Invited Review Article

ISSN (Print) : 0971-913X
ISSN (Online) : 2455–1244

Journal of Endocrinology and Reproduction, *Vol 21(1), 15-26, 2017, DOI: 10.18311/jer/2017/21026*

Differential Diagnoses and Prognoses of Stress-Induced Metabolic Changes by Stress Hormone Effects – A Synopsis of Our Recent Publications

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Abstract

The impact of a given amount of stress hormone upon about 12 different metabolic markers like blood gases, buffers, glucose, lactate and electrolytes shows a comprehensive pattern in a characteristic stress situation, fingerprinting both individual idiosyncrasies and the peculiar qualities of a certain stressful situation. According to HPLC data, norepinephrine correlates linearly and significantly with the mentioned stress hormone effects, underlining the feasibility of taking stress hormone effects for stress-diagnostic purposes rather than catecholamines themselves. Stress hormone effects – especially their correlative relations to each other – can also serve as prognostic tools, whereby effort and even performance in sports can be deduced from anticipatory arousal. Also, need of regeneration after a trial can be calculated from pre-challenge arousal. Even several days after a first parachute jump the personal feeling of success, of having been able to overcome the challenge efficaciously, correlates with the pre-challenge pCO_2. However, the beneficial values of this "future building capacity", that enables us to be nearly automatically prepared for future challenges, can be misused by unduly protracting such sympatho-adrenal anticipatory situations due to nonstop submaximal workload. Tissue oxygen depletion in oxygen–demanding situations is one of the resulting noxae. Determination of stress hormone effects furthermore allows educated guesses to distinguish, whether glucose irregularities, e.g. in metabolic syndrome, can be traced back to stressful situations or to the illness proper.

Keywords: Blood Gases, Correlations, Norepinephrine, Prediction, Stress Markers

1. Introduction

The technical term "stress hormones" is familiar to the layman mostly in form of adrenalin or epinephrine, or as cortisol, mainly connected with mental arousal. This becomes clearer when we consider that cortisol determination in humans out of saliva does not need invasive blood sampling anymore and is therefore open to non-medical investigators, meaning, for instance, that psychologists make use of the "hard" data that such stress hormone determinations provide to gain additional evidence for their questionnaire-scores.

But since cortisol as a target organ hormone is part of a feedback loop containing, e.g. ACTH as releasing factor[1], simultaneous ACTH determination, for which blood sampling is needed. Some of our own investigations dealt with standardized workloads of already severely loaded mountain guides after a difficult climbing test. It turned

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out that about one hour after a difficult climb their cortisol levels were extremely low, due to an effective negative feedback down from considerably increased levels immediately after the climb[1]. The difference between low cortisol in a relaxed state and low cortisol as a reaction to increased workload in the immediate past was the success of provoking cortisol within much less than the 15-20 minutes needed according to textbooks[2].

Thus, successful provocation, swifter than usual, most probably due to quick ACTH secretion, serves as differential diagnosis of otherwise easily confusable states of either relaxation or post – load feedback situations and should be taken into consideration, when trying to characterize low–cortisol situations by mere saliva – cortisol tests.

On the other hand, the classical catecholamine determination with HPLC is well known for its trickiness[3-8]. For correct determination of catecholamine in men, antecubital blood is needed whereas in rats even blood from cannulated tail arteries, a procedure that requires experience, would be suitable which holds true also for[9-12] the very sensitive HPLC determination.

In both cases, be it cortisol or catecholamines, an additional drawback is the unknown receptor situation, either that of nuclear receptors in the case of cortisol, or membrane receptors in the case of catecholamines. The expression of these receptors tends to change at least according to chronic increase or decrease of the concentration of the hormones in blood[1].

In the case of catecholamines an especially noteworthy example (unpublished) was an investigation into the catecholamine state of an anorectic young lady of 18 years of age. Due to her anorectic state, her hormonal state was confused, her sexual hormones were not sufficient to provide for her menarche, but her catecholamine state seemed to be perfectly normal. After some thinking we deduced, that her decidedly agitated state during blood sampling simply had to provoke catecholamines, so that her epinephrine concentration, deemed normal by us, was in her situation decidedly high. Chronic low catecholamines did obviously provoke/increase receptor expressions on the membrane, so that the "normal" catecholamine concentration hit upon an unphysiologically high number of membrane receptors, constantly expressed by her because of unsatisfactory blood catecholamine levels. What we deemed to be normal from the point of view of a healthy person must have been a veritable catecholamine onslaught for our patient.

It goes without saying that there is a whole bunch of other stress hormones, or hormones that are considered as stress hormones, in varying degrees by varying authors: testosterone along with all kinds of corticoids and even somatotropin have been incorporated into the greater family of stress hormones.

However, it suffices that we are in accordance that direct hormone determination for characterizing the stress state of an organism could have its snags in sampling as well as in determination and interpretation.

Already in 1992, we adopted a method, taken from Intensive Care Units to determine blood gases, buffer substances, pH, glucose, lactate and electrolytes out of about 100 microliters of capillary blood[13-20]. First, we checked whether these "stress hormone effects", as we called them, had any mathematical relation to the simultaneously determined real stress hormones, like e.g. norepinephrine. It turned out that there were mostly linear correlations between many of the effects and norepinephrine plasma levels proper[6, 7, 13].

Figures. 1, 2, 3. Correlations between metabolic parameters and free norepinephrine (HPLC) after sport.

