

A Personal Biography of a Physiological Misnomer^{*}: The Anaerobic Threshold

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Key words

anaerobic threshold, lactate threshold, ventilatory breakpoint, McArdle's disease

accepted 24.09.2021

ABSTRACT

In 1973 Wasserman, Whipp, Koyal, and Beaver published a groundbreaking study titled "Anaerobic threshold and respiratory gas analysis during exercise". At that time, respiratory gas analysis and laboratory computers had evolved such that more advanced respiratory exercise physiology studies were possible. The initial publications from this group on the onset of anaerobic metabolism in cardiac patients, the first breath-by-breath VO_2 system, the first description of the anaerobic threshold, and then later new methods to detect the anaerobic threshold have been and continue to be highly cited. In fact, their 1973 anaerobic threshold paper is the sixth and their 1986 paper is the second most cited paper ever published in the *Journal of Applied Physiology*. The anaerobic threshold concept has also generated > 5500 publications with the rates increasing over time. The publication of two papers that help to refute the "anaerobic" explanation for this phenomenon had no effect on the rates of citations of the original anaerobic threshold papers or the number of anaerobic threshold papers published since. Thus, despite now substantial evidence refuting the proposed anaerobic mechanisms underlying this phenomenon, these papers continue to be highly influential in the discipline of exercise physiology and, perhaps even more explicitly, clinical exercise physiology.

In 1973 Wasserman, Whipp, Koyal, and Beaver published a groundbreaking study titled "Anaerobic threshold and respiratory gas analysis during exercise" [2]. The objective of the present paper is to provide the history, context, and outcomes associated

with this single exercise physiology phenomenon - the "anaerobic threshold".

Historical Background

Lactate has long been known to be a critical metabolic molecule, initially because of its role in fermentation. Later its involvement in metabolism was elucidated and in 1808 lactate levels in the muscles of hunted stags that had been running were shown to be elevated [3]. Subsequently, increased blood lactate levels during and after exercise were demonstrated in humans in a number of 19th century studies. In a classic 1930 study, W. Harding Owles measured blood lactate levels after acute exercise of various intensities and durations, mainly in himself, concluding that "there seems to be some critical rate of walk, above which only did an increase in blood lactate follow the exercise" [4] – perhaps the first hint at a lactate or anaerobic threshold?

From the early 1800's until ~1950 exercise physiology research generally focused on human performance and basic exercise physiology concepts. For example, in 1913 Krogh and Lindhard published a landmark paper addressing "The regulation of respiration and circulation during the initial stages of muscular work" [5] – a prelude to Krogh's muscle capillary studies that resulted in his 1920 Nobel Prize. In 1923 AV Hill (another Nobel Prize awardee) and Lupton published one of the first studies addressing VO_2max titled "Muscular exercise, lactic acid and the supply and utilization of oxygen" [6]. Margaria, Edwards and Dill in 1933 also published a classic paper describing the alactacid and lactacid O_2 debts following a range of work rates [7]. In 1938 Robinson published his Harvard Fatigue Lab dissertation assessing the responses of 93 males 6–91 yrs old to progressive exercise in one of the first aging exercise physiology studies [8]. In 1939 Christensen and Hansen published perhaps the classic human performance study as a series of five papers in the *Skandinavian Archives of Physiology* showing that the sub-

strates used during exercise were dependent on work rate, work duration, previous diet, and state of training [9].

Although hardly a clear delineation, around ~1950 substantial research began to focus on clinical exercise physiology. For example, in the 1940's exercise testing was used to assess cardiovascular (CV) function and physical work capacity in patients with various CV diseases. In the late 1950's and early 1960's research began to document the benefits of exercise training for individuals with a wide range of CV diseases [10, 11]. A similar progression also occurred relative to pulmonary testing and diseases, with exercise spirometry testing to assess lung diseases first appearing in the 1950's [12–15] and the benefits of exercise training for a number of pulmonary pathologies being documented beginning in the 1960's [16].

Thus, the evolution of exercise physiology research resulted in an environment in the late 1960's/early 1970's where it had begun to address the spectrum from basic exercise physiology to human performance to clinical exercise physiology. Also, at the same time, there were rapid advances in respiratory gas analyzers and laboratory computers, both of which contributed to a dramatically expanded capacity to assess a wider range of exercise physiology variables.

Evolution of Respiratory Gas Analyses

Analysis of the respiratory gases has received substantial attention since the early 1800's as a result of their involvement in mammalian metabolism. In 1898 John Haldane described improvements on a previous respiratory gas analysis method [17]. The apparatus consisted of a series of calibrated glass components to quantify fractions of O_2 and CO_2 in an unknown sample. Essentially, the volume of the total gas sample was assessed at baseline. The CO_2 was then removed in a closed environment via reaction with potas-

^{*} the author acknowledges the initial usage of this term by Dr. George Brooks [1].

sium hydroxide and the new volume was used to calculate the CO₂ fraction. Similar procedures were then employed using potassium pyrogallate to absorb the O₂ and the new volume was used to calculate the O₂ fraction in the sample. In 1948, Scholander published a micro-method using a much smaller device to accurately assess gas fractions in samples as small as 0.5 ml using similar volumetric methods [18]. BB Lloyd in 1958 developed the Lloyd-Gallenkamp device, a new volumetric respiratory gas analyzer that improved upon the Haldane analyzer. When reading the exercise physiology literature, you will find that many papers up until the late 1980's indicated that commercial O₂ and CO₂ mix gas tanks were first validated versus the Lloyd-Gallenkamp or Scholander methods prior to their use in calibrating the new electronic respiratory gas analyzers.

