JEPonline
Journal of Exercise Physiologyonline

Official Journal of The American Society of Exercise Physiologists (ASEP)

ISSN 1097-9751
An International Electronic Journal
Volume 4 Number 1 January 2001

Review

AN EXERCISE PHYSIOLOGIST'S "CONTEMPORARY" INTERPRETATIONS OF THE "UGLY AND CREAKING EDIFICES" OF THE VO_2MAX CONCEPT

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ABSTRACT

ROBERT A. ROBERGS **An Exercise Physiologist's "Contemporary" Interpretations Of The "Ugly And Creaking Edifices" Of The VO_2max Concept**. JEPonline**,** 2001 4(1):1-44. The recent debate over the validity of traditional interpretations of the concept of VO_2max has prompted the writing of this commentary. Rather than provide another "classic" interpretation of how VO_2max is interpreted within exercise physiology (1), a more "contemporary" interpretation than that of Noakes (2-4) is provided by an exercise physiologist well-trained and widely published in exercise physiology and biochemistry. It is this author's contention that Noakes (2-4), as well as Bassett and Howley (1), have over-emphasized the classic research of Hill and related physiological interpretations pertaining to VO_2max. Nevertheless, Noakes deserves to be commended for his candor in constructively criticizing how the field of exercise physiology has researched and interpreted findings on the concept of VO_2max. Despite Noakes' criticisms of the validity of the concept of a VO_2 plateau at VO_2max, a thorough review of research, as well as the presentation of original data in this manuscript, indicates that the VO_2 plateau is a measurable phenomenon in most subjects. Noakes' alternative theories for limitations to VO_2 during incremental exercise to volitional exhaustion are challenged based on past research evidence. The limitations to VO_2 during incremental exercise are shown to be population and environmental condition specific, and the concept of main determinants of VO2max for all people and conditions is shown to be an oversimplification and inaccurate. Novel interpretations of recent research are presented to provide a more systems oriented and research-based approach to understanding the determinants of the limitation to the continued increase in VO_2 during incremental exercise testing. The challenges that confront exercise physiologists are to better define their profession, increase the standards and quality of academic preparation, improve research design, and better justify certain physiological interpretations when researching VO_2max and related topics.

Key Words: Aerobic Capacity, Anaerobic Capacity, Anaerobiosis, Deoxygenation, Hypoxia, Oxygen Deficit, Endurance, Exercise Performance, Oxygen Delivery, Scientific Method

INTRODUCTION

During the last three years the reviews and commentaries by Bassett and Howley (1) and Noakes (2-4) have provided reading that has been entertaining, enlightening, and at times very disturbing. These publications have concerned fundamental topics associated with the administration and interpretation of exercise testing for the purpose of quantifying the maximal rate of oxygen consumption (VO_2max). Given that VO_2max is arguably the single most performed test in exercise physiology, with considerable application to numerous clinical specialties, this debate is of importance to how exercise physiologists and other professionals explain and interpret human physiology and biochemistry during incremental exercise. This fact was clearly emphasized by Peter Raven in an editorial commentary to the most recent of Noakes' publications (5). Raven stated, "*I encourage all of our members and readers to become aware of the issues raised and in the future to accept or reject the concepts developed by Noakes based upon the weight of scientific evidence generated*."

I have decided to contribute my interpretations of physiology and biochemistry during exercise to the topics debated by Noakes (2-4) and Bassett and Howley (1). The contents of this review will be beneficial to contrast against what I view to be the over "classical" interpretations of Bassett and Howley, and the loosely defined "contemporary" interpretations of Noakes.

What is Exercise Physiology and Who is An Exercise Physiologist?

The debate developed by Noakes (2-4) and Bassett and Howely (1) is not confined to interpretations of research evidence. For example, Noakes' originally claimed that, "*The belief that oxygen delivery alone limits maximal exercise performance has straightjacketed exercise physiology for the past 30 yr*." (2). In additional commentaries, Noakes stated, "*I wish to review some contentious claims in exercise physiology*", and that, "*the focus* (of the challenging beliefs) *will be on exercise physiology*" (3). Finally, when concerned with the ability of exercise scientists to adequately scrutinize past and present research, Noakes' claimed that "*the concept of refutability is not always eagerly accepted in all areas of our discipline*" (3).

Clearly, there is a need to briefly explain the current condition of the discipline and profession of exercise physiology within the United States. As I will explain, an understanding of the status of exercise physiology aids in the explanation for why the field of exercise physiology, and those who call themselves exercise physiologists, may be open to criticism.

First of all, it is important to realize that exercise physiology is not a profession in the U.S., and there are currently no widely accepted definitions and standards of what is exercise physiology and who is an exercise physiologist. It was as recent as 1997 that the first and only professional exercise physiology organization was founded, The American Society of Exercise Physiologists (ASEP). Although ASEP has developed nationwide academic standards (ie: course accreditation) and external certification, these programs are in their infancy. In addition, ASEP is working with numerous state exercise physiology associations to develop consistent state-specific licensure, but as yet only Louisiana has licensure protection of the term and scope of practice of an "exercise physiologist" (6). How do these traits reflect on exercise physiology as a viable academic and research entity? The answer is clearly negative. Current and past academics and researchers of exercise physiology have considerably divergent training and competencies. In addition, the Ph.D. degree in exercise science in the U.S. is still based on academic content with only a single research experience (doctoral dissertation) required in most programs. Consequently, it is no surprise that exercise physiologists can be claimed to be poorly trained and/or competent in research inquiry. It is also no surprise that authors of textbooks on exercise physiology may have eagerly accepted "attractive" theories without adequately scrutinizing their merit in order to develop a broader scientific-based academic content. University-based exercise physiologists may have then continued this acceptance in order to justify their presence in the university setting. These suggestions are best reflected by the need to continue to justify the scientific presence of the exercise sciences in many university departments within the U.S. This justification still occurs despite

documented evidence that the scientific evaluation of exercise, athletics, sports and general physical activity can be traced to the late 19th century (7,8), and therefore be justified by more than a century of research-based inquiry and accumulated knowledge.

A good example of the lack of direction in defining who an exercise physiologist is can be found in Brooks' 1994 summary of the last 40 years of basic exercise physiology research (9). Brooks identified the need to define exercise physiology research early in his manuscript, and chose to use the self admitted "*extremely broad definition*" of, "*either the use of exercise to better understand human physiology, or the use of physiology to better understand human exercise*". I have extreme professional dissatisfaction for how Brooks' definitions allow anybody who uses exercise in a research model to be doing exercise physiology research, and therefore that anybody trained in physiology who conducts research involving exercise can be an exercise physiologist. However, the topic of who is an exercise physiologist is not central to this commentary. Rather, Brooks' inability to provide a sound definition of exercise physiology, and of who an exercise physiologist is, clearly exemplifies the lack of accepted academic, research and professional definitions within exercise physiology.

A definition of exercise physiology more congruent with accepted interpretations within the discipline itself is that exercise physiology involves the scientific study of how exercise alters human systemic and cellular physiology both during and immediately after exercise, as well as in response to exercise training (10). As such, exercise physiology encompasses study and competencies in, but not restricted to, systems physiology, cellular biochemistry, nutrition, body composition, research design and statistics, and exercise specific topics such as ergometry, calorimetry, ergogenic aids, mechanisms of fatigue, environmental stresses, and clinical applications. The breadth of these academic courses is covered in most exercise science degrees, thereby indicating that an exercise science degree is a preferred, and perhaps should be the only recognized route of training to become an exercise physiologist.

The previous definition of exercise physiology reveals that an exercise physiologist must be trained in multiple systems physiology, cellular biochemistry, and the classic exercise sciences. **It is the diverse knowledge and skill base of an exercise physiologist that differentiates such a scientist or academic from a physiologist who has specialized in one aspect of human physiology and has an academic and research interest in how exercise interacts with this specialization**. Recognition of the multiple systems and levels of regulation that influence human physiology during exercise cannot be overemphasized. For example, viewing one line of evidence without fully recognizing other competing influences can lead to erroneous interpretations and conclusions. As I will reveal in this review, Noakes (2-4) repeatedly used evidence from research to support his "contemporary" interpretations, and even developed his own theories that have not been researched. However, when this evidence is compared to the evidence of multiple physiological and biochemical responses to exercise, I will explain how many of Noakes' theories are erroneous.

Finally, Noakes' criticisms and alternate interpretations stress the need exercise physiologists to be open to, and even invite constructive criticism from outside disciplines. Such criticism can strengthen, refine or redefine previously formulated theories, with the net result of strengthening the scientific framework of the discipline. Obviously, this is a good thing, and as previously explained, definitely needed by the discipline of exercise physiology. Exercise physiologists, like all scientists of a specific discipline, should be more willing to research the validity of any challenging concept so that no valid arguments can be made against the measurements and interpretations that define the knowledge and skill base of the discipline.

The Scientific Method

Before starting on a review of the issues at question, comment is required on the process of the scientific method. Noakes (3) went to great lengths to expound the virtues of good science vs. bad science. In simpler terms than provided by Noakes, the scientific method is based on the ability to raise questions that have not yet been answered. The potential answers to the questions serve as the basis for hypotheses, which are just as

important for their role in proposing outcomes as they are for identifying other potential outcomes and to rationalize why they may not eventuate. The researcher then attempts to design a study around these hypotheses in an attempt to show the proposed outcome(s). However, the objective of a scientist is to not just show how one hypothesis is correct. Science can never prove anything outright. Statistics only give the researcher a range of probabilities for findings to support or reject hypotheses, and given this scientists need to have the realization that science is never exact. There are always alternate explanations for research findings, and as each of Popper (11), Katch (12) and Noakes (3) have all correctly described, good science is not just identifying an association between variables, or speculating further on a cause-effect interaction, it is also disproving any alternate explanations. Katch (12) correctly described this requirement of science as a researcher's "burden of disproof".

The nature of science therefore allows anybody to come up with alternative theories. In fact, one could gauge the poor quality of the scientific base of a discipline by the number of alternate theories that arise. The more alternate theories, the less clear past research has been on disproving alternate theories, and the poorer the scientific base of the discipline. Therefore, the most disturbing feature of Noakes' (2-4) interpretations, which are in opposition to the general accepted train of thought, is their potential to reflect the poor scientific basis of the science of exercise physiology. However, as I have previously commented, science is defined by the inability to totally prevent alternative explanations. Therefore, what needs to be decided is how valid are the criticisms of Noakes and the arguments within the rebuttal from Bassett and Howley (1).

Bassett and Howley (1) attempted to refute the interpretations of Noakes (2-4). However, I have to agree with Noakes (4) that many of the explanations used by Bassett and Howley suffer from a circular argument. This is especially true for the explanation of an oxygen limitation to skeletal muscle (not necessarily an anaerobiosis as Noakes interprets). Any argument will fit Noakes' circular argument descriptor if it is based on inadequate research: inadequate not just in the quality of individual studies, but also the ability to refute alternate explanations. Ironically, Noakes can also be criticized for circular arguments as he also provided explanations that do not necessarily refute the positions of Bassett and Howley, and some explanations simply cannot be researched at this time (eg. intramuscular kinetics of oxygen diffusion). Thus we have two sides debating over issues, each performing circular arguments, with no net progress being made on resolving any issue.

The circular argument approach is where I have some discontent with the response of Basett and Howley (1) to the "edifices" proposed by Noakes (3,4). Bassett and Howley did provide detailed evidence for their belief of the validity of current thinking in exercise physiology. However, they used one-sided evidence of the "classic" perspective of data interpretation and did not provide any evidence at all on research data that would refute the alternative explanations proposed by Noakes. For example, in the section on "Factors Limiting VO_2max", Bassett and Howley presented evidence to support a central cardiovascular limitation that included evidence from at least 5 different lines of research inquiry. However, no evidence was presented that directly refuted the alternate explanations raised by Noakes. Approaching this topic with "good science" should have resulted in a section that provided evidence of whether or not Noakes' alternate explanation was supported by past research; that of a central nervous system, central cardiovascular, or intramuscular response that dampens muscle ATP demand to prevent exceeding the oxygen supply. As Bassett and Howley did not do this, Noakes has been able to respond in a rebuttal (4) that Bassett and Howley are guilty of a circular argument. Of course, Noakes is correct in regard to the circular argument issue, but that does not mean that his argument is correct, especially when he himself does not provide any concrete evidence to support his claims. Rather, Noakes obtained research findings from a vast array of different studies involving tests of VO_2max as well as other metabolic capacities. When concerned with research of VO_2max, Noakes selected evidence from research that used subjects that were either aged, sedentary and/or diseased. Obviously, there are fundamental concerns with the generalizability of the results of these studies to the topic of VO_2max in healthy recreationally active to highly trained individuals. This scenario is consistent with each of the "edifices" that were at question. Ironically, Noakes did not address the issue of generalizability in any of his manuscripts (2-4).

The remaining task at hand is to decide how much credence one should give to alternate hypotheses. It is this issue that has been the most disturbing of the commentaries of Noakes (2-4). Typically, the scientific method would require one to raise alternate hypotheses and put them to the test of research. This process would require a thorough review of past research to formulate the hypotheses. Research would then be designed to test these hypotheses. If results indicated that an alternative explanation needed to be accepted, then publication in peer reviewed journals would be the process to be pursued. Noakes has not done this with many of his alternate explanations to previously accepted fact. Furthermore, Noakes has arrived at alternate explanations with at times what appears to be a one-sided or incomplete evaluation of past research. This has been a short cut to the scientific method, and as I will reveal, one that has fueled a debate that is futile. No side of this debate, that of the presence and determinants of a VO_2 plateau during incremental exercise testing, is totally correct unless new research is conducted that empirically answers the issues at question. As my previous comments have indicated, the fact that a debate could occur on a topic in science is fairly good evidence that the topic has been poorly researched, and any effort at reaching a consensus will be based more on speculation that fact. A better contribution to science would be to identify the research that needs to be done to decrease speculation. I will attempt to do just that in the sections that follow.

The Edifices of Exercise Physiology: Fact or Fiction?

When reading the articles of Noakes (2-4), Bassett and Howley (1), and Howley et al. (13), there are key topics that Noakes has described as "edifices". For the point of clarification, an edifice is a "large abstract structure", with an emphasis that the structure is important for holding together a larger point of reference (14). In Noakes' use of the word "edifice", he is referring to several key accepted interpretations of exercise physiology that have been used to form an important knowledge base for the discipline and developing profession. The following sections present research that either refute or support the edifices that Noakes identified that pertain to VO_2max measurement and interpretation. Noakes grouped his concerns of the measurement and interpretations of VO_2max into two edifices; that of the VO_2 plateau interpretations of Hill that Noakes believed led to the generally accepted "cardiovascular/anaerobic model" of VO_2max, and that the development of muscle hypoxia limits VO_2max. However, I have separated the first edifice into two; *the VO_2 plateau coincides with VO_2max,* and *VO_2max is limited by oxygen delivery and therefore maximal cardiorespitory function and capacities.* The third edifice remains intact; *the development of an intramuscular hypoxia during incremental exercise to VO_2max.*

"Edifice"#1: A plateau in VO_2 coincides with maximal oxygen consumption

The classic research of Hill and Lupton

Each of Bassett and Howley (1) and Noakes (2-4) have gone to great lengths to dissect the classic research of Hill and Lupton from 1923 (15). For example, almost 5 pages of the 10 written in Noakes' initial commentary on exercise testing (2) dealt with research of or immediately associated with the work of Hill and Lupton (15) and Hill (16). In his 1997 manuscript from the JB Wolffe lecture (3) Noakes devoted 2.5 pages to this material, and almost 10 pages in his recent rebuttal (4). Why is there all this attention to research that is between 50 and 75 years old? Noakes argued that it is this research that has framed the illogical assumption of a maximal oxygen consumption limited by oxygen delivery. Conversely, Bassett and Howley (1) argued that this classic research deserves to be recognized for its insights of applying indirect calorimetry (an old science even in those days) (8) to better understanding the capacity of the human body during exercise, and for how this capacity influences muscle metabolism and exercise performance.

What were the findings and interpretations of the original research manuscripts that investigated and interpreted VO_2max? Each of Noakes (2-4) and Bassett and Howley (1) have published lengthy interpretations of this work, as well as quotes from the manuscripts. Given the prior intricate dissection of this research, added interpretations are not warranted. However, the more important of the quotes from this research were from Hill (15), Taylor et al. (17) and Mitchell and Blomqvist (18). Hill (15) stated that,

"*In running the oxygen requirement increases continuously as the speed increases, ….; the actual oxygen intake, however, reaches a maximum beyond which no effort can drive it. The oxygen intake may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory system*."

Taylor et al. (17) stated that,
"*There is a linear relationship between oxygen intake and workload until the maximum oxygen intake is reached. Further increases in workload beyond this point merely result in an increase in oxygen debt and a shortening of the time in which work can be performed*."

Mitchell and Blomqvist (18) stated that,
"*Maximal oxygen uptake is the greatest amount* [rate] *of oxygen a person can take in during physical work and is a measure of his* [/her] *maximal capacity to transport oxygen to the tissues of the body. It is an index of maximal cardiovascular function …… and, therefore, is valuable in the evaluation of abnormal cardiovascular function*".

The repercussions of these interpretations are still seen in the most recent of exercise physiology textbooks, which claim that VO_2max represents the maximal cardiorespiratory capacity, and that central cardiovascular function represents the main limitation to VO_2max (10,19-22). No mention is made in any textbook of the limitations in the original research that resulted in these interpretations. However, one textbook does mention the recent recognition of the controversy surrounding the VO_2max concept (20).

