THE ROLE OF HYPEROSMOLALITY AND HEMODYNAMIC ALTERATIONS IN RADIOCONTRAST NEPHROPATHY

Naci DUMAN, M.D., Aytül NOYAN, M.D., Ali ANARAT, M.D., Ayşe DOĞAN*, M.D., Rüksan ANARAT**, M.D.

Çukurova University, Faculty of Medicine, Department of Pediatric Nephrology and Physiology* Adana, Turkey
Düzen Laboratories Adana, Turkey
Gazi Medical Journal 7 : 67-71, 1996

SUMMARY : In the present study we determined the hemodynamic parameters that are formed in rats with reduced renal mass (70-75 %) when radiocontrast material, hypertonic and isotonic solutions are infused. The rats from all three groups had statistically the same indirect blood pressures prior to nephrectomy and after the nephrectomy the indirect blood pressure levels increased to the same level in all three groups. For all three groups the pulse rates exhibited no change after the nephrectomy. The direct blood pressure values obtained from the transducer in the A. Femoralis were same for all three groups. During the infusion the direct systolic and diastolic blood pressures of the rats that received radiocontrast material and 4.5 % NaCl exhibited statistically significant drops and lasts for three to five minutes. After the infusion, the BUN and serum creatinine levels of group that received radiocontrast material were significantly higher than that of the other groups. Consequently we can emphasize that hyperosmolality and the associated hemodynamic changes are not directly responsible for contrast associated nephropathy.

***Key Words :** Radiocontrast Nephropaty, Hemodynamic Changes.*

INTRODUCTION

Contrast nephropathy can be defined as an acute impairment of renal function that follows exposure to radiocontrast materials and for which alternative explanations for renal impairment have been eliminated (2). The incidence of contrast associated nephropathy (CAN) varies from 0 to 22 % based on several studies (6, 15, 16). This wide variation can be traced to differences in design among studies as well as differences in criteria for significant renal impairment. Recently, CAN, the third most common cause of hospital acquired renal insufficiency, is getting increased and estimated that these agents are responsible for 12 % of the cases of hospital acquired acute renal failure (10). Whether the incidence of CAN is reduced with non-ionic agents remains contrversial (5, 9). It was proposed that interference with renal perfusion, altered perm-selectivity, direct tubular injury, intraluminal obstruction and immunological mechanisms are responsible for the etiopathogenesis of CAN; however none has been achieved universal acceptance (2, 11, 14, 17, 19). Recently, it has been reported that endothelin excretion and concentration were elevated after radiocontrast infusion (8).

In the present study we studied the hemodynamic parameters that are formed in rats with reduced renal mass (70-75 %) when radiocontrast material, hypertonic and isotonic solutions are infused.

MATERIALS AND METHODS

Animals : 35 male Wistar Albino rats were

employed. All rats fed with normal rat chow (containing 0.2 % Na) and tap water for 1 week prior to the study. During this period, the rats were housed in five or six to a cage at room temperature and were subjected to 12 hr light / dark cycles. After this period indirect blood pressures, pulses and weights of all rats were measured. Rats weighing between 280-400 gr were anesthetized with ketamine (130 mg / kg BW) and right total, left 50 % nephrectomy was performed. After this operation, the rats were kept under observation for six to eight weeks, at the end of the period which the experiments described below were performed.

Experimental Procedure : The rats were anesthetized with 50 mg / kg sodium pentobarbital and subjected to tracheostomy, during which V. jugularis, V. Femoralis and A. Femoralis were catheterized. 0.9 % NaCl was infused into the V. Jugularis at the rate of 0.02 ml / min by a Cole - Palmer infusion pump to prevent insensible loss. The drug with its vehicle was infused from the V. Femoralis and subsequently blood samples were drawn by the same way. The catheter in the A. Femoralis contained a pressure transducer that was used monitoring the systolic and diastolic pressures in real time. In addition, the urinary bladder was also catheterized by suprapubic incision to collect urine samples.

After the operation, the arterial pressure was monitorized continously until stabilisation period (30-45 minutes). At this point the rats were randomly separated into three groups. Group I rats were infused with 8.9 ml / kg (or 2.9 gr of iodine / kg of body weight) Na diatrizoate (Urovision, 1500 mosm / kg). Group II rats were infused with 0.9 % NaCl in an equal volume with radiocontrast material. Group III rats (the control group) were given 4.5 % NaCl that was in same volume and osmolality with radiocontrast material. Two hours after the drug infusions, blood and accumulated urine samples were collected from all the rats and tested for BUN, creatinine, uric acid, electrolytes, calcium and phosphorus in the laboratory. For all cases, the mean standart deviations were calculated and compared using the Student's test.

