial^2 z}{\partial p^2}\right), \qquad (1)$$

where p is the partial pressure or concentration of oxygen, m is the resting or basal metabolic rate of oxygen consumption, K is the diffusion constant for O_2 in muscle tissue, x, y, z are rectilinear spatial coordinates, and t is time.

Changing to cylindrical coordinates (r, θ, z) and aligning the z-coordinate with the longitudinal axis of the muscle (Assumption *a*) leads to the following simplifications (Assumptions *b* and *c*):

$$\frac{\partial p}{\partial t} + m(r, t) = K\left(\frac{\partial^2 p}{\partial r^2} + \frac{1}{r}\frac{\partial p}{\partial r}\right). \qquad (2)$$

Since the transient response to stretch is not of interest, but only the steady-state basal metabolism before and after the stretch (i.e., $\partial p/\partial t = 0$), a final simplification arises:

$$\frac{d^2 p}{dr^2} + \frac{1}{r}\frac{dp}{dr} - \frac{m(r)}{K} = 0. \qquad (3)$$

Eq. 3 is identical to Hill's (1928) equation 6.4.3(1), except that he considered m to be a constant, whereas in the current study the resting metabolism m is not assumed to be constant. It is rather assumed to depend on the oxygen partial pressure, p, which in turn depends on the radial displacement r, from the central longitudinal axis. More formally, solution of diffusion Eq. 3 gives p as a function of r: $p = p(r)$. Hence $m = m[p(r)]$; hence $m = m(r)$, as written in Eq. 3, or $m = m(p)$. As justified in the Introduction, the dependence of m on p is assumed to be sigmoidal and is described as follows:

$$m(p) = m_o\,(1 - e^{-m_1 p})^{m_2}, \qquad (4)$$

where m_o, m_1, and m_2 are arbitrary constants (five examples are shown for $m_o = 1$ in Fig. 2). The degree of arbitrariness is constrained by the mean value of $m(p)$, $\overline{m}$, being simply the observed or measured basal

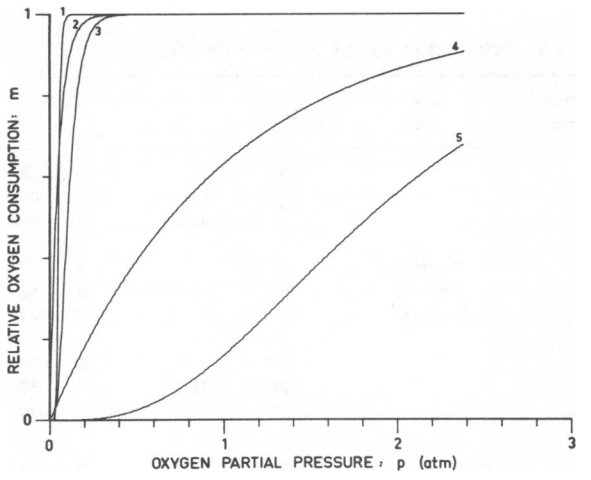

FIGURE 2 Examples of possible functions relating oxygen consumption (arbitrarily scaled to 1.0) and its concentration or partial pressure, achieved by varying the values of m_1 and m_2 in Eq. 4 (see text). Values of parameters (m_1, m_2): (100, 100), (20, 1), (20, 5), (1, 1), and (1, 4) in curves 1–5, respectively.

metabolic rate averaged throughout the volume of the muscle. That is,

$$\overline{m} = \frac{1}{p_o - p_a} \int_{p_a}^{p_o} m_o(1 - e^{-m_1 p})^{m_2}\, dp, \tag{5}$$

where p_o is the oxygen partial pressure at the surface of the muscle, and p_a is the oxygen partial pressure on the central longitudinal axis.

Solving Eq. 5 for m_o and then substituting into Eq. 4 yields

$$m(p) = \frac{\overline{m}\,(p_o - p_a)(1 - e^{-m_1 p})^{m_2}}{\int_{p_a}^{p_o}(1 - e^{-m_1 p})^{m_2}\, dp}. \tag{6}$$

It is to be emphasized that Eq. 6 establishes the link between the arbitrary simulation parameters m_1 and m_2 and the observed value of resting metabolism (as measured and shown in Fig. 1, for example). Substitution of Eq. 6 into Eq. 3, permitted since $m(p) = m[p(r)]$ as explained above, requires that solution of the following equation be sought:

$$\frac{d^2p}{dr^2} + \frac{1}{r}\frac{dp}{dr} - \frac{\overline{m}\,(p_o - p_a)(1 - e^{-m_1 p})^{m_2}}{K\int_{p_a}^{p_o}(1 - e^{-m_1 p})^{m_2}\, dp} = 0. \tag{7}$$

Solution of the Diffusion Equation

A digital computer program was written to solve Eq. 7 for the arbitrary parameters p_o (the P_{O_2} at the surface of the muscle), r_o (muscle radius), $\overline{m}$ (basal oxygen consumption), and m_1 and m_2, which determine the shape of the oxygen consumption/P_{O_2} relation. It should be noted that solution of Eq. 7 yields p as a function of r, $p = p(r)$, and hence explicitly gives the P_{O_2} value on the axis: $p_a \equiv p(0)$. But since p_a is previously required in the third term of Eq. 7, in order to find the solution, it is clear that an iterative solution procedure is demanded.