When reviewing the criticisms of Noakes (2-4), and the support provided by Bassett and Howley (1) for Hill's findings and interpretations, it becomes clear that Hill's research methodologies and data interpretations were at fault. Despite Noakes' claim of circular reasoning, and Bassett and Howley's response that both they and Hill did not do this (hardly a scientific presentation refuting Noakes' criticisms), the scientific facts are clear on this issue. As Noakes claimed, Hill did not empirically test the plateau phenomenon to be true, and had research methodology that would not be accepted by today's standards of scientific inquiry. For example, Hill (15) used multiple bouts of exercise performed for several minutes to acquire steady state and end-exercise (for non-steady state conditions) VO_2 values. Hill did not collect data for running speeds above what he perceived to be the maximal rate of VO_2 possible while running (4 L/min at 16 km/h) – a value we now know not to be "maximal"! Hill also used multiple data points (1-3) from 7 different subjects to acquire a sufficient number of unaltered data points to ascertain the existence of a plateau phenomenon. I agree with Noakes' (4) concerns, "*I remain unconvinced that one can reasonably expect to identify a 'plateau phenomenon' and hence sustain an influential physiological theory from a total of three measurements of VO_2 in each of four athletes, and one each in another two*." Similar methodological flaws were evident in the pivotal manuscripts that followed the work of Hill (17,18,23,24), and functioned to further cement the concept of a VO_2 plateau and VO_2max into exercise physiology and clinical exercise testing interpretations.

Despite the shortcomings of the early research on VO_2max, exercise physiologists need to know that criticism of the original research of VO_2 during incremental exercise does not necessarily refute the entire concept of the VO_2 plateau phenomenon and the existence of a VO_2max. The reality of the critical evaluation of past research is that no matter how finicky we get at scrutinizing the original research on the concept of VO_2max, inadequacies will be found due to the date of the work. We should not expect perfect research from the pioneers of our field. In fact, I cannot think of any pioneering research that was not flawed in some way due to aspects of research design, methodology, or inadequate experimental control. We should recognize Hill and Lupton (15), as well as the other original researchers of exercise physiology (17,18,23,24), for their commitment to raising questions about exercise physiology, and their perseverance in being able to answer them – even if some of their answers and interpretations were wrong. The challenge of these pioneering

researchers was not to answer all the questions about the increase in VO_2 during incremental exercise, but to introduce the concept.

The challenge to determine the mechanisms for the VO_2max phenomenon belongs to the physiologists who came after Hill and Lupton (15). Therefore, what is most important to the measurement and understanding of VO_2max is the body of knowledge that has more recently added to our understanding of this topic, and how we have interpreted this research. As I have mentioned earlier, if there are faults in how we measure and interpret VO_2max, then criticism needs to be directed at more recent exercise physiologists than Hill and Lupton! The fact that we are arguing over research that is more than 50 years old to establish the current validity of the VO_2max concept in exercise physiology can be interpreted several ways. This debate could be explained by the topic being complex and extremely difficult to research. Alternatively, there may be major inadequacies in research (content and number) on this topic, with equally inadequate interpretations. As will be clear in this manuscript, I am convinced that the compilation of research on the VO_2mnax remains to be inadequate, and there has been an equally inadequate acceptance of the findings of this research to be true, unquestionable and complete.

Is there a plateau in VO_2 during incremental exercise to volitional exhaustion?

A concise explanation of the stance of Noakes (2-4) is that a plateau in VO_2 is not always evident in subjects who perform incremental exercise to volitional exhaustion. Consequently, the peak VO_2 attained during an incremental exercise test cannot be assured to be maximal, and the interpretation of a cardiovascular limitation to an increasing VO_2 can be questioned. This deviates from the accepted understanding that a plateau in VO_2max is an important criterion for establishing the validity of the measurement. According to Noakes, exercise physiologists believe that 1) a plateau in VO_2 at VO_2max occurs in all individuals, and 2) that such a plateau is caused by insufficient oxygen delivery to contracting skeletal muscle (3,4).

Careful reading of all sides of this debate reveals that there is no difference of opinion with the first conjecture. Bassett and Howley (1) correctly indicate that a plateau in VO_2max is not seen in all subjects tested, even when healthy and endurance trained. For example, researchers have shown a plateau phenomenon in 33% (25), 43% (26), 50% (27), 75% (28,29), 94% (17), 28% (18,23), 50-60% (30), 40% (31) and …% (32) of subjects tested. These variable results have been explained by differences in the test protocol (30,33-35), the fitness and age of the subjects tested (27,28), the criteria used for establishing a VO_2 plateau (17) and the data collection and analysis procedures used in the research (32).

The important distinction between the interpretations of Noakes (2-4) and Bassett and Howley (1) is that Bassett and Howley indicate that a VO_2 plateau is not necessary for the interpretation of a cardiovascular limitation to VO_2max. Nevertheless, I find the justifications and explanations used to reach a consensus on the issue of a VO_2 plateau from both parties to be very inadequate. For example, why is there a plateau found in some subjects and not others? Does the inconsistency of the plateau in past research mean that it is physiologically irrelevant? Is the fact that a VO_2 plateau is an inconsistent finding real, or a result of research methodology? Do explanations exist for a VO_2 plateau that is not related to traditional interpretations of oxygen delivery?

Before being able to answer the aforementioned questions and provide an alternate explanation for the VO_2max phenomenon to those of Noakes (2-4) and Bassett and Howley (1), the metabolic and cardiorespiratory physiology that occurs during incremental exercise to volitional exhaustion needs to be presented. With this basic information clarified, an additional interpretation to the VO_2max and plateau phenomenon can be presented to contrast with the contemporary interpretations of Noakes and the traditional viewpoints of Bassett and Howley.

<u>Metabolic and Cardiopulmonary Changes During Incremental Exercise To Volitional Exhaustion</u>

Today the exercise protocol most commonly used by research exercise physiologists for the quantification of VO_2max is the ramp, or pseudo-ramp protocol. Typically, a true ramp protocol is not performed due to the equipment constraints of having a computer generated ramping function. Thus, researchers commonly use

protocols that have a frequent small increase in mechanical power output (O_2 cost) (pseudo-ramp), such as a one minute incremental protocol. As well reviewed by Howley et al. (13), to increase the validity of the protocol to detect a true VO_2max, such a protocol must be developed to cause volitional exhaustion in 8 to 10 min following a 5 min warm up, and this total duration dictates the increment in O_2 cost/stage. For example, a person who can perform cycle ergometry to 400 Watts at volitional exhaustion during incremental exercise testing would require an increment of approximately 30 Watts/min for a 14 min test (includes the warm up). Each of Noakes (2-4) and Bassett and Howley (1) clearly revealed that the early research on the VO_2max concept did not involve continuous incremental exercise testing like that used today. It is therefore useful to compare changes in the VO_2 responses from intermittent and continuous protocols to reveal the reality of present day issues of the change in VO_2 during incremental exercise. Figure 1 reveals the change in VO_2 for a single subject during cycle ergometry exercise for different relative exercise intensities that range from 20 to 100% VO_2max, as well as a ramp protocol to VO_2max. The subject and technicians were instructed to continue

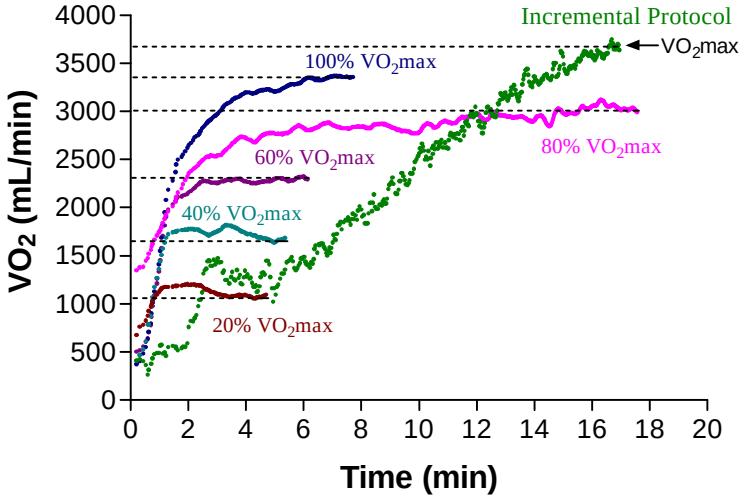

Figure 1: Comparisons between the change in VO_2 during incremental exercise to VO_2max, and each of exercise to steady state or fatigue for 20, 40, 60, 80, and 100% of the power output at VO_2max exercise intensities. The incremental exercise protocol involved 2 min of rest, 3 min at 50 Watts, followed by 25 Watt/min increases in exercise intensity.

data collection at each exercise intensity until a steady state was attained (no shorter than 4 min for 20-60% VO_2max), or until volitional fatigue (80 and 100% VO_2max).

There are several important findings from this data;

1) for low intensity increments in exercise intensity, there is an overshoot in the VO_2 response followed by a decrease in VO_2 to true steady state.
2) as the subject progresses from steady state to non-steady state intermittent exercise, the VO_2 response does not plateau,
3) for this subject the time to fatigue decreased as the relative power output increased for relative intensities ≥ 80% VO_2max,
4) due to the anaerobic component of exercise intensities greater than the lactate threshold, the peak VO_2 value obtained from the single bout non-steady state exercise intensities must be less than the actual VO_2 cost,
5) VO_2max from the ramp protocol exceeded the peak VO_2 obtained from the continuous exercise at the exercise intensity at 100% VO_2max,
6) there was a decrease in the VO_2-time slope of the ramp protocol after approximately 10 min,
7) the incremental exercise test induced a slower increase in VO_2 relative to the single bout %VO_2max power outputs, and
8) the peak VO_2 from the intermittent protocol (3372 mL/min) was attained at 90% of the continuous test VO_2max value (3752 mL/min).

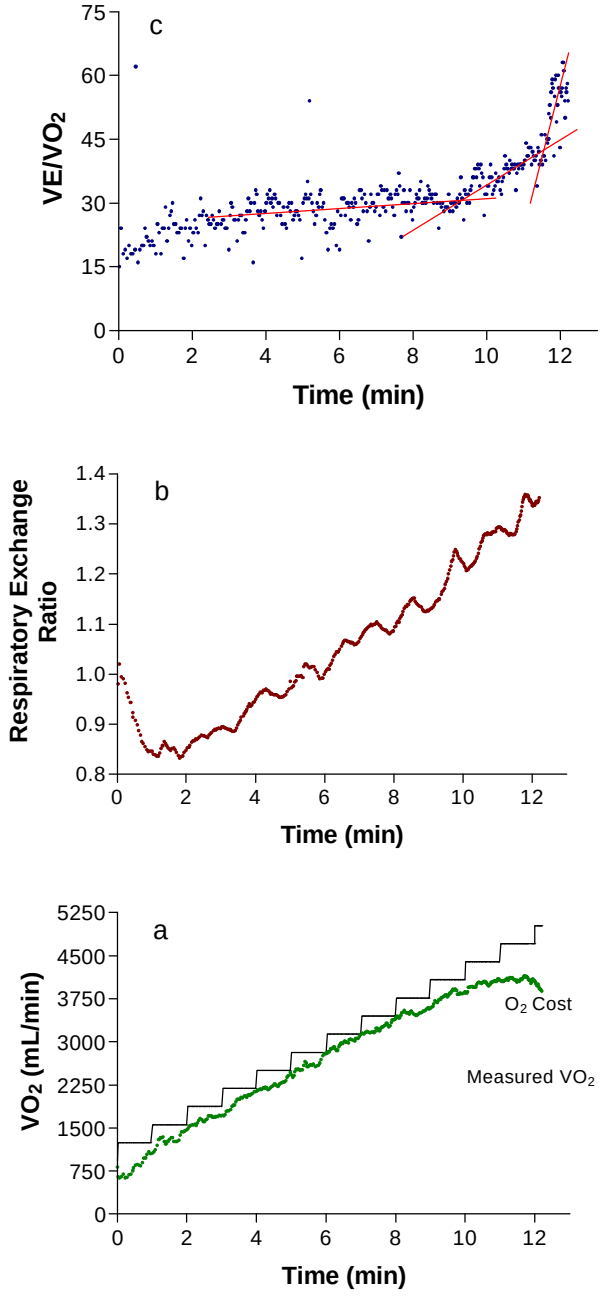

Figure 2: The graphical representation of a) the measured and calculated oxygen cost of a 30 Watt/min incremental cycle ergometer exercise test for the measurement of VO_2max. The oxygen cost of each stage was calculated from a previously determined VO_2-Watts relationship of the subject (rest, 50, 110, and 150 Watts). Data are also presented for b) the respiratory exchange ratio (RER), and c) the ventilatory equivalent for oxygen (VE/VO_2).

Clearly, using intermittent protocols dispersed over days, as performed by Hill and Lupton (15), Taylor et al. (17) and Wyndham et al. (24) is not a suitable procedure for assessing VO_2max as it can underestimate VO_2max and artificially generate a VO_2 plateau when combining multiple single bouts of exercise.

Cardiopulmonary and Muscle Metabolic Changes During Incremental Exercise Testing?

Figure 2 presents original data from an incremental exercise test to VO_2max. The first feature to note is that the subject incurred an increasing oxygen deficit with an increase in exercise intensity. The size of the deficit increased linearly with the increase in VO_2 until approximately 2 min after the attainment of an RER > 1.0 (Figure 2b) and the ventilatory threshold (Figure 2c), after which the oxygen deficit increased exponentially. Furthermore, this subject demonstrated a marked plateau in VO_2. Thus, near the end of an incremental exercise test to volitional exhaustion, the likelihood for a cardiovascular limitation to exercise competes with peripheral muscle fatigue induced by the increasing oxygen deficit. The peripheral fatigue could result from the potential combination of metabolic acidosis, an altered adenylate charge of the contracting muscle fibers, a decreased capacity to consume oxygen due to a greater involvement of fast twitch glycolytic motor units, or impaired excitation-contraction coupling. Furthermore, if any condition limits a person's ability to develop a large oxygen deficit during incremental exercise, they will not be able to sustain high intensity non-steady state exercise for long enough to exhibit a plateau in VO_2. Based on this data, the limitations to the VO_2 attained at the end of an incremental exercise test to volitional exhaustion will depend on the exercise protocol, the health and fitness status of the subject, and involve not just a high aerobic capacity but also a well developed anaerobic capacity.

Each of Noakes (2-4), Bassett and Howley (1), and Howley et al. (13) also commented that to remove the variability in VO_2 during small interval or breath-by-breath testing, data need to be averaged over at least 60 s to provide a true representative VO_2 value. However, this approach is intuitively wrong. Any averaging

function applied to VO_2, when VO_2 is changing from a linear to curvilinear response, will make the VO_2 change more linear (Figure 3a-d). This is especially true when the non-linear component of the VO_2-intensity curve may be confined to the last 1 to 3 min of the test.

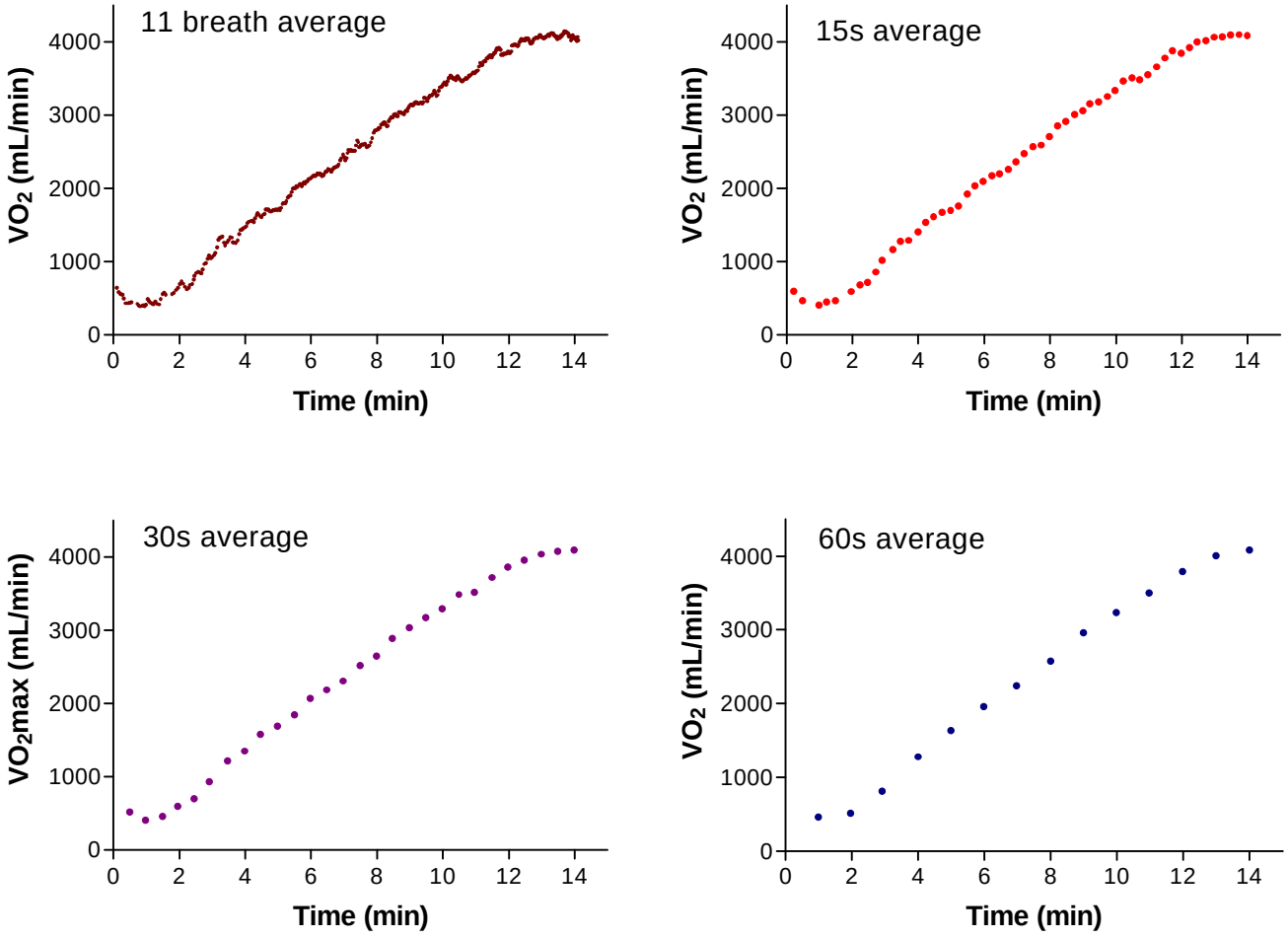

Figure 3: The same data for a given subject presented as 4 different average functions. The shorter the averaging function, the greater the ability to visually and computationally detect a VO_2 plateau.

