MODIFIED SEQUENTIAL HEMODIALYSIS VERSUS STANDARD SEQUENTIAL HEMODIALYSIS IN OVERHYDRATED UREMIC PATIENTS

THESIS

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بسم الله الرحمن الرحيم

INTRODUCTION
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INTRODUCTION AND AIM OF WORK

Patients with chronic renal failure requiring treatment with the artificial kidney usually require reduction of their total body water in conjunction with their dialysis. Removal of this excess fluid during hemodialysis by ultrafiltration,usually accomplished by negative pressure on the dialysate compartment (Kobayashi et.al.,1972; Ing et.al.,1975),often causes arterial hypotension or muscle cramps or both(Bergström et.al.,1976) in particular when relatively large amounts of fluid have to be removed in brief periods of time.Bergström and co-workers (1976) observed by chance that rapid ultrafiltration was much better tolerated (without significant fall in blood pressure) when performed without simultaneous dialysis, i.e.,when negative pressure was applied with the dialysis fluid bypassing the dialyzer. They successfully introduced a dialysis protocol of sequential ultrafiltration and dialysis : in this way even large amounts of fluid (e.g. 4 liters or more in one hour) could be removed without discomfort to the patient and without a fall in blood pressure. This was soon confirmed by other clinical investigations (Shaldon,1976;Ivanovich et.al.,1977; Jones et.al.,1977).

Rosenzweig and Rosansky(1983) studied a new form of sequential hemodialysis ,modified sequential hemodialysis, to see if it improved blood pressure stability as compared to standard dialysis techniques. They concluded that it is superior to regular hemodialysis with respect to blood pressure maintenance and superior to standard sequential hemodialysis with respect to urea and creatinine clearance. Consequently, they claim that this new form of treatment may prove to be the optimal method of hemodialysis in the future.

The aim of this work is to evaluate this technique of hemodialysis compared to standard sequential hemodialysis described earlier by Bergström et.al., 1976.

REVIEW OF LITERATURE

KINETICS* OF HEMODIALYSIS

The purpose of maintenance hemodialysis is to palliate the failure of the excretory and hydroelectrolyte functions of a diseased kidney. However, it is evident that the artificial kidney cannot obviate the failure of endocrine and metabolic functions of the kidney (Scribner et.al.,1960; Hegstrom et.al.,1961).

Dialysis is achieved by discontinuous exchange between patient plasma and a dialysis solution across a semipermeable membrane. The electrolyte composition of the dialysate is similar to an ultrafiltrate** of normal plasma. Thus, diffusible solutes pass into the dialysis fluid, while blood proteins and formed elements remain in the plasma. Increasing the hydrostatic pressure between the blood and the dialysate removes excess water and sodium accumulated by the patient between dialyses (Murray et.al.,1948).

The principles underlying hemodialysis are the physical and chemical laws governing mass transfer across semipermeable membranes (Wolf et. al.,1951).

MASS TRANSFER ACROSS SEMIPERMEABLE MEMBRANES (Man & Jungers ,1979).

Schematically, a hemodialyzer is made of a semipermeable membrane separating two compartments in which blood and dialysate flow (Fig. 1).

Mass transfer is defined as the quantity of solute trans-

*Kinetics=the study of the turnover, or rate of change, of a specific factor, commonly expressed as units of amount per unit time (Dorland's Illustrated Medical Dictionary, 25th. edn., W.B. Saunders-Igaku Shoin, 1974)

**Ultrafiltration entails separation of plasma water from macromolecular constituents such as protein and cellular elements via its passage through a semipermeable membrane. An ultrafiltrate is the fluid that has passed through a semipermeable membrane.

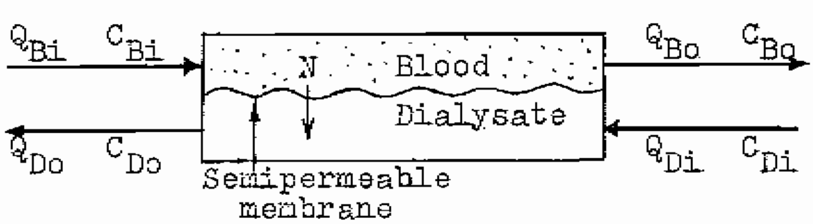

Figure 1. Schematic diagram of a hemodialyzer.