These chemical volumetric methods all required 4–6 minutes for the analysis of an unknown sample, with duplicate analyses requiring ~10–15 min, with consecutive respiratory gas samples also needing to be “stored” in some way without leakage or diffusion while samples were analyzed. These methods also required a high degree of technical proficiency and they all required the use of mercury, a chemical now known to have severe toxic effects.

In the 1950's, the age of electronics ushered in a new era of dramatically enhanced respiratory gas analysis methods. The first two major developments were the nondispersive infrared LB-1 and LB-2 CO₂ analyzers and the polarimetric OM-11 O₂ analyzer from Beckman Instruments, which rather rapidly became the gold standard in exercise physiology labs. Interestingly, this CO₂ analyzer was initially developed to monitor CO₂ levels on submarines. The O₂ analyzer was based on a World War II design by Linus Pauling and was later used in American spaceflights. The primary benefit of these analyzers was that they had very short delay times and very fast response times. Thus, they were **DRAMATICALLY** faster than the previous respiratory gas analyzers, which opened entirely new opportunities for physiologists in terms of measuring O₂ and CO₂ fractions. Another marked advance in respiratory gas analysis occurred in the 1970's when Perkin-Elmer introduced its

mass spectrometer medical gas analyzer which gave very rapid and stable results and also could measure a wider range of gases.

Thus, the evolution of respiratory gas analyzers over the last ~100 yrs was also at a point by the 1960's where they could assess gas fractions very rapidly and accurately. This represented a huge advancement, but initially these benefits couldn't be fully utilized because these analyzers were still being used to simply measure gas fractions in mixed expired gases collected over 30–60 sec periods or the values were recorded on graphical recorders to later identify the end tidal fractions for each breath. At roughly the same time, dramatic advances were also made in computer technology, especially in terms of incorporating them into labs where substantial amounts of data could then be “collected”, analyzed, and utilized to their full extent.

Evolution of Laboratory Computers

To put history in context a bit, the “computer” age actually “began” in 1801 when a French inventor developed a weaving loom that was run by a type of punched cards. Then from 1833–1871 Charles Babbage designed the Babbage Differential Engine which could calculate tables of data, although he realized that it could eventually be “programmed” to perform a wide range of calculations. Later the US government realized it had a major problem because, as a result of population expansion, the 1880 Census took 7 yrs to analyze by hand! They then hired Herman Hollerith, an American statistician and inventor, who developed an electromechanical device based on punch cards to tabulate the ever-expanding census data much more rapidly. Hollerith went on to found IBM and is still memorialized in programming circles by Hollerith strings and constants. In 1936 Alan Turing invented the Turing Machine – a device “capable of computing anything that is computable”. In 1943 researchers at the University of Pennsylvania developed what many call the first “true” programmable computer – the Electronic Numerical Integrator and

Calculator (ENIAC), a device that filled a 20 ft by 40 ft room.

Obviously, these initial computers were very large, which provided the impetus to develop a smaller “mini-computer” – which rather than meaning a miniature computer actually meant a minimal computer, i. e. - that it contained the minimal components to be considered a computer. One key initial step in this process was the 1957 formation of the Digital Equipment Corporation (DEC) with a goal to develop “interactive computing” devices which individuals could program and interact with to generate input and output. DEC delivered their initial PDP-1 (Programmed Data Processor-1) in late 1959. The PDP computers went through numerous advancements over time with the PDP-16 released in 1972. At one time in the late 1960's DEC computers were second only to IBM in terms of computer sales. These devices were also useful as laboratory computers as they could accept input from various devices through analog to digital convertors and because at ~4.5 ft long × 7 ft high × 3 ft deep they could fit in a lab setting. The Varian Corporation also shipped their first 620/i mini-computer in 1967, which was the device Whipp and Wasserman used for their breath-by-breath VO₂ system [19, 20].

Intersection of the Evolution of Exercise Physiology and Technology Developments

Thus, by the late 1960's and early 1970's respiratory gas analysis systems and laboratory computer technology had developed to the point where the physiological questions raised by basic and clinical exercise physiologists could be extended to much more precise and rapid analyses of respiratory gases and laboratory computers also become available to truly capitalize on the amount of data this new generation of respiratory gas analyzers could generate.

Initial Anaerobic Threshold Publications

Karlman Wasserman, the senior author on the initial seminal AT publication [2], published ~360 manuscripts over his career as a pre-eminent respiratory physiologist and physician (total citations ~33 000, ISI h-index 85). He already had ~50 publications prior to his seminal 1973 AT publication [2]. Dr. Wasserman published 89 manuscripts in collaboration with Brian Whipp starting in 1969 and Dr. Whipp published another 137 manuscripts over the course of his distinguished career (total citations ~24 000, ISI h-index 74). Dr. Wasserman began the line of research that led to the AT paper with a 1964 publication titled “Continuous measurement of ventilatory exchange ratio during exercise” to detect “when oxygen supply is inadequate” [20]. In this study ventilatory exchange ratio was quantified based on the end-tidal gas fractions determined from graphical records. They concluded that “the level of work at which the RER increases appreciably above its resting level corresponds to the level at which arterial lactate increases and plasma bicarbonate falls.” They noted that at low levels of work the $\Delta R/VO_2$ was almost constant or increased only slightly. “The curve then rose steeply as the workload increased” [20]. In this paper no mention was made of a “threshold” or an “anaerobic threshold”. They also concluded that “the usefulness of R as an indication of anaerobic metabolism is a result of oxygen deficiency and NO OTHER FACTORS” (capitals mine) – already defining the phenomenon based on a proposed, yet still unstudied, underlying mechanism. To be complete and perhaps a bit more fair, they were basing their “conclusion” on substantial evidence showing that low oxygen levels (i. e., hypoxia, altitude, etc.) led to increased blood lactate concentrations.

