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Scientific Progress or Regress in Sports Physiology?

Invited Commentary

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ABSTRACT

In modern societies there is strong belief in scientific progress. But unfortunately a parallel partial regress occurs because of often evitable mistakes. Mistakes are mainly forgetting, erroneous theories, errors in experiments and manuscripts, prejudice, selected publication of “positive” results and fraud. An example for forgetting is that methods introduced decades ago are used without knowing the underlying theories: basic articles are no longer read nor cited. This omission may cause incorrect interpretation of results. For instance false use of actual base excess instead of standard base excess for calculation of the number of hydrogen ions leaving the muscles raised the idea that an unknown fixed acid is produced additionally to lactic acid during exercise. An erroneous theory led to the conclusion that lactate is not the anion of a strong acid but a buffer. Mistakes occur after incorrect application of a method, exclusion of unwelcome values, during evaluation of measurements by false calculations, or during preparation of manuscripts. Coauthors as well as reviewers do not always carefully read papers before publication. Peer reviewers might be biased against a hypothesis or an author. A general problem is selected publication of positive result. An example of fraud in sports medicine is the presence of doped subjects in groups of investigated athletes. To reduce regress it is important that investigators search both original and recent articles on a topic, and examine conscientiously the data. All coauthors and reviewers should read the text thoroughly and inspect all tables and figures in a manuscript.

Key words: forgetting, erroneous theories, mistakes in experiments and manuscripts, selected publication, fraud

In modern societies there is strong belief in scientific progress. But unfortunately a parallel partial regress in scientific publication including sports physiology can occur because of often evitable mistakes. These errors are mainly forgetting or oversights, erroneous theories, mistakes in experiments and manuscripts, selected publication of "positive" results, prejudice, and fraud. Some mistakes can be detected by a careful reader, while other mistakes need special expertise to identify or clarify.

In this contribution typical examples detected by the author in the area of sports physiology are presented.

Forgetting

Often basic articles for methods introduced decades before are no longer read or cited. Also modern apparatus present "ready-made" results which formerly had to be calculated step-by-step. Without knowledge of the underlying theories incorrect interpretation of results may occur. In the following I describe some typical examples.

B**ase excess:** False use of actual base excess (derived from blood titration with acid and base in vitro) instead of standard base excess (corrected for in vivo conditions, i.e. considering the equilibration of blood with the interstitial fluid) for quantifying the number of hydrogen ions leaving the muscles raised the idea that an unknown fixed acid is produced additionally to lactic acid during hard exercise.[1] In contrast the decrease of standard base excess fits well to the increase of [lactate].[2,3]

Efficiency: Gross efficiency during cycling has been compared in untrained and trained subjects for equal percentages of maximal power without considering its dependence on metabolic rate and pedal rate. This shortcomimg led to the belief (in contrast to the classical opinion) that metabolic efficiency can be markedly improved by training.[4-6] Fig. 1 from Böning et al.[7] shows that gross efficiency (upper panel) changes with absolute power (because the relative contribution of basal metabolism to total energy consumption decreases with power) and pedal rate (mainly because of the changing contribution of idling). There is only a small overall difference between untrained and trained subjects. Net efficiency also varies with pedal rate (lower panel), but the maximal value is independent of power; training most likely has no significant effect. Therefore comparisons are only valid if these simple facts are considered.

Often efficiency is even not calculated but decreases in oxygen uptake are taken as proof for an improvement, e. g. during an altitude stay[8] or after intake of nitrate in form of beetroot juice.[9] But for a correct calculation of energy turnover the consideration of CO_2 production is also necessary to determine the relation of fat and carbohydrate consumption by use of the respiratory exchange ratio.[10] Altitude acclimatization causes a reduction in fat combustion![11] Strangely in spite of routine measurement of both O_2 and CO_2 in modern equipment this calculation is often omitted. An additional possible mistake is to neglect anaerobic metabolism which plays a role at intensities above the maximal lactate steady state.[12]

Literature Searches: Relevant articles are not always found. In former years scientists mainly relied on their institutional library collections which never were complete; e. g. some important European journals were not present in American universities and vice versa. Today most researchers search references in PubMed, which also presents only a selection of scientific journals. Additional use of Google scholar and other sources is helpful.

