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CSA – Clinical Stress Assessment

Sepp Porta et al.[*]
[1]*Institute of Applied Stress Research, Judendorf – Strassengel,*
[2]*Institute of Pathophysiology, Medical University of Graz,*
[3]*Institute of Mathematics and Scientific Computing, KFU Graz,*
[4]*Rehabilitation Clinique of the AUVA, Tobelbad,*
[5]*Theresianische Militärakademie, Wiener Neustadt,*
[6]*St. Anna Hospital, Herne,*
[1,2,3,4,5]*Austria*
[6]*Germany*

1. Introduction

1.1 Theoretical background – Outlook to applications

What is stress?

Although stress may be defined seemingly differently by endocrinologists, physiologists, psychologists, a.s.o. prefering the tools of their own, specialized trades, the general denominator and most important fact to remember is, that stress never ever impacts somehow upon you or threatens you from somewhere. Stress is always and only your individual typical reaction to something beginning with a menace and ending perhaps with a slight challenge typical for everyday life. Your personal reaction to such provocations is called stress. The provocation itself is not at all a stress but is called "stressor". Those two technicalities are regrettably often confused by journalists, so that the word "stress" became an exceedingly wooly term.

But if we once agree upon the reactive nature of stress, further reasoning is simple: If your efforts to remove a provocation turn out to be too feeble, the provocation remains and your unsuccessful efforts become chronic – chronic stress ensues. Although perhaps a bit too feeble to remove the provocation, your stress efforts are still using up more than the portion of energy which you have allotted to the routine running of events. Thus your whole system needs more fuel over a longer time, which in its turn tends to exhaust your energy reserves. Your efforts grow feebler still – burnout threatens.

[*] Gertrud W. Desch, Harald Gell, Karl Pichlkastner, Reinhard Slanic, Josef Porta, Gerd Korisek, Martin Ecker and Klaus Kisters
1 *Institute of Applied Stress Research, Judendorf – Strassengel, Austria,*
2 *Institute of Pathophysiology, Medical University of Graz, Austria,*
3 *Institute of Mathematics and Scientific Computing, KFU Graz, Austria,*
4 *Rehabilitation Clinique of the AUVA, Tobelbad, Austria,*
5 *Theresianische Militärakademie, Wiener Neustadt, Austria,*
6 *St. Anna Hospital, Herne, Germany.*

It is interesting, that such reasoning describes on the one hand the well known development of chronically increased energy turnover into exhaustion and burnout. On the other hand it shows, that increasing exhaustion also increasingly curtails successful reactions to immanent provocations, meaning that those provocations cannot be fought with adequate reactions any more – an exhausted subject cannot mobilize enough reserves to fend off a challenge – there is not enough stress available to cope successfully. Thus one could appreciate the nonsense of statements repeated in journals over and over again, to "dismantle your stress" or "let your stress phase out". Far from getting rid of a personal reaction which may successfully release you from an impending menace, one has to fight the menace itself, which can be only done by successfully mobilizing ones reserves.

All those different reactions of the organism, due to differing workload intensities and different duration leading to the symptoms just described, can be quantified by a multiple parameter assessment called CSA.

Physiological aspects of stress and their utilization for stress assessment

Stress situations incite changes of Adrenaline and Noradrenaline which, in their turn effect variations in blood pH, CO2, O2, buffer parameters like BE or HCO3, lactate and blood glucose as well as electrolytes like K, Na, Ca and Mg. Since we could show as far back as 1991 (1, 2), that those stress hormone effects do correlate highly significantly with adrenaline and noradrenaline changes themselves, the tedious, costly and time consuming catecholamine determination by HPLC could – at least for the purposes with which we tend to deal in this chapter – be abandoned in favour of a much quicker method for determination of stress induced metabolic changes. Estimation of those metabolic effects has the additional benefit, that the obstacle of the receptor situation, which influences hormonal effects and thus restricts the meaningfulness of catecholamine determination as a tool for assessing stress intensity is avoided, since all of our parameters depict post receptor effects.

Those non hormonal parameters therefore show interdependent stress hormone effects, which, when determined simultaneously, can be laid over an organism like a data net by especially designed online software which can be taken as the basis of an individually adaptable multi parameter stress index.

In the simplest case of a physical workload e.g., we find workload dependent change in blood glucose, increase in lactate, accompanied by adaptive changes in pCO2 and/or HCO3 and baseexcess, softening the lactate impact upon pH. Moreover, typical shifts in Ca, Mg and K provide us with information about the intensity and duration of stress. When e.g. more sensitive parameters like pCO2 or less sensitive ones like HCO3 and blood glucose, are determined at the same time in the same sample, they can give a good idea about the duration of the stress, depending upon the relative involvement of the said parameters.

Likewise, change of electrolytes can tell – together with either pH or pCO2 about the momentary inclination to sportive performance, about the intensity of symapthoadrenal expectation situations or even about the individually felt efforts of competition and – in the long run – even help to diagnose and quantify a possible state of exhaustion. Chronic sympathoadrenal impact upon metabolism could also be detectable in psychopathological diseases like depressive disorders, where the question arises, whether the patients' mental exhaustion may not affect metabolic processes too.

Also, those interconnections of multiple metabolic effects can be used to uncover hitherto less well understood parameter interactions in metabolic diseases like the metabolic syndrome or even diabetes. There the quantity of electrolyte deficiency and its relation to the idiosyncratic behaviour of a chronically affected metabolism may open new aspects of diagnosis and therapy. Finally, diagnosis of mental and physical load leading to exhaustive stress can not only be used in managers and sports persons, but also to the purpose of being better able to judge upon correct treatment of livestock.

In most cases one has to take pains to collect pre- and post workload data.

The hardware used for such an assessment consists of well established determination systems, implemented in most ICUs all over the world. Due to the easy transportability, at least of those two examples shown below in fig.1 and fig.2., they have been used in assessment campaigns, ranging from determination of psychical workload of teachers in schools or managers in industrial plants to the evaluation of fitness of professional ski racing teams in mountain ranges and assessment of the impact of sleep deprivation in soldiers far away from human habitations.
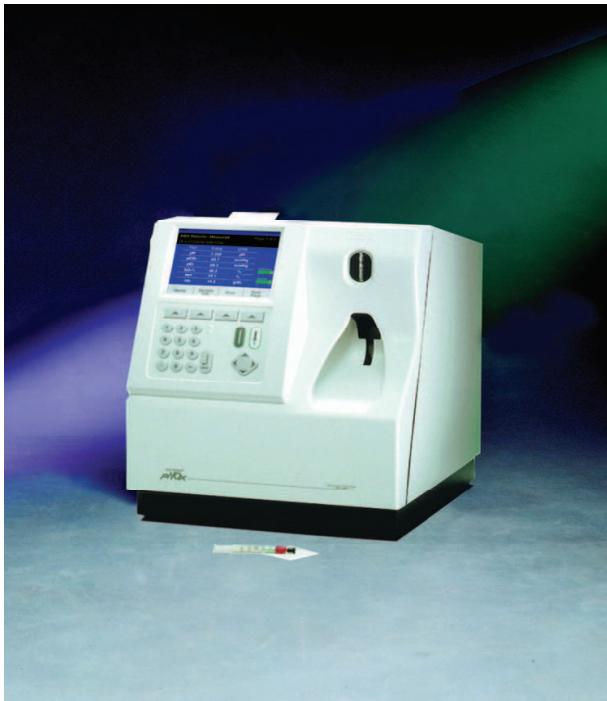

Fig. 1. NOVA CCX (Critical Care Express)   Fig. 2. NOVA Phox - M

Fig. 1. and 2. Two types of transportable ICU analyzers (dimensions estimable by the syringe in the foreground)

1.2 Practical implementation

Sampling and sample determination – Single persons

Thus, a persons' or an animals' workload, stress compatibility, duration of stress and also the intensity and the kind of stress can be determined within 3 minutes by collecting about 100 microliters of capillary blood, usually from the finger tip. The sample is routinely analyzed for pH, pCO_2, pO_2, O2saturation, ionized magnesium, ionized potassium, ionized calcium and ionized sodium, lactate, blood glucose, baseexcess and HCO_3 (optionally

hemoglobine and hematocrit) using a CCX (Crital Care Express, fig.1)) analyzer (NOVA Biomedical) or a Phox – M (fig.2) of the same producer (NOVA Biomedical), with about the same functions but smaller and even easier transportable and CSA (Clinical Stress Assessment) software. Both devices are widely applied all over the world in Intensive Care Units (ICUs), the software for online data evaluation and interpretation however has been developed by an Austrian corporation (PLK, Judendorf - Strassengel).

Healthy persons are usually checked before and after a standardized ergometric workload, mainly 80 Watts during 8 minutes, or before and after absolving sporting activities, or before and after a standardized psychical load like a Shapiro – test or any kind of training routine the impact of which stands in question. Additionally, the effects upon a persons' metabolism by so called wellness activities - from steam bath to sauna baths, massages etc. - can be investigated, applying the same protocol. In other fields of application even single determinations can be useful e.g. in the course of daily glucose profiles from diabetic patients in rehabilitation hospitals.

