

Effects of Low Chloride versus High Chloride Infusion on Glomerular Filtration Rate and Renal Plasma Flow in Healthy Volunteers—A Randomized, Controlled, Crossover Study

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Abstract

Background: Previous studies have shown that chloride liberal fluids may be associated with worse renal outcomes. Deterioration of kidney function during hyperchloremia/chloride overload is believed to be induced by disturbances in renal perfusion, but exact mechanisms of chloride nephrotoxicity are unclear. The purpose of this randomized, crossover study was to investigate the effect of chloride loading on renal plasma flow (RPF), filtration fraction (FF) and glomerular filtration rate (GFR) in order to elucidate potential nephrotoxic mechanisms of chloride infusion. **Methods:** Fifteen healthy males were investigated twice after treatment with 2L isotonic saline and plasma-lyte with a wash-out period of at least 10 days. Within 15 mins after completion of infusion, the kidney parameters (RPF, FF and GFR) were estimated by Technetium-99m diethylenetriamine penta-acetic acid (99-mTc-DTPA) renography. **Results:** 99-mTc-DTPA renography showed reduction in both mean GFR (114 ± 13 ml/min vs. 119 ± 12 ml/min, $p = 0.04$) and RPF (977 ± 272 ml/min vs. 1066 ± 197 ml/min, $p = 0.19$) and increasing FF ($12\% \pm 2\%$ vs. $11\% \pm 2\%$, $p = 0.19$) after 0.9% saline comparing to Plasma-lyte, but only GFR reduction was statistically significant. Reduction in GFR and RPF and increasing in FF after 0.9% saline was observed in 10 subjects while in 5 others the reverse trend was shown. There were no statistically significant differences between mean systolic and diastolic blood pressure (BP) before and after each infusion except baseline diastolic BP. Weight changes (Δ weight)

were similar after each infusion. **Conclusions:** We have demonstrated that high chloride infusion can affect kidney function in healthy subjects and seems to lead to impairment in both RPF and GFR.

Keywords

Chloride Nephrotoxicity, Renal Plasma Flow, Glomerular Filtration Rate, Renography

1. Background

Fluid therapy is widely used in critically ill patients and surgical patients treated in intensive care units (ICU), but the choice of fluid remains controversial. Isotonic sodium chloride with chloride concentration of 154 mmol/l is the most commonly used crystalloid in ICU. Some studies indicate that chloride overload secondary to large infused volumes of saline leads to hyperchloremia and metabolic acidosis [1] [2]. Both human and animal studies show that hyperchloremia in turn is associated with decreased renal perfusion [3] [4] [5] [6] [7], impaired immune function [8] [9] and increased mortality [10]. Many observational studies show that use of chloride restrictive fluids may be associated with better renal outcomes [11] [12] [13] and decreased risk of death [14] [15] compared with chloride liberal regimes. Large randomized controlled trials show conflicting results [16] [17] [18].

In the light of existing data, deterioration of kidney function during hyperchloremia/chloride overload is believed to be induced by disturbances in renal perfusion, but exact mechanisms of chloride nephrotoxicity are unclear. The purpose of our study was to investigate the effect of chloride loading on renal plasma flow (RPF), filtration fraction (FF) and glomerular filtration rate (GFR) in order to elucidate potential nephrotoxic mechanisms of chloride infusion. We designed a randomized, crossover study to compare the effects of intravenous infusion of 0.9% saline and Plasma-Lyte on kidney function in healthy subjects using ^{99m}Tc-DTPA gamma-camera renography. Renography with ^{99m}Tc-DTPA allows simultaneous measurements of RPF, FF and GFR [19] [20]. We aimed to determine whether chloride loading related to use of 0.9% saline (chloride concentration = 154 mmol/l) would affect renal hemodynamic parameters compared to Plasma-lyte (chloride concentration = 98 mmol/l).

2. Materials and Methods

2.1. Study Design

The trial was performed as a randomized, crossover study in healthy subjects. Study intervention was blinded for observers who evaluated renography. Fifteen healthy males were investigated twice after treatment with 2 L isotonic saline and plasma-lyte with a wash-out period of at least 10 days.