Others had previously investigated the possibility that gas exchange measures might provide additional insights into aerobic as well as anaerobic metabolism during exercise. Nearly a century ago now, Hill, Long, and Lupton indicated that “a study of the respiratory quotient, if undertaken with sufficient caution, may throw light, not so much on the bodies being oxidized as on

the acid-base changes occurring as a result of exercise and recovery” [21].

Also in 1964 Wasserman and Mclroy published “Detecting the threshold of anaerobic metabolism in cardiac patients during exercise” [22] in which they sought to determine if assessing the onset of anaerobic metabolism during progressive exercise could quantify the CV fitness of this population without requiring a maximal exercise test. They used the same methods as in their previous 1964 paper described above and concluded that “the measurement of the ventilatory gas exchange ratio during exercise is a useful test of cardiovascular function. It answers the question of how much work a subject can do before the heart fails to meet the tissue oxygen requirements” [22]. In the paper the authors consistently called this critical point “the threshold of anaerobic metabolism” or “the onset of anaerobic metabolism”. However, they did use the term “anaerobic threshold” in the text in describing the results of their Case Studies 2 and 3 and also in the captions of their original **Figs. 2 and 7**.

In 1973 Beaver, Wasserman, and Whipp published another critical paper titled “Online computer analysis and breath-by-breath graphical display of exercise function tests” [19]. Based on their previous work, they believed it would be useful to make “continuous calculations of respiratory variables over the duration of extended physiological studies” which they clearly indicated was now made possible with the new generation of respiratory gas analyzers and the lab computers [19]. In this paper they described and validated the first breath-by-breath VO_2 system based on a Beckman LB-1 CO_2 analyzer, a Westinghouse Model 211 O_2 analyzer, and a Fleisch pneumotachograph. But the key was that they were linked via analog inputs to a Varian 620/i computer that had 12 000 (yes – 12k, not 12 mb or 12gb) 16-bit words of memory in which to run the actual program and store the data. And the sampling was done at 50 Hz, when previously only one sample could be determined per breath! Clearly this system represented a quantum leap forward in the assessment of respiratory variables during exercise.

Later in that same year Wasserman et al. published the seminal AT paper titled “Anaerobic threshold and respiratory gas exchange during exercise” [2], wherein they stated that they were able to take advantage of “the development of rapidly responding gas analyzers and automated data processing computers” [2]. Their goal was to describe and validate an exercise test to assess the AT – which they defined as “the level of work or O_2 consumption just below that at which metabolic acidosis and the associated changes in gas exchange occur”. They again used the Beckman CO_2 analyzer and a Westinghouse M211 O_2 analyzer, but they indicated that later in their study they used a Perkin-Elmer mass spectrometer for their gas analyses. From these data they generated the classic AT detection criteria during progressive exercise of 1) a nonlinear increase in V_E , 2) a nonlinear increase in VCO_2 , 3) an increase in end-tidal pO_2 without a decrease in end-tidal pCO_2 , and 4) an increase in R, although they did indicate that the increase in R was the least sensitive of these criteria. They concluded that “The anaerobic threshold is a useful concept. Its application during exercise testing should considerably increase the information gained regarding cardiovascular function in health and disease” [2].

In 1986 Beaver, Wasserman, and Whipp published a follow-up paper titled “A new method for detecting anaerobic threshold by gas exchange” with the goal to “study the changes in respiratory gas exchange during an incremental exercise test to derive an objective mathematical method to reliably locate the anaerobic threshold” [23]. In this paper they developed and validated the V-slope method to detect the AT, by mathematically quantifying the point at which VCO_2 increased out of proportion to VO_2 during progressive exercise. They found that their new method yielded the same results as those from the visual inspection of the same data by 6 reviewers experienced with these assessments. However, they noted that the V-slope method yielded a coefficient of variation for the AT VO_2 that was ~20% that of the panel average. Thus, they concluded that “...the V-slope analysis, which detects the increased CO_2 production from buffering metabolic acid, addresses the central

mechanism of the anaerobic threshold and is therefore more widely applicable” [23].

The Author’s Personal Side of the Anaerobic Threshold

In 1972 I began graduate school at the University of Wisconsin with Drs. Fran Nagle, John Mullin, and Bruno Balke. In that same year Whipp and Wasserman became the first to assess the kinetics of VO_2 and other respiratory variables on a breath-by-breath basis at the onset of exercise [24] and then in 1973 at the offset of exercise [25]. They found that the overall kinetics at the onset of exercise were generally slower at higher absolute exercise intensities and that at moderate to higher intensity exercise the rapid exponential increase in VO_2 during the first 1–2 mins of exercise was followed by a further slow increase in VO_2 over the subsequent 3–4 mins [23]. They also made a brief point that increased fitness might be associated with more rapid exercise VO_2 kinetics at the same absolute work rate based on comparing the responses of two men with $\text{VO}_{2\text{max}}$ values of 19 and 40 ml/kg/min. I was intrigued by these findings because as a runner, I had noted that pretty much as hard as you were breathing in the first five mins or so of a run, was generally how hard you were going to be breathing for the remainder of the run if you maintained the same pace. Also, I wondered if their “fitness” comparison with a 40 yr old with a $\text{VO}_{2\text{max}}$ of 19 ml/kg/min might have been affected by additional pulmonary and CV issues that could have altered his exercise responses above and beyond his lack of fitness.

