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The role of pneumoperitoneum in the glomerular filtration in an experimental model with 2/3 reduction of the renal mass

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ABSTRACT. Objective: To evaluate the influence of the CO_2 pneumoperitoneum in the glomerular filtration in a rat model with a 2/3 reduction of renal parenchyma. Methods: Adult Wistar male rats (n = 50) were subjected to right nephrectomy and a 2/3 ligature of the renal left vascular branch. Animals were randomly distributed as follows: GI (n = 10) - simulated, GII (n = 20) – 8 mm Hg pneumoperitoneum, and GIII (n = 20) – 15 mm Hg pneumoperitoneum. After two (GIIA and GIIIA) and three (GIIB and GIIIB) hours of insufflation, and one hour of disinsufflation, they were evaluated for the following aspects: mean blood pressure (MBP), microhematocrit, urinary volume and inulin clearance. Results: The microscopic aspects showed signs of glomerulosclerosis that caused proteinuria. Renal function with 8 mm Hg pneumoperitoneum after two hours of disinsufflation (Δ% = 202.68) was better than after three hours (Δ% = 10.89). With 15 mm Hg pneumoperitoneum, the renal function was damaged by both procedures, that is, two (Δ% = -3.57) and three hours (Δ% = -3.25). Conclusion: Inulin clearance evidenced renal insufficiency in the model with a 2/3 reduction of renal mass, and depending on both the increase of the exposure time and the pressure intensity, it can be more intensified.

Keywords: inulin, kidney failure, pneumoperitoneum, video-assisted surgery.

O papel do pneumoperitônio na função renal em um modelo experimental de redução de 2/3 do parênquima renal

RESUMO. Este estudo tem como objetivo avaliar a influência do pneumoperitônio induzido CO_2 sobre a função renal em um modelo em ratos com redução de 2/3 de sua massa renal. Em relação à metodologia, ratos Wistar (n=50), machos, adultos, foram submetidos à nefrectomia direita e ligadura de 2/3 do pedículo vascular renal esquerdo. A seguir, foram aleatoriamente distribuídos em GI (n=10)– Simulado, GII (n=20) com pneumoperitônio de 8 mmHg e GIII (n=20) compneumoperitônio de 15 mmHg, por uma hora. Após duas (GIIA e GIIIA) e três (GIIB e GIIIB) horas da desinsuflação, foram avaliadas a pressão arterial média (PAM), micro-hematócrito, volume urinário e *clearance* da inulina. Os resultados da microscopia mostraram que o rim remanescente apresentou sinais de glomeruloesclerose, caracterizada pela proteinúria. A função renal com pneumoperitônio de 8 mmHg após duas horas da insuflação (Δ%=202,68) foi melhor do que com três horas (Δ%= 10,89). Com o pneumoperitônio de 15 mmHg tanto com duas (Δ%=-3,57) quanto três horas (Δ%=-3,25), a função renal esteve prejudicada. Concluiu-se que o*clearance* da inulina mostrou haver um comprometimento da função renal no modelo de redução de 2/3 do parênquima e que, dependendo do volume e do tempo de pneumoperitônio, pode ser agravada.

Palavras-chave: inulina, insuficiência renal, pneumoperitônio, cirurgia vídeo-assistida.

Introduction

Although the renal transplant frequently allows a better quality of life to chronic renal patients, the donor is still the limiting factor. The number of patients waiting for a transplant is a universal problem. The donor candidate does not always satisfy the ideal criteria of health state for such cases. There is a global tendency to expand the group of renal donors by using the so-called marginal donors: people with diabetes, hypertension, glomerulosclerosis, some types of cancer, and some cardiopathies (Bloom et al., 2005; Merion et al., 2005).

The increase of living donors, due to the facility of video-assisted surgery associated with the use of marginal donors, has supported the importance of the problem of eventual deleterious effects of the pneumoperitoneum in these particular cases (Hazebroek et al., 2002).

Nature and temperature of the gas used (Saad, Minor, Mohri, & Nagelschmidt, 2001; Farias et al., 2011; Berganza & Zhang, 2013), as well as the pressure (Berguer, Gutt, & Stiegmann, 1993), the speed of insufflations and maintenance, hemodynamic repercussions, and the eventual diffusion of microorganisms have been exhaustively studied (Sorbello et al., 2003).

Renal changes depend on the pressure intensity; however, it is transitory and ends after the release of pneumoperitoneum. There is no evidence of either histopathological injuries or tubular lesions. Both renal function and diuresis return to normal state without long-term sequels (Dunn & McDougall, 2000).