Blood and dialysate flow rates are respectively depicted as Q_B and Q_D ,with indices i(inlet) or o(outlet).Corresponding blood and dialysate solute concentrations are $C_B$and C_D,with the same indices.

ported from the blood to the dialysate, or vice versa,per time unit. Hydrostatic pressure between the blood and dialysate and the solute concentrations of each determine the direction of solute exchanges. Solute mass removed from the blood stream per time unit(N)may be expressed as the difference between solutes present in the inflowing blood and those in the outflowing blood(Michaels,1971):

$$N = (Q_{Bi} \times C_{Bi}) - (Q_{Bo} \times C_{Bo}) \quad ....(1)$$

When ultrafiltration is low or nil,the flow rate of outflowing blood is very close to that of inflowing.Q_{Bi} and Q_{Bo} may be assumed to be equal, and equation(1)may be simplified as follows:

$$N = Q_B (C_{Bi} - C_{Bo}) \quad ....(1A)$$

According to the same principle, solute mass transferred from blood to dialysate per time unit may be expressed as follows:

$$N = (Q_{Do} \times C_{Do}) - (Q_{Di} \times C_{Di}) \quad ....(2)$$

The solute mass(N)extracted from the blood is necessarily equal to that transferred to the dialysate during the same time, and equation(1)equals equation(2)(Michaels,1971).

Mass transfer across a semipermeable membrane is based on two mechanisms,diffusion and ultrafiltration.Diffusion, or conduction transfer,is a passive transfer of solutes across the membrane;for a given solute the amount of diffusion depends on the surface area and chemical nature of the membrane and on the concentration gradient of the solute. Ultrafiltration,or convection transfer,is simultaneous transfer of solutes and solvent across the membrane under the influence of a hydrostatic pressure gradient between the blood and the dialysate;its degree depends mainly on the hydraulic permeability* of the membrane for various solutes.

DIFFUSIVE MASS TRANSFER

Hemodialysis is a diffusion-based mass transfer process between blood and dialysis fluid modulated by a semipermeable membrane.In most instances,the direction of solute movement is from blood to dialysis fluid(Henderson,1983).The solute mass transferred across the membrane by diffusion per time unit (N_d)depends on three factors:mass transfer coefficient of the dialyzer(K_o),active membrane surface area(A),and mean concentration gradient for the individual solute($\overline{\Delta C}_M$):(Michaels,1971)

$$N_d = K_o \times A \times \overline{\Delta C}_M \qquad \ldots\ldots\ldots\ldots\ldots\ldots(3)$$

During hemodialysis,other factors may influence solute movement by diffusion across the dialysis membrane(Henderson, 1983).There is an orderly relationship between solute molecular size and its rate of transport;large solutes diffuse more slowly than small ones.Solutes that are protein-bound or present within the blood cell,e.g.,calcium,potassium,will not obey this orderly relationship,but depend on their binding con-

* Hydraulic permeability or ultrafiltration coefficient is a physical property of a given membrane,related to its solvent transfer rate per unit time(Man &Jungers,1979).

stants and/or cell membrane permeability to determine their rate of removal by dialysis. Solute charge has also been determined to be important for transport across synthetic and biological membranes,especially for solutes above 500 daltons in size.For these"middle molecules",i.e.molecules larger than the commonly identified uremic toxins(larger than 500 daltons but smaller than proteins),the configuration of the molecule is also important in determining its rate of movement across the dialysis membrane (Henderson,1983).

Equation(3)indicates that transfer efficiency is maximal under the following conditions: (Man & Jungers ,1979)

*Solute concentration gradient across the membrane must be as high as possible. In the case of single-pass dialysis, this is the case when the dialysate is devoid of the given solute. The countercurrent dialysate system(Fig. 1),which improves the transfer rate,is used in most dialyzers, associated with active turbulence to mix dialysate layers along the membrane.

*Active membrane surface area must be as large as possible. Unperfused or channelling areas may be reduced by improving dialyzer design and by using two or more dialyzers in parallel or dialyzers with a high surface area membrane.However, these possibilities entail a high extracorporeal blood volume.In this respect,hollow-fiber dialyzers have the best surface-to-volume ratio (Gotch et.al.,1972).

*Overall transport coefficient for waste solutes must also be as high as possible. This coefficient depends on the resistance to solute transfer not only of the membrane itself but also of the blood film and the dialysate.

Mass Transfer Resistance:

In order for a solute molecule to diffuse during extracorporeal hemodialysis(ECHD) from well-mixed plasma water in the blood path to well-mixed dialysis fluid, it must traverse serially three resistances to its movement(Fig.2). These are the resistances presented by poorly mixed plasma water adjacent to the dialysis membrane(R_B), that of the membrane itself(R_M), and that for poorly mixed dialysis fluid adjacent to the membrane(R_D)(Leonard et. al.,1960). Overall transfer resistance, R_O, is equal to the sum of the above resistances, or:

$$R_O = R_B + R_M + R_D \qquad \ldots\ldots\ldots\ldots\ldots (4)$$

As permeability is inversely related to resistance, it results:

$$R_O = \frac{1}{K_O} = \frac{1}{K_B} + \frac{1}{K_M} + \frac{1}{K_D}$$

Improvement of diffusion transfer requires a reduction of these individual resistances(Man & Jungers ,1979).

-R_B may be reduced by decreasing blood channel height. It has been decreased from 400µm in the standard Kiil to 150µm newer disposable plate dialyzers and to less than 100 µm in the hollow-fiber kidney.

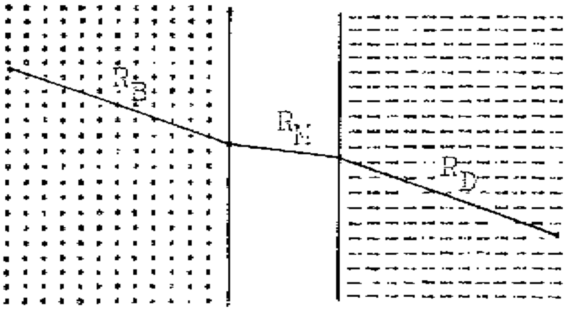

Figure 2. Mass transfer resistances in a hemodialyzer : blood resistance(R_B),membrane resistance(R_M), and dialysate resistance(R_D).

-R_D may be reduced by high dialysate flow rates. This creates turbulence in the dialysate stream, which increases washout of the superficial dialysate layer. Dialysate flow ranges from 500 to 1000 ml/min. in most parallel flow diayzers. Dialysate compartment resistance may also be lowered by improving support sructure design, such as in "multipoint" Kiil dialyzers (Edson et. al., 1972).

-For a given membrane, R_M may be reduced by diminishing membrane thickness. The Cuprophan membrane was progressively reduced from about 30 μm to 11 μm, but mechanical resistance of the membrane precludes further progress. Newer membranes, such as polyacrylonitrile (Kirkwood et. al. ,1978), polycarbonate, and Amicon XM-50 (Henderson et. al. ,1973), have become available; these membranes are more permeable than Cuprophan for all molecules tested, especially for solutes with molecular weights over 300 daltons. Thus, they have lower membrane resistance to "middle molecules".

Respective Influence of R_B, R_M, and R_D on Solute Transfer:

The comparative contribution of each of the several resistances differs with membrane format. The greater the degree to which a given format and its resulting flow pattern causes high sheer rates and "turbulent" flow over the membrane, the greater the resultant membrane "scrubbing" effect that occurs, reducing the thickness of the stagnant fluid films and respective contributions to R_O. The larger the solutes, the greater the effect of R_M and the less the collective contributions of R_B and R_D (Henderson , 1983). Data from Babb et.