Sampling and sample determination – Groups

Such determinations can therefore characterize the reaction of a single person but they also can do the same with a whole group of people. In the latter case the group reaction may serve as a mirror of the typical demands of a certain task on a sample of persons. Thus information about e.g. the usefulness of a bout of training for defined purposes can be collected. All data won from the 100 microliter sample are analysed simultaneously within two minutes, so that total measuring time from blood sampling until the printout of the online processed data takes no more than 3 minutes. Calculations of averages, standard errors of means (SEM), delta values between the groups and linear correlations between all sampled parameters with their regression coefficients are software immanent. This means, that basic group statistics are available immediately after the testing of the last group member. The automatic correlation of every single parameter with all others comes in useful in many ways as we will see during the progress of the chapter. It allows us to look behind the equalizing group averages, thus enabling us to quantify the position of every group member from the point of view of a certain parameter combination. Moreover, the automatically emphasized numbers of significant regression coefficients in the correlation table creates a quickly recognizable pattern of typical group behaviour, as explained in fig. 3. Seen for the first time, this coefficient tables seem somehow crowded with data, but after a short acclimatisation one appreciates the quick oversight over all relevant interconnections of the measured parameters under different conditions:

In the first table (correlations day 1 before load) there are 7 significant linear correlations between stress related parameters. In the second table, describing the correlative situation of the same parameters and the same group, but this time after workload (military obstacle run – HIB), the number of correlations more than doubles to 15. Especially the increase of correlations with lactate and pCO_2 after workload and the occasional difference in plus/minus signs are noteworthy. As we will endeavour to demonstrate, such correlative views can show at a glance, whether the present workload of a group still allows overcompensation (see below) or whether the group seems to be on the brink of exhaustion already. The usefulness of this tool in preventive medicine is obvious. The results of more than 2000 patients and experiments have been recorded in our data banks and published in about 60 papers and printed abstracts, thus providing comparative material for easier interpretation of results.

Data correlation before and after workload

Correlations from Day 1 Before Load

pH	-0,2504	0,481831	0,333402	0,433029	0,583413	-0,5074	0,25455	-0,01633	-0,32217	**-0,63423**	-0,24493
	pCO₂	0,726923	0,828486	-0,20617	-0,29714	-0,04356	-0,09519	-0,06547	-0,35569	-0,06392	0,035502
		BE	0,986333	0,139369	0,161857	-0,40704	0,102724	-0,06267	-0,53472	-0,49239	-0,12316
			HCO₃	0,069993	0,063736	-0,33665	0,05957	-0,06223	-0,52028	-0,41705	-0,0929
				pO₂	0,964941	-0,42371	0,190862	0,006544	0,192812	0,168397	0,594032
					O₂sat	-0,44238	0,220152	0,015527	0,143388	0,047916	0,439431
						Na	-0,15078	0,436357	0,348535	0,322723	-0,30305
							Ca	0,762729	0,159733	-0,16922	-0,1855
								Mg	0,225335	-0,02046	-0,28541
									K	0,289389	0,289389
										Lactate	0,642421
											BS

n=
p<0.05   0,6
p<0.01   0,6411
p<0.001   0,7604

*** Blue cell indicates correlation always seen

Correlations from Day 1 After Load

pH	-0,63133	0,222844	-0,00479	-0,13636	0,296601	-0,21557	-0,36304	-0,28804	0,228092	**-0,62068**	0,000522
	pCO₂	0,648703	0,811668	-0,45956	**-0,66746**	0,506397	0,1739	0,223456	-0,23483	0,026883	0,160047
		BE	0,9723	-0,6818	-0,49137	0,401231	-0,15568	-0,02538	-0,02401	**-0,55603**	0,21133
			HCO₃	-0,65535	-0,55363	0,45704	-0,06946	0,033726	-0,05444	-0,41068	0,207617
				pO₂	0,853721	-0,33658	0,133764	0,009547	0,210286	0,760339	-0,12479
					O₂sat	-0,43265	-0,09908	-0,22285	0,449271	0,459362	0,060453
						Na	0,773358	0,843156	0,019402	-0,25188	-0,18683
							Ca	0,914917	0,123339	0,085249	-0,37858
								Mg	0,111536	-0,03408	-0,41609
									K	-0,07662	0,282364
										Lactate	-0,08128
											BS

n=
p<0.05   0,5
p<0.01   0,6411
p<0.001   0,7604

Outprint of CSA – software immanent automatic correlations of all the parameters measured.
Upper triangle: before workload,
Lower triangle: after workload
Red numbers: significant correlation coefficients.

Fig. 3. Example of two tables of regression coefficients of a group before and after workload, useful for quick overall estimation of the changes of interparametric dynamics.

Ethical aspects

All participants in the investigations presented in this chapter consented to the anonymous use of their data after being carefully informed about the aim of the study according to the Helsinki Charter (*http://www.wma.net/e/ethicsunit/helsinki.htm.*). The most recent submission to and passing of our experimental intentions by the ethical commission of the Austrian Federal Ministry for Defence and Sports (BMfLVS) dated from Dec. 13th, 2010.

1.3 Application of CSA

Our own experience of CSA application ranges from investigations into the behaviour of teachers, students, triathletes, aircraft pilots, bungee jumpers, military combat groups, special police units, rescue teams, sleep deprivation, free radical research, patient's stress in rehabilitation clinics to the impact of wellness treatments, even to the exhaustion of farmers providing holidays for tourists additionally to their usual tasks.

The following four applications that will be discussed in the course of the chapter form a concentrated substrate, presented to make the reader think about own, customized applications:

1. Determination of the impact of sport training or training of so called "first responders", like military training units, special police groups, fire fighters and others. We maintain that it is not only possible to link changes of blood parameters with sportive success but also to predict success chances before competition or deployment.
2. Determination of the quantity of mental stress.
3. In the field of internal medicine mainly idiosyncrasies of diabetic metabolism, especially those due to the newly found importance of mineral deficiencies in type2 diabetics

which, by CSA application, we were able to link up with the deterioration of other metabolic disturbances.

4. Qualification and quantifications as well as predictions of success chances in competing animals like horses or camels and also prevention of cruelty to animals by stress documentations are one our next step of development.

ad 1: Determination of the impact of sport training or training of so called "first responders", like military training units, special police groups, fire fighters and others

Up to now the decision about a persons' fitness for a certain competition mainly rests upon the trainers' subjective adjudication, bolstered by lactate tests or even more demanding workout procedures and a more or less profound experience. Thus the availability of a hardly molesting, objective, in depth assessment of competitors and first responder personnel concerning their momentary ability to perform a certain task (3, 4, 5) comes in useful. Investigations in that area revealed not unexpectedly, that the metabolic situation of a person before a contest contributes decisively to the degree of the later success. Therefore it could be advantageous if we would be able to quantify the metabolic turnover before the contest in each case. Because, by quantifying pre contest metabolic situations, both the individual position within a group of contesters could be determined and eventually significant deviations of possible group outsiders could be marked down, understood and subsequently discussed with the person in question. That e.g. exhausted soldiers or sportsmen are no more able to perform satisfactorily is a truism. However, there are unsatisfactory performances which are less well explainable. The most common reasons are mostly privately known to the performer but not eagerly revealed to the trainer or group commander like lack of sleep due to entertainments during the previous evening.

But also unexpected bouts of good or bad performances occur, unexplainable to both performer and trainer. Moreover, the very same scores obtained easily by performer A could have been demanding for performer B, so that equal scoring may not mean equal potential at all. Even slight influences during the pre contest situation which are hardly felt and therefore frequently ignored, like temperature differences or even the changing of a routine can be reasons for a significant shift in interdependencies of electrolytes and metabolic parameters with measurable impact upon the performance to follow. Especially correlative changes between Mg, K, the Ca/Mg quotient or, to a lesser extent Ca alone with H^+ donors like lactate and the consecutive pH and blood buffer situation react rather sensibly to changes of the sympathoadrenal situation in man and even in horses (3,4,5,6). Since in our experience the demand for such determination focuses upon comparatively small groups and their individual members, we tried to offset the comparatively small number of experiments by software immanent statistics from diverse points of view to keep results controlled as strictly as possible.

Since our assessment provides us with at least 24 interconnected data per person (from determinations before and after workload), a more comprehensive description than that by the widely used lactate test or by catecholamine assay alone is possible.

It is remarkable, that nearly the same small amount of capillary blood which is still routinely used for lactate tests could easily yield eleven times more information instead of the single lactate determination. As an example we would like to show an investigation of 14 Ensigns of the Theresianische Militärakademie in Wiener Neustadt, Austria before and after a demanding military obstacle race of 3 – 5 minutes duration. It turned out that the metabolic changes in the experiments due to that military obstacle race were considerable, although the overall duration did not exceed five minutes:

Changes in group averages before and after the obstacle race (*military steeplechase, Hindernisbahn - HIB*) are shown in table 1: An expected significant change in stress dependent parameters like pH, pCO2, BE, HCO3 and K, due to severe exertions was visible. The averages of Mg and Ca however did not change significantly.

	pH	pCO$_2$	BE	HCO$_3$	pO$_2$	O$_2$sat	Na	Ca	Mg	K	Latate	BS
Averages before HIB	7,433	34,714	-1,114	23,400	68,293	94,164	145,886	1,135	0,514	4,339	1,793	102,357
+ / - SEM	0,005059	0,568578	0,419295	0,383162	1,5218	0,522737	0,429906	0,008238	0,008228	0,077598	0,11117	1,99892
Averages after HIB	7,257214	26,14286	-15,3643	12,01429	92,59286	96,29286	146,3714	1,140714	0,515	3,805	12,98462	151,2857
+ / -SEM	0,020643	0,53171	1,048002	0,72323	2,565461	0,215464	0,39103	0,009167	0,009931	0,093631	0,864019	6,807743

Average group values before and after sports +/- standard errors of means (SEM). Changes in pH, pCO2, BE, HCO3, pO2, O2sat., K, Ca, lactate and blood glucose are highly significant (two sided t- tests (p<0,01), (7))

Table 1. CSA outprint, example of the change of group averages due to a military obstacle race (HIB).