Erroneous Theories

Robergs et al.[13] proposed in 2004 that lactate is not the anion of a strong acid but a buffer. Besides using a new controversial concept of “metabolic buffering” the apparently supporting calculations (number of liberated H^+, muscular buffer capacity) were erroneous.[2,14]

The widely accepted theories of Peter Stewart (e. g. described in[15,16]) are partly based on a conceptual error. He and his followers consider a balance equation of cation and anion concentrations, characterized by the equality sign, e. g.

$$[Na^+] + [K^+] + [H^+] = [Cl^-] + [HCO_3^-] + [OH^-]$$

like a chemical reaction equation, characterized by a flash, e. g.

$$HCl \rightarrow H^+ + Cl^-$$

and thus return to concepts (e. g. Cl^- considered as an acid) already abandoned ate beginning of the 20th century.[2] Additionally the large number of measured electrolyte concentrations in plasma and red cells cause scattering and make practical application laborious. Therefore I myself did not publish similar measurements during respiratory acidosis and alkalosis in man.

Mistakes in Experiments and their Evaluation

Mistakes may occur after incorrect application of a method, during evaluation of measurements, by false calculations, or exclusion of unwelcome values (extreme values sometimes point to subjects with unexpected properties). In the following section I describe examples mainly from own investigations. Some examples (mainly from own investigations) are useful for illustrating common mistakes.

Discarding of “improbable” results. Head-out immersion causes diuresis, but the effect is reduced in endurance-trained athletes.[17] Therefore some athletes could not void every 30 min in our experiments. The student performing the measurements originally discarded all zero values thus eliminating the significance of the training effect.

Moreover single outliers are not always caused by measurement or evaluation errors but may be indicative for a special biologic effect. **Ende Durchsicht**

In subjects with cystic fibrosis a slightwards right shift of the standard oxygen dissociation curve of hemoglobin (measured as increase of the half saturation pressure P_{50} at 40 mmHg

PCO_2, pH 7.4, 37°C) is generally observed.[18] A statistically confirmed outlier in the patients (Fig. 2) is no measurement error, but caused by low 2,3-biphosphoglycerate concentration. This points to an optimal adaptation for combined hypoxia-hypercapnia in this patient, because binding of O_2 to blood in the lungs is facilitated. Moles living under similar conditions inspiring air with reduced O_2 and increased CO_2 content are perfectly adapted possessing a low standard P_{50}.[19] Interestingly in other publications on cystic fibrosis similar outliers can be detected.

Similarly at altitude the typical but not optimal human acclimatization reaction is a rightward shift of the standard oxygen dissociation curve in contrast to a leftward shift in well-adapted animals like llamas. But "human llamas" have been detected occasionally.[20,21] An interesting example for an outlier is also the famous mountaineer Reinhold Messner.[22,23] He reached an arterial oxygen saturation of nearly 93% during exercise (90 W, ventilation 34.4 l/min) in artificial hypoxia (inspiratory PO_2 77 mmHg corresponding to 5500 m of altitude). In contrast 5 other mountaineers ventilated approximately 41 l/min, but showed average saturations of only 72%. Messner's high saturation can only be explained by a low half saturation pressure like in llamas – or a leak in the system. Unfortunately I lost the reference with his data years ago and I hesitated too long to contact him for some measurements (blood gases and acid base status, BPG metabolism, Hb type). Now (age 71 years) he is not willing to take part.

"Responders" and "Nonresponders". Chapman et al.[24] have grouped athletes after altitude training according to their improvement in running time. Athletes with performance improvements better than the mean value were called responders, runners without improvement were called nonresponders, the rest was omitted. Consequently after this manipulation changes in erythropoietin concentration and total red cell volume were significantly different between responders and nonresponders. With this evaluation technique not extreme but intermediate values are excluded. It appears a scientist can produce herewith a s of significant effects, but are they real?

False calculations. The concentration of lactate is higher in plasma than in erythrocytes for three reasons: 1) lactate is present only in the water space which amounts to approximately 70% in the cells, 2) the distribution of lactate is controlled by a Donnan equilibrium with lowered anion concentrations in the cell water, 3) transport by monocarboxylate channels needs several minutes until equilibrium. Comparing results of different investigations without considering these issues may lead to erroneous conclusions.[25,26]

Mistakes in Manuscripts

Astonishingly coauthors as well as reviewers do not always carefully read the papers before submission and publication. For example the striking difference between leg O_2 delivery and the product CaO_2 x leg blood flow (both values must be equal) in the same table was missed by the authors[27] causing contrasting interpretations about erythropoietin effects. Fortunately the mistake was corrected after a letter to the editor.[28,29] As an example of various mistakes in an otherwise excellent publication examining the influence of erythropoietin on maximal O_2 consumption in mice[30], the animals had a resting heart rate of 514/min but 160/min at exhaustion. Only the resting value seems to be correct because it is negatively correlated to body mass in mammalia; during exercise heart rate rises usually in mice as in other animals. None of 7 authors had seen this error and various other mistakes. Surprisingly the corresponding regression equations yielded realistic values.[31] Also surprisingly the journal did neither accept a letter to the editor nor publish a correction.