RESULTS

The following observations were obtained;

1) The rats from all three groups had statistically the same indirect blood pressures prior to nephrectomy ($p > 0.05$). After the nephrectomy the indirect blood pressure level increased to the same level in all three groups ($p > 0.05$). When compared the indirect blood pressure levels of the three groups before and after nephrectomy, there is a statistically significant increase in groups after nephrectomy ($p < 0.001$) (Table 1).

2) For all three groups the pulse rates exhibited no change after the nephrectomy and were statistically equal ($p > 0.05$) (Table 2).

3) The direct blood pressure values obtained by using the transducer in the A. Femoralis after the stabilisation period were same for all three groups for both systolic ($F = 0.019$, $p > 0.05$) blood pressu-

Group	Prior to nephrectomy* (mm Hg)	After the nephrectomy** (mm Hg)	t	p
I	110.0 ± 6.3	168.3 ± 14.7	14.15	< 0.001
II	109.5 ± 6.0	167.5 ± 15.7	11.02	< 0.001
III	106.0 ± 5.2	170.5 ± 10.1	17.96	< 0.001

* The rats from all three groups had statistically the same indirect blood pressures prior to nephrectomy (ANOVA) ($F=1.53$, $p> 0.05$).
** After the nephrectomy the indirect blood pressures increased to the same level in all three groups (ANOVA) ($F=0.126$, $p> 0.05$).

Table 1 : Mean indirect blood pressures prior to nephrectomy and 6-8 weeks after nephrectomy.

Group	Prior to nephrectomy*	After the nephrectomy**	t	p
I	320.0 ± 24.5	333.0 ± 14.1	1.78	> 0.05
II	327.0 ± 22.1	337.5 ± 17.7	1.17	> 0.05
III	324.0 ± 12.6	334.5 ± 22.4	1.29	> 0.05

* The rats from all three groups had statistically the same pulse rates prior to nephrectomy (ANOVA) ($F=0.34$, $p> 0.05$).
** After the nephrectomy the pulse rates increased to the same level in all three groups (ANOVA) ($F=0.192$, $p> 05$).

Table 2 : Mean pulse rates prior to nephrectomy and 6-8 weeks after the nephrectomy.

res, indicating that this factor did not depend on the drug / vehicle combinations used (Table 3 and 4).

4) During the infusion the direct systolic and diastolic blood pressures of the rats that received radiocontrast material (Group I) and 4.5 % NaCl (Group III) exhibited statistically significant drops ($p < 0.001$) (Table 3 and 4). Three to five minutes after the infusion period ended, these values increased to their pre-infusion levels. No statistically significant changes were observed in the systolic or diastolic blood pressures of the Group II rats ($p > 0.05$).

5) For Groups I and III, the pulse rates exhibited no corresponding changes during the infusion and were statistically equal to those of the Group II rats (Table 5).

6) After the infusion, the BUN levels of Group I (68.5 ± 46.1 mg / dl) and Group III (47.8 ± 14.1 mg / dl) were statistically equal. Both of these levels were higher than that of Group II (39.9 ± 5.6 mg / dl) ($p < 0.05$).

7) After the infusion, the serum creatinine (Scr) levels of Group I (0.17 ± 0.13 mg / dl) were significantly higher than that of Group II (0.94 ± 0.30 mg / dl) and Group III (0.97 ± 0.43 mg / dl) ($t = 2.53$ and $t = 2.25$ respectively, $p < 0.05$).

8) After the infusion, the creatinine clearence (Ccr) levels of Group I (0.17 ± 0.13 ml / min) were statistically lower than that of Group II (0.37 ± 0.28 ml / min) ($t = 2.12$, $p < 0.05$) but equal with Group III (0.25 ± 0.19 ml / min) ($t = 1.15$, $p > 0.05$).

9) After the infusion, the urinary protein levels of Group I (1.61 ± 0.01 mg / h) were significantly higher than Group II (0.84 ± 0.34 mg / h) ($p < 0.05$), but there wasn't a statistically significant difference

Group	Prior to infusion SBP (mmHg)* X ± SD	During the infusion SBP (mmHg) X ± SD	After the infusion SBP (mmHg)** X ± SD
I	174.7 ± 22.4	107.0 ± 26.0	177.3 ± 25.2
II	169.0 ± 17.9	180.5 ± 18.9[a]	181.5 ± 20.1
III	172.5 ± 24.7	122.5 ± 18.4	174.5 ± 23.6

* The difference of the SBP levels of the groups were insignificant (ANOVA) ($F=0.199$, $p> 0.05$).
** After the infusion the difference of the SBP levels of the groups were insignificant (ANOVA) ($F=0.22$, $p> 0.05$).
a During infusion mean SBP levels of the group II were significantly higher than group I and group II ($t= 8.18$, 6.95 respectively and $p<0.001$).