Breath-by-breath VO_2 data, when appropriately smoothed to account for discrepant breaths, is theoretically the most sensitive method to detect a plateau phenomenon. In fact, when reviewing our data set from tests involving the determination of VO_2max from breath-by-breath methods (Medical Graphics Corporation, CPX-D, St. Paul, Minnesota) (n=37) incorporating treadmill and cycle ergometer protocols (Table 1), the proportion of tests conducted that demonstrate a true plateau (delta VO_2 increase ≤50 mL/min for VO_2max and the neighboring data point) in healthy, moderately to highly trained individuals is 86.5, 75.7, 56.8 and 11.1 % for 11 breath, 15 s, 30 s and 60 s data averaging, respectively. When the plateau criteria of Taylor et al. (17) were used (<150 mL/min increase in VO_2 during the last minute) the proportion of tests that demonstrated a plateau were 100, 100, 94.6 and 54 % for 11 breath, 15 s, 30 s and 60 s data averaging, respectively.

Table 1: Details of the changing VO_2-Power slope during incremental exercise, and the influence of the duration of time averaging on VO_2max.

	*VO_2max** (mL/kg/min)	*VO_2 Slope* (20-60%)	*VO_2 Slope* (90-100%)	*DVO_2* (last 60s)[g]	*DVO_2* (last 30s)[g]	*DVO_2* (last 15s)[g]	*DVO_2* (11 breath)[g]	*Plateau*[¶]
1.	44.7[C]	163.3	159.0	140.3	87.3	62.0	20.1	✓
2.	48.4[C]	166.6	175.8	189.8	81.3	13.3	3.6	✓
3.	32.2[T]	161.4	13.0	63.5	30.0	74.9	0.2	✓
4.	64.7[C]	401.5	161.8	196.6	30.0	46.4	56.9	✗
5.	55.0[C]	258.5	152.1	239.3	60.9	83.7	10.4	✓
6.	54.2[C]	220.1	67.94	245.4	79.9	25.9	115.5	✗
7.	48.1[T]	327.9	70.21	58.6	11.2	33.3	1.2	✓
8.	51.5[T]	405.3	47.74	118.4	10.0	71.2	57.9	✗
9.	47.8[C]	320.7	110.2	83.2	9.6	8.8	2.3	✓
10.	47.6[C]	171.2	127.8	132.4	84.3	66.2	14.4	✓
11.	40.0[T]	259.9	49.57	13.3	40.3	34.0	12.4	✓
12.	49.2[T]	181.8	186.3	207.5	84.1	23.8	45.2	✓
13.	55.8[T]	297.8	110.6	161.4	59.6	9.2	2.7	✓
14.	51.6[T]	169.6	139.5	177.9	47.5	37.3	0.3	✓
15.	40.2[T]	251.2	75.41	107.1	1.0	35.5	51.4	✗
16.	42.0[T]	309.7	62.33	62.0	6.7	7.8	1.9	✓
17.	41.9[C]	219.5	45.35	62.2	10.5	7.8	0.9	✓
18.	54.7[C]	193.6	226.1	173.7	8.2	23.5	26.5	✓
19.	52.4[T]	330.5	98.84	165.8	18.3	45.1	5.0	✓
20.	31.2[T]	212.3	72.64	85.9	7.8	22.4	10.9	✓
21.	50.1[T]	150.7	64.0	65.5	20.8	9.6	0.6	✓
22.	47.8[C]	296.5	89.61	79.8	27.8	17.6	12.5	✓
23.	28.4[C]	224.8	74.76	265.0	59.5	111.5	53.9	✗
24.	44.6[C]	161.1	334.0	188.7	155.9	79.7	26.2	✓
25.	37.7[C]	163.9	119.1	216.6	113.2	22.7	34.2	✓
26.	54.5[C]	172.1	90.67	71.5	106.4	75.4	22.6	✓
27.	45.9[C]	164.3	120.9	161.9	86.4	30.4	27.9	✓
28.	36.7[C]	375.2	176.1	228.3	40.1	38.5	8.5	✓
29.	38.0[C]	196.3	84.4	221.4	94.6	36.6	14.4	✓
30.	39.2[C]	188.4	92.16	104.2	28.7	16.1	32.0	✓
31.	44.3[T]	218.8	249.5	200.4	167.8	48.5	25.1	✓
32.	50.6[T]	276.8	54.73	48.0	9.3	14.6	27.2	✓
33.	46.1[T]	298.6	95.65	92.2	50.2	59.6	5.3	✓
34.	50.4[C]	1440	108.1	97.0	24.8	46.4	8.1	✓
35.	38.8[C]	261.9	79.7	57.6	22.6	14.2	2.4	✓
36.	53.2[T]	428.1	58.21	2.2	39.9	3.3	10.2	✓
37.	46.0[C]	226.4	202.1	220.5	150.0	18.4	24.8	✓
Incidence (%)								86.5
Mean ± SD		277.3 ± 211.3	113.9 ± 66.1	135.3 ± 71.7	53.7 ± 44.6[χ]	37.2 ± 26.3[χ]	21.2 ± 23.3[χφ]	

* from an 11 breath average ; [g] for VO_2max and the closest neighboring data point of the respective averaging interval ; [C] = cycle ergometry ; [T] = treadmill ; [χ] significantly different 60s ; [φ] significantly different 30s ; [∂] Based on ΔVO_2 ≤50 mL/min for VO_2max and closest neighboring data point.

Based on the data of Table 1 and Figures 2 and 3, differences in the time averaging used during data collection and the criteria used for accepting a VO_2max value both influence the ability to detect a VO_2 plateau. If VO_2 data are averaged in 30s or 60s intervals during an incremental exercise test, most subjects will not have sufficient time at near VO_2max intensities to establish a VO_2 plateau. For example, minute averaged data would require that subjects maintain exercise for between two to three minutes at metabolic intensities at and above VO_2max to demonstrate a VO_2 plateau. This is difficult and perhaps impossible for most people to accomplish during an incremental exercise test, no matter what their level of training. Furthermore, if the subject from the data in Figure 3 ended the test more than 30 s earlier, a VO_2 plateau would have only been detected by the 15s and 11 breath averaged data.

An additional implication of a large time average is that it will underestimate the true VO_2max. Figure 4 is based on the data of Table 1 and presents the VO_2max that results from each of the time average conditions. All means are significantly different from each other, with the smaller time average interval yielding larger values for VO_2max. These differences are not just based on added "noise" in the data, for as shown by the mean data of the delta VO_2 values of Table 1 and Figure 5, the smaller time averaging interval was associated with less variability in neighboring values at VO_2max.

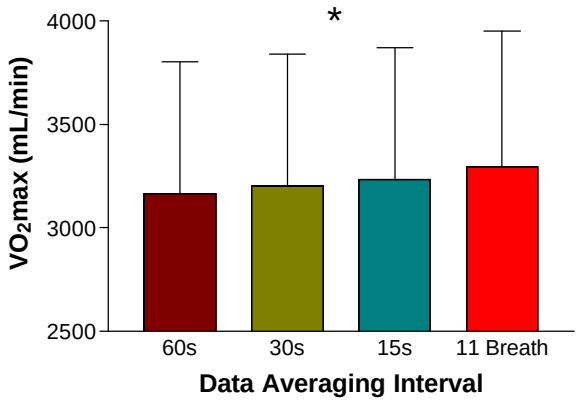

Figure 4: The mean±SD VO_2max values for the data set presented in Table 1. All means are significantly different (*=p<0.01) from each other using the Tukey HSD test.

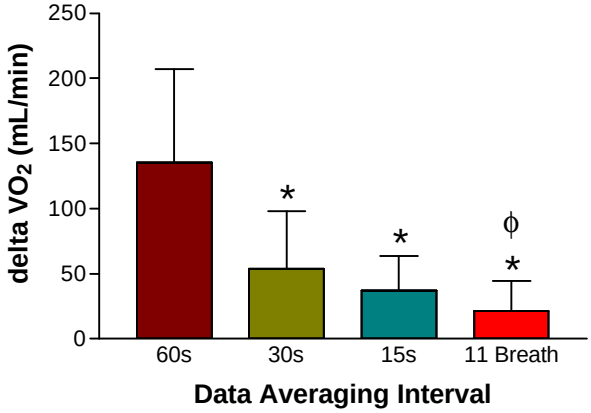

Figure 5: The mean±SD deltaVO_2 values for VO_2max and the closest neighboring data point for the data set presented in Table 1. * = significantly (p<0.01) different from 60s averaging ; $^{\phi}$ = significantly (p<0.01) different from 30s averaging.

These findings are in direct opposition to the theoretical arguments against small time interval averaging raised by Noakes (2-4) and Howley et al. (13). Based on these facts, the following comment by Noakes (2) can be viewed to be unrealistic and probably impossible; "*It would seem that the minimal criteria for identifying a true plateau phenomenon would be a failure of oxygen consumption to rise during exercise of increasing intensity lasting at least 5 min or during interrupted testing in which the maximum workloads are sustained for at least 3 to 5 min.*" Similarly, the following recommendation of Howley et al. (13) is equally misleading, "*It is preferable to use collection periods of 60s, or if that is not feasible, to average at least two consecutive* [30s] *values. If this is not done, it is possible to introduce errors of 200 ml·min^{-1} or greater in maximal exercise, and most will overestimate the actual value*". There is obviously a bias in why Howley et al. (13) view the "actual value" to be that from a one minute average. In addition, they totally overlook the likelihood that such an approach will artificially lower VO_2max in most subjects.

Perhaps the problem with the VO_2 plateau criteria is not that it cannot be identified in all subjects, but that it was raised by Hill and Lupton (15) in the first place. Hill and Lupton chose to focus on a plateau because it was a visual method that was easy (not necessarily correct) to apply to their data as a reflection of a limitation. As Noakes (2-4) correctly identified, Hill and Lupton did not follow their interpretations through with additional research to verify that VO_2 did plateau with further increases in exercise intensity, or that the limitation to continued increases in VO_2 was the cardiorespiratory capacity. However, the reality of the issue here is that Hill and Lupton did not have the instrumentation to truly show a VO_2 plateau during continuous incremental exercise, and interpretations and criticisms of their data need to be cognizant of this fact. Hill and Lupton tried to explain their data with the concept of a VO_2 plateau, and although this approach has questionable scientific merit due to the constraints imposed by their methodology, their greatest hallmark was their ability to rationalize the concept of a VO_2 plateau. Noakes chose to focus on the inadequate methodology of Hill and Lupton to discredit the generally accepted cardiorespiratory limitation to VO_2max. An alternative strategy is to

recognize the methodological flaws of the earlier research and conclude that intermittent protocols and relatively large time averaged (30s to 60s) data procedures are too insensitive to detect a VO_2 plateau that does occur in most individuals at the end of continuous incremental exercise to volitional exhaustion.

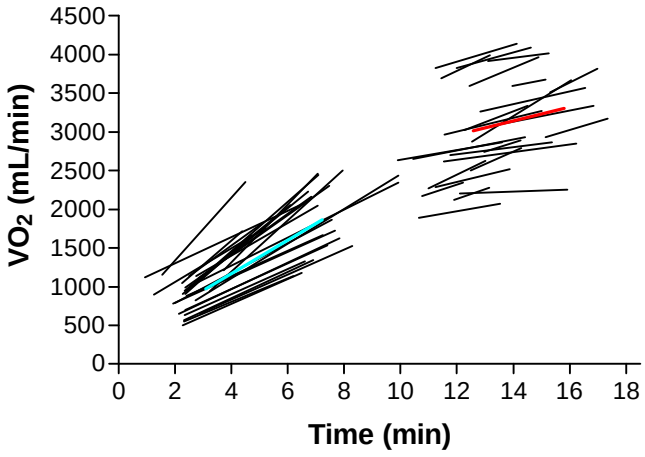

Figure 6: The linear regression lines of best fit for the 20 to 60% VO_2max and 90% to 100% VO_2max data sets of Table 1. The colored lines within each data set represent the mean slope, and clearly show the significant decrease in the VO_2-time slope that occurs in most individuals during incremental exercise to VO_2max (treadmill and cycle ergometry protocols).

For the 37 subjects from our lab that comprised the VO_2max data set (Table 1), the slope for the data obtained during two segments of the test (25-60% VO_2max and 90-100% VO_2max) differed significantly. The visual depiction of these results is provided in Figure 6, which clearly shows the decrease in slope in the VO_2-time curve close to VO_2max. Two subjects that represent the extremes of this analysis are shown in Figure 7. This original data reveals that depending on the person there can be a change from linearity in the VO_2-time curve during incremental exercise testing, and that this change is depicted by a decreasing slope that continues to decrease as a curvilinear function to VO_2max. These results differ to those of Myers et al. (36,37), who demonstrated a repeated increase and decrease in the slope (determined from 30 eight breath average data points, repeated each successive breath) of the VO_2-time curve throughout a ramp exercise test to VO_2max. Added comment on the data of Myers et al. will be presented later in this section. Nevertheless, the data presented in this manuscript clearly reveals that, depending on the person, VO_2 does not increase linearly with an increase in power output during exercise, and that the start of a slope trend towards a plateau is detected with breath-by-breath data several minutes prior to volitional fatigue.

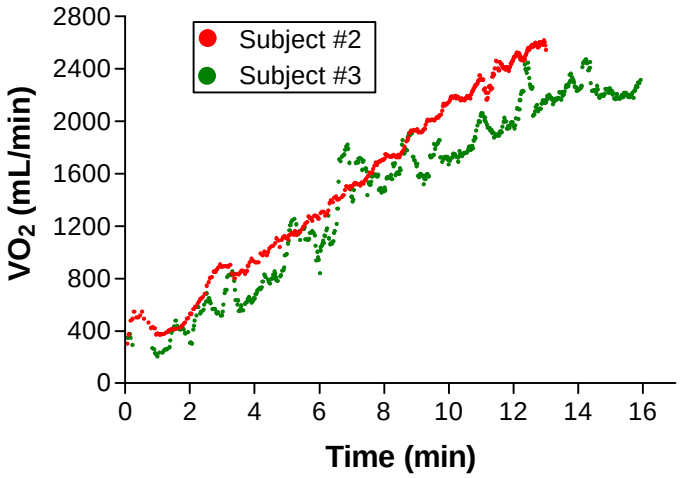

Figure 7: Representative data for subjects 2 and 3 from Table 1. As reported in Table 1, subject 2 had a similar VO_2-time slope throughout the test. However, subject 3 had a significant decrease in the VO_2-time slope that can be visualized to commence after 8 min of the incremental protocol.

Ironically, the non-linear increase in VO_2 during exercise to VO_2max has been shown in earlier research of VO_2max (24), and was recognized by Noakes (2). Nevertheless, the implications of this profile have been largely ignored within exercise physiology. This oversight is unfortunate as such a fundamental observation adds to the physiological interpretations of an exercise test to VO_2max, and can be explained by sound applications of biochemistry and motor unit recruitment. For example, once the lactate threshold (LT) is reached and there is an increase in anaerobic metabolism, there is obviously a smaller increase in VO_2 for a given increase in power output (Figure 8a, b and c). The more the exercise intensity increases beyond the LT, the greater the anaerobic component of the test, and the slope of the VO_2-time curve must decrease. This reduction in VO_2 slope is not caused by an oxygen delivery limitation, but by the increase in fast twitch motor unit recruitment (38-41). In addition, skeletal muscle must incur an oxygen deficit to

increase rates of mitochondrial respiration (of any motor unit type) from increased cytosolic concentrations of ADP, Pi, and NADH (42). An attractive hypothesis would be that the greater the muscle mitochondrial density (endurance trained, or large type I motor unit proportion) the later in a protocol to VO_2max that a decrease in the slope of the VO_2-time curve would occur. Added discussion of the physiological implications of the change in the VO_2-time curve occurs within the section on edifice #2.

In summary, the concept of a VO_2 plateau at VO_2max is a real phenomenon that has been inconsistently reported due to time averaging constraints imposed by methodologies used in past research. Unfortunately, despite more than 75 years of research since the pioneering studies of Hill and Lupton (15), there is still no uniformity in criteria used to verify VO_2max, and insufficient evidence for how one or a combination of variables are valid for use as verification criteria (13). It is likely that such criteria may be different for time averaging vs. breath-by-breath methodologies due to the greater temporal sensitivity of the breath-by-breath methodology. Clearly, recommendations are needed for the combination of the exercise protocol and method of data acquisition and presentation that is most conducive to *causing* and *detecting* a plateau in VO_2. For instances when a plateau in VO_2 is not detected, criteria are needed that verify that the peakVO_2 is sufficiently similar to the peak VO_2 attained in a plateau (VO_2max). These inadequacies of the measurement of VO_2max are unfortunate, as the error of the method in VO_2max measurement (≥3%) (13) can result in peak VO_2 values that occur without a plateau to be similar to what could be a true VO_2max (with a VO_2 plateau) (Figure 3).