Selected publication of “positive” results

This problem is difficult to solve. It is most important in pharmacological studies, where negative results are frequently ”forgotten”. But generally neither authors nor editors like experiments without the expected effect. As a countermeasure a Journal of Negative Results in Biomedicine has been founded.

Prejudice

The problem is demonstrated by a citation:

“All peers are equal, but some peer reviewers are more equal than others.”

(George Orwell 1945 modified) and a comic (Fig. 3). The reviewer should check manuscripts for importance, clarity, completeness and mistakes. The style for different fields and journal prescriptions is mainly a matter of personal taste. The frequency of inappropriate reviewer comments is often increased if the reviewer is not a real expert for the topic.

Fraud

An example especially of fraud in sports medicine is the presence of doped subjects in a group of investigated athletes. Thus artificially changed performance or physiological variables might be considered as normal. It is necessary to be aware of this when selecting subjects for scientific project. A related problem is that athletes taking part in a scientific project involving prohibited substances (e. g. EPO injections) cannot go to competitions before any effect has disappeared. These questions have been discussed recently. [33-35]

Conclusions

To reduce regress in physiological and performance studies it is important that investigators search not only for recent articles on a topic, examine conscientiously the data and ensure that all coauthors read both the text thoroughly and check tables and figures in a manuscript. Reviewers have the same obligations. Journals should repeatedly invite readers to submit letters to the editor for clarification which is best possible immediately after publication. Frequent open discussions about important topics are essential.

References

1. Juel C, Klarskov C, Nielsen JJ, Krustrup P, Mohr M, Bangsbo J. Effect of high-intensity intermittent training on lactate and H^+ release from human skeletal muscle. *Am J Physiol Endocrinol Metab*. 2004;286:E245-E251.

2. Böning D, Maassen N. Point: Lactic acid is the only physicochemical contributor to the acidosis of exercise. *J Appl Physiol*. 2008;105:358-359.

3. Böning D, Klarholz C, Himmelsbach B, Hütler M, Maassen N. Causes of differences in exercise-induced changes of base excess and blood lactate. *Eur J Appl Physiol*. 2007; 99:163-171.

4. Böning D, Pries AR. Pitfalls of efficiency determination in cycling ergometry. *J Appl Physiol*. 2013; 115:1862.

5. Hopker JG, Coleman DA, Gregson HC et al. The influence of training status, age, and muscle fibre type on cycling efficiency and endurance performance. *J Appl Physiol*. 2013; 115.

6. Hopker JG, Coleman DA, Passfield L. Reply to Boning and Pries. *J Appl Physiol*. 2013; 115:1863.

7. Böning D, Gönen Y, Maassen N. Relationship between work load, pedal frequency, and physical fitness. *Int J Sports Med*. 1984; 5:92-97.

8. Gore CJ, Clark SA, Saunders PU. Nonhematological mechanisms of improved sea-level performance after hypoxic exposure. *Med Sci Sports Exerc*. 2007; 39:1600-1609.

9. Bailey S.J., Vanhatalo A, Winyard PG, Jones AM. The nitrate-nitrite-nitric oxide pathway: Its role in human exercise physiology. *Eur J Sport Sci*. 2012; 12:309-320.

10. Böning D. “Biodoping“ with beetroot? Speculations about improved efficiency. Editorial. *Dtsch Z Sportmed*. 2012; 63:337-339.

11. Roberts AC, Butterfield GE, Cymerman A, Reeves JT, Wolfel EE, Brooks GA. Acclimatization to 4,300-m altitude decreases reliance on fat as a substrate. *J Appl Physiol*. 1996; 81:1762-1771.

12. Beneke R, von Duvillard SP. Determination of maximal lactate steady state response in selected sports events. *Med Sci Sports Exerc.* 1996; 28:241-246.

