THE EFFICACY OF GINSENG TO HAEMODYNAMIC PARAMETERS DEPENDENT TO THE VEGETATIVE SYSTEM

A. A. Bettermann, C. Bettermann
Hamburg, W/Germany

SUMMARY

To find out the effects of ginsenosides to some parameters of the haemodynamic and gas exchange depending to the autonomic nervous system - and to border it against the psychosomatic nervous ways was the idea of these studies. The lot of the effects are very differentiated, so that we have to find out the special ginsenoside receptors in that system.

INTRODUCTION

After having visited the 3rd International Ginseng Symposium we had a lot of questions to this very magnificent but for the European medical style really unusual kind of therapy.

To analyse why the Ginseng drug is everyday such helpfull in the Southeast - Asian - Countries but not comparable to the effects in the Europeans. Even though we have no comparable medical help in and around here, by using Ginsenosides. Now we know, that in some parts it is a problem of the quality and quantity of the stomach acid.

In between some German companies capsized their Ginseng products, because they had trouble with the pesticides in the preparationes. That is the reason, why we had to find out our first injectable Ginseng preparation. Because we had a lot of problems with purifiing the commercial market Ginseng stuff - we mixed up some weight and some red Ginseng extracts, finding out a nearly ideal mixture - the WANDREDMAN GINSENG.

Having this new product we had to make sure, that there is a reproducable efficacy without any side effects. Therefore we made a lot of experiences in biochemistry and clinical trials, from which I would like to give you two examples.

In the last few years the most medical scientists informed about an only psychological effect of the Ginsenoside - me too. Now we postulate the vegetative power of the Ginsenosides we mixed - and we will make it sure and for everybody available with the following results.

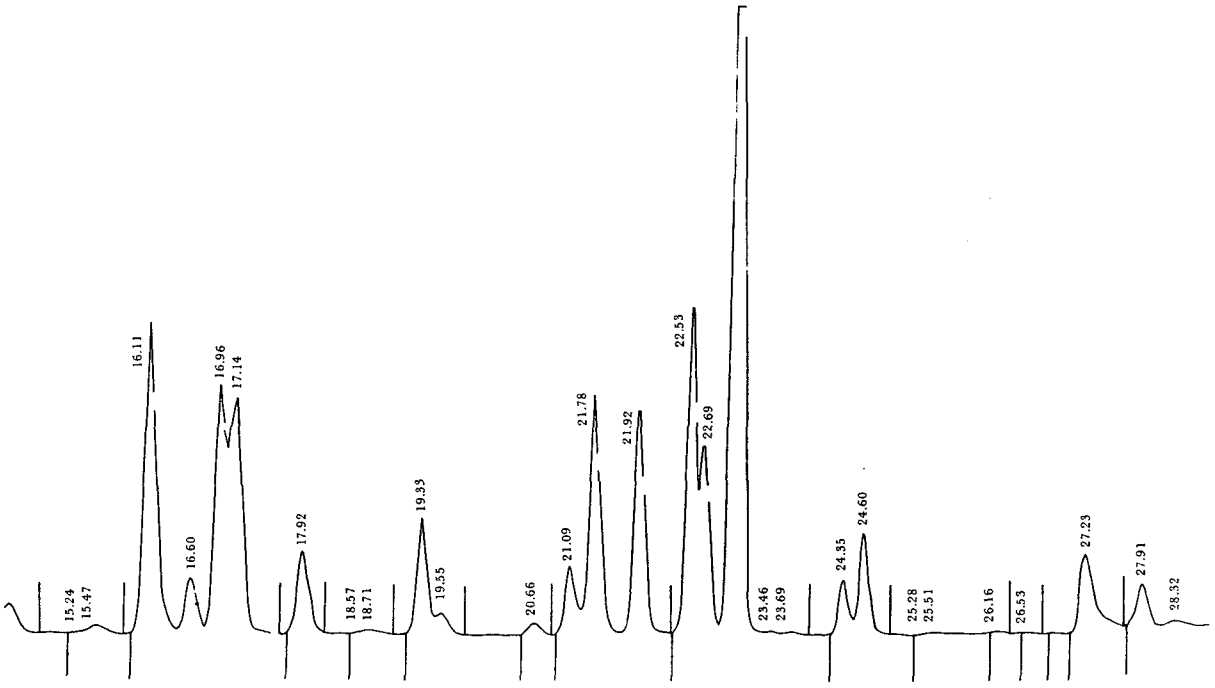
MATERIALS AND METHODS

For the controle of purifiing and standardizing our Wandreman Ginseng we used the HPLC modified by Cansell and Sadeé (Cancer Treatm. Rep. 64 (1980) 165). In comparison to a well known Ginseng preparation - the *Panax Ginseng* C.A. Meyer - the Tab. 1 and 2 are shown the different Ginsenograms - how we call it since the time of our first own Ginseng preparation. Comparing it to other Ginseng products from the German market, we had trouble with the proof of ginsenosides in blood. So we took the Gastrointestinal Resorption Model from H. Stricker

Table 1. Ginsenogram of wandredam ginseng.

14 47 25 Chart 2.00 CM/MIN
Run #6
Column Solvent
External standard quantitation

Peak #	Amount	RT	Exp. RT	Area	RF
	741.00800	2.00		741008 F	0.000000E0
	47.18600	2.16		47186 L	0.000000E0
	196.06700	2.74		196067 L	0.000000E0
	343.66700	13.95		343667 L	0.000000E0
	1227.19000	14.42		1227198 L	0.000000E0
	59.65500	15.24		59655 F	0.000000E0
	357.25900	15.47		357259 L	0.000000E0
	11632.50000	16.11		11632588 F	0.000000E0
	2016.86000	16.60		2016867 F	0.000000E0
	8829.28000	16.96		8829327 F	0.000000E0
	8874.86000	17.14		8874911 L	0.000000E0
	2783.45000	17.92		2783463 L	0.000000E0
	85.58300	18.57		85583 F	0.000000E0
	155.87600	18.71		155876 L	0.000000E0
	4033.11000	19.33		4033124 F	0.000000E0
	784.57900	19.56		784579 L	0.000000E0
	407.70300	20.66		407703 L	0.000000E0
	2268.63000	21.09		2268640 F	0.000000E0
	8485.36000	21.38		8485412 F	0.000000E0
	7317.42000	21.92		7317456 L	0.000000E0
	10151.60000	22.53		10151717 F	0.000000E0
	5475.03000	22.69		5475056 F	0.000000E0
	33492.00000	23.08		33492284 F	0.000000E0
	81.30800	23.46		81308 F	0.000000E0
	61.46500	23.69		61465 L	0.000000E0
	1715.36000	24.35		1715368 F	0.000000E0
	3090.22000	24.60		3090229 L	0.000000E0
	39.58700	25.28		39587 F	0.000000E0
	119.68600	25.51		119686 L	0.000000E0
	52.61500	26.53		52615 L	0.000000E0
	3339.91000	27.23		3339930 L	0.000000E0
	1414.82000	27.91		1414827 F	0.000000E0
	153.53300	28.32		153533 F	0.000000E0
	149.39400	29.16		149394 L	0.000000E0
Total	119984.00000				



(Pharm. Ind. 38,2,232-234,289-295(1976)) to find out, under which circumstances the resorptional optimum will be reached for the different Ginsenosides. The stomache acid in a concentration of more than 2 Mval/h BAO (Basic Acid Output) or 30 Mval/h MAO (Maximum Acid Output) wrecks nearly all Ginsenosides. Thats the reason why in our country the Ginseng products are loosing a lot of their effects.

During that proof-proceedings we measured pesticides in some Ginseng preparationes - the HPLC showed some strange peaks first - and than we made a lot of analyses to check out, what it means, to have such peaks in a Ginsenogram. Since that time we never used any oral Ginseng and made power to the development of an injectable Ginseng, we got ready late in 1982. In the purified and standardized wight and red Ginseng we never found any pesticides lateron. The biochemical, pharmakokinetic and pharmakodynamic tests did not show different results to earlier analysis with other well known Ginseng products. There is a maximum of bioavaliability and a typical dose effect graph.