I was working with the University of Wisconsin distance runners at the time, so I had a ready and available highly-trained population (Lucky Point #1). Now, all I had to do was to get the breath-by-breath VO_2 system – clearly no small problem. However, as luck would have it (Lucky Point #2) my advisors had contacts at the University of Wisconsin Medical School who were also interested in developing a computer-based respiratory gas exchange analysis system. Working with the equations from Beaver, Wasserman, and Whipp [19], for my master’s thesis we developed what was perhaps the third breath-by-

breath VO_2 system in the world. However, this system simply integrated the expired gas fraction curves to derive “mixed” expired gas fractions that were not weighted for their instantaneous flow signals; but the steady-state VO_2 values generated by this system did validate against both those predicted for the work rates and Douglas bag (i. e. - the timed collection of expiratory gases in rubberized neoprene bags and later meteorological balloons for subsequent gas and volume analyses) values. We found that VO_2 kinetics were clearly slowed at higher work intensities and that the highly-trained individuals ($\text{VO}_{2\text{max}} = 70$ ml/kg/min) had more rapid VO_2 kinetics at the onset of exercise than untrained individuals ($\text{VO}_{2\text{max}} = 50$ ml/kg/min) at the same absolute work rates, but the differences were only of borderline significance at the same relative work rates [26].

I presented these results at the 1975 FASEB meetings, where the first person to the microphone following my talk was Brian Whipp. I was shaking in my boots when I saw him, but he winked at me as he approached the microphone, I breathed a huge sigh of relief, and he complemented me on the study and asked a pretty easy question. Also at that meeting, I had lunch with Dr. John Holloszy, where he pretty much indicated that the study I had presented was the first one they wanted to do in their new human exercise physiology lab at the Washington University School of Medicine. Oh, and by the way, would you like to come work with us as a postdoctoral fellow (Lucky Point #3)?

As I wanted to continue this VO_2 kinetics research for my doctoral dissertation, we had to develop a true breath-by-breath VO_2 system where the instantaneous expired gas fractions were weighted by the time-aligned flow signals. More luck for me as the lab where I worked in the Medical School had just purchased a Perkin-Elmer respiratory mass spectrometer (Lucky Point #4). Also, my major professor advised me to take an undergraduate Introduction to Computing course (remember – 1973) because “I think computers are going to be important in the future” (Lucky Point #5)! The course introduced FORTRAN programming and I was hooked!

Given this “massive” background I then taught myself machine language programming on my first PDP 12 minicomputer. It took me a year of programming to develop a validated breath-by-breath VO_2 system. During this time, I was in contact with Brian Whipp who generously gave me further insights into the complex analysis algorithms. I then conducted my dissertation study wherein we assessed the exercise and recovery VO_2 responses at three relative exercise intensities and two exercise durations finding no evidence for lactate underlying either the second slow component of the exercise or the recovery VO_2 response [27, 28].

In 1976 I arrived at the Washington University School of Medicine as a new PhD to begin an NIH post-doctoral fellowship with Dr. Holloszy. During this time, again as luck would have it, both financially and scientifically (Lucky Point #6), I was also supported by Dr. Michael Brooke and the Jerry Lewis Neuromuscular Disease Center. Every Tuesday I tested their patients using both acute and prolonged exercise protocols with and without prior manipulation of diet or substrate stores to assess the physiological impact of their disease [29–31].

Dr. Holloszy’s group had a Friday data presentation/journal club involving postdoctoral fellows and researchers from both the human and the animal research labs – thus, a wide range of exercise physiology topics was addressed. One Friday, I presented exercise test data on various neuromuscular disease patients with one of them having McArdle’s disease. After I explained the underlying pathology, John Ivy asked “So, did that patient have an anaerobic threshold?” I responded that we didn’t actually use a test appropriate to assess the AT. But then he asked the key question “OK, but from the beginning to the end of their exercise test, did they hyperventilate?” And the answer was a clear and resounding YES. So, he asked if we thought we could get more such patients? To which I responded, “I hope so!”

McArdle’s disease, a rare neuromuscular disease with most cases going undiagnosed, was first identified in the medical literature in 1951 by the British physician Brian McArdle [32]. The pathology in these

patients is the complete or relative lack of the phosphorylase enzyme in skeletal muscle. Thus, their rate of skeletal muscle glycogen breakdown is reduced to the point where all of the diminished rates of pyruvate generation can be processed via the Krebs Cycle rather than going to lactate to maintain skeletal muscle NAD⁺ levels. The initial case described by McArdle was “diagnosed” by performing a handgrip exercise test with occluded arm blood flow. As you can well imagine, this would elicit a huge increase in blood lactate levels in healthy individuals, but lactate levels did not increase whatsoever in this, and all other, McArdle’s disease patients [32]. The lack of skeletal muscle phosphorylase and the inability to break down glycogen at high rates were subsequently verified in skeletal muscle biopsy samples from these patients.

My discussions with Dr. Brooke indicated that they had two McArdle’s patients in the St. Louis area and two others in Indianapolis and West Virginia (Lucky Point #7). As I indicated in the eventual paper, 4 participants doesn’t sound like a very substantial sample size. However, at the time these 4 patients accounted for 10% of the total world McArdle’s disease population described in the medical literature. So, from an alternative point of view, how many studies include 10% of the total world population, however it is defined?