13. Robergs RA, Ghiasvand F, Parker D. Biochemistry of exercise-induced metabolic acidosis. *Am J Physiol Regul Integr Comp Physiol*. 2004; 287:R502-R516.

14. Kemp G, Böning D, Strobel G, Beneke R, Maassen N. Explaining pH change in exercising muscle: lactic acid, proton consumption, and buffering vs. strong ion difference. *Am J Physiol Regul Integr Comp Physiol*. 2006; 291:R235-R237.

15. Lindinger MI, Heigenhauser GJ. Counterpoint: Lactic acid is not the only physicochemical contributor to the acidosis of exercise. *J Appl Physiol*. 2008; 105:359-361.

16. Stewart PA. *How to Understand Acid-Base. A Quantitative Primer for Biology and Medicine.* New York: Elsevier; 1981.

17. Böning D, Skipka W. Renal blood volume regulation in trained and untrained subjects during immersion. *Eur J Appl Physiol*. 1979; 42:247-254.

18. Böning D, Littschwager A, Hütler M, Beneke R, Staab D. Hemoglobin oxygen affinity in patients with cystic fibrosis. *PLoS ONE*, 2014; 9:e97932.

19. Campbell KL, Storz JF, Signore AV, Moriyama H, Catania KC, Payson AP, Bonaventura J, Stetefeld J, Weber RE. Molecular basis of a novel adaptation to hypoxic-hypercapnia in a strictly fossorial mole. *BMC Evol Biol.* 2010; 10:214-228.

20. Hebbel RP, Eaton JW, Kronenberg RS, Zanjani ED, Moore LG, Berger EM. Human llamas: Adaptation to altitude in subjects with high hemoglobin oxygen affinity. *J Clin Invest.* 1978; 62:593-600.

21. Beall CM, Decker MJ, Brittenham GM, Kushner I, Gebremedin A, Strohl KP. An Ethiopian pattern of human adaptation to high-altitude hypoxia. *Proc Natl Acad Sci USA.* 2002; 99:17215-17218.

22. Cerretelli P, di Prampero PE, Brückner J, Ferretti G, Capelli C, Howald H, Oelz O. Respiratory and metabolic characteristics of elite Alpine climbers. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Cold*. New York: Praeger Publishers; 1987: 457-463.

23. Oelz O, Howald H, di Prampero PE, Hoppeler H, Claaassen H, Jenni R, Buhlmann A, Ferretti G, Bruckner JC, Veicsteinas A, Gussoni M, Cerreteli P. Physiological profile of world-class high-altitude climbers. *J Appl Physiol*. 1986; 60:1734-1742.

24. Chapman RF, Stray-Gundersen J, Levine BD. Individual variation in response to altitude training. *J Appl Physiol* 1998; 85:1448-1456.

25. Myburgh KH, Viljoen A, Tereblanche S. Plasma lactate concentrations for self-selected maximal effort lasting 1 h. *Med Sci Sport Exer* 2001; 33:152-156.

26. Böning D. Differences between whole blood and plasma lactate concentrations have to be considered when comparing various studies. *Med Sci Sports Exerc* 2001; 33:1411-1412.

27. Lundby C, Robach P, Boushel R et al. Does recombinant human Epo increase exercise capacity by means other than augmenting oxygen transport? *J Appl Physiol* 2008; 105:581-587.

28. Böning D, Maassen N, Pries A. No proof for augmented arterial oxygen content as only factor influencing exercise capacity after Epo doping. *J Appl Physiol* 2008; 105:1988.

29. Lundby C. Reply to Böning, Maassen and Pries. *J Appl Physiol* 2008; 105:1989.

30. Schuler B, Arras M, Keller S, Rettich A, Lundby C, Vogel J, Gassman M. Optimal hematocrit for maximal exercise performance in acute and chronic erythropoietin-treated mice. *Proc Natl Acad Sci USA*. 2010;107:419-423.