Beyond the information which the average group values provide, we were able to uncover four different facts by correlating appropriate parameters of the pre- contest situation.

a. The phenomenon of "overcompensation" in the pre contest phase can be detected and its effect upon the assessment of a persons' fitness and sportive compatibility can be discussed.

b. The impact of pre contest sympathoadrenal arousal upon the metabolism of each group member can be quantified. If outliers are present, they can be characterized and marked down for interviews

c. Connections between the now quantifiable position of each group member in the pre contest phase and the definite scoring during the contest can be established. Success/effort relationship can be characterized.

In other words, the answers to those four points provide the trainer with comprehensive information about the individual pre contest situation of each group member, whether the adrenergic arousal before contest remains within beneficiary boundaries or already uses up too much energy which would be more profitable employed later during the contest. They detect outsiders and even provide the trainer with scoring - chance predictions for the contest to follow. How is it done? First of all we have to become familiar with the usual state of affairs before a contest, the knowledge of which seems to be not usual at all. We call it "overcompensation". Different group members tend to express it in differing quantities.

a. Overcompensation

Slight to moderate mental or physical load frequently results in metabolic overcompensation. Simplified, the well known respiratory compensation of metabolic acidity can become over efficient, so that persons with increased lactate or other H$^+$ donors end up with a more alkaline pH brought about by a disproportionally increased breathing frequency, connected of course with an equally disproportional loss of CO2. The benefit of this seemingly wasteful behaviour is a kind of run up into higher pH regions to premeditate a later fall into dangerous acidity by an eventually more demanding workload in the immediate future which the organism seems to prudently forestall. Accumulation of O2 in the blood because of the more alkaline conditions points the same way. A good example of such a reaction is the pre contest situation before the military steeplechase concerning pH/pCO2 relationship. (fig. 4). This figure deals with and quantifies an "over successful" removal of acidity from the blood by increased breathing frequency.
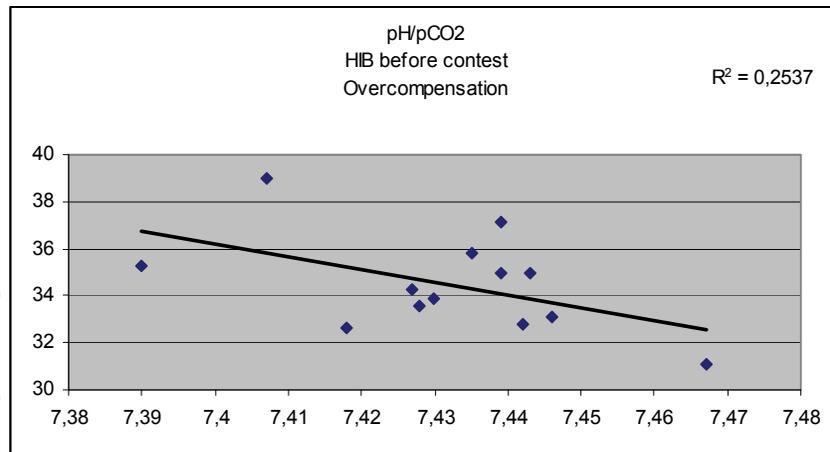
Abscissa: pH
Ordinate: pCO2 in mmHg
P< 0,05, significant
Situation before the military steeplechase contest.

Fig. 4. Situation before contest: Increased breathing frequency leads to diminishing pCO2 and consecutive pH increase.

The highest breathing frequency, borne out by the most pronounced loss of CO2 leads to the most alkaline pH. This means, that here the most pronounced metabolic activity, expressed by the highest breathing frequency, paradoxically yields the highest pH values (fig. 4)
The picture is completely contrary to the familiar concomitant fall in pH and pCO2 during pronounced physical action (contest), which is shown in the next graph to underline the striking differences between the "warming up"(fig.4) and the real contest situation (fig.5):
pH / pCO2 after workload
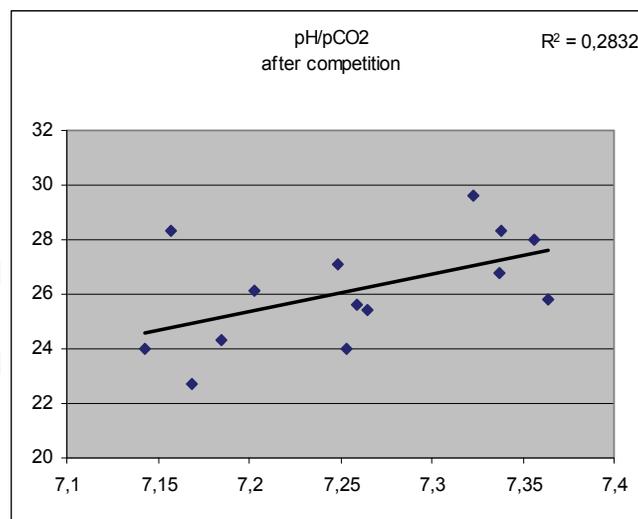
Abscissa: pH
Ordinate: pCO2 in mmHg
P< 0,01, highly significant
Situation after the military steeplechase contest.

Fig. 5. During the demanding military exercise pH/pCO2 relation turns around, CO2 release is now unable to prohibit the fall in pH (note the extremely low pH and pCO2 values due to the heavy workload).

The adrenaline induced slight, individually different lactate increase in the pre contest situation should lead to a concomitant decrease in pH. But since at the same time H ions are indirectly got rid of by increased breathing, proportional pH decrease along with lactate increase is counteracted. Consequently, in the pre contest situation, pH and lactate do not correlate positively any more – as they do during the contest – due to the increased loss of CO_2 during the said overcompensation, as shown in fig.6.

pH/lactate before HIB

$R^2 = 0,0546$
not significant
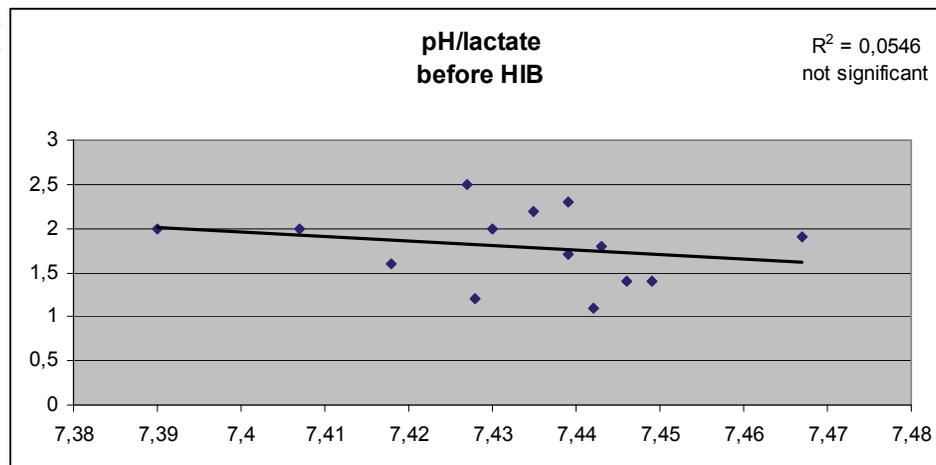
Abscissa: pH
Ordinate: lactate in mM/l
p>0,05, not significant
Situation before the military steeplechase contest.

Fig. 6. Due to successful CO_2 control of pH before contest, pH/lactate relationship vanishes.

Consequently again, all our following correlative graphs of pre contest situations dealing at least with either pCO_2 or pH have to be interpreted as situations, when the highest pH and the lowest pCO_2 occur in the person with the most clearly increased metabolism. Having ourselves used those automatic correlative evaluations regularly, we came across overcompensation surprisingly frequently, mostly in pre contest situations or other moments of sympathoadrenal arousal. Therefore we would like to forward the supposition that overcompensation is a general feat of adaptation to probable demands in the future and thereby possibly an important part of evolutionary survival strategy.