2.2. Randomization

Subjects were randomized to treatment using block randomization conducted at <http://www.randomization.com/>. There was equal probability to receive 0.9% saline or Plasma-lyte on the first study visit.

2.3. Recruitment

Healthy volunteers were recruited by advertising in public institutions and private companies in period 1 April 2015 to 31. January 2016.

2.4. Subjects

Inclusion criteria

Healthy, adult male volunteers between 18 and 45 year, with BMI between 18.5 - 30 kg/m.

Exclusion criteria

Arterial hypertension (blood pressure 140 mmHg systolic and/or >90 mmHg diastolic), history or clinical signs of neoplastic disease or disease of the heart, lungs, kidneys or endocrine organs, drug or alcohol abuse (*i.e.* >14 units a week), significant abnormalities in laboratory screening test (*i.e.* abnormal hemoglobin, white cell count, plasma sodium, plasma potassium, plasma creatinine, plasma alanine aminotransferase, serum cholesterol, plasma bilirubin and plasma albumin, and urine samples (*i.e.* albuminuria or glucosuria), abnormal electrocardiogram.

Withdrawal criteria were development of one or more of the exclusion criteria or lack of compliance.

2.5. Effect Variables

Glomerular filtration rate (GFR), renal plasma flow (RPF) and filtration fraction (FF) obtained by ^{99m}Tc-DTPA renography.

2.6. Number of Subjects

Fifteen healthy subjects were included. The sample size was calculated based on a minimally relevant difference in renal plasma flow (RPF) of 50 ml/min (about 10%) and expected standard deviation of 67 ml/min [19], $\alpha = 5\%$, $\beta = 20\%$.

2.7. Treatment Intervention

0.9% Sodium chloride Baxter A7S and Plasma-lyte Baxter A/S were provided by Herning Hospital Pharmacy (Table 1).

2.8. Ethics

This study was approved by The Central Denmark Region Committees on Healthy Research Ethics (case number: 1-16-02-264-15). The study was conducted in accordance with principles of declaration of Helsinki. Written informed consent was obtained from all subjects.

Table 1. Characteristics of the 2 crystalloid infusions.

	0.9% saline	Plasma-lyte 148
Sodium (mmol/L)	154	140
Chloride (mmol/L)	154	98
Potassium (mmol/L)	-	5
Magnesium (mmol/L)	-	1.5
Acetate (mmol/L)	-	27
Gluconate (mmol/L)	-	23
Strong ion difference	0	50
pH	5.4	7.4
Theoretical osmolarity (mOsm/L)	308	294.5
Total solute weight (g/L)	9	14.6
Na: CL ratio	1:1	1.43:1

2.9. Interventions/Experimental Procedure

The study took place at The University Clinic of Nephrology and Hypertension, and Dept. of Nuclear Medicine, Regional Hospital West Jutland, Denmark in period 1, April 2015 to 31, January 2016. Participants met at 7.30 hours following a fast from midnight, after having abstained from alcohol and caffeine (24 hours). They did not eat or drink for the duration of the study. After voiding, height, weight and blood pressure was measured. After randomization, two 1-L bags of 0.9% saline or Plasma-Lyte 148 (**Table 1**) were infused over 1 hour using 2 MRI-compatible infusion pumps (Cardinal Health, Asena GW). Measurements of body weight and blood pressure were repeated at the end of the infusion. Within 15 min after completion of infusion, the renography was initiated. Participants were permitted to void as needed and, in all cases, at the end of infusion before and after the renography. The time of each micturition was noted, and urine volume after renography was measured.

2.10. Measurements/Renography Protocol

The kidney parameters (RPF, FF and GFR) were estimated from renographies obtained by a single-headed gamma camera (Bodyscan; MiE medical imaging electronics, Seth, Germany) in the posterior position over the lower thoracic/upper abdominal area with the patient in the supine projection. At the time of the bolus injection (6 MBq Tc99m-diethylenetriaminepentaacetic acid (DTPA)/kg bodyweight in a cubital vein), a dynamic acquisition was initiated (1 frame per second in the first minute and 1 frame per every 10 seconds during the subsequent 20 minutes).

