PART IV

GUEST LECTURE

Chairmen:  V Cambi
            N K Man
CONVECTIVE MASS TRANSPORT IN DIALYSIS

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The purpose of this paper is a discussion of the clinical effects and applications of convective mass transport in haemodialysis and other treatment modalities of terminal renal failure. As this presently is an area of controversy, speculation and hypothetical thoughts are inevitable.

Nevertheless, some quantification of the subject is indicated: in haemodialysis with tight membranes such as cuprophane the contribution of convection to overall mass transfer of uraemic solutes of 500 daltons or less is negligible in comparison to diffuse transport. The convective clearance of larger molecules across these tight membranes is significantly affected by sieving. For instance for a three litre fluid removal over four hours of haemodialysis with a cuprophane membrane the clearance of inulin, because of a sieving coefficient of 0.3, only amounts to 4ml/min [1]. The situation is different with modern high flux membranes with larger pore radii. In an in vitro study with a polysulfone hollow fibre capillary dialyser Schmidt et al [2] could show that at blood and dialysate flows of 200ml and 500ml respectively the clearances of urea and creatinine only changed insignificantly when ultrafiltration rate was increased from 0 to 100ml/min. In contrast this increase or ultrafiltration was accompanied by a 50 per cent rise of inulin clearance. The negligible effect of convection and small molecule clearance is also valid for the in vivo situation. Streicher and Schneider [3] using the same polysulfone capillary dialyser in patients only saw a marginal increase of urea and creatinine clearances of one per cent and three per cent respectively when they increased ultrafiltration rate from 0.50ml/min.

The cause for the interest of nephrologists in convection as an alternative to diffusive removal of uraemic retention products — especially of the larger molecular range — is partly historic and partly futuristic. It was the middle molecule hypothesis which spurred the demand for an increase of convective mass transport. As convective mass transfer, in contrast to diffusion, is not necessarily dependent on molecular size it offered the possibility to remove larger molecular species, which were thought to play a primary role in the pathogenesis of the uraemic syndrome. Thus great expectations accompanied
the introduction of haemofiltration, a treatment modality solely based on convection. Even though experimental data had suggested a link between retention of larger molecules and the uraemic syndrome the clinical experience was rather disenchanted. In the majority of studies haemofiltration was no better cure of uraemia than haemodialysis [4] and single claimed benefits were muddled by controversy. It was in this situation of doubt that neglected small molecule removal was reinstated and coupled with convective mass transfer. The name of the pragmatic marriage was haemodialfiltration. One may consider this treatment modality as a therapeutic insurance policy or as an indication of a scientific stalemate. We should not forget, however, that the excursion into convection did yield one very positive finding: Volume removal during treatment modalities with convective mass transfer was accompanied by better cardiovascular stability than during haemodialysis with mainly diffusive transport. In a way this observation was a rediscovery. Already in 1976 Shaldon, Bergström and others described that weight removal in haemodialysis patients by pure ultrafiltration – that means only convective mass transfer takes place – is accompanied by remarkable cardiovascular stability superior to isovolaemic haemodialysis [5]. Quellhorst was the first to demonstrate clinically a similar cardiovascular stability in haemofiltration, another pure convective process [6]. Subsequently Leber reported that even mixing convective and diffusive mass transfer by performing haemodiafiltration results in an improvement of cardiovascular stability in comparison to predominantly diffusive haemodialysis [7]. This effect is presently utilized by von Albertini who, as yet in a small number of patients, is performing ultra-short high efficient haemodiafiltration with adequate volume removal without serious cardiovascular instability [8].