In the first study we made an animal trial - even though it is contested in our country to go this way. But everybody in here will tolerate it, because the cerebral-death-model is only reproducable in animals. We chosed this model because it is the only possibility to check out the effects to the autonomic nervous system without any superimposing from the psychological part of the central nervous system. In the human body you can only use anaesthesia conditions but this is not independent from psychological and psychosomatic side effects for instance of our dreams.

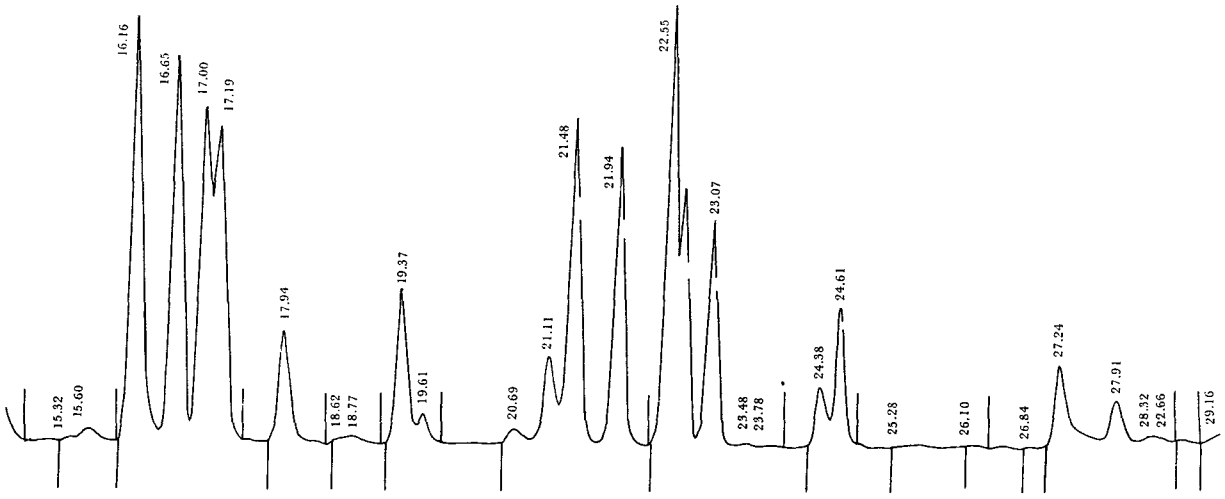
RESULTS

In the Fig. 1 and 2 you see the effects to the haemodynamicand gas - change - parameters in normal conditions. On line we measured the mean aortic pressure, the mean-pressure in the arteria pulmonalis, the heart rate and the oxygen absorption capacity from the blood gas analyse. All the other parameters are calculated by the well known methods. Here you only see a selection of allover 23 datas. In this two figures you have a direct comparison to the effects of Brenzkatachin (Dopamin). A comparable damped kind of an action you see for the ginsenosides but it

Table 2. Ginsenogram of panax ginseng C.A. meyer

16 33 52 Chart 2.00 CM/MIN
Run #9
Column Solvent
External standard quantitation

Peak #	Amount	RT	Exp. RT	Area	RF
	184.84200	2.02		184842 L	0.000000E0
	316.80200	3.76		316802 L	0.000000E0
	256.22300	9.69		256223 L	0.000000E0
	142.22800	11.80		142228 L	0.000000E0
	475.77700	14.10		475777 L	0.000000E0
	1700.99000	14.56		1700996 L	0.000000E0
	94.78000	15.32		94780 F	0.000000E0
	423.39300	15.60		423393 L	0.000000E0
	15513.90000	16.16		15514023 F	0.000000E0
	13682.90000	16.65		13683017 F	0.000000E0
	12430.00000	17.00		12430068 F	0.000000E0
	11361.30000	17.19		11361431 L	0.000000E0
	3960.98000	17.94		3960997 L	0.000000E0
	113.03000	18.62		113030 F	0.000000E0
	226.74100	18.77		226741 L	0.000000E0
	5441.12000	19.37		5441153 F	0.000000E0
	1104.22000	19.61		1104227 L	0.000000E0
	612.89400	20.69		612894 F	0.000000E0
	3048.16000	21.11		3048176 F	0.000000E0
	11781.70000	21.40		11781854 F	0.000000E0
	9921.97000	21.94		9922022 L	0.000000E0
	13875.00000	22.55		13875079 F	0.000000E0
	7350.96000	22.72		7351006 F	0.000000E0
	7527.14000	23.07		7527179 F	0.000000E0
	59.59700	23.48		59597. F	0.000000E0
	45.77200	27.70		45772 L	0.000000E0
	1845.41000			1845419 F	0.000000E0
	4043.42000	24.61		4043442 L	1.000000E0
	3585.22000	27.24		3585242 F	0.000000E0
	1684.95000	27.91		1684953 F	0.000000E0
	304.44600	28.32		304446 L	0.000000E0
	34.04000	28.66		34040 L	0.000000E0
	340.35000	29.16		340350 L	0.000000E0
Total	133488.00000				



seems to be a similar kinetic. N means the starting point wihout any drug effect. Measuring-point 1 documents the low-dose effect after 15 minutes, point 2 and 3 the medium and high-dose-effects even after 15 more minutes and N (Index) shows the ending measurement even 30 minutes after giving the last injection ore ending up the permanent infusion.

In this kinetics of the haemodynamic parameters it is generally noticed that the highest dosage showes a kind of satuating. In statistics you may see the increasing blood pressure as a sign of the so called afterload - with a little less of an increase in the preload (P_{PA}), but without any influence to the heart rate. This is really economic for the heart muscle which is evidently in the increasing of the heart-minute volume. This is not regulated as usual by the TPR and RPA, which is shown in the Fig. 2, even more from blood - volume and Haematokrit which is shown in the Fig. 7-10.

The decreasing of oxygen capacity and arteriovenous shunt volume is not significant - the regulation in normal conditiones is independent from the ginsenosides.

The dosage of the WANDREDMAN GINSENG we measure in Miliunits. The equivalent for 1 mU = 4,7μg purified ginsenosides. We used as a low dose 4 mU, as a medium dose 7 mU and as a high one 10 mU per kg body weight.

In Fig. 3 and 4 you see the same dogs under anesthesia conditions - comparing the ginsenosides to Adrenalin and the so called cardioselective Beta-Blocker. The proceeding is exactly the same as under normal conditions. The effect to the preload (P_{PA}) is nearly like an adrenergic stimulation, which is not undangerous for an insufficient heart muscle. None effect to the HR but even more to the oxygen capacity where the ginsenosides are working like the Adrenalin even though in the arterio-venous shunt volume effecting as a Beta - Blocker, what is logically similar to the resistence in the pulmonal arteria. It shows that the ginsenosides are able to load the heart on one hand (preload) and to release it on the other hand with special effects to the respiratory tract. In the last figures of this clinical trial (Fig. 5 and 6) you see the very interesting effects of the ginsenosides without any superimposing of the central nervous system. Now the aortic blood pressure is decreasing, while the heart rate is increasing. Here the heart rate regulates the HMV, TPR and RPA regulates the blood pressures. By the way the HMV was measured by thermodilution method.

It is noticable that the effects to haemodynamic parameters during the conditions of cerebral death are converted in some parts comparing it to normal and anesthesia conditions.

