Liberation of Kinins During Extracorporeal Circulation?

In patients undergoing open heart surgery by means of extracorporeal circulation the fibrinolytic potential of the plasma is increased (FISCHER[1], FISCHER et al.[2], VON KAULLA and SWAN[3], MAMMEN[4,5], MARKGRAF[6,7], MATIS[8], THIES[9], TICE et al.[10,11], TSUJI et al.[12]). Already EISEN[13] suggested that the activation of fibrinolysis is related to kinin formation.

Severe hypotension and shock occurring in the course of open heart operations were believed to be due partly to the liberation of vasoactive substances into the circulating blood (HOLLENBERG et al.[14]). During extracorporeal circulation a decrease of plasma kininogen was measured and accordingly liberation of kinins was suggested (WIEGERSHAUSEN et al.[15]). But from the decrease of kininogen in plasma, the conclusion that kinins are liberated is not to be drawn (BERRY et al.[16], HABERMANN[17]). Therefore the problem of kinin liberation associated with extracorporeal circulation has been newly investigated.

Methods. The studies were carried out in 10 patients aged from 35 to 64 years (6 females, 4 males), who underwent operations with extracorporeal circulation for different reasons (mitral valve replacements (5), aortic valve replacements (4) and combined aortic-mitral valve replacement (1)). During various phases of these operations, the concentration of protein and kininogen in plasma and the concentration of kinin in whole blood were measured. A bubble oxygenator according to RYGG-KYVSGAARD and a roller pump according to DE BAKEY were used. The average perfusion volume was 2.2 l/m² body surface area × min. The body temperature was normotherm during extracorporeal circulation. The oxygenator was primed with 1000 ml of a lactated Ringer solution and 1000 ml of 5% dextrose solution.

Blood samples were obtained before and after induction of anaesthesia, following injection of heparin and at various phases during the course of extracorporeal circulation and, finally, after the termination of bypass. Blood was drawn through a catheter placed in the radial artery, except during bypass, when it was taken from the oxygenator after being arterialized.

Plasma kininogen was determined according to FREY et al.[18], kinin in whole blood according to ZACEST and MASHFORD[19]. In our hands the method of ZACEST and MASHFORD worked with a 73% yield. Total protein in plasma was estimated by the biuret reaction.

Results and discussion. One patient's course of plasma kininogen, whole blood kinin and plasma protein in absolute values is shown in Figure 1. As this figure illustrates, the plasma level of kininogen decreased, however the plasma protein and blood kinin did, too.

Estimations of kininogen, kinin and protein carried out repeatedly following induction of anaesthesia did not show different values as during bypass. For this reason only 1 trias of columns for a particular phase of the surgical procedure was used in the graph. The analytical values in each case were related to the starting level (= 100%).

Up to the beginning of the bypass kininogen, kinin and protein seemed obviously to be unaltered (Figure 2). Neither the anaesthesia itself, which should be responsible for haemodilution and correspondingly decreased protein levels in plasma (BOND and PARSONS[20], RUDOLPH et al.[21]) nor the injection of heparin, which can act against an inhibitor of plasminogen activation and might ease the activation of fibrinolysis (BULUK and JANUSZKO[22]), caused a significant change in plasma kininogen.

After the heart-lung machine had been connected to the patient, plasma kininogen decreased to 48 ± 12% (S.D.) of the starting level, but plasma protein did fall in the same direction to 57 ± 5% (S.D.) of the starting level. Kinin also fell to about the same degree, namely to 64 ± 25% (S.D.) of the starting level.

Obviously neither the contact of blood with foreign surfaces in the heart-lung machine nor the enhancement of fibrinolysis or coagulation, respectively (BLOOM[23], DE

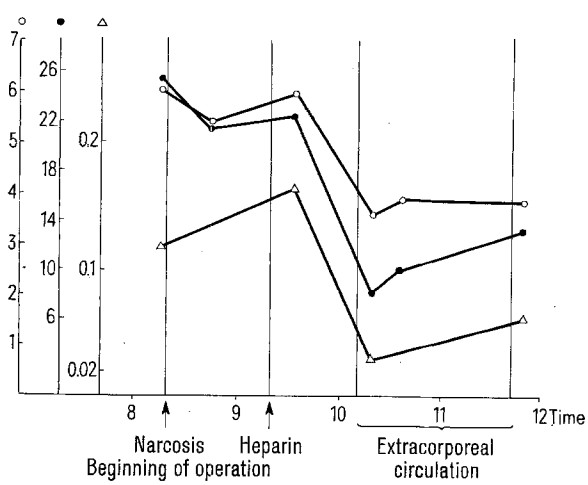

Fig. 1. Protein in g/100 ml (○), kininogen in µg bradykinin equivalents /ml plasma (●) and bradykinin in ng/ml blood (△) of a patient during various phases of open heart surgery.

