GASTROCYSTOPLASTY AND CHRONIC RENAL FAILURE: AN ACID-BASE METABOLISM STUDY

LUIZ GONZAGA DE FREITAS FILHO, JOSÉ CARNEVALE, JOVELINO Q. S. LEÃO, NESTOR SCHOR AND VALDEMAR ORTIZ

From the Department of Surgery and Nephrology of Universidade Federal de São Paulo, Escola Paulista de Medicina, São Paulo, Brazil

ABSTRACT

Purpose: To verify in an experimental model whether gastrocystoplasty may protect patients with chronic renal failure from acid loading associated acidosis a wedge-shaped portion of the middle stomach was used to improve bladder capacity in animals with chronic renal failure.

Materials and Methods: An experimental model was used to study 112 adult female Wistar rats (EPM-1) weighing between 156 and 259 gm. The animals were randomly assigned to groups, including 41 controls, 24 undergoing five-sixths nephrectomy to create chronic renal failure, 26 undergoing gastrocystoplasty and 21 undergoing gastrocystoplasty and five-sixths nephrectomy to create renal failure. To provide an acid overload a 5% NH_4Cl diet was administered to a subgroup of each group. Two months after surgery 24-hour urine was collected, and volume and pH were measured as well as the amount of bicarbonate, ammonium, titratable acidity and chloride. The animals were then exsanguinated through an abdominal aorta puncture. The blood was used for blood gas analysis and to measure sodium, potassium, chloride, ionized calcium and creatinine.

Results: When undergoing an acid overload, the animals with gastrocystoplasty had no acidosis since acid radicals were eliminating in the urine as NH_4Cl. When given the same acid overload, metabolic acidosis developed in the animals with gastrocystoplasty and chronic renal failure.

Conclusions: Gastrocystoplasty protected healthy rats from acidosis when they were given an acid overload but failed to protect the rats with chronic renal failure under the same conditions.

KEY WORDS: kidney; bladder; urinary diversion; rats, Wistar; acidosis

Diseases affecting the capacity of the bladder to store urine at low pressure led surgeons to consider the bowel as an alternative in the construction of a reservoir. At first the principle was not widely used but it became more widely used after Lapides et al popularized the idea that the contents of urinary reservoirs may be emptied periodically by clean nonsterile material.[1] Growing experience with such diversions resulted in several reports of frequent urinary tract infections and the development of metabolic acidosis, particularly in patients with already impaired renal function.[2]

To prevent such hyperchloremic acidosis Sinaiko performed an experimental study in 1956 to divert the ureters to a pouch constructed from the gastric body.[3] Rudick et al constructed urinary diversion pouches from the gastric body of dogs and demonstrated that the gastric acid environment prevented urinary tract infection with little formation of mucus.[4] The pouches, which were bathed in a solution containing urea, only showed some absorption when the concentration was 30-fold higher than that usually found in urine. Piser et al compared the transmural flow of ions in the colon and stomach when used to augment vesical capacity.[5] They observed that animals with colocystoplasty tended to absorb water and electrolytes, whereas those with gastrocystoplasty tended to secrete them. Kennedy et al performed a comparative study in animals with gastrocystoplasty or colocystoplasty in which urinary tract obstruction had previously been created by irrigating the urinary diversion with ammonium chloride, which leads to metabolic acidosis.[6] Animals with gastrocystoplasty were found to tolerate the overload better and hyperchloremia did not develop.

Because renal failure and acidosis develop in a large number of patients with lower urinary tract uropathy, the use of stomach for partial or total replacement of the bladder, was aimed at taking advantage of the capacity of the gastric parietal cells to secrete H^+ and Cl^- to obtain an extrarenal source of acid radical elimination. We assessed the ability of gastrocystoplasty to eliminate acid radicals through the extrarenal route in patients with chronic renal failure. We studied the acid-base metabolism of rats that underwent gastrocystoplasty in the presence and absence of an acid overload in an experimental model of renal mass reduction that leads to chronic renal failure.[7]

