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INHIBITION OF ANAPHYLATOXIN RELEASE BY COOLING THE BLOOD WITHIN THE DIALYSER

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Summary

Release of anaphylatoxin C_{5a} during cuprophan haemodialysis can be inhibited by lowering blood temperature in the dialyser to 24°C. As a result of the lower anaphylatoxin generation, intra-dialytic leucopenia is markedly reduced.

Introduction

The interaction between cuprophan membrane and blood leads sequentially to complement activation by the alternate pathway, generation of the anaphylatoxin C_{5a} and C_{3a} and aggregation and embolization of granulocytes within the pulmonary vascular bed [1,2]. It is this pulmonary leucosequestration which causes the profound leucopenia occurring early in dialysis. Like other enzyme cascades, complement activation is temperature dependent [3,4]. We previously showed that cooling the blood in the dialyser markedly reduces intra-dialytic leucopenia [5]. We present here the findings of a study aimed at directly assessing both in vitro and in vivo the effect of blood cooling on anaphylatoxin release.

Patients and methods

In vitro generation of C_{5a} antigen was assessed by incubating the serum from two normal subjects in revolving plastic tubes for one hour with cuprophan membrane (1ml per 20cm^2 of membrane) at temperatures of 23, 30 and 37°C respectively.

In vivo studies were carried out on eight patients (4 males and 4 females) on regular dialysis treatment from one to seven years (average 2.7) and aged 25–59 years (average 50). Diagnosis of renal disease was interstitial nephropathy (3), unknown aetiology (3), diabetic nephropathy (1), renal vascular disease (1). In a cross-over design each of them underwent one standard haemodialysis with dialysate temperature set at 37°C, and one cool haemodialysis. The latter was accomplished by lowering pre-dialyser blood temperature through a 200cm

coil immersed in a bath of running tap water, and by using unwarmed dialysate. Blood was then rewarmed before being returned to the patient by another coil inserted in the venous line and immersed in a thermostatic bath. Blood lines of similar length and conformation were employed both in cool and standard haemodialysis. In all treatments cuprophan hollow fibre dialysers were used. Temperature was monitored by means of thermocouple needles (Ellab) placed in the blood and dialysate circuits. Blood temperature within the dialyser was estimated as the average of the pre- and post-dialyser blood temperature. Leucocyte and differential count were determined in duplicate on blood drawn from the arterial line at 0, 15, 30, 60, 120 and 240 minutes of haemodialysis. At the same time points we also determined C_{3a} and C_{5a} antigens in both the arterial and venous blood of extracorporeal circuit. C_{5a} and C_{3a} antigens were determined by RIA (Upjhon, Kalamzoo), white blood cell and differential count by a manual method. Dialyser urea and creatinine clearances were determined by standard methods at the end of the second hour of haemodialysis. Blood gases were determined by Radiometer ABL2 gas analyzer.

Statistical analysis was performed by paired Student's 't' test and linear regression analysis.

Results

The in vitro studies showed that C_{5a} release was significantly related to the temperature of the incubation (Figure 1) ($r=0.90$ $p<0.001$).

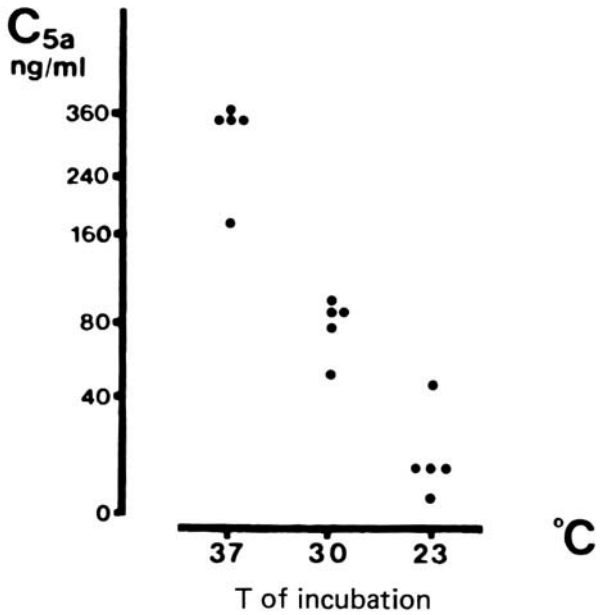

Figure 1. Relationship between temperature of incubation and C_{5a} release in vitro, $r=0.90$, $p<0.001$, $y= -477+20.3x$

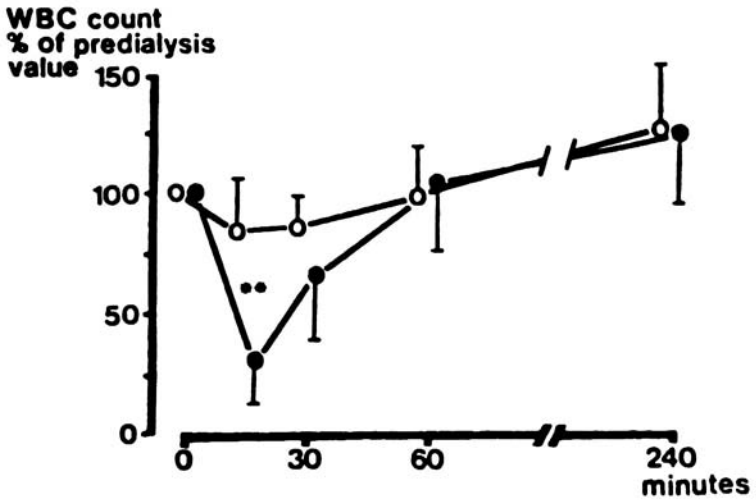

Figure 2. White blood cell count during cool (○) and standard (●) haemodialysis, **p<0.001