To make sure what is happened with that results we made another clinical trial with 10 patients under anesthesia and postoperative

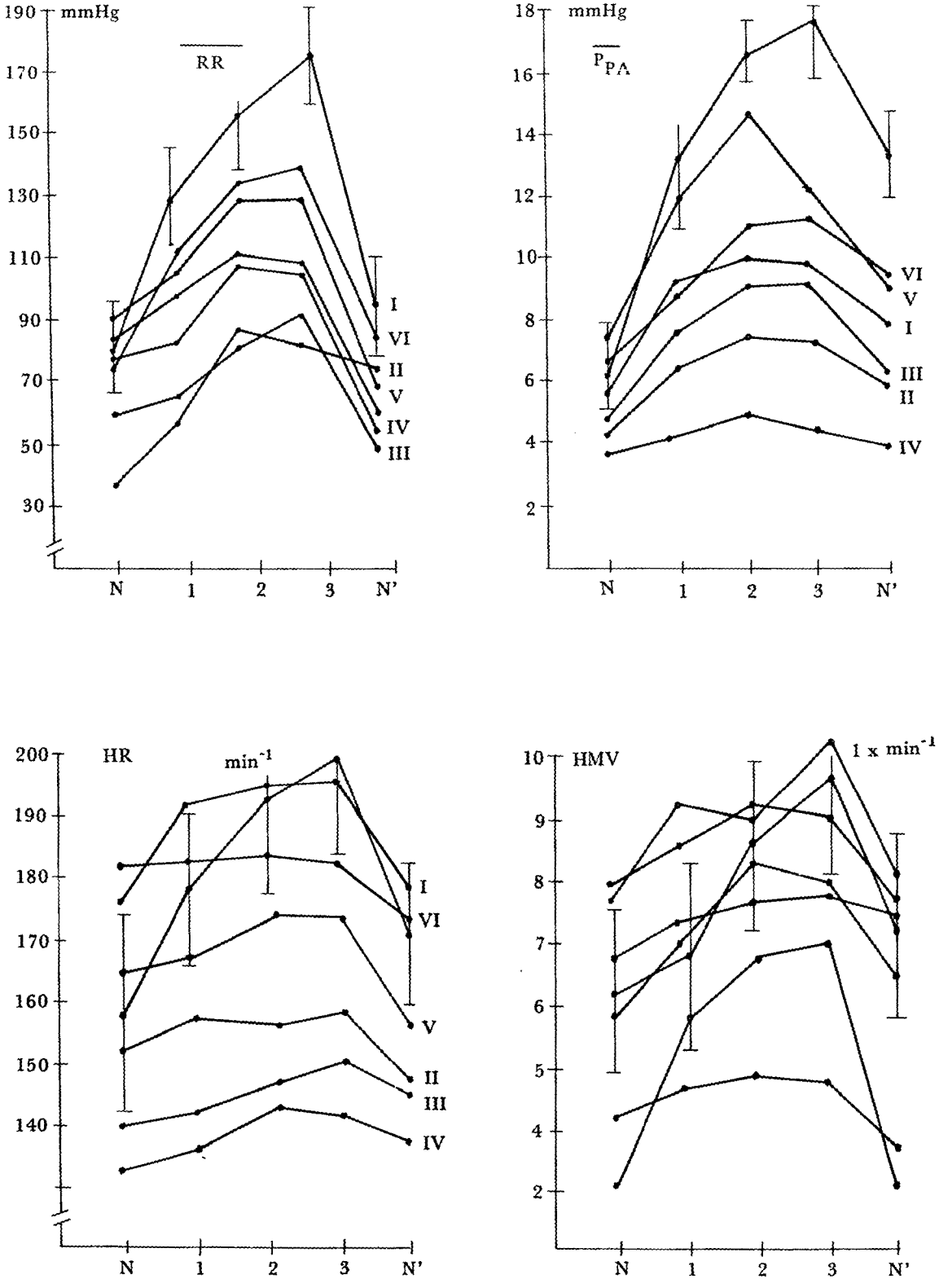


Fig. 1. Normal conditions in dogs / n = 6 / red = Brenzkatechin.

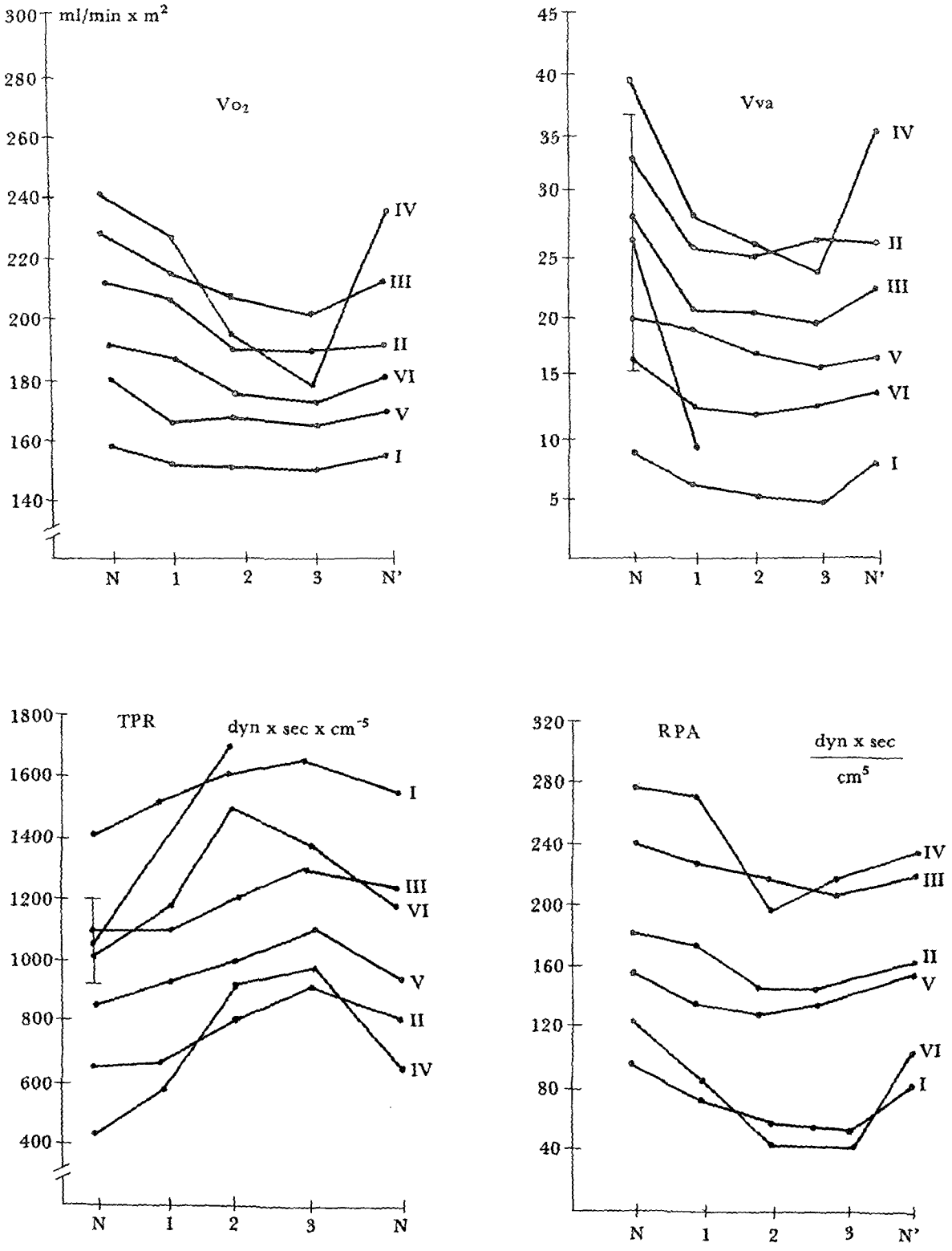

300
ml/min x m²
280
260
240
220
200
180
160
140
Vo₂
IV
III
II
VI
V
I
N
1
2
3
N'
45
40
35
30
25
20
15
10
5
Vva
IV
II
III
V
VI
I
N
1
2
3
N'
1800
TPR
dyn x sec x cm⁻⁵
1600
1400
1200
1000
800
600
400
I
III
VI
V
II
IV
N
1
2
3
N
320
RPA
dyn x sec
cm⁵
280
240
200
160
120
80
40
IV
III
II
V
VI
I
N
1
2
3
N'

Fig. 2. : Fig. 1.