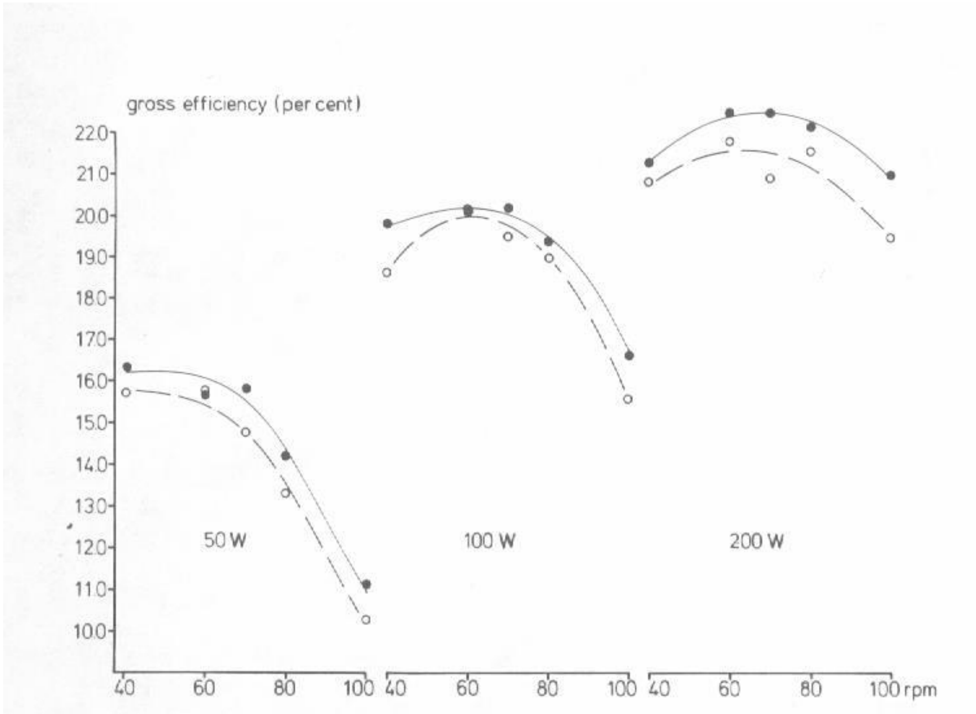
31. Böning D, Maassen N, Pries A. The hematocrit paradox--how does blood doping really work? *Int J Sports Med*. 2011;32:242-246.

32. Appell HJ, Atkinson G, Duarte JA, Houmard JA. Doping and physiological research--hostile brothers or unwanted twins? *Int J Sports Med*. 2008;29:623.

33. Böning D, Steinacker JM. Problems with doping in scientific articles? *Int J Sports Med*. 2008;29:699.

34. Roecker K, Dickhuth.H.-H. Answer to D. Böning's and J. M. Steinacker's Letter to the Editor "Problems with doping in scientific articles?". *Int J Sport Med*. 2008; 29:700.