We clearly demonstrated that our four McArdle’s patients had ventilatory responses

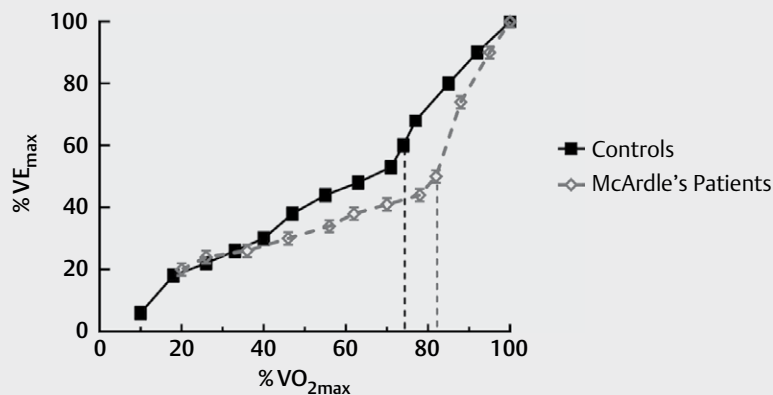
with progressive exercise that were similar to those of 26 normal healthy individuals (► Fig. 1), with a ventilatory breakpoint (“anaerobic threshold”???) at $81 \pm 5\%$ $\text{VO}_{2\text{max}}$ versus $73 \pm 2\%$ $\text{VO}_{2\text{max}}$ in the controls [33]. These similar ventilatory responses occurred despite the McArdle’s patients exhibiting no increase in their blood lactate levels whatsoever during or following the maximal exercise test (► Fig. 2). Given the heavy reliance of Drs. Whipp and Wasserman on arterial blood gas measurements in their initial AT studies, Ed Coyle raised the possibility of obtaining similar samples in our patients. While we couldn’t obtain arterial blood gas samples, we did assess venous H⁺ levels. And thank goodness we did because the results clearly showed the markedly disparate responses between the two groups at work intensities exceeding the ventilatory breakpoint, with venous [H⁺] increasing markedly after this point in the healthy participants (a respiratory alkalosis not able to completely overcome the underlying metabolic acidosis) whereas venous [H⁺] decreased markedly in the patients after this point (a respiratory alkalosis without an underlying metabolic acidosis)(thank you Jerry Dempsey) (► Fig. 3) – a rather clear demonstration that this critical physiological breakpoint does not appear to be directly caused by the metabolic acidosis.

This study was presented at the 1981 Miami, FL American College of Sports Medicine meeting. Now 40+ yrs later, I think it

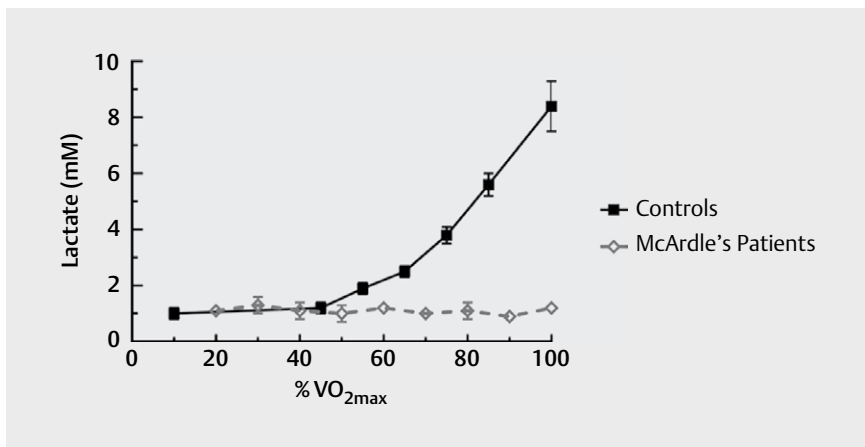
is appropriate for me to apologize for my over-exuberance in this abstract. The title of the abstract was “Ventilatory threshold without increasing blood lactate levels in McArdle’s patients – Anaerobic Threshold?” I should have ended the title before the final phrase “- Anaerobic Threshold?”. Also, in the first sentence of the abstract in the phrase “commonly (yet misleadingly) termed the anaerobic threshold” the “yet misleadingly” should not have been there as by that point in the abstract the statement was clearly premature. Finally, in the last sentence stating that the relationship others had observed between the changes in ventilation and blood lactate levels during progressive exercise “were fortuitous” is hardly consistent with any scientific hypothesis. At the meetings other investigators approached me (Steven Lewis most prominently) to indicate that after seeing our abstract, they had tested a McArdle’s disease patient and found that they also hyperventilated markedly with increases in exercise intensity.

A second apology is also necessary here. One of the reviewers of this original McArdle’s paper [33] contacted me before it was published and requested the figures for an upcoming debate with one of the proponents of the AT. I sent the graphs and heard later that the AT proponent was totally blindsided when these graphs were presented, especially since the graphs were not available to the general scientific community at that time. This was not appropriate on my part and my answer should have been “No” to that request.