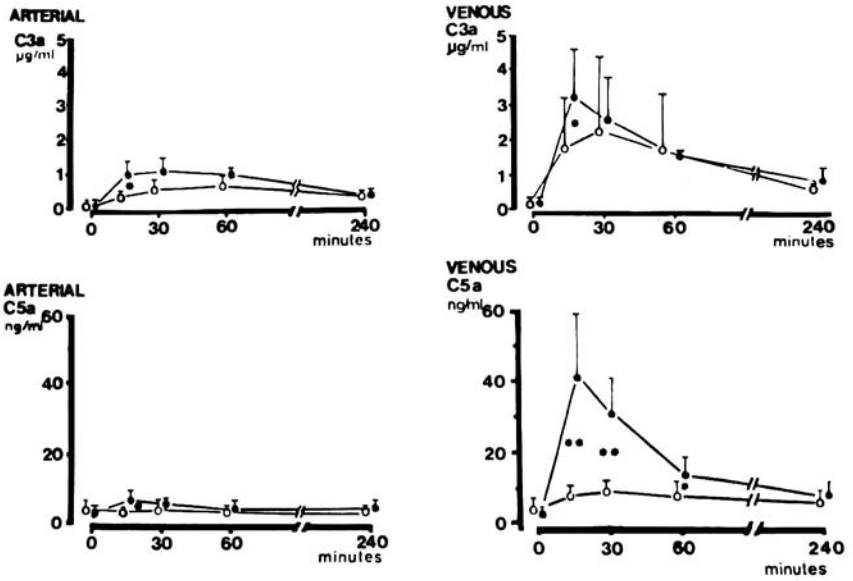

Figure 3. $C_{3}a$ and $C_{5}a$ in the arterial and venous blood of extracorporeal circuit during cool (○) and standard (●) haemodialysis, *p<0.05 **p<0.001

The in vivo studies agreed with the in vitro observations. Thus when compared to a standard haemodialysis (estimated dialyser blood temperature, 35.3±1.0°C), cool haemodialysis dialyser blood temperature, 24.9±1.3°C) brought about a marked reduction in the degrees of both leucocyte reduction (Figure 2) and C_{5a} generation (Figure 3). Much less marked appeared the effect of blood cooling on C_{3a} release (Figure 3).

There was a trend for arterial PO_2 to decrease less during cool haemodialysis (Figure 4) than during standard haemodialysis, while $PaCO_2$ changes were similar.

In standard haemodialysis urea and creatinine clearance were 182±21 (SD) and 152±16ml/min; in cool haemodialysis values were significantly lower: 150±14 and 126±15ml/min, respectively ($p<0.001$)

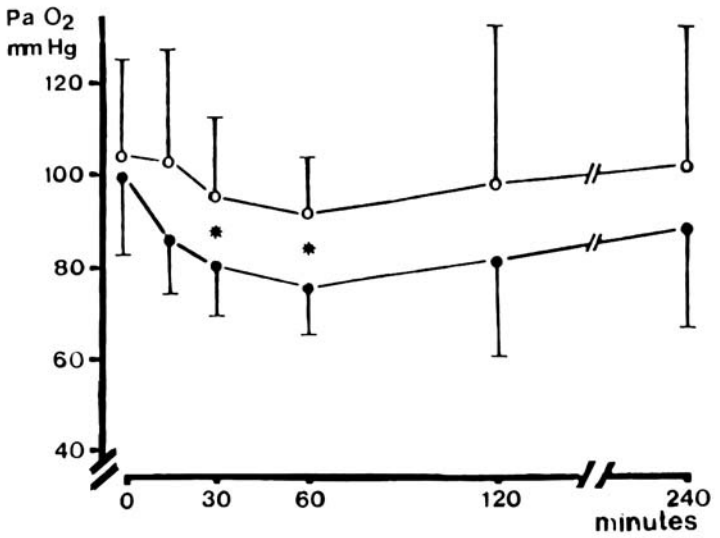

Figure 4. PaO_2 changes during cool (○) and standard (●) haemodialysis, *$p<0.02$

Discussion

Cooling the blood in the dialyser strongly reduced the degree of complement activation and anaphylatoxin release. With lower anaphylyatoxin release the degree of leucopenia was markedly blunted. This observation adds further support to the concept that C_{5a} generation is the cause of intra-dialytic leucopenia. The less marked effect of blood cooling on C_{3a} generation remains to be explained. According to some authors a pathophysiological correlate of dialysis induced complement activation is, at least in part, arterial hypoxia [6]. We observed a better preservation of arterial PaO_2 during the cold treatment, but the data are still insufficient to allow the conclusion that this finding reflects a slower rate of complement activation.

Proper adjustment of blood temperature represents a simple measure for reducing or avoiding complement activation not only during cuprophan haemodialysis, but probably also in other settings of extracorporeal circulation.

References

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