Optimum Level of Combined Adrenergic Blockade for the Experimental Study of Hemorrhagic Shock[1]

Alpha receptor blockers protect against the metabolic consequences of experimental hemorrhagic shock[2]. This may be due to their vasodilating effects, which require an increased circulating blood volume. Protection against the metabolic consequences of hypotension is therefore obtained at the expense of an increased sensitivity to blood volume loss, a fact which creates therapeutic problems. Conversely, isolated blockade of β-receptors aggravate the course of experimental hemorrhagic shock[3]. However, in conjunction with certain additional pharmacological measures, β-blockade may apparently be protective, too. Inhibition of pulmonary and splanchnic blood pooling[4], as well as a structural and functional protection of the heart, have been demonstrated[5,6]. This communication reports the effects of an unidirectional or combined adrenergic blockade of varying intensity on the course of a standardized hemorrhagic hypotension.

Materials and methods. 48 rabbits were anesthetized with Nembutal® 30 mg/kg. A hemorrhagic shock at a constant blood pressure of 40 mm Hg was induced and maintained (by withdrawal or infusion of a few millilitres of blood) for 30 min. The animals were heparinized with 0.5 ml heparin in 1.5 ml saline. A 2^4 factorial design was adopted, permitting the study of each blocker alone and the combination of both at all dosage levels, as compared with untreated controls.

α-blockade was produced with Dibenzyline® at 4 different dosage levels: 0, 1.0, 2.5 and 4.0 mg/kg, designated as A_0, A_1, A_2 and A_3. β-blockade was effected with Trasicor® in dosages of 0, 0.1, 0.15 and 0.20 mg/kg, designated as B_0, B_1, B_2 and B_3. Thus, A_0B_0 was the untreated control group. The α-blocker was injected 45 min and the β-blocker 20 min prior to the start of bleeding. The 48 rabbits were allocated at random to the 16 experimental groups of 3 animals each. The blood loss at the end of the shock period, arterial pH, pCO_2, base excess, lactate and pyruvate were measured (methods, cf. 2, 5). Blood samples were drawn before bleeding, at the end of shock and 3 h after retransfusion of $^2/_3$ of blood volume loss.

The results were subjected to an analysis of variance on a Bull Gamma 30 s computer. Statistical significances were assessed at the 5% and 1% level ($p < 0.05$ or < 0.01, respectively).

Results and discussion. Figure 1 shows the average blood loss at the end of the hypotensive period for each of the 16 experimental groups. Increasing levels of α-blockade reduces blood loss ($p < 0.01$). Additional β-blockade increases blood loss, particularly so at the lowest dosage level of the β-blocker and less markedly with increasing levels of α-blockade ($p < 0.05$). A significant interaction is not demonstrable. The closest approximation to the blood loss of the untreated group (A_0B_0) is obtained with the lowest level of combined α- and β-blockade (A_1B_1), with absolute averages of 27.6 and 24.2 ml/kg, respectively.

There were no differences of pre-bleeding metabolic control values. The metabolic status at the end of the 30-minute hypotensive period is shown in Figure 2. Metabolic acidosis is inhibited at all levels of α-blockade, whereas it is pronounced in the A_0B_0 group and following pure β-blockade. The effect of α-blockade is significant with $p < 0.01$ for pH, pCO_2 and base excess. However, the smaller blood loss produced by increasing levels of

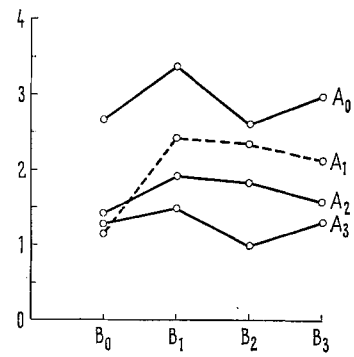

Fig. 1. Average blood volume loss in percent of body weight at the end of 30 min of hypotension at 40 mm of mercury for the 16 experimental groups. $A_{0,1,2,3}$ = Dibenzyline. 0; 1.0; 2.5; 4.0 mg/kg $B_{0,1,2,3}$ = Trasicor. 0; 0.1; 0.15; 0.20 mg/kg.