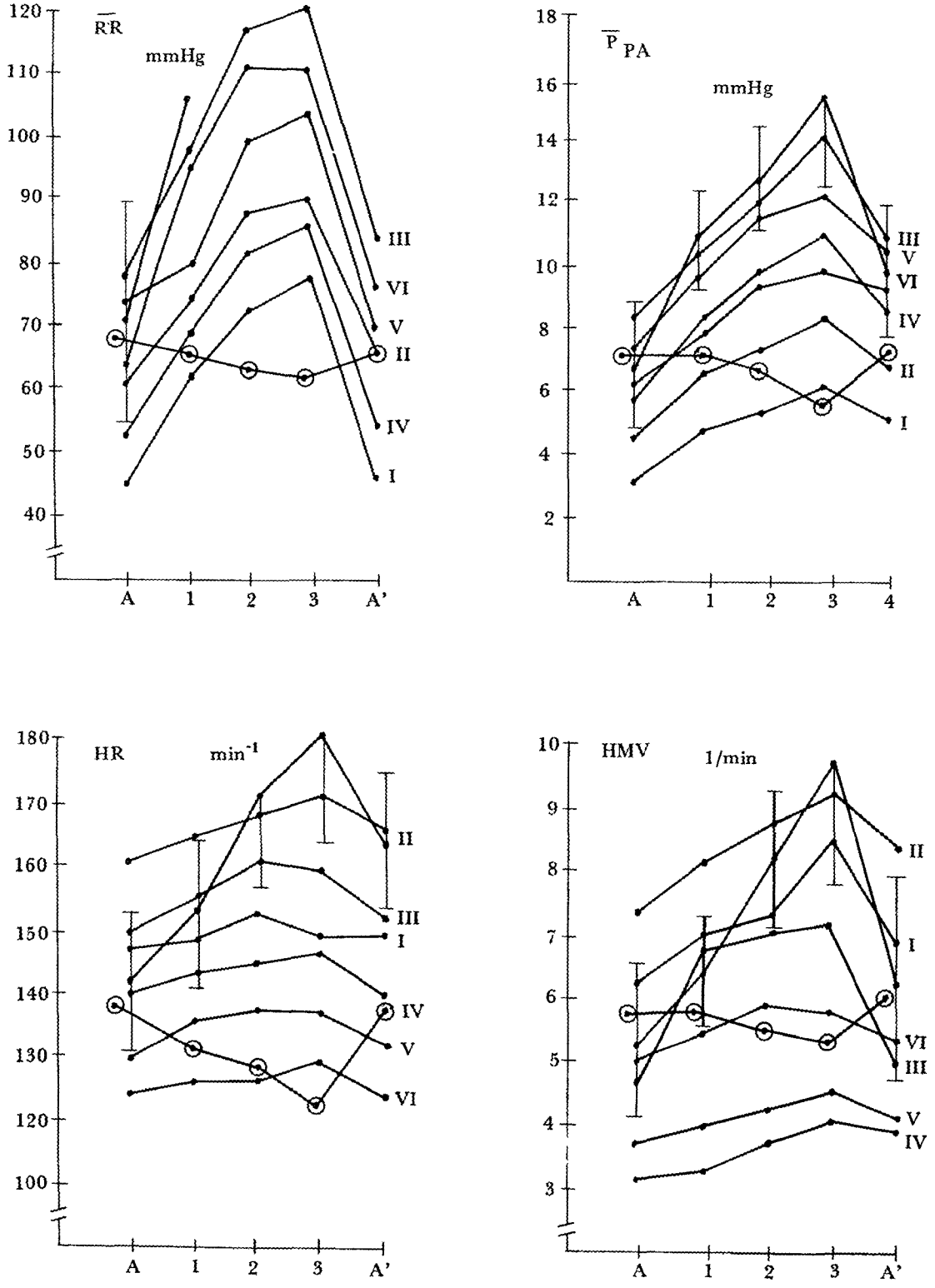


Fig. 3. Anesthesia conditions in dogs.
/red = Adrenalin / blue = β-Blocker.

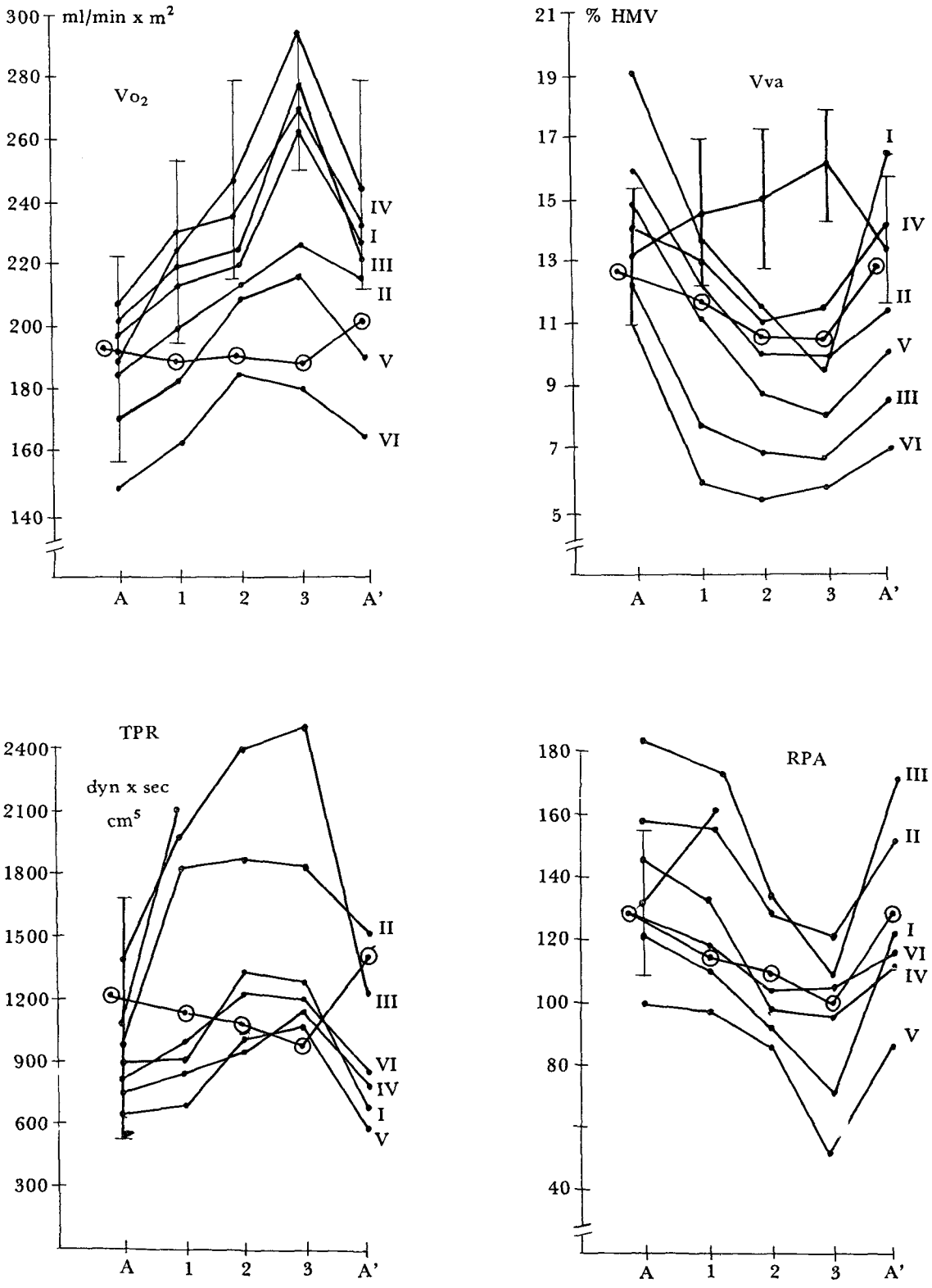

300
280
260
240
220
200
180
160
140
ml/min x m²
Vo₂
IV
I
III
II
V
VI
A
1
2
3
A'
21
19
17
15
13
11
9
7
5
% HMV
Vva
I
IV
II
V
III
VI
A
1
2
3
A'
2400
2100
1800
1500
1200
900
600
300
TPR
dyn x sec
cm⁵
II
III
VI
IV
I
V
A
1
2
3
A'
180
160
140
120
100
80
40
RPA
III
II
I
VI
IV
V
A
1
2
3
A'

Fig. 4. : Fig. 3.