Data processing was performed in the commercial software MEDIC 2000 XP, ver. 5.9.1. GFR, FF and RPF were calculated for each kidney separately and the single-kidney results summarised to create the total renal parameters.

The clearance of DTPA approaches GFR because the tracer is excreted almost

exclusively by free filtration. Hence, single-kidney GFR was calculated from the uptake index in each kidney 60 - 120 seconds after the bolus injection using a modification of the Rutland-Patlak method [20].

RPF was calculated as the ratio of GFR, determined as described above, and FF of DTPA estimated from the first passage through the kidney approximately 10 - 45 seconds after the bolus injection. In this time interval, the software estimated FF by comparing the background corrected kidney activity with the calculated activity from the convolution integral, minimizing the sum of squared differences using an iterative approach. The analyses were performed by two nuclear medicine physicians blinded to knowledge of whether the patient had received Saline or Plasmolyte.

2.11. Statistics

Students paired *t* test was used to compare the two groups, with significant difference at $P < 0.05$. We performed statistical analyses by using IBM SPSS statistics version 20.0.0 (SPSS Inc., Chicago, IL, USA) and STATA statistical software.

3. Results

3.1. Demographics

Fifteen males with a median age of 26 year (range 18 - 46 years), body mass index of $24.5 \pm 3 \text{ kg/m}^2$, P-creatinine of $82 \pm 8 \text{ }\mu\text{mol/L}$, office systolic BP of $130 \pm 9 \text{ mmHg}$ and diastolic BP of $68 \pm 7 \text{ mmHg}$ completed the study. P-potassium was $3.8 \pm 0.2 \text{ mmol/L}$, P-sodium $140 \pm 3 \text{ mmol/L}$ and hemoglobin $9.5 \pm 8 \text{ mmol/L}$. All had normal renograms. None reported adverse effects.

3.2. Changes in Body Weight and Blood Pressure

There were no statistically significant differences between mean systolic and diastolic blood pressure (BP) before and after each infusion except baseline diastolic BP. Weight changes (Δ weight) were similar after each infusion (Table 2).

3.3. Renal Parameters

Mean glomerular filtration rate GFR, renal plasma flow (RPF) and filtration fraction (FF):

⁹⁹mTc-DTPA renography showed reduction in both mean GFR ($114 \pm 13 \text{ ml/min}$ vs. $119 \pm 12 \text{ ml/min}$, $p = 0.04$) and RPF ($977 \pm 272 \text{ ml/min}$ vs. $1066 \pm$

Table 2. Body weight and blood pressure baseline and after intervention.

Intervention	Mean BP baseline (mmHg)		Mean BP after (mmHg)		Mean weight baseline (kg)	Mean weight after (kg)	Δ weight (kg)
	Systolic	Diastolic	Systolic	Diastolic			
Plasma-lyte	131 ± 9	70 ± 8	125 ± 7	66 ± 6	82 ± 14	83.3 ± 15	1.9 ± 0.4
0.9% saline	129 ± 11	66 ± 7	126 ± 8	66 ± 8	82.1 ± 14	83.1 ± 14	1.9 ± 0.2
P value	0.11	0.023	0.46	0.89	0.93	0.46	0.96

197 ml/min, $p = 0.19$) and increasing FF ($12\% \pm 2\%$ vs. $11\% \pm 2\%$, $p = 0.19$) after 0.9% saline comparing to Plasma-lyte, but only GFR reduction was statistically significant (**Table 3**).

Changes in GFR, RPF and FF after 0.9% saline versus Plasma-lyte in each subject.

Figures 1-3 show individual changes in GFR, RPF and FF after 0.9% saline and Plasma-lyte respectively. Reduction in GFR and RPF and increasing in FF after 0.9% saline was observed in 10 subjects while in 5 others reverse trend was shown.