b. Quantification of pre- contest conditions and characterization of outliers

Following up our suppositions of a possible impact of the pre- contest situation upon the contest proper, we checked as a first step the K/pH proportions of the experimentees, because a possible sympatho – adrenal arousal in expectation of the contest may well lead to an individual increase of lactate values (the average increase being only a slight one, see tab.1), consequently to increased H ions, which would be exchanged with K ions from the tissue in a rate presumably proportional to the H ion production and therefore proportional to catecholamine impact. Indeed, a highly significant, but negative correlation between pH and Ionized K ensues, positioning the most pronounced K loss along with the highest metabolic turnover, characterized in this overcompensating situation by the highest pH and lowest K values. A combination of electrolyte- and metabolic parameters therefore are seemingly able to characterize typical group idiosyncrasies (overcompensation in this case) as well as the individual position of the participants within the group (fig.7):
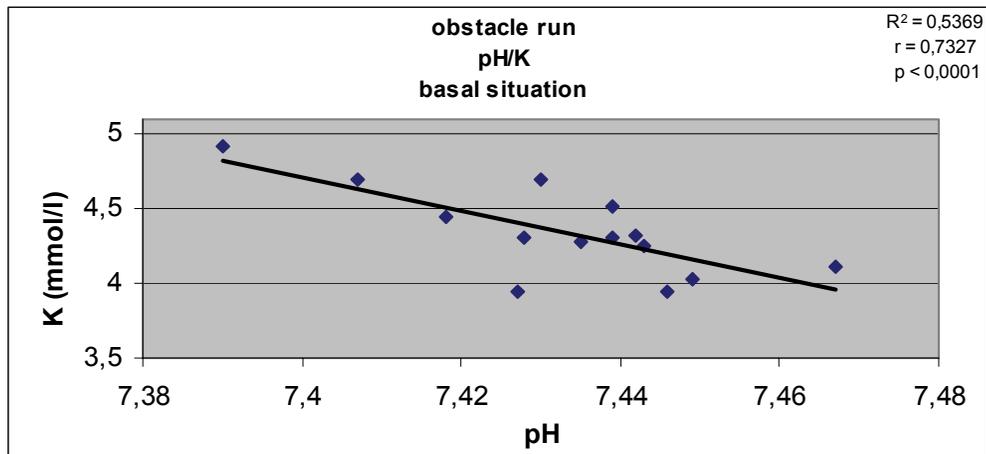
Abscissa: pH
Ordinate: K in mM/l,
p<0,001, highly significant
Correlation between pH and potassium before sports.

Fig. 7. Sympathoadrenal arousal before contest incites overcompensation, also shown by significant inverse pH/K relationship.

In such an adrenergic state of expectation, a further correlation can be expected, namely a proportional behaviour of pH and ionized magnesium, because adrenaline increase changes of pH via the mechanism mentioned above and can also increase ionized Mg in blood (8,9).
However, no significant correlation could be found. This could have been due to two outliers which are marked by an oval inclusion in the graph below (fig.8):
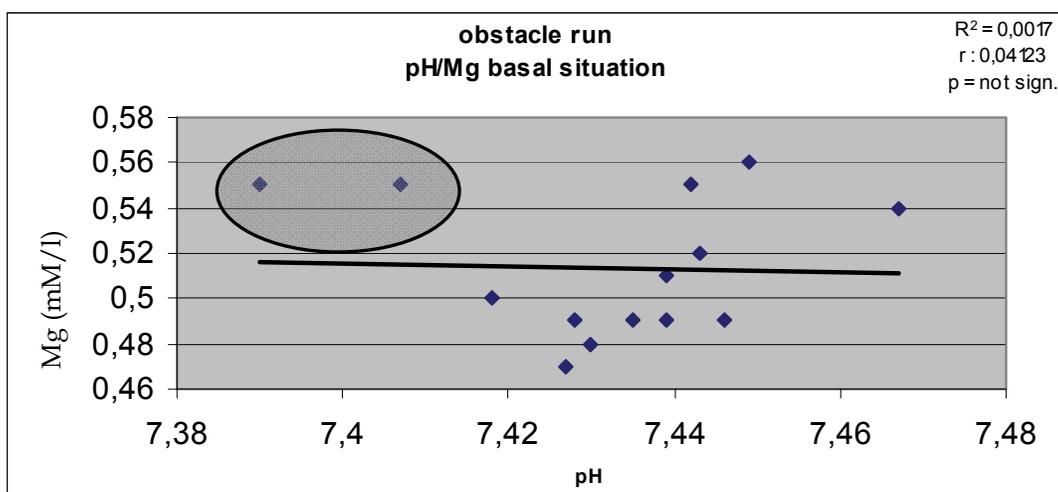
Abscissa: pH
Ordinate: Mg in mM/l,
p>0,05, not significant
points within the elliptic figure: presumptive outliers

Fig. 8. Positive pH/Mg correlation is disturbed by two outliers.

When the outliers are removed, a highly significant positive correlation between ionized Mg and pH in the blood of the pre-contest experimentees evolved (fig.9):
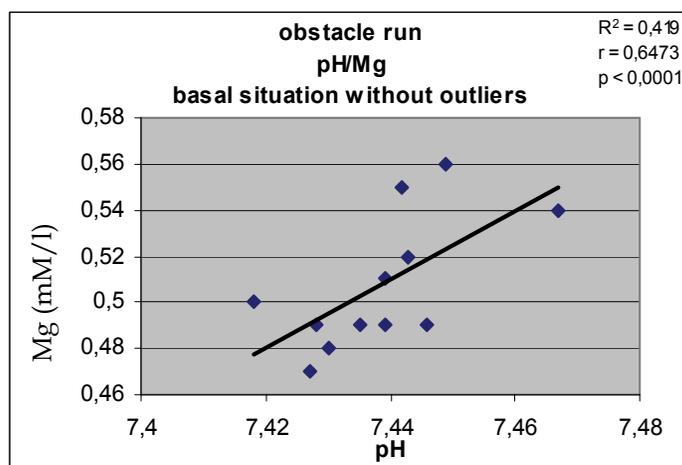
Abscissa: pH
Ordinate: Mg in mM/l,
p<0,001
Correlation between pH and magnesium before sports without outliers.

Fig. 9. Removal of the outliers leads to restored pH/Mg correlation.

Similar as in fig.8, the highest Mg turnover (here Mg increase) goes along with the most pronounced metabolic turnover, again characterized by pH increase, due to overcompensation, provided the outliers have been removed. However, to characterize and/or remove the outliers out of purely statistical reasons is not correct, although it seems obvious, that they are not part of the sample. They both show high Mg values at concomitantly low pH which does not fit the group behaviour at all. On the contrary, this combination of parameters points towards an already most active metabolism before sports, which may not be able any more to meet the subsequently further increased energy turnover, necessary for high scoring. It follows, that they do not develop any sign of overcompensation, as does the rest of the group, since their high Mg values exist concomitantly with low pH, a feat that does nowhere occur in the rest of the overcompensating group. The pre – contest diagnosis of a prematurely increased metabolism of the outliers is consistent with some of the outliers' values *after* sports, forming a different multi parameter pattern:
1. very high BE values after sports
2. very high pCO2 values after sports
3. very high HCO3 values after sports
4. low scoring (ranking on 12th respectively 13th position within a group of 14).
According to this additional information, we felt justified to separate those two participants from the other members of the group, which – without those two - forms the mentioned well definable, highly significant pH/Mg relationship (fig.3). At least for practical reasons the information of their outlying position - which is only shown by the correlation analysis and would never have come forth by group average calculations alone - should on no account be discarded and at least used for closer observation and extended interviews with the two experimentees.

c. Prediction of success chances by quantitative evaluation of pre- contest conditions

Investigations into interdependencies between basal K and awarded scores (fig.10).For the first time we introduce non CSA values in our correlative interpretations – the awarded

scores for the obstacle run, which are nearly identical with ranking of the period of time needed for its absolution.
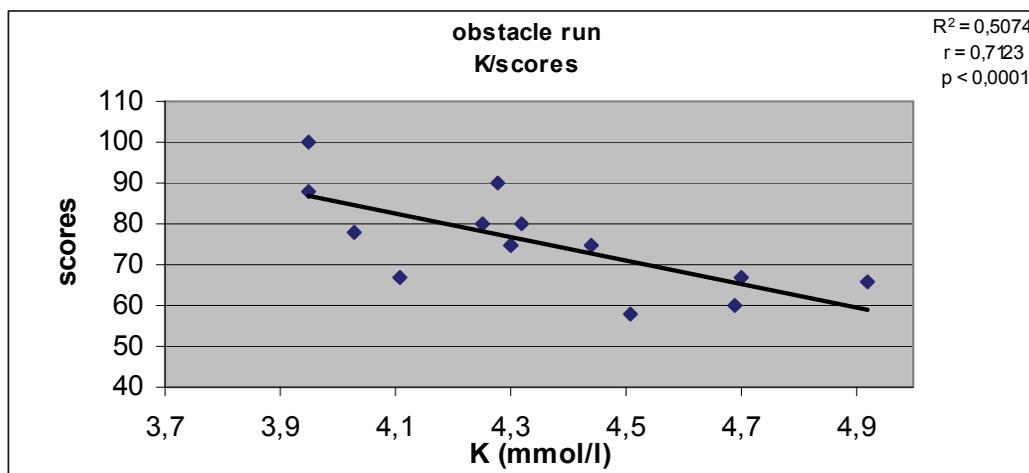
Abscissa: Basal K in mM/l
Ordinate: awarded scores
p<0,001

Fig. 10. Blood K levels before contest possibly predict chances of scoring at the contest proper.