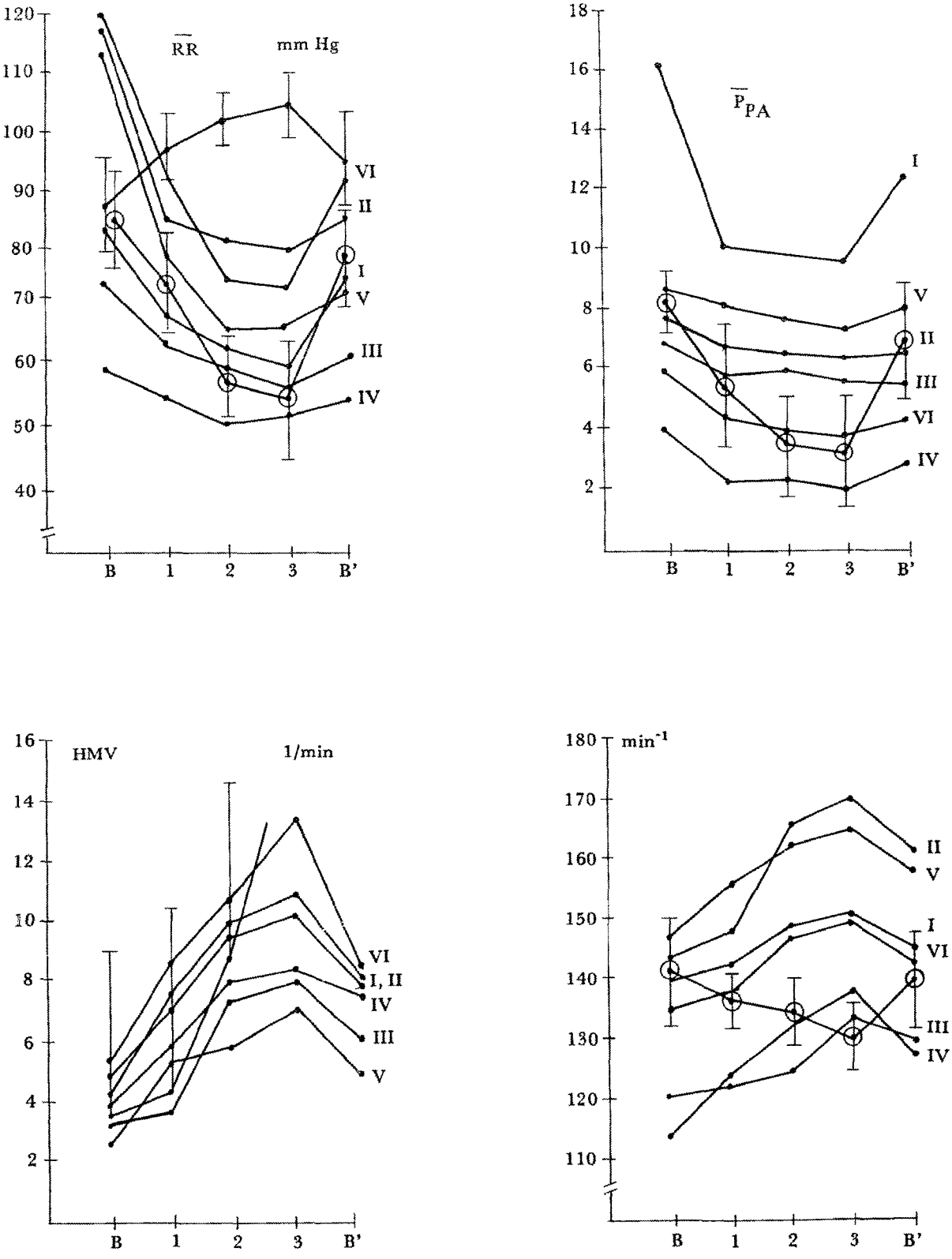


Fig. 5. Braindead dogs / red = Adrenalin / blue — β Blocker.

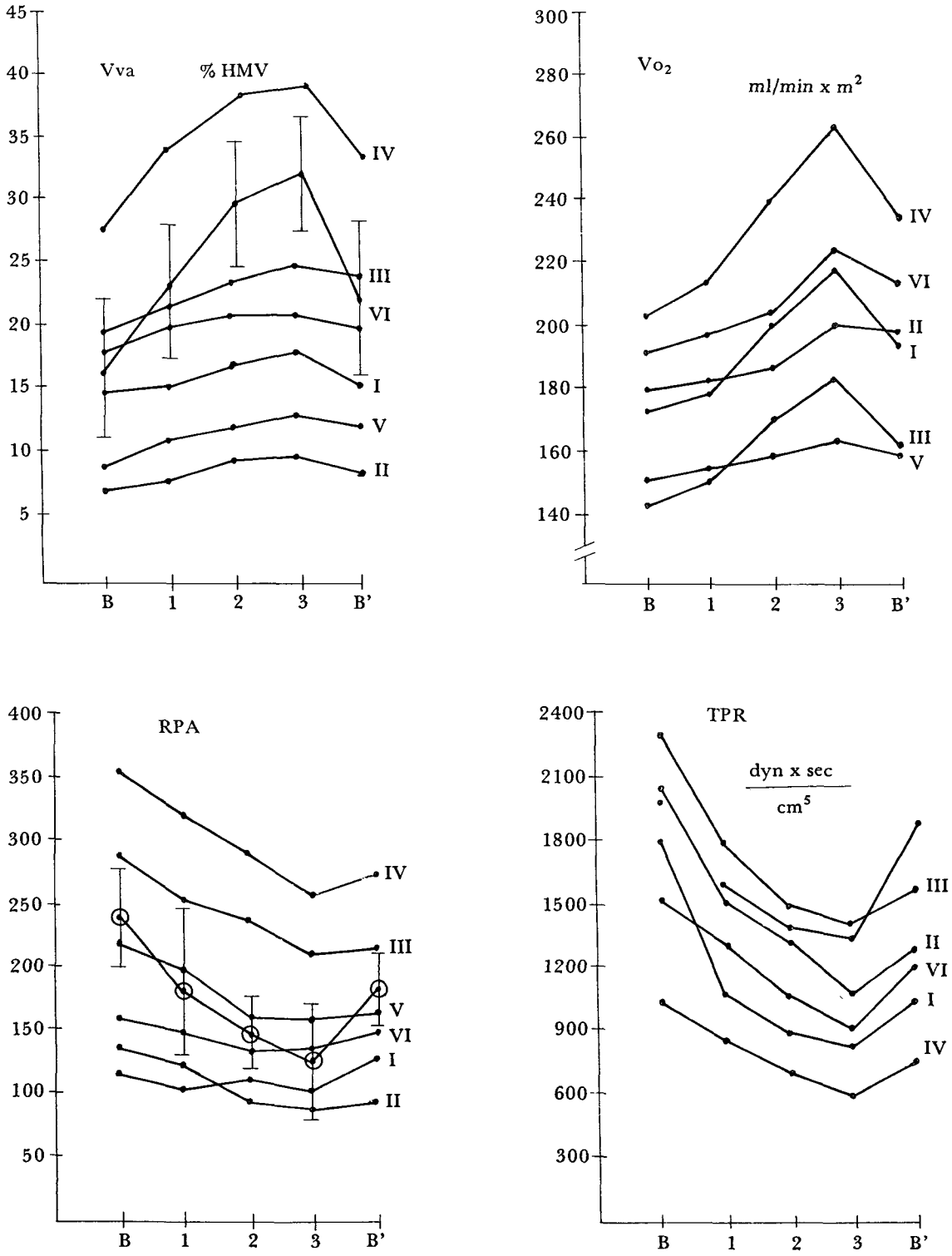

Vva
% HMV
45
40
35
30
25
20
15
10
5
IV
III
VI
I
V
II
B
1
2
3
B'
Vo2
ml/min x m2
300
280
260
240
220
200
180
160
140
IV
VI
II
I
III
V
B
1
2
3
B'
RPA
400
350
300
250
200
150
100
50
IV
III
V
VI
I
II
B
1
2
3
B'
TPR
dyn x sec
cm5
2400
2100
1800
1500
1200
900
600
300
III
II
VI
I
IV
B
1
2
3
B'

Fig. 6 : Fig. 5.