Numerical integration of Eq. 7 makes use of a Runge-Kutta method applied to a branching problem (Celia, 1969); i.e., one in which both $p(0)$ and $dp/dr(0)$ are known. Since the model assumes radial symmetry (Assumption *c*), $dp/dr(0) = 0$. The initial estimate of $p_a \equiv p(0)$ is set to zero and the solution determined as r runs from 0 to r_o (muscle radius) in arbitrary steps of Δr ($10^{-4} r_o$). When $r = r_o$, a check is made to see if $p \geq p_o$. If $p(r_o) < p_o$ then r is reset to zero, p_a is increased by Δp_a (10^{-6}–10^{-3} p_o), and the equation solved again. This process is repeated until $p \geq p_o$ when $r = r_o$. Clearly, by suitable choice of Δr and Δp_a, the value of $p(r_o)$ can be made arbitrarily close to p_o, subject only to consideration of computation time.

Solution of Eq. 7, for the parameters r_o, p_o, $\overline{m}$, m_1, m_2, and K, yields $p = p(r)$ (Fig. 3) and, in particular, the value p_a (the partial pressure of O_2 on the axis). This represents the prestretch solution. The muscle of arbitrary chosen length, l_o, is then stretched by some arbitrary amount Δl. This yields a new value of muscle radius:

$$r_o' = r_o\,[l_o/(l_o + \Delta l)]^{1/2}. \tag{8}$$

Eq. 7 is then solved again as described above, yielding a new poststretch oxygen partial pressure on the axis, p_a'. Since, for any nonzero stretch, $p_a' > p_a$, convergence to the poststretch solution is speeded considerably by setting the initial estimate of p_a' equal to p_a rather than to zero as in the prestretch case. An example of both the pre- and poststretch solutions of Eq. 7 is given in Fig. 3. Given the poststretch value of axial oxygen partial pressure, p_a', and the assumed relation between oxygen consumption and oxygen partial pressure (Fig. 2 and Eq. 4), the poststretch value of oxygen consumption, $\overline{m}'$, can be calculated according to Eq. 5. Throughout the remainder of this paper the value of

$$\Delta m = (\overline{m}'/\overline{m} - 1) \times 100, \tag{9}$$

i.e., the percentage increase in metabolic rate due to stretch, is the variable of interest.

RESULTS

The stretch-induced percentage increment in the metabolic rate of oxygen consumption, Δm, was examined for a

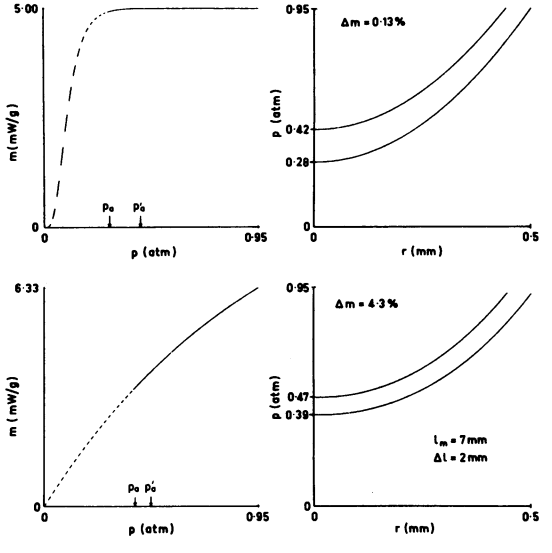

FIGURE 3 Simulated response of a 7-mm muscle, with a prestretch resting metabolism of 5 mW/g in 0.95 atm O_2, to a 2-mm elongation under two different oxygen consumption (m)/concentration (p) profiles (left-hand panels): (m_1, m_2) = (20, 5) and (1, 1) in upper and lower trace, respectively. Pre- and poststretch values of oxygen partial pressure on central axis given by p_a and p_a', respectively. Right-hand panels show pre- and poststretch (lower and upper trace of each pair, respectively) solutions of Eq. 7 (see text) corresponding to the m/p profile shown at left. In upper panels stretch raises axial O_2 concentration from 0.28 to 0.42 atm, but causes only a negligible stretch effect (Δm) since muscle operating on the flat portion of the m/p profile (left-hand panel). In lower panels stretch raises axial O_2 concentration from 0.39 to 0.47 atm, but causes an approximately 30-fold greater Δm because muscle operating over a steep portion of the O_2 consumption/concentration relation.