Pre contest K concentrations and the scores awarded after steeplechase correlated negatively in a highly significant manner, meaning that persons with lowest pre- contest K values cherish the best chances for high scoring in the subsequent contest. Lowest K concentrations on the other hand coincide with highest pH levels in the overcompensating group (fig.1), which – under those circumstances – mark high metabolic activity. Within reason therefore, those who have been most successfully mentally "warming up" themselves, stand to be rewarded with better scoring chances. It is important, not to be led astray by the high scoring of contestants with an alkaline starting position, Slightly alkaline pH in this context is definitely not a sign of low metabolic turnover, but, as we have already been able to demonstrate, a feat of increased energy turnover by sympathoadrenal arousal, what we just called "mental warming up". Summing up the information of the graphs hitherto presented, the pre contest metabolic pattern of a presumable high scorer seems to be:

1. Low potassium (fig. 7)
2. High pH (fig 1))
3. High Mg (fig. 9)
4. Low pCO2 (fig. 4)

This multi parameter pattern shows, that increased metabolism characterized by the most pronounced loss of CO2, increases Mg clearance from the tissue and also increase blood pH. Since pre- contest pH is already increased by excessive CO2 loss, there is no urgent need for cation exchange, which is underlined by the low blood K values. Roughly spoken, K seemingly is allowed to stay put within the tissue, regardless of increased metabolism. Such a tissue reserve of readily exchangeable K ions however, could facilitate a more successful H ion removal into tissues later, during the demanding contest expected. That lactate values did not enter our multi parameter pattern more prominently can be explained by the failing

correlation between lactate and pH. Increased breathing frequency obviously buffers direct lactate impact. Also – during the predominantly mental stress before contest – a participation of free fatty acids from catecholamine induced beta oxidation is to be expected and can indeed be roughly calculated by subtracting lactate values from baseexcess (both in mM/l)

### d. Characterization of success/effort relationships

The role of certain electrolytes in blood, changed by the psychic arousal of the pre- contest situation could be shown already by correlating them with metabolic parameters like pH or pCO2. But they play a further role – again together with metabolic parameters - as indicators of competition success, part of which we have already exemplarily shown by the predictive power of K changes before competition. During our investigations of blood samples before and after the military obstacle run (HIB), however, we found connections of lactate and Mg changes with running times and scoring which contributed substantially to a better understanding of a contestants' attitude to the task. This may come in useful for basic research about the role of Mg in energy turnover but also has practical importance in such cases when one wants to check effort and performance of tasks where other means of objectivation cannot be applied or one is simply not present.

Therefore let us have a look into the Mg/lactate relationship, which we purport to be especially apt to reveal the individual attitude towards the contest: Although individual Mg+ changes were rather pronounced, no corresponding *average* Mg+ increase or decrease was visible because Mg+ changes often pointed in opposite directions. This individual behaviour of the Mg+ changes however correlates highly significantly with lactate changes. Fig.11 shows, that sometimes more information can be gained by using the – also automatically compiled – delta values, the changes between the values before and after workload and not the measured values themselves. Thus clear proportionalities between effort and electrolyte turnover could be shown.
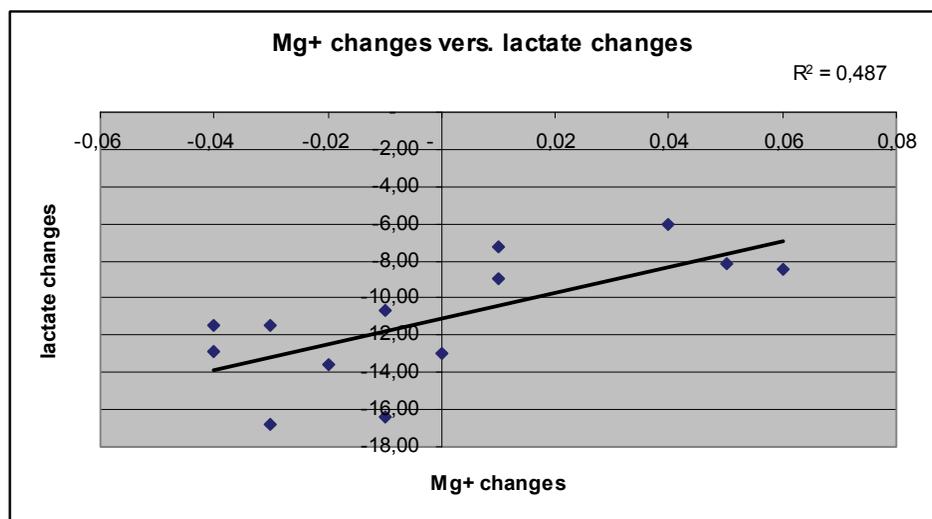
Abscissa: Mg+ changes (delta values: Mg+ before exercise minus Mg+ after exercise)
Ordinate: Lactate changes (delta values: lactate before exercise minus lactate after exercise)
P< 0,001, highly significant

Fig. 11. Documentation of delta values sometimes are better able to reveal parameter interactions than absolute concentrations.

Higher lactate increases beyond 11 mM/l correspond with Mg+ increase, lactate changes below that value corresponds with Mg+ decrease in blood. That lactate changes do not correlate with both awarded scores and running time is not surprising, since it is common knowledge that subjects with better fitness may score higher with less lactate increase than less well trained subjects with higher lactate increase (3). But unexpectedly, Mg+ changes (automatically computed delta values) did correlate with awarded scores and running times as well, highly significantly in a polynomial curve of the 2nd order. Fig. 12 shows, that Mg changes not only correlate with lactate changes (effort) but also with awarded scores, but now in a different, polynomial manner.
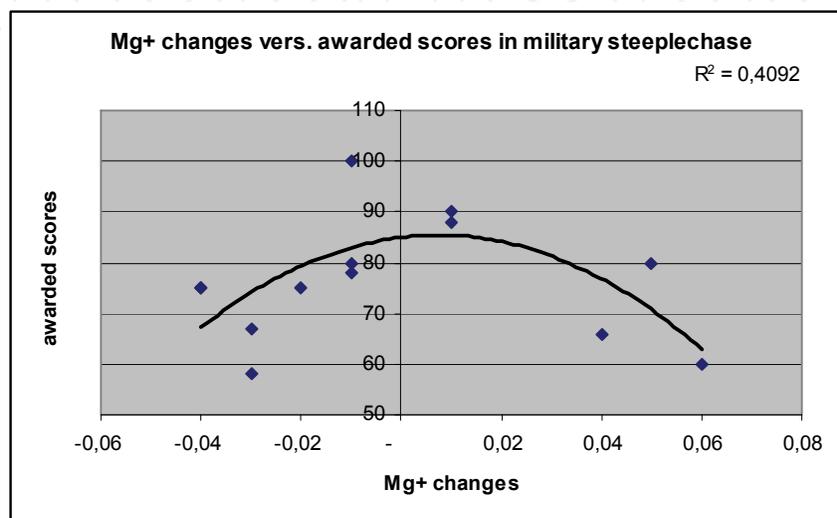
Abscissa: Mg+ changes (delta values)
Ordinate: scores awarded
P< 0,001, highly significant

Fig. 12. Mg delta values this time plotted against scores, once more prove their usefulness.

Since changes in blood Mg+ are to be considered as subtractions of Mg+ influx from tissue and Mg+ redistribution (10) by clearance from the blood, people with the best balanced Mg+ in- and efflux show nearly zero deviation. And it is exactly this group that has been shown to have the best chances for highest scores and shortest running times. Moreover, the supposed unpredictability of positive or negative Mg+ changes, at least during short term exercise with high energy turnover, may be qualified by the existence of this polynomial correlation between both scores and running times and the Mg+ changes in question.
Distinctly increased Mg+ blood concentrations therefore, went along with the high lactate increases beyond 11 mM/l, mostly in participants with low scores. Contrarily, low scores and long running times went together with pronounced decreases in Mg+ along with comparatively low lactate increases otherwise seen in high scorers, but then with hardly any Mg+ changes.
Thus, a typical combination of lactate and the obviously quicker Mg changes is characteristic not only for a certain score, but also provides more information about the reason for low scoring, when one combines the information of fig.4 and fig.5: High Mg+ increase is mostly associated with pronounced lactate increase and pronounced Mg+ decrease with a relatively small lactate increase for this demanding kind of exercise. All the high lactate increases therefore are on the side of Mg+ increase and vice versa. Moderate lactate increase, along with moderate Mg+ change seem to characterize the reaction of a well trained subject.

One is tempted to deduce, that in our short and demanding exercise the mark of an average delta value of 11mM/l of lactate may be the turning point between a preponderance of Mg+ clearance from the blood during the first stages of the exercise and a consecutively increased Mg+ influx into the blood, overcoming the clearance rate, because of considerably increased demand upon muscular tissue.