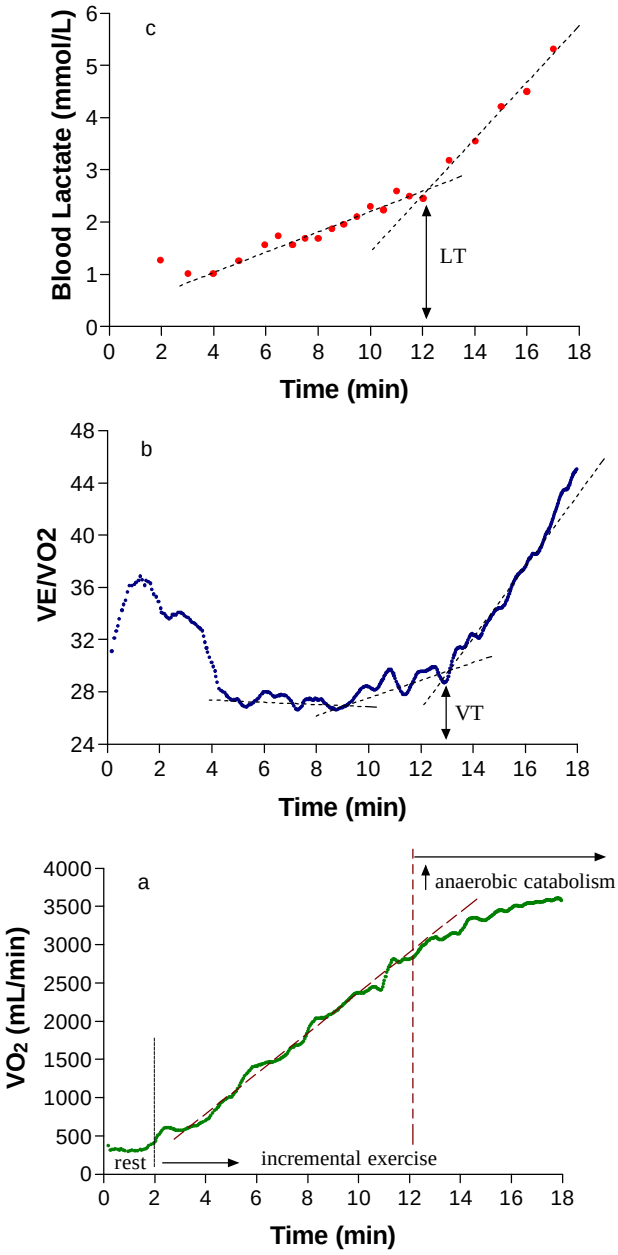

Figure 8: Data from subject 23 of Table 1 that presents (a) VO_2, (b) the ventilatory equivalent for oxygen (VE/VO_2), and (c) blood lactate responses to incremental exercise. The increasing anaerobic catabolism that occurs after the lactate threshold (LT) coincides with a decrease in the VO_2-time slope. In addition, a clear VO_2 plateau is apparent.

Specific Responses to Noakes' Arguments Against a VO_2 Plateau

Based on the previous explanations of the VO_2 plateau phenomenon, what were Noakes' key explanations for why a plateau is physiologically irrelevant? Specific responses to Noakes' explanations are needed to reveal and explain which are valid and which are invalid. As best as I could understand, Noakes' used two arguments to refute the VO_2 plateau/VO_2max concept; 1) it was originally based on flawed research methodologies and interpretations, and 2) it does not occur in all individuals, and is not a reliable physiological marker for maximal effort.

1. The poor research base of the VO_2 plateau and VO_2max concept

In the preceding sections I have provided thorough explanations for why this argument is correct for a 1 min averaging duration. However, based on the data presented in Table 1 and Figures 4-7, shorter duration data averaging results in a significantly higher incidence of a VO_2 plateau at VO_2max. Consequently, the previously

reported low incidence of a VO_2 plateau using 1 minute data averaging does not discredit the concept or refute the occurrence of a VO_2 plateau at VO_2max. The key argument of Noakes that requires clarification is the one that follows.

2. A VO_2 plateau is not a reliable physiological marker for maximal effort

Noakes based this argument almost solely on the results of Myers et al. (36,37), which he described as, "[the only study that] *has attempted to directly determine whether oxygen consumption during progressive, ramp exercise reaches a maximum*" (3). Obviously, the study methodology and results of Myers et al. need to be evaluated with equal scrutiny that Noakes has applied to research that accepted the VO_2 plateau concept. The key study of Myers was that published in 1990 (37).

Myers et al. (37) used breath-by-breath indirect calorimetry during each of steady state treadmill exercise (52% VO_2max) (n=10) and a treadmill ramp protocol (n=6) to determine the variability in VO_2. All VO_2 data were initially smoothed as repeated 8 breath averages. In addition, steady state data were averaged an additional 9 ways to determined the method with least variability. For the steady state data, the breath-by-breath methodology was shown to be the most variable with a standard deviation of 4.5 mL/kg/min, with almost linear reductions in variability as the sampling interval was increased to 60s averages with a standard deviation of 0.8 mL/kg/min. For the ramp protocol data, VO_2-time slopes were determined on 30 consecutive 8 breath average data points, with this procedure repeated for each successive data point. Myers et al. also showed that the inherent variability in breath-by-breath data, even when 8 breath averaged, causes repeated increases and decreases in the slope of VO_2-time data throughout the protocol, and that there was no evidence of a zero slope attained at or near VO_2max. Myers et al. concluded that, "*considerable variability in the slope of the change in VO_2 occurs with a constant change in external work, regardless of the sampling interval used, suggesting that the plateau concept needs to be reevaluated*".

There are subtle assumptions underlying both Myers' and Noakes' interpretations of this data. First of all, when concerned with the steady state data, how should the variability in VO_2 from different collection procedures be interpreted? If it is assumed that the more linear depiction with less variability is best, then obviously the minute averaging approach makes sense and should be used. However, what is the rationale for being biased to choosing one minute averaging and data presentation that has less variability? I would argue that because our predecessors used one minute averaging, more from methodological constraints than anything else, we are somewhat biased to use the same. After all, a less variable data presentation looks nice, and is consistent with a model that simplifies the body's VO_2 to a more linear function. However, is this a valid mind-set to have when measuring and interpreting changes in VO_2 during incremental exercise? Conversely, does breath-by-breath data show true physiological variability? I would argue that it does, and in fact, Myers' (37) own steady state data, when used in a multiple regression model to account for this variability, showed that a model including ventilation rate, tidal volume and metabolic intensity accounted for 95% of the variance in steady state VO_2. Clearly, the variability in VO_2 from breath-by-breath methodology is related to physiological causes, and this fact needs to be considered in any attempt to average data causing less variability. There becomes a point in time when averaging causes the "real" physiological sensitivity of data to be lost. I think this point was made very clearly in preceding sections on the decreased sensitivity of detecting a VO_2 plateau when using time averaged data. As such, less variability is not necessarily more accurate, and in fact can mask what may be important physiological responses to steady state and incremental exercise.

The second issue raised by Noakes using the data of Myers et al. (37) is that the variability in VO_2-time slopes from 30 successive 8 breath averages makes the concept of a VO_2 plateau solely at VO_2max a mute point. For example, if a VO_2 plateau (slope not significantly different from zero) occurs in repeated intervals throughout an incremental exercise test, and there is no consistent finding of a plateau at VO_2max, then how can a VO_2 plateau be a valid criteria in documenting VO_2max? The first impression when assessing the data of Myers et al. is that Myers and Noakes have very good arguments. However, at closer inspection of the data, it becomes apparent that the data can be interpreted with completely opposite meaning depending on the biases you have in

the concept of a VO_2 plateau and how you interpret breath-by-breath data. For example, a presentation of changing VO_2-time slopes during a VO_2max test with breath-by-breath data collection will reveal changes in slopes repeatedly throughout the test. However, such changes do not, by themselves, invalidate the development of a VO_2 plateau. This is because it is difficult, if not impossible, to interpret the VO_2-time slope data without evidence of the change in absolute VO_2 that is occurring during the exercise protocol.

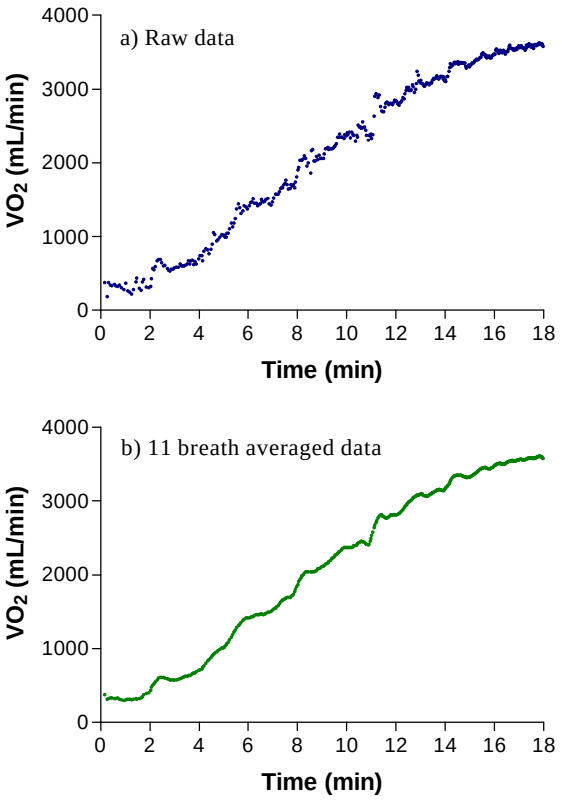

Figure 9: A representative data set from one subject that compares (a) breath-by-breath data to (b) 11 breath smoothed data. For this subject, there was minimal breath-by-breath variability in VO_2, and the data clearly reveals that not all subjects have high variability in physiological responses during this method of indirect calorimetry.

Interpretation of the data in figures 2-8 of Myers et al. is further compromised by the presentation of data during only the last 3-6 min of the respective tests. I would argue that many of these figures reveal data that support a VO_2 plateau (Figures 2, 3, 5, 6, 8 from Myers et al., 1990), as slope data are either decreasing towards zero, or have already distributed themselves close to or equally around the true plateau line (slope=0) (Figures 2, 3, 6 from Myers et al., 1990). Furthermore, if the initial data (all > 8 min) of Figure 3, 4, 5 and 7 (from Myers et al., 1990) were presented, then the presence of VO_2-time slope data above zero in the range of values presented may have more clearly illustrated trends for or against a plateau during the final minutes of each test. This fact is highlighted in the data of subject #3 of Figure 7, who also shows considerably large variability in VO_2, yet the total test reveals a trend for an exponential VO_2-time curve, with a plateau at the end of the test.

Finally, comment needs to be directed at the extreme variability in the data of Myers et al. (37). The maximal VO_2-time slope values for the eight breath averaged data of Myers et al. approximated 20 mL/kg/min, which calculates to be a rate of increase in VO_2 approximating 1.5 L/min for a 75 kg person. One must assume that the actual breath-by-breath data were more extreme! A rate of VO_2 increase of 1.5 L/min is difficult to comprehend when the estimated rate of VO_2 demand from their protocols averaged 292 mL/min. Furthermore, the data of Figure 9 show a) breath-by-breath and b) 11 breath smoothed data for another subject (Table 1, subject 35) from one of our research studies. The average rate of change in VO_2 for the protocol (25 W/min ramp cycle ergometry =290.6 mL/min) between minutes 5-10 was 260.7 mL/min, and the greatest rate of change in VO_2 for any 30 data point period of the raw (unaveraged) data was 380 mL/min. It is logical to conclude that perhaps the subjects of Myers et al. (37) were unfamiliar with breathing through a mouthpiece, or exercising on a treadmill, which combined to make their breathing patterns unrealistically variable. Scientists who routinely work with breath-by-breath indirect calorimetry data know that some subjects breath with more variability than others, which is reflected as increased "noise" of breath-by-breath VO_2 data (subject 3 of Figure 7). It is poor science to conclude that six subjects who show abnormal variability in breathing during an exercise protocol are representative of all people, and that the results invalidate a physiological construct that has been argued to exist in more than 70 years of previous research.

"Edifice"#2: VO_2max Is Limited By Maximal Cardiorespiratory Function and Capacities

Noakes (3) originally emphasized the need to develop models from which to test and solidify current research evidence. For example, Noakes quoted Steven Hawking, "*How can we know what is real, independent of a theory or model with which to interpret it?*" For physiology, the challenge is to obviously develop a model that is based on components that as accurately as possible resemble in vivo conditions. What have been the models exercise physiologists have and currently use to recognize and explain cardiovascular limitations to VO_2max? The answers to this question are fundamental to understanding the emergence of the oxygen delivery limitation interpretation to VO_2max, and the validity and invalidity of many of Noakes' criticisms. As with edifice #1, a specific assessment of Noakes' criticisms will be presented at the end of this section.

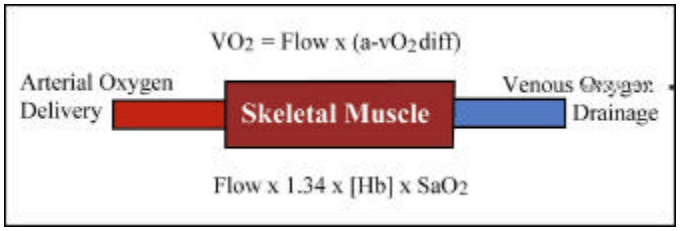

Figure 10: The traditional model used to explain limitations to VO_2max. The model is based on the Fick equation, portrays skeletal muscle as a "black box", and has two main components – oxygen delivery, and oxygen extraction.

Figures 10-12 present models that have been used to identify the importance of key features that can influence VO_2max. The first model (Figure 10) has been used for decades in exercise physiology, and has correctly been referred to as the Fick model. The Fick model assumes that no limitation exists in central cardiopulmonary function, and that the only variables of importance to VO_2 are arterial blood oxygen content (CaO_2), blood flow, and oxygen extraction by muscle measured as the arterial – venous oxygen difference (a-$vO_2\Delta$). The Fick model assumes that contracting skeletal muscle is a "black box" that has homogenous metabolic demand and oxygen delivery features. In addition, as venous drainage from contracting skeletal muscle at VO_2max was originally shown to still retain a small amount of oxygen, this evidence was first used to reflect the peripheral limitation (inability to extract oxygen) to VO_2max. This is obviously a simple model. However, even today, as evidenced by the Noakes (2-4) and Bassett and Howley (1) publications, there is debate on the contributions of peripheral oxygen extraction and central cardiopulmonary function and capacities to the limitations to VO_2max.

The second model (Figure 11) is modified based on the original findings of Dempsey (43,44) where some individuals experience a worsening hypoxemia during exercise close to VO_2max, thereby lowering CaO_2 and total circulatory oxygen delivery. However, the assumptions of the "black box" approach to oxygen delivery within skeletal muscle are retained.

The third model (Figure 12) has been promoted by Wagner (45,46), Rowell (47), Ferretti (48) and di Prampero (49), and includes central and peripheral cardiovascular capacity limitations as well as peripheral oxygen diffusion limitation in the flux of oxygen from blood to skeletal muscle. However, as with the models of Figures 10 and 11, skeletal muscle remains a "black box". Although this model is arguably the most accepted in application to the limitations to VO_2max, with more recognized validity during hypoxia (50,51), the "black box" assumption of skeletal muscle function during exercise at VO_2max remains a major weakness. Such models that treat skeletal muscle as a "black box" intuitively lend support to the oxygen delivery

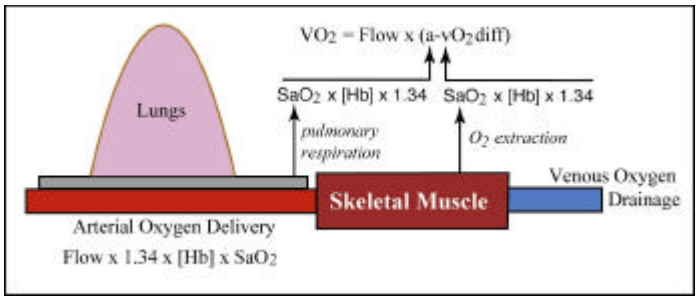

Figure 11: The first research based modification to the Fick model of VO_2max. Here, the work of Dempsey (42) and others (43) resulted in the need to alter oxygen delivery due to the evidence for a sea level hypoxemia at VO_2max in some subjects.

limitations to VO_2max, as no other intramuscular components exist in the model. Thus**, herein lies the cause of the popularity or widespread acceptance of the cardiorespiratory explanations for the limitations to VO_2max; no past or current model allows any intramuscular component to be considered a limiting factor**!

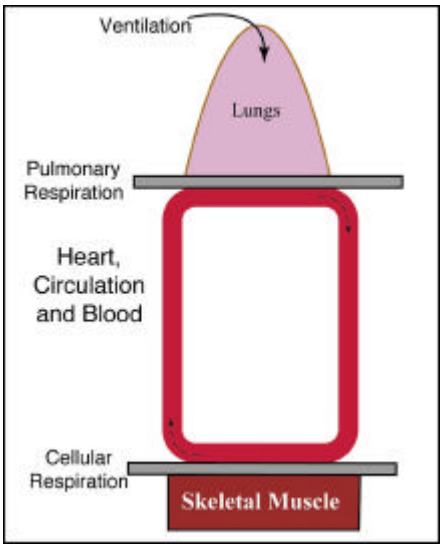

Figure 12: A model proposed by Wagner (1996) that also adds peripheral oxygen diffusion to the list of potential factors that influence VO_2max. However, as with prior models, skeletal muscle remains a "black box".

Wagner has recognized the weakness of the "black box" approach for modelling intramuscular factors that contribue to VO_2max, yet because of methodological limitations to measuring actual intramuscular blood flow, tissue oxygenation, tissue oxygen demand conditions, and oxygen provision/tissue demand relationships, he has argued that it is difficult to adopt an alternate model of oxygen demand and extraction by contracting skeletal muscle (50,51). This is a reasonable approach to take, yet the identification of the limitations of the "black box" model of muscle oxygen demand during exercise provides a useful focus on the possible complications of understanding what limits VO_2max and therefore what causes a VO_2 plateau at VO_2max.