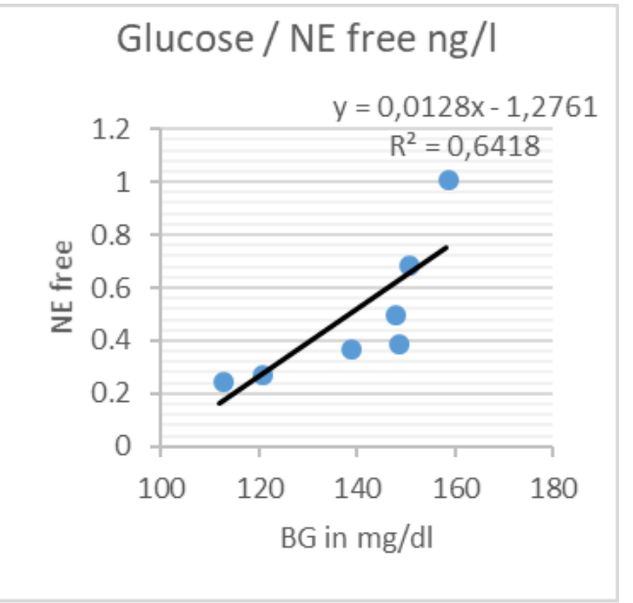


Figure 1. Legend: Ordinate: Free Norepinephrine

Interestingly, the linear regression lines between hormone and hormonal effects had different slopes, dependent upon the kind of load that has been applied to a person or a group of persons. Also, different kinds of load – roughly mental or physical – could create correlations with different hormone effects and likewise effects of different intensities of load varied in both the correlation

partner and the steepness of the slope[21, 23, 24]. To illustrate the matter in a simple way, let us imagine the difference in correlative behaviour hormones versus hormone effects in mental versus physical strain.

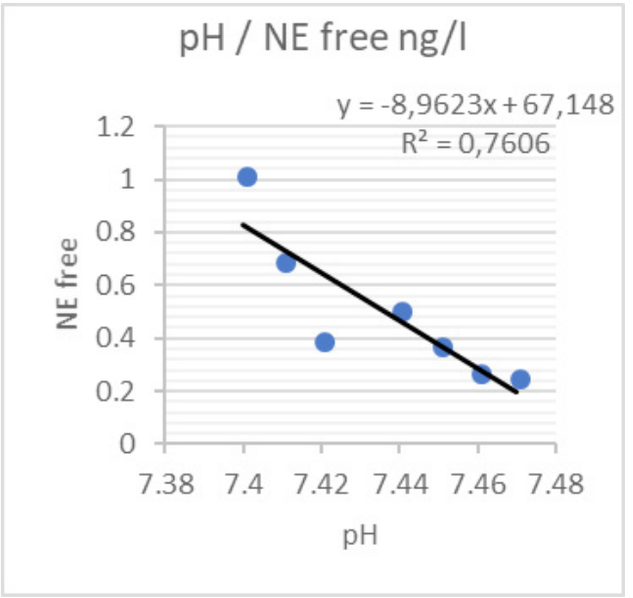


Figure 2. Abscissa: pH
Ordinate: norepinephrine in pg/ml

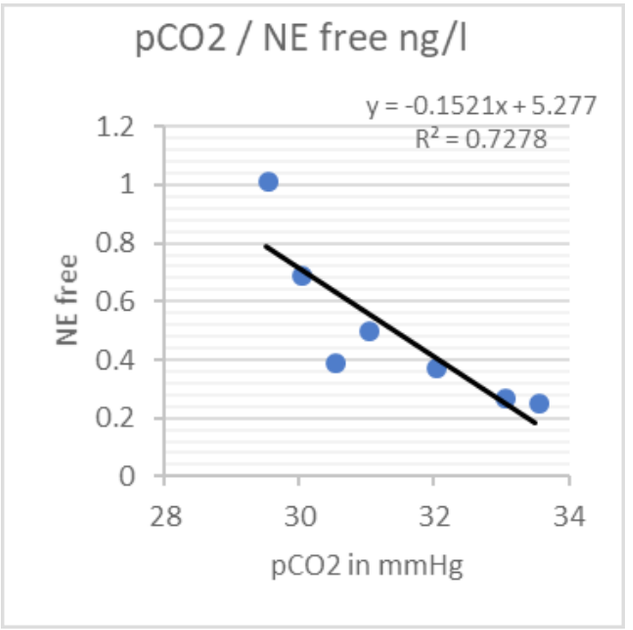


Figure 3. Abscissa: pCO_2 in mmHg
Ordinate: norepinephrine in pg/ml

During a physical load, like a 2400m run, linear proportionalities between norepinephrine increase and lactate increase are well known. In mental strain, norepinephrine does increase rather along with calculated free fatty acids and not so much with lactate. The latter, however, may well happen, when the mental strain becomes so intensive that more and more physical systems are involved as is the case in sleep deprivation[22] or long-term pressure[25, 26].

The ensuing exhaustion in its turn expresses an even more different pattern of slope steepness and correlation partners than during workload and concomitant stress[24].

The possibilities of interpreting the relations between hormones and their effects, changing with the quantity and quality of a challenge are manifold, so that it took us a considerable time to realize the meaning of certain behavioural correlative patterns. Especially, since we did no longer include stress hormones themselves in our correlation design but instead assessed and evaluated the correlations between the individual stress hormone effects (usually 12 such parameters per person and blood sample), between those effects and psychological scores or parameters of performance like running times a.s.o.