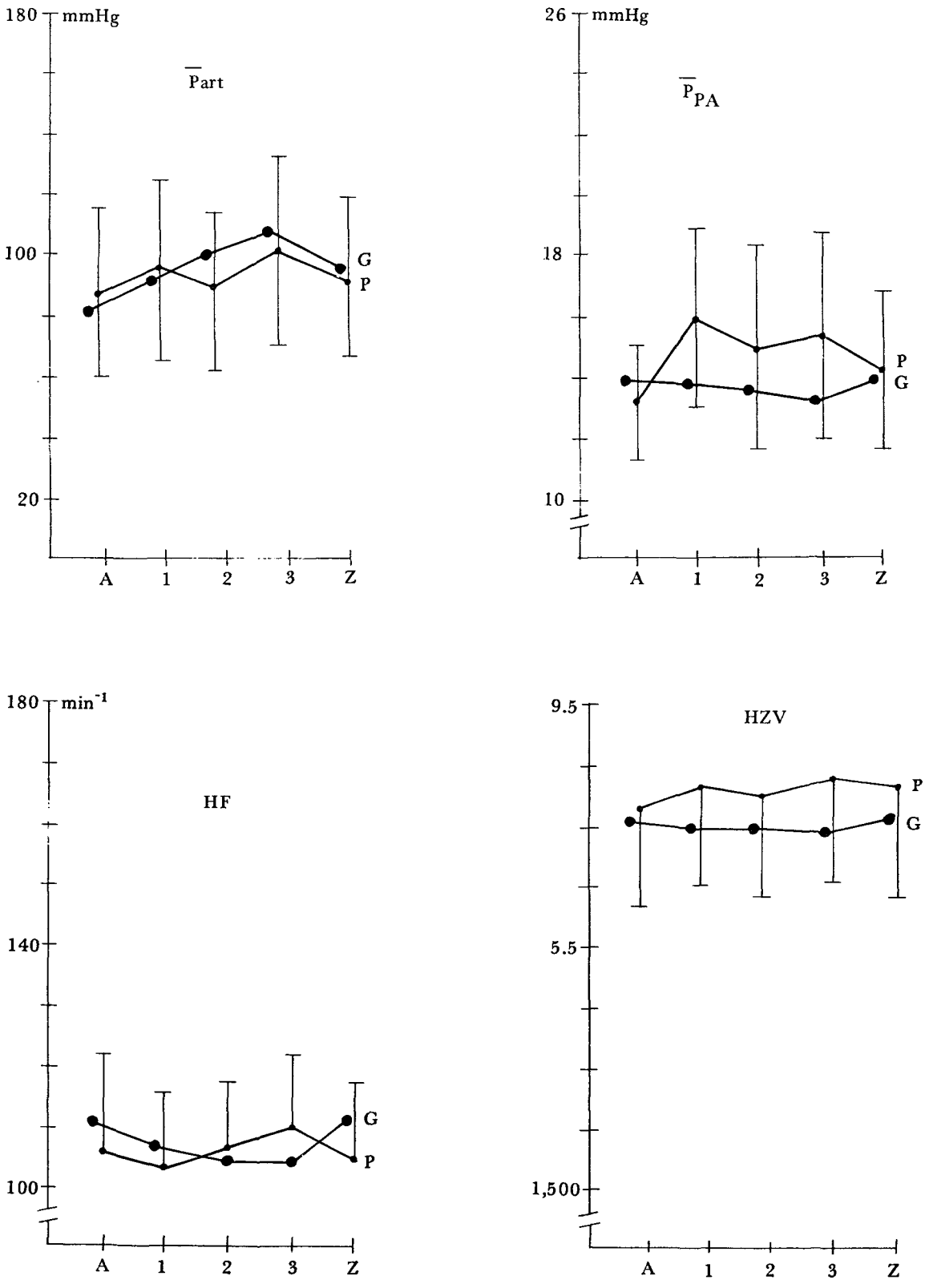
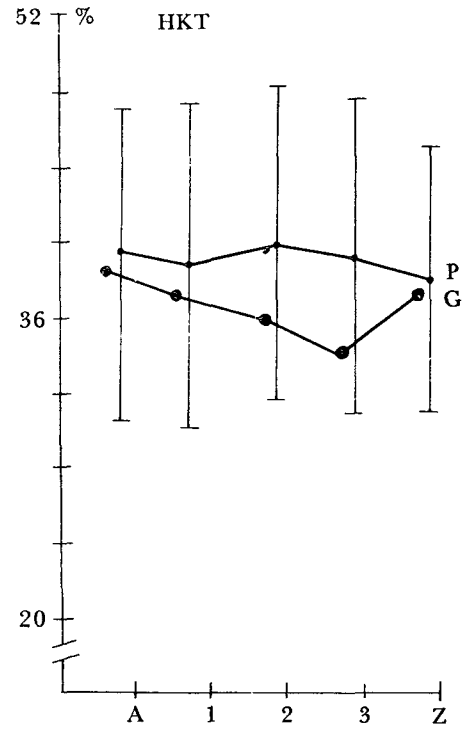
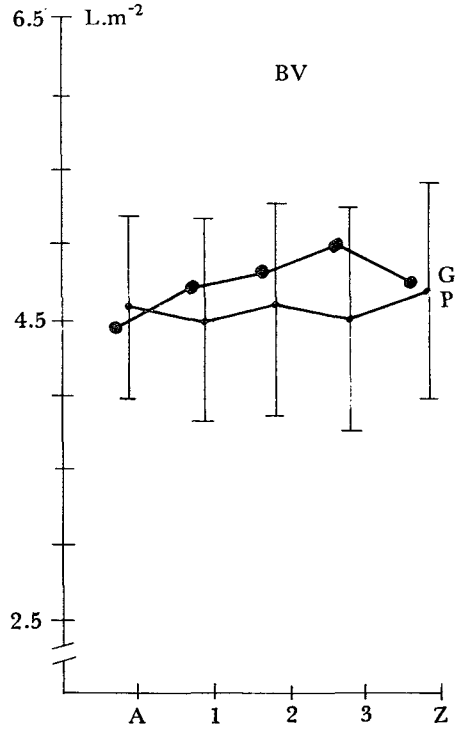
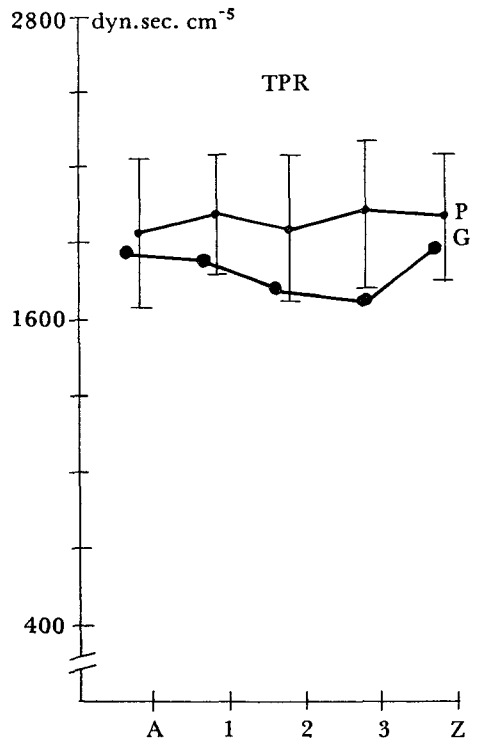