[1] Work supported by Research Grant No. 4423 from the Swiss National Foundation for the Advancement of Scientific Research.

[2] M. NICKERSON, in *Shock, Pathogenesis and Therapy* (Springer, Berlin 1962), p. 398.

[3] G. ZIEROTT, C. MEYER and P. LUNDSGAARD-HANSEN, Z. Kreislaufforsch., in press (1969).

[4] J. L. BERK, J. F. HAGEN, W. H. BEYER, G. R. DOCHAT and R. LA POINTE, Surgery Gynec. Obstet. *125*, 311 (1967).

[5] M. L. ENTMAN, D. B. HACKEL, A. M. MARTIN, E. MIKAT and J. CHANG, Arch. Path. *83*, 392 (1967).

[6] P. LUNDSGAARD-HANSEN, C. MEYER, H. RIEDWYL and G. ZIEROTT, Z. Kreislaufforsch. *58*, 623 (1969).

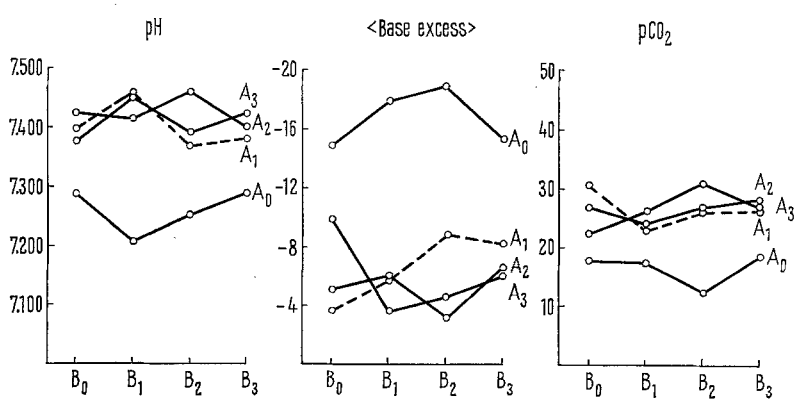

Fig. 2. Changes of acid-base status in arterial blood at the end of the 30 min hypotensive period. Means of 16 experimental groups, cf. Figure 1.

α-blockade has almost no further effect on metabolic acidosis. Conversely, the increased blood loss effected by additional β-blockade does not aggravate the metabolic status ($p > 0.05$). These findings are amplified by the changes of lactate/pyruvate metabolism depicted in Figure 3. Without treatment and with pure β-blockade, tissue perfusion is impaired following shock, as witnessed by an average arterial L/P ratio of 75. At all levels of α-blockade, the ratio remains low ($p < 0.01$). Again, the blood loss increment produced by additional β-blockade causes no metabolic deterioration.

Three hours after reinfusion, metabolic recovery as judged by arterial pH and base excess was better following combined blockade than after α-blockade only, as seen from the Table. A significant interaction ($p < 0.05$) between α- and β-blocker was, however, present. At all levels of α-blockade (A_1, A_2, A_3), metabolic acidosis decreased with a small dose of β-blocker (B_1), whereas it increased again with higher levels of β-blockade (B_2 and B_3).

Combined adrenergic blockade at the lowest dosage level employed in this study (1.0 mg/kg α-blocker + 0.1 mg/kg β-blocker) thus increases tolerance to an acute blood loss as compared with pure α-blockade, without sacrificing the metabolic protection provided by that measure. It therefore represents an optimum in the sense that it combines a minimum decrease of tolerated blood loss with a maximum inhibition of its metabolic sequels. The results obtained with this regimen in shocked dogs will be reported separately[7].