As determination of 12 stress hormone effects takes about 100 microliters of finger-tip capillary blood and is ready and done in about three minutes, contrasting to 10 mL antecubital blood and hours of determination time with HPLC, our method has its merits.

Since an important feature of our workload and stress characteristics are both linear and polynomial correlations, we had to consider the correlation immanent feature of prediction[27]. By calculating the slope of a given linear correlation, say between lactate and pH, it is not only possible but inevitable to predict the probable position of a higher lactate value in relation to a lower pH.

Likewise, correlations between lactate values before and after a sporting challenge have intrinsic predictive powers of the effort needed to overcome the trial, i.e. after having calculated this relationship for once, reliable approximations can be made about the effort needed at a comparative challenge. Even blood gas determination immediately before a challenging event like the very first parachute jump correlates with subjective feelings of success a considerable time after the jump, which sounds exceptional, but is explainable[28] in so far as pCO_2 before the challenge specifies breathing frequency, breathing frequency can be connected with mental arousal and those, who are the most exited before the jump could well be the most contented afterwards, being proud to have successfully overcome their excitement.

And last not least a problem concerning the transition or even overlapping of metabolic workload reactions,

(mental) load and metabolic illness like the metabolic syndrome came to our attention.

We wanted to characterize a group of persons in a rehabilitation clinic by arranging them statistically according to their glucose/insulin quotient (HOMA Index), a common practice for the assessment of the severity of aberrations of the carbohydrate metabolism. However, it is well known[29-36] that adrenalin increase suppresses insulin production and secretion[37, 38] and increases blood glucose not only by this mechanism but also by increased glycogenolysis, a behaviour that has distinct bearings upon the HOMA index. Our question now was whether we could get some rough estimation about the HOMA index of a person being more affected by metabolic illness or by acute agitation. Possibly a juxtaposition of HOMA indices and some of our correlations, depicting stress – prone situations could be helpful.

Now we would like to get down to exemplary results and their interpretation, beginning with a possible diagnostic value of correlative assessments of stress hormone effects.

2. Stress Hormone Effects as Diagnostic Tools

2.1 Stress Hormone Effects

Calculable connection between mental and physical strain and prognosis of effort.

Figures 4 and 5. Effort depends upon anticipation

Anticipation: Mental Load

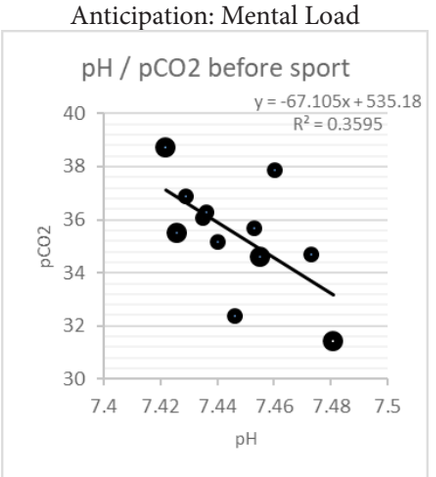


Figure 4. Most intense anticipation (lower right)
Abscissa: pH
Ordinate: pCO2

Sport: Physical Workload

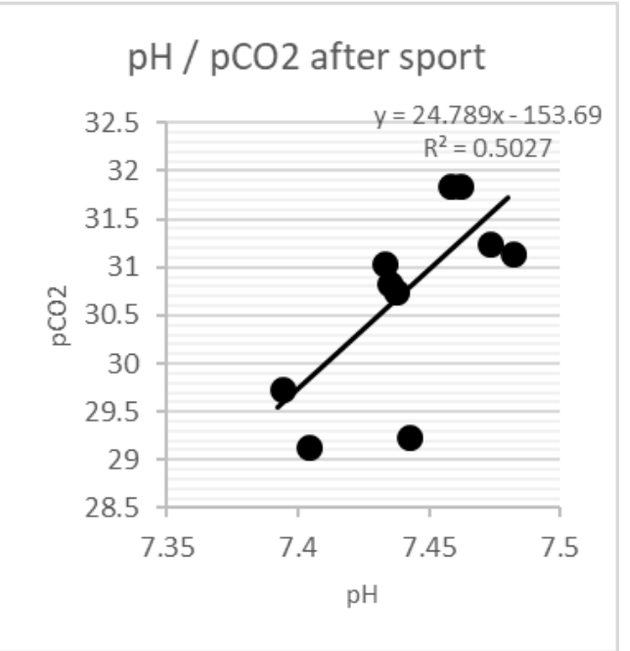


Figure 5. lowest effort needed (upper right)
Abscissa: pH
Ordinate: pCO_2

The intensity of metabolic anticipation of a future challenge is individual, but still expressible by correlative systems. In general, more the CO_2 is being lost from the blood by more intense breathing, the more alkaline the blood would get. This is mainly true for situations with negligible muscle participation, because appreciable lactate production can be excluded. Therefore, increased breathing during mental anticipation of a (sportive) challenge tends to increase pH values. This reaction, that can be found so regularly, that it constitutes a hallmark of mental arousal, we call a super-compensation or over-compensation, because of the seemingly unwarranted and energy wasting increase of pH beyond the normal range[27, 39].

It turned out, however, that the generated alkaline pH in mental or submaximal physical workload serves two purposes, which are beneficial for the prospected workload:

- pH seems to take a kind of in-run, anticipating and avoiding the danger of a subsequent perilous fall by excessive lactate production during the following physical load; and
- alkaline pH binds more oxygen, so that in case of a later acidification an increased amount of oxygen can be released in a situation when increased

oxygen supply is needed by (heart) muscle tissues.