Fig. 7. Anesthesia conditions in men / n = 10 /


52
%
HKT
36
20
P
G
A
1
2
3
Z


6.5
L.m-2
BV
4.5
2.5
G
P
A
1
2
3
Z


2800
dyn.sec. cm-5
TPR
1600
400
P
G
A
1
2
3
Z

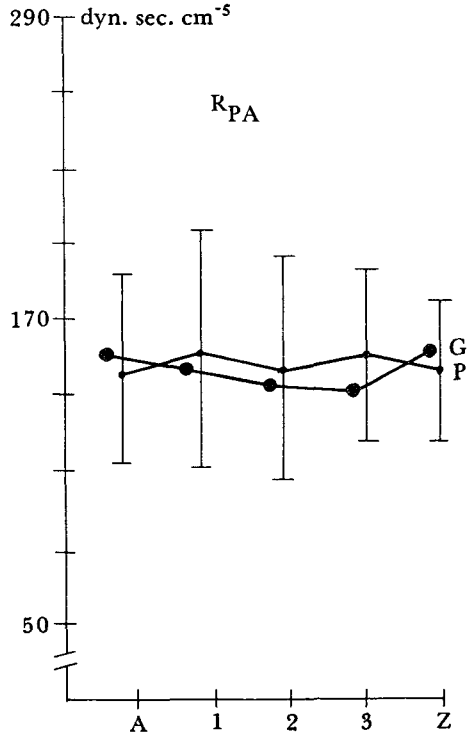

290
dyn. sec. cm-5
RPA
170
50
G
P
A
1
2
3
Z

Fig. 8.: Fig. 7.

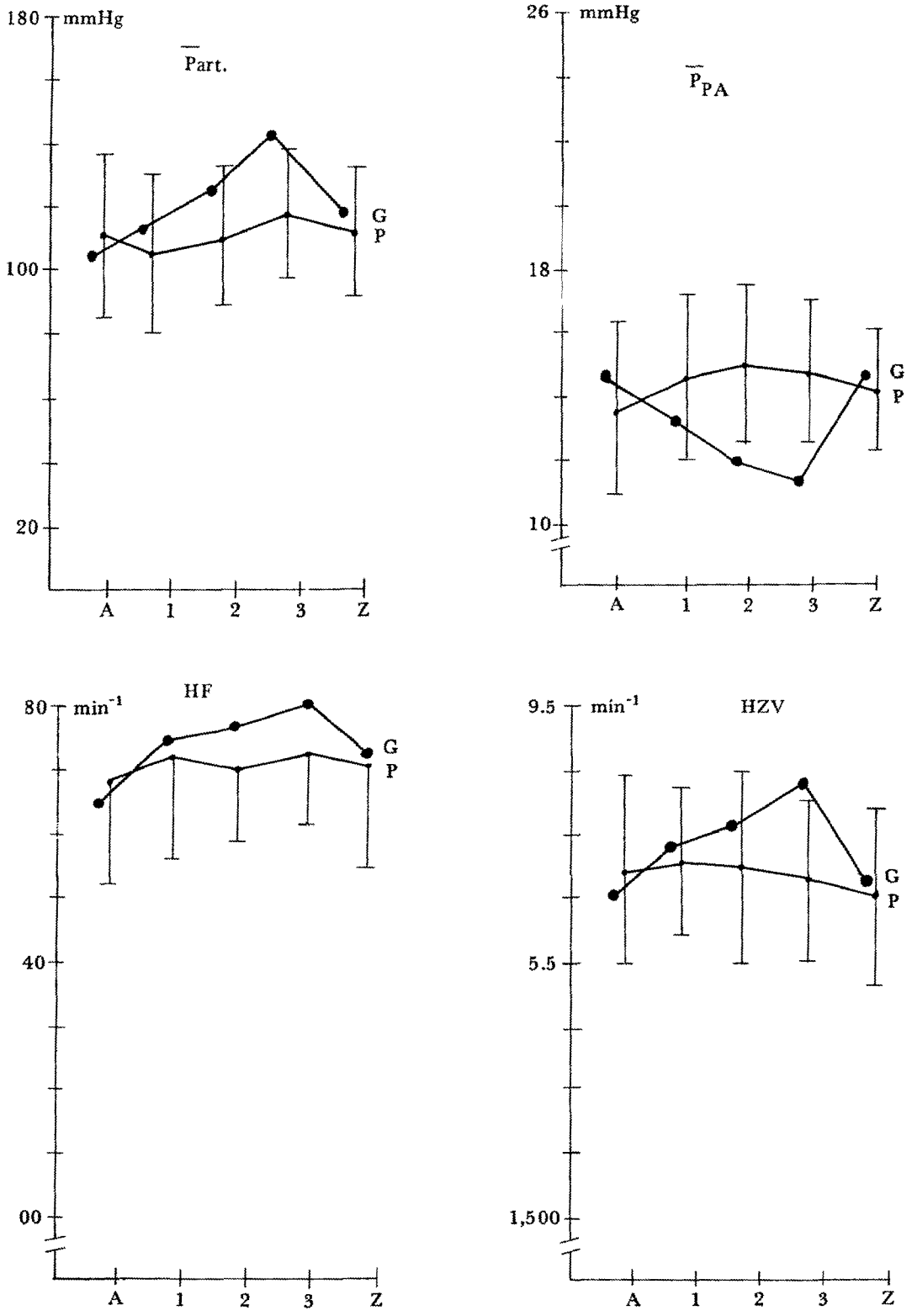
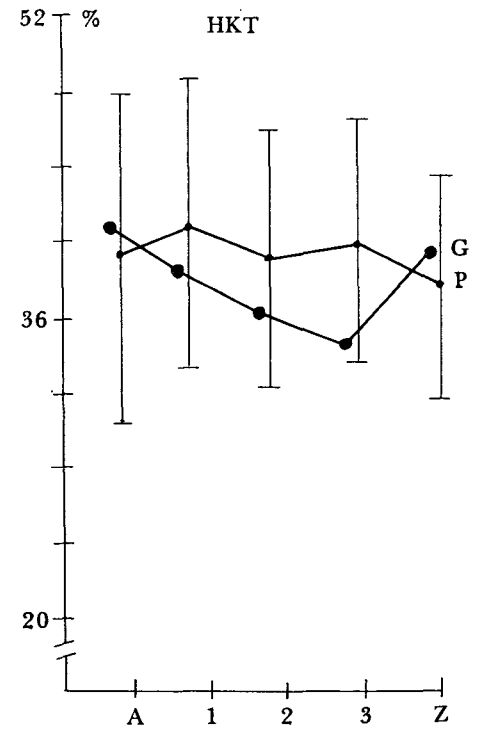
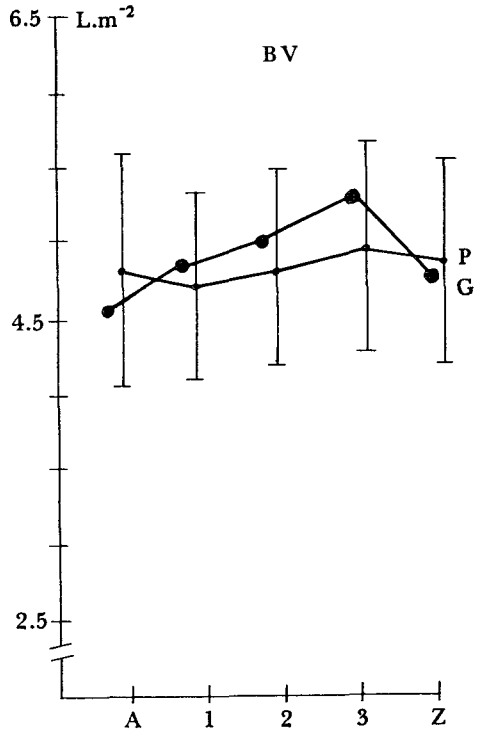
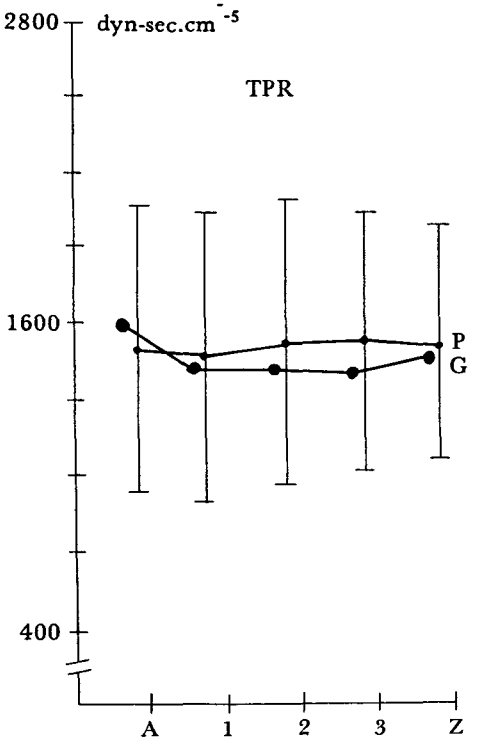