MATERIALS AND METHODS

A total of 112 adult female Wistar rats (EPM-1) weighing between 156 and 259 gm. were randomly assigned to 4 groups, of which each was divided into 2 subgroups depending on whether an acid overload was induced. Five days before sacrifice the animals in the subgroups with an acid overload were given a diet in which the food was ground and mixed with NH_4Cl in a ratio of food-to-NH_4Cl of 19:1 (5%). The rats were given a known amount of food prepared in this manner and the amount ingested was weighed daily. Animals that failed to ingest an amount deemed the minimum required to develop acidosis were not included in the study. Of the remaining rats 27 in a control subgroup underwent urine and plasma determinations for use as benchmarks for all animals, 14 in a control subgroup underwent acid overload, 10 underwent five-sixths nephrectomy to induce chronic renal failure, 11 underwent five-sixths nephrectomy plus acid overload, 13 underwent gastrocystoplasty, 13 underwent gastrocystoplasty plus acid overload, 11 underwent gastrocystoplasty plus five-sixths nephrectomy, and 10 underwent

gastrocystoplasty plus five-sixths nephrectomy plus acid overload.

The animals were anesthetized intraperitoneally with 30 mg./kg. pentobarbital sodium and 10 mg./kg. chloral hydrate. After identification the rats in the control and control plus acidosis subgroups were maintained on a warm table to maintain rectal temperature at around 37C until they recovered from anesthesia. They were then maintained in individual cages for a 2-month period. The animals in the remaining groups were also placed on a warm table and underwent median laparotomy. The rats in the groups with chronic renal failure, chronic renal failure plus acidosis, gastrocystoplasty plus chronic renal failure and gastrocystoplasty plus chronic renal failure plus acidosis underwent five-sixths nephrectomy according to a previously accepted model.[7] The animals in the groups with gastrocystoplasty, gastrocystoplasty plus acidosis, gastrocystoplasty plus chronic renal failure and gastrocystoplasty plus chronic renal failure plus acidosis underwent gastrocystoplasty according to the technique described by Adams et al.[8] At the end of surgery the rats were maintained in individual cages under the conditions previously described. They were placed in Nalgene metabolic cages (Nalge Co., Rochester, New York) 24 hours before sacrifice. The 24-hour urine sample was collected into a vessel containing a liquid petrolatum film, volume was measured and it was prepared for laboratory determination. The rats were then weighed, anesthetized and prepared as described for the first surgery. The abdominal aorta was isolated and punctured, leading to sacrifice by exsanguination. Part of the blood was immediately introduced into the enclosure of the Model 993 Automatic Blood Gas System device (AVL, Roswell, Georgia) for blood gas determination. The remainder was centrifuged at 2,000 rpm for 10 minutes and the supernatant was collected for plasma measurement of Na, K and Ca ionized through the automated selective Model 9140 Na, K, Ca analyzer ion electrode (AVL). Plasma Cl was determined by photometry.[9] Plasma creatinine was measured by the alkaline picrate method.[10]

After 24-hour urinary volume determination certain measurements were obtained. Urinary HCO_3^- excretion (CO_2 pressure) was determined by placing 1 ml. of urine in the Van Slyke device. The value in mm. Hg was multiplied by the proportionality constant value 0.03 at 37C to convert the result into mmol./l. using the Henderson-Hasselbach equation. To determine titratable acidosis excretion the amount of 0.1 N NaOH in ml. necessary to raise pH to 7.4 was measured, transformed by the rule of 3 into a 1 N solution and then multiplied by 1,000 to obtain the result in μEq. per minute.[11] Ammonium excretion was measured by the direct Nesslerization method in μEq. per minute.[12] As in the plasma determination, chloride was measured by photometry.[9] The Kruskal-Wallis test was done for statistical analysis among the groups and the Mann-Whitney test was performed for comparisons between the groups with and without

acid overload with statistical significance considered at the 5% level ($p < 0.05$).