Moreover, it turned out that the more intensive the breathing before the physical challenge has been, the less the breathing frequency increased at an acute challenge in a linearly predictable way[27].

It is symptomatic for the state of art of stress hormone effect determination that e.g. research in acidity or alkalosis of the blood in mental or environmental load, is not at all well developed in humans but – not totally surprising – much better known in the poultry- or general farming ambient[47-51, 53, 54, 55]. Blood gas- or pH analyses in human medicine are mostly restricted to intensive care medicine, or pulmonology, eventually including comprehensive checks of professional sportsmen. Those situations are not favourable to recognize "super compensatory" reactions in day-to-day life as our cooperation partners and we do in approximatively 4000 cases per year[46, 52].

Similarly, determination and juxtaposition of some selected stress hormone effects like pH before and after sport, RR before sport with lactate after sport or HCO_3^- before sport with pCO_2 after sport show significant linear relations, advocating the mentioned probability of forecasting effort from anticipatory behaviour (Figures. 6-8).

Figures 6, 7 and 8. Prediction of Future Effort from Anticipating (Supercompensating) Metabolism

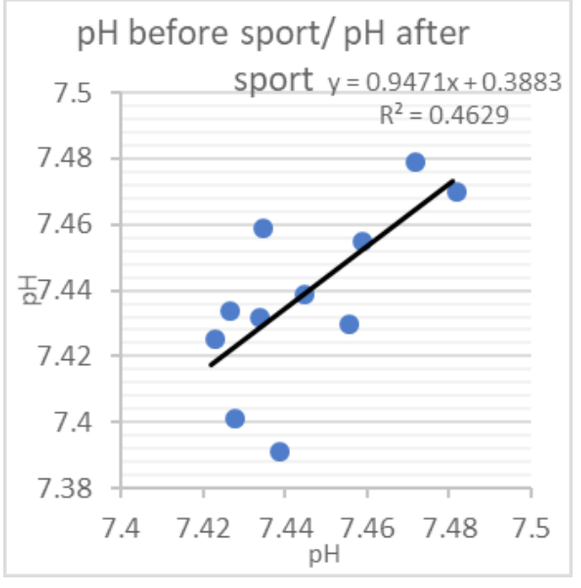


Figure 6. Abscissa: pH
Ordinate: pH

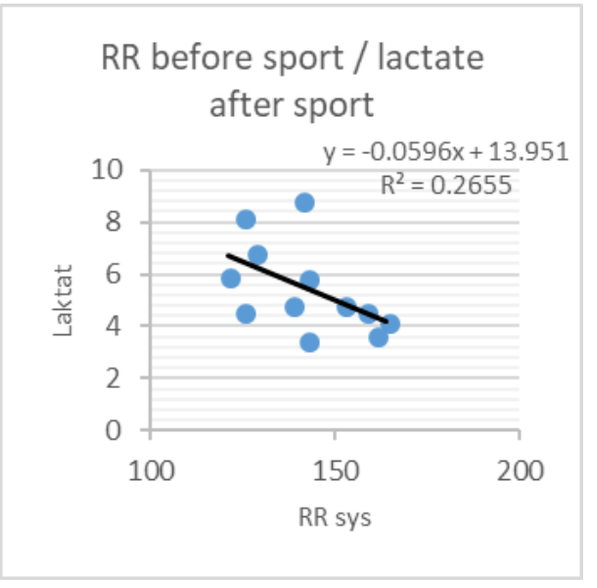


Figure 7. Abscissa. RR sys in mmHg
Ordinate: Lactate in mM/l

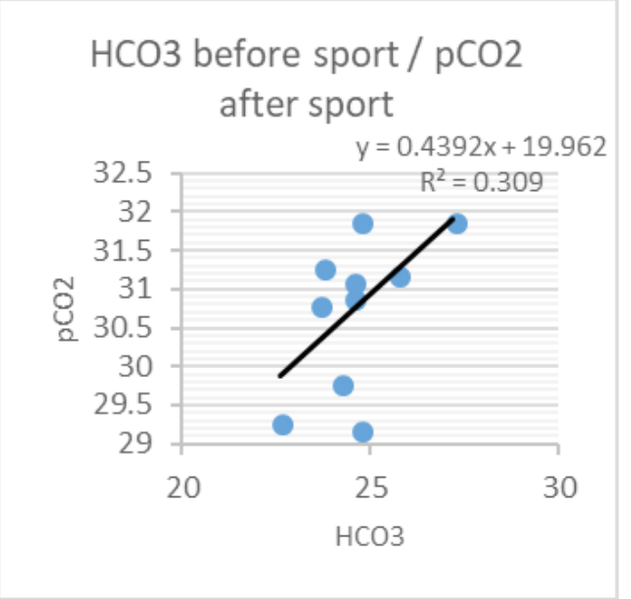


Figure 8. Abscissa: HCO_3^- in mM/l
Ordinate: pCO_2 in mmHg

2.2 Stress Hormone Effects: Prognosis of Performance

Figures 9, 10 and 11. Prediction of Future Performance from Supercompensating Metabolism

