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Time Course of Bradykinin Generation during LDL Apheresis

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In LDL apheresis using a dextran-sulfate-cellulose (DSC) column, the initial contact phase of the intrinsic coagulation pathway is activated by the negative charges of the DSC, leading to prominent production of bradykinin accompanied by consumption of factor XII, prekallikrein (PK), and high-molecular-weight kininogen (HMWK).[1] The time course in the blood levels of bradykinin showed a peak level at around 1,000 ml of plasma treatment and decreased thereafter.[2] The aim of the present study was to determine the mechanism for this decrease in bradykinin levels after the 1,000 ml point.

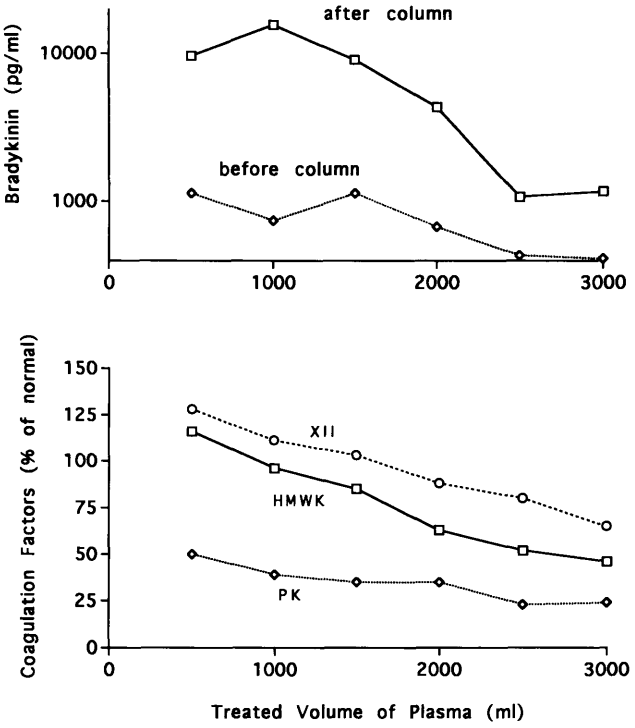

Fig. 1 Time courses of the levels of bradykinin in the plasma before and after the dextran-sulfate-cellulose column and factor XII (XII), prekallikrein (PK), and high-molecular-weight kininogen (HMWK) in the plasma before the column. All the factors decreased toward the end of LDL apheresis.

Patient and Methods

A 57-year-old man with heterozygous familial hypercholesterolemia has been treated fortnightly with LDL apheresis for the past 2 years. The treated volume of plasma is 3,500 ml in each LDL apheresis. The time course of bradykinin generation was examined in one of these procedures. Plasma samples were taken

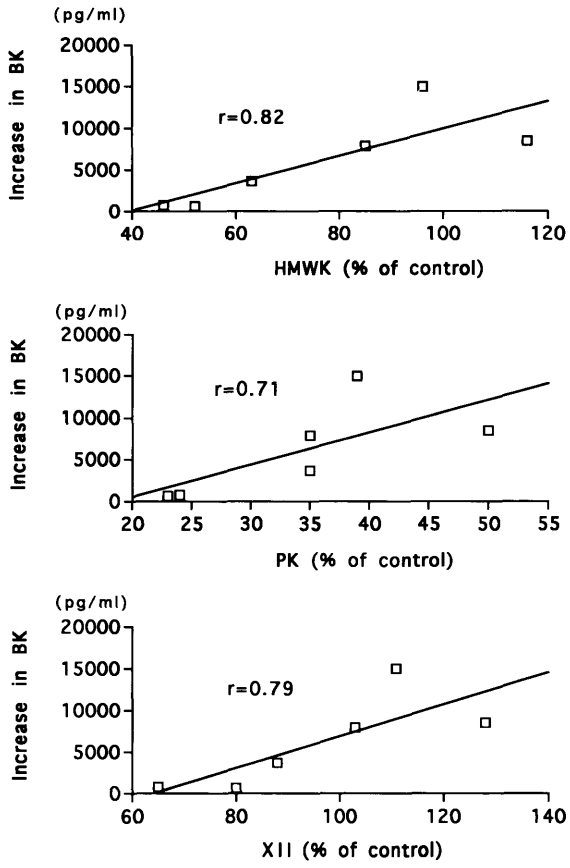

Fig. 2 There are positive correlations between the decrease in coagulation factors and bradykinin generation. In particular, there is a significant correlation ($r=0.82$, $P<0.05$) between the decrease in HMWK and bradykinin genaration. BK, bradykinin; XII, factor XII; PK, prekallikrein; HMWK, high-molecular-weight kininogen.

every 500 ml of treatment before and after the DSC column until the 3,000 ml plasma treatment point. The levels of bradykinin, factor XII, PK, and HMWK were measured in these samples. The difference in bradykinin levels in the plasma before and after the column indicates bradykinin generation. Bradykinin generation was related to reductions in factor XII, PK, and HMWK by passing of plasma through the column. The concentrations of factor XII, PK, and HMWK were expressed as the activity of plasma which decomposes the appropriate chromogenic substrates. The levels of bradykinin were measured by radioimmunoassay.

Results

All the factors participating in bradykinin generation decreased gradually and reached about one-half after 3,000 ml plasma treatment (Fig. 1). These factors decreased to almost null after the column. In accordance with this decline, levels of bradykinin in the plasma after the column decreased from more than 10,000 pg/ml to 1,000 pg/ml after 3,000 ml plasma treatment. There were positive relationships between bradykinin generation and reductions in factor XII, PK, and HMWK (Fig. 2). In particular, the correlation between bradykinin generation and the reduction in HMWK was statistically significant ($r=0.82$, $P<0.05$).

Discussion

Our previous study showed that blood levels of bradykinin declined toward the end of LDL apheresis despite an initial rise.[2] Kallikrein converted from PK cleaves HMWK to release bradykinin. The present study demonstrated that the decline in bradykinin levels was due to the consumption or exclusion of PK and HMWK. The present study was undertaken using a device, the MA01, which is equipped with two small DSC columns (LA15: total volume 150 ml). The two columns were used alternatively during the procedure: when one column was in use for LDL adsorption, the other column was regenerated by washing with 0.7 M saline and a physiological solution. The adsorbed coagulation factors are discarded with LDL during regeneration. If the single large DSC column (LA40: total volume 400 ml) were used, the coagulation factors adsorbed on the column might continue to produce bradykinin. Therefore, the time course of bradykinin might differ from that in the present study. If bradykinin generation is related to hypotension during LDL apheresis, the smaller column is preferred to the larger for stable hemodynamics.

References

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