Generic and trade names of drugs: Dibenzyline® = Phenoxybenzamine; Trasicor® = 1-Isopropylamino-3-(*o*-allyloxyphenoxy)-2-propanol-hydrochloride; Nembutal® = Pentobarbital.

pH and base excess 3 h after reinfusion $\bar{x}$ and 95% confidence intervals. No overlapping = $p < 0.05$

	Combined blockade mg/kg $1.0\alpha + 0.1\beta$	α-Blockade mg/kg 1.0	2.5	4.0
pH	7.447 (7.402–7.492)	7.323 (7.315–7.331)	7.345 (7.301–7.389)	7.255 (7.215–7.295)
BE	−2.1 (−1.1 to 3.1)	−8.9 (−8.3 to −9.5)	−8.5 (−7.8 to −9.2)	−11.5 (−10.5 to −12.5)

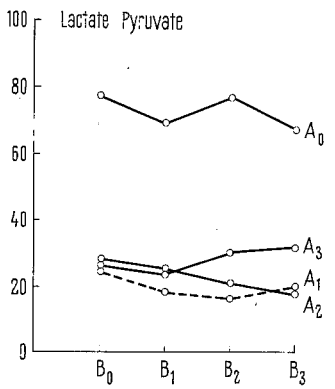

Fig. 3. Means of arterial lactate/pyruvate ratios in arterial blood at the end of the 30 min hypotensive period, cf. Figure 1.

Zusammenfassung. Die Kombination von 1,0 mg/kg α-Blocker und 0,1 mg/kg β-Blocker ergibt im experimentellen hämorrhagischen Shock die geringste Reduktion des tolerierten Blutverlustes zusammen mit einer maximalen Hemmung seiner metabolischen Konsequenzen und erscheint daher als optimal.

G. Zierott, H. Riedwyl
and P. Lundsgaard-Hansen

University Department of Experimental Surgery, Inselspital, and Institute of Mathematical Statistics, University of Bern, 3008 Bern (Switzerland), 1 April 1969.

[7] G. Zierott, E. Pappova and P. Lundsgaard-Hansen, Pflügers Arch. ges. Physiol. *310*, 1 (1969).

Preparation of 'New'-Vasoconstrictine (SVPx), a Vasoconstrictor Hormone of Plasma

A previously undescribed vasoactive hormone[1–4] has been separated from plasma by paparchromatography and counter-current distribution[5–7], and can be characterized by the following properties: (1) the material causes the isolated aorta of the rabbit to contract; (2) its contracting action is not antagonized by serotonin antagonists[6]; (3) unlike catecholamines, it leads to a contraction of intestinal muscle of the rabbit; and (4) it can be distinguished from histamine and from a number of commonly known vasoactive polypeptides[8].

Battelli (1905)[6] coined the term 'vasoconstrictine' for the constrictor material present in serum, for the most part the result of serotonin released from blood platelets during the clotting of the shed blood. We shall refer to the serum principle(s) as 'old'-vasoconstrictine. In contrast, when arterial blood is freshly collected in the presence of heparin, there is no evidence for newly formed constrictor material such as serotonin[9]. Since the plasma of heparinized blood incubated at 37 °C for as long as 1 h showed no additional constrictor activity, it appears reasonable to assume that the vasoconstrictor potency

[1] M. Wurzel, Fedn Proc. *21*, 112 (1962).
[2] M. Wurzel, Arch. int. Pharmacodyn *143*, 550 (1963).
[3] M. Wurzel, R. C. Bacon, R. Grant jr. and B. W. Zweifach, Pharmacologist *6*, 195 (1964).
[4] M. Wurzel and B. W. Zweifach, Arch. int. Pharmacodyn. *162*, 1 (1966).
[5] M. Wurzel and D. C. Blair, Fedn Proc. *26*, 378 (1967).
[6] M. Wurzel, B. W. Zweifach, L. C. Craig and W. I. Taylor, Experientia *23*, 486 (1967).
[7] M. Wurzel, L. C. Craig and B. W. Zweifach, Pharmacologist *10*, 211 (1968).
[8] M. Wurzel and B. W. Zweifach, Fedn Proc. *22*, 542 (1963).
[9] M. Wurzel and B. W. Zweifach, Fedn Proc. *23*, 120 (1964).