Studies on the effects of increased intra-abdominal pressure and volume expansion on renal function with the use of animals, such as rats (Hazebroek et al., 2003; Fagundes, Montero, Novo, & Bandeira, 2001; Lee et al., 1999), pigs (London et al., 2000; Lindberg, Bergqvist, Bjorck, & Rasmussen, 2003; Gudmundsson, Viste, & Myking, 2003), rabbits (Guler, Sade, & Kirkali, 1998; Bentes de Souza, Wang, & Chu, 2003) and humans (Hawasli et al., 2003; Nguyen, Perez, Fleming, Rivers, & Wolfe, 2002; Pérez et al., 2002), have brought new knowledge on oliguria, which occurs in laparoscopic procedures and how to reduce such deleterious effects.

The transitory and reversible oliguria without sequel in a kidney of a normal donor would have the same behavior in a previously injured kidney.

From this starting point, this study aimed to analyze the functional changes in experimental animals subjected to both a significant reduction of the renal mass and varying pneumoperitoneum pressures.

Material and methods

Methods

Renal function was evaluated in 50 male rats, aging 2-3 months and weighing 250-300 grams. They were subjected to right nephrectomy and a 2/3 ligature of the renal left vascular branch, as well as to induced CO_2 pneumoperitoneum.

Rats were randomly distributed in three groups (pressure intensity) and two subgroups (pressure time). Group I (n = 10) – without pneumoperitoneum; Group II (n = 20) – 8 mm Hg pneumoperitoneum and Group III (n = 20) – 15 mm Hg pneumoperitoneum. Animals of Groups II and III were reassigned to subgroups: IIA (n = 10) and IIIA (n = 10) with two hours of insufflation and one hour of disinsufflation; and IIB (n = 10) and IIIB (n = 10) with three hours of insufflation and one hour of disinsufflation.

The distribution of the animals in different groups is illustrated in the flowchart below (Figure 1).

After intramuscular anesthesia, a xiphopubic incision was performed with the identification of vessels near the emergence of the renal left artery, with inferior arterial branch ligature and nephrectomy to the right, for a 2/3 reduction of the renal mass. After the first week, 1% sodium chloride was added to speed up the level of glomerulosclerosis and proteinuria for about six weeks. Animals were subjected to diuresis control in metabolic cages for 24 hours for collecting the urine for proteinuria determination, and monitoring the chronic renal insufficiency.

After six weeks, animals were subjected to an anesthetic procedure and a preoperative preparation similar to the previous round to install and control the pneumoperitoneum, in addition to the dissection of the *carotis communis* artery and the left jugular vein, as well as the catheterization with polyethylene catheter (PE 50) in order to measure both the mean arterial pressure (MAP) and the saline solution infusion in pump at two millimeters per hour.

Once the first blood collection for the determination of microhematocrit was completed, a laparotomy with lower midline incision was carried out, with vesicostomy and purse-string suture for catheter fixation and insufflation of pneumoperitoneum according to the groups.

Inulin infusion at mL h^{-1} was performed through the jugular vein by keeping the animal in a thermal box at about 28ºC. Rectal temperature was measured with a digital thermometer.

Forty five minutes after establishing the pneumoperitoneum and beginning the inulin infusion, the urinary bladder was emptied (Figure 2); 60 minutes later, the arterial blood (0.2 mL) was collected for serum inulin dosage. Afterwards, a second blood sample was taken to determine the microhematocrit (hydration control). Sixty minutes after pneumoperitoneum disinsufflation, the urinary bladder was emptied once more, and 75 minutes after that, the arterial blood (0.2) was collected as before, so that the serum inulin was determined. After 90 minutes, a new urinary inulin dosage was performed.

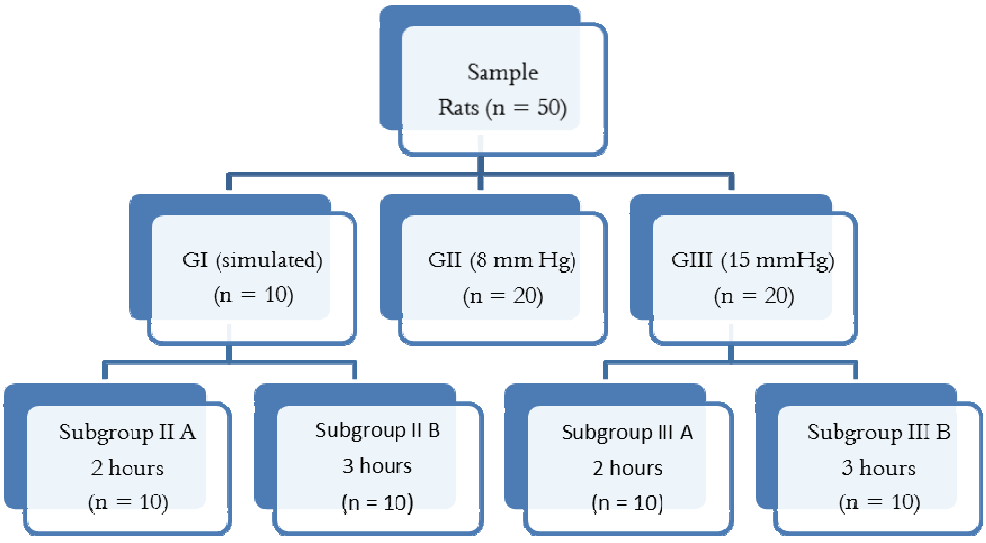

Figure 1. Scheme of the animals' distribution in the different groups studied.

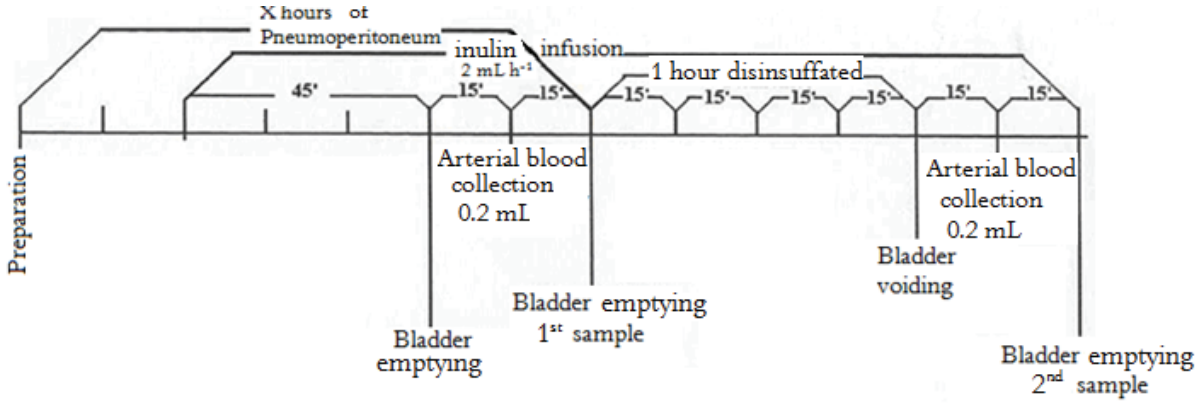

Figure 2. Procedures for establishing the pneumoperitoneum and data collection in the different groups.

In group I (sham), only the abdominal cavity was opened, with dissection of the carotid, jugular, vesicostomy and introduction of Veress needle (without pneumoperitoneum), as well as collection of blood and urine as previously reported to measure the inulin clearance.

After these procedures, euthanasia, exploratory laparotomy and nephrectomy of the left remaining kidney were performed, the kidney was subjected to a histological study. Qualitative and quantitative evaluations were carried out with the use of a computerized image analyzer to calculate the necrosis area percentage in the remaining left kidney.

Inulin clearance was calculated as follows: urine inulin concentration x urinary volume $min.^{-1}$ $inulin^{-1}$ concentration in plasma.

Wilcoxon's test, Analysis of Variance and Kruskal-Wallis' non-parametric test were used for data analysis.

Results

Once the inulin clearance measurement is difficult, the percentile variation of its values (Δ%) was chosen for statistic calculation. Tables 1 and 2 present the mean and standard deviations by using the tests mentioned above.

Table 1. Mean and standard deviation (expressed in mL $min.^{-1}$) of inulin in the initial and final exposure time. Δ% was also calculated.

	Pneumo (Initial)	Disinsufflation (Final)	Δ%
Groups			
Sham	0.1321 ± 0.3	0.4663 ± 0.14	277
II A	0.0633 ± 0.08	0.0712 ± 0.05	203
II B	0.0983 ± 0.02	0.1025 ± 0.02	11
III A	0.0941 ± 0.05	0.0807 ± 0.03	-3.57
III B	0.1071 ± 0.04	0.0962 ± 0.03	-3.25

Data were subjected to statistical analysis by using the following tests:

Wilcoxon's test evaluated the dependent variables (pneumoperitoneum x disinsufflation). Considering the control group, inulin values were significantly higher in the final exposure time, however, no significant differences were detected between groups IIA and IIB.

Mann Whitney's test (2 hours x 3 hours Δ%) did not evidence any significant difference.

Kruskal Wallis' test evaluated the independent variables (group Sham x Group II x Group III Δ%). The following sequence was registered: group Sham > II B and III A and IIIB.

Table 2. Mean urinary volume and standard deviation (expressed in mL min.$^{-1}$) in the initial and final exposure time. Δ% was also calculated.

	Pneumo (Initial)	Disinsufflation (Final)	Δ%
Groups			
Sham	1.05 ± 0.15	1.09 ± 0.16	4.53
II A	0.7 ± 0.17	0.64 ± 0.13	-6.01
II B	0.86 ± 0.12	0.93 ± 0.15	8.19
III A	0.93 ± 0.18	0.90 ± 0.17	-2.10
III B	0.95 ± 0.14	0.94 ± 0.14	-0.11

Wilcoxon's test evaluated the dependent variables (pneumoperitoneum x disinsufflation). No significant values were found.

In Mann Whitney's test (2 hours x 3 hours Δ%) Group II B > II A, however, no significant values were found in Group III.

Kruskal Wallis' test evaluated the undependable variables (group Sham x Group II x Group III Δ%). No significant values were observed.

Microscopic analysis

Non-specific interstitial nephritis, discrete tubular changes with focal dilatation containing proteinaceous material, and focal glomerulosclerosis were observed, which is typical of both renal insufficiency and onset of proteinuria (Figures 3 and 4).

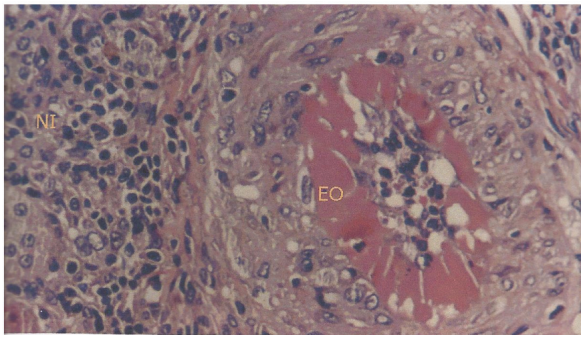

Figure 3. Photomicrography of the kidney of an animal of group I (sham) in the area not subjected to ischemia, showing the endarteritis obliterans (EO) associated with interstitial nephritis (IN). The aspects were similar in all the remaining animals of the three groups (HE – 400 x).

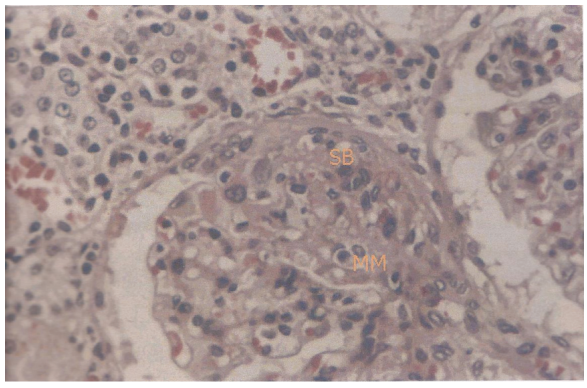

Figure 4. Photomicrography of the kidney of an animal of group I (sham) in the area not subjected to ischemia, showing focal glomerular change with a slight increase of the mesangial matrix and cellularity (MM), as well as synechia of both the parietal and visceral folium and Bowman's capsule (SB). The aspects were similar in all the remaining animals of the three groups (HE – 400 x).

Results and discussion

There still remains the doubt whether transitory and reversible oliguria without sequels in the kidney from a normal donor would have the same behavior as in a previously injured kidney.

The purpose of this study was to produce a rat model with functional and histopathological signs of renal insufficiency. After testing some situations in a pilot study, it was possible to standardize a procedure that allowed the establishment of renal failure that could lead the animal to simulate a chronic renal disease with loss of its glomerular filtration capacity.

Therefore, the population of functioning nephrons was reduced. Both the unilateral nephrectomy and the partial nephrectomy (2/3) of the contralateral kidney, shown in the pilot study, characterized a kidney with renal insufficiency at medium and long-term. However, the observation period necessary for such manifestations was long (over ninety days) and associated with a high morbidity rate, which made it difficult to acquire an adequate sampling.

The inclusion of an overload of sodium chloride to the diet caused a more evident renal insufficiency in a shorter period of time, without loss of animals.

The addition of sodium chloride to the diet has accelerated the glomerulosclerosis and increased the proteinuria rate. In the pilot study, without the addition of salt, the time for obtaining proteinuria was longer. Such addition occurred after the first week of nephrectomy, since if it was promptly performed, the mortality rate would increase during the post-operative period. After the sixth week, the histological evaluation showed evidences of glomerulosclerosis, which is the classical finding

that confirms the renal insufficiency and also the onset of proteinuria.

In order to characterize the renal insufficiency, a dosage of inulin, that is, a vegetable starch, was applied. Inulin clearance, according to Tanner (2003), is the virtual volume of plasma which contains inulin eliminated by the kidneys in a certain period of time. The inulin is neither secreted nor reabsorbed by the kidneys, consisting, thus, a freely filtered substance. It is considered the 'gold standard' for measuring the glomerular filtration (Feher, 2012; Takahira et al., 2001; Padrini & Palatini, 2003).

Inulin filtration test has proved to be efficient in several animal models, such as in dogs (Buranakarl, Kijtawornrat, Nampimoon, Chaiyabutr, & Bovee, 2003), cats (Haller et al., 2003; Miyamoto, 2001), pigs (Van Westen et al., 2002; Kriern et al., 2001; Bauer, Walter, & Zwiener, 2000), and rats (Schaeffer, Gratrix, Mucha, & Carbajal, 2002; Fischer, Bogoliuk, Ramirez, Sanchez, & Masnatta, 2000).

The inulin dose used (at the concentration of 16 mg per kilo of weight and with a speed of 2 mL per hour) was attested by similar studies in the literature (Schaeffer et al., 2002; Fischer et al., 2000).

The determination of hematocrit and average arterial pressure had the goal of ensuring that hemodynamic changes would not occur, which could alter the glomerular filtration rate.

Based on Wilcoxon's test, the dependent variables were evaluated considering the differences between the pneumoperitoneum and disinsufflation exposure time. A better glomerular filtration rate was verified in the control group in the final period. Therefore, it can be indirectly stated that during disinsufflation, the renal function is not totally recovered when using a pressure of 8 or 15 mm Hg for a two-three-hour-period of time, in addition to one hour of disinsufflation. These findings are not in accordance with Beduschi, Beduschi, Williams and Wolf (1999), who evaluated the renal function with serum creatinine, however, corroborate Moreira (2002) on hypertensive rats, which showed a potential renal insufficiency. Thus, it can be concluded that the pneumoperitoneum is more injurious to a kidney with renal insufficiency when compared to a normal kidney.

Kruskal Wallis' analysis of variance (Table 1) of independent groups, comparing the two-three-hour-period for the three groups, showed that the glomerular filtration rate is much more efficient in the control group than in group III, but is not significant in group II subjected to a lower pneumoperitoneum pressure. Nevertheless, when these same parameters were analyzed during the three-hour-period of time, these differences appeared in both groups, proving that the pneumoperitoneum is detrimental for kidney in a direct proportion to the time and pneumoperitoneum pressure.

In the literature, there is no study evaluating the glomerular filtration rate in rats with chronic renal insufficiency by using inulin in the presence of different pneumoperitoneum pressures and disinsufflation, thus, a comparative analysis is limited.

The evaluation of the urinary volume (Table 2) based on Wilcoxon's test showed no statistical difference concerning the pneumoperitoneum and disinsufflation exposure times. However, some changes were detected in the renal function when the evaluation was carried out with inulin, which corroborates the fact that diuresis is not a good parameter for the evaluation of renal function (Salas, Giacaman, & Vio, 2003; Schrier, Wang, Poole, & Mitra, 2004; Pickering & Endre, 2014).

The macroscopic evaluation of the fifty kidneys indicated a wide range of small depressions and color changes in the polar site, with reddish brown tint denoting tissue necrosis, represented by areas of collapse with hemorrhage spots and lesser consistency.

Such necrotic changes were confirmed under optical microscopy, in other words, a wide range of ischemic alterations occurred. Among these, representative fields were selected to confirm the established necrosis and the extension of the process with due quantification, which varied from 22 to 28% of the surface of the examined specimens.

Further studies are necessary to clarify the reversibility of the functional behavior of damaged kidneys, as well as those subjected to high pneumoperitoneum pressures, and verify how the procedures for kidney preservation for future transplant can be affected under such situations.

Conclusion

Inulin clearance evidenced that renal function is impaired when using the 2/3 reduction model of renal mass, and that it is directly related to both the pressure and the pneumoperitoneum exposure time.

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