What is the reason for the improvement of cardiovascular stability, when diffusion is replaced by convection or the two physical processes are mixed? Numerous mechanisms were discussed, most of them only circumstantially linked to convective mass transfer. The major issues in the debate were membrane biocompatibility, sodium balance, choice of buffer and treatment specific interference with the sympathetic response to volume removal. One of the earliest concepts was that better cardiovascular stability, characteristic of treatment modalities with significant convective mass transfer, was related to the improved biocompatibility of the high flux membranes employed [9]. Most of these membranes were non-cellulosic and showed less interaction with cellular and non-cellular blood constituents than cellulosic membranes [10]. Two observations very strongly speak against this concept: (1) the excellent cardiovascular stability during pure ultrafiltration across cuprophan membranes [11]; (2) haemodialysis still displays less cardiovascular stability than haemofiltration when the same non-cellulosic high flux membrane is used for both treatment modalities [12]. Controversy erupted about possible differences in sodium balance as the cause for differences in cardiovascular stability between haemodialysis and haemofiltration. Gotch advanced the proposition that the process of post-dilutional haemofiltration was more sodium retentive than conventional haemodialysis and that this improved sodium balance explained better cardiovascular stability during weight loss in post-dilutional haemofiltration [13]. He argued that due to ultrafiltration the average plasma protein concentration in
the blood circulating through the device is higher in post-dilutional haemo-
filtration than in haemodialysis. He then suggested that because the magnitude
of sodium retention increases with protein concentration, a lower sodium flux
occurs during post-dilutional haemofiltration than during haemodialysis. In
principle at least two clinical observations are in disagreement with his concept:
(1) vascular stability is also maintained in pre-dilutional haemofiltration [14],
where the average protein concentration in the haemofilter does not rise to
levels characteristic of post-dilutional haemofiltration; (2) symptoms which
accompany haemodialysis with high dialysate sodium such as excessive inter-
treatment weight gain, thirst and hypertension [15] are rarely observed in
haemofiltration. We ourselves demonstrated in two studies, an acute and a
chronic cross-over study, that the intra-treatment drop of mean arterial blood
pressure was higher in haemodialysis than in haemofiltration even though there
was no difference of sodium balance [15]. While sodium balance definitely
affects intra-treatment symptomatology in haemodialysis it obviously is not the
main cause for the different cardiovascular stability of haemodialysis and haemo-
filtration.

Generally in haemofiltration substitution fluid lactate is used as buffer in
contrast to acetate in dialysate. It was suggested that differences in intra-treatment
haemodynamics between the two treatment modalities may be related to differ-
ences in buffer chemistry. This issue was taken up by Shaldon, who in two
studies could demonstrate that even with acetate as a buffer in haemofiltration
infusate the characteristic superiority in haemodynamic stability over acetate
haemodialysis still prevailed [16,17].

As sympathetic activity is the main regulator of the response of total peri-
pheral resistance to volume removal the differences in changes of total peripheral
resistance during convective and diffusive blood purification may be an indicator
of treatment specific effects on sympathetic activity. This concept is supported
by results we obtained when we submitted the same patients to acetate and
bicarbonate haemodialysis, to haemofiltration and pure ultrafiltration with
identical weight loss per unit of time [11]. During convective mass transfer —
that means during haemofiltration and pure ultrafiltration — where total peri-
pheral resistance rose during volume removal there was an increase of plasma
noradrenaline concentrations signalling an increase of sympathetic activity. In
contrast during diffusive blood purification there was no change of plasma
noradrenaline concentration and either a drop (acetate haemodialysis) or a
small increase (bicarbonate haemodialysis) in total peripheral resistance. Our
data does not support the interpretation that the differences in noradrenaline
levels are just a consequence of differences in noradrenaline removal from the
extracellular fluid during haemodialysis and haemofiltration [11]. At the
present time however there is no plausible explanation by which mechanisms
convective and diffusive mass transfer might exert different effects on sympa-
thetic activity and thereby on total peripheral resistance. Therefore without
applicable hypothesis our findings have to be considered as empirical observations
of unknown relevance.

This is the fate of all findings so far brought forward in this debate. As
empirical observations their scientific value remains dubious until they have been
fitted into scientifically well secured explanatory hypotheses. We are not lacking in measurements but in need of a hypothesis. This need may be fulfilled by a very interesting concept introduced by Shaldon [18], which provides new impulses for future investigation and very cleverly mixes transport physics with biology. The centre role in the hypothesis is ascribed to the monocyte, which, when stimulated, activates a multitude of biological processes. In most instances the initiating mediator is the monokine interleukin-1 [19]. Interleukin-1 (IL-1) stimulates antibody production of B-cells, interleukin-2 release by T-cells, fibroblast proliferation and formation of collagen, hepatic synthesis and release of acute phase reactants such as haptoglobin, fibrinogen and serum amyloid A protein [19,20]. IL-1 also induces synthesis of PGE₂ in the hypothalamic area [19] and in skeletal muscle [21] and of PGI₂ in endothelial and smooth muscle cells [22,23]. If by mechanisms discussed below patients’ monocytes are stimulated during haemodialysis the known effects of IL-1 can be linked in many aspects to clinical symptomatology not uncommon in patients on regular haemodialysis: fibroblast proliferation and collagen production together with the formation of serum amyloid A protein may cause carpal tunnel syndrome and scapulohumeral peri-arthritis [24], acute phase proteins may be responsible for hypercatabolism and increased urea generation [19], muscle proteolysis could be mediated by PGE₂ [21] and last but not least both PGE₂ and PGI₂ as vasodilators may play a primary role in haemodialysis hypotension.