Table 3 : Mean systolic blood pressures of the groups prior, during and after the radiocontrast infusion.

Group	Prior to infusion DBP (mmHg)* X ± SD	During the infusion DBP (mmHg) X ± SD	After the infusion DBP (mmHg)** X ± SD
I	104.7 ± 22.7	51.7 ± 20.8	102.7 ± 25.2
II	103.0 ± 15.4	104.5 ± 20.5[a]	105.5 ± 22.5
III	106.5 ± 22.7	67.0 ± 15.1	108.0 ± 19.6

* The difference of the DBP levels of the groups were insignificant (ANOVA) ($F=0.019$, $p> 0.05$).
** After the infusion the difference of the SBP levels of the groups were insignificant (ANOVA) ($F=0.16$, $p> 0.05$).
a During infusion mean SBP levels of the group II were significantly higher than group I and group II ($t= 6.27$, $p<0.001$ and $t= 3.83$, $p<0.01$) respectively and $p<0.001$).

Table 4 : Mean diastolic blood pressures of the groups prior, during and after the radiocontrast infusion.

Group	Prior to infusion* X ± SD	After the infusion** X ± SD
I	343.0 ± 26.5	352.0 ± 22.6
II	326.0 ± 22.6	348.0 ± 22.1
III	331.5 ± 30.4	336.0 ± 49.1

* The difference of the pulse rates of the groups were insignificant (ANOVA) ($F= 0.587$, $p>0.05$).
** After the infusion the difference of the pulse rates of the groups were insignificant (ANOVA) ($F= 0.759$, $p>0.05$).
Table 5 : Mean pulse rates of the groups before and after the radiocontrast infusion.

between Group I and Group III (1.25 ± 0.84 mg / h) ($p > 0.05$).

DISCUSSION

Until the mid 1970s high dose contrast procedures were considered safe in spite of few reports of toxicity, particularly among dehydrated patients with diabetes. By the late 1970s however reports of the potential nephrotoxicity of contrast exposure began accumulating in the literature (1, 5, 7). Clinicians were suddenly aware of the potential toxicity. However, the fear of precipitating renal failure by contrast studies was probably exaggerated. It is now apparent that toxicity from contrast agents is a significant risk only for a small minority of the millions of patients who undergo these procedures. It is therefore important to identify those individuals who are at greatest risk to develop contrast nephropathy as well as to identify those factors which contribute to the increased risk for this complications.

In this study we studied the effects of hyperosmolality and hemodynamic parameters in rats with radiocontrast nephrotoxicity. Since generally it is quite difficult to cause radiocontrast nephrotoxicity in healthy laboratory rats, the renal functions of these animals were impaired through partial nephrectomy following the procedure published by Heyman et al (9). The renal hemodynamic changes of the rats were inferred from blood pressures and pulse rates measured in real time during the experiment. The solutions described in the experimental procedure were infused to the rats in 1-2 minutes. During the infusion the direct systolic and diastolic blood pressures of the rats that received the radiocontrast material and 4.5 % NaCl solution exhibited statistically significant drops ($p<0.001$), indicating a decrease in renal blood flow. This decrease started 30 seconds after the end of the infusion and lasted about 3-5 minutes. This sequence is termed the biphasic response in the literature and is quite well known (11, 13, 17). On the other hand there is no consensus on the onset and duration of the biphasic response. Katzberg and co-workers reported that the biphasic response starts within 2 minutes and lasts for 10 minutes (11). Given the above, it appears that while the occurence of the biphasic response can be considered a sign of CAN, further studies are needed to correlate the parameters of the biphasic response with the degree of CAN.

Scr values are most sensitive criteria of CAN in several reports (15, 16). After radiocontrast infusion 30-50 % or 1 mg/dl increment is a reflection of CAN (8, 15). In our study we did not measure basal Ccr but accept the Ccr of group II as control Scr. Mean Scr values of group I were higher than the group II and III indicating the CAN.