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VRIES et al.[24], MAMMEN[5]), are associated with increased kinin formation.

Obviously all changes in plasma kininogen and blood kinin during different phases of open heart surgery are caused by haemodilution. In fact the average values (in %) of protein (pr) are highly correlated to kininogen (kg) and kinin (kn): $r_{pr-kg} = 0.96$, $r_{pr-kn} = 0.98$; $p < 0.01$.

It has already been shown that activation of endogenous plasmin by streptokinase in human plasma led to kinin formation only, if the protease inhibitors are widely eliminated (SEIDEL et al.[25]). A comparable situation does not exist in vivo. Probably plasmin once activated is inactivated so rapidly (FISCHER[1]), that it does not cause an increase of kinin liberation. Indeed HAMBERG[26] and HAUSTEIN and MARKWARDT[27] found a plasmin dependent formation of kinins in human plasma, but HAMBERG destroyed protease inhibitors by acidification for a certain period of time and HAUSTEIN and MARKWARDT put additional plasminogen into their plasma incubates. Although BULUK et al.[28] found an activation of the fibrinolytic and the kinin system during venostasis, these results do not prove a systemic formation of kinins in the course of enhancement of the fibrinolytic potential.

The results presented are in contrast to WIEGERSHAUSEN et al.[15]. Unfortunately it is not possible to discuss their communication in detail because they did not measure the degree of haemodilution in their patients. Moreover, they did not inform about the volume of perfusion which, being small, leads to a larger extent of fibrinolysis activation than being high (VON KAULLA and SWAN[3]).

Possibly the controversial results are due to different types of oxygenators used in extracorporeal circulation. In WIEGERSHAUSEN's study a disc oxygenator was applied, which was observed to cause a stronger activation of fibrinolysis than a bubble oxygenator (EKERT et al.[29]). In addition the denaturation of γ-globulins in disc oxygenators (PRUITT et al.[30]) possibly leads to liberation of kinins (BOREHAM and GOODWIN[31], MOVAT[32,33]).

Zusammenfassung. Bei 10 Patienten, die sich einer Operation am offenen Herzen unterzogen, verliefen die Plasmakininogen- und Blutkininspiegel parallel zum Plasmaprotein. Das spricht gegen eine exzessive Aktivierung des Kinin-bildenden Systems im Plasma während extrakorporaler Zirkulation.

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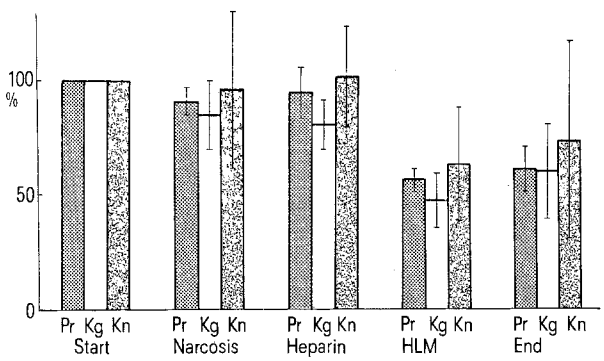

Fig. 2. Total plasma protein (Pr), kininogen (Kg) and kinin (Kn) during various phases of open heart surgery. Values before (start) and after induction of anaesthesia (narcosis), following heparin injection (heparin), during extracorporeal circulation (HLM) and after termination of bypass (end). Average values ± S. D. ($n = 10$).

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Saccharin Preference of Butyraldoxime-Treated C57BL Mice

Butyraldoxime, chronically administered via the drinking fluid, has been shown to elicit the following in C57BL mice: 1. marked blockade of hepatic aldehyde dehydrogenase, 2. accumulation of substantial concentrations of acetaldehyde in blood following an ethanol dose, and 3. pronounced decrease in the natural ethanol preference of these animals[1,2]. Since increased acetaldehyde levels can produce toxic effects[3], we have attributed the strong and sustained decrease in ethanol preference of the C57BL mice during, and after, butyraldoxime ingestion to a learned aversion based upon the noxious effects of increased acetaldehyde levels[2].

Recently NACHMAN et al.[4] reported that i.p. administration of butyraldoxime following the ingestion of saccharin is effective in producing a conditioned aversion to saccharin, i.e., reducing the saccharin intake during a test run several days later. They concluded that 'Since the substantially lower dosages used in these experiments were sufficient to cause a learned aversion to solutions other than alcohol, ...the effects on the self-selection of alcohol previously reported for ... [butyraldoxime[1]] ... are based,

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