This turning point should be demonstrable by a polynomial curve, which indeed it has been. It furthermore may even serve as a kind of standardization mark, beyond which additional lactate increase (effort) does correspond less and less with effectiveness. A possible practical application of the combined information of fig.4 and fig.5 could be i.a. an objectivation of subjective adjudications of any persons' effort and success. Hitherto, mostly increases of Mg+ blood concentrations during short term exercise have been advocated, while Mg+ decrease has been mainly associated with longer lasting workloads (11, 12, 13) Biphasic Mg+ changes, at least during short term exercises have not been described up to now. As mentioned above, the results of such an investigation allow basic considerations about new aspects of the role of electrolytes as well as pave the way towards some practical progress in adjudication of success and effort relationship.

ad.2: Metabolic changes due to mental stress in depressive patients

Having been able to show that the predominantly psychically induced change in metabolic parameters before a contest can be measured and thus quantification of psychical arousal by metabolic determinations can be attempted at least proportionally, we would like to show an application of this idea at psychiatric in - patients. Our clinical study included 19 patients (17 females and 2 males) with a mean age of 44 years (range from 24 to 65, with a median of 44). All of them were suffering from major depressive disorders (Hamilton depression scale from 18 to 33). We compared them with a group of .46 subjects (35 males and 11 females, nearly equally aged) Before and after a slight ergometric effort (60 watts for 6 minutes) capillary blood samples were drawn as described above and the resulting group averages
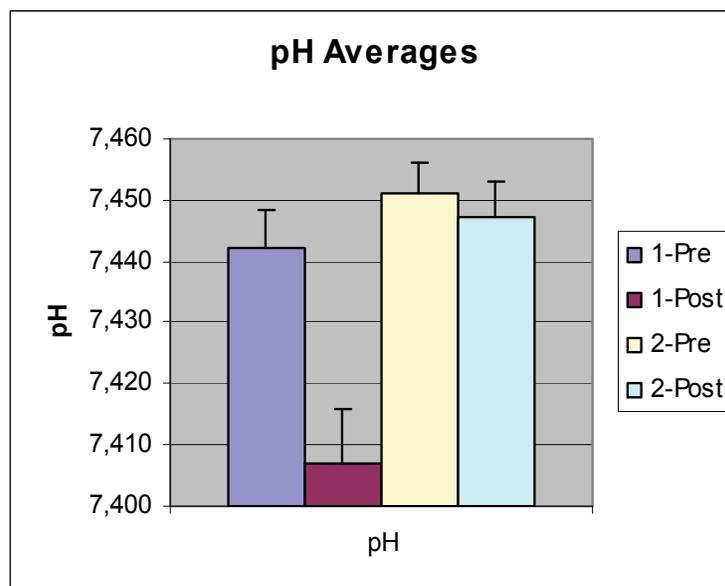

Abscissa: determination situations (see text)
Ordinate: pH

Fig. 13.

for pH, pCO2, Basexcess and Magnesium are shown in the next four automatically generated graphs. The first two columns of each graph show the group averages before (col.1) and after workload (col.2) of the psychiatric patients, columns 3 and 4 show the group averages of the equally treated healthy group

Fig. 13: Figs. 13, 14, 15 and 16 deal with the average changes of pH (fig.13), pCO2 (fig.14), base excess (fig.15) and magnesium (fig.16) of psychiatric in – patients (blue and red column) and a matched control group from our data banks (yellow and green columns). Remark the much more sensible reaction of the patients to workload.
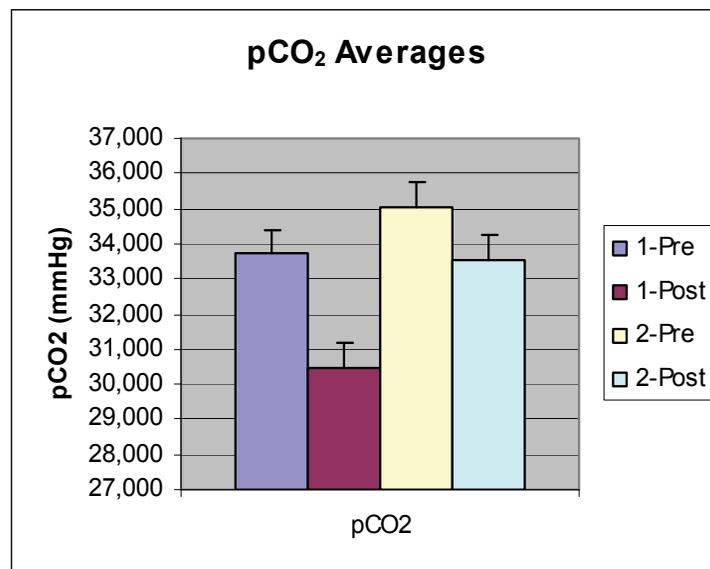
Abscissa: determination situations (see text)
Ordinate: pCO2 in mmHg

Fig. 14.
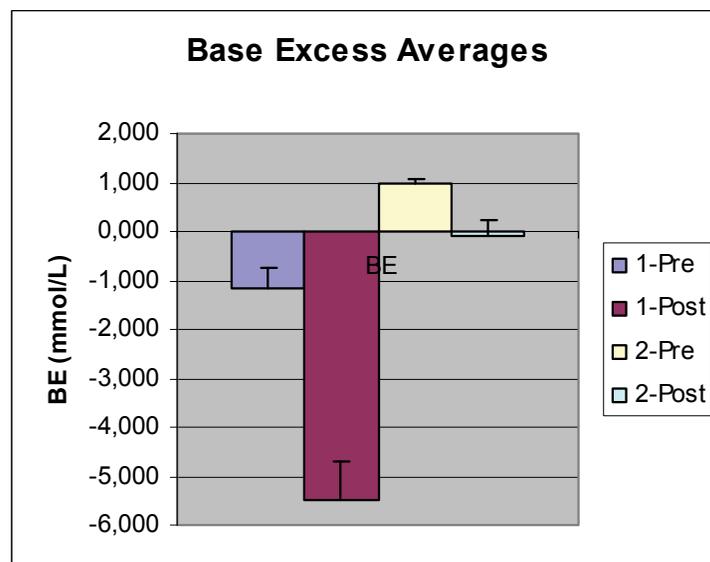
Abscissa: determination situations (see text)
Ordinate: Baseexcess in mM/l

Fig. 15.
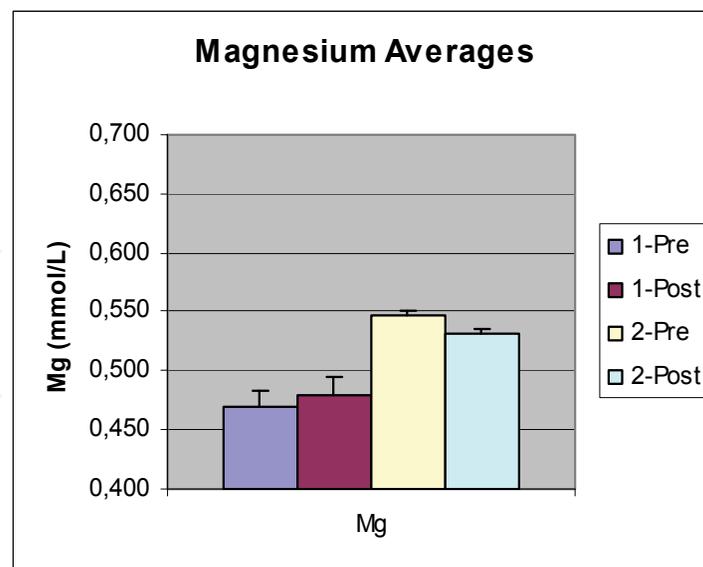
Abscissa: determination situations (see text)
Ordinate: Ionized Mg in mM

Fig. 16.

With the exception of the baseexcess there were no significant differences in the basal situation between the depressive and the healthy group. Since the significantly lower buffer capacity, shown by the baseexcess values of the depressive group (fig. 15, col.1 and col. 3) cannot be due to acutely increased breathing, (fig. 14, col.1 and col.3) it has to be acknowledged as a chronic buffer diminishment of longer standing, developed in the course of the illness. This is underlined by the significantly and clearly more intensive reaction to the slight workload by the depressive patients. Their pCO2, their pH and their baseexcess react disproportionately sensitive to the moderate workload. Such an expected accumulation of over sensitive reactions to daily demands may well have been the reason for a chronic decrease of their total buffer capacity in the course of the illness. Accordingly, our investigations into the differences of metabolic reaction between depressive and healthy people yield – just by glancing at the automatically generated graphs and average statistics - two general results:

- The well known unwillingness of depressive patients or burnout patients to perform bodily feats is obviously not only due to depressive moods but also to a handicapped metabolism, demonstrable mainly by a disproportional reaction to provocation. Careful attempts to increase bodily fitness of the patients may be rewarded.
- Although metabolic tests can never be used diagnostically in mental illnesses, repeated checks of the metabolic situation could be helpful for documentation and quantification e.g. of the progress of medication.

ad 3: Idiosyncrasies of the diabetic metabolism, especially those due to the newly found importance of mineral deficiencies in type2 diabetics uncovered by CSA diagnosis

The blood glucose status of diabetic in - patients is routinely checked by a daily glucose profile, which consists of glucose determination from capillary blood at three different times. With nearly the same small amount of blood and the same effort we could determine not only glucose but also 11 additional parameters. The results of those investigations have been published in some full papers and several congress abstracts. We could show i.a. that

not only type1 diabetics but also about 36% of the nearly tenfold higher number of type2 diabetics suffer from severe loss of electrolytes, especially from hypomagnesemia. However, the magnesium state of type 2 diabetics has not been considered to be crucially important for the patients' wellbeing up to now, since only easily treatable cramps were thought to ensue from magnesium deficiency. But by correlatively combining of some of our simultaneously determined parameters, we could show, that diabetic hypomagnesemia seems to be responsible not only for the said cramps, but for a whole series of negative influences upon the already strained diabetic metabolism:

Let us direct, e.g. our attention to some differences in metabolic behaviour in patients with Mg levels below and above the hypomagnesemic threshold of 0,45mM/l ionized Mg in blood (hypomagnesemic threshold according to the Austrian Consensus Conference as well as the Deutsche Gesellschaft für Ernährung – German Society for Nutrition) and exemplarily look at some facts accompanying those differences: As already mentioned above, severe deficits in ionized blood magnesium became increasingly conspicuous during investigations into interactions of blood glucose, buffers and electrolytes during daily glucose profiles of type2 diabetic patients, since we had the opportunity of magnesium determination with ion sensitive electrodes (NOVA CCX, CSA). This fraction, according to our knowledge, has not been compared yet with blood glucose metabolism in type2 diabetic patients to any larger extent.