CONCLUSION

In the occurence of CAN, a lot of factors such as direct cellular toxicity, hyperosmolarity, changes in the renal hemodynamics, tubular obstruction etc. are expected to play roles (2, 8, 11, 14, 17, 19). However, a definitive etiological study has not been completed. In our study we examined the roles of hyperosmolality and changes in the hemodynamic functions. We observed the same hemodynamic changes in the groups that received the radiocontrast agents or 4.5 % NaCl solution. However, only the group that received the radiocontrast agent exhibited Scr increases and Ccr decreases. Consequently, we can summarize that hyperosmolality and the associated hemodynamic changes are not directly responsible for CAN, rather additional factors play a major part in this type of pathogenesis.

Correspondence to : Dr.Aytül NOYAN
Çukurova Üniversitesi Tıp Fakültesi
Pediatrik Nefroloji Bilim Dalı
01330 ADANA - TÜRKİYE
Phone : 322 - 458 40 63

REFERENCES

1. Anseri Z, Baldwin DS : Acute renal failure due to radiocontrast agents. Nephron 1976 ; 17 ; 28-40.
2. Berkseth RO, Kjellstrand CM : Radiologic contrast-induced nephropathy. Med Clin North Am 1984 ; 68 ; 351-370.
3. Brezis M, Greenfeld Z, Herman M, et al : Experimental nephrotoxicity of the radiocontrast agents iohexol, ioxaglate and iothalamate : An in vitro and invivo study. Invest Radiol 1991; 26 ; 325-331.
4. Brezis M, Rosen S, Silva P, Epstein FH : Selective vulnerability of the medullary thick ascending limb to anoxia in the isolated perfused rat kidney. J Clin Invest 1984; 73 ; 182-190.

5. Buyan N, Arab M, Hasanoğlu E, Gökçora N, Ercan S : The effects of contrast media on renal function in children : Comparison of ionic and non-ionic agents. Ped Nephrol 1993; 7 : C45.
6. D'Elia JA, Gleason RE, Alday M, et al : Nephrotoxicity from angiographic contrast material : A prospective study. Am J Med 1982; 72 : 719-725.
7. Diaz-Buxo JA, Wagoner RD, Hattery RR, Palumbo PJ : Acute renal failure after excretory urography in diabetic patients. Ann Intern Med 1975; 83 : 155-158.
8. Hentschel M, Gildein P, Brandis M, Zimmerhackl LB : Endothelin is involved in the contrast media induced nephrotoxicity in children with congenital heart disease. Clin Nephrol 1995; 43 : S12-S15.
9. Heyman SN, Brezis M, Reubinoff CA, et al : Acute renal failure with selective medullary injury in the rat. J Clin Invest 1988; 82 : 401-412.
10. Hou SH, Bushinsky DA, Wish JB, et al : Hospital-acquired renal insufficiency : A prospective study. Am J Med 1983; 74 : 243-248.
11. Katzberg RW, Morris TW, Schulman G, et al : Reactions to intravenous contrast media. Part II : Acute renal response in euvolemic and dehydrated dogs. Radiology 1983; 147 : 331-334.
12. Katzberg RW, Morris TW, Lasser EC, et al : Acute systemic and renal hemodynamic effects of meglumine / sodium diatrizoate 76 % and iopamidol in euvolemic and dehydrated dogs. Invest Radiol 1986; 21 : 793-797.
13. Katzberg RW, Schulman G, Meggs LG, et al : Mechanism of the renal response to contrast medium in dogs : Decrease in renal function due to hypertonicity. Invest Radiol 1983; 18 : 74-80.
14. Nicot GS, Merie LJ, Charmes JP, et al : Transient glomerular proteinuria, enzymu ria and nephrotoxic reaction by radiocontrast media. JAMA 1984; 252 : 2432-2434.
15. Parfrey PS, Griffiths SM, Barrett BJ, et al : Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. N Engl J Med 1989; 320 : 143-149.
16. Porter GA : Contrast-associated nephropathy. Am J Cardiol 1989; 64 : 22E-26E.
17. Reed JR, Williams RH, Luke RG : The renal hemodynamic response to diatrizoate in normal and diabetic rats. Invest Radiol 1983; 18 : 536-540.
18. Schultz SG, Lavelle KJ, Swain R : Nephrotoxicity of radiocontrast media in ischemic renal failure in rabbits. Nephron 1982; 32 : 113-117.
19. Spinler AS, Goldfarb S : Nephrotoxicity of contrast media following cardiac angiography : Pathogenesis, clinical course and preventive measures, including the role of low-osmolality contrast media. Ann Pharmacother 1992; 26 : 56-64.