Figure 13 includes the research proven factors that are involved in tissue oxygen consumption that are precluded with the "black box" model of muscle oxygen consumption. During incremental exercise there is an increase in fast twitch motor unit recruitment, which in turn causes an increasing heterogeneity (increasing anaerobic bias) in the metabolic characteristics of the muscle fibers used to sustain the exercise intensity (38-41). In addition, as the force generation of single muscle contractions increase there is an increasing temporal inhomogeneity in blood flow to the working skeletal muscle (52). Taken together, these two events must also increase the mismatch in oxygen supply and demand within the contracting muscle, thereby raising or dampening the decreases in the oxygen content of venous blood draining the muscle

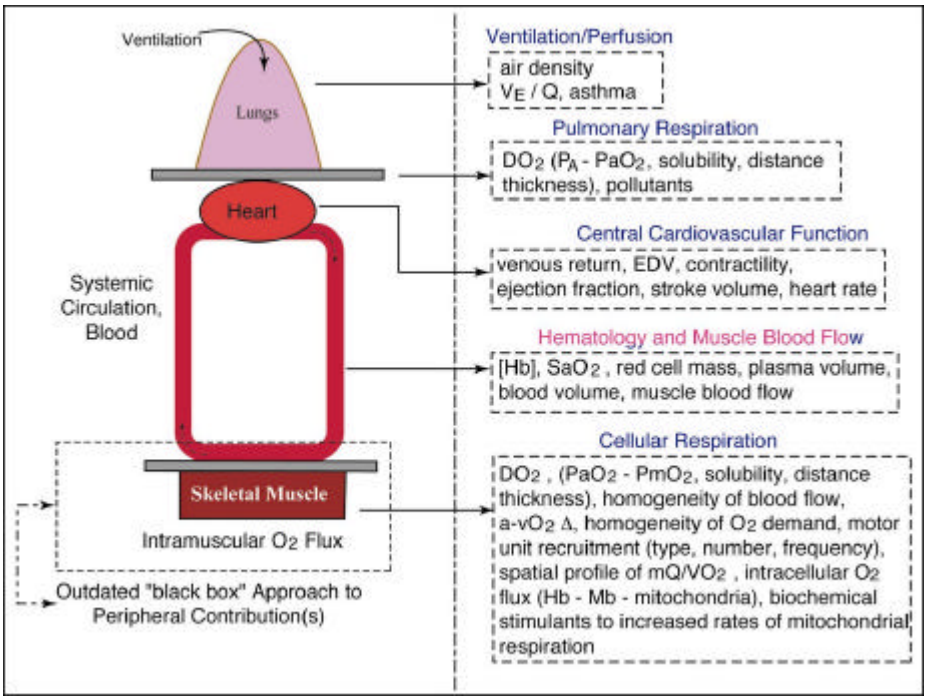

Figure 13: A more research-based model of the oxygen associated determinants of VO_2max in humans. The main difference with this model compared to previous versions is the representation of skeletal muscle as a conglomerate of independent factors that can alter the capacity for cellular, muscle and whole body VO_2.

mass. Consequently, the presence of oxygen in venous blood draining skeletal muscle at exercise intensities approaching VO_2max can be explained by a number of conditions, and should not be interpreted as a simple reflection of excess oxygen delivery and the presence of adequate muscle oxygenation.

Figure 13 also groups the determinants of given physiological capacities involved in the consumption of oxygen. Traditionally exercise and pure physiologists have used the term "oxygen delivery" without providing a definition. Based on the content of Figure 13, if oxygen delivery is defined as the acquisition and transport of oxygen into skeletal muscle where it is available for mitochondrial respiration, oxygen delivery is dependent on each of ventilation, pulmonary perfusion, pulmonary respiration, central cardiovascular function, blood hematology, systemic blood flow redistribution, muscle blood flow, oxygen diffusion into cells, and cellular oxygen diffusion kinetics. The importance of the latter components has been well modeled by Severinghaus (53). It seems appropriate to recommend that physiologists not use the generic term of "oxygen delivery" in relation to interventions that alter muscle or whole body VO_2, but define the components they are referring to within the total oxygen delivery cascade and use these more specific terms of reference.

Despite the use and acceptance of the first three models (Figures 10-12) of cardiovascular and pulmonary limitations to VO_2max, Noakes (4) specifically challenged Bassett and Howley (1) "… *to contest the refutations to the cardiovascular/anaerobic model that I presented, not to ignore these and instead rehash conventional arguments that 'prove' the traditional model* ..." This challenge was a little late, as it came within Noakes' rebuttal to the response of Bassett and Howley to Noakes' prior publications (2,3). Nevertheless, I have recognized this challenge. Based on the previous presentation of research models used to explain the determinants of VO_2max, arguments against Noakes' should not be based on models 1, 2 or 3 (Figure 10-12), but on the scientific evidence that negates his alternate explanations when considering the multifaceted presentation of model 4 (Figure 13). In particular, attention needs to be given to the research that has focused on the intramuscular diffusion of oxygen at VO_2max.

I am surprised that neither of Noakes (2-4) nor Bassett and Howley (1) elaborated on the research and theoretical models of Wagner et al. (45,46,50,51), or cited the findings of additional human and animal research that has revealed the importance of peripheral (interstitial and intracellular) oxygen diffusion as a determinant of VO_2max (54-65). I find these omissions and the oversight of the importance such research has had on the improved understanding of the determinants to VO_2max to be very surprising. For example, use of animal hindlimb preparations has shown that raising the partial pressure gradient for oxygen diffusion into contracting skeletal muscle without altering oxygen delivery (Flow x CaO_2) increases O_2 extraction and VO_2max (54,58). Similarly, hyperoxia increases VO_2max in this model despite peak blood flow values during normoxia that far exceed those reported in humans during larger multiple muscle group exercise (60). Conversely, reducing the partial pressure gradient for peripheral oxygen diffusion, while maintaining flow and circulatory oxygen delivery, lowers VO_2max (55). These findings are supported by human subjects research where hyperoxia is accompanied by reductions in maximal blood flow to contracting muscle, such that cardiovascular oxygen delivery is normalized (66). However, hyperoxia still causes a significant increase in VO_2max, which must be due to a greater net a-v$O_2\Delta$ caused by the improved diffusion of oxygen based on a much larger partial pressure gradient. Collectively, in both animal and human subject research, experimental evidence supports the existence of a peripheral O_2 diffusion limitation to VO_2max during normoxia that is independent of circulatory oxygen delivery and blood flow.

An understanding of the importance of oxygen supply to contracting skeletal muscle in humans has developed from comparisons of whole body to regional body exercise models. For example, exercise confined to the human quadriceps (2.5 kg) has been shown to cause the largest reported blood flow to contracting muscle (240 mL/min/100 g) (57,59,60), with these rates exceeding the theoretical maximal capacity of the cardiovascular system to increase muscle blood flow during large muscle mass exercise (~140 mL/min/100 g for Q = 35 L/min, muscle blood flow = 0.8 x Q, muscle mass = 20 kg) (47). Despite these conditions, VO_2max during

knee-extension exercise still increases during hyperoxia (59), which has been interpreted as evidence that skeletal muscle mitochondrial capacities during large muscle mass exercise must far exceed that at VO_2max. These findings are similar to the studies used by Bassett and Howley (1) to support an oxygen supply limitation to VO_2max, which included combined arm and leg exercise (67,68), hypoxemia at both sea level and during hypoxia (43,44,69-71), and cross-sectional studies comparing endurance trained and untrained individuals (47). In addition to this body of knowledge can be added the increased VO_2max resulting from plasma volume expansion (72) and erythrocythemia (73-76). However, such interpretations from these prior research studies are based on models 1-3 of Figures 10-12, for as previously explained, if a model is used that prevents further exploration of intramuscular factors that limit VO_2max, cardiovascular oxygen delivery limitation can be the only interpretation of the results. What is important to conceptualize is how the same data can be viewed using the components of model 4 (Figure 13).

Table 2 lists the physiological changes that occur during incremental exercise to VO_2max. Research-based support for the consequences of the physiological changes are provided, as well as inferred interpretations that, although yet to be proven by research due to methodological limitations, offer logical consequences that have importance to model 4 (Figure 13).

Table 2: The physiological and muscle biochemical characteristics that occur in the minutes prior to VO_2max.

Physiological Alteration	*Research-Based Consequence*	*Inferred Consequence*
- Fast Twitch Motor Unit Recruitment	*¯ Slope of VO_2-Time curve*	*- Mismatch in O_2 Supply-Demand* *- Heterogeneity of O_2- Demand* *¯ Rate of Increase in O_2 Extraction* *¯ Rate of Decrease in vO_2*
- Force and Frequency of Muscle Contraction	*- Heterogeneity of Blood Flow* *- temporal* *- spatial*	*¯ Rate of Increase in O_2 Extraction* *¯ Rate of Decrease in vO_2*
- Oxygen Deficit	*- Acidosis* *- ADP, - Pi, - NADH + H^+* *- Stimulation of Mitochondrial Respiration* *Developing Muscle Fatigue*	
¯ Intramuscular PO_2		*Impaired Cellular Diffusion of O_2* *Mismatch in O_2 Supply-Demand*
- Cardiac Output to Near Maximal	*- O_2 Circulatory Delivery*	
- Ventilation	*Improved Pulmonary Ventilation/Perfusion*	
Compromised Pulmonary Function	*- A-aPO_2D* *¯ SaO_2 and CaO_2*	*Mild Edema*

During incremental exercise an increasing fast twitch motor unit recruitment and increasing force and frequency of muscle contractions are important as they indicate altered muscle function during the progression from mild exercise to intensities approaching that at VO_2max. As indicated, both events would constrain the continued increasing rate at which skeletal muscle can consume oxygen, even in the presence of adequate oxygenation. Regardless of the oxygen supply to contracting skeletal muscle, the slope of the VO_2-power curve will decrease with an increase in fast twitch motor unit recruitment (Figures 8 and 14). This response is due to the relatively lower mitochondrial mass of fast twitch muscle. An increased recruitment of fast twitch motor units will cause an inevitable increase in the proportion of total muscle ATP hydrolysis that occurs from non-mitochondrial

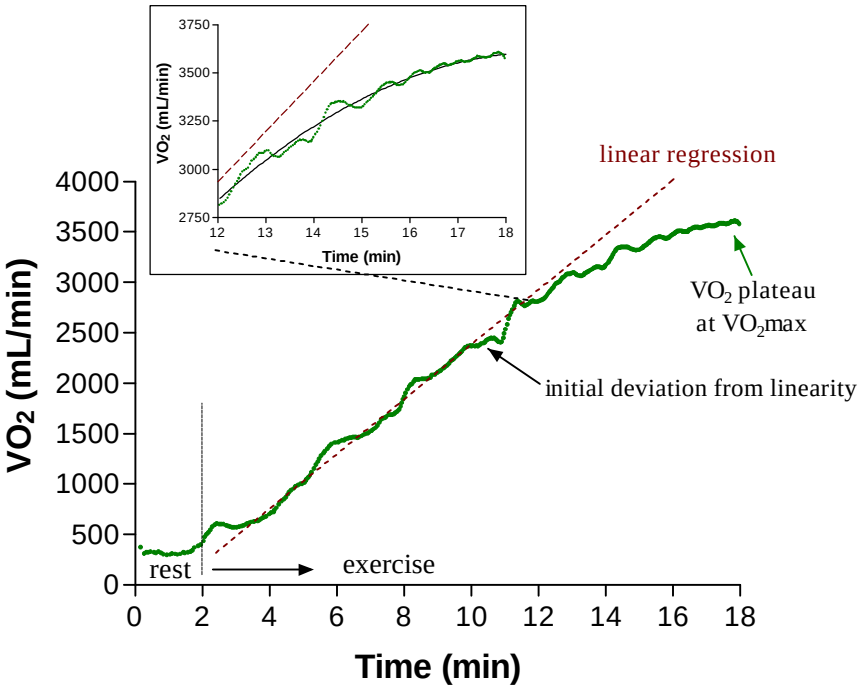

Figure 14: Data from subject 23 of Table 1, and also Figure 9. The change in the VO_2-time slope is seen as a deviation from linearity after approximately 11 minutes. Data from the final 6 minutes of the test are presented in the insert figure and is fit with a nonlinear regression model. This individual data, along with individual and mean data of Table 1 and Figures 2-8 reveal the nonlinearity of the VO_2-time curve during continuous incremental exercise testing to VO_2max.

sources. The net result is a reduced rate of VO_2 increase for a given increase in power output. Noakes identified this response in his original 1988 manuscript (2), but did not address this important concept in the later papers (3,4).

The increasing recruitment of fast twitch motor units is clearly revealed in the data of Lucia et al. (39) (Figure 15). Lucia measured the root mean squares of EMG (rmsEMG) signals during a cycle ergometer ramp (5 Watts/12 s) protocol and demonstrated 2 breakpoints in the EMG data, similar to the VT responses. Chwalbinska-Moneta et al. (38) reported similar findings that included significant nonlinear correlations between rmsEMG data, blood lactate and catecholamines. Additional results exist that support (40,41) and refute (77) a clear association between an EMG threshold and the blood or ventilation thresholds. However, there is agreement across several research laboratories for an increase in EMG activity after the LT, and that this activity partly reflects an increased recruitment of fast twitch motor units.

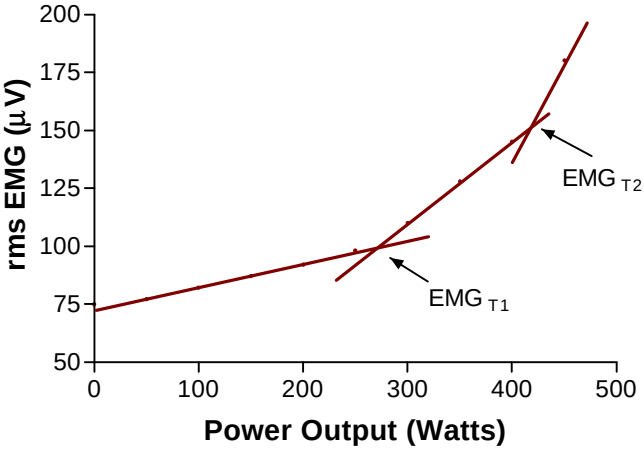

Figure 15: A redrawn figure from Lucia et al. (38) showing the change in rmsEMG activity and time during incremental exercise to VO_2max. A clear threshold pattern is shown for the EMG data, and it is tempting to associate this change with the decreased slope of the VO_2-time curve during the latter half of a test to VO_2max.

As power output increases during the last 5 min of an incremental exercise test to VO_2max, the slope of the VO_2–time curve either continues to decrease or remains linear until near the end of the test where data will plateau or cease without a plateau due to volitional exhaustion. The reasons for the individual variability in this pattern have yet to be explained by research, as discussed previously for edifice #1. However, based on prior discussion (edifice #1) that a VO_2 plateau will indeed occur in almost all healthy and moderately endurance trained people, what content of Table 2 could explain a continued decline in the rate of increase in VO_2 during these conditions?

During incremental exercise, each of an increase in the mismatch in the O_2 supply-demand relationship, an increase in the heterogeneity of O_2 demand, and an increase in the heterogeneity of O_2 supply (temporal and spatial) would reduce the ability of the working muscle to sustain a high rate of VO_2. To date, none of these factors has been included in any previously published model of the determinants to VO_2max, and as I have previously explained, this fact has been the real "straightjacket" that has constrained our understanding of VO_2max. For example, the measure of VO_2max is a rate variable. A plateau in this variable despite increasing exercise intensities can crudely be interpreted (Figures 10-12) as a balance between O_2 supply and demand across an entire working muscle mass. A decline in VO_2 would infer that O_2 supply is insufficient to meet demand across an entire working muscle mass. Within this scheme are multiple variables connected in series that could be potential limiting factors (ventilatory, pulmonary, cardiovascular) (Figure 13), as well as numerous entities within skeletal muscle that may or may not be the true limiting variables to VO_2max in the healthy to trained individual. The intramuscular issues pertinent to the cellular provision of oxygen to and within the mitochondria are illustrated in Figure 16. The implications of these variables to limitations to VO_2max will be incorporated into the responses to the arguments raised by Noakes.

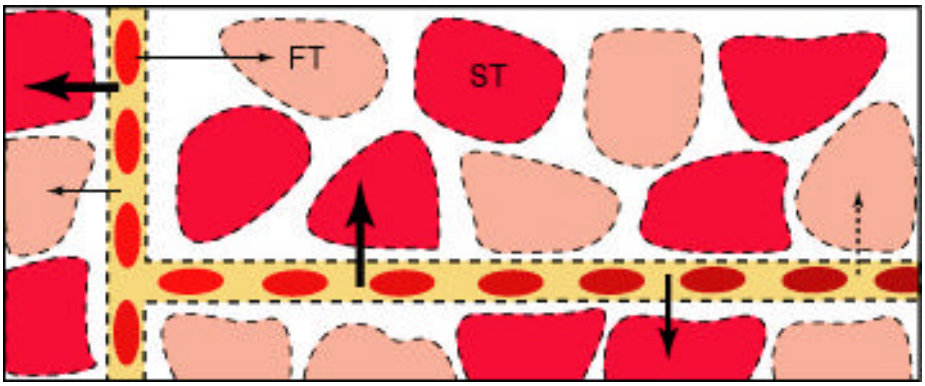

Figure 16: The intramuscular issues pertinent to the provision and consumption of oxygen by skeletal muscle at VO_2max. Note the differences in muscle fiber types and oxygen demand, diffusion distances, and decreased blood oxy-hemoglobin saturation near the distal regions of the capillaries.

Specific Responses to Noakes' Arguments Against a Cardiorespiratory Limitation to VO_2max

As best as I could understand, the collective arguments from the three manuscripts of Noakes (2-4) that were used to refute the VO_2 plateau/VO_2max concept are presented in Table 3.