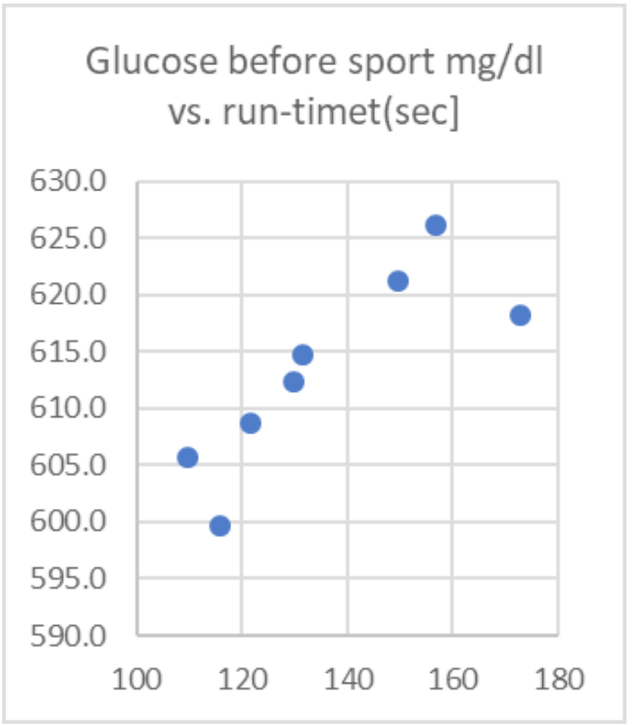


Figure 9. Abscissa: glucose in mg/dl
Ordinate: runnng time in seconds

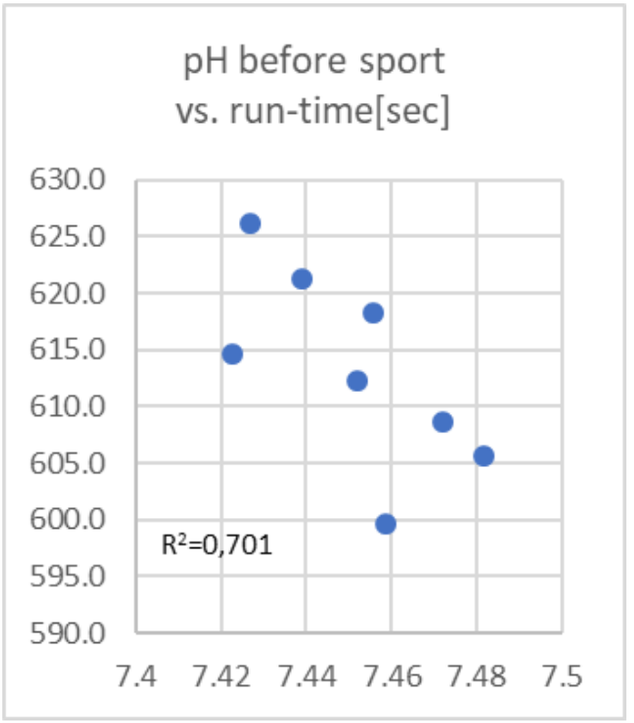


Figure 10. Abscissa: pH
Abscissa: running time in second

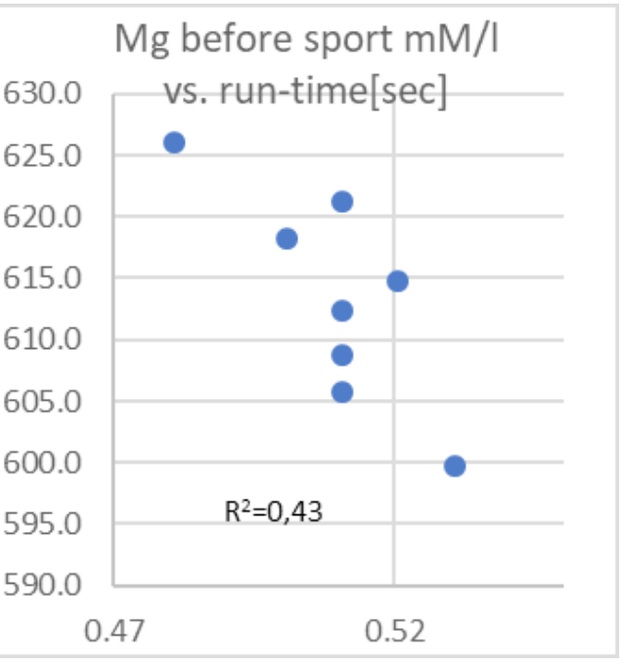


Figure 11. Abscissa. Ionized Mg in mM/l
Ordinate: running time in seconds

Performance (run-time 2400m) obviously also depends on supercompensation beforehand (glucose, pH, Mg)

Obviously, not only future effort, but also probable future performance can be predicted from correlations of metabolic data before sport and similar performance markers during sport.

Those participants with the most overcompensated (increased) pH values beforehand perform the 2400m run quickest (see also Figures 9, 10 and 11). At the same time, their glucose and magnesium concentrations are comparatively the lowest, meaning that they are well within the normal range. Less trained performers show comparatively low pH along with high glucose (up to 170 mg/dl) and low magnesium values already during the anticipation phase.

It seems that increased pH beforehand, brought about by overcompensating, increased breathing frequency, is beneficiary for the subsequent performance, so long as more consequential pathways like glucose metabolism or magnesium concentrations are not yet involved. This behaviour of stress hormone effects means, that a certain anticipatory excitement promotes future performance, but one has to draw a line at untimely glucose or magnesium mobilisation, which probably would indicate improper and therefore useless and noxious overcompensation[46, 6, 7].

2.3 Stress Hormone Effects: Prognosis of Recreation Time

When we claim that probable future effort as well as probable future performance can be construed from the behaviour of stress hormone effects during the anticipatory phase, it seems feasible that intensity or time needed for recreation also could be calculated even from individual anticipatory reactions before a challenge.