wide range of oxygen consumption/concentration profiles (m_1 and m_2, see Fig. 2), external oxygen concentrations (p_o), oxygen diffusion coefficients (K), muscle radii (r_o), prestretch metabolic rates ($\overline{m}$), and stretch extents (Δl). Since Δm is a function of seven variables, a comprehensive graphical presentation of results would require a plot in eight dimensions; only two-dimensional plots are presented throughout. It is not the form of the function $\Delta m = \Delta m$ (m_1, m_2, p_o, K, $\overline{m}$, r_o, Δl), but rather its maximal value which is of interest.

In all simulations the value of l_o was 7 mm. When not themselves variables, the values of r_o, p_o, and $\overline{m}$ were usually 0.5 mm, 0.95 atm, and 5 mW/g (0.015 ml O_2/g/min)—common values for stretch experiments using papillary muscles at 27°C (Gibbs, 1978; Loiselle, 1979*a*). When not a variable, Δl was usually set at 2 mm, yielding $\Delta l/l \doteq 30\%$, about the largest value sustainable by a papillary muscle without injury (Loiselle, 1979*a*). The appropriate value of K, the oxygen diffusion coefficient, is open to some question (Kawashiro et al., 1975; Mahler, 1978; for a review, see Gibbs, 1978). When not itself a variable, the value of K was chosen to be 1.4×10^{-5} cm^2 · min^{-1} · atm^{-1}, as in Krogh (1918). In accordance with Assumption *c*, K was considered to be independent of r.

p_o Dependence

The effect of varying the external oxygen partial pressure upon the simulated stretch effect is shown for various conditions in Fig. 4. In the course of performing these simulations, the need to extend the range beyond 0.95 atm (the usual experimental choice) in order to determine the general shape of the relation soon became apparent. Hence the simulated p_o ranged from 0 to 2.375 atm (i.e., to 2.5 times the usual experimental value). As can be seen in Fig. 4 the general shape of the $\Delta m - p_o$ relation and the location of its maximum depends on the remaining variables (m_1, m_2, K, r_o, Δl, and $\overline{m}$) but in no case does the simulated stretch effect (Δm) exceed 6.5% for normobaric conditions. The rough appearance of some of the curves depends not only on the number of abscissal solutions of Eq. 7 (usually 100) but also on the values of Δr and Δp_a within the program. Smoothing of the curves could have been achieved, but at the expense of increased computation time.

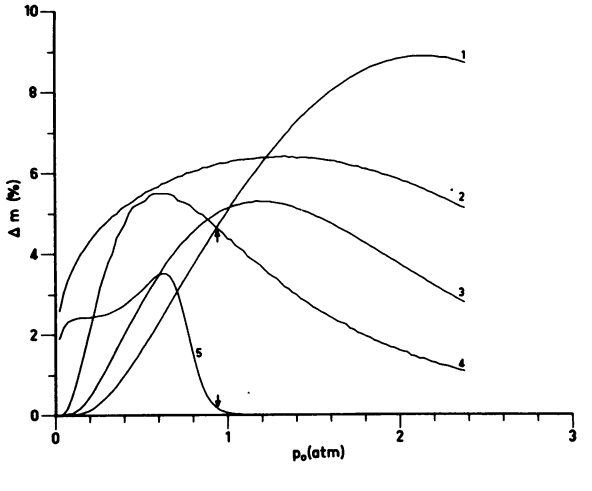

FIGURE 4 Simulated increase in basal metabolism (Δm) of a 7-mm-long papillary muscle of radius 0.5 mm stretched by 2 mm under various external oxygen concentrations (p_o). Prestretch basal metabolism ($\overline{m}$) = 20, 5, 10, 5, and 5 mW/g, and m/p profile parameters (m_1, m_2) = (1, 1), (1, 10), (1, 1), (1, 1), and (20, 5) in curves 1–5, respectively. Arrows on curves 4 and 5 at p_o = 0.95 atm correspond to Δm = 4.3 and 0.13% in lower and upper panels, respectively, in Fig. 3.