Induced Erythrocythemia or Hyperoxia

The question of whether increasing the oxygen content of the blood increases VO_2max is simple, and research has clearly answered that VO_2max does increase with increased O_2 availability, whether by hyperoxia (59,60,66,78), erythrocythemia (73-76), or improved peripheral oxygen diffusion (54,55,58). Nevertheless, Noakes asserts that this evidence is far from compelling due to the absence of the control of blood acid-base balance in past research, that the increase in VO_2max is small compared to the increased oxygen supply, and that there is still no direct proof of intramuscular hypoxia. The latter argument has been the crux of Noakes' stance. Thankfully, recent research has shed more light on the development of an intramuscular hypoxia, and this topic is expanded in the section on edifice #3. However, at this time it is important to state that there is overwhelming evidence for the development of an intramuscular hypoxia, or myoglobin deoxygenation, during incremental exercise to VO_2max (59). Consequently, there is now definitive experimental evidence that shows that Noakes' belief that there is no rationale for even raising the issue of the need for an increased oxygen delivery/supply at VO_2max to be incorrect.

Table 3 : Arguments used by Noakes* for refuting a cardiorespiratory limitation to VO_2max.

Topic	*Rationale*
1. Induced Erythrocythemia or Hyperoxia increases VO_2max (1988)	• No control of blood acid-base balance • Increase in O_2 delivery exceeds increase in VO_2max • No clear evidence of tissue hypoxia
2. Tissue oxygenation indirectly limits VO_2max by directly acting on factors other than mitochondrial ATP regeneration (1988)	• Lactate paradox during acute and chronic hypoxia • Lower VO_2max during cycling than running • Potential for impaired intracellular calcium transport or myosin ATPase activity
3. Individuals with disease and/or muscle weakness are not centrally limited during incremental exercise (1988, 1997)	• Most subjects do not demonstrate a plateau, or expected values for heart rate or ventilation at exhaustion • Training improvements in VO_2max are more coincident with peripheral not central cardiovascular adaptations • Strength and power training also increases VO_2max • Detraining/taper decreases muscle oxidative capacity, yet increases muscle power and performance • Individuals with diseases/illness such as renal failure, heart failure and cardiac transplantation all show histological evidence of impaired skeletal muscle contractile function
4. Fatigue develops rapidly at or near VO_2max (1997)	• Skeletal muscle oxygen-independent reactions that regenerate ATP are not fully taxed at and following VO_2max • This implies that factors cause exhaustion before the maximal capacity for oxygen-independent ATP regeneration is reached
5. Skeletal muscle rates of ATP use are regulated to prevent large variance in the skeletal muscle ATP concentration (1997)	• Muscle ATP does not decrease by more than 50% at VO_2max, even despite complete ischemia and excessive contraction from artificial electrical stimulation • VO_2max decrement at altitude • Presence of a lactate paradox during acute and chronic hypoxia • Motor unit recruitment is decreased during acute hypoxia
6. The hypothesis that skeletal muscle blood flow regulates skeletal muscle contractile function (1997)	• Peripheral blood flow is regulated to maintain central arterial blood pressure
7. Central cardiovascular function does not limit VO_2max (1998)	• No evidence for a plateau in cardiac output at VO_2max and therefore a central cardiac limitation to VO_2max • If a central cardiac limitation was evident, this would present itself as coronary ischemia and related symptoms of cardiac fatigue. There is currently no evidence for these developments

* from Noakes (2-4)

One cannot discuss the evidence from studies of hyperoxia and erythrocythemia without once again commenting on the model used to interpret evidence of how increasing oxygen supply increases VO_2max. If the models from Figures 10-12 are used, then researchers would be forced to conclude that any increase in VO_2max resulting from erythrocythemia or hyperoxia must be evidence of a oxygen delivery limitation that has been overcome by the intervention. Conversely, if the models from Figure 13 and 16 are used as a research reference, then added questions need to be answered. Does the added oxygen content of the blood improve the homogeneity of oxygen provision (temporal and spatial) within the contracting muscle? Does erythrocythemia alter blood volume and central cardiovascular function? Does hyperoxia or erythrocythemia alter additional functions that also influence cellular respiration, such as acid-base balance? Is there a clear relationship between the amount of added circulatory oxygen delivery and an increase in VO_2max?

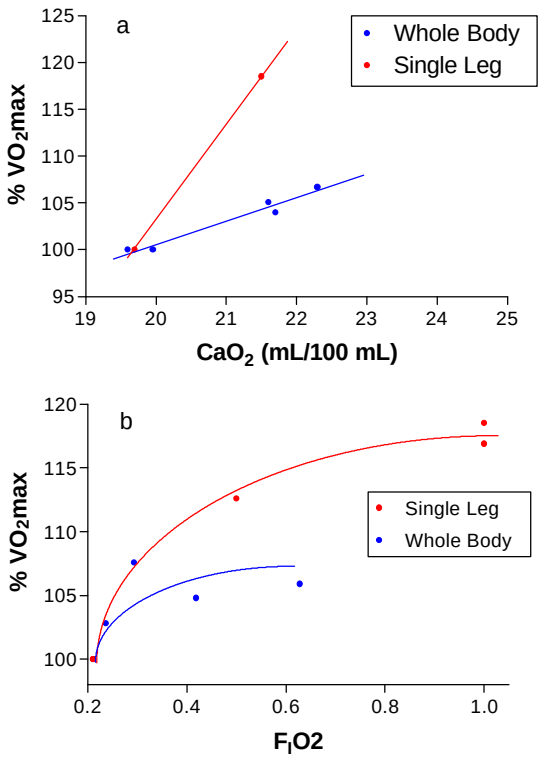

Figure 17: Data of the change in VO_2max (%VO_2max) from studies using human subjects that have increased oxygen delivery via hyperoxia or erythrocythemia using single (58) or double leg exercise (65,72,77). A greater increase in VO_2max is evident when performing single leg exercise, regardless of whether the improved oxygen condition is expressed as a) blood oxygen content (CaO_2) or b) the inspired fraction of oxygen (F_IO_2).

Strong evidence of an oxygen limitation to VO_2max during erythrocythemia or hypoxia would result if a relationship between blood oxygen content and increases in VO_2max could be shown. I have tried to do this from past research (59,66,73,78), and data are presented in Figure 17. Based on this data, a linear relationship does exist between the increase in VO_2max and blood oxygen content. The data that are used to document this relationship are derived from both hyperoxia (59,66,78) and erythrocythemia (73). It is clear from Figure 17 that the slope of the %VO_2max – CaO_2 relationship is appreciably larger for single leg (knee extension) exercise than conventional two-legged cycle ergometry. This difference is explained by the larger relative blood flow at VO_2max during single leg knee extension exercise than during cycle ergometry (56,57,59-62). Researchers interpret these findings using the "black box" model of Figure 10, resulting in evidence for an improved extraction of oxygen and for a mitochondrial capacity that exceeds "normal" oxygen supply (57,59,60). Although it is obvious that net oxygen extraction must increase, the question of why it increases has yet to be answered. For example, based on Figures 13 and 16, it remains uncertain whether the increased VO_2max during artificially increased oxygen supply is caused by a reduced heterogeneity of oxygen supply within the working muscles, improved oxygen diffusion kinetics, or both. Regardless of the exact cause, the fact that added oxygen supply increases VO_2max in proportion to increased blood oxygen content, and presumably oxygen delivery, is compelling data that supports the importance of oxygen supply, even with an uncompromised central circulation, in determining VO_2max.

Noakes (4) criticized Bassett and Howley (1) for interpreting studies of single conditions of hyperoxia or erythrocythemia based on the inability of these studies to control extraneous factors that could also improve exercise tolerance and VO_2, such as acid-base balance. Noakes based this argument solely on the interpretations of Welch et al. (66). However, the comments of Welch were not directed at VO_2max but to continuous exercise performance at submaximal and high exercise intensities. In fact, the acid-base argument of Noakes disintegrates based on the evidence of clear relationships between VO_2max and CaO_2 for multiple exercise conditions (Figure 17). If factor(s) other than oxygen supply were to explain the increases in VO_2max,

then these variables would need to be positively interrelated to CaO_2 during both hyperoxia and erythrocythemia. I am unaware of any evidence that supports this association at this time.

The final argument of Noakes was that increasing oxygen supply also increases venous blood oxygen content. Noakes interpreted this condition as evidence that refutes a prior oxygen limitation, and stated that, "*.. the active muscles had no use for the surplus oxygen provided after blood doping*." This interpretation is clearly based on a "black box" or Fick model (Figures 10-12) of VO_2. I hope I have clearly revealed how misleading this approach is as it ignores the peripheral cardiovascular and respiration limitations to VO_2max independent of circulatory oxygen delivery (Figure 13). Furthermore, the fact that venous PO_2 does increase with hyperoxia and erythrocythemia is added evidence for the presence of an oxygen supply-demand heterogeneity that is raised in Figure 13. If one accepts the fact that such heterogeneity can impair net cellular VO_2, even in the presence of seemingly adequate oxygen delivery, then an increase in venous oxygen content following increased oxygen delivery is exactly what will be predicted. An increased VO_2 would also result based on the potential for increased oxygen supply to improve peripheral oxygen diffusion. In fact, each of Hogan (54,55), Richardson (57-60), and Roca (56) have tested the importance of peripheral oxygen diffusion using animal hindlimb models or single leg muscle contraction in humans. Their data indicate that it is the diffusive aspects of increased oxygen supply to contracting muscle that are most important for increases in VO_2max, as such increases are more for a given oxygen delivery when partial pressure gradients for oxygen are increased compared to blood oxygen content or blood flow. The earliest of these studies was published in 1988 and may have been too late for Noakes to include in his first manuscript. However, Noakes did not recognize these findings in either of his additional manuscripts published in 1997 and 1998 (3,4).

Tissue Oxygenation and Mitochondrial ATP Regeneration

As I have organized my rebuttal to Noakes on this topic as another edifice (#3), comment on this topic occurs in a later section.

Individuals with Disease and/or Muscle Weakness

Noakes (2-4) presents strong evidence for how individuals that are extremely deconditioned and/or have certain disease processes are not able to sustain incremental exercise to a VO_2 plateau. As such, they attain a peak VO_2 and not a true VO_2max. There is no controversy on this issue. The concern that I have with the rationale used by Noakes is that he clumps this evidence from unhealthy human conditions, along with other "unusual" physiological characteristics, into a collective body of evidence that he applies to "disprove" the VO_2max concept in healthy and trained individuals. Such a process is a fundamental violation of the concept of generalizability in research design and analysis. Data from individuals with cardiac failure or disease, heart transplantation, renal disease, kidney transplants, symptoms of over-training (2,3,79,80), or individuals exposed to heat stress or acute and chronic hypoxia (3,4,81-83) should only be applied to individuals with or exposed to the same characteristics. The rationale for such a restricted application of findings is that the prevailing condition of these subjects specifically alters processes, including or in addition to oxygen transport and utilization, that influence the ability to attain VO_2max.

At best, the data Noakes used to argue against an oxygen supply limitation indicates that the term VO_2max should not be applied to the peak VO_2 attained without a VO_2 plateau by individuals with select diseases, or who have been sedentary.

Fatigue and Non-Mitochondrial ATP Regeneration at VO_2max

Noakes (3) illustrated his thoughts on the use of non-mitochondrial sources of ATP regeneration during incremental exercise (Figure 5, p. 580) by showing an increasing oxygen deficit predominantly confined to the period of a VO_2 plateau at VO_2max. Despite presenting an alternate, more correct illustration in the same manuscript (Figure 7, p. 583), Noakes argued that the duration of a plateau was insufficient to fully tax a skeletal muscle maximal rate of "oxygen independent ATP production" (~ 500 mmol/min greater than VO_2max). Noakes' interpreted these facts as evidence that exercise to VO_2max is prematurely terminated, raising the possibility that a cause of limitation to VO_2max may be muscle contractile function.

Noakes' (3) evidence and logic are incorrect. As shown in Figures 8 and 14 of this manuscript, and in Figure 7 from Noakes (p. 583), a gradual development of an oxygen deficit occurs throughout the entire incremental protocol, and a more rapid increase in the deficit is evident after the lactate threshold. Consequently, an oxygen deficit is not confined to the duration of the VO_2 plateau.

The expectation of a maximal rate of anaerobic ATP regeneration at the end of a test to VO_2max is not supported by past research, which shows that this "maximal" rate is very short lived, occurs during the initial seconds of "all out" exercise, and then decreases until eventual fatigue (84-88). A more important topic of research is to compare the maximal accumulated anaerobic capacity to that obtained during an incremental exercise test. Unlike Noakes' theory, there is greater physiological rationale for an oxygen deficit from an incremental exercise test to VO_2max to be less than the "maximal" value. This would indicate that fatigue was not induced by exhausting the full capacity of anaerobic metabolism, which can be argued to support and not contradict an oxygen limitation.

It is also questionable to infer that the fatigue at the end of a test to VO_2max to fatigue is similar to the fatigue at the end of a bout of "all out" exercise. I would propose that the metabolic acidosis and additional intracellular markers of muscle fatigue would be less indicative of muscle fatigue after a test of VO_2max than a 2-3 min bout of all-out exercise. However, I am not aware of such comparisons in past research, or the quantification of the accumulated oxygen deficit during incremental exercise. Nevertheless, Chwalbinska-Moneta et al. (89) reported minimal decreases in muscle pH from 7.04 to 6.99 at 50 Watts above the onset of blood lactate accumulation (75 %VO_2max). Furthermore, Sahlin et al. (90) reported moderate decreases in muscle pH to 6.6 at intensities and durations similar to incremental exercise to VO_2max, with muscle lactate increasing to ~13 mmol/kg wet wt. Knuttgen et al. (91) reported increases in muscle lactate to ~20 mmol/kg wet wt at 90% VO_2max. These changes in muscle pH and lactate accumulation coincide with increases in muscle NADH. Ren et al. (92) reported 50-150% increases in cellular NADH at 75 and 100% VO_2max in both type I and II muscle fibers during cycle ergometry. The aforementioned alterations in muscle metabolites at VO_2max are not as extreme as the metabolic perturbations evident after short-term intense exercise to exhaustion (Table 4) (93-99).

The fatigue at the end of a test to VO_2max is more correctly described as a result of a progressive development of a metabolic imbalance between the rate of ATP demand and supply, resulting in the need to lower the exercise intensity to a value that allows for adequate recovery. A "maximal" rate of anaerobic ATP regeneration does not occur during these conditions due to the duration of anaerobic metabolism that has already occurred, which past research shows to be important in determining the "peak" rate of anaerobic energy production (84,86,99). Until additional research is completed, exercise physiologists should be aware of the development of an oxygen deficit during incremental exercise and devise protocols that limit this deficit, especially for individuals who are likely to have a compromised anaerobic capacity such as the sedentary or individuals with disease.

Conservation of Muscle ATP Concentrations

Noakes (3) hypothesized that because muscle ATP concentrations never fall below 50% of resting values, even after extreme ischemia and electrical stimulation to contractile failure (99), there must be a metabolic protection of tissues so that contracting muscle cannot demand more ATP (oxygen) than is able to be supplied (metabolism) to it. This interpretation is based on an incorrect view that muscle ATP is a store of energy that can be used by the cell if needed. Noakes also supported this "new model" with evidence of compromised exercise tolerance at extreme altitude (81), reduced blood lactate during exercise with chronic hypoxia (82), a similar reduced blood lactate in individuals with metabolic or organ diseases (79,80), and a central nervous system limitation to exercise during acute hypoxia (83).

Before providing alternate explanations for the aforementioned findings, or clarifying Noakes' interpretation of them, it is important to first summarize basic biochemical principles of metabolic control. Noakes' belief that

muscle ATP is a store of energy is strong evidence of his lack of understanding of muscle biochemistry and cellular metabolic regulation. Skeletal muscle, like all tissues with a high demand for energy, functions optimally under certain biochemical conditions. Typically, these conditions reflect resting concentrations of substrates, products, and enzyme cofactors within a cell (Table 4). The regulation of skeletal muscle metabolism during exercise functions to maintain these concentrations as best as possible. Deviations from these metabolite concentrations reflect cellular conditions that can no longer maintain this cellular milieu, and if not corrected by a reduced rate of ATP demand, will eventually result in muscle fatigue. There is still debate over the exact causes of this fatigue, but increases in cellular ADP, Pi, H^+, and NH_3, as well as neuromuscular electrolyte imbalances, have been reported to be candidates for dampened ATP regeneration and/or impaired contractile function (85,86-88,93,98,99).

Table 4: Concentrations of key metabolites within skeletal muscle at rest, at VO_2max, and after 2-3 min of intense exercise to fatigue.

Molecule	*Metabolite Concentrations* (*mmol/kg wet wt.*)		
	Rest	***VO_2max***	***Severe Muscle Fatigue***
Creatine Phosphate (CrP)	26.0	10.0	3.0
Adenosine Triphosphate (ATP)	8.0	7.5	5.0
Adenosine Diphosphate (ADP)	0.003	0.005	0.02
Creatine (Cr)	3.0	19.0	26.0
Inorganic Phosphate (Pi)	3.0	19.0	26.0
pH	7.0	6.6	6.02
NADH	0.02	0.04	0.06
Protons (H^+)	0.0001	0.000135	0.00095
Lactate (La^-)	1.0	6-15.0	25-35.0

adapted from references (84-88,90-95,98,99)

The experimental evidence for the importance of maintaining a stable muscle ATP concentration is based on biochemical estimates of the phosphorylation potential (100) or adenylate charge (101) of the cell (equations 1 and 2).

Phosphorylation potential = [ATP] / [ADP] (equation 1)

Adenylate charge = ([ATP] + ½[ADP]) / ([ATP + ADP + AMP]) (equation 2)

These measures reflect the ability of the cell to transfer free energy from the adenylate molecules and creatine phosphate, thereby supporting the energy requirements of cellular work. Given that the free energy release of ATP, or any high energy cellular intermediate, is based on the standard change in Gibbs free energy ($\Delta G°'$) and cellular concentrations of substrates and products (equation 3), a fall in cytosolic ATP and increase in ADP would dramatically reduce the free energy release of ATP hydrolysis. This in turn would decrease the energy available for cell work, as well as impair the regeneration of ATP during the two ADP coupled reactions of phase 2 (3 carbon intermediates) of glycolysis. Thus, it is a metabolic impossibility for cell ATP concentrations to fall dramatically, as this would reflect a total impairment of the ability to transfer phosphates throughout the cell, as well as to use the free energy of hydrolysis to fuel cell work.