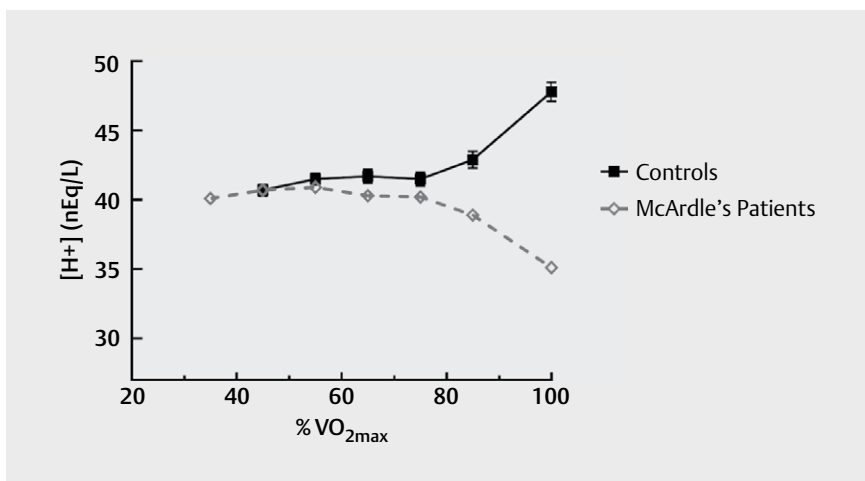
Sometime after publication, I received a Letter to the Editor from Dr. Whipp and asked if I would like to respond. However, while I cannot remember all of the details of the initial letter, I responded that I did not think the letter was appropriate because it accused me of using “legerdemain” to generate the results in the McArdle’s patients. The Oxford Dictionary definition of legerdemain is “skillful use of one’s hands when performing conjuring tricks”, so perhaps you can see why I wanted no part of responding to such a letter. A revised version of the letter came to me much later and I think we had a useful exchange of points of view [34, 35].



► Fig. 1 Ventilatory responses to progressive exercise in McArdle’s disease patients (circles, dashed line) and healthy control participants (closed squares, solid line) [33].



► **Fig. 2** Blood lactate responses to progressive exercise in McArdle's disease patients (diamonds, dashed line) and healthy control participants (closed squares, solid line) [33].



► **Fig. 3** Venous [H⁺] responses to progressive exercise in McArdle's disease patients (diamonds, dashed line) and healthy control participants (closed squares, solid line) [33].

So Jim, you did some interesting work with one- and two-component exercise and recovery VO₂ kinetics curves for your dissertation with a major focus on the potential role of blood lactate as a mechanism underlying the second component of the recovery VO₂ response. Since you showed that your McArdle's patients didn't alter their blood lactate levels with maximal exercise, what did their recovery VO₂ kinetics show? Uh (stumble, stumble) – we took them off the VO₂ system at the end of the maximal exercise test. So, they had to recover anyway, but you didn't measure their recovery VO₂ responses? Yes – aren't we brilliant scientists?

Thus, in a follow-up we studied five McArdle's patients, only one of whom was in the previous study, age-matched healthy controls, and older healthy individuals VO_{2max}-matched to the McArdle's patients [36]. They underwent progressive exercise to their maximal capacity; VO₂ was assessed for 6 mins prior to, during, and for 15 mins after exercise. These McArdle's patients again showed a ventilatory threshold similar to that of the two control groups, again without any increase whatsoever in their blood lactate levels. In addition, the recovery VO₂ kinetics in all three groups were best fit by a two-, rather than a one-, component exponential model, with there being no differences between any of the groups in terms of the time course and magnitude parameters, providing further ev-

idence that the second slower recovery VO₂ component may well not have a "lactacid" mechanism underlying it.

Subsequent History of the "Anaerobic Threshold"

We concluded our first McArdle's disease patient's paper by stating "Clearly, further research is necessary to determine which signal or signals results in the altered cardiovascular, respiratory, and metabolic responses occurring at or very near the point where ventilation increases abruptly" [33]. And wow - was that an understatement for what followed!

Since then, there have been untold numbers of symposia, poster sessions, oral sessions, and publications addressing the AT. In fact, at the 2019 national ACSM meeting in Orlando, FL a symposium was held titled "Anaerobic Threshold: 50+ Years of Controversy", the general contents of which were also published recently in the *Journal of Physiology (London)* [37]. The symposium was chaired by Michael Hogan (California – San Diego) and presentations were given by researchers focused on lactate metabolism and the physiological and applied aspects of the AT. Perhaps the best summary of this Symposium, and maybe of all AT research, was provided by a quote from Brian Whipp relayed via Harry Rossiter (UCLA) – "the term anaerobic threshold seems to polarize investigators into those who believe it to be a milestone and those who believe it to be a millstone" [38]. On the millstone side, Bruce Gladden (Auburn) made the strong statement that "Anaerobic threshold is an inappropriate term because it implies a mechanism that is refuted by several lines of evidence" [39]. Also on the millstone side, David Poole (Kansas State) indicated that "Thresholds represent fundamental "tipping points", teaching us physiological control mechanisms BUT problems of definition, measurement, and interpretation create confusion" [40]. On the milestone side in terms of human performance, Harry Rossiter cited data from Faude et al. [41] indicating that a substantial number of studies have reported strong linear correlations between the lactate

threshold and distance running performance, a point initially raised in 1970 by Dave Costill with directly measured blood lactate levels during submaximal exercise [42]. From a clinical perspective, Dr. Rossiter summarized a substantial body of research showing that a patient's AT is strongly and inversely related to their development of post-surgical complications, especially CV events [43, 44]. Thus, this critical "tipping" point during submaximal exercise is clearly of substantial physiological, clinical, and performance significance, although the mechanisms underlying it continue to be debated.