RESULTS

The animals in the subgroups on acid overload had pH, HCO_3 and CO_2 total plasma values smaller than those in the control subgroup, except for the animals in the gastrocystoplasty plus acidosis subgroup (table 1). When the groups undergoing the same surgical procedure with and without acid overload were compared, no differences were found in the rats with chronic renal failure and those with gastrocystoplasty. However, when the gastrocystoplasty plus chronic renal failure and gastrocystoplasty plus chronic renal failure plus acidosis groups were compared, the values of pH (U = 3/U critical = 26, $p < 0.05$), HCO_3 (U = 11/U critical = 26, $p < 0.05$) and total CO_2 (U = 11/U critical = 26, $p < 0.05$) were always smaller in the animals on acid overload (table 1). Chloride plasma levels in the animals in the control and control plus acidosis groups were higher in the rats with than without acid overload. However, such a difference between the overload and no overload groups was not found in the animals in the remaining groups. Sodium and calcium plasma levels showed no significant difference among the groups compared. For plasma potassium and creatinine all subgroups with chronic renal failure had values higher than those of the animals in the standard control subgroup (table 1).

The rats in the subgroups with acidosis had urinary pH and HCO_3 values smaller than those of the animals in the control subgroup, except for the rats with gastrocystoplasty plus acidosis and gastrocystoplasty plus chronic renal failure plus acidosis (table 2). Such animals also had pH and HCO_3 levels higher than those of the remaining rats with acid overload (control plus acidosis and chronic renal failure plus acidosis) (H = 43.46/H critical =11.07, $p < 0.05$). The animals without acid overload in the chronic renal failure subgroup had pH and HCO_3 urinary levels less than those in the remaining groups (H = 13.68/H critical = 9.49, $p < 0.05$). Comparing the rats with chronic renal failure with and without acid overload showed that acidosis reduced urinary pH (U = 0/U critical = 26, $p < 0.05$) and urinary HCO_3 (U = 2/U critical = 26, $p < 0.05$) (table 2). The acid overload failed to reduce urinary pH and HCO_3 in the groups with gastrocystoplasty, gastrocystoplasty plus acidosis, gastrocystoplasty plus chronic renal failure and gastrocystoplasty plus chronic renal failure plus acidosis. The animals on acid overload had titratable acidity levels higher than those in the control subgroup except for the rats with gastrocystoplasty plus acidosis and gastrocystoplasty plus chronic renal failure plus acidosis. Of the animals without acid overload only those with chronic renal failure had levels of titratable acidity in the urine higher than those in the control subgroup. The animals in all subgroups with and without acid overload had levels of

TABLE 1. *Plasma values in the various groups*

Subgroups	Mean pH	Mean HCO_3 (mMol./l.)	Mean Total CO_2	Mean Na	Mean K	Mean Ca	Mean Cl	Mean Creatinine (mg./dl.)
Control	7.246	16.2	17.4	138	3.8	1.23	102	0.6
Control, acidosis	6.985*	8.3*	9.4*	138	4.1	1.35	118*	0.7
Chronic renal failure	7.198	14.9	16.0	138	4.4*	1.17	109	1.0*
Chronic renal failure, acidosis	7.105*	11.6*	12.8*	140	4.4*	1.27	106†	1.0*
Gastrocystoplasty	7.253	15.2	16.3	138	4.0	1.24	109	0.6
Gastrocystoplasty, acidosis	7.182†	13.0†	14.0†	136	4.2	1.21	107†	0.7
Gastrocystoplasty, chronic renal failure	7.247	16.2	17.3	137	4.5*	1.24	108	0.9*
Gastrocystoplasty, chronic renal failure, acidosis	7.068*,‡	9.8*,‡	10.8*	131	4.8*	1.20	110	1.1*

* Versus control p <0.05.

† Versus control plus acidosis p <0.05.

‡ Versus gastrocystoplasty, chronic renal failure plus acidosis p <0.05.

TABLE 2. *Urinary values in the various groups*

Subgroups	Mean pH	Mean HCO_3 (mMol./l.)	Mean Titratable Acidity (μEq./min.)	Mean NH_4 (μEq./min.)	Mean Chloride (mMol./24 hrs.)
Control	7.4	26.8	0.008	0.212	1.77
Control, acidosis*	5.7	1.3	0.530	3.402	6.75*
Chronic renal failure	7.1*,†	14.0*,†	0.055*,†	0.266†	1.53
Chronic renal failure, acidosis	5.9*,†	3.4*,†	0.295*,†	1.291*,†,‡	2.16‡
Gastrocystoplasty	7.8	29.4‡	0.026	1.285*,†	1.90
Gastrocystoplasty, acidosis	7.0†	15.9†,‡	0.178‡	2.430*,†	4.12*,‡
Gastrocystoplasty, chronic renal failure	7.8	31.1	0.092	2.225*	2.18
Gastrocystoplasty, chronic renal failure, acidosis	7.7‡	25.3‡	0.113‡	2.021*	2.96‡

* Versus control p <0.05.
† Versus plus acidosis p <0.05.
‡ Versus control plus acidosis p <0.05.

total urinary ammonium that were higher than those in the control subgroup except for the rats with chronic renal failure and without acid overload. In these animals levels of total ammonium in the urine were smaller than in the remaining subgroups (H = 30.63/H critical = 9.49, p <0.05, table 2). Urinary chloride showed no significant differences among the rats without acid overload but it was higher in the control subgroup with acidosis and the groups with gastrocystoplasty plus acidosis. In the animals with gastrocystoplasty and gastrocystoplasty plus acidosis the urinary parameters showed that acid overload reduced the levels of HCO_3 (U = 8.5/U critical = 45.0, p <0.05) and increased the levels of acid secretion due to ammonium (U = 38/U critical = 45, p <0.05, table 2). When gastrocystoplasty was performed in the animals with chronic renal failure with and without acidosis, acid overload caused neither a reduction in urinary pH nor increased acid secretion as titratable acidity and ammonium (table 2). Tables 1 and 2 show the mean plasma and urinary values, respectively, in the animals studied in the various groups.

DISCUSSION

The use of bowel for complete or partial bladder replacement has enabled the construction of low pressure reservoirs of greater capacity. The possibility of emptying its contents by periodical catheterization virtually made its use universal in all cases in which replacement of the lower urinary tract was required.[1] However, as experience with bowel diversions increased, complications arose, including mucous formation with the consequent predisposition to bacterial colonization and spontaneous perforation, tumor potential and given the great reabsorption capacity the development of hyperchloremic acidosis.[2,13,14]

Much effort has been devoted toward explaining and understanding the actual mechanism of intestinal diversion hyperchloremic metabolic acidosis. The latest and most accepted attempt is that of Koch and McDougal.[15] They experimentally showed that when the intestinal segment is in contact with urine, it reabsorbs chloride, potassium and ammonium. In their study they speculate that ammonium would be partially absorbed as its NH_3-free conjugated basis (diffusible) and the released H^+ would be reabsorbed with chloride or excreted as titratable acid. Thus, one may say that although the actual hyperchloremic acidosis production mechanism of intestinal diversions is not yet completely understood, it is to a large extent associated with the reabsorption of ammonium and to a lesser extent with the secretion of bicarbonate in the urine.

Based on the capacity of gastrocystoplasty constructed with the gastric body to maintain the chloropeptic secretion of parietal cells this model was initially designed to study the acid-base metabolism of animals in chronic renal failure in a renal mass reduction model.[7] We observed whether gastrocystoplasty would protect such animals from acidosis by creating an H^+ radical extrarenal clearance source, as in the study of Kennedy et al[6] in which chronic renal failure developed in the animals due to obstructive uropathy.

In contrast to obstructive uropathy models that compromise all nephrons from the start, in the chronic renal failure model used the remaining nephrons suffer structural and functional hypertrophy, increasing the single nephron glomerular filtration rate in response to the work required to offset renal mass reduction. Similarly major tubular changes occur to produce and reabsorb the increased filtered volume. With time there is progressive and pathological tubular dilatation as well as interstitial inflammation and fibrosis, leading to glomerulosclerosis. This process is accompanied by azotemia, proteinuria and hypertension, taking the inexorable course toward chronic renal failure.[7] In this model the glomerular filtration rate is reduced by 30% to 50%.[7,16] We ascertained the adequacy of the model used by observing high serum creatinine and potassium values in the animals in the subgroups with chronic renal failure, chronic renal failure plus acidosis, gastrocystoplasty plus chronic renal failure and gastrocystoplasty plus chronic renal failure plus acidosis in relation to the control group (table 1).

Because the rats in the subgroups receiving no acid overload ingested a vegetal origin protein diet, a urinary acidification defect developed due to hyperactivity of the intercalary β cells of the collecting tubules, accounting for the secretion of HCO_3^- of the tubular lumen through an HCO_3^-/Cl^- protein exchanger and H^+ of the peritubular capillaries, thus, losing a large amount of HCO_3^- in the urine (table 2). On the other hand, animals with chronic renal failure due to increased anionic retention triggered by the reduced glomerular filtration rate start to lose less bicarbonate, thus, decreasing urinary pH (table 2).

Despite a major renal mass reduction the remaining nephrons were able to maintain pH, HCO_3^- and total CO_2 plasma levels (table 1). Only the urinary parameters showed the adaptive changes in acid-base metabolism (table 2). By aiming to establish a more extreme acidosis situation a new experimental model was created (the acidosis subgroups), in which, similar to the technique in the experiment of Kennedy et al,[6] the animals were given a chronic NH_4Cl overload, giving rise to acidosis.

The plasma levels and urinary determinations in the control subgroup plus acidosis corroborated the suitability of the new model for developing hyperchloremic metabolic acidosis. We then proceeded to verify whether gastrocystoplasty, which is known to maintain the acid and chloride secretion capacity of the gastric cell when implanted into the bladder, would protect the animals with chronic renal failure from acid overload. The transplanted gastric mucosa capacity to maintain chloropeptic secretion is stressed as one of the qualities explaining the use of stomach in urinary diversion in patients with hyperchloremic acidosis.[16] Therefore, testing the capacity of gastrocystoplasty to protect patients with chronic renal failure from acidosis represented an effort to verify the validity of its main indication since complications

found with experience and in comparison to other forms of bowel diversion have increasingly curbed its use.[13, 17-20] Creating acid overload in the chronic renal failure plus acidosis subgroup showed that in this model pH, HCO_3^- and CO_2 total plasma levels were maintained. Therefore, no overt acidosis developed because ammonium genesis was not yet compromised and the acid radicals were still cleared. Despite the renal mass reduction a major compensating increase in the total excretion of acids as titratable acid and ammonium was found, as already noted by MacClean and Hayslett (table 2).[21] Likewise, when the subgroup of animals in which gastrocystoplasty was performed were given an acid overload, no overt acidosis developed when pH, HCO_3^- and total CO_2 plasma levels were compared with those in animals gastrocystoplasty but without the overload. In this case the capacity of the parietal cells to secrete H^+ and Cl^- taken to the bladder made possible the elimination of the acid overload as NH_4^+ and Cl^-. Since the NH_3/NH_4^+ buffer pK is 9.15, the elimination of H^+ was possible with no great variations to urinary pH and, thus, between the subgroups with gastrocystoplasty and gastrocystoplasty plus acidosis no difference in such levels was found. Such findings allow one to state that gastrocystoplasty proved capable of protecting animals without chronic renal failure from metabolic acidosis triggered by acid overload. Nevertheless, gastrocystoplasty failed to protect the rats with gastrocystoplasty plus chronic renal failure plus acidosis from acidosis triggered by acid overload. Nonhyperchloremic acidosis (uremic acidosis) caused by acid overload in those animals (since there is retention of ions other than chlorides) (table 2) and the likely reduction in NH_3 synthesis by the tubular cells prevented the acid overload from being cleared as NH_4^+ and Cl^-. In this subgroup with gastrocystoplasty plus chronic renal failure plus acidosis the increased relative capacity to clear acids was not enough to prevent acidosis. Because uremic acidosis is known to be accompanied by the retention of ions other than chloride as well as the fact that in such individuals the tubular cells lose a great deal of NH_3 synthesis capacity, it is recommended that more long-term studies should be performed for the further assessment of the role of gastrocystoplasty in such cases. To our knowledge no type of urinary derivation outweighs any other at the moment. When urothelial tissue is unavailable for vesical amplification, ileocystoplasty, colocystoplasty or gastrocystoplasty are the options. Although the benefits of gastrocystoplasty are currently known,[2] the experience is still recent and an in-depth evaluation is necessary to elucidate its role in the management of lower urinary tract diseases.

REFERENCES

1. Lapides, J., Diokno, A. C., Silber, S. J. et al: Clean, intermittent self-catheterization in the treatment of the urinary tract disease. J Urol, 107: 458, 1972
2. Nguyen, D. H. and Mitchell, M. E.: Gastric bladder reconstruction. Urol Clin North Am, 18: 649, 1991
3. Sinaiko, E. S.: Artificial bladder from segment of stomach and study of effect of urine on gastric secretion. Surg Gynecol Obstet, 102: 433, 1956
4. Rudick, J., Schonholz, S. and Weber, H. N.: The gastric bladder: a continent reservoir for urinary diversion. Surgery, 82: 1, 1977
5. Piser, J. A., Mitchell, M. E., Kulb, T. B. et al: Gastrocystoplasty and colocystoplasty in canines: the metabolic consequences of acute saline and acid loading. J Urol, part 2, 138: 1009, 1987
6. Kennedy, H. A., Adams, M. C., Mitchell, M. E. et al: Chronic renal failure and bladder augmentation: stomach versus sigmoid colon in the canine model. J Urol, part 2, 140: 1138, 1988
7. Hostetter, T. H., Olson, J. L., Rennke, H. G. et al: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol, 241: F85, 1981
8. Adams, M. C., Mitchell, M. E. and Rink, R. C.: Gastrocystoplasty.: an alternative solution to the problem of urological reconstruction in the severely compromised patient. J Urol, 140: 1152, 1988
9. Zall, D. M., Fisher, D.and Garner, M. Q.: Photometric determination of chlorides in water. Anal Chem, 28: 1665, 1956
10. Bonsnes, R. W. and Taussky, H. H.: On the colorimetric determination of creatinine by the Jaffe reaction. J Biol Chem, 158: 581, 1945
11. Jørgensen, K.: Titrimetric determination of the net excretion of acid/base in urine. Scand J Clin Lab Invest, 9: 287, 1957
12. Connerty, H. V., Briggs, A. R. and Eaton, E. H., Jr.: Determination of preformed urinary ammonia (nitrogen) by means of direct nesslerization. Am J Clin Pathol, 28: 634, 1957
13. Bauer, S. B., Hendren, W. H., Kozakewich, H. et al: Perforation of the augmented bladder. J Urol, 148: 699, 1992
14. Blyth, B., Ewalt, D. H., Duckett, J. W. et al: Lithogenic properties of enterocystoplasty. J Urol, 148: 575, 1992
15. Koch, M. O. and McDougal, W. S.: The pathophysiology of hyperchloremic metabolic acidosis after urinary diversion through intestinal segments. Surgery, 98: 561, 1985
16. Bregman, R., Boim, M. A., Santos, O. F. et al: Effects of systemic hypertension, antidiuretic hormone and prostaglandins on remnant nephrons. Hypertension, suppl., 15: I72, 1990
17. Sheldon, C. A., Gilbert, A., Wacksman, J. et al: Gastrocystoplasty: technical and metabolic characteristics of the most versatile childhood bladder augmentation modality. J Pediatr Surg, 30: 283, 1995
18. Gold, B. D., Bhoopalam, P. S., Reifen, R. M. et al: Gastrointestinal complications of gastrocystoplasty. Arch Dis Child, 67: 1272, 1992
19. Kinahan, T. J., Khoury, A. E., McLorie, G. A. et al: Omeprazole in post-gastrocystoplasty metabolic alkalosis and aciduria. J Urol, 147: 435, 1992
20. Nguyen, D. H., Bain, M. A., Salmonson, K. L. et al: The syndrome of dysuria and hematuria in pediatric urinary reconstruction with stomach. J Urol, 150: 707, 1993
21. MacClean, A. J. and Hayslett, J. P.: Adaptive change in ammonia excretion in renal insufficiency. Kidney Int, 17: 595, 1980