Free energy change (ΔG) = $\Delta G°' + R \cdot T \cdot \ln$ ([products] / [substrates]) (equation 3)

For ATP hydrolysis: $\Delta G = \Delta G°' + R \cdot T \cdot \ln$ ([ADP] [Pi]) / ([ATP])]* (equation 4)

Example 1: rest conditions:

$\Delta G = -7.3 + [\ 0.00198589 \cdot 310 \cdot [\ln ([0.000003]\ [0.003]) / [0.008]\ ]$ (equation 5)

$= -7.3 + [\ 0.6156259 \cdot (\ln 0.000001125\ )]$

$= -7.3 + (0.6156259 \times -13.6977)$

$= -7.3 + (-\ 8.42765)$

$= -15.72$ Kcal/mol

Example 2: extreme muscle fatigue following 2-3 min "all-out" intense exercise:

$\Delta G = -7.3 + [0.00198589 \cdot 310 \cdot [\ln ([0.003 + 0.023] / [0.004]\ ]$ (equation 6)

$= -7.3 + [\ 0.615629 \cdot (\ln 0.01725\ )]$

$= -7.3 + (0.615629 \times -4.0599)$

$= -7.3 + (-2.4994)$

$= -9.8$ Kcal/mol

*Note that the H^+ of ATP hydrolysis is not included in these calculations

The correct interpretation of even a 50% reduction in cellular ATP is that it is not protecting the cell, but evidence of metabolic events that have exceeded the cell's capacity for ATP regeneration (equations 5 and 6). Such a reduction in ATP, and accompanied changes in the products of ATP hydrolysis, are associated with a meaningful decrease in free energy release. Interestingly, the conversion of 2 ADP to AMP (adenylate kinase reaction), which is then converted to IMP within the purine nucleotide cycle (AMP deaminase), prevents large increases in ADP and partially conserves the free energy release from ATP hydrolysis despite decreasing muscle ATP concentrations. Nevertheless, unlike Noakes' interpretation, a 50% decrease in the cellular ATP concentration is not a sign of protection against demand outstripping supply, but the exact opposite. A near 50% decrease in cellular ATP is an extreme situation for the cell. This condition coincides with a reduced free energy release from ATP hydrolysis and therefore decreases the energy available for cell work, slows the rates of ATP hydrolysis coupled reactions, and thereby compromises the ability of the cell to do work. If demand did not outstrip supply, then muscle ATP would be well maintained and not forced to compromise free energy transfer. Such biochemical explanations of metabolic regulation clearly reveal that the cellular ATP concentration is not an energy store, but a condition within the cell that needs to be maintained as best as possible for optimal metabolic function and regulation.

Comment also needs to be given to the research findings Noakes chose to support his "new model", which I hope to have already clearly disproven based on sound biochemical logic and the application of the laws of bioenergetics. Nevertheless, it must be emphasized that the topic at question is the cause of limitation to VO_2max during incremental exercise. Surely the evidence that Noakes needed to present should have been during the metabolic demands at VO_2max and not during the extreme conditions the he mostly chose to use.

The research of Spriet et al. (99) reveals the muscle contractile and metabolic failure that results from perturbations in cellular ATP concentrations and related biochemical and metabolic conditions (eg. acidosis, ADP, Pi, ammonia) during short term high intensity exercise. Spriet's findings, in light of the aforementioned biochemical explanations of cellular ATP flux and the fact that such fatigue occurred from exercise at intensities far greater than at VO_2max, should not be used as evidence for a premature muscle fatigue at VO_2max. The research of the lactate paradox during hypoxia remains poorly explained and inconsistently documented in the literature. For example, the research from Operation Everest II (OEII) is based on a gradual continuous exposure to decreasing pressure (hypobaric hypoxia). Thus, the data from OEII reflect chronic altitude exposure, which support other data in showing a reduced blood lactate at VO_2max (81,82). Conversely, during acute exposure to hypoxia, submaximal blood lactates are higher than during normoxia (102). However, it is likely that these alterations during acute hypoxia are due more to increased blood catecholamine concentrations than any connection to limitations in cellular oxygen supply and utilization (103,104). Once again there is no rationale to apply these findings to muscle metabolic conditions at VO_2max in healthy people during normoxia.

The only evidence Noakes used that pertained directly to VO_2max was the data of Kayser et al. (83) that showed a reduced muscle EMG activity at VO_2max during hypoxia compared to normoxia. However, the reduction in EMG activity during hypoxia is not evidence for a CNS limitation to VO_2max at sea level. A study more suited to this conclusion would have involved a normoxia to hyperoxia comparison, where results showed that EMG activity was greater during hyperoxia.

When viewing the aforementioned alternate explanations to Noakes' theories that pertain to the anaerobic contributions to VO_2max and the relative ATP conservation during muscle fatigue, it becomes apparent that the muscle fatigue at VO_2max is not extreme at all. As already indicated, the fatigue at VO_2max is really an imbalance in the demand and supply of ATP to the contractile proteins within skeletal muscle. Unless there are other disease or functional limitations, test termination from volitional fatigue at VO_2max simply results from the need to lower the exercise intensity to reduce the rate of ATP demand. The fact that muscle metabolic fatigue is not severe, and that the full anaerobic capacity of skeletal muscle is not taxed during incremental exercise to VO_2max, lends indirect support to other factors that limit VO_2max in healthy individuals, such as oxygen supply. The difference in the interpretations of this data between Noakes and myself is clear evidence of the danger of research interpretation by Noakes without an appropriate understanding of the metabolic biochemistry and physiology of exercise.

<u>Skeletal Muscle Blood Flow Regulates Contractile Function</u>

Noakes rationalized this theory based on the capacity of skeletal muscle to receive an extraordinarily large percentage of the cardiac output during exercise. This capacity is even more revealed during single muscle group unilateral limb exercise, which receives a relative blood flow (to tissue mass) far greater than previously reported for contralateral limb or whole body exercise (56,57,59-61,63,65). Noakes hypothesized that the capacity of skeletal muscle to receive a high rate of blood flow must be intimately connected to the regulation of systemic blood pressure. If this were not the case, then muscle blood flow during large muscle group exercise would exceed the capacity of the cardiovascular system to maintain blood pressure (47), resulting in a dramatic fall in each of systemic blood pressure, cardiac blood flow and performance, and cerebral blood flow.

Although this is an intriguing hypothesis, Noakes provides no experimental evidence to support it. Such evidence would consist of impaired muscle metabolism and contractile function with reduced flow but sustained oxygen supply. The only research evidence that this author could find that is close to this experimental design provides evidence that contradicts such a hypothesis. Exercise with altered blood oxygen content, from either hypoxia or hyperoxia, results in an alteration of maximal blood flow to normalize net oxygen supply to working muscle (56,57,59,62,66). In addition, the work of Wagner (50,51), Hogan (54,55), and Richardson (57-60) indicate that the cellular conductance of oxygen within the contracting muscle is of additional importance to each of net circulatory oxygen delivery and blood flow. These research findings indicate a regulation of cellular oxygen consumption that is more dependent on the cellular availability of oxygen than blood flow.

<u>Central Cardiovascular Function Does Not Limit VO_2max</u>

Noakes (2-4) rationalized the inability for central cardiovascular function to limit VO_2max on the belief that if such a limitation existed it would also involve a plateau in cardiac output at VO_2max. Noakes further rationalized that if there was evidence of central cardiovascular limitations they would be accompanied by impairment to myocardial blood flow, the development of myocardial ischemia, and decreased cardiac performance. Ironically, Noakes once again obtained the evidence for his belief that exercise physiologists perceive that there is a central cardiovascular compromise at VO_2max from the writing of Hill (16), who stated, "*When the oxygen supply becomes inadequate, it is probable that the heart rapidly begins to diminish its output, so avoiding exhaustion; the evidence for this, however, is indirect, and an important field of research lies open in the study of the recovery process in heart muscle… It would seem possible that a deciding factor in the capacity of a man for severe prolonged exercise may often be the efficiency of his coronary circulation.*"

When confined to apparently healthy individuals, there is obviously no development of myocardial ischemia during incremental exercise to VO_2max, even when as previously explained, these individuals develop a VO_2 plateau at VO_2max. An uncompromised central cardiovascular function to VO_2max is also seen in severe hypoxia (105). Noakes clearly and correctly reveals that no data exist to support a plateau in cardiac output at or near VO_2max. However, Noakes failed to document that the measurement of cardiac output during exercise at or near VO_2max is extremely difficult, even for invasive and arguably more direct methods of measurement (cardiac catheterization). Despite this difficulty, given the importance of this topic it is ironical that despite Hill's implied statement of the need for added research on cardiac output near VO_2max, such studies have not been performed by exercise physiologists or cardiologists in the ensuing 75 years since Hill's statement.

Obviously, Noakes is correct in his criticisms of the possibility for myocardial limitations to VO_2max. However, this fact does not discredit an oxygen supply limitation to VO_2max, which previous explanation has revealed probably exists within contracting skeletal muscle and can have little to do with central cardiovascular function. To conceptualize this fact, one must realize that skeletal muscle blood flow during exercise is a fraction of total cardiac output. Although this fraction is extraordinarily large during exercise to VO_2max (>80%), the crucial question is whether or not the oxygen provision from this amount is adequate to continue to increase VO_2 at VO_2max.

Research clearly indicates the development of an increasing anaerobic ATP regeneration during incremental exercise that begins as early as 60-80% VO_2max (Figures 8 and 14). When viewing this basic fact, and adopting a philosophical attitude towards the design of human physiology, perhaps the need to generate an oxygen deficit and develop metabolic symptoms of ensuing muscle fatigue while increasing VO_2 towards VO_2max is the protection our body has for excluding a myocardial limitation to exercise. To this can be added the increasing heterogeneity within contracting muscle for oxygen supply and demand (Table 2), causing peripheral oxygen diffusion limitations to VO_2. Consequently, despite the lack of evidence to support a central cardiovascular limitation to oxygen supply, oxygen supply may still be limiting to contracting skeletal muscle and VO_2max based on peripheral circulation and oxygen diffusion limitations. These issues were clearly identified in Figures 13 and 16.

Reinterpretation of An Oxygen Limitation To Contracting Skeletal Muscle

The issue that is clear from the publications of Noakes (2-4), Bassett and Howley (1), and the numerous other manuscripts that are cited in this commentary is that it is wrong to expect to find the same single or multiple limiting factor(s) to VO_2max in all people (Figure 18). There is a pulmonary diffusion limitation in some but not all people at sea level (43,44), a peripheral muscle anaerobic capacity/muscle power limitation in the sedentary and diseased (79.80), and an oxygen provision limitation that could be caused by declines in central circulatory function but is most likely based on inadequate peripheral oxygen diffusion in the endurance trained (50,51,59-61). Added to these specific cases is the existence in all healthy and active people of an overall inability to supply oxygen at a sufficient rate to maximize cellular mitochondrial respiratory capacities (59).

The problem of arguing whether there is or is not an oxygen limitation to VO_2max is not the proof of either side of the argument, but whether the question is inappropriate due to the multiple contributions to VO_2max. If exercise physiology, as well as most medical and physiological sciences, has been straight jacketed by anything over the past decades it has been by the belief that the multi-system functioning of the human body can be simplified into one main determinant in almost anything that we study. I propose that we should not view research as a quest to find the single most important physiological determinant to whatever is our topic of inquiry, but to better understand the multiple factors that cause individual differences in the physiological response of interest. The latter approach requires a redirection of inquisitiveness, and altered research practices that include increased sample sizes, increased statistical power, modified research designs, and an arsenal of statistics that go beyond t-tests and factorial analysis of variance.

"Edifice"#3: VO_2max Is Associated With an Intramuscular Anaerobiosis

Intertwined within Noakes' interpretations of the standard interpretations of a VO_2 plateau at VO_2max is his perception that exercise physiologists believe that the VO_2 plateau is caused by the development of intramuscular hypoxia (3). Noakes referred to this interpretation as the "cardiovascular/anaerobic model of exercise physiology" (4). As an exercise physiologist, I am perplexed that Noakes perceives that exercise physiologists believe this hypothesis to be true to the extent that muscle becomes completely anaerobic. Such a model results from the "black box" approach to modeling the determinants of VO_2, and as such, is extremely over-simplistic and therefore misleading.

As previously stated, during incremental exercise there is an increasing heterogeneity in intramuscular blood flow and intramuscular oxygen demand, causing a widening mismatch in blood flow/oxygen demand. This condition, even if oxygen delivery to muscle is maintained, would result in a decrease in the rate of muscle VO_2 without any change in intramuscular oxygenation. This is seen clearly in Figures 2, 6-8, and 14. In fact, muscle oxygenation could increase slightly during these conditions due to the steady increased rate of systemic oxygen delivery yet reduced rate of increase in VO_2. During these conditions, a plateau in VO_2 will not be associated with anaerobiosis. This fact is analogous to lung ventilation, where a decrease in pulmonary oxygen diffusion will increase alveolar PO_2, yet arterial PO_2 can fall. Why is it that when it comes to peripheral gas exchange physiologists make interpretations that simple pulmonary physiology precludes? The answer is an over-reliance on the "black box" approach to understanding the determinants to regional and whole body VO_2.

Katz and Sahlin (93) published an excellent review on the interpretations of muscle biochemical data that either refutes or supports the development of an intramuscular hypoxia. Despite what I would describe as an interpretation of muscle metabolism from a homogenous "black box" mentality, which is necessitated by mixed fiber assay obtained from muscle biopsy, their interpretation of a large body of experimental evidence was that a reduced oxygenation of skeletal muscle does occur during incremental exercise to VO_2max. This evidence was based on the consistent reports of an increase in total muscle NADH (predominantly from the mitochondria) at intensities as low as 60-80% VO_2max.

Recently, Richardson et al. (59) reported compelling data supporting the deoxygenation of myoglobin in contracting skeletal muscle using ^{1}H magnetic resonance spectroscopy (^{1}H MRS). The oxygen desaturation of myoglobin was used to estimate an average intramuscular PO_2 at VO_2max of approximately 3.0 Torr (55% Mb-O_2) during normoxia and 2.3 Torr during acute hypoxia (60% Mb-O_2) (F_IO_2 = 0.12, P_B ~ 740 mmHg). To better understand the meaning of this finding, the limitations of ^{1}H MRS must be explained. Muscle MRS involves the detection of a radio-frequency signal from a select region of muscle. This region, especially when using a large peripheral surface coil (7 cm) applied to the rectus femoris as done by Richardson et al. (59), acquires signal from whatever tissue lies within its signal field (stated to be 100 cm^3). For the region over the rectus femoris, this involves the muscle fibers (from heterogenous motor units; recruited and not recruited) falling within this field, which the authors stated to "*predominantly*" be from the rectus femoris. However, based on structural and functional anatomy, the rectus femoris is a relatively thin muscle and signal must have also been acquired from the vastus intermedius. This acquired signal is therefore an average for the sampled regions of these muscles. By definition, and especially when applying the data of model 4 (Figure 13), such an average would be from the sum of regions that have a lower and larger intramuscular PO_2 than the stated value. The reported value of 3.0 Torr for the intramuscular PO_2 at VO_2max during normoxia must therefore be interpreted as an average of regions that would be less and more oxygenated. This is strong evidence for the existence of regions within contracting skeletal muscle that have extreme (< 3 Torr) deoxygenation at metabolic rates close to VO_2max. What is even more interesting is that this data results from a small exercised muscle mass during rates of blood flow that are the highest recorded in the literature. These are the conditions that would suit a higher than typical intramuscular oxygenation if circulatory oxygen delivery was the only determinant to VO_2max!

Do the results of Richardson et al. (59) support the development of an intramuscular anaerobiosis during incremental exercise to VO_2max? The answer depends on the definition of "anaerobiosis". Consequently, what does Noakes mean when he uses the term "*anaerobic*" in the term "*cardiovascular/anaerobic model*"? In a later section of one manuscript, Noakes (4) stated that such a term applied to, "*when it's* [skeletal muscle] *oxygen supply is inadequate*". This is a fair definition, and one that clearly does not imply the absence of oxygen. The term "anaerobiosis" is therefore inappropriate. What then is an insufficient supply of oxygen to contracting skeletal muscle to support continued increases in the rate of VO_2, and why does it develop?
The first part of the aforementioned question is impossible to answer at this time. However, some aspects of the question can be discussed. For example, a VO_2 plateau at VO_2max implies that a continued increase in the rate of VO_2 is no longer possible, despite continued increases in exercise intensity. To even maintain this rate of VO_2, oxygen must be present, otherwise there would be a drastic (more extreme than an overshoot phenomenon) fall in VO_2. As this does not happen, it is logical to assume that there comes a point in time when intramuscular PO_2 falls to values that are no longer supportive of continued increases in VO_2 for a muscle mass of heterogenous oxygen supply and demand. The data of Richardson et al. (59) support this assumption better than an alteration of muscle contractile function as proposed by Noakes. Future research, exploiting as yet undeveloped intramuscular research methodologies is needed to prove "*causation and exclude association between apparently related phenomena*" (4) on this topic. For example, we currently do not know the intracellular PO_2 values needed to optimize the flux of oxygen between myoglobin and mitochondria in vivo. Consequently, the question to answer is how much of a fall in intramuscular oxygen is needed to blunt continued increases in VO_2? Until we have methodology to better research *in-vivo* intracellular oxygen kinetics during multiple exercise intensities, I propose that researchers and educators avoid using the terms "anaerobic" and "anaerobiosis". A term that is more applicable is the development of an "intramuscular deoxygenation" at increasing exercise intensities.