Indeed, individual pH and individual pCO_2 during the anticipation phase correlate linearly and significantly with their counterparts after recreation. For instance, lower pH before sport, which correlates with slower running time afterwards correlates with comparatively normal pH after recreation, probably because the exertion of this individual has not been exceptional and therefore recreation has been quicker (Figures 12, 13).

Figures 12, 13. Prediction of Recreation Time Needed

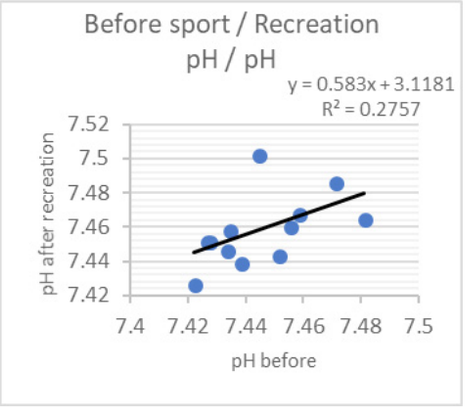


Figure 12. Abscissa: pH before sport
Ordinate: pH after recreation

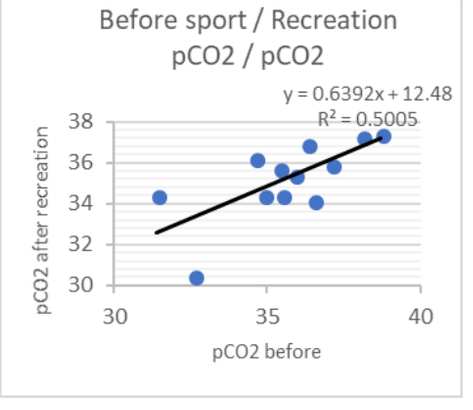


Figure 13. Abscissa: pCO_2 before sport
Ordinate: pCO_2 after recreation

The more anxiety has been overcome, the greater is the subjective success.

2.4 Stress Hormone Effects and Post – HOC Psychology

Figures 14, 15. Do Blood Parameters Before Para-Jump Correlate with Subjective Feeling Afterwards?

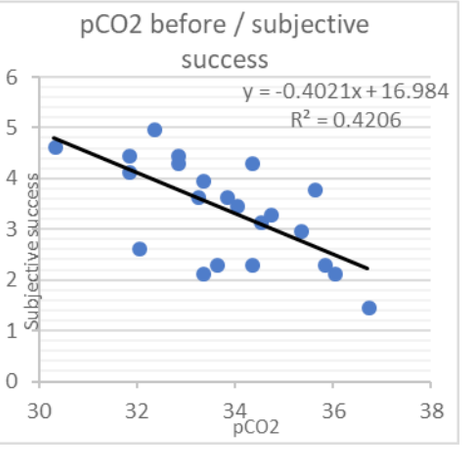


Figure 14. Abscissa: pCO2 in mM/l
Ordinate: subjective success scores

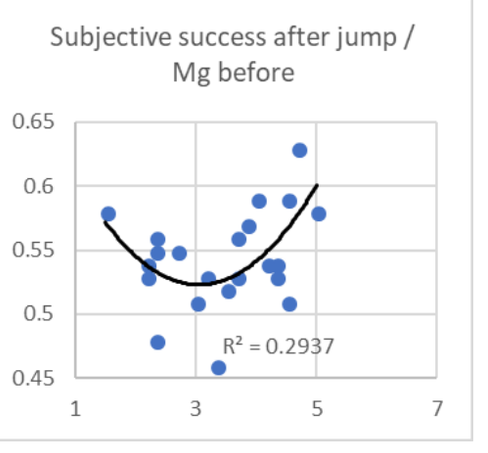


Figure 15. Abscissa: subjective success scores
Ordinate: ionized Mg in mM/l
Mg shows "borderline of coolness"

Three days after the very first para – jump, the participants have been asked about their feeling of success due to the performance of the jump. A highly significant correlation between pCO_2 before the jump and the personal feeling of success days afterwards emerged, which has been commented upon already. Additionally, the concomitantly determined values of ionized magnesium show that Mg concentrations in blood taken during the anticipatory phase decrease in people with lower scores of individual success up to a score of about 3, while beyond that score – in those participants who had higher exci-

tation values beforehand - magnesium levels increase. The nadir of this polynomial curve could be taken as the borderline between the calmer and the more agitated participants. (more concerning Mg behaviour in stress later).

3. Misuse of future building

Overcompensation or supercompensation, evolving not only during mental arousal before a physical challenge, but also during submaximal physical or mental exertions, has been characterized by us as being beneficiary for future more severe challenges, insofar as it paves the way for them beforehand (pH increase, increased oxygen binding), thus attenuating future effort and therefore attenuating the stressful response to a given task.

This "future building capacity", as we call it, is beneficiary only, if its maintenance does not become chronic. If so, a lingering, dangerous situation develops. The beneficiary, forward looking, quasi automatic future building system degenerates into a perilous situation brought about by a nearly non-stop submaximal activity level.

Roughly, increasing agitation (up to a certain degree of course), leads to increased breathing frequency and therefore increased alkaline pH, and therefore increased oxygen binding. We should be aware that oxygen binding of alkaline blood also means a curtailed tendency to liberate oxygen into tissues. This means further, that the more frequent and agitated breathing becomes, the more oxygen is bound within the blood, oxygen that is progressively withheld from the increasingly demanding, increasingly labouring tissues – a vicious cycle, which can be interrupted only by pauses or by pH lowering, arduous sport. This is precisely, what laypersons usually mean, when they talk about the unpleasantry of stress.