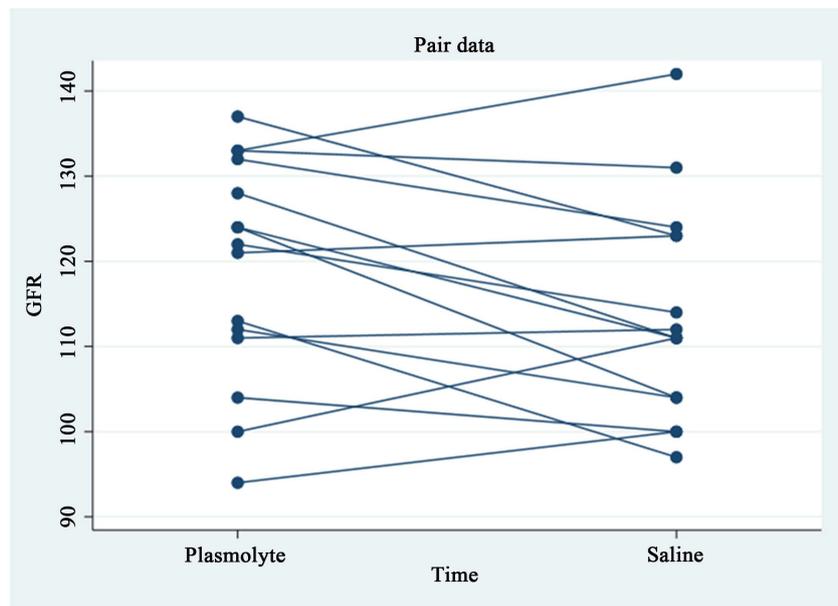


Figure 1. Changes in GFR after 0.9% saline versus Plasma-lyte in each subject.

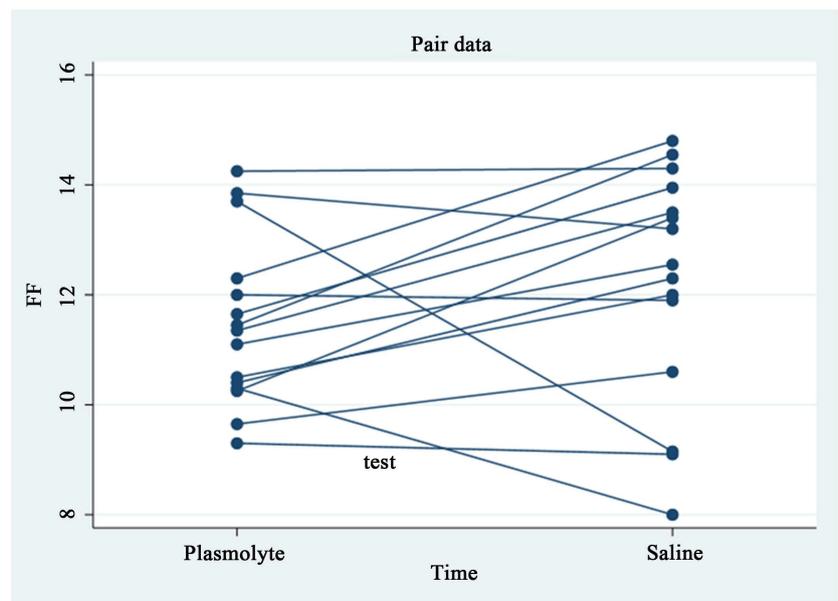


Figure 2. Changes in FF after 0.9% saline versus Plasma-lyte in each subject.