Scientific Impact of the Anaerobic Threshold Concept

Another important question is whether the AT concept had an impact on the field of exercise physiology. One imperfect but widely used method to assess the impact of a paper is its citation rate. The original Wasserman et al. AT paper [2] is clearly highly impactful having been cited 1555 times through the end of 2019, or ~32 citations/yr over the past 45 yrs (► Fig. 4). Furthermore, their 1986 paper [23] on newer methods to detect the AT has been cited ~2700 times, a rate of 77 citations/yr. And Wasserman's initial 1964 [22] paper on AT in cardiac patients has also been cited nearly 600 times, a rate of ~11 citations per yr since its publication. Together these three seminal AT papers have been cited a total of ~5000 times, which averages out to a rate of ~120 citations per year since they were published, or once every three days. All three of these papers also continue to be cited at very high rates with the averages amounting to 17, 45, and 135 (total ~200) citations per yr over the last 10 yrs for the three papers. These averages for the last 10 yrs are ~40% greater than their average citation rates over their entire history, indicating that they continue to be cited at very high rates.

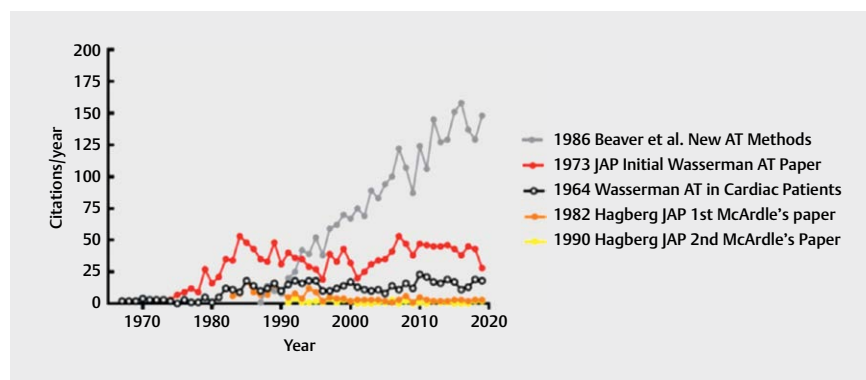
Another further and dramatic demonstration of the impact of these papers is that the 1986 Wasserman paper on new methods to identify the AT [23] is the most cited exercise physiology paper and the second most cited article ever published in the

Journal of Applied Physiology. Furthermore, its citation rate is ~75% higher than the second most cited exercise physiology article published in that Journal. Also, the original 1973 Wasserman AT paper [2] is the third most cited exercise physiology article ever published in the Journal of Applied Physiology.

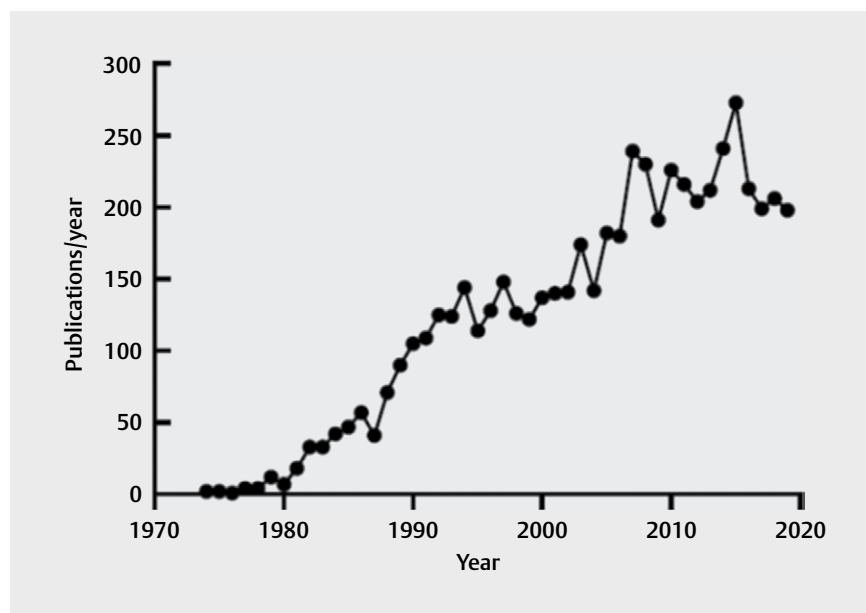
Another measure of the impact of a concept, especially in the case of a newly-coined term, is the number of papers generated related to the concept. These data also continue to strongly substantiate the impact of the AT on the discipline. A PubMed search for "anaerobic threshold" identified ~5650 papers published since 1973 until the end of 2018, which averages

~120 such publications each yr since 1973 – or one every three days for the past ~50 yrs (► Fig. 5). Also, the number of such publications in the last 10 yrs averages 217 papers/yr – well above the average across all the yrs since the original AT publication [2](► Fig. 5). Thus, the AT concept has generated a substantial number of papers and they continue to appear at high rates.

So, how impactful were the two McArdle's patient papers that questioned the mechanism proposed to underlie the AT? Relative to this, the initial 1982 McArdle's disease patient paper [33] has been cited 182 times since its publication (► Fig. 4). To put this in perspective, this amounts to only 11% of the citations for the original Wasser-



► Fig. 4 Citation histories of the key anaerobic threshold publications.