Illustrative are Figures 16 and 17, which show the increasing slope between pH and pCO_2 along with the duration of chronically fatiguing sleeplessness.

Figures 16 and 17. Misuse of Future Building Capacity

As we could demonstrate (21, 26, 39, 40) that the tiring fight against sleep during sleep deprivation increases metabolism (although the outward impression of a fatigued person does not support it) by progressive demands on epinephrine secretion because the fight against sleep gets more and more exhausting with increasing duration of sleep deprivation. Here, as in submaximal occupations, increasing blood pH binds oxygen (Figure 8), that is at the same time badly needed in the epinephrine stimulated tissues.

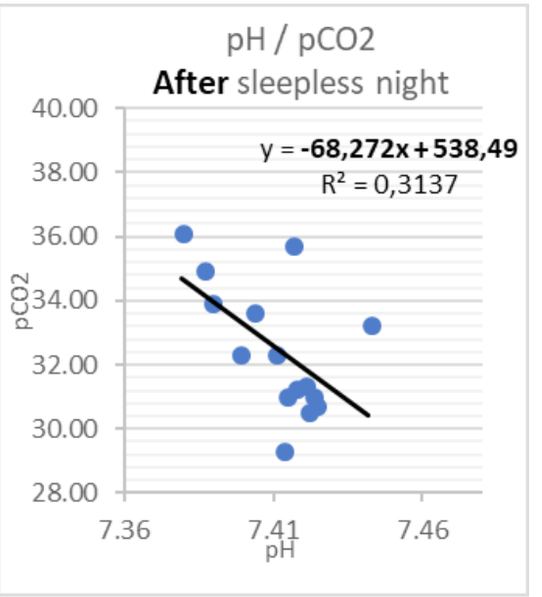


Figure 16. Abscissa: pH
Ordinate: pCO_2 in mmHg

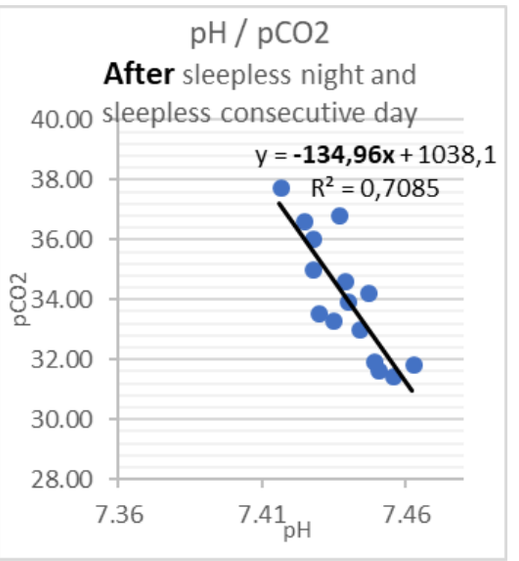


Figure 17. Abscissa: pH
Ordinate: pCO_2 in mmHg

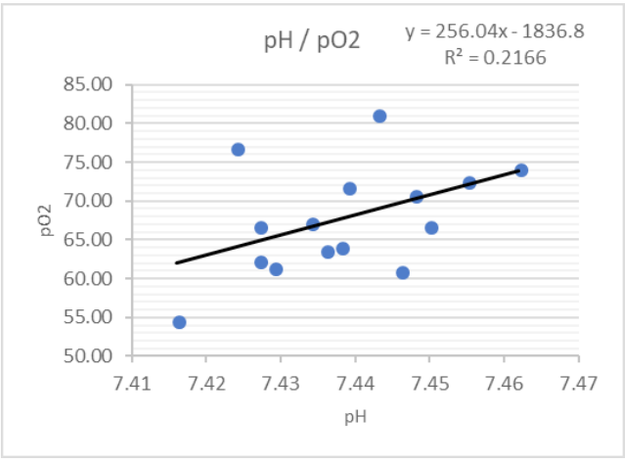
Both lack of oxygen and lack of magnesium impede energy turnover in similar ways[26].

3.1 Metabolic syndrome: How much do stress hormone effects falsify the diagnosis?

A widely used indication of abnormalities of the carbohydrate metabolism is the quotient blood glucose/insulin, the so called HOMA index[30].

Trying out the applicability of our stress hormone effect determination in a different field, we investigated 17 patients of a rehabilitation centre where they underwent mostly dietary interventions due to carbohydrate metabolism irregularities. Out of approximately 100 microliters of blood we determined the stress hormone effects mentioned in the introduction, additionally their plasma insulin and calculated their non- lactate acidity in blood, by subtracting lactate values (mM/l) from the total acid compensation (base-excess, also in mM/l). A comparison between the individual HOMA indexes and base excess values resulted in a highly significant polynomial curve ($r = 0.684$, $p < 0.01$)