Fig. 9. Normal conditions in men / n = 10 /


52
%
HKT
36
20
G
P
A
1
2
3
Z


6.5
L.m-2
BV
4.5
2.5
P
G
A
1
2
3
Z


2800
dyn-sec.cm-5
TPR
1600
400
P
G
A
1
2
3
Z

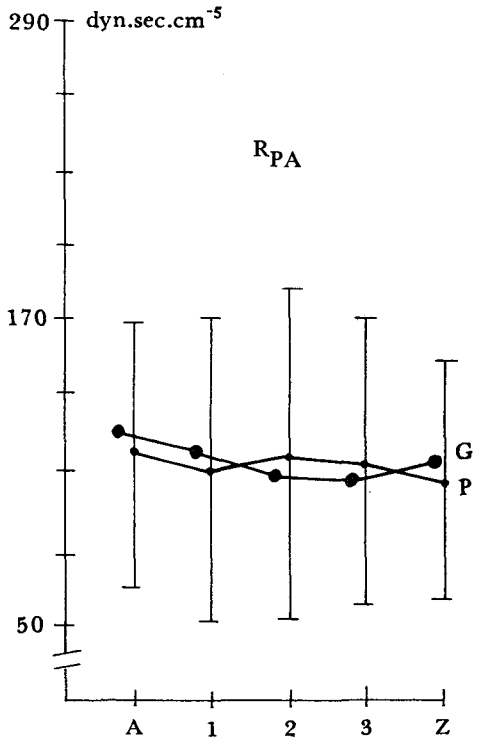

290
dyn.sec.cm-5
RPA
170
50
G
P
A
1
2
3
Z

Fig. 10. : Fig. 9.

(nearly normal, stabil haemodynamics) conditions.

The different dosage we gave to the human body were 2, 5 and 8 mU per kg body weight. The blood volume was measured by a special body plethysmographie. All other handlings are even the same as in the former study, but the time inbetween the measuring points were only 5 minutes. Also we checked out a placebo row in the same procedure with the same patients. So you have a direct comparison between the ginsenosides and a placebo during the same stbil time of anaesthesia.

Fig. 7 and 8 are showing the results - there are no significant effects but you may recognize the typical up and down in the placebo group and a dose-effect-kinetic from the ginsenoside - that might be dependent to a higher dose as we used right now. Even remarkable are the effects to be Haematokrit and the blood volume, so that we postulate a special regulation to this parameters as central ones in the haemodynamics. These effects are more abundant without soothing the autonomic nervous system as shown in Fig. 9 and 10.

Fulder: I want to ask you about sympathetic and parasympathetic tone. Could you make any comments as to whether ginseng actually change sympathetic and parasympathetic relationships? Can you make any conclusion with that kind of studies?

Bettermann: Yes, let's say, it is more effective to the parasympathetic receptors and maybe that, from these figures, it can be said that the effect is a bit more on the side of the parasympathetic system.

Fulder: Are you intending to do any studies on the comparing of adrenergic and cholinergic receptors?

Bettermann: I think that the adrenergic stimulation is nearer to the effect of ginsenosides.

Tso: I'm very much interested in the very first comment you made about the effect of ginseng in Asian people versus Europeans. Did you say that the difference lies in adicity? I'd like to hear more about that.

Bettermann: We found out that there is a difference in the absorption of ginseng depending on the stomach acid. It is well known that, for instance, the mean acid output, the so-called basic acid output of Japanese is really lower than that of European people.

I.P. Lee: What I'd like to ask you is that did you compare the receptor affinity of the dopamine p-receptor versus propanolol instance or the ginsenoside? What about the efficacy of these two based on the concentration as well as the duration of the β-blocking effect?

Bettermann: I think that there is a β-blocking effect in one of our models, because even in this dissociated braindead model, there is a bit more β-blocking effect as I have shown in the comparison. But I can't say about that effect in normal condition.

Soldati: I can't understand your explanation about the acidity in the stomach between Japanese and European people. Anyway, my question is that the ginsenosides, as we have seen in pharmakokinetic studies on pigs, are not absorbed as interginsenoside. From that point of view I think that, the molecular weight of ginsenoside is too big to be absorbed directly as a substance. And I don't see any difference in pH between Japanese and European people. We know that ginsenosides are reabsorbed as a metabolite. We have seen yesterday in a speech, though I don't remember who presented it, that abosrption of inter-ginsenoside is very poor.

Bettermann: Yes, we can't say whether stomach acid disturbs the ginsenoside or not. But I can say that maybe it disturbs the metabolism. We measured the resorption of ginsenoside at a level higher than the basic acid output. The maximum acid output is decreasing from 60 to 10% if the acid ratio is over this level. So maybe it depends not only on the pH but on the quantity of the acid.

F.J. Lee: Could you give me the difference in the volume and in acidity between European and Japanese or Oriental People?

Bettermann: That is not the difference in pH. The

only difference between European and Oriental people is the quantity, the so-called basic acid output and maximum acid output. The level is 2 millimolar per hour for basic acid output and 30 millimolar per hour for the maximum acid output.

F.J. Lee: Do you mean that then, the main difference is not the acidity itself but the volume of the acid?

Bettermann: Yes, you are right.

Joo: You injected ginseng preparation because you doubted the absorption of ginsenoside. Can you tell me the dosage of one injection? How much did you inject?

Bettermann: In human bodies, about 150mg for one injection per 70kg body weight were used.

Joo: Did you find any dose-dependant difference?

Bettermann: We observed that there was not any dose-dependant difference. Increase in dose did not always elevated the effect. I think there might be optimum dosage.

자율신경계에 관여하는 혈행동력학적 지수에 미치는 인삼의 효과 연구

A. A. Bettermann
서독 함부르크대학

제 3 차 국제 인삼 심포지움 이래로, 첫번째 연구로서, 본 저자는 혈행동력학적 지수와 가스 교환 지수를 정상적인 개와(n=6) 뇌사상태의 개(n=6)를 사용하여 측정하였다. 뇌사상태를 자율 신경이 없는 상태라고 정의한다면, 지능이 낮은 개에 대하여 인삼 효능을 얻을 수 없을 것이다.

그러나 자율적으로 조절되는 순환 지표에 대한 인삼의 효과가 카테콜, 아드레날린·베타-차단제에 버금가는 놀라운 결과를 얻었다.

몇가지의 진세노사이드들의 위장관내 흡수에 의구심이 있어서, 저자들에 의하여 정제되고 표준화시킨 "주사용 인삼"을 처음으로 사용하였다.

이상과 같은 동물실험 결과, 부작용이 발견되지 않아서, "주사용 인삼"을 laporotomy 환자에 투여하여 혈행동력학적 지수와 가스 교환 지수에 미치는 영향을 조사하였다. 한번은 마취 상태에서 실험하였고, 정상 상태하의 1일후에 투여하여 실험하였다.

뇌사 상태의 개의 경우의 모델과 사람의 혈행동력학은 큰 차이를 보였다. 결론적으로 인삼은 순환계를 포함한 자율신경계에 직접 영향을 미친다고 할 수 있다.