Similarly, investigations about the behaviour of ionized calcium in type2 diabetics seem at least to be rare. Its average values in our patients are, like those of magnesium, very low. Also remarkably low were the base excesses of the patients, though lactate concentrations in blood did not exceed normal elevations found on moderately busy days.
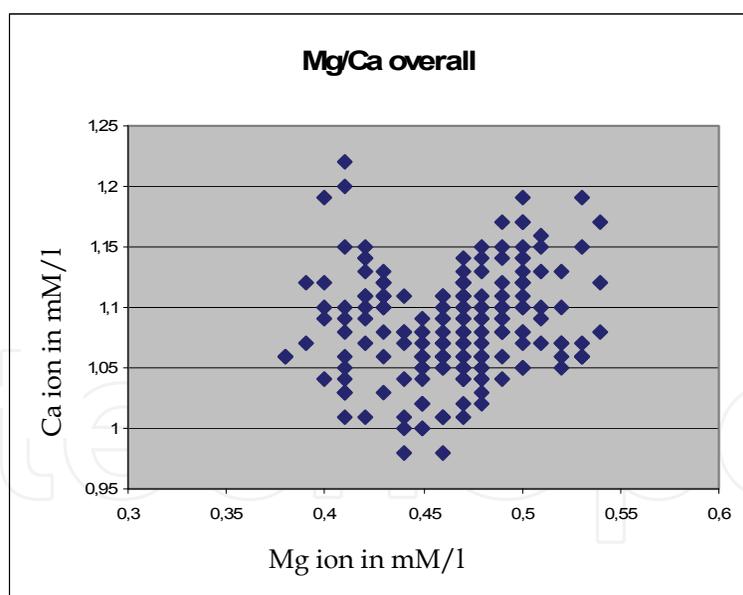
Abscissa. Ionized Ca in mM/l
Ordinate: ionized Mg in mM/l

Fig. 17. Remarkable change of relationship of Mg and Ca in the blood of diabetics nearly exactly at the point of the hypomagnesiemic threshold.

Magnesium and calcium averages give the impression to be inversely proportional to the concomitant blood glucose values, a feat that has been already mentioned by others together with magnesium and blood glucose or insulin sensitivity (17). But when we put together all

single values of all our patients, regardless of sampling times, there was no significant inverse correlation between ionized magnesium and blood glucose. Still, the pattern of the individual points in the Ca/Mg graph was exceptional (fig.6). Exactly at the Mg value of 0,45 mM/l (the agreed hypomagnesemic threshold) the Ca/Mg relationship seemed to switch directions. Fig.17 shows the turnaround of the relationship of ionized Ca with ionized Mg. Obviously, only from the hypomagnesemic threshold (0,45mM/l) upwards a significant, positive correlation has developed.

Even without indrawn regression lines one can observe, that the Ca/Mg ratio takes an opposite course nearly exactly above and below the hypomagnesemic threshold of 0,45 mM/l. We acknowledged this ambivalent behaviour by splitting the sample along this threshold of 0,45 mM/l into a high- and a low Mg subgroup. Consequently, we found a highly significant positive correlation between Mg and Ca in the higher Mg subgroup but no correlation at all in the lower subgroup. This finding encouraged us to look for more correlations, not within the overall sample but again within the subgroups above and below the hypomagnesemic threshold, trying to find at least some hints for the reason of the very low Mg values in our diabetics, where 36 % had Mg concentrations of 0,45mM/l and lower, since the mechanism of low magnesium values in NIDDMs seems to be unclear, Some authors (18,19) discuss a recurrent metabolic acidosis, along with episodes of osmotic diuresis as possibilities among others for magnesium diminishment in the diabetic patients, while stating that this diabetic hypomagnesemia seems to merit poor attention by physicians anyway. Shaffie et al (20) observed a lowering of bicarbonate along with low tissue pCO_2 and hyperventilation.

Indeed, pCO_2 values in our patient sample are low. Additionally, correlations between pH and pCO_2 overall and in the subgroups showed a significantly inverse behaviour, most clearly expressed in the low Mg subgroup, with a slope more than double as steep (y=59x) as in the higher Mg subgroup (y=23,6x) , pointing to an increasing need for respiratory compensation along with diminishing Mg concentrations. Thus, pH seems to be kept at an average of 7, 43 by constant loss of CO_2, obviously slightly overcompensating a steady input of anions.
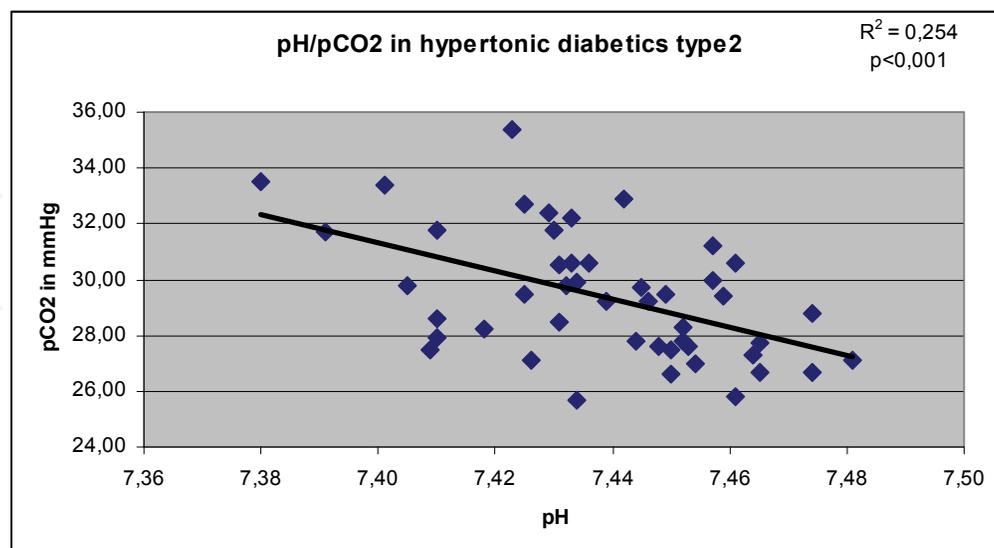

Abscissa. pH
Ordinate: pCO_2 in mmHg
P<0,001 highly significant

Fig. 18. Increasingly lower pCO_2 creates more and more alkaline pH in hypertonic diabetics.
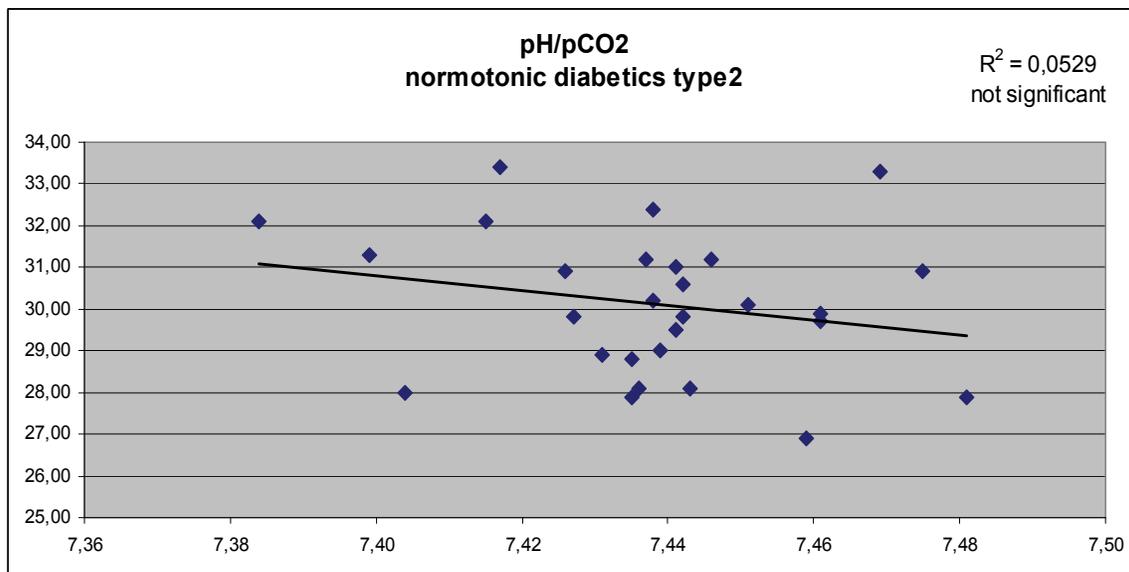
Abscissa. pH
Ordinate: pCO2 in mmHg
P>0,05 not significant

Fig. 19. Normotonic diabetics do not show any relationship between pH and pCO2 (see fig. 18) at all.
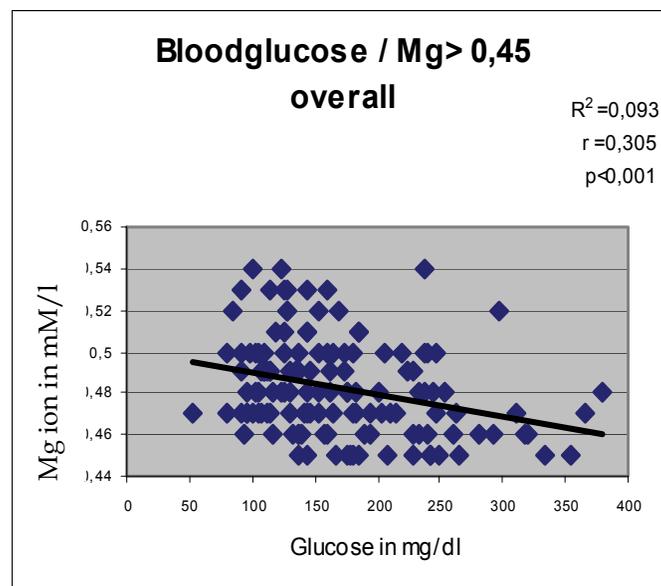
Abscissa. Glucose in mg/dl
Ordinate: ionized Mg in mM/l
P<0,001 highly significant

Fig. 20. Above the hypomagnesiemic threshold blood glucose increases along with lower Mg levels – a good argument for substitution.