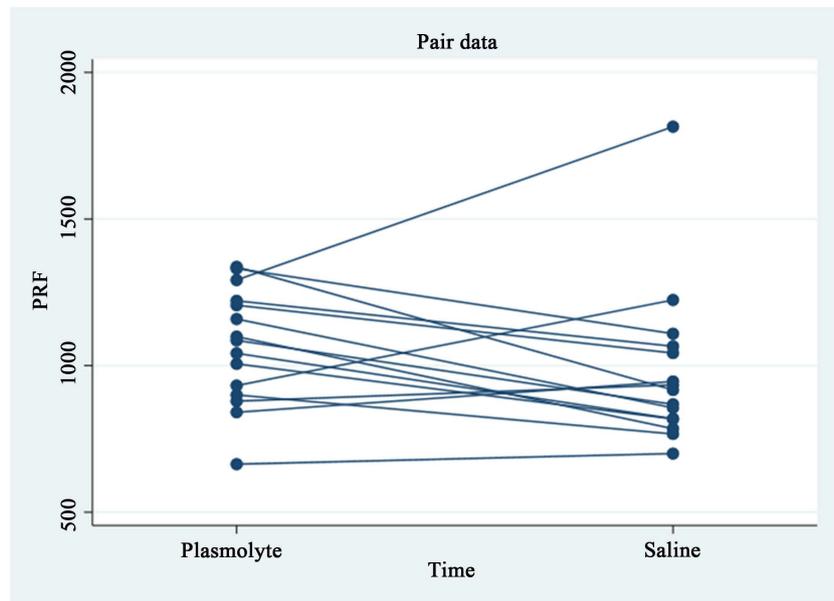


Figure 3. Changes in RPF after 0.9% saline versus Plasma-lyte in each subject.

Table 3. Mean glomerular filtration rate GFR, renal plasma flow (RPF) and filtration fraction (FF) after Plasma-lyte and 0.9% saline.

	Plasma-lyte (n = 15)		0.9% saline (n = 15)		
	Mean	SD	Mean	SD	
GFR (ml/min)	119	12	114	13	P = 0.04
RPF (ml/min)	1066	197	977	272	P = 0.19
FF (%)	11	2	12	2	P = 0.19

The inter- and intra-assay variation coefficient for GFR, RPF and FF.

The inter- and intra-assay variation coefficient was calculated as $SD/X * 100$ where X is mean value of GFR, RPF and FF and SD denotes standard deviation. The inter-assay variation coefficient for GFR was 10% after Plasma-lyte and 11% after 0.9% saline; for RPF was 18% after Plasma-lyte and 28% after 0.9% saline; for FF was 18% after Plasma-lyte and 24% after 0.9% saline.

4. Discussion

We found a slight, but significant, impairment in GFR after saline-infusion compared to Plasmolyte. The impact of saline on FF and RPF are not significant but apart from two outliers there is a tendency. Our findings support the existing data that the chloride overload from 0.9% saline infusion, affects renal hemodynamics and may have negative effect on renal function. Such a hypothesis has been suggested in previous animal and human studies.

In the 1980s Wilcox *et al.* [4] have shown that intrarenal infusion of chloride solution (0.9% saline, NH_4Cl) in dogs led to decreased renal plasma flow and GFR because of renal chloride-induced vasoconstriction. Another study demonstrated that lowering the luminal chloride concentration reduced renal vascular

responsiveness to angiotensin II, vasopressin and phenylephrine in rats [21]. A later study conducted by a Danish group in rabbits has also indicated that in the absence of chloride, the vasoconstrictive effects of angiotensin II and potassium were abolished [5] and that K-induced contraction of smooth muscle cells in the renal afferent arteriole is strongly chloride-dependent [6]. Some data indicate that chloride transport through macula densa is involved in tubuloglomerular feedback and increased chloride delivery to the distal nephron leads to decreased GFR [22]. Furthermore chloride infusion may induce vasoconstriction related to thromboxane release [7]. Altogether these data indicate an essential role of chloride in regulation of vascular resistance (primary afferent arteriole) and renal microcirculation and suggest that disturbances in chloride balance can affect kidney function.

The negative effect of chloride overload in the form of 0.9% saline infusion on kidney hemodynamics has been confirmed by human studies. In healthy volunteers intravenous infusion of 0.9% saline results in hyperchloremia and unfavorable changes in renal cortical perfusion measured using magnetic resonance imaging compared to Plasma-lyte [3].

Our study results from healthy volunteers are in line with the negative effect of Chloride on kidney function as we detected a significant decrease in glomerular filtration rate and a subtle decrease in renal plasma flow after 0.9% saline infusion compared to Plasmolyte. The non-significant results for RPF rely on the two subjects in whom RPF increased excessively after Saline (**Figure 3**). This paradoxical response could not be explained technically, but may very well reflect the sensitive but indirect, and therefore quite imprecise estimation of RPF. Exclusion of those two subjects from statistical analysis rendered the changes in RPF highly significant ($p = 0.002$). Furthermore, the lack of significant drop in RPF after 0.9% saline could be due to too few study subjects as the SD for RPF used in the power calculation was much lower than observed in the study. Another issue that may affect results of our study is differences in the intra-assay variation for RPF of 18% after Plasma-lyte versus 28% after 0.9% saline. This reflects the sensitive but imprecise estimates of quantitative data from renography.