Figure 18. Chronic pH Increase = Oxygen Trapping



Abscissa: pH
Ordinate: pO_2 in mmHg

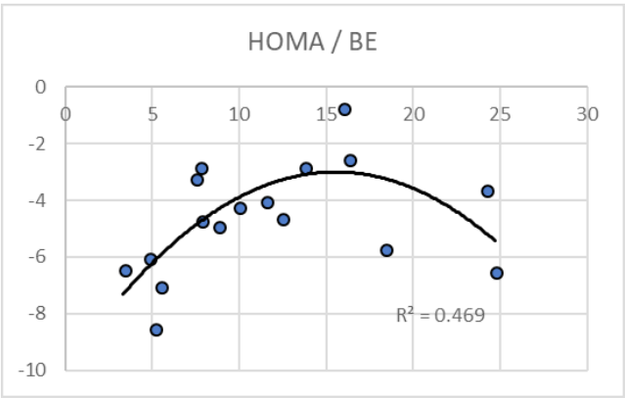


Figure 19. Abscissa: HOMA index Ordinate: base excess in mM/l

The graph shows that in the ascending branch the HOMA index is the smaller (the "better"), the lower the base excess, meaning the higher the acidity has been. After a short puzzling about the result, we realized that the patients nearly all underwent dietary restrictions so that increased acidity should mean increased ketone bodies, and decreased food uptake and therefore lower blood glucose levels and most probably therefore lower insulin concentrations (see Figure 20).

The descending branch represents those patients, whose blood acidity is not so much due to ketone increase by metabolic illness, but probably to acute epinephrine increase, thereby increasing free fatty acids and decreasing base excess. Around the apex of the curve, a mixed influence can be postulated. About 4 – 6 persons of the investigated group therefore had a comparatively high HOMA index, without a tangible metabolic syndrome (at least not tangible within the reach of our methodology).

Figure 20 shows that indeed non - lactate acidity (negative values here mean increased acidity) must be the main source for base excess decrease (pH/lactate relation was not significant), so that the instrument of polynomial correlation between base excess and pH, by showing the dynamics of the change and not – as usual - the static mean values, has decisive influence on our ability of rightly adjudging the situation.

We are, at present, only able to show the difficulties of relying on a HOMA index exclusively and in addition to show the possibility of a way out. More in-depth investigations however would demand a somewhat bigger sample.

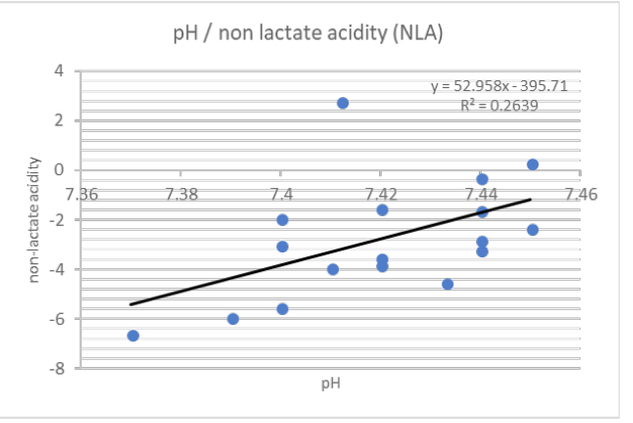


Figure 20. Abscissa: pH Ordinate: non – lactate acidity

We would not like to close our deliberations about the feasibility of using stress hormone effects for workload or stress determination, without pointing explicitly to the usefulness of electrolytes, especially magnesium as stress

markers. Although we have already shown significant correlations between Mg and performance indicators like feeling of success or running times, there are many more that we frequently use.

The basic idea to do so stems from a commentary of Klaus Dörner in Lothar Thomas "Labor und Diagnose"[41], stating that ionized Mg determination is fickle and unreliable, since ionized Mg changes quickly and unexpectedly along with metabolic changes – a statement we would well endorse[1]. But what if we know for certain the amount of metabolic changes by using our stress hormone effects like pH, like base excess, like glucose, lactate, pCO_2 or HCO_3^- as correlation partners and reference values? In this way, we can embed ionized Mg concentrations and their changes within a reliable and net – like ambient and furnish them with a host of calculable collateral parameters, underlining the feasibility of using such correlations as sensitive markers of workload and stress intensity[19, 41-45].

4. Summing up

1. Norepinephrine, according to HPLC results, correlates linearly and significantly with stress hormone effects like pH, blood glucose or pCO_2, underlining the feasibility of taking easier detectable stress hormone effects for stress-diagnostic purposes than catecholamines themselves.
2. Stress hormone effects moreover serve – because of their correlative behaviour – also as prognostic tools, whereby, e.g. sporting effort can be deduced from anticipatory arousal.
3. Not only effort but even performance capacity can be deduced from pre- sport situations comparing them with, e.g. running times.
4. Last not least, pre- challenge arousal also enables us to calculate regeneration needs.
5. Even several days after a special challenge, the personal feeling of success of having been able to overcome the challenge correlates with the acute pre-challenge situation.
6. However, the beneficial values of this "future building capacity", enabling us to be nearly automatically prepared for future challenges, can be misused by unduly protracting such sympatho - adrenal anticipatory situations by nearly nonstop submaximal working. Tissue oxygen depletion in oxygen – demanding situations is one of the resulting noxae.
7. Determination of stress hormone effects furthermore allows educated guesses, how far glucose irregularities, e.g. in metabolic syndrome, can be traced back to stressful situations or to the illness proper.
8. Thus, the impact of a given amount of stress hormone rise upon about 12 different metabolic markers with different quantity and quality constitutes a comprehensive pattern of a characteristic stress situation, fingerprinting both individual idiosyncrasies and the peculiar qualities of a certain stressful situation.

5. Acknowledgment

The authors gratefully acknowledge the enthusiastic participation of the Austrian officer trainees at the Theresan Military Academy, the prudent technical assistance of Mrs. G. Porta and the meticulous editing of Mr. T. Porta.

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