35. Wagner PD. When worlds collide--elite sport, doping, and scientific research. *J Appl Physiol.* 2013;114:1359-1360.



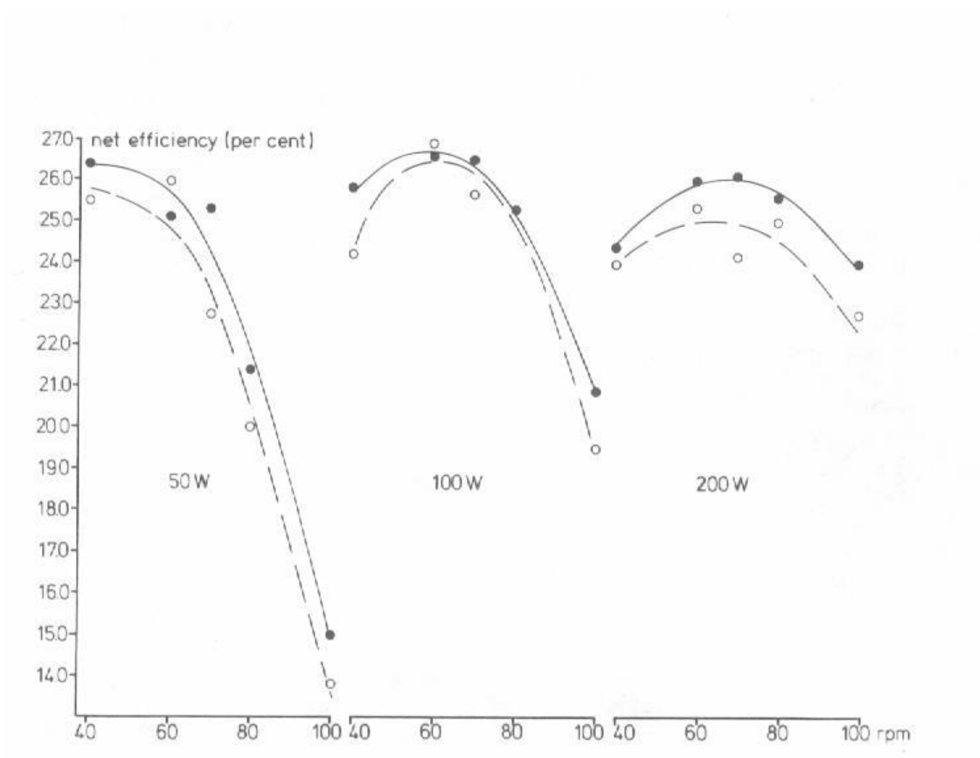


Fig. 1. Gross (upper panel) and net (lower panel) efficiency in dependence on work load and pedal rate (rpm) in untrained (empty circles) and trained (filled circles) males. From Böning et al. (1984)[7] with permission.

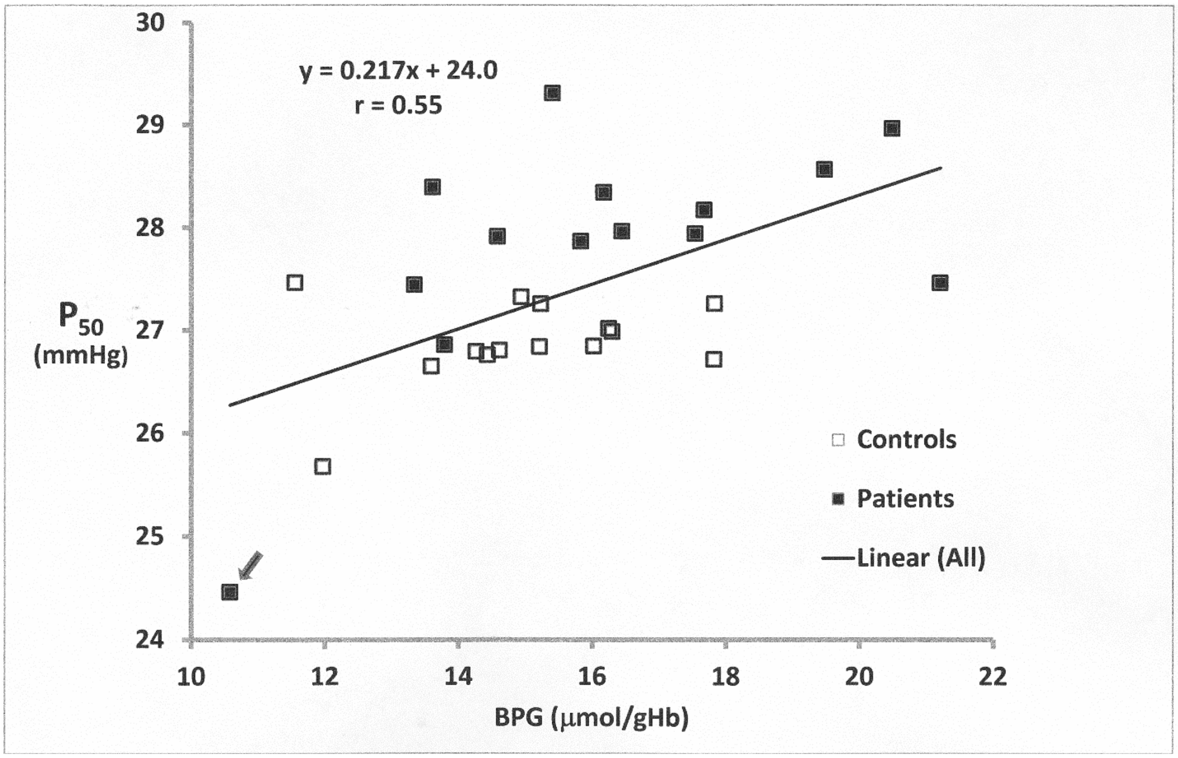


Fig. 2. Standard half saturation pressure (P50 at 40 mmHg PCO_2, pH 7.4, 37°C) in patients with cystic fibrosis and healthy controls in dependence on 2,3-biphosphoglycerate (BPG) concentration. One patient's value (arrow) is very low (24.4 mmHg). From Böning et al. (2014)[18] with permission.

Fig. 3. Peer reviewing since the Stone Age (from Aries Systems Corporation with permission, http://creativecommons.org/licenses/by-nc-nd/3.0/deed.en_US).