Despite these preclusions, our results support the hypothesis that using low chloride fluids could be associated with more favorable renal outcomes. We were focused on changes in GFR, FF and RPF and did not measure biochemical parameters during the study. Hence, the mechanism by which chloride affects renal haemodynamics cannot be elucidated further from our data.

It should be clarified that, as the study subjects were healthy males, the conclusion is limited to this population and may not be directly extrapolated to critically ill patients or females.

The importance of these findings in clinical practice remains unclear. Observational studies have shown that the use of chloride-restrictive intravenous fluid strategy was associated with better renal outcomes in critically ill and surgical patients [11] [12] [13] [23] although large randomized controlled trials show conflicting results. The SPLIT study [16] did not show significant decrease in the

incidence of acute kidney injury after 0.9% saline infusion versus Plasma-lyte among patients in the intensive care unit. On the contrary, a recent, randomized study (SMART) have shown that use of balanced crystalloids (Plasma-lyte og lactated Ringer's solution) as intravenous fluid treatment had favorable effect on the composite outcome of death and major adverse kidney events compared with 0.9% saline in critically ill patients [17]. Published at the same time, SALT-ED study in patients hospitalized outside an ICU has demonstrated results consistent with SMART study [18]. The conclusions from large clinical studies are not equivocal, however, and it should be pointed out, that the studies were heterogeneous both regarding patient populations and the interventions, especially infused fluid volumes, which may significantly affect the results.

Strengths and Limitations

The major strength of the study is the strong study design (randomized, crossover-controlled, single-blind trial). Only men were included to eliminate sex differences.

Furthermore, the study conditions were standardized regarding food and water intake, coffee and alcohol consumption to avoid any confounding of the results. The crossover design minimizes the effect of other confounders such as smoking and anatomical conditions.

Ideally, renal haemodynamics should be measured from infusion techniques with double isotope technique with suitable tracers for GFR and RPF. Such a set up was not accessible in our institution at that time. DTPA fulfills the criteria for GFR measurements, but the use of this tracer to calculate RPF is cumbersome and imprecise which is reflected in the large SD intervals. The absolute calculated RPF values must be interpreted with precaution, but due to the cross-over design inter-individual variations are eliminated.

5. Conclusion

We have demonstrated that high chloride infusion can affect kidney function in healthy subjects and seems to lead to impairment in both RPF and GFR. Our results are consistent with previous preclinical and observational data. The clinical relevance of these observations in patients is unclear, especially in the light of recent large randomized controlled trials.

Further studies are needed to clarify this issue.

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Ethics Approval and Consent to Participate

This study was approved by The Central Denmark Region Committees on Healthy Research Ethics (case number: 1-16-02-264-15). The study was con-

ducted in accordance with principles of declaration of Helsinki. Written informed consent was obtained from all subjects.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and analysed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no competing interests.

Author's Contributions

All authors have contributed to the publication. A. E. Oczachowska-Kulik, M.H. Malmberg, J. J. Jensen and J. N. Bech designed the project. A. E. Oczachowska-Kulik and M.H. Malmberg performed the experiments. A. E. Oczachowska-Kulik, J. J. Jensen and J. A. Ejlersen performed laboratory analysis. A. E. Oczachowska-Kulik and J. A. Ejlersen performed statistical analysis. A. E. Oczachowska-Kulik, J. A. Ejlersen and J. N. Bech wrote and edited the manuscript.

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List of Abbreviations

BP: Blood Pressure, eGFR: estimated Glomerular Filtration Rate, RPF: Renal Plasma Flow, FF: Filtration Fraction, 99-mTc-DTPA: Technetium-99m Diethylenetriamine Penta-Acetic acid, SD: Standard Deviation.