Regarding possible mechanisms of monocyte induction during haemodialysis at least three well established principles have to be considered: monocytes adhering to the dialyser membrane may be exposed to complement fractions C₅a, a resultant of complement activation on the membrane surface [10]. Monocytes may also phagocytose granulocytes aggregated at the membrane after interaction with C₅a and they may be exposed to active subunits of endotoxin able to pass from dialysate to blood through the dialyser membrane. All three factors, C₅a, endotoxin fragments and phagocytosis will induce the monocyte to produce IL-1 [19,25]. In addition dialysate derived solutes such as acetate that confront the monocyte at the membrane blood interface in unphysiological high concentrations may also induce IL-1 production. This is a realistic assumption since it has been shown that substances such as silica and urate induce IL-1 production [19].

So the blood membrane interface may represent a bioreactor in which the magnitude of response is controlled by the effective concentrations of inducers of IL-1. Effective inducer concentrations at the bioreactor interface should be highest in haemodialysis, where there are possible dialysate derived inducers such as acetate and endotoxin fragments and where concentrations of blood derived inducers such as C₅a are not decreased by convective fluid flow. In pure ultrafiltration and haemofiltration with no dialysate derived inducers and only C₅a and aggregated granulocytes being operative as inducers the effective bioreactor interface, because of convective flow, will be reduced to a minimum.

As pointed out before the known effects of IL-1 postulated to be released at the bioreactor interface very well fit acute intra-treatment symptomatology in haemodialysis. This especially applies for hypotension, which following Shaldon’s hypothesis is a consequence of IL-1 mediated release of vasodilating
prostaglandins from tissues such as endothelium and smooth muscle. The model also gives a plausible explanation for the reduction of cardiovascular instability by the introduction of convection into uraemic blood purification. The concept which suggests a thrice weekly induction of an acute phase response may also be a key to the understanding of chronic effects of haemodialysis.

Already investigators are able to provide data supporting the hypothesis. Port could show by in vivo bioassay that measurable quantities of IL-1 appear in the blood during haemodialysis [26]. Lonnemann from our group demonstrated in in vitro studies that when endotoxin is recirculated on the dialysate side of a 15μ cuprophan capillary dialyser significant induction of IL-1 occurs after four hours in the recirculated donor blood [27].

Figure 1 relates to the possible role of acetate at the bioreactor interface and shows very recent preliminary data obtained by Bingel in our laboratory. She incubated human monocytes with phythaemagglutinin (PHA) as control, with 20 and 40mmol/L acetate, with 0.5ng/ml endotoxin and with 20 and 40mmol/L-acetate plus 0.5ng/ml endotoxin. IL-1 was measured by the lymphocyte activating factor (LHF)-Assay [19] and its concentration is expressed as ³H-Thymidine incorporation in cpm. Whereas acetate alone compared to the PHA control had no effect, there was a small but significant response to the low endotoxin dose and a very dramatic response when monocytes were incubated with endotoxin plus acetate. The response increased with rising concentrations of acetate. Interpretation of the data can only be limited before additional experiments are performed. As a preliminary conclusion I suggest that acetate is synergistically potentiating the IL-1 response of the monocyte to endotoxin.

![Figure 1](image-url)

**Figure 1.** The in vitro effect of acetate on interleukin 1 (IL-1) induction of human monocytes, n=12; X ± 1 SE; p<0.0001, unpaired 't' test. For further details see text.
Conclusions

Convective mass transport was introduced into the extracorporeal treatment of uraemia with the intent to improve treatment results by removal of higher molecular weight toxins. Even though this concept is still short of being proven, an improvement of intra-treatment symptomatology was achieved. This effect may be due to the modification of the acute phase response at the blood membrane interface by convection. While acute benefits have been established chronic advantages of convective mass transport for the patient can be envisaged.

References

PART V

GUEST LECTURE

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