O_2 Consumption/Concentration Relation (m_1 and m_2) Dependence

Fig. 5 shows the effect of various values of m_1 and m_2, which govern the shape of the oxygen consumption/concentration relation, upon the simulated stretch effect. A family of curves is shown in each panel spanning values of m_1 or m_2 from 0.01 to 20 (values outside this range caused computational difficulties despite the use of double precision arithmetic—a fact of little consequence since the stretch effect is essentially nil for $m_1 = m_2 > 20$). It can be seen that, despite a varying influence of these two parameters upon Δm, the magnitude of the stretch effect never exceeded about a 6.5% increase in resting metabolism. The optimizing values of (m_1, m_2), i.e., those values which

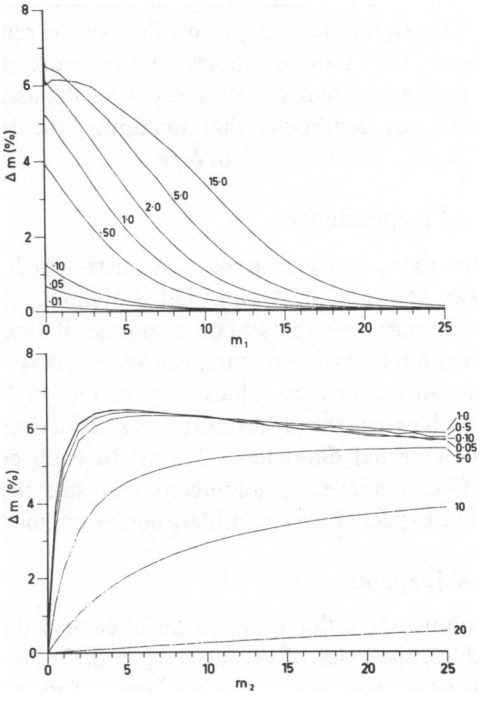

FIGURE 5 Influence of parameters m_1 and m_2, which describe (Eq. 4, text) the oxygen consumption/concentration relation, upon the simulated stretch effect (Δm), of a papillary muscle of dimensions: l_o = 7 mm, r_o = 0.5 mm, stretched by 2 mm in 0.95 atm O_2. Upper panel: influence of m_1 for values of m_2 ranging from 0.01 to 15.0. Lower panel: influence of m_2 for values of m_1 ranging from 0.05 to 20.0.

maximize Δm, can be seen to be about (1, 4), corresponding to curve 5 of Fig. 2. Because it is unlikely that this corresponds to the true oxygen consumption/concentration relation (see Fig. 2) the values $m_1 = m_2 = 1$ were usually chosen for succeeding simulations although no conclusions would be altered by this choice.

r_o Dependence

Fig. 6 shows the variation of Δm, the simulated stretch response, with the muscle radius r_o, for a variety of $\overline{m}$, p_o, and Δl conditions. The effect of stretch is strikingly dependent on muscle radius but once again the magnitude of the effect is moderate. The peak stretch effect occurs at lower external oxygen concentrations and higher basal metabolic rates, the thinner the muscle. Even quite unphysiological stretches ($\Delta l/l \doteq 60\%$) only cause about a 10% increase in basal metabolism. It is curious that for values commonly encountered in papillary muscle studies (basal metabolism = 5 mW/g; $p_o = 0.95$ atm) the peak stretch effect occurs with a muscle of diameter ~ 1 mm, the commonly accepted upper limit in order to avoid the problem of diffusion limitation (for a review, see Gibbs, 1978).

$\overline{m}$ Dependence

The increment in metabolic rate with stretch depends on the magnitude of the prestretch metabolic rate $\overline{m}$, as shown in Fig. 7. The dependence of Δm on $\overline{m}$ again passes through a maximum for any given values of the remaining parameters. The four examples shown were selected because they gave approximately equal results and represent the (r_o, p_o) conditions that maximize the response when $m_1 = m_2 = 1$ and $\overline{m} = 5$ mW/g.

Δl Dependence

In all the above considerations, the unstretched muscle length was constant at 7 mm. The simulated effect of stretches of various extents upon a muscle of this length with a prestretch resting metabolism of 5 mW/g in 0.95 atm is shown for various values of r_o in Fig. 8. For any given stretch extent the largest effect is seen to occur for a muscle of external diameter 1.2 mm. In each case the stretch effect increases monotonically with stretch extent, as would be expected from consideration of the model.

K Dependence

In determining the influence upon Δm of each of the above six variables, the value of K, the oxygen diffusion coefficient, was held constant at 1.4×10^{-5} cm$^2 \cdot$ min$^{-1} \cdot$ atm^{-1} (Krogh, 1918). The question arises whether the stretch effect of the model is sensitive to the value of K. Fig. 9 shows the dependence of Δm upon K for approximately optimizing values of the remaining seven parameters. It can be seen that the Krogh value (1.4×10^{-5} cm$^2 \cdot$ min$^{-1} \cdot$ atm^{-1}) lies close to the optimum for the given conditions and that the relationship falls off quite steeply on either side of the maximum.

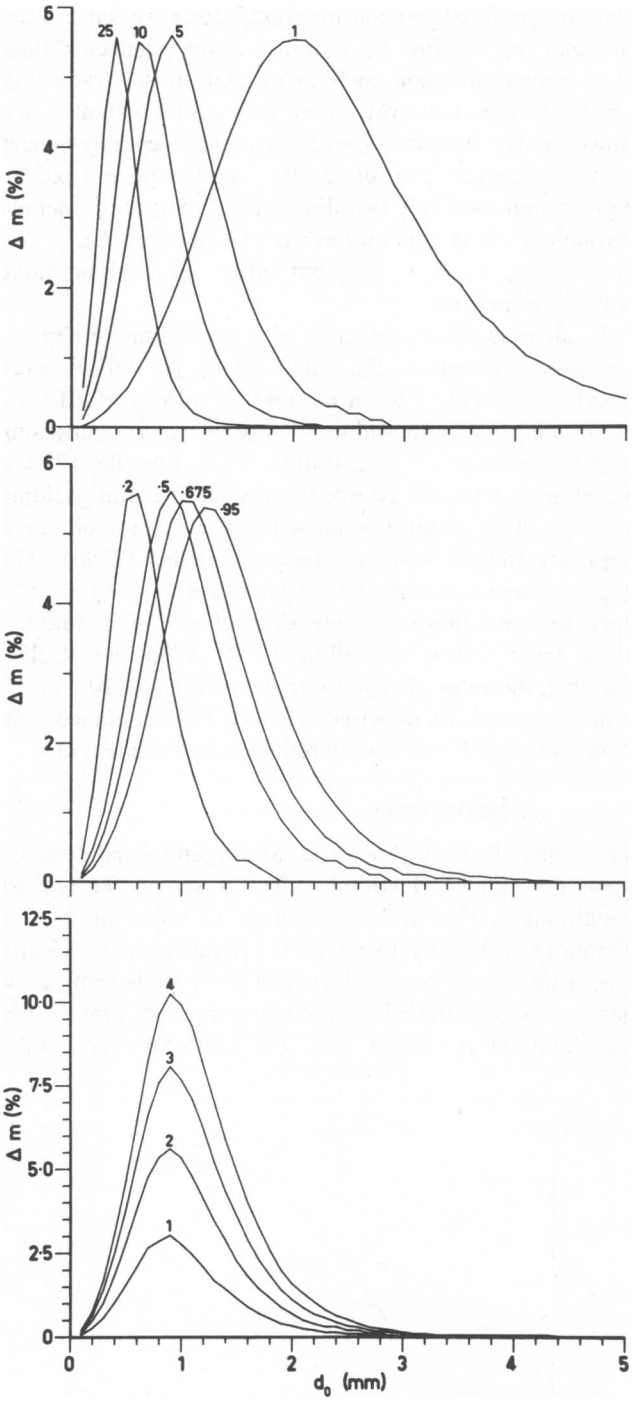

FIGURE 6 Influence of muscle diameter (d_0) upon the simulated stretch response (Δm) of a 7-mm papillary muscle. Upper panel: muscles of various prestretch metabolic rates ($\overline{m}$) in 0.5 atm O_2. Middle panel: $\overline{m}$ = 5 mW/g; muscles in various p_0 (atm) conditions. Lower panel: $\overline{m}$ = 5 mW/g; p_O = 0.50 atm; muscles stretched by 1–4 mm. In all cases the m/p profile described by $(m_1, m_2) = (1, 1)$.

DISCUSSION

The results of simulated stretches of the muscle model are unequivocal. Despite a wide range of oxygen consump-

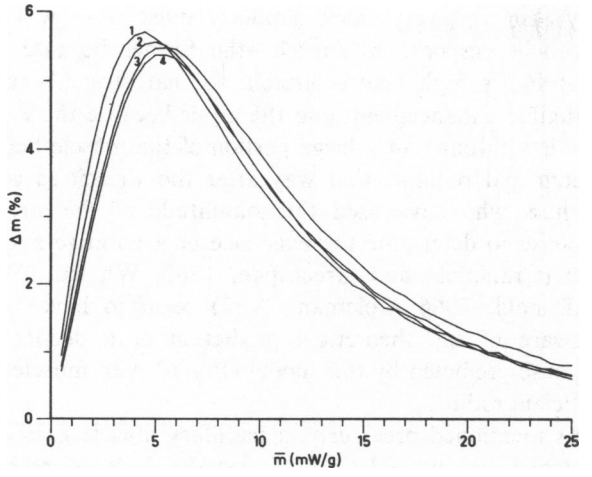

FIGURE 7 Effect of prestretch metabolic rate ($\bar{m}$) upon simulated stretch effect (Δm) of muscles of length 7 mm subjected to stretches of 2 mm when d_o = 0.6, 0.9, 1.0, and 1.2 mm, and p_o = 0.20, 0.50, 0.675 and 0.95 atm (curves 1–4, respectively). These combinations of parameters were chosen since they maximize Δm for an m/p profile described by (m_1, m_2) = (1, 1). (see middle panel, Fig. 6).