The Importance of Skeletal Muscle Hypoxia at VO_2max to Research of Increased Oxygen Supply
To date, the traditional interpretation of increases in VO_2max during hyperoxia or erythrocythemia has been that muscle mitochondrial capacities are not fully taxed during exercise to VO_2max during normoxia, even in highly trained endurance athletes (59-62). However, this interpretation is based on the "black box" model of VO_2 (Figures 10-12). Given that additional potential contributors to limitations in VO_2 at VO_2max exist (Figure 13), and that recent research has revealed that a muscle deoxygenation does develop progressively as one approaches VO_2max, how should the findings of increased VO_2max during hyperoxia or erythrocythemia be interpreted?

The interpretation that the increase in VO_2max with increased oxygen supply reveals an excess mitochondrial capacity can no longer be viewed to explain all of the increase in VO_2max. One should not ignore the possibility that providing added oxygen might also improve the equality of net oxygen diffusion within contracting skeletal muscle, which in turn would improve net oxygen supply/demand relationships, which would then support a higher rate of VO_2 prior to a plateau (Figure 18). Once again the simplicity of the Fick models may have caused physiologists to propose and accept over-simplistic explanations for research findings, and retard the development of a better understanding of exercise physiology at VO_2max.

A New Model For Explaining Limitations to VO_2max
Given the fallibility of the explanations used by Noakes' to explain oxygen supply-independent limitations to VO_2max, and my arguments for the inadequacies of the use of the Fick or "black box" model to explain VO_2max, a new model is needed. Such a model should include all known physiological contributors to VO_2max that are supported by research. I have developed this model and presented it as Figure 18. The structure of the model is based on the importance of oxygen supply and tissue oxygen demand, and how these components are distributed throughout the working muscle mass. After all, these are the basic requirements that govern VO_2 for a given exercise condition. On the oxygen demand side of the model, the peak oxygen demand is dependent on the peak exercise intensity, which in turn is dependent on interactions between motor unit

recruitment, muscle fatigue, and muscle anaerobic capacity and endurance. These components are then dependent on muscular strength and power, muscle mitochondrial density, etc.

The utility of this model is that the components are revealed that research has shown to alter the ability of individuals to attain a VO_2 plateau and thereby a peak VO_2 that represents VO_2max. In addition, components are present that can be altered to increase or lower the VO_2 at which a plateau occurs, thereby changing VO_2max. Furthermore, the real relevance of this model is that components are shown that clearly identify the multifaceted determinants of VO_2max, and in so doing, provide the exercise physiologist, pure physiologist, or clinician with a more complete framework from which to interpret the peak VO_2 attained from incremental exercise testing.

This model is not final or complete. Future research will no doubt require additional components to be added, or require the alteration of the place or connections made to several components. However, all models need to be dynamic; changing with recent scientific discoveries that further improve the accuracy of model. As previously commented, the Fick approach to modeling VO_2max has been used for too long, and this has been the greatest indictment against the scientific quality of the interpretation of VO_2max.

RECENT RESPONSES TO NOAKES' CHALLENGES TO CONVENTIONAL THEORIES ON THE LIMITATION TO VO_2max

Immediately prior to the submission of this manuscript, additional responses (106-110) to the manuscripts of Noakes (2-4) were published. Three options were possible: to ignore these latest references, include content from these new manuscripts into the main body of the manuscript, or add a short commentary at the end. After reading these manuscripts I decided that they did not add to the content of this manuscript as they present material that either reinforces my emphasis on the importance of peripheral oxygen diffusion (108,109) and a more integrated approach to understanding VO_2max (111), or provide further examples that justify Noakes' criticisms of generally accepted thinking in exercise physiology (106,107).

I am astounded that Bassett and Howley (106), in a second opportunity to challenge Noakes' theories and interpretations of past research, once again fail to critically evaluate the topic of the limitations to VO_2max in a manner that soundly refutes Noakes' arguments. Similarly, Bassett and Howley have not applied the constructive criticisms of Noakes to reevaluate their own thinking on the concept of VO_2max. For example, Bassett and Howley once again presented their interpretation of the work of Hill (15,16), they remained fixed in their use of the Fick model to interpret VO_2max during whole body or large muscle group exercise, and they did not provide any research evidence that refuted any of Noakes' rationale. Furthermore, Bassett and Howley stated that; "*…. It is estimated that 70-85% of the limitation in VO_2max is linked to maximal cardiac output*….", but did not provide any scientific research-based evidence to support this fact (106).

Although there are numerous additional examples of how Bassett and Howley have inadequate interpretations and explanations of VO_2max, the best example of their illogical thinking is seen in their discussion of mitochondrial density, peripheral oxygen diffusion, and VO_2max. Bassett and Howley (106) state,

> "*Their* (Honig et al., 1992 [111]) *overall conclusion is that VO_2max is a distributed property, dependent on the interaction of O_2 transport and mitochondrial O_2 uptake. We agree with this conclusion. However, this model cannot determine which of these two factors limits VO_2max in the intact human performing maximal exertion. …… If one talks about the intact human being performing maximal, whole body exercise, then the cardiorespiratory system is the limiting factor*."

I do not understand why Bassett and Howley can recognize the importance of peripheral oxygen diffusion (111), yet discount that it is influential in determining VO_2max (even to a small degree) during whole body exercise. Furthermore, how can there be an acknowledgement to a dependence on the interaction between

cardiovascular oxygen delivery and intramuscular oxygen diffusion and transport, followed by the belief that one variable remains to be the most important limitation in all non-diseased active humans? Once again I have to state my support of Noakes criticisms of this line of thinking, and reiterate my interpretation that such thinking is constrained by the persistent confinement of thought on VO_2max within exercise physiology to the components of the Fick models (Figures 10-12).

The second manuscript of Bassett and Howley (106) can be further criticized based on additional content within this manuscript? When concerned with Noakes' criticisms of the low incidence of a VO_2 plateau at VO_2max, Bassett and Howley commented that, "*Failure to achieve a plateau does not mean that these subjects have failed to attain their 'true' VO_2max….. a subject may fatigue just as VO_2max is reached. Thus a plateau may not be evident … For these reasons a plateau in VO_2 cannot be used as the sole criterion for achievement of VO_2max*." No comment is given to the assumption inherent in this line of reasoning that a one minute average is the only means to detect an accurate VO_2 at VO_2max. Furthermore, no argument is made for why Noakes' belief of a low incidence of a VO_2 plateau, and the research of Myers (37) that he uses to support his argument, may be questionable from methodological and subject characteristic issues.

Similar criticisms can be applied to the manuscript of Bergh et al. (107). Rather than reflect on how exercise physiologists interpret VO_2max and make appropriate corrections, these authors once again attacked the rationale Noakes used to explain his alternate theories. As I have mentioned in this manuscript, I also believe that Noakes has not based his opinions on scientific logic. However, that does not mean that Noakes is unjustified in his criticisms of how VO_2max is interpreted in exercise physiology. In my opinion Noakes simply used the incorrect rationale to support his valid criticisms.

I hope that my manuscript reveals that not all exercise physiologists think according the logic presented by Bassett and Howley (1,106) or Bergh et al. (107). Exercise physiologists must realize that application of recent research in cardiovascular and respiratory physiology reveals that there are multiple determinants to VO_2max. The question of what is the single most important determinant to VO_2max may have been acceptable 20 years ago. However, this question is no longer valid today. As I illustrate in Figure 18, there are multiple variables that can influence VO_2max, and the importance of many variables change with different subject and environmental characteristics. As stated by Wagner (110), "*There is clearly no single factor limiting O_2 transport. ….. This is exactly what is expected of an integrated O_2 transport system whose elements are managed in series*." To those who remain in question of all the evidence that leads one to accept this line of reasoning, what is so difficult in the process of realizing the accuracy of this approach, and then accepting it as a valid educational strategy or model for future research inquiry? Is the Fick model so engrained into exercise physiology dogma that we have no resourcefulness to adapt our models and our line of thinking to be more congruent with contemporary research?

SUMMARY AND CONCLUSIONS

Noakes is to be commended for his openness in challenging exercise physiologists to better study and interpret research findings pertaining to VO_2max. Nevertheless, as previously stated, constructive criticism is only meaningful if the criticisms have validity. For example, Noakes began the critical sections of past research in each of his manuscripts with a commentary on the classic research that has developed the notion of a VO_2 plateau at VO_2max (2-4). Based on the poor scientific quality of investigation in these early studies, Noakes argued that there was no proof of a VO_2 plateau that coincides with VO_2max and an oxygen supply limitation to contracting skeletal muscle. Consequently, Noakes proposed his own explanations for a limitation to VO_2 during incremental exercise. The interpretation of the fallibility of the VO_2 plateau concept was the central framework from which Noakes developed all of his hypotheses. Noakes stated; "*If one accepts uncritically that each VO_2max test is always limited by tissue oxygen deficiency, then inappropriate conclusions may be drawn in those tests in which no plateau in oxygen consumption develops*…" (2). "*If the basis for the model* [a VO_2 plateau supporting an oxygen limitation to VO_2max] *is in doubt, then it behooves us to question vigorously the*

further predictions of that original model." (3). "*The cardinal point is that, without the 'plateau phenomenon', the cardiovascular/anaerobic model has no greater claim to be the sole and authentic explanation of exercise physiology and athletic performance than does any other competing model*." (4). Noakes illustrated this line of reasoning in Figure 3 of the final rebuttal manuscript (4).

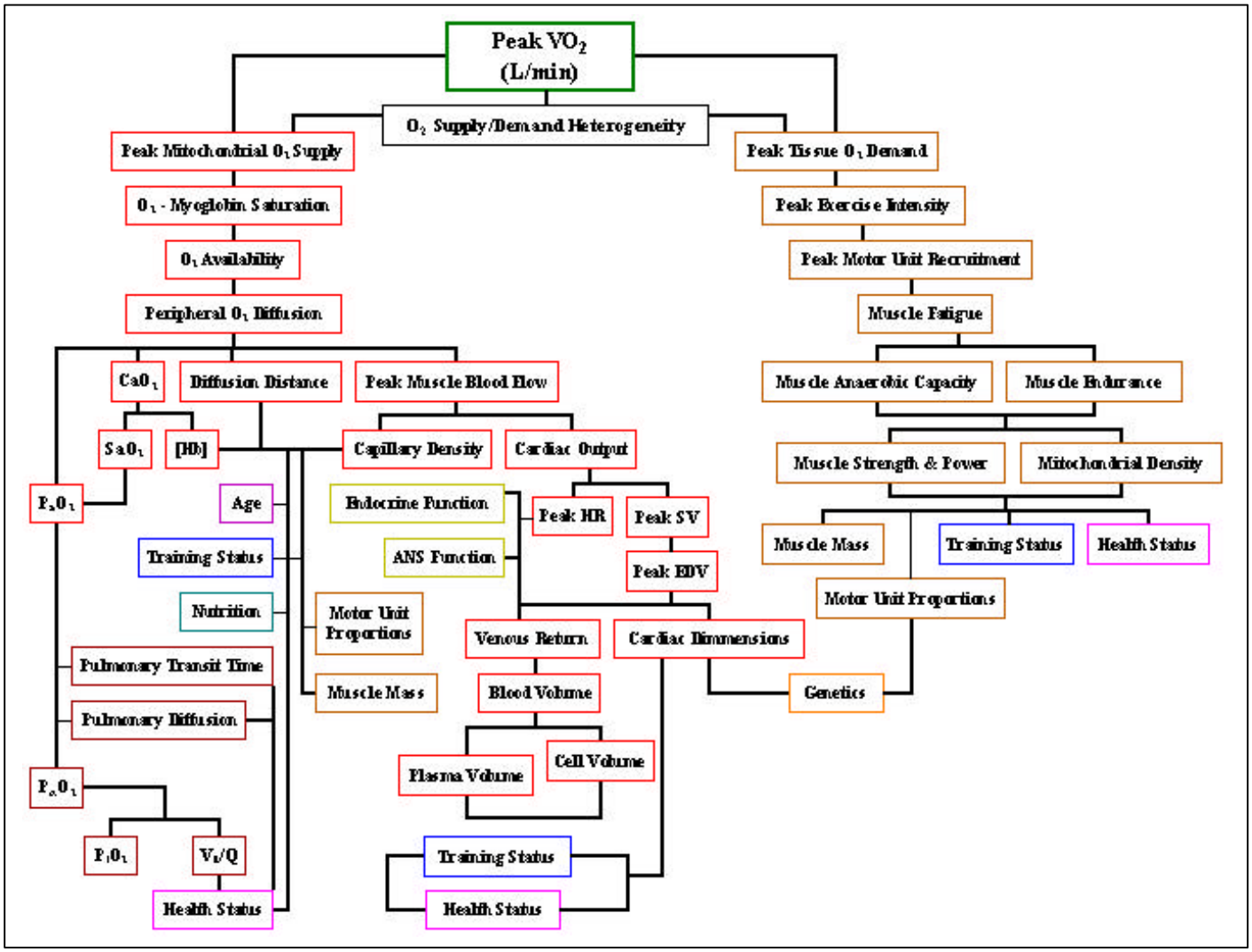

Figure 18: Flow chart illustrating the components of human physiology that combine to influence the capacity of the peak VO_2 attained during incremental exercise testing. Note the identification of training, genetics, health and disease states, and how they can influence determinants of both peak oxygen supply and demand. Components are color coded to show similar physiological origin such as oxygen supply (red), pulmonary function (brown), skeletal muscle characteristics (tan), etc.

Clearly, any evidence that shows that Noakes has been incorrect in his interpretation of data that undermines the existence and documentation (not necessarily the same) of a VO_2 plateau would remove the pillar that supports all of Noakes' alternate explanations. Herein lies the importance of the data I present on the influence of the time averaging interval used to measure VO_2 during incremental exercise. Based on the original data of Table 1, most healthy and active people regardless of training status, gender, age, and test mode (treadmill vs. cycle ergometry), develop a VO_2 plateau at VO_2max when using time averaging durations < 15 s. This is true even when using criteria for a plateau (≤50 mL/min) that is three times as stringent as has been used in the past (17). Clearly, the arguments of Noakes against a VO_2 plateau are incorrect, and the alternate explanations, although interesting, must be viewed with skepticism due to the poor rationale used to justify their existence.

Each of Noakes alternate explanations (Table 3) has been shown to be invalid. The message from this rebuttal to Noakes and Bassett and Howley's exchange (1-4,106) is simple. There is no single determinant to VO_2max as it is a capacity that is influenced by numerous factors (Figure 18), and this fact has been proposed and supported in research by Peter Wagner and his collaborators for almost a decade. The individual importance of these factors varies with training and health status. Nevertheless, for healthy and active to elite-trained individuals, there is overwhelming evidence for an oxygen supply limitation that coincides with a VO_2 plateau when using short interval data averaging (< 15s). This oxygen supply is dependent on each of cardiovascular delivery and peripheral oxygen diffusion from blood hemoglobin to muscle myoglobin. It is likely that the kinetics of oxygen flux from myoglobin to the mitochondria is also important, but as yet no methodology exists to study this component in vivo.

This inquiry into the concept of a VO_2max has revealed several important conclusions;

1) Interpretations of the topic of VO_2max within the discipline of exercise physiology has been too easily directed by superficial physiological assumptions from dated research;

2) The majority of past research of the physiological demands of incremental exercise testing to VO_2max are outdated, use methodology that has questionable application to current computerized methodologies, and have not answered many fundamental questions;

3) The low incidence of a VO_2 plateau reported in past research may be more dependent on data averaging procedures than limitations imposed by cardiorespiratory physiology and muscle biochemistry;

4) The lack of research supported guidelines to measure VO_2max may contribute to errors in measurement and interpretation;

5) The models used by exercise and pure physiologists to explain limitations in the rates of VO_2 are over-simplistic, biased to show a cardiovascular oxygen delivery limitation, and are no longer supported by contemporary research;

6) The peak VO_2 attained at the end of an incremental exercise protocol to volitional exhaustion is explained by multiple variables, which vary in importance depending on the health and fitness status of the subject, and environmental conditions;

7) In healthy individuals, breath-by-breath data should detect a VO_2 plateau, the peak VO_2 attained represents VO_2max, and this value may be associated with a significant intramuscular hypoxia;

8) In healthy recreationally active to elite-trained individuals, the VO_2 plateau at VO_2max is best explained by an oxygen supply limitation that involves multiple components that connect pulmonary respiration to mitochondrial respiration within contracting skeletal muscle. Nevertheless, the intracellular in vivo kinetics of oxygen transfer between hemoglobin and myoglobin and the mitochondria of skeletal muscle that has a

heterogenous profile of oxygen demand and capacity for VO_2 remain unknown due to methodological constraints.

Despite the 77 years since the pioneering published research of Hill and Lupton (15), it is obvious that exercise physiologists need to continue to research the population-specific occurrence and limitations to VO_2max. Based on the data from this manuscript, the VO_2 plateau should be expected to occur in healthy subjects, and may be the only valid criteria to verify VO_2max. Research needs to be completed using today's electronic and computerized technologies to establish valid verification criteria for VO_2max. In addition, the model I propose in Figure 18, as with future models, should be scrutinized and where appropriate, specific components put to the test of research and modified when needed. Exercise physiologists should ensure that models used in research, or to explain research findings, are as close to in vivo conditions as possible so that future facts used in exercise physiology remain facts and cannot be refuted as edifices.

ACKNOWLEDGMENTS

I need to thank my Ph.D. students and fellow faculty at the University of New Mexico for their critical comments and assistance during the writing of this manuscript. This manuscript is written with an honest, and I hope, a professional tone. At times I criticized how exercise physiologists have collected and interpreted data on the topic of VO_2max. In addition, critical comments were directed at specific manuscripts, and as a result to specific researchers. However, I have total respect for all my colleagues, and I feel that the tone of this manuscript is more professional and impartial than any of the key manuscripts (1-5,106,107) that prompted me to write this document. We as exercise science/physiology professionals must realize that constructive criticism is a component of professionalism, and that if we respond correctly, criticism functions to make our field stronger by refining the physiological constructs on which our field is developed. The discipline of exercise physiology needs more criticism, for the uncertainty over how exercise physiologists measure and interpret VO_2max is just one example from many of the questionable research base of the discipline.

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