Such chronic processes accompanied by a moderately increased breathing frequency may slowly but successfully waste the magnesium (and calcium) resources of the patient. The interesting observation, that patients with Mg concentrations below 0,45mM/l do not

seem to show correlations with blood glucose any more, may indeed point towards a certain exhaustion, for which low Mg concentrations are usually characteristic. But low Mg in those patients may be not only a marker of increasing metabolic exhaustion, but could actively contribute to wasteful anaerobic glycolysis by limiting ATP – ADP turnover. At least in non diabetic patients, we could show that low magnesium concentrations before extensive liver surgery deteriorate the prognosis about the final outcome significantly (21). The most important result concerning type2 diabetics is unquestionably the highly significant negative correlation between Mg levels and blood glucose above the hypomagnesemic threshold.

It means that diabetic patients with lower Mg levels are prone to higher blood glucose values.
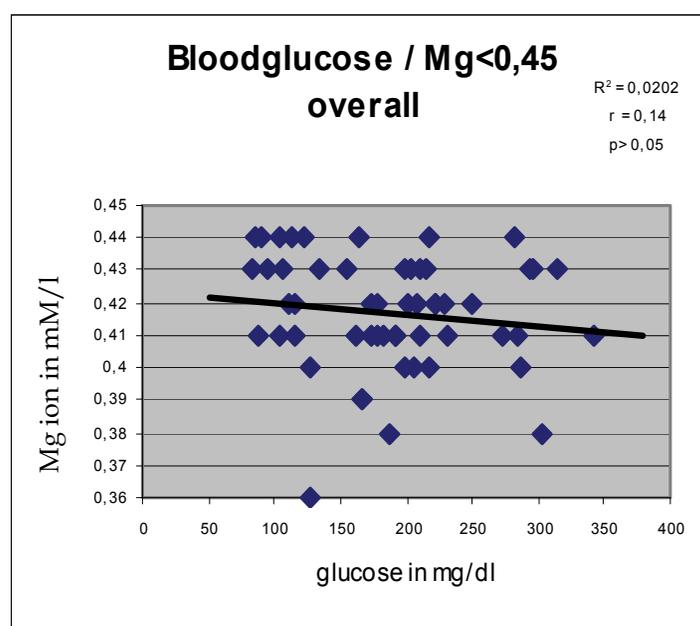
Abscissa. Glucose in mg/dl
Ordinate: ionized Mg in mM/l
P 0,05 not significant

Fig. 21. Below the hypomagnesiemic threshold the calculable Blood glucose/ Mg relationship vanishes, but the number of patients with high glucose values is remarkable.

Therefore we think that Mg determination, especially, that of the more active ionized fraction, should be included into the monitoring at least of hospitalized diabetic patients. When interpreted together with blood glucose levels and other CSA parameters, it reveals a much deeper insight into the metabolic state of the patient. In our opinion, increased knowledge of physicians about the impact of Mg deficiency upon the diabetic (and also non–diabetic) metabolism would increase the demand for magnesium determination and also for magnesium medication.

Consequently, we can see, that without increased effort, just by substituting a more up to date measuring device coupled with appropriate software, the daily glucose profile, a routine diagnostic method of very long standing, could be changed into a much more sensitive investigative tool, capable of quickly unearthing new knowledge about metabolic dynamics for the benefit of the patients.

ad 4: CSA application in animals (outlook)

About 15 years ago we investigated the catecholamine state of immobilized rats and of pigs in abattoirs. Immobilisation of animals led to dramatic increase in catecholamines and to vastly diminished stress compatibility (22, 23) Catecholamine levels of pigs before slaughtering in abattoirs have been found to be an incredible hundred thousand fold higher than normal.

Both, immobilisation and the pre- slaughtering situation are widely common in the treatment of pigs, since mother sows are often kept practically immobilized in very small cages. Objectivation of the effects of the demonstrated catecholamine increase upon the metabolic parameters provided by simple and scarcely molesting CSA testing could reveal at least electrolyte changes in blood, most probably vastly increased electrolyte input into muscle tissue. Low quality, watery meat could well be the outcome. In immobilized mother sows the metabolic effects of catecholamine elevation may also have a whole bunch of negative effects, easily imaginable (24). At the very least CSA metabolic investigation may provide prove, that cruelty to animals does not pay, in fact actually decreases profits of husbandry.

Concerning the application of CSA tests in the training of e.g. racing animals like horses, dogs or camels, it seems easy to adapt our methods and results from our investigations in humans.

It is obviously an asset for both animals and trainers to be able to adjudge the pre contest condition, thereby the contest chances and the metabolic changes during a given contest of a specific animal. The familiarity of a good trainer with animals in his care, by which up to now subjective judgement has been delivered, could be supplemented by objective testing. Hitherto surprising reactions during the contest may thus be more successfully avoided, momentary fitness state of the animal more correctly adjudicated, latent illnesses better anticipated as benefits for animal, trainer and owner.

2. General outlook

By providing therapists, trainers or commanders of first responder units with a multi – parameter pattern of stress hormone effects and their statistics within minutes, an objective support of decisions which range from selection of specific treatments, adaptation of training efforts or educated guesses about success chances of teams to detection of team *outliers* is provided.

Still, the decision making responsibility of the physician, the trainer or the commander remains untouched. On the one hand, the intricate pattern of the interwoven parameters provides a rather sensitive metabolic picture, which can be broadened by additional correlations with sociological and psychological scores (for which free spaces in our correlation tables are already provided). But the same multi parametric intricacy prohibits – at least at the moment – a mathematical overall calculation including all changing parameters according to their momentary importance. It turned out, that pure multiple regressions of the bulk of all data are not stable enough, so that factor analyses have to be applied in advance. Some smaller problems could be already solved in this way, but generally the best way to use our tool at the moment is a one days course in interpretation with lots of practical applications and some theoretical background, which in nearly all cases enables the user to proceed successfully on her or his own.

3. Summing up

Stress hormone changes correlate significantly with their also changing effects like lactate, blood gases, buffer capacities and electrolyte concentrations. About twelve of those

parameters can be determined simultaneously by easily transportable ICU equipment from 100 microliter of capillary blood within three minutes and the data be transferred on line by CSA (Clinical Stress Assessment) software into data banks. Individual statistics or group statistics are automatically calculated, so hat a kind of data net is spread over the proband or a whole group of probands. Changing of sensitive parameters like pCO_2 or Ca are indicative of acute effects, while changing of less sensitive values like HO_3 or blood glucose point towards more chronic developments.

Application of CSA has been found fruitful i.a. to detect and quantify:

- The pre – contest stress situation of sports persons or pre deployment situation of first responders like soldiers or fire fighters, thereby being able to select outliers and calculate scoring changes preliminarily. A persons' success/effort relationship can be quantified.
- Since mental stress imprints its quantity in nearly all cases upon metabolic changes, those changes and their idiosyncrasies can be quickly measured and taken as sensitive pointers for e.g. a gradual effectiveness check of medical treatment.
- Inclusion of CSA application in diabetic check ups can provide the physicians with a more then 10 – fold increased information about blood glucose changes within the individual metabolic ambient of a patient, out of nearly the same small amount of blood within 3 minutes. It enabled us at least to find hitherto hardly suspected deficiencies and interactions of electrolytes and glucose in type2 diabetics, with a significant further deterioration in hypertonic diabetics.
- Concerning the predictive and in depth assessing capabilities of CSA concerning sports and first responders, it hits the eye that those very capabilities could be applied successfully in training of competing animals as well as in the control of unnecessary stress of husbandry situations.

4. Acknowledgment

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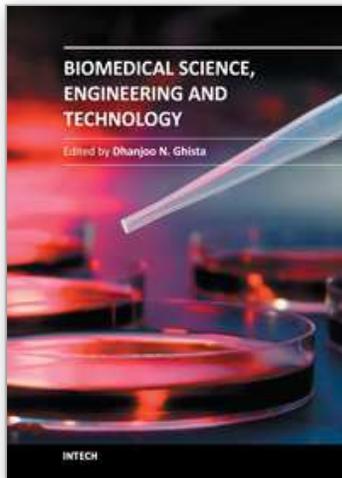
Biomedical Science, Engineering and Technology
Edited by Prof. Dhanjoo N. Ghista

This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytomedicinal plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering coves topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

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