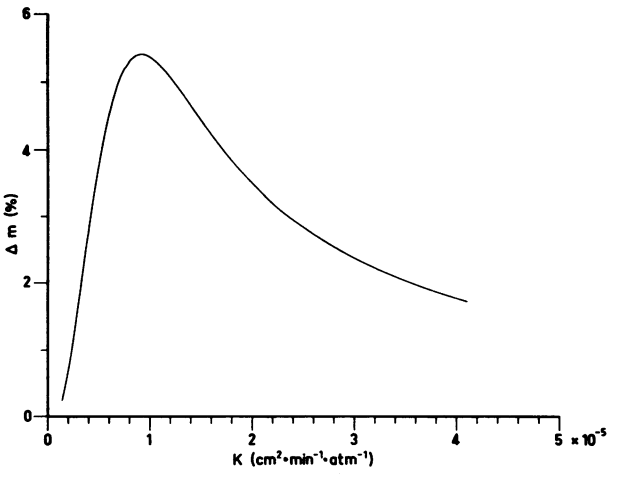

FIGURE 9 Effect of value of the Krogh diffusion constant (K) upon simulated stretch effect (Δm) for a 7-mm papillary muscle of 1-mm diameter stretched by 2 mm in 0.95 atm O_2. Oxygen consumption/concentration relation described by (m_1, m_2) = (1, 1).

tion/concentration profiles applied to a wide range of external oxygen concentrations, oxygen diffusion coefficients, basal metabolic rates, and muscles dimensions, simulated stretches of even quite improbable extents yield increments in basal metabolic rate considerably less than those seen experimentally in vitro (Feng, 1932; Euler, 1935; Lee, 1960; Whalen, 1960; Cranefield and Greenspan, 1960; Gibbs et al., 1967; Poole and Sonnenblick, 1967; Clinch, 1968; Loiselle, 1979*a*; see also Fig. 1 and Table I). Since the magnitude of the stretch effect (Δm) depends on seven distinct parameters and since numerical solution of Eq. 7 requires considerable computation time, no attempt was made to determine the absolute optimal stretch conditions. The effect of varying each parameter

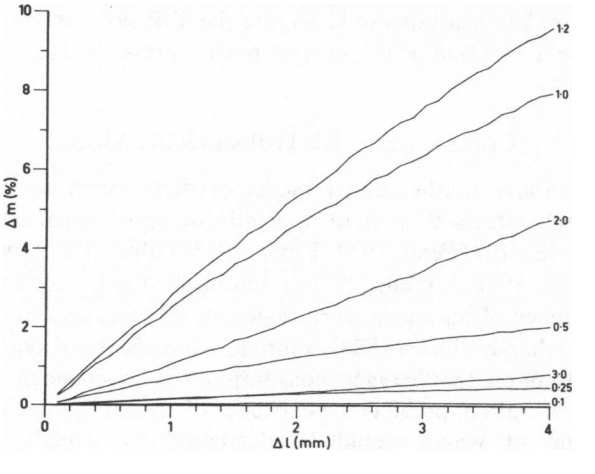

FIGURE 8 Effect upon simulated stretch response (Δm) of a stretch of Δl imposed upon 7-mm-long papillary muscles ranging in diameter from 0.1 to 3.0 mm. Muscles had prestretch basal metabolic rates of 5 mW/g in 0.95 atm O_2. Note that these parameters maximize Δm for a muscle of diameter 1.2 mm, in accordance with Figs. 6 (middle panel) and 7.

over a wide range (holding the remaining parameters fixed) will be considered separately.

p_o

Independent of the values of the remaining parameters, the dependence of Δm (the effect of stretch upon the basal metabolism) on the P_{O_2} of the bathing solution always has the same general form (Fig. 4): a monotonic increase from zero to some maximum followed by a monotonic decrease that asymptotically approaches zero. The general shape of the $\Delta m = \Delta m\ (p_o)$ relation (i.e., the appearance of a maximum) shown in Fig. 4 can be explained as follows. When the external oxygen concentration is very low, the concentration at all points within the muscle will likewise be low, and reducing the radius secondary to elongation will have a negligible effect because of the negligible P_{O_2} gradient. Similarly when the P_{O_2} is extremely high at the surface of the muscle, it will be likewise extremely high on the axis and stretch will increase it only marginally. At intermediate values of p_o, on the other hand, the oxygen concentration on the axis will be low or moderate and in these cases elongation will raise the axial value considerably, owing to the steeper P_{O_2} gradient. There will consequently be a much greater relative effect on the basal metabolism.

O_2 Consumption/Concentration Profile (m_1 and m_2)

In his analysis of oxygen diffusion into tissues, Hill (1928) assumed that O_2 consumption was independent of concentration. In the current model a variable consumption/concentration relation was incorporated since a sigmoidal relation is not only more plausible but receives experimental support (Kempner, 1937; Hill, 1948; Stainsby and Otis, 1964; Stainsby, 1965; Gore and Whalen, 1968; Rakusan, 1971; Wilson et al., 1977). By varying the values

of parameters m_1 and m_2, the O_2 consumption/concentration profile may be altered dramatically from simple exponential through sigmoidal to rectangular hyperbolic. But even the most extreme rectangular hyperbola, which can be made to approximate Hill's independence assumption arbitrarily closely (see Fig. 2), has a profound effect on the "anoxic core" implication. For no matter what the form of the relation, provided it approaches zero smoothly, since the O_2 consumption on the axis can only approach zero but can never reach it, an anoxic core is an impossibility.

The effect of varying m_1 and m_2 upon the stretch response is, of course, p_o-dependent (see Fig. 4); but in Fig. 5, which shows $\Delta m = \Delta m\ (m_1, m_2)$, p_o was held constant at 0.95 atm (the usual experimental value). Realistic papillary muscle dimensions were also chosen ($r_o = 0.5$ mm, $l_o = 7.0$ mm, and $\Delta l = 2.0$ mm); yet the greatest simulated increase in resting metabolism was <7%, which occurred with values of m_1 and m_2 approximately equal to 1 and 4, respectively. The unlikely oxygen consumption/concentration profile corresponding to these values is shown in Fig. 2 (curve 5).

The recent findings of Jöbsis and colleagues (Jöbsis, 1974; Rosenthal et al., 1976, Jöbsis et al., 1977), relating to the redox state of the terminal cytochrome of the respiratory chain in vivo, may bear on the shape of the oxygen consumption/concentration relation. They have found that increasing the partial pressure of oxygen to 1 atm causes increasing oxidation of the cytochrome with no sign of a plateau in the percentage oxidation/oxygen partial pressure relation. If there were a one-to-one correspondence between the redox state of the terminal cytochrome and the overall rate of oxidative phosphorylation, the most realistic oxygen consumption/concentration relation might lie somewhere between curves 3 and 4 of Figure 2, i.e., with the critical P_{O_2} in the region of hyperbaric oxygen partial pressures. This extreme interpretation seems unlikely, however, in view of the complexity of the oxidative phosphorylation system and, consequently its likely ability to buffer the rate of oxygen consumption against falling oxygen concentrations.

Basal Metabolism ($\overline{m}$)

As can be seen in Fig. 7, the effect of the prestretch resting metabolism $\overline{m}$ on the stretch effect is again unimodal. It is not immediately obvious that the function $\Delta m = \Delta m\ (\overline{m})$ should display a sharp maximum but this is indeed the case, since for small $\overline{m}$, $p_a \rightarrow p_o$, whereas for large $\overline{m}$, $p_a \rightarrow 0$. In either case p'_a approximates p_a. For intermediate value of $\overline{m}$, p_a lies intermediate between 0 and p_o, so that p'_a becomes dissimilar to p_a. The argument is analogous to the p_o dependence discussed above.

Muscle Geometry (r_o and Δl)

The effect of muscle radius r_o upon Δm (Fig. 6) is similar to that of p_o; i.e., a smooth unimodal relation results. Both very thin and very thick papillary muscles show little metabolic response to stretch—the former because the axial P_{O_2} is high before stretch, so that stretch causes negligible enhancement, and the latter because the P_{O_2} is very low throughout a large portion of the muscle before stretch and remains that way after the stretch as well. Authors who have used the magnitude of the stretch response to determine the existence of a putative anoxic core (Cranefield and Greenspan, 1960; Whalen, 1961; McDonald, 1966; Coleman, 1967) seem to have been unaware of the theoretical prediction of a decline in response predicted by this model (Fig. 6) with muscles of sufficient radius.

As mentioned previously, a papillary muscle passively stretched beyond ~30% of l_o usually fails to recover completely (i.e., it remains somewhat elongated and shows diminished force production). Figs. 6 (lower panel) and 8 show the effect of varying the extent of stretch (Δl) upon the stretch response. As expected, increasing Δl increases Δm, but it is to be emphasized that, for the simulated muscle of length 7 mm, stretches beyond about 2-mm extent (which yield simulated increments in basal metabolism of only ~7%) would be unphysiological.