► Fig. 5 Publications per year identified via PubMed searches on the term "anaerobic threshold".

man AT paper [2] and only 7% of the citations for the 1986 Wasserman new AT methods paper [23]. The second McArdle's disease patient paper [36] has only been cited 34 times since its publication. Thus, the original Wasserman AT papers were clearly cited substantially more, in fact at 10–14 times higher rates, than the two papers that questioned the mechanism proposed to underlie the AT.

Given the supposed self-correcting nature of science, another important question is whether the McArdle's disease papers had any impact on the citation histories of the seminal AT publications. Clearly if a scientific finding was subsequently found to be incorrect, in terms of the methods, the data, or the mechanistic explanations, it would be expected that the citations to the original publications would decrease after that point in time. However, as shown above, the citation histories of these papers clearly show that the highest citation rates for these papers have all been in the last ~10 yrs, well after the publication of the McArdle's disease patient papers (► Fig. 4). The same trend also holds for the number of AT papers being published, with the rates again being the highest in the last 10 yrs. This provides strong evidence that the McArdle's disease papers actually had no discernable effect on these two outcomes relative to the impact of the AT concept.

Thus, clearly the citations for the seminal Wasserman AT papers and the number of publications related to this concept have increased substantially over time and both remain at very high levels, despite strong evidence that the phenomenon is actually misnamed. However, the data relative to the continued high rates of AT publications also shed some further light on where much of the continued interest in this phenomenon is derived. As indicated above (► Fig. 5), a substantial number of AT articles have continued to appear in the scientific literature. Linear regression analyses of these data indicate there is a highly significant increase in the rates of "AT" publications over time since the original 1973 publication as evidenced by an average increase of ~6 such publications each yr over the last 45 yrs, with a correlation of 0.97 ($P < 0.00001$). On the other hand, the rate of increases in AT papers over time in the two exercise physiology journals

► **Table 1** Rates of increase in anaerobic threshold publications over time in various sources.

Publication Source	Slope *	Correlation (p-value)	Total Citations
All Sources	5.9	0.97 ($p < 0.00001$)	5650
European Journal of Applied Physiology	0.3	0.60 ($p < 0.00001$)	360
International Journal of Sports Medicine	0.2	0.67 ($p < 0.00001$)	267
Journal of Applied Physiology	0.1	0.26 ($p = 0.85$)	255
Medicine and Science in Sports and Exercise	0.1	0.36 ($p = 0.015$)	241
Journal of Sports Medicine and Physical Fitness	0.1	0.58 ($p = 0.00003$)	183
British Journal of Sports Medicine	0.1	0.68 ($p < 0.00001$)	60
Six Exercise Physiology Journals Above	0.9	–	1366

* slope is expressed in the increase in citations in that source per yr from 1973 until the end of 2019 as determined by simple linear regression.

with the most "AT" papers (European Journal of Applied Physiology, International Journal of Sports Medicine) have increases of only 0.3 and 0.2 papers/yr, respectively, over this same general time frame (► Table 1). In addition, the next four exercise physiology journals in terms of published "AT" papers over time all have rates of increases which, while generally highly statistically significant, amount to 0.1 paper/yr. And the increases in AT papers over time in these six leading exercise physiology journals amounts to a total of slightly less than 1 paper/yr. Thus, the rates of increase in AT papers per yr published in the general literature are 20–60 times higher than the rates of increases in AT papers in the six leading exercise physiology journals and the rates of increase in AT papers/yr in the total literature is still ~6 times the combined rate of increase across the six leading exercise physiology journals. Thus, the overwhelming majority of AT papers (~85%) are appearing in non-exercise physiology journals, with many to most of these journals being related to clinical exercise physiology.

Exercise Physiology Texts and the Anaerobic Threshold

All exercise physiology textbooks since the mid 1980's have addressed the AT concept. In fact, in 1984 Brooks and Fahey referred to the AT as a "misnomer" and termed it the lactate inflection point using the McArdle's patient data as one of the primary pieces of evidence [45]. All of the exercise physiology texts generally address both the milestone vs millstone issues surrounding the AT. On the millstone side, they all question

the proposed underlying "anaerobic" mechanism and raise issues with the terminology of this inflection point. On the milestone side of the ledger, they also quite consistently acknowledge that this exercise intensity represents an inflection point that is of critical physiological and metabolic significance.

Summary and Conclusions

Roughly 50 yrs ago, Wasserman and colleagues published their groundbreaking AT study. Their study represented the culmination of the evolution of respiratory gas analysis and laboratory computers to the point where such physiological studies were now possible. The initial publications from this group continue to be highly cited, with two of them being the second and fourth most cited papers ever published in the Journal of Applied Physiology. Further evidence of its impact is the fact that the AT concept has generated >5500 publications with the rates also continuing to increase over time. The publication of two papers that seriously question the "anaerobic" mechanism for this critical physiological phenomenon [33, 36] had no discernible effect on the rates of citations of the original AT papers or the number of AT papers published since. Thus, despite substantial evidence refuting the proposed "anaerobic" mechanisms underlying this phenomenon, these papers continue to be highly influential in the discipline of exercise physiology and perhaps even more explicitly in the discipline of clinical exercise physiology.

Acknowledgements

This paper is dedicated to Dr. Brian J. Whipp and Jeffrey Miller, who both left us FAR too early and to the 2020 passing of Dr. Karlman Wasserman.

Conflict of Interest

The author has no conflicts of interest relative to this manuscript. The author asserts that the manuscript is consistent with the IJSM ethical standards [46].

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published online 08.12.2021

Bibliography

Int J Sports Med 2022; 43: 391–400
DOI 10.1055/a-1664-8854
ISSN 0172-4622
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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany