The physiological response to isovolemic hemodialysis, isolated ultrafiltration and sham-dialysis in healthy man. A short overview

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RESPUESTA FISIOLOGICA A LA HEMODIALISIS ISOVOLEMICA. ULTRAFILTRACION AISLADA Y DIALISIS SIMULADA EN VOLUNTARIOS SANOS

RESUMEN

Los pacientes urémicos pueden presentar diversos grados de neuropatía, miocardiopatía, anemia, desnutrición y otros tipos de complicaciones que pueden modificar la respuesta fisiológica normal del individuo al procedimiento de diálisis. Para valorar adecuadamente estos fenómenos se estudiaron cuatro grupos de sujetos sanos que fueron tratados con diferentes técnicas de diálisis: hemodiálisis isovolémica (IHD), ultrafiltración aislada hipervolémica (hiper IUF) e hipovolémica (hipo IUF) y diálisis simulada (SHD). La IHD se realizó en siete individuos durante ciento veinte minutos con una concentración de acetato en el líquido de diálisis de 40 mmol/l. La hiper IUF se efectuó en ocho casos después de haber infundido previamente una solución de Ringer, equivalente al 3 % del peso corporal, con una tasa de ultrafiltración de 25 ml/min. La hipo IUF se hizo en siete sujetos durante ciento veinte minutos sin infusión previa y con un volumen de ultrafiltrado de 1.000 c.c. En 18 individuos se realizó SHD. La IHD produjo un descenso de las resistencias vasculares periféricas (RVP) que fue compensado por un incremento del índice cardíaco debido a una elevación de la frecuencia cardíaca (FC). Durante ambos procesos de IUF se observó una disminución del volumen plasmático con un descenso del volumen sistólico y del gasto cardíaco sin modificaciones de la FC con tensión arterial estable debido a un incremento de las RVP. Durante la SHD se objetivó una activación del complemento y leucopenia sin hipertensión pulmonar ni hipoxemia. En conclusión, la adaptación cardiovascular a la IUF y a la IHD son fenómenos diferentes y presentan respuestas en direcciones opuestas. Durante la IHD, la tensión arterial depende principalmente de la posición pretratamiento de la curva de Frank-Starling y de la tasa de reposición del volumen plasmá- reducción del volumen plasmático. Una FC mantenida durante la IUF es la respuesta fisiológica normal a una reducción del volumen plasmático. La monitorización de la FC en la IUF carece de utilidad para valorar el grado de deshidratación del individuo.

Palabras clave: ***Biocompatibilidad. Diálisis isovolémica. Diálisis simulada. Hemodinámica. Ultrafiltración aislada.***

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SUMMARY

Uremic patients may have different degrees of neuropathy, cardiomiopathy, anemia, signs of malnutrition, and other adverse effects of uremia, which may modify the physiological response to dialysis. We have performed 4 different studies isovolemic dialysis (IHD), hypervolemic isolated ultrafiltration (Hyper IUF), hypovolemic isolated ultrafiltration 'hypo IUF) and sham-dialysis (SHD) in healthy male volunteers to asses the normal physiological response to these procedures. IHD was performed in 7 subjects during 120 minutes with acetate (40 mmol/l). Hyper IUF in 8 individuals after an infusion of Ringer solution equal to 3 % of the body weight, with a ultrafiltration rate of 25 ml/min. Hypo IUF was performed in 7 subjects during 60 minutes without prior infusion, the total ultrafiltrate volume was one liter. Eighteen healthy volunteers underwent SHD. The IHD provoked a decrease of systemic vascular resistences which was compesated by an increased cardiac index owing to an increment of heart rate. During both the IUF studies the central blood volume decreases and this decreases the stroke volume and cardiac output with no changes in heart rate making blood pressure stability dependent of vasoconstriction. Although SHD induced complement activation and leukopenia neither pulmonary hypertension nor arterial hypoxemia were observed. We may conclude that the cardiovascular adaptation to IUF and isovolemic dialysis with acetate act in opposite directions. During convectional HD these cardiovascular adaptative forces may counteract each other, making blood pressure highly dependent on the pre-treatment position on the Frank-Starling curve and the plasma refilling rate during treatment. An unchanged heart rate during IUF is the normal physiological response to a reduction in the central blood volume. Monitoring of heart rate cannot show whether a subject is becoming moderately underhydrated during IUF. The question whether pulmonary hypertension constitute any real problem during HD in man cannot, so far, be answered.

Key words: ***Biocompatibility. Hemodynamics. Isolated ultrafiltration. Isovolemic hemodialysis.***

Introduction

The dialyzer and the dialysate constitute together with the patient a complex system where incompatibility within the system may result in various symptoms and complications. Factors that may be associated with complications are diffusive transport across the dialyzer membrane, transport of fluid by convection and contact between blood and foreign materials in the tubing set and the dialyzer membrane. Uremic patients may also have different degrees of neuropathy, cardiomyopathy, anemia, signs of malnutrition and other adverse effects of uremia, which may modify the physiological response to dialysis. We have studied isovolemic hemodialysis (IHD), isolated ultrafiltration (IUF) and blood-membrane contact (sham-dialysis) in healthy subjects to assess the normal physiological response to these procedures.

Material and methods

The healthy male volunteers (mean age 27, range 20-39 years) were studied after they gave their informed consent. The investigation was approved by the Ethics Committee of Karolinska Institute at Huddinge University Hospital.

Four different studies were performed where cardiovascular function and blood gases were studied:

A) *Isovolemic hemodialysis (IHD).* Seven subjects were studied during 120 minutes of IHD with acetate (40 mmol/l) as buffer source in the dialysate.

B) *Hypervolemic isolated ultrafiltration (Hyper IUF).* Eight subjects were studied during isolated ultrafiltration after an infusion of Ringer solution equal to three per cent of the body weight. The ultrafiltration rate was 25 ± 2 ml/min.

C) *Hypovolemic isolated ultrafiltration (Hypo IUF).* Seven subjects were studied during one hour of isolated ultrafiltration without prior infusion of any fluid. The ultrafiltration rate was 17 ml/min and the total ultrafiltrate volume was one liter.

D) *Sham-dialysis (SHD).* Eight subjects underwent SHD during 150 minutes and 10 subjects during 30 minutes in order to investigate the effect of the dialyzer membrane on the blood gases, the white blood cell count, the complement system and the cardiovascular function.

IHD and IUF were preceded by a recirculation period of 30 minutes in order to achieve a hemodynamic adaptation to the extracorporeal circulation.

Detailed description of the methods used have been reported elsewhere [1-3]. Right heart catheterization was performed with a Swan-Ganz thermodilution catheter for measurements of pulmonary arterial blood pressure, pulmonary capillary wedge pressure (SHD and Hypo IUF studies), cardiac output and central blood temperature. Arterial blood pressure was recorded through a catheter in a brachial artery.

Blood access was obtained by introducing a catheter into a femoral vein and a needle into a brachial vein. The dialysis monitor was Gambro AK 10 UDM and a cuprophan 1.2 m^2 hollow fiber dialyzer (Gambro 120 M) was used. The blood pump speed was 200 ml/min.

Arterial blood samples were repeatedly collected for determination of plasma acetate and blood gases.

In the SHD study blood for total white blood cell count (WBC) was sampled from the inlet side of the dialyzer every 10 minutes during the first 30 minutes (n = 18) and thereafter every 30 minutes (n = 8). The absolute numbers of the different white cells were calculated. The complement factor C_{3d} (as per cent of a standard, by Brandslund et al's method [4]) in blood from the inlet and the outlet side of the dialyzer, collected every 10 minutes during the first 30 minutes of SHD (n = 10).

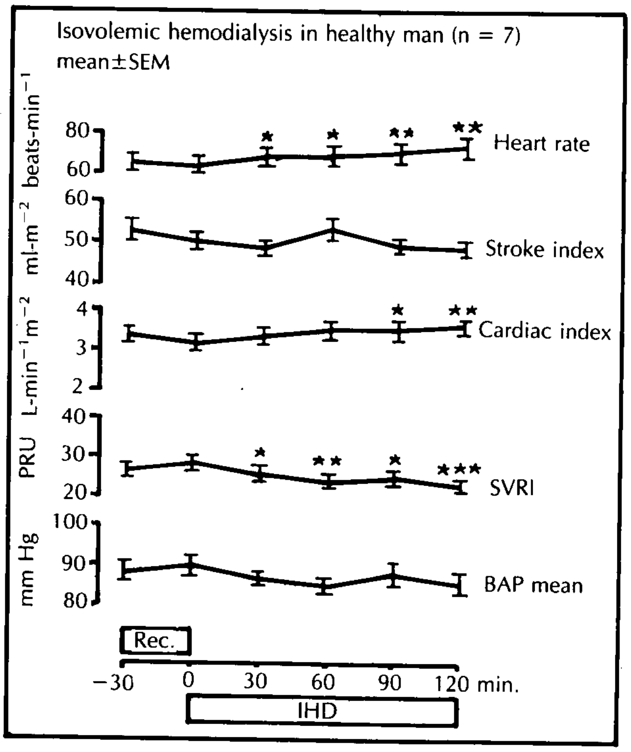

*Fig. 1.—Circulatory data in seven healthy men at start and end of recirculation (=Rec.) (−30 minutes to 0) and during the subsequent 120 minutes of isovolemic hemodialysis (IHD). Asterisks indicate significance in changes between 0-120 minutes. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. SVRI = systemic vascular resistance index. BAP mean = mean brachial arterial blood pressure. Mean ± SE.*

Results and discussion

Isovolemic hemodialysis

IHD in healthy man provokes a dilatation of the vascular system, as the systemic vascular resistance index decreased significantly, which was compensated by an increased cardiac index owing to an increased heart rate, stroke index being unchanged; the blood pressure remaining unchanged (fig. 1). This vascular dilatation was most likely due to the dilatory effect of acetate [5-7], as the plasma acetate increased to 2.51 ± 0.30 mmol/l.

Similar circulatory pattern, as in the IHD study, has also been observed in *uremic patients* during IHD [8, 9], although the blood pressure decreased in some patients, despite isovolemia [8, 10]. The plasma acetate levels during IHD in our healthy subjects were lower than those previously reported in many uremic patients [11-13]. One explanation may be that the normal subjects were healthy young men with a larger lean body mass than most hemodialysis patients. In such patients the steady state arterial acetate concentration is significantly lower in men than in females and it is negatively correlated to body size, suggesting that the size of the lean body mass is of importance for the efficacy of acetate metabolism (Danielsson A, Gutiérrez A, Bergström J, unpublished observations).

There was slight but significant reductions, during IHD, in $PaCO_2$ (decreased by an average of 3.6 mmHg at end of IHD) and plasma bicarbonate (decreased during the first 30 min of IHD by 0.9 mmol/l) with a tendency to a decrease in PaO_2 but no change in pH. This is mainly in agreement with observations within the first 120 minutes of acetate hemodialysis in non-uremic patients treated for schizophrenia [14]. Acetate dialysis in *uremic patients* has yielded more varied results. However, most authors report a decrease in the arterial PO_2 (for a review, see [15, 16]).

Isolated ultrafiltration

During the pre-ultrafiltration infusion, in *the Hyper IUF study,* the pulmonary arterial blood pressure increased by about 50 % and cardiac index and stroke index by 19 % and 16 %, respectively, and at the end of IUF, mainly, returned to the pre-infusion values. During the *Hypo IUF study,* plasma volume decreased by 11 % calculated from changes in total plasma protein. The mean pulmonary capillary wedge pressure and pulmonary arterial blood pressure decreased by 33 and 25 %, respectively. Pulmonary vascular resistance index did not change significantly. At end of IUF heart rate had increased by only 4 ± 1

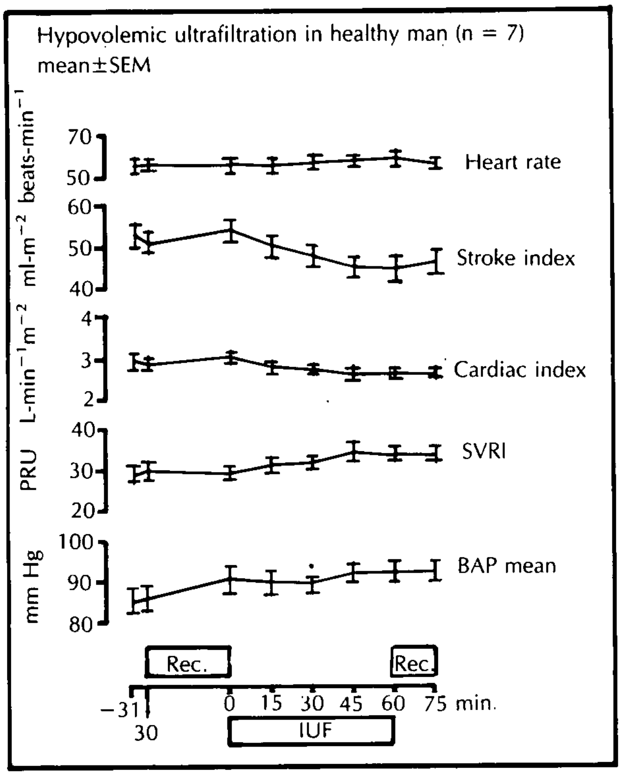

*Fig. 2.—Systemic circulatory data in seven healthy men during the connection of the dialyzer and tubing set to the subjects (−31 to −30 minutes), during recirculation (Rec.) (−30 minutes to 0), the subsequent isolated ultrafiltration of one liter (IUF) (0 to 60 minutes) and in five subjects during post-ultrafiltration recirculation (60 to 75 minutes). Ultrafiltration was performed with the subjects in a normohydrated state at the start of IUF. SVRI = systemic vascular resistance index. BAP mean = mean brachial arterial blood pressure. Asterisks indicate significant changes compared to 0 minutes. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Mean ± SE.*

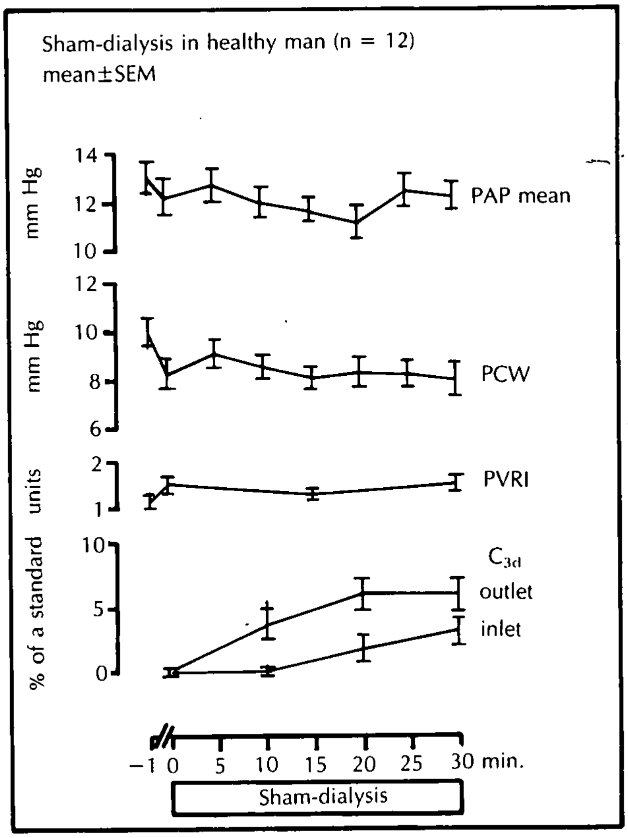

*Fig. 3.—Changes in mean pulmonary arterial blood pressure (PAP mean), mean pulmonary capillary wedge blood pressure (PCW), pulmonary vascular resistance index (PVRI) and complement factor C_{3d} during 30 minutes of sham-dialysis in 12 healthy men. C_{3d}, in plasma from the inlet and the outlet sides of a dialyzer, was measured as per cent of a standard (n = 10). Asterisks indicate significant changes compared with the start (0 min) and between the outlet and the inlet sides of the dialyzer at each point of time. Significant changes in hemodynamics were determined between «−1» and «0» min (during gradual filling of the dialyzer with blood) and between «0» and 5-30 min (n = 12). PAP mean was recorded continuously. * $p < 0.05$, ** $p < 0.01$. Mean ± SE.*

beats per minute ($p < 0.05$), but no significant changes occurred earlier during IUF (fig. 2). During both the IUF studies, the blood pressure was maintained by vasoconstriction which compensated for the falling cardiac output, in turn due to decreasing stroke volume and unchanged heart rate. During IUF the central blood volume decreases and this decreases the stroke volume and cardiac output making blood pressure stability dependent of vasoconstriction. The unchanged heart rate during IUF is obviously a normal physiological phenomenon. An unchanged heart rate has been reported in non-uremic subjects when hypovolemia was induced by experimental hemorrhage [17]. Bergenwald et al. suggested that the unchanged heart rate might be due to a lowering of the set point of the arterial varoreflexes through interaction with baroreceptors in the low pressure region.

The hemodynamic response to IUF in *uremic patients* is characterized by a peripheral vasoconstriction, a constant blood pressure and an unchanged heart rate [8, 18-21]. This absence of heart rate increase in uremic patients has been suggested to be a sign of autonomous neuropathy [20]. However, the present results show that this is also the circulatory response in healthy man. Theoretically, small fluctuations in blood temperature may also contribute to the blood pressure regulation. Maggiore et al. have suggested that the vasoconstriction during isolated ultrafiltration is provoked as a compensation for a falling blood temperature [22, 23] and some evidence for this has also been found in the dog [24]. However, it is not probable that a fall in body temperature contributed to any extent to vasoconstriction in our study, as the blood temperature changes were negligible. Central blood temperature, measured with the Swan-Ganz catheter, was at end of Hyper IUF 0.15 ± 0.05° C lower than before study ($p < 0.05$) and during Hypo IUF temperature was unchanged at end of IUF compared with start of study.

Oxygen tension did not change after overhydration or during the two IUF procedures in uremic patients a decrease in PaO_2 has been reported [25, 26], but unchanged [27] and increased [28] oxygen tensions have also been found.

Sham-dialysis

Both in the IHD and Hyper/Hypo IUF studies we have purposely used a recirculation period before the effect of dialysis (diffusive transport) or ultrafiltration (convective transport) were studied, considering that most membrane-related events occur during the first 30 minutes of blood-membrane contact [29]. However, it was important to clarify the effects of blood-membrane interaction during the first 30 minutes of blood-membrane contact, as pulmonary hypertension has been reported after the injection of cuprophan-incubated plasma in the sheep [30] and during cuprophan sham-dialysis in patients with chronic uremia [31].

During 150 minutes of SHD heart rate, stroke index, cardiac index, systemic vascular resistance index and brachial and pulmonary arterial blood pressures remained unchanged. In the 12 subjects in whom more frequent measurements were made during the first 30 minutes of SHD the only essential hemodynamic changes were in response to the reduction in the intravascular blood volume during the filling of the extracorporeal circuit with blood (fig. 3).

In the SHD study the release of complement factor C_{3d}, as well as marked leukopenia, was detected early after the beginning of sham-dialysis. After 10 minutes of blood-membrane contact the C_{3d} level in the outlet blood of the dialyzer had increased significantly, compared to the initial value and to the concentration of the inlet blood at 10 minutes. Thirty minutes after the start of SHD the C_{3d} level had increased significantly in the inlet blood, but there was still a significant difference in the C_{3d} concentration between the inlet and the outlet blood in the dialyzer (fig. 3).

Total white blood cell count (WBC) decreased by 57 % during the first 20 minutes of SHD and reached after 20 minutes $2.3 \pm 0.2 \times 10^9$/liter ($n = 18$, $p < 0.001$). Thereafter, WBC increased to $6.7 \pm 0.5 \times 10^9$/liter at 150 minutes — i.e., a 35 % higher value than at the start ($n = 8$, $p < 0.05$). The significant decrease in WBC during the first 20 minutes of blood-membrane contact was due to a significant fall in segmented neutrophils, eosinophils, lymphocytes and monocytes by 83 ($p < 0.001$), 49 ($p < 0.01$), 13 ($p < 0.05$) and 76 ($p < 0.05$) per cent, respectively ($n = 18$). The various white blood cells then rose to basal values ($n = 8$). The leukopenia was of the same magnitude as that observed in uremic patients during cuprophan dialysis. The changes in differential counts of leukocytes were about the same as those observed in hemodialysis patients [29, 32-34]. The fall in monocytes suggests that monocyte activation occurred, which may be attributed to C_{5a} binding [35] or to the effect of pyrogens from foreign materials and fluids. Monocyte activation may result in the release of interleukin-1 [36] which, according to a proposed hypothesis, may be an important factor in the development of cardiovascular instability and hypotension [37]. However, no such reactions were observed in our healthy subjects.

Although SHD induced complement activation and leukopenia as in uremic patients, neither pulmonary hypertension nor arterial hypoxemia were observed in our healthy subjects. These results contrast with the observation by Schohn et al that cuprophan sham-dialysis in chronic uremic patients increases the pulmonary arterial pressure [31]. Patients with chronic uremia may be more prone to develop an increase in pulmonary arterial pressure and pulmonary hypertension for several reasons. One reason may be the pre-existing over hydration with pulmonar congestion at the start of dialysis. It is also possible that repeated contact with the dialyzer may increase the tendency to pulmonary vasoconstriction. Moreover, it cannot be excluded that the pulmonary response to complement activation might be enhanced by the uremic intoxication or via some other mechanism. That pulmonary hypertension is not an invariable response to dialysis in patients with uremia was shown by Walker et al.[38], who found that the pulmonary arterial pressure increased in only 3 of 7 patients with acute renal failure.

Species differences

Several studies have been performed using anesthetized and often mechanically ventilated *uremic or non-uremic animals.* Both when acetate is administered as an infusion or administered during isovolemic hemodialysis by diffusion the animals present falling blood pressure [39-44] at variance with our healthy subjects during IHD. Isolated ultrafiltration in dogs has resulted in increased heart rate [45] which is contrary to our findings in healthy man. The normal pulmonary vascular resistance found during our SHD study is in contrast with Walker et al's findings that, in the sheep, cuprophan-incubated plasma induces pulmonary hypertension and hypoxemia [30]. Differences between species may be of importance, it is known that sheep develop pulmonary hypertension during the infusion of complement-activated plasma, whereas rabbits do not [46]. Because of species differences and the experimental procedures including anesthesia and artificial ventilation results of animal studies should interpreted with caution and may not be entirely relevant for experimental and clinical situations in man.

Conclusion

We conclude that the cardiovascular adaptation to isolated ultrafiltration and isovolemic hemodialysis with acetate act in opposite directions. During conventional hemodialysis these cardiovascular adaptive forces may counteract each other, making blood pressure highly dependent or the pre-treatment position on the Frank-Starling curve and the plasma refilling rate during treatment [47]. An unchanged heart rate during ultrafiltration is the normal physiological response to a reduction in the central blood volume. Monitoring of heart rate cannot show whether a subject is becoming moderately underhydrated during isolated ultrafiltration. The question whether pulmonary hypertension constitute any real problem during extracorporeal treatment in man cannot, so far, be answered.

Acknowledgements

These studies were supported by grants from the Karolinska Institute, the Swedish Society of Medicine and Gambro AB, Lund, Sweden. We are grateful to Ingrid Witikainen, RN, and Ellen Bauge, RN, and her staff for technical assistance.

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