Oxygen Diffusion Coefficient (K)

The stretch effect is remarkably sensitive to K (Fig. 9), with the peak value occurring in the vicinity of the value reported by Krogh (1918) for skeletal muscle. As reviewed by Gibbs (1978), several modern estimates of oxygen diffusivity in cardiac muscle exceed the Krogh value by a factor of ~2. However, even should oxygen diffusion in cardiac tissue be facilitated by the presence of myoglobin (Lentini, 1964; Wittenberg, 1970; Fletcher, 1980), Fig. 9 shows that the resulting increased diffusivity of oxygen would not enhance the metabolic effect of stretch. (This is, of course, an oversimplification; Wittenberg [1970] has shown the P_{O_2} dependence of facilitated oxygen flux. Thus, a complete analysis would require the diffusion coefficient to be a function of the oxygen partial pressure, i.e., $K = K(p)$.)

Comparison with Hill's (1928) Model

The above mathematical model predicts much smaller stretch effects than those typically observed experimentally in vitro (Feng, 1932; Euler, 1935; Gibbs et al., 1967; Clinch, 1968; Loiselle, 1979*a*), but implicitly disallows the existence of an anoxic core region in the muscle. On the other hand, Hill's (1928) solution, which is based on the assumption that oxygen consumption is independent of concentration, predicts the existence of an anoxic core, the extent of which would be decreased by stretch. As discussed above, several authors have used the experimentally observed dependence of the stretch effect on the muscle radius as evidence in support of the anoxic core hypothesis. Although Fig. 6 would suggest caution in this regard, it is remarkable that the anoxic-core implication of

Hill's model has, apparently, never been quantified. What is the predicted magnitude of the stretch effect according to Hill's model? Hill's (1928) solution of the diffusion equation is:

$$r_c^2 [\ln (r_o^2/r_c^2) + 1] = r_o^2 - 4Kp_o/m_o, \qquad (10)$$

where m_o is the basal metabolic rate (uninfluenced by oxygen concentration) and r_c is the critical radius (i.e., the radius at which the oxygen concentration p drops to zero).

In this model, for given values of m_o, p_o, and r_o, m depends only on the volume of oxygenated tissue (a cylinder when $r_c = 0$ and an annulus when $r_c > 0$); i.e., m $(p > 0) = m_o$ and p $(r < r_c) = 0$. Elongation, by reducing r_c, increases the oxygenated volume and hence increases the mean basal metabolic rate when averaged over the total muscle volume. Fig. 10 shows the relative stretch effect predicted by the Hill model as a function of muscle radius r_o for various values of p_o and m_o. The essential difference with this model, of course, is the absence of a stretch effect if the muscle radius is less than some critical value. The stretch effect varies directly with m_o and inversely with p_o, but, even in simulated muscles that would be deemed to have unacceptably large radii for in vitro studies, it achieves values of only ~12%, which is much less than those observed experimentally (see Fig. 1 and Table I). Even the Hill model, which predicts the existence of an anoxic core due to oxygen diffusion limitation, is unable to account for the magnitude of the stretch effect seen experimentally in vitro.

Thus, the results of both the Hill model (in which oxygen consumption is independent of oxygen concentration) and a more realistic model incorporating a sigmoidal relation between oxygen consumption and concentration are in agreement. If the cores of isolated papillary muscles are indeed anoxic, as many authors have suggested, the observation that stretch increases the basal metabolic rate of those muscles cannot be used as supporting evidence. As exploration of both of these models has shown, attributing the effect of stretch purely to oxygen diffusion considerations is qualitatively in the correct direction but quantitatively of insufficient magnitude. It seems safe to conclude, as Feng (1932) did many years ago from studies of amphibian skeletal muscle, that stretch has a metabolic effect per se upon mammalian cardiac muscle.

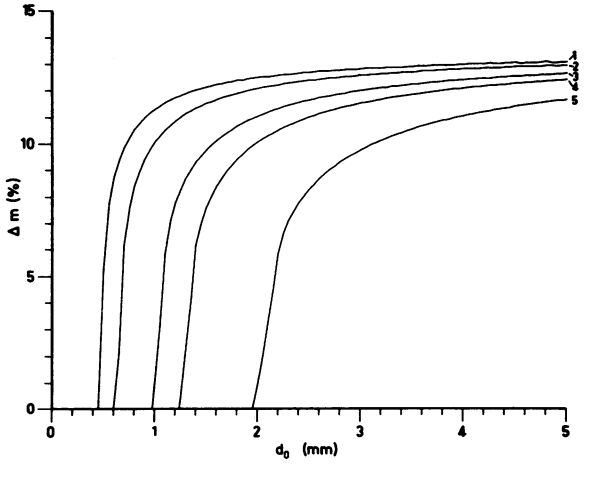

FIGURE 10 Simulated stretch effect, for a 7-mm papillary muscle elongated by 2 mm, according to Hill's diffusion model (Eq. 10, text). Prestretch metabolic rate = 20, 20, 20, 5, and 5 mW/g, and p_O = 0.50, 0.95, 2.375, 0.95, and 2.375 atm in curves 1–5, respectively; K = 1.4 $cm^2 \cdot min^{-1} \cdot atm^{-1}$.

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